Comparative Quantification of Health Risks

Global and Regional Burden of Disease Attributable to Selected Major Risk Factors

Volume 1

Edited by

Majid Ezzati, Alan D. Lopez, Anthony Rodgers and Christopher J.L. Murray

World Health Organization
Geneva

WHO Library Cataloguing-in-Publication Data

Comparative quantification of health risks : global and regional burden of disease attributable to selected major risk factors / edited by Majid Ezzati . . . [et al.].

2 v. + v.3 in 1 CD-ROM.

Contents: vol. 1, Childhood and maternal undernutrition—Other nutrition-related risk factors and physical activity—Addictive substances—vol. 2, Sexual and reproductive health—Environmental and occupational risks—Other selected risks—Distribution of risks by poverty—Data analysis and results—Multi-risk assessment.—Annex tables CD-ROM, Population attributable fractions, mortality and disease burden for selected major risk factors.

1. Risk factors 2. Cost of illness 3. Risk assessment
4. Comparative study I. Ezzati, Majid. II. Title: Global and regional burden of disease attributable to selected major risk factors.

ISBN 92 4 158031 3 (NLM Classification: WA 105)

Typeset in Hong Kong
Printed in Switzerland

Contents

Volume 1

CD-ROM

Annex tables

Population attributable fractions, mortality and disease burden for selected major risk factors

List of authors

H. Ross Anderson, St George's Hospital Medical School, University of London, London, England (randerso@sghms.ac.uk).

Gavin Andrews, WHO Collaborating Centre for Evidence in Mental Health Policy, St Vincent's Hospital, Sydney, Australia (gavina@crufad.unsw.edu.au).

Natasha Andronova, Department of Atmospheric Sciences, University of Illinois at Urbana-Champaign,Urbana, IL, USA (natasha@uiatma.atmos.uiuc.edu).

Gregory L. Armstrong, Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, GA, USA (GArmstrong@cdc.gov).

Timothy P. Armstrong, Chronic Diseases and Health Promotion, World Health Organization, Geneva, Switzerland (armstrongt@who.int).

José Luis Ayuso-Mateos, Servicio de Psiquiatria, Hospital Universitario de la Princesa, Madrid, Spain (joseluis.ayuso@uam.es).

Jamie Bartram, Protection of the Human Environment, World Health Organization, Geneva, Switzerland (bartramj@who.int).

Robert E. Black, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (rblack@jhsph.edu).

Tony Blakely, Department of Public Health, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand (tblakely@wnmeds.ac.nz).

Monika Blössner, Nutrition for Health and Development, World Health Organization, Geneva, Switzerland (bloessnerm@who.int).

Fiona C. Bull, School of Sport & Exercise Sciences, Loughborough University, Loughborough, Leicestershire, England (F.C.L.Bull@lboro.ac.uk).

Diarmid Campbell-Lendrum, Protection of the Human Environment, World Health Organization, Geneva, Switzerland (campbelllendrumd@who.int).

Laura E. Caulfield, Department of International Health, Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (lcaulfie@jhsph.edu).

Louise Causer, European Centre on the Health of Societies in Transition, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, European London, England.

John Cleland, Centre for Population Studies, London School of Hygiene and Tropical Medicine, London, England (john.cleland@lshtm.ac.uk).

Aaron J. Cohen, Health Effects Institute, Boston, MA, USA (acohen@healtheffects.org).

Martine Collumbien, Centre for Population Studies, London School of Hygiene and Tropical Medicine, London, England (martine.collumbien@bigfoot.com).

Marisol Concha-Barrientos, Asociación Chilena de Seguridad, Gerencia de Salud, Santiago, Chile (gsamcb@gw.achs.cl).

Justine Corry, WHO Collaborating Centre for Evidence in Mental Health Policy, St Vincent's Hospital, Sydney, Australia (j.corry@unsw.edu.au).

Carlos Corvalan, Protection of the Human Environment, World Health Organization, Geneva, Switzerland (corvalanc@who.int).

Mercedes de Onis, Nutrition for Health and Development, World Health Organization, Geneva, Switzerland (deonism@who.int).

Louisa Degenhardt, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia (l.degenhardt@unsw.edu.au)

Tracy Dixon, Cardiovascular Disease, Diabetes and Risk Factor Monitoring Unit, Australian Institute of Health and Welfare, Canberra, Australia (tracy.dixon@aihw.gov.au).

Timothy Driscoll, School of Public Health, University of Sydney, Sydney, Australia (elmatom@optushome.com.au).

Sally Edwards, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, England (edwardss@who.int).

Paul Elliot, Department of Epidemiology and Public Health, Imperial College of Science Technology and Medicine, London, England (p.elliot@ic.ac.uk).

Majid Ezzati, Harvard School of Public Health, Boston, MA, USA (mezzati@hsph.harvard.edu).

Lorna Fewtrell, Centre for Research into Environment and Health, University of Wales, Aberystwyth, Wales (lorna@creh.demon.co.uk).

Marilyn A. Fingerhut, National Institute for Occupational Safety and Health, Washington, DC, USA (mfingerhut@cdc.gov).

Steven M. Fishman, Department of International Health, Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (sfishman@jhsph.edu).

Ulrich Frick, Addiction Research Institute, Zurich, Switzerland (ulrich.frick@isf.unizh.ch).

Makeda Gerressu, Department of Primary Care and Population Sciences, Centre for Sexual Health and HIV Research, Royal Free and University College Medical School, London, England (mgerressu@gum.ucl.ac.uk).

Gerhard Gmel, Swiss Institute for the Prevention of Alcohol and Drug Problems, Lausanne, Switzerland (ggmel@sfa-ispa.ch).

Kathryn Graham, Centre for Addiction and Mental Health, London, Canada (kgraham@uwo.ca).

Kersten Gutschmidt, Protection of the Human Environment, World Health Organization, Geneva, Switzerland (gutschmidtk@who.int).

Simon Hales, Department of Public Health, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand (shales@wnmeds.ac.nz).

Wayne Hall, Institute for Molecular Biosciences, University of Queensland, Brisbane, Queensland, Australia (w.hall@imb.uq.edu.au).

Sandra Ham, Centers for Disease Control and Prevention, Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Atlanta, GA, USA (svh6@cdc.gov).

Anja M. Hauri, Staatliches Untersuchungsamt Hessen, Dillenburg, Germany (a.hauri@suah-ldk.hessen.de).

Miguel Hernan, Harvard School of Public Health, Boston, MA, USA (mhernan@hsph.harvard.edu).

Yvan J.F. Hutin, Essential Health Technology, World Health Organization, Geneva, Switzerland (hutiny@who.int).

Adnan A. Hyder, Department of International Health, Health Systems and Management Program, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (ahyder@jhsph.edu).

Cathy Issakidis, WHO Collaborating Centre for Evidence in Mental Health Policy, St Vincent's Hospital, Sydney, Australia (cathyi@crufad.unsw.edu.au).

Rachel Jackson-Leach, International Obesity Task Force, London, England (rleach@iotf.org; rachjacklea@aol.com).

W. Philip T. James, International Obesity Task Force, London, England (jeanhjames@aol.com).

David Jernigan, Health Policy Institute, Georgetown University, Washington, DC, USA (djernigan@aol.com).

Eleni Kalamara, International Obesity Task Force, London, England (obesity@iotf.org).

David Kay, Centre for Research into Environment and Health, University of Wales, Aberystwyth, Wales (Dave@crehkay.demon.co.uk).

Charlotte Kieft, Department of Public Health, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand.

Sari Kovats, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, England (Sari.Kovats@lshtm.ac.uk).

Michal Krzyzanowski, European Center for Environment and Health, World Health Organization, Bonn, Germany (mkr@ecehbonn.euro.who.int).

Nino Künzli, Division of Occupational and Environmental Health, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA (e-mail: Kuenzli@usc.edu).

Philip J. Landrigan, Department of Community & Preventive Medicine, Mount Sinai School of Medicine, New York, NY, USA (phil.landrigan@mssm.edu).

Malcolm R. Law, Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Barts and The London, Queen Mary's School of Medicine and Dentistry, London, England (M.R.Law@qmul.ac.uk).

Carlene M.M. Lawes, Clinical Trials Research Unit, University of Auckland, Auckland, New Zealand (c.lawes@ctru.auckland.ac.nz).

David Le Sueur (Deceased), Medical Research Council, Durban, South Africa. Deceased.

James Leigh, Centre for Occupational and Environmental Health, School of Public Health, University of Sydney, Sydney, Australia (jleigh@bigpond.com).

Karen Lock, European Centre on the Health of Societies in Transition, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, England (Karen.Lock@lshtm.ac.uk).

Alan D. Lopez, School of Population Health, University of Queensland, Brisbane, Queensland, Australia (e-mail: a.lopez@sph.uq.edu.au).

Michael Lynskey, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia.

Stephen MacMahon, Institute for International Health, University of Sydney, Sydney, Australia (smacmahon@iih.usyd.edu.au).

Mirjam Maeusezahl-Feuz, Division of Epidemiology and Infectious Diseases, Swiss Federal Office of Public Health, Bern, Switzerland (mirjam.maeusezahl@bag.admin.ch).

Colin D. Mathers, Measurement and Health Information, World Health Organization, Geneva, Switzerland (mathersc@who.int).

Martin McKee, European Centre on the Health of Societies in Transition, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, England (martin.mckee@lshtm.ac.uk).

Anthony McMichael, National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia (Tony.McMichael@anu.edu.au).

Sumi Mehta, Health Effects Institute, Boston, MA, USA (smehta@healtheffects.org).

Maristela Monteiro, Pan American Health Organization, Washington, DC, USA (monteirm@paho.org).

Luke Mullany, Department of International Health, Disease Prevention and Control Program, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (lmullany@jhsph.edu).

Christopher J.L. Murray, Harvard University Initiative for Global Health, Cambridge, MA, USA (christopher_murray@harvard.edu).

Andrea Neiman, Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA (afn1@cdc.gov).

Deborah Imel Nelson, School of Civil Engineering and Environmental Science, University of Oklahoma, Norman, OK, USA (imel@ou.edu).

Cliona Ni Mhurchu, Clinical Trials Research Unit, University of Auckland, Auckland, New Zealand (c.nimhurchu@ctru.auckland.ac.nz).

Robert Nicholls, Flood Hazards Research Centre, University of Middlesex, Enfield, England (r.nicholls@mdx.ac.uk).

Chizuru Nishida, Nutrition for Health and Development, World Health Organization, Geneva, Switzerland (nishidac@who.int).

Bart Ostro, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Oakland, CA, USA (bostro@oehha.ca.gov).

Kiran Dev Pandey, World Bank, DECRG-IE, Washington, DC, USA (kpandey@worldbank.org).

Richard Peto, Clinical Trial Service Unit and Epidemiological Studies Unit, Medical Sciences Division, University of Oxford, Oxford, England (richard.peto@ctsu.ox.ac.uk).

Joceline Pomerleau, European Centre on the Health of Societies in Transition, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, England (Joceline.Pomerleau@lshtm.ac.uk).

Arden Pope, Department of Economics, Brigham Young University, Provo, UT, USA (arden_pope@byu.edu).

Michael Pratt, Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA (mxp4@cdc.gov).

Annette Prüss-Üstün, Protection of the Human Environment, World Health Organization, Geneva, Switzerland (pruessa@who.int).

Laura Punnett, University of Massachusetts, Lowell, MA, USA (Laura_Punnett@UML.edu).

Jürgen Rehm, Centre for Addiction and Mental Health, Toronto, Canada (jtrehm@aol.com).

Nina Rehn, UNODC—United Nations Office on Drugs and Crime, Viet Nam Field Office, Hanoi, Vietnam (nina.rehn@unodc.org).

Amy L. Rice, Department of International Health, Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (arice@jhsph.edu).

Neville J. Rigby, International Obesity Task Force, London, England (nrigby@iotf.org).

James Robins, Harvard School of Public Health, Boston, MA, USA (robins@hsph.harvard.edu).

Anthony Rodgers, Clinical Trials Research Unit, University of Auckland, Auckland, New Zealand (a.rodgers@ctru.auckland.ac.nz).

Isabelle Romieu, National Institute for Public Health, Cuernavaca, Mexico (iromieu@correo.insp.mx).

Robin Room, Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden (Robin.Room@sorad.su.se).

Jonathan M. Samet, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (jsamet@jhsph.edu).

Michael Schlesinger, Department of Atmospheric Sciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA (schlesin@atmos.uiuc.edu).

Christopher T. Sempos, University at Buffalo, Buffalo, NY, USA (sempos@buffalo.edu).

Maryam Shayeghi, International Obesity Task Force, London, England (obesity@iotf.org).

Uwe Siebert, Institute for Technology Assessment, Massachusetts General Hospital, Boston, MA, USA (usiebert@hsph.harvard.edu).

Tim Slade, WHO Collaborating Centre for Evidence in Mental Health Policy, St Vincent's Hospital, Sydney, Australia (tims@crufad.unsw.edu.au).

Emma Slaymaker, Centre for Population Studies, London School of Hygiene and Tropical Medicine, London, England (emma.slaymaker@lshtm.ac.uk).

Kirk R. Smith, School of Public Health, University of California, Berkeley, CA, USA (krksmith@berkeley.edu).

N. Kyle Steenland, Rollins School of Public Health, Emory University, Atlanta, GA, USA (nsteenl@sph.emory.edu).

Rebecca J. Stoltzfus, Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA (rjs62@cornell.edu).

Heather Swanston, WHO Collaborating Centre for Evidence in Mental Health Policy, St Vincent's Hospital, Sydney, Australia (heathers@crufad.unsw.edu.au).

Sang Woo Tak, University of Massachusetts, Lowell, MA, USA (SangWoo_Tak@student.uml.edu).

Frank Tanser, Africa Centre for Population Studies and Reproductive Health, Mtubatuba, South Africa (tanserf@mrc.ac.za).

Stephen Vander Hoorn, Clinical Trials Research Unit, University of Auckland, Auckland, New Zealand (svande@ctru.auckland.ac.nz).

Neff Walker, Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland (walkern@unaids.org).

Matthew Warner-Smith, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia.

Keith P. West Jr, Department of International Health, Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (kwest@hsph.edu).

Paul Wilkinson, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, England (Paul.Wilkinson@lshtm.ac.uk).

Nick Wilson Department of Public Health, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand (nwilson@actrix.gen.nz).

Theresa Wilson, University of Middlesex, Enfield, England (Theresa7@mdx.ac.uk).

Alistair Woodward, School of Population Health, University of Auckland, Auckland, New Zealand (a.woodward@auckland.ac.nz).

Basia Zaba, Centre for Population Studies, London School of Hygiene and Tropical Medicine London, England (basia.zaba@lshtm.ac.uk).

Acknowledgements

This book is the product of more than four years of collaborative effort involving a large group of scientists across the world. This collaboration, led by the World Health Organization (WHO) and known as the comparative risk assessment (CRA) project, is one of the largest and most comprehensive research projects ever undertaken by WHO. The successful completion of the project, and this book, would not have been possible without great effort from a number of individuals and organizations.

More than 150 scientists, experts on the various risk factors and methodological aspects, reviewed the chapters in this book with great care, many of them multiple times, to ensure the scientific integrity, completeness and plausibility of the material and the conclusions. Many individuals and organizations donated their unpublished data to the project to fill some of the existing data gaps. Stephen Vander Hoorn played a key role in the design of the conceptual and methodological framework for the analysis. The literally millions of calculations leading to the disease burden estimates reported in these volumes are the result of his invaluable technical and statistical abilities and perseverance. Our colleagues David Evans, Emmanuela Gakidou, Mie Inoue, Carlene Lawes, Rafael Lozano, Doris Ma Fat, Susan Piccolo, Chalapati Rao, Joshua Salomon, Kenji Shibuya and Niels Tomijima, provided substantial motivational and intellectual support and assistance with the Global Burden of Disease databases. We are especially grateful to Marie-Claude von Rulach for her extraordinary efforts in helping to manage the network of contributors and the collaborators meetings, and for secretarial support. Technical discussions on burden of disease methodology with Colin Mathers and Claudia Stein contributed greatly to improving the scientific basis of the estimates.

The final editing and production of a book of this magnitude, with contributions from numerous authors, is a challenging and complex task. Kaarina Klint and Kai Lashley have managed that process with great care and commitment. Editorial assistance from Stanislava Nikolova, Anna Moore and Margaret Squadrani is highly appreciated. Our thanks also to our technical and copy editors Andrew Colborne, Heidi Mattock, Gillian Stanbridge and Frank Theakston for their efforts to ensure consistency of style across chapters originally written with varied disciplinary and personal styles. Colin Mathers, David Evans

and Ties Boerma generously and efficiently coordinated the production process in its final stages.

The initial concept of the cover artwork was developed by Saied Ezzati; the final arrangement of the cover design was done by Mark Forrest and Emmanuela Gakidou.

The research published in this book forms part of the larger Global Burden of Disease 2000 project, funded by a grant from the National Institute on Aging (PO1-AG17625). Their support is gratefully acknowledged.

Foreword

During the twentieth century reliable cause-specific mortality statistics became available for many countries, culminating in the Global Burden of Disease project which, during the 1990s, provided estimates for different regions of the world (with, obviously, varying degrees of reliability) of the numbers of deaths due to major diseases, and of the amounts of "disability-adjusted" loss of healthy life from those diseases. The present study goes further, and seeks to estimate the amounts of death and disability due to the main avoidable causes of those diseases. Its preliminary conclusions underlay the 250-page World Health Organization report on "Reducing Risks" (2002), the aim of which was to summarize, for the first time, the amount of death and disability in each of 14 subregions of the world that is attributable not to particular diseases, but to particular avoidable risk factors.

Such attributions of causality throw up, of course, many more difficulties than were encountered in the previous studies of the Global Burden of Disease, which merely tried to classify deaths by the one main disease (or type of accident or violence) that underlay them. For, one death may have several avoidable causes. For example, if a poorly nourished child dies of measles, should "the cause" be thought of as exposure to the virus, or as the lack of measles vaccination (in that child or in the community), or as the poor diet (low in protein, energy and certain micronutrients) that prevented recovery from the illness? The most appropriate answer, if we want to prevent such deaths, is that each of these factors should be thought of as "a cause" of a certain proportion of the childhood deaths from measles. That is what the authors of the *World health report 2002* tried to do, and in the present much more detailed series of monographs they explain to the interested (or disputative) reader much more about their main conclusions, and about how they reached those conclusions. This is important, because over the years some of the conclusions may need to be revised, as more detailed studies are undertaken or as exposure and disease patterns evolve.

For many decades it has been recognized increasingly clearly by those concerned with global health that much can affordably be achieved even in relatively poor countries if resources are directed to the major diseases of childhood and early adult life, and more recently the affordable avoidability of much other adult mortality and morbidity has been recognized

(see *The Health of Adults in the Developing World*). Ten years ago, the 1993 World Bank report, *Investing in health* (together with its companion volume, *Disease Control Priorities in Developing Countries*) was extremely influential in consolidating these ideas and getting them accepted, and acted upon, by the major international economic institutions.

But, any such cost-effectiveness calculations require, among other things, reliable estimates of effectiveness, and the present report goes further than any other in providing estimates of just how much mortality and morbidity could be avoided by addressing particular causes of disease. In many parts of the world (the main exceptions being where political disruption or HIV predominate) the risk of premature death has been reduced by more than half over the past few decades, and premature death can be halved again over the next few decades if the major intervention options are pursued to control disease and injury, and their causes.

This book will greatly facilitate such progress. It is well organized, stimulating and is an important part of a political and scientific process that is already preventing many millions of deaths a year, and will prevent many more millions of deaths a year in the future.

Sir Richard Peto
Professor of Medical Statistics and Epidemiology
University of Oxford, England

Preface

A clear understanding of the role and relative magnitude of diseases, injuries and their underlying causes—and effective and affordable interventions to reduce them—should guide policies and programmes for health development. Over the centuries, the health of populations has improved because science has helped us understand the main causes of disease affecting large populations, and how technologies or programmes can be delivered to reduce hazards among those affected or at risk.

While the monitoring and analysis of diseases and mortality in populations has been largely undertaken by actuaries and demographers, much of the work on causes of disease has emanated from research in fields such as epidemiology, toxicology and physiology, which focus on micro-level analysis. By its very nature, this research has quantified hazards in the study population, with its specific characteristics. This body of knowledge has had tremendous application in reducing the established causes of disease, from smoking to iodine deficiency, in many populations. The broader, policy-relevant issue of population effects of exposure to risks, however, has remained under-explored relative to our documentation of established diseases. Thus, while there has been decades of epidemiological research into the leading causes of many major diseases, from childhood diarrhoea to ischaemic heart disease, there have been few attempts to estimate the population-level effects of various exposures, either for specific countries and groups of countries, or for the world and its major regions.

During the last quarter of the twentieth century, a number of works have addressed both the methodological and empirical aspects of population-wide effects of major *causes* of diseases. Examples include the development of cancer risk models and methods to forecast the health of ageing populations based on their causal determinants, and the estimates of mortality due to risk factors such as smoking, asbestos and childhood malnutrition. This gradual establishment of "risk assessment" or "risk quantification" has been driven partly by the academic curiosity of individual researchers and partly by the demands of regulatory agencies and public policy for better quantitative evidence on the health implications of certain risk exposures.

This book provides a comprehensive assessment of the health effects caused by a range of exposures that are known to be hazardous to human

health. Its origins lie in the expressed need by policy and advocacy groups for comparable data on risk factor exposure and effects in populations. The only previous attempt to quantify risk factor burden worldwide, the Global Burden of Disease (GBD) 1990 project, was affected by a lack of conceptual and methodological comparability across risk factors; the analysis of each risk was constrained by its own disciplinary tradition. It nonetheless stimulated debate about the crucial role of risk factor assessment as a cornerstone of the evidence base for public health action: for instance, the leading risk factor in 1990, malnutrition, accounted for substantially more disease burden worldwide than the leading cause of disease at that time, acute lower respiratory infections.

A key concern of the current work on risks to health is to provide a degree of conceptual and methodological consistency and comparability across risk factors. The results reported in this book, therefore, differ in a number of important ways from those of GBD 1990: a new analytical framework and consistent set of definitions on "risk factor exposure" have been used to enhance comparability; the number of exposures assessed has more than doubled; and the analyses have benefited from more recent and thorough research into causality and geographical variations in population exposures and health effects.

The scope of risks to health studied in this book covers many of the most important hazards to health addressed by various fields of scientific enquiry. Arguably, there are hundreds of risk exposures that are harmful to health; and there are important implications for better understanding the disease burden they cause across the world. We have selected only a relatively small number of exposures for quantification in this book, largely determined by the availability of scientific research about their prevalence and health effects in different parts of the world. It was also important to make choices about the definition of each risk factor. Given the close interrelationships among diet, exercise and physiological risks on the one hand, or among water, sanitation and personal hygiene on the other, the exact definition of what a "risk factor" is, itself requires careful attention. That a particular risk factor like dietary fat intake does not appear in this book does not, of course, imply that it is of limited relevance; or that exposure to lead has been assessed separately from urban air pollution does not override their close linkages. Rather, we have limited ourselves to risk factors for which there was good potential for satisfactory quantification of population exposure distributions and health effects using the existing scientific evidence and available data, and for which intervention strategies are available or might be envisioned to modify their impact on disease burden.

The chapters in Volumes 1 and 2 of this book fall into two broad categories: those that address specific risk factors, and those that provide conceptual, methodological or empirical links across risks. The book begins with a description of some of the important conceptual and methodological issues in quantifying risk factor burden in a consistent

and comparable framework. This is followed by twenty-two chapters, organized under six broad sections, each of which present the background and the scientific evidence and empirical findings for individual risks. These are followed by an attempt to quantify the distributions of some risks by poverty levels. While much is known about the relationship between poverty and health, it is undoubtedly too complex and population-specific to be adequately assessed in a single quantification effort. The research reported here is therefore limited to a simple mapping of risks by poverty, based on existing data. Following the risk factor chapters, the calculus of estimating the burden of disease attributable to each risk factor from exposure and hazard data is presented, followed by a chapter that summarizes the results for individual risk factors.

Many policies and programmes affect multiple risks simultaneously, motivating an assessment of the disease burden from multiple risk factors. The focus on joint exposures and hazards is particularly important because diseases and injuries are almost always caused by multiple risk factors, which may act together on disease processes, or have effects mediated through each other. We have therefore included two chapters on the joint effects of multiple risk factor exposures. The final chapter of the book provides conclusions and recommendations for future research, based on the analytical findings presented in the book, as well as the gaps in data and scientific knowledge that increased uncertainty in quantifying risk factor burden reported here.

The specific risk factor chapters have been grouped according to clusters of exposures likely to be of similar scientific or policy interest. Volume 1 begins with four chapters on childhood and maternal undernutrition, which collectively cause a significant proportion of the childhood infectious disease burden worldwide. With substantial reductions in child mortality over the past few decades in many countries, the focus of scientific enquiry has progressively moved to improving our understanding of the causes of disease and injury among adults. The next five chapters address the various distal (e.g. exercise), more proximal (e.g. overweight and obesity), and physiological (e.g. suboptimal cholesterol levels) risks that are clustered together under the label of nutrition and physical activity. The last section in Volume 1 and the first section in Volume 2, addictive substances and sexual and reproductive health, include the major lifestyle and behavioural risks that are widespread in many societies and, despite being the subject of scientific enquiry and public health intervention for decades, present a range of complexities in risk quantification.

The risk factors that are a part of the physical environment of households (e.g. indoor air pollution from household solid fuel use), communities (e.g. urban air pollution), or specific subgroups (e.g. occupational risk factors) are the next group of risks assessed in Volume 2. The next two chapters, childhood sexual abuse and contaminated medical injec-

tions, do not fall into any of the above broad categories and are presented independently. These two chapters, each representing a risk factor that affects multiple important diseases, illustrate the potential for risk assessment as an analytical tool for improving the public health evidence base across a wide spectrum of health concerns.

In each of the specific risk factor chapters, the authors have provided a definition of the risk factor and introduced an "exposure variable" that best reflects the distribution of hazards in the population. The complexity of disease causation mechanisms (e.g. sexual behaviour and sexually transmitted infections), and the limitations posed by available data and epidemiological studies (e.g. physical inactivity or indoor smoke from solid fuels) have been important factors in the choice of exposure variable. Coupled with this is the choice of a "theoretical-minimum-risk population exposure distribution", which can serve as a consistent baseline for assessing attributable disease burden across difference risks. For some risks such as smoking or childhood abuse, the theoretical-minimum-risk population exposure distribution is obviously zero exposure for the whole population; for others the choice of baseline exposure distribution is less obvious, either because zero exposure is not definable (e.g. blood pressure) or because it may not lead to the lowest risk level in some populations (e.g. alcohol). Each chapter includes current estimates of exposure distributions by age and sex for 14 epidemiological subregions. The chapters also examine in detail the evidence for health outcomes, including the evidence for causality and the estimates of hazard (disease-specific) associated with each level of exposure. Each chapter then concludes with summary results of the burden of disease and injury in 2000 attributable to the risk factor, and when possible using existing evidence and knowledge, estimates of projected future exposure to the risk.

The CD-ROM attached contains detailed tables on the various components of disease burden (i.e. deaths, years of life lost [YLL] due to premature mortality, and disability-adjusted life years [DALYs]) attributable to each risk factor by age, sex and the 14 epidemiological subregions of the world used by the World Health Organization (WHO) in the *World health report 2002*. The 191 Member States of WHO were divided into five mortality strata on the basis of their levels of child mortality (under five years of age) and 15–59-year-old male mortality. When these mortality strata are applied to the six WHO regions, they produce 14 epidemiological subregions, which are used throughout this book (Table 1).

This book is the culmination of over four years of scientific enquiry and data collection, collectively known as the comparative risk assessment (CRA) project, coordinated by WHO and involving over 100 scientists worldwide. The book is also one of the several planned outputs of the GBD 2000 project which includes multiple analytical and empirical perspectives on global population health. The importance of the collaborative effort in the CRA project goes beyond having leading

Table 1 The 14 GBD epidemiological subregions

WHO region	*Mortality stratum*[a]	*Countries*
AFR	D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo
	E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
AMR	A	Canada, Cuba, United States of America
	B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
	D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
EMR	B	Bahrain, Cyprus, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
	D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
EUR	A	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
	B	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Serbia and Montenegro, Slovakia, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan
	C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
SEAR	B	Indonesia, Sri Lanka, Thailand
	D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal
WPR	A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore
	B	Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

[a] A: very low child mortality and very low adult mortality; B: low child mortality and low adult mortality; C: low child mortality and high adult mortality; D: high child mortality and high adult mortality; E: high child mortality and very high adult mortality. High-mortality developing subregions: AFR-D, AFR-E, AMR-D, EMR-D and SEAR-D. Low-mortality developing subregions: AMR-B, EMR-B, SEAR-B, WPR-B. Developed subregions: AMR-A, EUR-A, EUR-B, EUR-C and WPR-A. This classification has no official status and is for analytical purposes only.

researchers for multiple risk factors working simultaneously on the same project. Rather, the interactions of these researchers, with a core network of scientists applying a common analytical framework and methods, has ensured greater consistency and comparability in using and evaluating scientific evidence across risks. As a result, our understanding of the comparative extent of disease burden caused by various exposures worldwide has advanced, and key areas of scientific enquiry necessary to better inform policies to reduce risks have been elucidated. Health advocates and those entrusted with policy and programme development to promote better health now have a more comparable empirical assessment of the hazards to health worldwide, and thus a firmer basis for public health action. We hope that the methodological and empirical findings reported in these volumes will indeed serve as the stimulus for global, regional and national policy action to reduce key hazards to health for decades to come.

Majid Ezzati
Alan D. Lopez
Anthony Rodgers
Christopher J.L. Murray

Chapter 1

Comparative quantification of health risks: conceptual framework and methodological issues

Christopher J.L. Murray, Majid Ezzati, Alan D. Lopez, Anthony Rodgers and Stephen Vander Hoorn

1. Introduction

Detailed description of the level and distribution of diseases and injuries, and their causes are important inputs to strategies for improving population health. Data on disease or injury outcomes alone, such as death or hospitalization, tend to focus on the need for palliative or curative services. Reliable and comparable analysis of risks to health, on the other hand, is key for preventing disease and injury. A substantial body of work has focused on the quantification of causes of mortality, and more recently, the burden of disease (Murray and Lopez 1997; Preston 1976). Analysis of morbidity and mortality due to risk factors, however, has frequently been conducted in the context of methodological traditions of individual risk factors and in a limited number of settings (Kunzli et al. 2000; Leigh et al. 1999; McGinnis and Foege 1993; Peto et al. 1992; Single et al. 1999; Smith 2000; Smith et al. 1999; Willet 2002). The principal conclusions of this body of work are as follows:

- Causal attribution of morbidity and mortality to risk factors has been estimated relative to zero or some other constant level of population exposure. This single, constant baseline, although illustrating the total

 Population Health Metrics, 2003, 1:1.

magnitude of the risk, does not provide visions of population health under other alternative exposure distribution scenarios.

- Intermediate stages and interactions in the causal process have not been considered in the causal attribution calculations. As a result, attributable burden could be calculated only for those risk factor–disease combinations for which epidemiological studies had been conducted (often limited to individual risks).
- Causal attribution has often taken place using exposure and/or outcome at one point in time or over an arbitrary period of time (for notable exceptions see the works of Manton and colleagues [Manton et al. 1993b, 1994; Yashin et al. 1986] and Robins [Robins 1986, 1987, 1999a, 1999b; Robins and Greenland 1991; Robins et al. 1999]). Such "counting" of adverse events (such as death) has not been able to clearly distinguish between those cases that would not have occurred in the absence of the risk factor and those where occurrence would have been delayed. More generally, this approach is unable to consider the accumulated effects of time-varying exposure to a risk factor—in the form of years of life lost prematurely or lived with disability.
- The outcome has been morbidity or mortality due to specific disease(s) without conversion to a comparable unit, making comparison among different diseases and/or risk factors difficult.

To allow the assessment of risk factors in a unified framework while acknowledging risk-factor specific characteristics, the comparative risk assessment (CRA) module of the Global Burden of Disease (GBD) 2000 study is a systematic evaluation of the changes in population health which would result from modifying the population distribution of exposure to a risk factor or a group of risk factors (Murray and Lopez 1999). This unified framework for describing population exposure to risk factors and their consequences for population health is an important step in linking the growing interest in the causal determinants of health across a variety of public health disciplines from natural, physical, and medical sciences to the social sciences and humanities. In particular, in the CRA framework:

- The burden of disease due to the observed exposure distribution in a population is compared with the burden from a hypothetical distribution or series of distributions, rather than a single reference level such as the non-exposed population.
- Multiple stages in the causal network of interactions among risk factor(s) and disease outcome are considered to allow making inferences about combinations of risk factors for which epidemiological studies have not been conducted, including the joint effects of changes in multiple risk factors.

- The health loss due to risk factor(s) is calculated as a time-indexed "stream" of disease burden due to a time-indexed "stream" of exposure.
- The burden of disease and injury is converted into a summary measure of population health, which allows comparing fatal and non-fatal outcomes, also taking into account severity and duration.

It is important to emphasize that risk assessment, as defined above, is distinct from intervention analysis, whose purpose is to estimate the benefits of a given intervention or group of interventions in a specific population and at a specific time. Rather, risk assessment aims at mapping alternative population health scenarios to changes in distribution of exposure to risk factors over time, irrespective of whether exposure change is achievable using existing interventions. Therefore, while intervention analysis is a valuable input into cost-effectiveness studies, risk assessment contributes to assessing research and policy options for reducing disease burden by changing population exposure to risk factors.

Summary measures of population health (SMPH) and their use in burden of disease analysis are discussed elsewhere (Murray 1996; Murray et al. 2002). The next three sections of this chapter address the conceptual basis and methodological issues for the remaining three points above. We then discuss the sources and quantification of uncertainty.

2. Causal attribution of SMPH to risk factors

Mathers et al. (2002) describe two traditions for causal attribution of health determinants, outcomes, or states: categorical attribution and counterfactual analysis. In categorical attribution, an event such as death is attributed to a single cause (such as a disease or risk factor) or group of causes according to a defined set of rules (hence 100% of the event is attributed to the single cause or group of causes). The International Classification of Disease system's (ICD) attribution of causes of death (WHO 1992) and attribution of some injuries to alcohol or occupational conditions are examples of categorical attribution. In counterfactual analysis, the contribution of one or a group of diseases, injuries or risk factors to a summary measure of population health is estimated by comparing the current or future levels of the summary measure with the levels that would be expected under some alternative hypothetical scenario, including the absence of or reduction in the disease(s) or risk factor(s) of interest. This hypothetical scenario is referred to as the counterfactual (see Maldonado and Greenland 2002 for a discussion of conceptual and methodological issues in the use of counterfactuals).

In theory, causal attribution of a summary measure to risk factors can be done using both categorical and counterfactual approaches. For

example, categorical attribution has been used in attribution of diseases and injuries to occupational risk factors in occupational health registries (Leigh et al. 1999) and attribution of motor vehicle accidents to alcohol consumption. In general however, categorical attribution of SMPH to risk factors overlooks the fact that many diseases have multiple causes (Rothman 1976). The epidemiological literature has commonly used the counterfactual approach for the attribution of a summary measure to a risk factor, and compared mortality or disability from the current distribution of exposure to the risk factor to that expected under an alternative exposure scenario.

The dominant counterfactual exposure distribution in these studies has been zero exposure for the whole population (or a fixed non-zero level where zero is not possible such as the case of blood pressure when defined as presence or absence of hypertension). The basic statistic obtained in this approach is the population attributable fraction (PAF) defined as the proportional reduction in disease or death that would occur if exposure to the risk factor were reduced to zero, *ceteris paribus* (Cole and MacMahon 1971; Eide and Heuch 2001; Greenland 1984; Levin 1953; MacMahon and Pugh 1970; Miettinen 1974; Ouellet et al. 1979; Rockhill et al. 1998; Uter and Pfahlberg 2001).[1] The attributable mortality, incidence or burden of disease due to the risk factor, *AB*, is then given as $AB = PAF \times B$ where B is the total burden of disease from a specific cause or group of causes affected by the risk factor with a relative risk of RR:

$$PAF = \frac{P(RR-1)}{P(RR-1)+1} \tag{1a}$$

The exposed population may itself be divided into multiple categories based on the level or length of exposure, each with its own relative risk. With multiple (n) exposure categories, the PAF is given by the following generalized form:

$$PAF = \frac{\sum_{i=1}^{n} P_i(RR_i-1)}{\sum_{i=1}^{n} P_i(RR_i-1)+1} \tag{1b}$$

Although choosing zero as the reference exposure may be useful for some purposes, it is a restricting assumption for others. The contribution of a risk factor to disease or death can alternatively be estimated by comparing the disease burden due to the observed exposure distribution in a population with that from another *distribution* (rather than a single reference level such as non-exposed) as described by the generalized

"potential impact fraction" equation (Drescher and Becher 1997; Eide and Heuch 2001; Walter 1980).

$$PIF = \frac{\int_{x=0}^{m} RR(x)P(x)dx - \int_{x=0}^{m} RR(x)P'(x)dx}{\int_{x=0}^{m} RR(x)P(x)dx} \tag{2a}$$

where $RR(x)$ is the relative risk at exposure level x, $P(x)$ is the population distribution of exposure, $P'(x)$ is the counterfactual distribution of exposure, and m the maximum exposure level. The first and second terms in the numerator of Equation 2a therefore represent the total exposure-weighted risk of mortality or disease in the population under current and counterfactual exposure distributions. The corresponding relationship when exposure is described as a discrete variable with n levels is given by:

$$PIF = \frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P_i' RR_i}{\sum_{i=1}^{n} P_i RR_i} \tag{2b}$$

In addition to relaxing the assumption of the no-exposure group as the reference, analysis based on a broader range of distributions has the advantage of allowing multiple comparisons with multiple counterfactual scenarios. Equation 2a can be further generalized to consider counterfactual relative risks (i.e. relative risk may depend on other risks, new technology, medical services, etc.). For example the relative risk of injuries as a result of alcohol consumption may depend on road conditions and traffic law enforcement. Similarly, people employed in the same occupation may have different risks of occupational injuries because of different safety measures. Therefore, a more general form of Equation 2a is given by:

$$PIF = \frac{\int_{x=0}^{m} RR(x)P(x)dx - \int_{x=0}^{m} RR'(x)P'(x)dx}{\int_{x=0}^{m} RR(x)P(x)dx} \tag{2c}$$

2.1 Counterfactual exposure distributions

Various criteria may determine the choice of the counterfactual exposure distributions. Greenland (2002) has discussed some of the criteria for the choice of counterfactuals, arguing that the counterfactuals should

be limited to actions that can be implemented (e.g. anti-smoking campaigns), rather than the effects of removing the outcomes targeted by those actions (e.g. smoking cessation) because, in practice, the implementation of counterfactuals for one risk factor or disease may affect other risks. The solution to Greenland's concern, however, is better analytical techniques for estimating joint risk factor effects, rather than abandoning non-intervention-based counterfactuals which, as argued by Mathers et al. (2002), is a limiting view. Estimating the contributions of risk factors to disease burden and the benefits of their removal, even in the absence of known interventions, can provide an understanding of their role in population health and visions of population health under different scenarios of risk factor exposure. This knowledge of risk factor effects can provide valuable input into public health policies and priorities, as well as research and development.

Murray and Lopez (1999) introduced a taxonomy of counterfactual exposure distributions that, in addition to identifying the size of risk, provides a mapping to policy implementation options. These categories include the exposure distributions corresponding to *theoretical* minimum risk, *plausible* minimum risk, *feasible* minimum risk and *cost-effective* minimum risk. Theoretical minimum risk refers to the exposure distribution that would result in the lowest population risk, irrespective of whether currently attainable in practice. Plausible minimum refers to a distribution which is imaginable, and feasible minimum is one that has been observed in some population. Finally, cost-effective minimum considers the cost of exposure reduction (through the set of known cost-effective interventions) as an additional criterion for choosing the alternative exposure scenario.

In addition to illustrating the total magnitude of disease burden due to a risk factor, the theoretical-minimum-risk distribution (or the current difference between theoretical and plausible or feasible risk levels) can guide research and development resources towards those risk factors for which the mechanisms of reduction (i.e. interventions) are currently underdeveloped. For example, if the reduction in the burden of disease due to improved medical injection safety is high and the methods for risk reduction are well-known, so that plausible/feasible and theoretical minima are identical, then current policy may have to be focused on the implementation of such methods. On the other hand, if there are large differences between plausible/feasible and theoretical minima risk levels for blood lipids or body mass index (BMI) (Powles and Day 2002), then research on reduction methods and their implementation should be encouraged. For this reason the total magnitude of the burden of disease due to a risk factor, as illustrated by the theoretical minimum, provides a tool for considering alternative visions of population health and setting research and implementation priorities.

Biological principles as well as considerations of equity would necessitate that, although the exposure distribution for theoretical minimum

risk may depend on age and sex, it should in general be independent of geographical region or population. Exceptions to this are, however, unavoidable. An example would be the case of alcohol consumption, which in limited quantities and when drunk in certain patterns has beneficial effects on cardiovascular mortality, but is always harmful for other diseases such as cancers and accidents (Puddey et al. 1999). In this case, the composition of the causes of death as well as drinking patterns in a region would determine the theoretical-minimum-risk distribution. In a population where cardiovascular diseases are a dominant cause of mortality, the theoretical-minimum-risk exposure distribution may be non-zero with moderate drinking patterns, whereas in a population with binge drinking and a large burden from injuries the theoretical minimum would be zero. Feasible and cost-effective distributions, on the other hand, may vary across populations based on the current distribution of the burden of disease and the resources and institutions available for exposure reduction.

The above categories of counterfactual exposure distributions are based on the burden of disease in the population as a whole. Counterfactual exposure distributions may also be considered based on other criteria. For example, a counterfactual distribution based on equity would be one in which the highest exposure group (or the group with the highest burden of disease) would be shifted towards low exposure values. Further, such equitable counterfactual distributions for each risk factor may themselves be categorized into theoretical (most equitable), plausible, feasible and cost-effective as described above. Similarly, a counterfactual distribution that focuses on the most susceptible groups in the population is one that gives additional weight to lowering the exposure of this group. Therefore, by permitting comparison of disease burden under multiple exposure distributions based on a range of criteria—including, but not limited to, implementation and cost, equity and research prioritization—relaxing the assumption of a constant exposure baseline provides an effective policy and planning tool.

2.2 Exposure distribution for theoretical minimum risk

In one taxonomy, risk factors such as those in the GBD project (Ezzati et al. 2002; see also the risk factor chapters in this book) can be broadly classified as physiological, behavioural, environmental and socioeconomic. Some general principles that guide the choice of theoretical-minimum-risk exposure distribution for each category are:

1. *Physiological risk factors*: This group includes those factors that are physiological attributes of humans, such as blood pressure or blood lipids, and at some level result in increased risk. Since these factors are necessary to sustain life, their "exposure–response" relationship is J-shaped or U-shaped, and the theoretical-minimum-risk distribution is non-zero. For such risk factors, the choice of optimal exposure

needs to be based on empirical evidence from different scientific disciplines. For example, epidemiological research on blood pressure and cholesterol have illustrated a monotonically increasing dose–response relationship for mortality even at low levels of these risk factors (Chen et al. 1991; Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998; MacMahon et al. 1990; Prospective Studies Collaboration 1995). But, given the role of these factors in sustaining life, this relationship must flatten and reverse at some level. In the blood pressure and cholesterol assessment, a theoretical-minimum-risk exposure distribution with a mean of 115 mmHg for systolic blood pressure and 3.8 mmol/l for total cholesterol (each with a small standard deviation) were used (Ezzati et al. 2002). This distribution corresponds to the lowest levels at which the dose–response relationship has been characterized in meta-analyses of cohort studies (Chen et al. 1991; Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998; MacMahon et al. 1990; Prospective Studies Collaboration 1995). Further, these levels of blood pressure and cholesterol are consistent with levels seen in populations which have low levels of cardiovascular disease, such as the Yanomamo Indians (Carvalho et al. 1989) and rural populations in China (He et al. 1991a, 1991b), Papua New Guinea (Barnes 1965; Carvalho et al. 1989), and Africa (Mann et al. 1964). Although meta-analyses of randomized clinical trials have indicated that blood pressure and cholesterol levels may be lowered substantially with no adverse effects (LaRosa et al. 1999; Pignone et al. 2000), it is difficult to justify an optimal exposure distribution lower than that measured in population-based studies, since lower levels in individuals may be caused by factors such as pre-existing disease. Arguments from evolutionary biology would also support the choice of a lower bound on the optimal distribution based on historical survival of populations who are not substantially exposed to factors that raise blood pressure or cholesterol.

2. *Behavioural risk factors*: The exposure–response relationship for this group of risk factors may be monotonically increasing or J-shaped. For risk factors with a monotonic exposure–response relationship, such as smoking, the optimal exposure would be zero unless there are physical constraints that make zero risk unattainable. For example in the case of blood transfusion, there may be a lower bound on the safety of the blood supply process even using the best monitoring technology. With a J-shaped or U-shaped exposure–response relationship, the minimum risk would occur at the turning point of the exposure–response curve. An example of this is alcohol consumption in adult populations with high cardiovascular disease rates, since moderate consumption may result in a reduction in ischaemic heart disease (IHD) in some age groups (Corrao et al. 2000). With a

J-shaped exposure–response curve, similar to physiological risk factors, empirical evidence would have to be used to determine the theoretical minimum risk.

Finally, some behavioural risks are expressed as the absence of protective factors such as physical inactivity or low fruit and vegetable intake. In such cases, optimal exposure would be the level at which the benefits of these factors would no longer continue. With a monotonic exposure–response relationship or without detailed knowledge about a possible turning point, the theoretical-minimum-risk exposure distribution should be chosen based on empirical evidence about the highest theoretically sustainable levels of intake or exposure (for example very active life style or a purely vegetarian diet).

3. *Environmental risk factors*: The toxicity of most environmental risk factors is best described as a monotonically increasing function of exposure (potentially with some threshold). Therefore, the theoretical-minimum-risk exposure distribution for this group would be the lowest physically achievable level of exposure, such as background particulate matter concentration due to dust.

4. *Socioeconomic "risk factors"*: Socioeconomic status and factors—such as income (including levels and distribution) and associated levels of poverty and inequality, education, the existence of social support networks, etc.—are important determinants of health, often through their effects on other risk factors. The effects of each of these factors on health are, however, highly dependent on other socioeconomic variables as well as the policy context, including accessibility and effectiveness of health and welfare systems. For this reason, the theoretical-minimum-risk exposure distribution, even if meaningfully defined, is likely to change over time and space depending on a large number of other factors. Given this heterogeneity, the effects of socioeconomic variables are best assessed relative to counterfactual distributions defined based on policy and intervention options in specific times and settings, as discussed by Greenland (2002).

3. Risk quantification models

Prediction implicitly assumes the use of a conceptual model which infers the value of the variable of interest at a point in time or space based on knowledge from a different time, or another location. Predictive models can be divided along a continuum between *aggregate* and *structural* categories. A completely aggregate model uses the previous trend of the variable of interest as the basis for predicting its future value. A structural model, on the other hand, identifies the components—and the relationships among them—of the "system" that determines the variable of interest. It then uses the knowledge of the system for predicting the value of

the variable of interest. Most predictive models lie between the two extremes and use a combination of aggregate and structural modelling.[2]

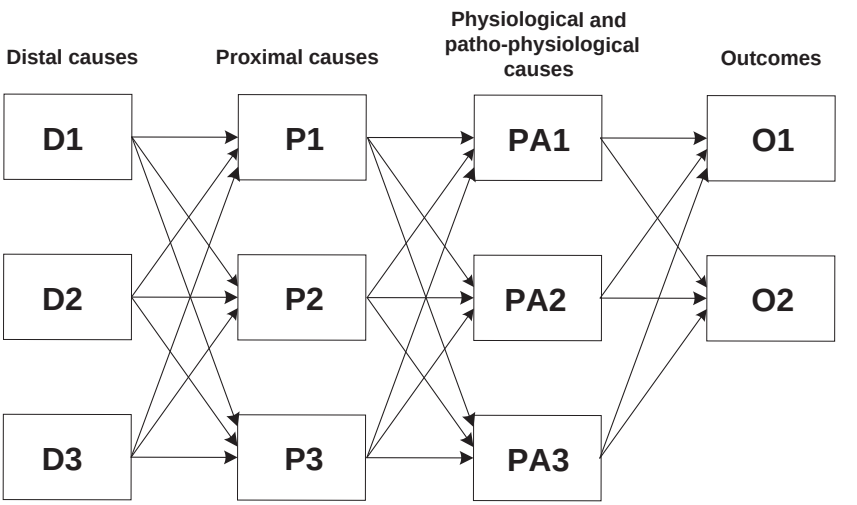
Consider for example predicting the future population of a city or the future ambient concentration of a pollutant. An aggregate model would extrapolate the historical levels to predict future values. Even in this case the model may include some structural elements. For example, the model may use a specific functional form—linear, exponential, quadratic or logarithmic—for extrapolation which involves an assumption about the underlying system. A structural model, in the case of population prediction would consider the age structure of the population, fertility (which itself may be modelled using data on education and family planning programmes), public health variables and rural–urban migration (which itself can be modelled using economic variables). In the case of air pollution, a structural model may consider demographic variables (themselves modelled as above), the structure of the economy (manufacturing, agriculture or service), the current manufacturing and transportation technology and effects of research and development on new technology, the demand for private vehicles, the price of energy and the atmospheric chemistry of pollution. Once again, in both examples the models may include some aggregation of variables by using historical trends to predict the future values of individual variables in the system, such as funding for family planning or research and development of new technologies.

The comparative advantage of structural and aggregate models lies in the balance between theoretical precision and data requirement. Structural models offer the potential for more robust predictions, especially when the underlying system is complex and highly sensitive to one or more of its components. In such cases, a shift in some of the system variables can introduce large changes in the outcome, which may be missed by extrapolation (such as the discovery of antibiotics and infectious disease trends or the change in tuberculosis mortality after the HIV epidemic). Aggregate models, on the other hand, require considerably less knowledge of the system components and the relationships among them. These models can therefore provide more reliable estimates when such information is not available, especially when the system is not very sensitive to inputs.

3.1 Models for risk factor–disease relationship

Using the above aggregate, structural taxonomy, it is also possible to classify models that are used to predict changes in death or disease as a result of changes in exposure to underlying risk factors. Murray and Lopez (1999) described a "causal-web" which includes the various distal (such as socioeconomic), proximal (behavioural or environmental) and physiological and patho-physiological causes of disease, as shown in Figure 1.1. While different disciplinary traditions—from social sciences

Figure 1.1 Simplified schema for a causal-web illustrating various levels of disease causation

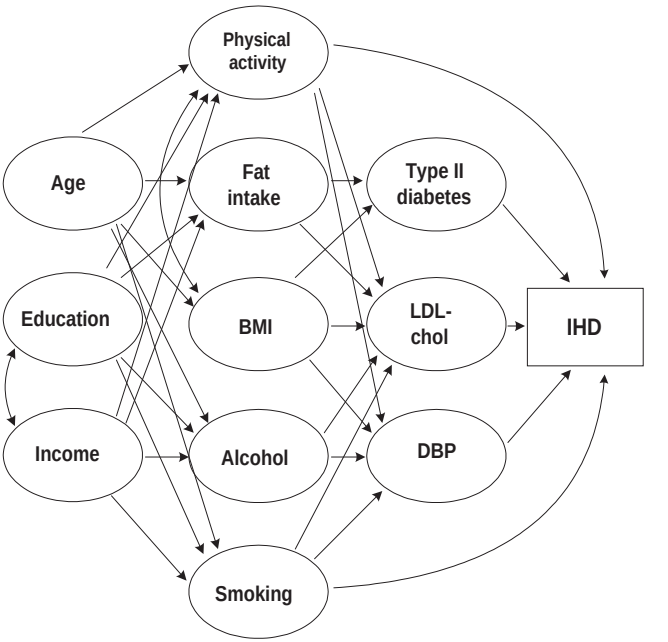


Note: Feedback from outcomes to preceding layers may also exist. For example, individuals or societies may modify their risk behaviour based on health outcomes.

and humanities, to the physical, natural and biomedical sciences—have focused on individual components or stages of these relationships, in a single multi-layer causal model with interactions the term "risk factor" can be used for any of the causal determinants of health (Mathers et al. 2002; Yerushalmy and Palmer 1959).[3] For example, poverty, location of housing, lack of access to clean water and sanitation, and the existence of a specific pathogen in water can all be considered the causes of diarrhoeal diseases, providing a more complete framework for assessment of interventions and policy options. Similarly, education and occupation, diet, smoking, air pollution, physical activity, BMI and blood pressure are some of the risk factors at various levels of causality for cardiovascular diseases.

Compared to a causal-web, Equations 1 and 2 that use relative risk estimates from epidemiological methods (e.g. the Cox proportional hazard or other regression models) lie further towards aggregate modelling. In general, in such methods, relative risks are estimated so that they incorporate the aggregation of the various underlying relationship (ideally, but not always, controlling for the appropriate confounding variables)[4] without considering intermediate relationships as separate causal stages. On the other hand, if specified and estimated correctly, considering the complete set of causal pathways which include multiple

Figure 1.2 A possible causal diagram based on established relationships for estimating the incidence of ischaemic heart disease



DBP Diastolic blood pressure.

Note: Other interactions may also be possible.

risk factors will allow making inferences about combinations of risk factors and risk factor levels for which direct epidemiological studies may not be available.

As discussed earlier, the appropriateness of the two approaches to estimation of attributable burden depends on the specific risk factor(s), outcomes and available data. For example, the relationship between smoking and lung cancer has been shown to be highly dependent on smoking intensity and duration which, with appropriate indicators of past smoking (Peto et al. 1992), can be readily estimated using the relative risk approach of Equations 1 and 2. Consider, on the other hand, the relationship among age, socioeconomic status and occupation, behavioural risk factors (such as smoking, alcohol consumption, diet, physical activity), physiological variables (such as blood pressure and cholesterol level) and IHD shown in Figure 1.2. Given the multiple complex interactions, IHD risk may be best predicted using a structural (causal-web) approach, especially when some risk factors vary simulta-

neously, such as smoking, alcohol and diet, requiring joint counterfactual distributions. Using a multi-risk model would also allow considering situations for which direct epidemiological studies may not have been conducted, such as the effects of physical activity on those people who have diets different from the study group or those who take medicine to lower blood pressure.

The health effects of global climate change provide another example where a structural approach to risk assessment may be appropriate. Economic activities (including manufacturing, agriculture and forest use, transportation and domestic energy use) affect the emissions of greenhouse gases (GHG). Changes in precipitation, temperature and other meteorological variables due to atmospheric GHG accumulation alter regional ecology, which in turn results in changes in agricultural productivity, quantity and quality of water, dynamics of disease vectors and other determinants of disease. All these effects are in turn modulated by local economic activities, land-use patterns and income (Patz et al. 2000; Reiter 2001; Rogers and Randolph 2000). A model based on the atmospheric physics/chemistry of GHG emissions and accumulation, climate models, plant and vector ecology and human activity might provide the optimal basis for the prediction of the health effects of climate change.[5]

Specifying the causal-web

Assuming for the moment no temporal dimension in the relationship between the different variables in the causal system (temporal aspects are discussed below), each layer of a causal-web may be characterized by the equation:

$$\mathbf{X}^n = f(\mathbf{B}(\mathbf{X}^{n-1}, \mathbf{X}^n), \mathbf{X}^{n-1}) \tag{3a}$$[6]

where $\mathbf{X}^n$ is the vector of the variables in the nth layer of the causal-web (which can be causal or output such as **D**, **P**, **PA**, or **O** using the notation of Figure 1.1); f is the functional form connecting the $(n-1)$th layer to the nth layer; **B** is a matrix of coefficients for f which itself may be dependent on the variables in the $(n-1)$th and nth layers ($\mathbf{X}^{n-1}$ and $\mathbf{X}^n$)[7] (as well as time as we discuss below).

The attributable fraction of disease or mortality due to a single risk factor in the causal-web is then obtained by integrating the outcome (**O**) over the current ($P(\mathbf{x})$) and counterfactual ($P'(\mathbf{x})$) population distributions of exposure, as for Equation 2.

$$AF = \frac{\int_{P(x)} \mathbf{O}(\mathbf{x}) - \int_{P'(x)} \mathbf{O}(\mathbf{x})}{\int_{P(x)} \mathbf{O}(\mathbf{x})} \tag{4}$$

3.2 Joint risk factor changes

The attributable fraction relationships described in Equations 1 and 2 are based on individual risk factors. Disease and mortality are however often affected by multiple, and at times correlated, risk factors (Rothman 1976; Walter 1980). Estimating the joint effects of multiple distal and proximal risks is particularly important because many factors act through other, intermediate, factors (Murray and Lopez 1999; Yerushalmy and Palmer 1959), or in combination with other risks. It is therefore important to consider how the burden of disease may change with simultaneous variations in multiple risk factors. Analysis of joint risk factor changes implicitly acknowledges that the disease causation mechanism involves multiple factors, and is therefore suited to a causal-web framework, with $P(\mathbf{x})$ and $P'(\mathbf{x})$ in Equation 4 being the joint distributions of the vector of risk factors, $\mathbf{x}$. Alternatively, when using Equations 1 or 2, knowledge of the distribution of *all* relevant risk factors and the relative risk for each risk factor, *estimated at the appropriate level of the remaining risk factors*,[8] is required. Therefore, in Equation 2a, RR and P may represent joint risks and exposure distributions for multiple risk factors (Eide and Heuch 2001). In this case, the estimates from Equations 2a and 4 may in theory be identical.

Additivity of attributable fraction

Many users of risk assessment desire information characterized by additive decomposition. In other words, users would like to know what fraction of the disease burden is related to any risk factor or group of risk factors, independent of the changes in other risk factors. As discussed by Mathers et al. (2002), additive decomposition is a property of categorical attribution and, in general, not of counterfactual attribution because many diseases are caused by the interaction of multiple risk factors acting simultaneously and therefore can be avoided by eliminating any of these factors (Rothman 1976; Rothman and Greenland 1998; Yerushalmy and Palmer 1959). Consider for example infant and child mortality due to acute respiratory infections (ARI), which are especially high among malnourished children, as a result of exposure to indoor smoke from solid fuels (Rice et al. 2000; Smith et al. 2000). In this case, removal of either risk factor can reduce mortality, some of which can therefore be attributed to both factors. Similarly the risk of mortality due to cardiovascular diseases among some of those who are exposed to smoking, low physical activity and poor diet may be reduced by elimination of any combination of these risk factors. Counterfactual causal attribution of disease and injury to individual risk factors does not normally allow additive decomposition and the sum of attributable fractions or burdens for a single disease due to multiple risk factors is therefore theoretically unbounded.

Although epidemiologically unavoidable and conceptually acceptable, the lack of additivity presents additional policy complexity and implies great caution is necessary when communicating and interpreting the estimates of attributable fraction and burden. With multiple attribution, the reduction of one risk factor would seem to make other, equally important risk factors potentially irrelevant from the perspective with a limited scope on quantification. At the same time multi-causality offers opportunities to tailor prevention based on availability and cost of interventions. It also necessitates the development of methods to quantify the effects of joint counterfactual distributions for multiple risk factors.

4. Temporal dimensions of the risk factor–disease relationship

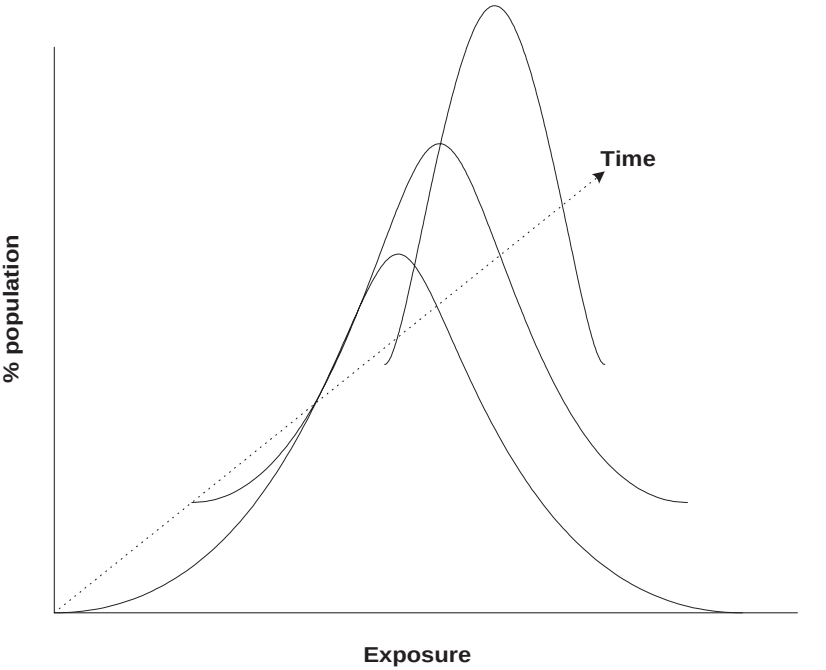
Both exposure to a risk factor and the health outcomes due to exposure include a time dimension. This can be described by a modified version of Equation 3 in which exposure and outcome as well as the model parameters (**B**) are dependent on time. In the following two sections we consider the temporal characteristics of exposure and health outcomes, respectively.

4.1 Temporal characteristics of exposure

With the exception of acute hazards (e.g. injury risk factors) exposure to a risk factor affects disease over a time period. As a result, the distributional transition between any two exposure distributions includes a temporal dimension as illustrated schematically in Figure 1.3. The transition path is of little importance if exposure changes over a short time interval, especially relative to the time required for the effect of exposure on disease. Over long time periods, however, there is sufficient time for contributions from the intermediate exposure values, and the actual path of transition may be as important as the initial and final distributions in determining the disease burden associated with change in exposure. For example, the effects of reducing the prevalence of smoking or exposure to an occupational carcinogen by half in a population would be markedly different if the change takes place immediately, gradually over a twenty-year period or after twenty years. Therefore, the health effects of exposure to many risk factors depend on the complete profile of exposure over time, and may be further accompanied by a time lag from the period of exposure. Also, for some risk factors there may be complete or partial reversibility, with the role of past exposure gradually declining.

To capture the effects of exposure profiles over time, we begin by considering the role of temporal dimensions of exposure at the level of individuals (or groups of individuals with similar exposure) before considering the whole population.

Figure 1.3 A (three-dimensional) representation of a time-indexed distributional transition of population exposure to a risk factor, with a decreasing central tendency



Suppose that at time T the relative risk of a disease, RR, for individuals exposed to a risk factor (compared to the non-exposed group) depends on the complete *profile or stream of exposure* between time T_0 and T, denoted by $x(t)$, with some lag, L, between exposure and effect. Then, there is some function, $f(x)$, which can be used to describe the contribution of exposure at any point in time between T_0 and T to the relative risk (RR). In mathematical notation:

$$RR(x(t))|_{T_0}^{T} = RR\left(\int_{T_0}^{T} f(x(t-L))dt\right) \qquad (5)^{9}$$

The quantity $\int_{T_0}^{T} f(x(t-L))dx$ is an *equivalent exposure*[10] between T_0 and T and is dependent on: i) the profile of exposure (i.e. level of exposure at any point in time) described by $x(t)$; and ii) the contribution of previous exposure to current hazard characterized by $f(x)$, an *accumulative risk function*.[11] Some common forms for the accumulative risk function, $f(x)$, are given in Table 1.1.

Table 1.1 Possible forms for the accumulative risk function, $f(x)$

Accumulative risk function, f(x)	*Interpretation*	*Relative risk*	*Potential example*
1. $f(x) = \begin{cases} 1 & \text{if } t = T \\ 0 & \text{otherwise} \end{cases}$	RR depends only on current exposure, with no contribution from past exposure	$RR(x(t))\Big\|_{T_0}^{T} = RR(x(\mathrm{T}))$	Instantaneous poisoning as a result of exposure to high levels of toxic chemicals; injuries or death in accidents due to binge drinking; infection with Hepatitis B or C as a result of an infected injection
2. $f(x) = 1$	RR depends on the accumulated exposure (or average exposure if normalized with respect to exposure time), without any effects from the temporal distribution of exposure	$RR(x(t))\Big\|_{T_0}^{T} = RR\left(\int_{T_0}^{T} x(t)dt\right)$	Cancer risk from lifetime exposure to carcinogens which have no threshold level
3. $f(x) = \begin{cases} \frac{1}{K} & \text{if } t > T - K \\ 0 & \text{otherwise} \end{cases}$	RR depends on current and past exposures. But the role of past exposure lasts for a limited time, K, and declines as a linear function of time	$RR(x(t))\Big\|_{T_0}^{T} = RR\left(\int_{T_0}^{T} \frac{(t - T + K)}{K} x(t)dt\right)$	Reduction in cardiovascular events after lowering blood pressure[a]
4. $f(x) = e^{\alpha(t-T)}$	RR depends on current and past exposures. But the role of past exposure decays as an exponential function of time	$RR(x(t))\Big\|_{T_0}^{T} = RR\left(\int_{T_0}^{T} e^{\alpha(t-T)} x(t)dt\right)$	Reduction in cardiovascular events after lowering blood pressure[a]

[a] Example is applicable in illustrating gradual reduction in risk after exposure is reduced. The exact functional form of risk reduction may not necessarily be linear or exponential.

For simplicity of notation, in all these cases we assume that: i) $L = 0$. Including a lag is straightforward and can be done by replacing t with $(t - L)$ in the corresponding formulas; and ii) there is no threshold for exposure. Including the threshold level is also straightforward using the TRUE($x(z) \geq X$) function.

In scenarios 1, 3 and 4, where the effects of past exposure are absent or decline over time, risk reversibility can take place if exposure is reduced or removed. In scenario 1 there is immediate risk reversibility; in scenario 3, there is full reversibility after time K; in scenario 4, risk reversibility asymptotically approaches 100%. In scenario 2 there is no risk reversibility and the effects of past exposure remain for an indefinite period.

The above framework can be extended from individuals to populations, by indexing the exposure profile ($x(t)$) to individuals (i.e. representing the exposure of the ith individual as $x_i(t)$) and considering how the distribution of exposure in the population evolves over time.[12] This in turn provides the population distributions of equivalent exposure (current or expected future and counterfactual) which form the basis of calculating attributable fractions (i.e. the terms in the numerator of Equations 2a, 2b or 4).

It is reasonable to assume that if the exposure of one individual is greater than that of another over the whole exposure period (i.e. tracking) (Foulkes and Davis 1981), the *equivalent* exposure of the former is also greater than the latter. In other words, the accumulative risk function, $f(x)$, has the following property:

$$\int_{T_0}^{T} f(x_i(t))dt > \int_{T_0}^{T} f(x_j(t))dt \quad \text{if} \quad x_i(t) > x_j(t) \quad \forall\, t \in [T_0, T] \tag{6}$$

With this property, if the ordering of individuals in the exposure distribution remains unchanged over time (i.e. the rank-order correlation of individual exposures equals 1 between different points in time), the equivalent exposure will also have a distribution with the same ordering of individuals.

The method used by Peto et al. (1992) for estimating mortality due to smoking implicitly uses such as framework. It is well known that the accumulated hazards of smoking depend on a number of variables including the age at which smoking began, number of cigarettes smoked per day and cigarette type. Such data however are extremely rare. To overcome this problem, Peto et al. (1992) used the smoking impact ratio, *SIR*, which uses population lung cancer rates as a marker for accumulated hazard of smoking, to estimate the relative risk of the accumulated smoking exposure corresponding to the population. In the above notation:

$$RR(smoking(t))\Big|_{T_0}^{T} = RR\left(\int_{T_0}^{T} f(smoking(t-L))dt\right) = RR(SIR(T))$$

The temporal profile of exposure for some risk factors may be more easily available than the range of indicators that are needed to estimate the accumulated hazards of smoking. For example, exposure to indoor smoke from solid fuels is likely to remain unchanged as long as household fuel and housing conditions remain the same. Therefore, estimating the effects of long-term exposure may require only knowledge of household fuel, housing and participation in cooking. Similarly, in the case of blood pressure, it is known that blood pressure follows a predictable age pattern (Tate et al. 1995; Yong et al. 1993), unless severely affected by a changes in social (stress), behavioral (diet or smoking)

or medical circumstances. In this case, the usual blood pressure of an individual reflects the history of the person's exposure. On the other hand, the patterns of fruit and vegetable consumption, smoking, or exposure to urban air pollution may change rapidly in countries with high rates of economic growth and urbanization, requiring more detailed data.

The above discussion is based on two implicit assumptions:

1. It considers the effects of exposure to a single risk factor over time. This approach may be appropriate for some risk factor–disease relationships (e.g. the effects of accumulated exposure to carcinogens with site-specific effects). But the single equivalent exposure cannot characterize other risk factor–disease relationships where risk factor interactions are important over time (e.g. physical activity, BMI, smoking and cardiovascular diseases). Extending this temporal dimension to multiple risk factors requires considering the accumulated effects of the vector of risk factors as well as their interactions. In this case, Equation 5 would be expressed in terms of the vector of risk factors of interest. Few epidemiological studies, however, have gathered the data needed for assessing accumulated interactive effects.
2. It considers exposure to each risk factor as an exogenous variable (i.e. intermediate exposure at any time, $x(t)$, is not affected by disease or other risk factors) whose accumulated effect can be captured in a single value using the risk accumulation function. For some risk factors, this assumption may not be valid since exposure to behavioural as well as environmental risk factors may be affected by knowledge of their current effects—individuals may change their diet or activity levels based on knowledge of their weight or blood pressure and governments may introduce regulations based on the level of various contaminants in air or water.[13]

Manton et al. (1993a, 1994) have relaxed these assumptions using a diffusion model for forecasting cardiovascular disease mortality in the United States of America. In this model, it is the change in the outcome at any time, t, that is modelled as a function of all the other variables in the system (i.e. other risk factors as well as outcomes) and their interactions. Using the notation of Equation 3:

$$d\mathbf{X}(t) = \mathbf{u}(\mathbf{X}(t), t)dt \tag{7}$$

where $\mathbf{u}(\mathbf{X}(t), t)$ is a drift term whose value depends on the current value of all the variables in the system as well as their interactions (and can be described by a functional form similar to that in Equation 3).[14] Methods for estimation of such models using longitudinal data are discussed by Robins (1997, 1999b).

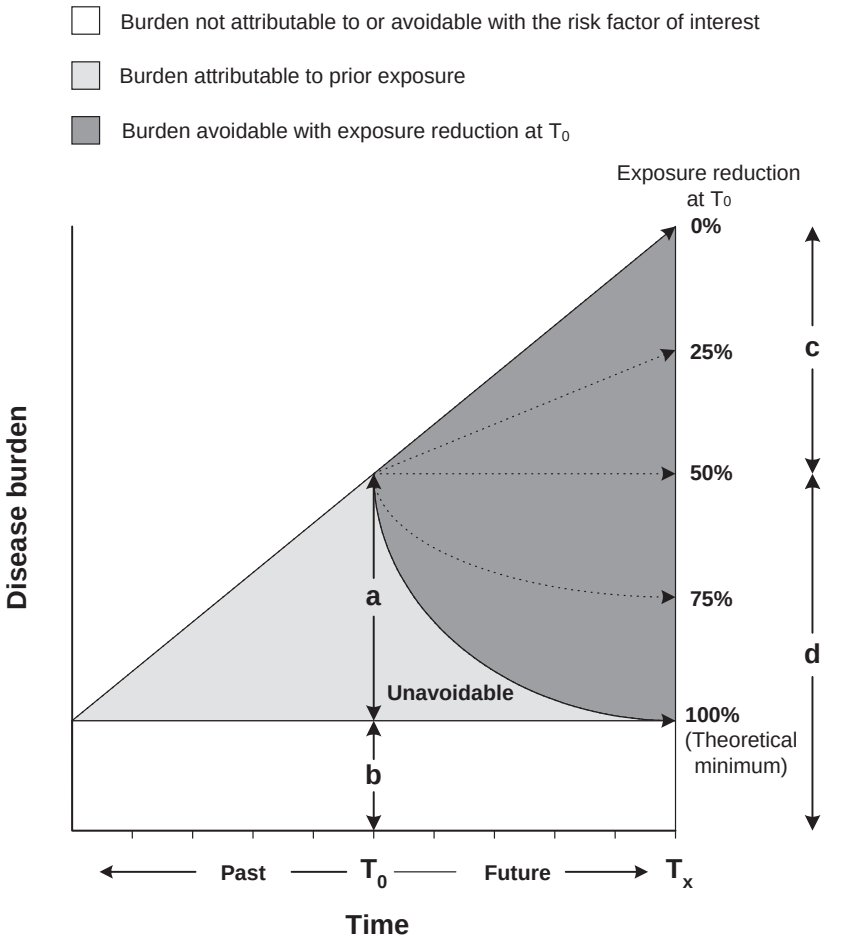
4.2 Temporal characteristics of health outcomes

If the outcome variable used in causal attribution of disease and mortality to a risk factor only involves counting of adverse events (such as disease incidence or death), it is not possible to characterize those cases whose occurrence would have been delayed in the absence of the risk factor (Greenland and Robins 1988; Robins and Greenland 1989, 1991). A major shortcoming with this approach is that it does not take into account the accumulated effects of exposure—in the form of years of life lost prematurely or lived with disability. Parameterizing the above relationships by age (or birth cohort) would allow estimating the effects of exposure to a risk factor, not as an event without time dimension, but as an event at a certain age and time. More broadly, considering the time-indexed stream of health losses due to a risk factor requires using a time-based (and not event-based) SMPH.

Murray and Lopez (1999) have provided an additional temporal distinction for the burden of disease due to a risk factor by introducing the concepts of "attributable" and "avoidable" burden. Attributable burden is defined as the reduction in *current and/or future burden* of disease if *past exposure* to a risk factor had been equal to some counterfactual distribution. Avoidable burden is the reduction in the *future burden* of disease if the *current or future exposure* to a risk factor is reduced to a counterfactual distribution. Attributable and avoidable burden are shown graphically in Figure 1.4. While attributable burden is easier to measure and more certain, avoidable burden is more useful for policy purposes. The distinction between attributable and avoidable burden becomes less significant as the time between exposure to risk factor and effects on disease burden decreases. In this case, attributable burden is a good predictor of avoidable disease burden.

Figure 1.4 also illustrates a conceptual complexity in defining and estimating avoidable burden. Attributable burden is defined based on the difference between (accumulated) current exposure and a counterfactual. Measuring current exposure, while difficult and uncertain, is conceptually well defined. Avoidable burden, on the other hand, depends on the expectation of future exposure and a counterfactual, with the former being analogous to current exposure. Consider for example a population exposed to rising levels of air pollution or rates of obesity. In this setting, interventions that would maintain pollutant concentrations or BMI at their current levels would result in avoiding disease and mortality; they reduce exposure from what it would be in their absence. Therefore, avoidable burden (i.e. how much of future burden could be prevented) by definition requires estimates of future exposure (i.e. how much of future burden there is). Projecting future exposure in turn raises the need to provide a projection framework. To provide visions of public health under various intervention and policy scenarios we suggest that the future exposure level, with respect to which avoidable burden is

Figure 1.4 Attributable and avoidable burden



a Disease burden at T_0 attributable to prior exposure.

b Disease burden at T_0 not attributable to the risk factor of interest (caused by other factors only).

The burden not attributable to the risk factor of interest (white area) may be decreasing, constant or increasing over time. The constant case is shown in the figure.

Dashed arrows represent the path of burden after a reduction at T_0.

c Disease burden avoidable at T_x with a 50% exposure reduction at T_0.

d Remaining disease burden at T_x after a 50% reduction in risk factor exposure.

estimated, be the expectation of exposure if the current policy and technological context were to continue, referred to as the "business-as-usual" exposure trend. Therefore avoidable burden is the burden of disease averted due to reduction in exposure to a risk factor beyond its expected trends. We emphasize that with this definition, avoidable burden is the difference between two exposure scenarios: the expectation of future trends (business-as-usual) and a reduction with respect to this trend towards theoretical minimum.

4.3 Cumulative vs period estimates of attributable and avoidable burden

Although analytically inconsequential, the starting point and the duration of the time interval over which attributable or avoidable burden is reported has policy implications because reductions in various risk factors may provide health benefits that occur after short or long delays and last for different periods. Consider for example the health benefits of reductions in binge alcohol consumption, smoking and GHG emissions. Reducing binge drinking would result in immediate health benefits from a drop in alcohol-related accidents and injuries (as well as medium- and long-term benefits from reduction in other diseases). Lowering smoking will have some short- and medium-term benefits from reduction of acute respiratory diseases and cardiovascular disease as well as longer-term benefits from lowering cancers and chronic obstructive pulmonary disease (COPD). The benefits of policies that reduce climate change as a result of GHG emissions are likely to be heavily concentrated in the future.

Consider these examples of health benefits in terms of duration: the distribution of a drug that lowers blood pressure, or food aid to reduce malnutrition; and programmes that promote and sustain increased physical activity, the introduction of a new agricultural technology which results in higher food yields, or automotive technology which eliminates the use of leaded gasoline. While the benefits of all these interventions may be equally large and important for the current cohort, the first two actions have one-time health benefits (unless repeated) while the latter three are likely to last indefinitely.

The above discussion would suggest reporting the estimates of avoidable burden in multiple ways including both period (e.g. annual) and cumulative estimates, as well as over short and long time frames. The issue of future estimates and their policy relevance is further complicated by the growing uncertainty of estimates with increasing length of the estimation interval. Therefore, while it may be preferable to increase the prediction horizon, it is important to emphasize that long-term predictions are inherently more uncertain.

4.4 Discounting future risk and health effects

Individuals may discount consumption or welfare within their own lifespan and exhibit a preference for benefits today over the future. The theoretical and empirical arguments for and against individual discounting with specific emphasis on health, including the possibility of negative discount rates, are summarized elsewhere (Murray 1996; Murray and Acharya 2002) and are directly incorporated in the calculation of a summary measure of population health. In addition to individual discounting and discount rates, policies dealing with risk confront the issue of addressing benefits to different populations across time. As a result, these policies must address ethical and analytical dilemmas related to the valuation of current and future health and welfare, in the form of social discount rates (Kneese 1999). Discounting future risks, benefits and welfare has been a subject of great debate (Howarth 1996; Lind 1982; Portney and Weyant 1999; Schelling 1995; Toman 1999), motivating some economists to conclude that

> maybe the idea of a unitary decision-maker—like an optimising individual or a wise and impartial adviser—is not very helpful when it comes to the choice of policies that will have distant-future effects about which one can now know hardly anything. Serious policy choice may then be a different animal, quite unlike individual saving and investment decisions. . . . "Responsibility" suggests something less personal (Solow 1999).

The arguments for and against discounting of future health and welfare, and their validity, have been discussed in detail elsewhere (Anand and Hansen 2002; Murray and Acharya 2002; Murray and Lopez 1996; Parfit 1984). According to one specific argument, "the disease eradication and health research paradox", not discounting future health would imply investing all of society's health resources in research programmes or programmes for disease eradication, which would result in an infinite stream of benefits, rather than in any programme that improves the health of the current generation. Such an excessive intergenerational "sacrifice" is a particularly powerful argument for discounting of future health (or more precisely for something that resembles discounting as we discuss shortly) (Parfit 1984). It is important to emphasize that this argument does not imply that future welfare or health is less valuable than current, but rather it uses discounting as a tool to avoid excessive sacrifice for the current generation, to the point of investing all resources in an infinite stream of future health. For this reason, Parfit (1984) argues that the issue of intergenerational distribution should be considered as an independent criterion, rather than explicitly discounting future benefits.

Koopmans (1960), Dasgupta and Mäler (1994) and Dasgupta et al. (1999), however, have shown that any preference-ordering defined over

a set of well-being paths over time can be represented by a numerical function with an *apparently* utilitarian form[15] and therefore includes what *resembles* positive discounting of future well-being. We emphasize that this notion is simply a consequence of considering the paths of well-being (or temporal distributions), rather than a statement about the value of current or future welfare. With this formulation, Dasgupta and Mäler (1994) and Dasgupta et al. (1999) consider the implications of the choice of discount rate as a "derived notion", as opposed to a value judgement. Dasgupta and Heal (1974) and Solow (1974b) have shown that if well-being is a result of consumption of an exhaustible resource, a zero discount rate would imply investing all available resources for the benefit of future generations, and hence no current consumption. This is because each unit sacrificed by the first generation would yield a finite loss to this generation, but an infinite stream of benefits to future generations (Arrow 1999) which, without discounting, would always be larger than the one-time sacrifice. Although the first generation cannot sacrifice everything,[16] the logical conclusion of this situation would be that "given any investment [for future benefits], short of the entire income, a still greater investment would be preferred" (Arrow 1999), or a potentially excessive intergenerational sacrifice (Murray 1996).

On the other hand, a positive discount rate would imply that in the long run consumption of resources should become zero. In this case, however, the additional requirement that well-being should never fall below a certain threshold would in turn require downward adjustment of the discount rate (Solow 1974a). The stricter requirement of non-declining consumption and well-being would require a discount rate lower than the productivity of capital (Dasgupta and Mäler 1994).[17] Based on these arguments, we suggest discounting of future attributable or avoidable disease burden due to risk factors, but with a low discount rate, to include the welfares of both current and future generations as described above.

5. Uncertainty

Quantitative risk assessment is always affected by uncertainty about the existence, magnitude and distribution of risk (Graham et al. 1988). Quantitative analysis of uncertainty greatly adds to the usefullness of the results because it shows not only the "best-estimate" of the magnitude and distribution of exposure to a risk factor, and the resulting burden of disease, but also the range of potential outcomes.

5.1 Sources of uncertainty in attributable fractions

Population distribution of exposure

An important source of uncertainty in risk assessment is characterizing population distribution of exposure. Due to complexity and cost, for

most risk factors, exposure is measured only in small samples and in a limited number of settings. As discussed earlier, because a risk factor can be represented in different layers of causality, variables for which data are more readily available can be used as exposure proxies. The use of exposure proxies is sometimes also necessary because epidemiological studies have used such proxies in estimating hazard size. For example, anthropometric variables such as height-for-age or weight-for-age are used as indicators of childhood nutritional status; the presence of clean water sources or sanitary latrines as indicators of faecal–oral transmission of pathogens; concentration of particles as the measure of exposure to the various pollutants in ambient air, and so on. In addition to reduced data requirements, the use of such indirect indicators of exposure (or exposure scenarios [Kay et al. 2000]) may provide direct mapping to existing interventions. At the same time, these indicators, which are often more distal than actual exposure, do not capture the variability of exposure within each scenario, unless combined with other indicators which affect this variability (Ezzati et al. 2000). For example people using the same water source may experience different levels of faecal–oral transmission of pathogens due to different storage and hygiene behaviours. Therefore, the use of indirect exposure proxies results in additional uncertainty in exposure characterization.

Even with the choice of exposure proxies, extrapolation of exposure between different populations or age groups is often necessary. Such extrapolation (or spatial prediction) can be based on models as simple as using the average of subgroups with data for a whole population, or more complex prediction models. For example, urban air quality monitoring systems provide data on particle concentrations in some but not all cities in each region. Models to predict ambient concentrations of particulate matter based on energy consumption, number of vehicles and level of industrialization can be used to predict ambient air pollution levels for cities where data are not available. Similarly, the level of physical (in)activity in a population may be predicted from a model that uses rural–urban population distribution, income, education, distribution across occupational categories and available transportation modes in each geographical region. Each such extrapolation adds to the uncertainty of exposure distributions.

Finally, as we discussed earlier, for many risk factors, hazards are associated with accumulated effects of sustained exposure. Indicators of accumulated hazard for those risk factors with changing exposure such as smoking, urban air pollution or BMI, are needed but not always available. Further, few epidemiological studies have considered the role of a temporal profile of exposure on disease (see Peto 1986 for an example of an exception). Therefore even if longitudinal data on exposure prevalence were available, they could not always be used together with epidemiological studies that consider a single exposure variable—at the beginning or end of the follow-up period, for example. At the same time,

if the ordering of individuals in the exposure distribution remains unchanged over time (see above), risk estimates from epidemiological studies with similar ordering may be applicable, but result in additional uncertainty.[18]

Risk factor–disease relationship

At the most fundamental level, quantifying the hazards associated with exposure to a risk factor requires identifying the diseases and injuries that are caused by a risk factor. The criteria for establishing disease causality have been the subject of interest and debate for over a century (summarized in Evans 1976, 1978; Hill 1965; National Research Council 1994; Yerushalmy and Palmer 1959). Epidemiological studies have successfully provided the basis for establishing causality between some risk factor–disease pairs. For other risk factor–disease combinations, where the measurement of exposure or disease has been difficult or the delay between exposure and health effects is very long, observational or experimental epidemiology has had less success in establishing causality (Evans 1976; Robins 1999a). For this reason, epidemiological evidence must often be complemented with inferences from other disciplines such as toxicology, physiology, parasitology and, increasingly, biophysics, in establishing disease causation.

Even when causality is established, the magnitude of the hazard due to a risk factor needs to be quantified. Although the statistical issues around establishing causality and estimating the effect size are similar (lack of causality is equivalent to zero excess risk) (Robins 1999a; Robins and Greenland 2000), in practice, with knowledge from multiple disciplines in establishing causality, it is often the latter that is the source of increased uncertainty in risk assessment. For example, the collectivity of scientific knowledge from disciplines such as economics and behavioural sciences, vector biology, physiology and bio-mechanics and epidemiology would confirm the possibility that climate change or socioeconomic inequality would increase disease, or whether the relationships between occupational factors or physical inactivity and lower back pain are causal. At the same time, risk assessment would require estimating the hazard magnitude for each of these relationships. Therefore, the complexity of the causal relationship, or lack of detailed data, would shift the debate from causality to hazard size.

Epidemiological studies that quantify hazards are often conducted in a limited number of settings, with emphasis on estimating the average effect size in the whole study group. While the robustness of relative risk measures has been confirmed for more proximal factors in studies across populations (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998; Law et al. 1994), their extrapolation is an important source of uncertainty for more distal risks (e.g. child sexual abuse) or for those whose effects are heterogeneous (e.g. alcohol and injuries vs alcohol and cancer) and has received less attention in the

epidemiological literature (Horton 2000). For some risk factors, it is likely that the magnitude of the hazard may depend on the levels of other variables (i.e. effect modifiers). Therefore, in extrapolating the results of individual epidemiological studies or meta-analyses, the very strength of the original study—applicability to the average person—would be the source of uncertainty if the population to whom the effect size is extrapolated has characteristics which would result in effect modification (Britton et al. 1999; Horwitz et al. 1990, 1996, 1998). The impact of alcohol drinking patterns on cardiovascular disease risk estimates (Britton and McKee 2000; Puddey et al. 1999) is an example of the importance of considering factors that modulate and modify hazards in risk extrapolation.

Risk factor and disease correlations

Because multiple risks and disease are correlated (e.g. higher malnutrition, unsafe water, sanitation and hygiene, indoor smoke and childhood mortality in poor rural households in developing countries; higher smoking, BMI and occupational risks in developed countries [Thun et al. 2000]), estimating attributable fractions would require stratified (e.g. by other risk factors) prevalence as well as disease data. Lack of stratified data is another source of uncertainty, in general leading to the underestimation of effects in the presence of positive risk factor correlations (Greenland 1984).

5.2 Characterizing and quantifying uncertainty

Various taxonomies of uncertainty have been used in risk assessment (National Research Council 1994) including:

1. classification based on information type such as uncertainty in hazard identification, exposure assessment, exposure–response assessment, as discussed above;

2. classification based on uncertainty type such as randomness, true variability, and bias; and

3. classification based on the approach to handling uncertainty which divides uncertainty into *parameter uncertainty* and *model uncertainty*. Parameter uncertainty includes the uncertainty quantifiable using random-variable methods such as the uncertainty due to sampling and measurement error. Model uncertainty is due to gaps in scientific theory, measurement technology and data (National Research Council 1994). It includes uncertainty in the knowledge of causal relationships or of the form of the exposure–response relationship (threshold vs continuous, linear vs non-linear, etc.), the level of bias in measurement, etc. Defined broadly, model uncertainty also includes extrapolation of exposure or hazard from one population to another. Uncertainty in risk assessment is overwhelmingly dominated by model

uncertainty, which arises due to a lack of direct studies on exposure, hazard and background disease burden.

We distinguish between uncertainty, which is due to gaps in knowledge, methods or data, and variability, which is a real property of the world and itself may be known with certainty or with uncertainty. Variability can nonetheless be a source of uncertainty in the absence of population-specific data on exposure or the exposure–response relationship. For many risk factors, data on exposure distributions are available for a limited number of populations or demographic groups. The exposure distribution for other populations are then extrapolated from the available data based on some model. As discussed earlier, the extrapolation model may be as simple as using the population-weighted average of the existing data or more complex (based on a number of predictors). In such cases, the statistical uncertainty of the estimator (e.g. the 95% confidence interval of the mean or regression coefficients) is an underestimation of true uncertainty in predicted values due to the unexplained variability in the data. More complex models can increase the predictive power and therefore reduce uncertainty but even the most sophisticated models are unlikely to fully explain the variability of the data, resulting in residual uncertainty. Variability can also be a source of uncertainty in the estimation and extrapolation of exposure–response relationships or relative risks that are measured in a limited number of settings. In the presence of multiple estimates of hazard, it is common to use meta-analytical approaches to obtain an overall estimate. At the same time, the differences between various estimates may reflect true variability in effect size, especially if obtained from different populations, resulting in uncertainty in hazard estimates.

Parameter uncertainty can be readily included in quantitative analysis using random-variable statistical methods (Morgan and Henrion 1990). While we have discussed the various sources of uncertainty, the important issue of extrapolation of exposure and hazard using models requires new approaches to quantifying uncertainty in the presence of limited data. Quantitative analysis of model uncertainty, by definition, would require considering the uncertainty of the models and assumptions used (including assumptions about disease mechanism or data/parameter extrapolation) using the methods of Bayesian statistics.

6. Conclusions

We have described a framework for systematic quantification of the burden of disease due to risk factors that attempts to unify the growing interest in health risks across a number of health, physical and social sciences. The key attributes of the framework, along with the corresponding methodological issues that arise in its application, are:

- comparing the burden of disease due to the observed exposure distribution in a population with the burden from a hypothetical distribution or series of distributions, rather than a single reference level such as non-exposed;
- considering the multiple stages of causality and interactions between risk factor(s) and disease outcome to allow inferences about combinations of risk factors for which epidemiological studies have not been conducted, including the joint effects of changes in multiple risk factors;
- calculating the health loss due to risk factor(s) as a time-indexed "stream" of disease burden due to a time-indexed "stream" of exposure, including consideration of discounting; and
- describing the sources of uncertainty in the risk assessment process.

For each of the above aspects, we have outlined the important conceptual and methodological issues and their implications for risk assessment. While this framework provides a means for considering risk factors in different layers of causality, with multiple counterfactuals (Ezzati et al. 2002; see also the risk factor chapters in this book), its application is limited by the availability of data on risk factors and hazards (Powles and Day 2002). The availability and form of data on both exposure and hazard are often determined by disciplinary boundaries as well as measurement difficulties. Analysis of selected risks highlights data and monitoring needs for better quantification and intervention strategies, especially more detailed data on exposure, hazard accumulation over time, and heterogeneity of risk factor–disease relationships.

For more effective and affordable implementation of a prevention paradigm, policies, programmes and scientific research should acknowledge and take advantage of the interactive role of major risks to health, across and within causality layers. Despite the methodological complexity and empirical difficulties, especially in estimating time-based multi-risk exposures, this framework provides a consistent basis for better and more comparable information about the various causes of disease and injury. In the remaining chapters of this book, the burden of disease due to a diverse set of risk factors is assessed according to this conceptual framework, with a detailed description of data sources and risk factor-specific methodological issues.

Acknowledgements

This work has been sponsored by the National Institute of Aging Grant 1-PO1-AG17625. The participants in the various CRA project collaborators meetings and two reviewers provided valuable comments. J. Powles and J. Barendregt provided extensive comments on an earlier draft.

Notes

1 As discussed by Greenland and Robins (1988), attributable fractions without a time dimension are not able to characterize those cases whose occurrence would have been delayed in the absence of exposure. The authors recommend the use of etiologic fractions with a time dimension to account for this shortcoming. Time-based measures are discussed in more detail below.

2 At the extreme, a structural model would attempt to use chemical or physical principles as the unit of analysis and modelling. This would of course be currently impossible in studying any system that involves population health.

3 The "driving force, pressure, state, exposure, effect" (DPSEE) model of Corvalan et al. (1999) does consider the multiple layers of causality. This model however focuses on the risk evolution process, which is less suitable for multi-risk factor interaction within and between layers. More complete discussions of causality and multiple causes are provided by Yerushalmy and Palmer (1959), Evans (1976, 1978) and Rothman and Greenland (Rothman 1976; Rothman and Greenland 1998).

4 The exception is those risk factors whose effects occur through intermediate variables which are themselves a risk factor for the outcome considered, such as the relationships between physical inactivity or obesity and IHD, which are mediated through blood pressure or cholesterol. In such cases, controlling for the intermediate risk factor would result in a bias (towards the null) in the estimation of total hazard of the distal factor (Greenland 1987).

5 There are no past studies on "climate change" as it is expected to take place in the future. For this reason, the relationship between climate change and health would always be based on a model which relates climate change to meteorological variables (e.g. temperature or rainfall). The relationship between these variables, disease vectors and disease could then be estimated from past data and vector biology (Craig et al. 1999; Martens et al. 1999; Rogers and Randolph 2000).

6 If the variables in the nth layer of the causal-web are affected directly by those in the $(n-2)$th layer in addition to the $(n-1)$th layer, or by variables within the nth layer itself (see Figure 1.2 for an example), Equation 3a can be expanded to include these links as well:

$$\mathbf{X}^n = f(\mathbf{B}_0(\mathbf{X}^n), \mathbf{X}^n; \mathbf{B}_1(\mathbf{X}^{n-1}, \mathbf{X}^n)\,\mathbf{X}^{n-1}; \mathbf{B}_2(\mathbf{X}^{n-2}, \mathbf{X}^n)\,\mathbf{X}^{n-2}) \tag{3b}$$

This can be extended to interactions across multiple causal layers, and in general any variable in the system can be affected by any other one as the concept of causal layer becomes more flexible.

7 In this case when some of the variables affect not only the other variables in the causal system but also the relationship(s) between variables, they are equivalent to "effect modification" in epidemiological literature (Rothman 1976). Graphically, in Figure 1.1 they would be represented as links (arrows) not between two variables but as links from one of the variables (the effect modifier) to another link in the system.

8 In other words the $RR(x)$ in Equations (2a) and (2b) are functions of the other covariates, referred to as effect modification earlier. Epidemiological

studies that stratify relative risks based on covariates other than age and sex are however rare.

9 The notation $|_{T_0}^{T}$ denotes "estimated between T_0 and T".

10 Equivalent exposure is an analytical concept and need not be physically realizable. In fact for many risk factors, such as carcinogens, where the effects are from life-long exposure, the equivalent exposure would be so high that its occurrence at a single instant would be impossible.

11 Further, if there is threshold, M, below which exposure has no effect:

$$RR(x(t))|_{T_0}^{T} = RR\left(\int_{T_0}^{T} f(x(t-L))(\text{TRUE}(x(t-L) \geq M))dt\right)$$

where

$$\text{TRUE}(x(t) \geq M) = \begin{cases} 1 & \text{if } x(t) \geq M \\ 0 & \text{if } x(t) < M \end{cases}$$

This framework can be easily modified to include cases where exposure has different effects below and above threshold by using TRUE($x(t) \geq M$) for the effect above the threshold and TRUE($x(t) < M$) for the effect below the threshold.

12 In this manner, the evolution of the exposure distribution is analytically similar to a "random process" in which a probability density function (PDF) describes a random variable which is a function of time. Exposure to a risk factor is not a random variable in the strict sense. But since a time-dependent exposure distribution has an accumulated distribution of 1.0, it has the same representation as a random process.

13 Robins (1999a) discusses this issue in the case of estimating the effects of a dynamic treatment regime whose dose is dependent on symptoms.

14 The diffusion model also includes a stochastic component to account for those interactive effects not described by the drift term.

15 The functional form is $\int_0^\infty W_i\alpha^t$ where $0 < \alpha < 1$ in Koopmans (1960) and $\int_0^\infty W_i\exp(-\delta t)$ where $\delta > 0$ in Dasgupta and Mäler (1994) and Dasgupta et al. (1999); α and δ are the social rate of discount.

16 The last unit of sacrifice will have infinite marginal utility therefore matching the future infinite stream of benefits.

17 These two additional constraints are external to the economic efficiency arguments as defined by maximizing aggregate welfare. In fact, these additional constraints of minimum acceptable or non-declining welfare result in an "inefficient" outcome in order to achieve better distribution across generations (Montgomery 1999). See Weitzman (1999) for another argument for the choice of lower discount rates.

18 If exposure is sustained for a longer time in the risk assessment population than in the study population and if the whole exposure period contributes to hazards, this would result in an underestimation of risk (and vice versa). For example, in many cohorts in current epidemiological studies, BMI

increased when the subjects were in their twenties or thirties. There is however increasing child and adolescent overweight or obesity in many regions of the world. If this continues into adult life, the hazards may be higher than subjects in the current study cohorts.

References

Anand S, Hansen K (2002) Age weights and discounting in disability-adjusted life years: a critical review. In: *Summary measures of population health*. Murray CJL, Salomon J, Mathers CD, Lopez AD, Lozano R, eds. World Health Organization, Geneva.

Arrow KJ (1999) Discounting, morality, and gaming. In: *Discounting and intergenerational equity*. Portney PR, Weyant JP, eds. Resources for the Future, Washington, DC.

Barnes R (1965) Comparisons of blood pressure and blood cholesterol levels in New Guineans and Australians. *Medical Journal of Australia,* **1**:611–617.

Britton A, McKee M (2000) The relationship between alcohol and cardiovascular disease in eastern Europe: explaining the paradox. *Journal of Epidemiology and Community Health,* **54**:328–332.

Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C (1999) Threats to applicability of randomised trials: exclusion and selective participation. *Journal of Health Services Research and Policy*, **4**:112–121.

Carvalho JJ, Baruzzi RG, Howard PF et al. (1989) Blood pressure in four remote populations in the Intersalt study. *Hypertension*, **14**:238–246.

Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W (1991) Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *British Medical Journal*, **303**:276–282.

Cole P, MacMahon B (1971) Attributable risk percent in case-control studies. *British Journal of Preventive and Social Medicine*, **25**:242–244.

Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K (2000) Alcohol and coronary heart disease: a meta-analysis. *Addiction*, **95**:1505–1523.

Corvalan CF, Kjellstrom T, Smith KR (1999) Health, environment, and sustainable development: identifying links and interactions to promote action. *Epidemiology*, **10**:656–660.

Craig MH, Snow RW, le Sueur D (1999) A climate-based distribution model of malaria transmission in sub-Saharan Africa. *Parasitology Today*, **15**:105–111.

Dasgupta P, Heal GM (1974) The optimal depletion of exhaustible resources. *Review of Economic Studies*, **41**.

Dasgupta P, Mäler K-G (1994) *Poverty, institutions, and the environmental resource base* (World Bank Environment Paper No. 9.) World Bank, Washington, DC.

Dasgupta P, Mäler K-G, Barrett S (1999) Intergenerational equity, social discount rates, and global warming. In: *Discounting and intergenerational equity*. Portney PR, Weyant JP, eds. Resources for the Future, Washington, DC.

Drescher K, Becher H (1997) Estimating the generalized impact fraction from case-control data. *Biometrics*, **53**:1170–1176.

Eastern Stroke and Coronary Heart Disease Collaborative Research Group (1998) Blood pressure, cholesterol, and stroke in eastern Asia. *The Lancet*, **352**:1801–1807.

Eide GE, Heuch I (2001) Attributable fractions: fundamental concepts and their visualization. *Statistical Methods in Medical Research*, **10**:159–193.

Evans AS (1976) Causation and disease: the Henle-Koch postulates revisited. *Yale Journal of Biology and Medicine*, **49**:175–195.

Evans AS (1978) Causation and disease: a chronological journey. *American Journal of Epidemiology*, **108**:249–258.

Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJL, Comparative Risk Assessment Collaborative Group (2002) Selected major risk factors and global and regional burden of disease. *The Lancet*, **360**:1347–1360.

Ezzati M, Saleh H, Kammen DM (2000) The contributions of emissions and spatial microenvironments to exposure to indoor air pollution from biomass combustion in Kenya. *Environmental Health Perspectives*, **108**: 833–839.

Foulkes MA, Davis CE (1981) An index of tracking for longitudinal data. *Biometrics*, **37**:439–446.

Graham JD, Green LC, Roberts MJ (1988) *In search of safety: chemicals and cancer risk*. Harvard University Press, Cambridge.

Greenland S (1984) Bias in methods for deriving standardized morbidity ratio and attributable fraction estimates. *Statistics in Medicine*, **3**:131–141.

Greenland S (1987) Quantitative methods in the review of epidemiologic literature. *Epidemiologic Reviews*, **9**:1–30.

Greenland S (2002) Causality theory for policy uses of epidemiological measures. In: *Summary measures of population health: concepts, ethics, measurement and applications*. Murray CJL, Salomon J, Mathers CD, Lopez AD, eds. World Health Organization, Geneva.

Greenland S, Robins JM (1988) Conceptual problems in the definition and interpretation of attributable fractions. *American Journal of Epidemiology*, **128**:1185–1197.

He J, Klag MJ, Whelton PK et al. (1991a) Migration, blood pressure pattern, and hypertension: the Yi migrant study. *American Journal of Epidemiology*, **134**:1085–1101.

He J, Tang YC, Tell GS, Mo PS, He GQ (1991b) Effect of migration on blood pressure: the Yi people study. *Epidemiology*, **2**:88–97.

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, **58**:295–300.

Horton R (2000) Common sense and figures: the rhetoric of validity in medicine (Bradford Hill memorial lecture 1999). *Statistics in Medicine*, **19**:3149–3164.

Horwitz RI, Singer BH, Makuch RW, Viscoli CM (1998) Clinical versus statistical considerations in the design and analysis of clinical research. *Journal of Clinical Epidemiology*, **51**:305–307.

Horwitz RI, Singer BH, Viscoli CM, Makuch RW (1996) Can treatment that is helpful on average be harmful to some patients? A study of the conflicting information needs of clinical inquiry and drug regulation. *Journal of Clinical Epidemiology*, **49**:395–400.

Horwitz RI, Viscoli CM, Clemens JD, Sadock RT (1990) Developing improved observational methods for evaluating therapeutic evidence. *American Journal of Medicine*, **89**:630–638.

Howarth RH (1996) Climate change and overlapping generations. *Contemporary Economic Policy*, **14**:100–111.

Kay D, Prüss AM, Corvalan CF (2000) *Methodology for assessment of environmental burden of disease. ISEE session on environmental burden of disease*. World Health Organization, Geneva.

Kneese AV (1999) The Faustian bargain. In: *The RFF reader in environment and resource management*. Oates WE, ed. Resources for the Future, Washington, DC.

Koopmans TC (1960) Stationary ordinal utility and impatience. *Econometrica*, **28**:287–309.

Kunzli N, Kaiser R, Medina S et al. (2000) Public-health impact of outdoor and traffic-related air pollution: a European assessment. *The Lancet*, **356**:795–801.

LaRosa JC, He J, Vupputuri S (1999) Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *Journal of American Medical Association*, **282**:2340–2346.

Law MR, Wald NJ, Thompson SG (1994) By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *British Medical Journal*, **308**:367–373.

Leigh J, Macaskill P, Kuosma E, Mandryk J (1999) Global burden of disease and injury due to occupational factors. *Epidemiology*, **10**:626–631.

Levin ML (1953) The occurrence of lung cancer in man. *Acta Unio Internationalis Contra Cancrum*, **9**:531–541.

Lind RC, ed. (1982) *Discounting for time and risk in energy policy*, Johns Hopkins University Press for Resources for the Future, Baltimore, MD.

MacMahon B, Pugh TF (1970) *Epidemiology: principles and method*. Little Brown and Company, Boston, MA.

MacMahon S, Peto R, Cutler J et al. (1990) Blood pressure, stroke, and coronary heart disease. Part I, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *The Lancet*, **335**:765–774.

Maldonado G, Greenland S (2002) Estimating causal effects. *International Journal of Epidemiology*, **31**:422–429.

Mann GV, Shaffer RD, Anderson RS, Sandstead HH (1964) Cardiovascular disease in the Masai. *Journal of Atherosclerosis Research*, **4**:289–312.

Manton KG, Dowd JE, Stallard E (1993a) The effects of risk factors on male and female cardiovascular risks in middle and late age. In: *Forecasting the health of elderly populations*. Manton KG, Singer BH, Suzman RM, eds. Springer-Verlag, New York.

Manton KG, Singer BH, Suzman RM (1993b) *Forecasting the health of elderly populations*. Springer-Verlag, New York.

Manton KG, Stallard E, Singer BH (1994) Methods for projecting the future size and health status of the US elderly populations. In: *Studies in the economics of aging*. Wise DA, ed. University of Chicago Press, Chicago, IL.

Martens P, Kovats RS, Nijhof S et al. (1999) Climate change and future populations at risk of malaria. *Global Environmental Change-Human and Policy Dimensions*, **9**:S89–S107.

Mathers CD, Ezzati M, Lopez AD, Murray CJL, Rodgers AD (2002) Causal decomposition of summary measures of population health. In: *Summary measures of population health: concepts, ethics, measurement and applications*. Murray CJL, Salomon J, Mathers CD, Lopez AD, eds. World Health Organization, Geneva.

McGinnis JM, Foege WH (1993) Actual causes of death in the United States. *Journal of American Medical Association*, **270**:2207–2212.

Miettinen OS (1974) Proportion of disease caused or prevented by a given exposure, trait or intervention. *American Journal of Epidemiology*, **99**: 325–332.

Montgomery WD (1999) A market-based discount rate: comments on Bradford. In: *Discounting and intergenerational equity*. Portney PR, Weyant JP, eds. Resources for the Future, Washington, DC.

Morgan MG, Henrion M (1990) *Uncertainty: a guide to dealing with uncertainty in quantitative risk and policy analysis,* Cambridge University Press, Cambridge.

Murray CJL (1996) Rethinking DALYs. In: *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol. 1. Murray CJL, Lopez AD, eds. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJL, Acharya A (2002) Age weights and discounting in health gaps reconsidered. In: *Summary measures of population health: concepts, ethics, measurement and applications*. Murray CJL, Salomon J, Mathers CD, Lopez AD, eds. World Health Organization, Geneva.

Murray CJL, Lopez AD, eds. (1996) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol. 1. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJL, Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. *The Lancet*, **349**:1436–1442.

Murray CJL, Lopez AD (1999) On the comparable quantification of health risks: lessons from the global burden of disease. *Epidemiology*, **10**:594–605.

Murray CJL, Salomon J, Mathers CD, Lopez AD, eds. (2002) *Summary measures of population health: concepts, ethics, measurement and applications*. World Health Organization, Geneva.

National Research Council (1994) *Science and judgment in risk assessment*. National Academy Press, Washington, DC.

Ouellet BL, Romeder JM, Lance JM (1979) Premature mortality attributable to smoking and hazardous drinking in Canada. *American Journal of Epidemiology*, **109**:451–463.

Parfit D (1984) *Reasons and persons*. Oxford University Press, New York.

Patz JA, McGeehin MA, Bernard SM et al. (2000) The potential health impacts of climate variability and change for the United States: executive summary of the report of the health sector of the US national assessment. *Environmental Health Perspectives*, **108**:367–376.

Peto R (1986) Influence of dose and duration of smoking on lung cancer rates. In: *Tobacco: a major international health hazard*. Zaridze D, Peto R, eds. (IARC Scientific Publication No. 7.) International Agency for Research on Cancer, Lyon.

Peto R, Lopez AD, Boreham J, Thun M, Heath C, Jr. (1992) Mortality from tobacco in developed countries. *The Lancet*, **339**:1268–1278.

Pignone M, Phillips C, Mulrow C (2000) Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials. *British Medical Journal*, **321**:983–986.

Portney PR, Weyant JP, eds. (1999) *Discounting and intergenerational equity*. Resources for the Future, Washington, DC.

Powles J, Day N (2002) Interpreting the global burden of disease. *The Lancet*, **360**:1342–1343.

Preston SH (1976) *Mortality patterns in national populations: with special reference to recorded causes of death*. Academic Press, New York.

Prospective Studies Collaboration (1995) Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 45 000 people in 45 prospective cohorts. *The Lancet*, **346**:1647–1653.

Puddey IB, Rakic V, Dimmitt SB, Beilin LJ (1999) Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors: a review. *Addiction*, **94**:649–663.

Reiter P (2001) Climate change and mosquito-borne diseases. *Environmental Health Perspectives*, **109**:S141–161.

Rice AL, Sacco L, Hyder A, Black RE (2000) Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. *Bulletin of the World Health Organization*, **108**:367–376.

Robins JM (1986) A new approach to causal inference in mortality studies with sustained exposure periods—application to control of the healthy worker survival effect. *Mathematical Modelling*, **7**:1393–1512.

Robins JM (1987) Addendum to "a new approach to causal inference in mortality studies with sustained exposure periods—application to control of the healthy worker survival effect". *Computers and Mathematics with Applications*, **14**:917–921.

Robins JM (1997) Causal inference from complex longitudinal data. In: *Latent variable modeling and applications to causality. Lecture notes in statistics (120)*. Berkane M, ed. Springer-Verlag, New York.

Robins JM (1999a) Association, causation, and marginal structural models. *Synthese*, **121**:151–179.

Robins JM (1999b) Marginal structural models versus structural nested models as tools for causal inference. In: *Statistical models in epidemiology*. Halloran E, ed. Springer-Verlag, New York.

Robins JM, Greenland S (1989) Estimability and estimation of excess and etiological fractions. *Statistics in Medicine*, **8**:845–859.

Robins JM, Greenland S (1991) Estimability and estimation of expected years of life lost due to a hazardous exposure. *Statistics in Medicine*, **10**:79–93.

Robins JM, Greenland S (2000) Comment on "causal inference without counterfactuals" by Dawid AP. *Journal of American Statistical Association—Theory and Methods*, **95**:477–482.

Robins JM, Greenland S, Fu-Chang H (1999) Estimation of the causal effect of a time-varying exposure on the marginal mean of a repeated binary outcome. *Journal of American Statistical Association*, **94**:687–700.

Rockhill B, Newman B, Weinberg C (1998) Use and misuse of population attributable fractions. *American Journal of Public Health*, **88**:15–19.

Rogers DJ, Randolph SE (2000) The global spread of malaria in a future, warmer world. *Science*, **289**:1763–1766.

Rothman KJ (1976) Causes. *American Journal of Epidemiology*, **104**:587–592.

Rothman KJ, Greenland S (1998) *Modern epidemiology.* Lippincott-Raven, Philadelphia, PA.

Schelling TC (1995) Intergenerational discounting. *Energy Policy*, **23**:395–401.

Single E, Robson L, Rehm J, Xie X (1999) Morbidity and mortality attributable to alcohol, tobacco, and illicit drug use in Canada. *American Journal of Public Health*, **89**:385–390.

Smith KR (2000) The national burden of disease from indoor air pollution in India. *Proceedings of the National Academy of Sciences*, **97**:13286–13293.

Smith KR, Corvalan CF, Kjellstrom T (1999) How much global ill health is attributable to environmental factors. *Epidemiology*, **10**:573–584.

Smith KR, Samet JM, Romieu I, Bruce N (2000) Indoor air pollution in developing countries and acute lower respiratory infections in children. *Thorax*, **55**:518–532.

Solow RM (1974a) The economics of resources or the resources of economics. *The American Economic Review*, **64**:1–14.

Solow RM (1974b) Intergenerational equity and exhaustible resources. *The Review of Economic Studies*, **41**:29–45.

Solow RM (1999) Foreword. In: *Discounting and intergenerational equity*. Portney PR, Weyant JP, eds. Resources for the Future, Washington, DC.

Tate RB, Manfreda J, Krahn AD, Cuddy TE (1995) Tracking of blood pressure over a 40-year period in the University of Manitoba follow-up study, 1948–1988. *American Journal of Epidemiology*, **142**:946–954.

Thun MJ, Apicella LF, Henley SJ (2000) Smoking vs other risk factors as the cause of smoking-attributable mortality: confounding in the courtroom. *Journal of American Medical Association*, **284**:706–712.

Toman MA (1999) Reconciling philosophy and economics in long-term discounting. In: *Discounting and intergenerational equity*. Portney PR, Weyant JP, eds. Resources for the Future, Washington, DC.

Uter W, Pfahlberg A (2001) The application of methods to quantify attributable risk in medical practice. *Statistical Methods in Medical Research*, **10**: 231–237.

Walter SD (1980) Prevention of multifactorial disease. *American Journal of Epidemiology*, **112**:409–416.

Weitzman ML (1999) Just keep discounting, but ... In: *Discounting and intergenerational equity*. Portney PR, Weyant JP, eds. Resources for the Future, Washington, DC.

Willet WC (2002) Balancing life-style and genomics research for disease prevention. *Science*, **296**:695–698.

WHO (1992) *International statistical classification of disease and related health problems. Tenth edition.* World Health Organization, Geneva.

Yashin AI, Manton KG, Stallard E (1986) Dependent competing risks: a stochastic process model. *Journal of Mathematical Biology*, **24**:119–140.

Yerushalmy J, Palmer CE (1959) On the methodology of investigations of etiologic factors in chronic diseases. *Journal of Chronic Disease*, **108**:27–40.

Yong LC, Kuller LH, Rutan G, Bunker C (1993) Longitudinal study of blood pressure: changes and determinants from adolescence to middle age. The Dormont High School follow-up study, 1957–1963 to 1989–1990. *American Journal of Epidemiology*, **138**:973–983.

Chapter 2

Childhood and maternal underweight

Steven M. Fishman, Laura E. Caulfield, Mercedes de Onis, Monika Blössner, Adnan A. Hyder, Luke Mullany and Robert E. Black

Summary

Undernutrition, as measured by underweight status, has been associated with substantially increased risk of childhood mortality worldwide, but the magnitude of its effect on specific causes of mortality and morbidity has been less well described. We reviewed extant data and conducted statistical meta-analyses in order to determine the relative risk of disease and death attributable to underweight status. We used these estimates in combination with estimates of underweight prevalence among children aged 0–4 years and women of reproductive age (15–44 years) to calculate the global burden of disease attributable to undernutrition.

Underweight was defined for children aged 0–4 years as low weight-for-age relative to the National Center for Health Statistics/World Health Organization (NCHS/WHO) reference median. The theoretical-minimum-risk distribution for this population was equivalent to the reference population distribution, wherein 2.3% of children have a weight-for-age below –2 standard deviations (SDs) (weight-for-age <–2 SDs, or weight-for-age *z*-score [WAZ] <–2) and are classified as underweight. The relationship between low weight-for-age among children and mortality was analysed as a multiple categorical variable having four levels of exposure: WAZ <–3, WAZ –3 to –2, WAZ –2 to –1 and WAZ >–1 (reference category). Morbidity was analysed as a dichotomous variable, comparing WAZ <–2 to WAZ >–2 (reference category). Underweight was defined for women of reproductive age as pre-pregnant body mass index (BMI) below 20 kg/m^2. The outcomes chosen for review were major diseases and disabilities commonly associated with nutritional deficiencies. Sufficient prevalence and risk data were available to analyse childhood underweight status as a risk factor for mortality due to diarrhoeal disease, measles, malaria and pneumonia.

Childhood underweight status was also analysed as a risk factor for increased incidence of these infectious diseases. Maternal underweight was considered as a risk for increased risk of conditions arising during the perinatal period. The relationships were considered causal on the basis of consistent evidence observed across different populations and settings, and persistence of the association after adjustment for recognized confounders and effect modifiers such as age, breastfeeding status and prior morbidity. Current prevalence and risk data were not suitable for deriving burden estimates relating to other outcomes or older populations, although this does not imply the lack of risk in those populations. We therefore reviewed and summarized two major areas of undernutrition research without calculating burden estimates: (i) effects of maternal underweight status during pregnancy on maternal mortality and fetal death; and (ii) the association between undernutrition and cognitive function.

Prevalence of undernutrition among children aged 0–4 years was obtained from the WHO Global Database on Child Growth and Malnutrition, derived from a systematic analysis of raw data sets from 310 nationally representative nutritional surveys that collected data on child anthropometry in 112 countries. Categorical underweight estimates for most subregions[1] were calculated using multilevel modelling that adjusted for variability between regions, countries and surveys. Prevalence of underweight status was highest in SEAR-B (25.8%), SEAR-D (45.9%), AFR-D (32.2%), AFR-E (31.1%) and EMR-D (25.1%). Projections based on national trends suggested declining prevalence in most subregions over the next 30 years but increasing prevalence in the African subregions.

Cause-specific mortality was estimated by extending the methods of Pelletier et al. (1994) to data obtained from the investigators of 10 cohort studies in which both weight-for-age category (<–3 SDs; –3 to –2 SDs; –2 to –1 SDs; and >–1 SD) and cause-of-death information were available. All studies contributed information on weight-for-age and risk of diarrhoea, pneumonia and all-cause mortality. However, only six studies contributed information on deaths due to measles, and only three studies contributed information on deaths due to malaria or, in some cases, fever. By calculating the logarithm of the mortality rates by cause and anthropometric status in each country and utilizing weighted random effects models, we estimated the relation between weight-for-age and risk of death and calculated the relative risk of dying for each cause and all-cause mortality from these models. The relative risks of mortality due to low weight-for-age were elevated for each cause of death. The attributable fractions of mortality associated with weight-for-age below –1 SD were 44.8% for measles, 57.3% for malaria, 52.3% for pneumonia and 60.7% for diarrhoea.

Estimation of cause-specific morbidity was based on statistical meta-analysis of published data identified through systematic literature

searches of Medline and other databases. We selected longitudinal studies that compared incidence data according to past anthropometric status. Underweight status among preschool-age children was significantly associated with subsequent risk of diarrhoea and pneumonia episodes, but the association with malaria was not statistically significant. There was no evidence that underweight status influenced susceptibility to measles infection. The overall attributable fractions of morbidity associated with weight-for-age below –2 SDs were 16.5%, 5.3% and 8.2% for pneumonia, diarrhoea and malaria, respectively.

Mortality due to perinatal conditions was calculated by estimating the attributable fraction of neonatal mortality due to intrauterine growth retardation (IUGR) and then multiplying the value by the estimated attributable fraction of IUGR due to low maternal pre-pregnancy BMI for each subregion. Attributable fractions were based on prevalence and risk estimates from available published and unpublished sources.

Overall, undernutrition in children aged 0–4 years, as reflected in underweight or low weight-for-age, caused 3 599 800 deaths, including 815 900 diarrhoea deaths, 1 042 900 pneumonia deaths, 261 300 measles deaths and 549 200 malaria deaths. There were an additional 148 400 low-birth-weight neonatal deaths associated with low maternal pre-pregnancy BMI. The total number of child deaths associated with maternal or child underweight status, 3 748 200, represented 34.7% of all child deaths in the age group 0–4 years. The loss in disability-adjusted life years (DALYs) associated with these deaths was over 126 million. An additional 879 900 DALYs were lost due to increased morbidity from pneumonia, diarrhoea and malaria. Of the total DALYs associated with undernutrition, 44 million (32.0%) were lost in SEAR-D, 30 million (21.7%) in AFR-D, 33 million (23.9%) in AFR-E, 16 million (11.5%) in EMR-D and 8 million (5.8%) lost in WPR-B. Altogether, these five subregions accounted for 95% of the total DALYs lost due to undernutrition.

The true burden of disease associated with undernutrition extends beyond the narrow focus of this analysis. In addition to the effects of poor pre-pregnancy BMI, inadequate weight gain during pregnancy can lead to IUGR. Fetal growth retardation, in turn, may be associated with impaired immunocompetence, as well as increased risk of chronic disease in later life. Chronic undernutrition, especially in conjunction with poor environmental stimulation, is associated with impaired cognitive development, and severe undernutrition during infancy may contribute to lasting intellectual deficits. Chronic undernutrition among adults can contribute to diminished work capacity. Additional research is necessary into the prevalence and impact of undernutrition throughout the life cycle.

1. Introduction

Child undernutrition—measured as poor anthropometric status—is internationally recognized as an important public health indicator for monitoring nutritional status and health in populations. Young children are most vulnerable to undernutrition and face the greatest risk of its adverse consequences. Those who suffer from growth retardation as a result of poor diets and/or recurrent infections tend to have more frequent episodes of severe diarrhoea and are more susceptible to several infectious diseases, such as meningitis and pneumonia (Man et al. 1998; Tomkins and Watson 1989; Victora et al. 1994). A number of studies have demonstrated the association between increasing severity of anthropometric deficits and mortality, and undernutrition is thought to be a contributing factor in over half of all child deaths in developing countries (Pelletier 1994; Pelletier et al. 1993; Rice et al. 2000; Schroeder and Brown 1994). There is strong evidence that poor growth is associated with delayed mental development (de Onis 2001; Mendez and Adair 1999; Pollitt et al. 1993; WHO 1999a), and several studies have shown a relationship between impaired growth status and poor school performance as well as reduced intellectual achievement (Martorell et al. 1992; PAHO 1998). In addition, growth retardation in early childhood is associated with significant functional impairment in adult life (Martorell et al. 1992) and reduced work capacity (Spurr et al. 1977), which in turn has an impact on economic productivity.

The purpose of this chapter is to describe our review and analysis of existing data in order to calculate relative risks of specific causes of death and morbidity attributable to undernutrition (defined by low weight-for-age or "underweight"), and to use the estimates, in combination with estimates of underweight prevalence from a comprehensive WHO database, to calculate the global burden of disease associated with underweight status.

1.1 Determinants of childhood undernutrition

Undernutrition has several levels of determinants. Poverty is a strong underlying determinant that leads to household food insecurity, poor childcare, maternal undernutrition, unhealthy environments and poor health care. These factors then lead to the immediate determinants of childhood undernutrition, that is, low birth weight, inadequate dietary intake of nutrients and frequent infectious diseases (Baqui and Black 2002). Low birth weight, primarily due to IUGR in developing countries, is a consequence of maternal undernutrition prior to and during pregnancy and subsequently contributes to undernutrition in infancy and childhood (Villar and Belizan 1982). This is especially important in areas such as South Asia, where there is a very high prevalence of low birth weight. The diets of many children in developing countries are inadequate, and children in the first two years of life are at particular risk.

During this period, children have a high rate of growth and demand for calories, protein, essential fats, vitamins and minerals. Breastfeeding provides excellent nutritional support for six months (Kramer and Kakuma 2002), but unfortunately many children in such settings are given fluids and other foods before this age, resulting in reduction of breast milk intake and exposure to infectious agents causing diarrhoea (Lutter 2000). After six months of age, even when breastfeeding is continued, children frequently lack sufficient dietary intake, or consume a diet that is of poor nutritional content (WHO 1998). Again, these dietary deficiencies may involve not only the macronutrients, but also the so-called micronutrients, that is, vitamins and minerals. In young children, the frequently contaminated environments and poor childcare practices cause high rates of infectious disease. These infections result in a reduction in nutrient intake, as well as increased utilization and loss of nutrients, such as vitamin A and zinc.

The relative importance of the three immediate determinants of undernutrition varies by setting. The percentage of growth faltering (compared with an international reference population) due to diarrhoea in developing countries in Latin America, Africa and Asia has been reported to range from 10% to 80% (Black 1991). A study in Bangladesh simultaneously examined the role of diarrhoea, other febrile illnesses and dietary intake on weight gain (Becker et al. 1991). In a model using data from this study, it was estimated that improving dietary intake to recommended levels would have a slightly greater effect than eliminating diarrhoea and febrile illness; however, doing both at the same time would be necessary to achieve growth equivalent to an international reference population. There are a number of factors specific to particular developing country settings that can moderate the effect of illness on growth (Black 1991). For example, the adverse effect of diarrhoea on growth is less in exclusively breast-fed children than in children after weaning. Furthermore, an adequate diet, such as that provided in supplementation programmes, may prevent the adverse effect of diarrhoea on growth in some (Lutter et al. 1989) but not all settings (Bhandari et al. 2001). Thus, undernutrition is due to a variety of determinants that act along a pathway from poverty to dietary deficiency and frequent infectious diseases of childhood.

1.2 Other age groups

Undernutrition is not limited to young children. Over 815 million people of all ages are considered undernourished (FAO 2001), including roughly 243 million adults in developing countries who are considered severely underweight (ACC/SCN 2000a). Poor anthropometric status among adults and adolescents has been associated with maternal complications, diminished work capacity and increased risk of mortality (Martorell et al. 1992; Rotimi et al. 1999; Spurr et al. 1977; WHO 1995b). However, prevalence data for most adults, school-age children, adolescents and the

elderly are scarce, and understanding of the health effects of undernutrition in these populations is incomplete. There is a need for further research on undernutrition throughout the life cycle, especially as populations in developing countries go through demographic and epidemiological transitions.

1.3 Exposure variable

The internationally recommended way to assess undernutrition at the population level is to take body or anthropometric measurements (e.g. weight and height). Based on combinations of these body measurements anthropometric indices are constructed. These indices are essential for the interpretation of measurements, as the value for body weight alone, for example, has no meaning unless it is related to an individual's age or height (WHO 1995b). In children the three most commonly used anthropometric indices are weight-for-height, height-for-age and weight-for-age. These anthropometric indices can be expressed in terms of *z*-scores, percentiles, or percentage of median, which can then be used to compare a child or a group of children with a reference population.

Weight-for-age was chosen as the index of child nutritional status for this analysis because it is the most widely used in developing countries, allowing for the inclusion of the largest number of studies. Although it does not distinguish between wasting and stunting, low weight-for-age (underweight) represents a combination of both aspects and has a high positive predictive value as an indicator for child malnutrition in developing countries (WHO 1995b). Underweight is defined internationally as the proportion of preschool children falling below –2 SDs (weight-for-age <–2 SDs, or WAZ <–2) from the NCHS/WHO international reference median value for weight-for-age (de Onis and Blössner 1997; WHO 1995b). The burden of disease estimates for mortality were based on four weight-for-age categories: <–3 SDs; between –3 and –2 SDs; between –2 and –1 SDs; and the reference category of >–1 SD. The estimates for morbidity were based on two categories: weight-for-age <–2 SDs and the reference category of >–2 SDs.

Although the terms are often used synonymously, "underweight" should be distinguished from the terms "malnourished" and "undernourished". "Undernourished" and "malnourished" refer to the internal, physiological state of nutriture. "Underweight" is an observable anthropometric marker for that state, while the internal process can only be inferred.

BMI was selected as the index of adult nutritional status recommended by the International Dietary Energy Consultative Group of the Administrative Committee on Coordination/Sub-Committee on Nutrition (Shetty and James 1994). BMI is less biased by height differences than other adult indicators, such as absolute weight, and correlates with

health-related outcome variables such as overall mortality risk. For evaluation of nutritional status in relation to pregnancy, only pre-pregnant BMI was considered. Unlike the classification of underweight status in children, there is no comparable international reference for BMI among adults. A BMI <18.5 kg/m^2 represents chronic energy deficiency, and the Institute of Medicine recommends a BMI cut-off of <19.8 kg/m^2 as the definition for underweight (Institute of Medicine 1990; Shetty and James 1994). The cut-off of 20 kg/m^2 is commonly used in studies of maternal risk, and, therefore, underweight status among women of reproductive age was defined as BMI <20 kg/m^2 for this analysis. Further details on BMI can be found in the chapter on overweight and obesity (chapter 8).

1.4 Considerations in choice of child anthropometric indicator

Nutritional status can be assessed using clinical signs of malnutrition, biochemical indicators and anthropometry. Inadequacies in nutritional intake eventually alter functional capacity and result in many adverse health outcomes that are distinct expressions of malnutrition's different levels of severity. Initially, children adapt to inadequate diets through reduced physical activity and slowed rates of growth. At moderate degrees of malnutrition, activity and growth rates are affected to a greater degree, and in addition signs of wasting and some biochemical abnormalities (e.g. reduction in serum albumin), begin to show. At advanced stages of severity, all linear growth ceases, physical activity is severely curtailed, body wasting is marked and clinical signs (e.g. oedema, hair and skin changes) are noticeable. Anthropometry thus has an important advantage over other nutritional indicators: body measurements are sensitive over the full spectrum of malnutrition, whereas biochemical and clinical indicators are useful only at the extremes. In addition, anthropometric measurements are non-invasive, inexpensive and relatively easy to obtain. The main disadvantage of anthropometry is its lack of specificity, as changes in body measurements are also sensitive to several other factors, including infection, altitude, stress and genetic background (de Onis 2000).

A child's body responds to malnutrition in two ways that can be measured by anthropometry: (i) a deceleration or cessation of growth, which over the long-term results in low height-for-age or stunting; and (ii) body wasting, which is a short-term response to inadequate intakes, commonly assessed by weight relative to height. Height-for-age and weight-for-height thus discriminate between different biological processes, unlike weight-for-age, which could be low because of stunting (short stature) and/or wasting (recent weight loss). The current estimates relied exclusively on weight-for-age, which reflects body mass relative to chronological age. It is influenced by both the height of the child (height-for-age) and her weight (weight-for-height). Hence weight-

for-age cannot discriminate between short- and long-term forms of malnutrition given that children classified on its basis are a mixed group in terms of their nutritional status. In the 1990s weight-for-height emerged as a very important indicator (WHO 1995b) and, in fact, several authors have identified low weight-for-height as the indicator of choice for screening malnourished children who are at increased risk of dying (de Onis 2000).

1.5 Theoretical-minimum-exposure distribution

The prevalence of underweight status is defined as the proportion of preschool-age children falling below –2 SDs indicated from the NCHS/WHO international reference median value (de Onis and Blössner 1997; WHO 1995b). The theoretical-minimum-risk distribution is equivalent to this distribution, wherein 13.6% of children aged 0–4 years have weight-for-age between –1 to –2 SDs and 2.3% have a weight-for-age <–2 SDs.

Anthropometric values are compared across individuals or populations in relation to a set of reference values based upon a healthy population. The choice of reference population to assess nutritional status has a significant impact on the proportion of children identified as being malnourished and, in turn, important implications for establishing relationships between nutritional status and functional outcomes (WHO 1995a). Much has been written about growth references, but unanswered questions remain about the many factors that determine human growth and indeed what constitutes "normal" growth. WHO has been recommending since the late 1970s the use of the NCHS/WHO international reference population *z*-scores for the comparison and presentation of child malnutrition data (Waterlow et al. 1977). A detailed account of the different growth references used prior to the current international reference is provided elsewhere (de Onis and Yip 1996). In the mid-1990s the NCHS/WHO international reference was found to have important technical and biological drawbacks (de Onis and Habicht 1996; de Onis and Yip 1996; WHO 1995a). Consequently, an international effort coordinated by WHO is under way to develop a new international growth reference for infants and young children (de Onis et al. 1997). The new international reference—which will be constructed from primary data collected for this purpose—includes a number of features that, taken together, will result in a reference population substantially different from the existing ones (de Onis et al. 2001). An important characteristic of this new reference is that it will be based on a truly international sample. Six countries, representing the major global geographic regions, are participating in this effort. Another notable feature is that it takes the breast-fed infant as the biological "norm", recognizing the health and nutritional benefits of breastfeeding. The extent to which the new curves differ from the current ones in shape and the spread of values around the mean will affect the relationship—established using the NCHS/WHO

reference values—between child anthropometry and functional outcomes such as morbidity and mortality.

Once a reference population has been selected, it is necessary to determine the limits of "normality". Current practice is to use a defined cut-off point using one of the three available classification systems for comparing a child, or a group of children, to the reference population: *z*-scores (SD scores), percentiles and percentage of median. The use of a statistically defined cut-off point (e.g. –2 SD *z*-score) is not unique to anthropometry; indeed, it is widely applied in many fields of biology and medicine. Nevertheless, it is important to bear in mind that using a cut-off-based criterion to define what is "abnormal" is arbitrary. In reality, there are not two distinct populations—one well nourished and the other malnourished—but rather a continuous gradation of nutritional status (de Onis 2000). The risk of undesirable health outcomes such as mortality does not change dramatically by simply crossing the cut-off line; risks are continuous within the "normal" range. For many purposes, the best descriptor of a population's nutritional status is the mean *z*-score, which in less developed environments is usually shifted to the left. This concept is based on data from many different countries which showed a high consistency in the SD of weight-for-height among young children (de Onis and Blössner 1997). Even under extreme conditions, such as during famines, where the mean *z*-score is two or three units below the reference, the value of the SD of *z*-scores is very close to unity. This shows that the entire distribution is shifted so that all individuals, not only those below a given cut-off point, are affected (Rose 1985). Taking such a population-approach resolves the problem of focusing solely on the severely malnourished subpopulation falling below a certain cut-off. In most instances, the mild and moderately malnourished subpopulations will be of greater importance from a public health perspective because there are many more children in these categories than in the severely malnourished one. For this reason, estimates are presented using low weight-for-age as both a dichotomous and multi-categorical variable when possible.

2. Prevalence of underweight among children

Over the years the WHO Department of Nutrition has been monitoring trends in child malnutrition using anthropometric data. A major difficulty has been the lack of comparability of survey results. Although many nutritional surveys have been conducted since the 1970s, many of them had used distinct definitions of malnutrition (i.e. different anthropometric indicators, reporting systems, cut-off points and reference values) making comparison among studies difficult. This lack of comparable data prompted the beginning of WHO's systematic collection and standardization of data on the nutritional status of the world's population of children <5 years. Initial results of this effort, published in 1993 (de

Onis et al. 1993), were updated in 1997 and presented together with estimates of trends in child growth retardation in developing countries (de Onis and Blössner 1997). A more recent analysis using multilevel modelling updated these earlier estimates, describing trends in child malnutrition from 1980–2005 (de Onis et al. 2000).

2.1 Data sources and quality control

Cross-sectional data on the prevalence of underweight were obtained from nationally representative nutritional surveys that collected data on child anthropometry and are included in the WHO Global Database on Child Growth and Malnutrition. This database was initiated in 1986 to compile, standardize and disseminate the results of nutritional surveys performed in both developing and developed countries (de Onis and Blössner 1997). A distinct feature of this database is the systematic analysis of raw data sets in a standard format to produce comparable results. Only nationally representative data have been used for the present analysis. Three hundred and ten national nutrition surveys from 112 countries carried out from 1965 onwards were analysed to estimate the prevalence of underweight in children. The majority of surveys were conducted by either the relevant national ministry of the country concerned, by the Demographic and Health Surveys (DHS) programme of Macro International, or by the Multiple Indicators Cluster Surveys (MICS) carried out by the United Nations Children's Fund (UNICEF). Appendix A lists all national surveys included in the present analysis by country in alphabetical order.

Survey data for inclusion in the WHO Global Database on Child Growth and Malnutrition are identified by various ways and mechanisms.

- An automated Medline search provides results according to the established search history following the weekly online Medline updates. Selected abstracts are reviewed and relevant surveys with data searched for in the library. Data are extracted and frequently the principal investigators and/or data holders are contacted to complement the data provided in the article and/or give clarification on methodological issues.
- A wide network of collaborators, including international organizations (e.g. UNICEF, Food and Agriculture Organization of the United Nations [FAO]), nongovernmental organizations (NGOs) (e.g. Helen Keller International), Ministries of Health and National Institutes of Nutrition, as well as independent institutions (e.g. Macro International) and individual researchers provide their data directly to the WHO Global Database. In case of queries on the data the same procedure as above takes place to clarify any unclear issues.
- Principal investigators contact the WHO Global Database to enquire about possible inclusion of their data into the Global Database.

- Other WHO database managers within WHO headquarters share data sets and survey documents with the Global Database.

The sampling methods for each of the survey data used in this analysis were carefully reviewed to ensure national representativeness. Multistage random sampling methods were applied for sample selection in the majority of countries. Only a few countries, such as Argentina, Chile, Croatia, Uruguay and Venezuela based their estimates on well-established national nutritional surveillance systems with high population coverage (country-specific details on sampling procedures are available from the authors on request). Surveys generally followed standard procedures of measuring length up to 24 months of age and height from 24 months onwards. The anthropometric measurement techniques used in each survey are described in the comprehensive survey reports, which are available on request. Some surveys included information on reliability of the measurements while others did not.

Survey results were checked for inconsistencies between the estimates based on height-for-age, weight-for-age and weight-for-height. The observed SDs of the *z*-score distribution were used to assess the quality of the survey results. With accurate age estimates and anthropometric measurements, the SDs of the observed height-for-age, weight-for-age and weight-for-height *z*-score distributions should be relatively constant and close to the expected value of 1.0 for the reference distribution (ranging within approximately 0.2 units). This nearly constant SD in height-based and weight-based *z*-score distributions provides an opportunity to assess data quality (WHO 1995b). Surveys with a SD outside the expected ranges were subjected to closer examination because of possible problems related to age assessment and anthropometric measurements. Surveys with inaccurate data resulting from measurement error or incorrect age reporting were excluded from this analysis.

2.2 Statistical analysis

The analysis followed three separate steps, which are described below. The number of countries and percentage of population aged <5 years covered by data for each subregion are listed in Appendix B. The population aged <5 years derived from the 1998 revision of the UN population estimates (UN 1999) for the particular survey year were added as population weights. As there were no significant differences observed between male and female child underweight prevalence, the model exercise included data only for sexes combined, and estimates were assumed to be the same for males and females.

Primary analysis of raw data sets

As an essential first step in producing subregional estimates, primary analysis of the 310 national raw data sets was conducted to produce

standardized estimates of prevalence of underweight as defined in section 1.1. This was necessary because many nutritional surveys used distinct definitions of malnutrition (i.e. different anthropometric indicators, reporting systems, cut-off points and reference values) making impossible the pooling of reported prevalences. There were three steps involved in this analysis: (i) identifying the data holder for each of the individual surveys; (ii) requesting re-analysis of the original data sets following the standardized definition, or otherwise, requesting a copy of the raw data set for standard analysis by the WHO Department of Nutrition; and (iii) initiating quality control procedures for each individual survey. Country-specific prevalences of child underweight by age, sex and subregion derived for each of the national surveys listed in Appendix A can be found on the web site of the WHO Global Database on Child Growth and Malnutrition at http://www.who.int/nutgrowthdb.

Subregional estimates: underweight as a dichotomous variable

The methodology applied to derive the underweight estimates depended on the availability of data points for the different subregions. In detail these were as follows: for AFR-D, AFR-E, AMR-B, AMR-D, EMR-B, EMR-D, SEAR-B, SEAR-D and WPR-B the underweight estimates were calculated using a multilevel model. Multilevel modelling allows for more than one component of variation, which in this case includes between subregions, between countries within subregions and between surveys over time within countries. This multilevel model is an extended form of regression, which separates estimates for the three levels of variation, and the total variation is obtained by combining over the three levels. To adjust for skewness in the distribution of prevalence, the model used the logit transform of the underweight prevalence, with the additional advantage of stabilizing the variance. Because estimates were calculated on the logistic scale, estimated prevalence and their CIs were derived by back-transformation. The nature of the logistic function ensured that all estimated prevalence and their CIs would lie above zero. CIs for prevalences close to zero were asymmetric, and were narrower than for values close to 50%—these are intrinsic properties of the logistic function (Armitage and Berry 1994).

Multilevel modelling was implemented in the Statistical Analysis System (SAS) Proc Mixed program, a procedure that accommodates both categorical and continuous covariates and incomplete series of time measurements, and allows for the added variability introduced by the multiple levels of analysis. Analyses were conducted separately for each subregion, given that the trend of underweight between subregions could differ substantially.

Separate analysis for each subregion required that two rather than three levels be modelled, thus reducing complexity of the model. An assumption of the analyses was that the extent of available data for countries was not related to the prevalence of underweight. In other

words, it was assumed that the trend of the prevalence over time for a subregion could be estimated in an unbiased manner from the data available. Under this assumption the model accommodated the variable patterns of available surveys for the countries. Countries with only one survey contributed information to the estimation of the overall intercept, whereas countries with more than one survey also contributed to the estimation of the regression coefficient(s) relating the trend to the survey year. The models specified a linear trend relationship between prevalence of underweight and survey year. Thus, these models assumed that the rate of change in the prevalence of underweight was constant.

Possible non-linear trends were examined by including quadratic and cubic polynomial terms. There was some evidence for non-linear relationship in only one of the subregions (SEAR-D), showing slightly larger differences between countries and indicating a better fit using the quadratic and cubic functions. However, due to unrealistic drops in prevalence the model outcome was discarded. Further explanation on the multilevel modelling approach to derive estimates has been described elsewhere (ACC/SCN 2000b; de Onis et al. 2000).

No modelling was possible in AMR-A, EUR-A, EUR-B, EUR-C and WPR-A due to lack of sufficient national survey data. To derive estimates for these subregions we proceeded as follows:

- In AMR-A and EUR-A, which are composed of developed countries, we assumed that children have a similar nutritional status as the reference population. Therefore, these two subregions were assigned the prevalence values derived from the international reference population, i.e. 2.3% (theoretical minimum). For these subregions no CIs were available and uncertainty was assumed as zero.
- In EUR-B, EUR-C and WPR-A, we calculated the weighted mean prevalence of underweight following the method of de Onis and Blössner (2000) for estimating prevalence and trends of overweight among preschool-age children in developing countries. Based on the available survey data the CIs fell within a 95% CI of: 0.1–15.5 in EUR-B; 0.1–5.1 in EUR-C; and 0.7–6.9 in WPR-A.

Subregional estimates: underweight as a multi-categorical variable

Growth in populations of children is normally distributed. In a standard normal distribution the SD is 1 and the mean is located at 0. As there is a relationship between the prevalence falling below the cut-off (<–2 SDs) and the mean *z*-score, to convert the mean *z*-score to a prevalence based on <–2 SDs, the probit function, which converts *z*-score values to cumulative percentiles, was used as recommended by an Expert Committee (WHO 1995b). To derive probability that the *z*-score of a child is between two cut-off points (<–3 SDs; –3 SDs to –2 SDs; –2 SDs to –1 SD; and >–1 SD), we calculated the difference between the two cumulative

probabilities obtained from the probit function. Prevalence data below –3 SDs were derived by subtracting the calculated values for the interval –3 to –2 SDs from the total of the prevalence below <–2 SDs provided by the categorical analysis (see Table 2.1 and section 4.2), which included all ranges below this cut-off.

2.3 Exposure estimates

The prevalence of low weight-for-age among children aged 0–4 years by subregion is listed as a dichotomous variable in Table 2.1 (a) and as a multi-categorical variable in Table 2.1 (b), below.

3. Prevalence of underweight among women of reproductive age

Subregional BMI estimates listed in Table 2.2 are from chapter 8. Underweight status is widespread among women of reproductive age in developing countries, especially in sub-Saharan Africa and South Asia. Of 26 sub-Saharan African countries with recent (<10 years old) survey estimates, 23 have greater than 30% prevalence of BMI <20 kg/m^2—five of which (Chad, Eritrea, Ethiopia, Madagascar and the Niger) have prevalence >50%. Among South Asian women, 70–76% in Bangladesh and India have a BMI <20 kg/m^2, along with 54–61% in Cambodia and Nepal. Low BMI is less common in the Americas, where prevalence of

Table 2.1(a) Underweight prevalence by subregion[a]

Subregion	*Prevalence of underweight (% below –2 SDs)*	*95% CI*
AFR-D	32.2	(26.7–38.2)
AFR-E	31.0	(24.7–38.0)
AMR-A	2.3	(2.0–2.6)
AMR-B	5.0	(3.8–6.6)
AMR-D	12.4	(7.7–19.6)
EMR-B	8.1	(5.4–12.1)
EMR-D	25.1	(14.5–39.7)
EUR-A	2.3	(2.0–2.6)
EUR-B	7.6	(0.1–15.5)
EUR-C	2.6	(0.1–5.1)
SEAR-B	25.8	(16.3–38.4)
SEAR-D	45.9	(40.7–51.2)
WPR-A	3.8	(0.7–6.9)
WPR-B	16.0	(12.7–19.9)

[a] Dichotomous estimate.

Table 2.1(b) Mean z-scores and underweight prevalence by weight-for-age category and subregion[a]

Subregion	Mean z-score	Percentage of children in weight-for-age category			
		<–3 SDs	>–3 to <–2 SDs	>–2 to <–1 SD	>–1 SD to <0
AFR-D	–1.54	7.1 (4.0–10.4)	25.1 (19.7–30.3)	38.3 (32.3–44.2)	23.3 (18.1–28.5)
AFR-E	–1.5	6.8 (3.1–10.3)	24.2 (18.1–30.4)	38.3 (31.3–45.3)	24.2 (17.9–30.2)
AMR-A	0	0.1 (0.1–0.2)	2.1 (1.9–2.4)	13.6 (13.0–14.3)	34.1 (33.3–35.1)
AMR-B	–0.35	0.5 (0.0–0.8)	4.5 (3.3–6.0)	20.8 (18.4–23.7)	37.9 (34.8–41.1)
AMR-D	–0.84	1.6 (0.0–3.8)	10.8 (5.3–16.5)	31.3 (23.1–39.8)	36.3 (27.6–44.9)
EMR-B	–0.6	0.8 (0.0–1.9)	7.3 (4.1–10.5)	26.3 (21.1–31.9)	38.1 (32.2–44.1)
EMR-D	–1.33	4.7 (0.0–10.9)	20.4 (8.7–32.1)	37.8 (23.7–51.9)	27.9 (14.9–41.0)
EUR-A	0	0.1 (0.1–0.2)	2.1 (1.9–2.4)	13.6 (13.0–14.3)	34.1 (33.3–35.1)
EUR-B	–0.57	0.7 (0.0–3.3)	6.9 (0.0–14.2)	25.7 (13.0–38.4)	38.2 (24.1–52.3)
EUR-C	–0.05	0.2 (0.0–0.8)	2.4 (0.0–4.9)	14.5 (9.1–20.2)	34.9 (27.5–42.5)
SEAR-B	–1.35	5.0 (0.0–10.4)	20.8 (10.6–31.1)	37.9 (25.7–50.2)	27.5 (16.2–38.7)
SEAR-D	–1.9	13.4 (9.9–17.1)	32.5 (27.5–37.3)	35.8 (30.6–40.7)	15.5 (11.8–19.4)
WPR-A	–0.22	0.3 (0.0–1.1)	3.5 (0.5–6.5)	18.0 (11.9–24.4)	36.9 (29.2–44.8)
WPR-B	–1	2.3 (0.8–3.8)	13.6 (10.3–17.1)	34.1 (29.6–38.9)	34.1 (29.4–38.7)

[a] Multi-categorical estimate.

Table 2.2 BMI distribution of women aged 15–44 years, by subregion

Subregion	Mean BMI (kg/m^2) (SD)		Percentage of women with BMI ≤20 kg/m^2	
	15–29 years	30–44 years	15–29 years	30–44 years
AFR-D	20.6 (3.5)	22.1 (3.9)	43.3	29.5
AFR-E	21.2 (3.9)	22.9 (4.8)	37.8	27.4
AMR-A	23.8 (5.7)	26.1 (7.1)	25.1	19.5
AMR-B	23.5 (4.7)	26.2 (5.1)	22.7	11.1
AMR-D	23.7 (3.1)	25.8 (4.4)	11.7	9.3
EMR-B	22.5 (4.4)	25.8 (5.1)	28.4	12.7
EMR-D	21.6 (6.3)	23.8 (8.5)	40.1	32.6
EUR-A	23.3 (4.1)	25.1 (4.7)	20.9	13.8
EUR-B	22.7 (3.9)	25.6 (5.2)	24.5	14.0
EUR-C	22.7 (3.9)	26.5 (5.0)	24.5	9.7
SEAR-B	20.5 (3.5)	22.7 (2.3)	44.4	12.1
SEAR-D	19.5 (3.0)	20.8 (4.0)	56.7	42.1
WPR-A	20.8 (3.5)	22.5 (4.1)	40.9	27.1
WPR-B	21.9 (4.2)	22.8 (4.1)	32.6	24.8

BMI <20 kg/m^2 among women of reproductive age is generally below 20% (ACC/SCN 2000b; DHS web site, http://www.measuredhs.com).

4. Risk factor–disease relationships

A synergistic relationship between malnutrition and infection has been recognized for decades (Scrimshaw et al. 1968), providing a foundation for the choice of health outcomes in this analysis, but the bi-directional nature of the relationship complicates attributing causality. The changes in body size used as a marker for undernutrition in this analysis are commonly the result, in part, of previous infections, raising the possibility that co-existing infection is responsible for some of the observed risk relationship. Age, sex, socioeconomic status, season, breastfeeding status and behavioural factors will also influence both anthropometric status and risk of infection (Pelletier 1994).

Undernutrition is most prevalent where poverty persists, and it is often difficult to isolate the effects of undernutrition from the complex web of environmental and socioeconomic factors that contribute to mortality and morbidity in such surroundings. In reviewing the various risk relationships, the likelihood of causality was considered according to Hill's standards (Hill 1965). In each case, there was judged to be sufficient biological plausibility and experimental evidence to support the relationship. We chose risk relationships that have been reported by multiple researchers in different populations under different circumstances. The associations generally, albeit not always, persisted after adjustment for prior morbidity and known confounders. Further, we selected for analysis only those studies in which anthropometric assessment clearly preceded the observed health outcome. In previous analyses (Pelletier 1994) and in our analysis, the consistency of the risk relationship between weight-for-age and mortality in different settings with quite different mortality rates and environmental conditions strongly suggests a causal rather than confounding relationship.

The relationship between undernutrition and disease may be mediated through many biological mechanisms. The lack of adequate protein and energy is associated with numerous immunological effects, including impairment of antibody and complement formation; atrophy of the thymus and other lymphoid tissues; reduction in T-lymphocytes; depressed lymphocyte activation; decreased secretory immunoglobin A (IgA) concentrations; and delayed cutaneous hypersensitivity reaction (Rivera and Martorell 1988; Scrimshaw and SanGiovanni 1997). Undernutrition is associated with impaired turnover and maturation of intestinal epithelial cells and compromised epithelial tissue integrity (Patwari 1999). Other anatomic barriers and secretory forms of protection such as lysozymes and mucus are also altered by undernutrition (Scrimshaw and SanGiovanni 1997).

In the course of the review, several health outcomes were dropped from further consideration toward the final burden of disease estimate. In many instances, there was insufficient published evidence within a developing country setting to support a causal relationship between low weight-for-age or BMI and the outcome, although the relationship might be more widely supported given a different choice of anthropometric indicator. Ultimately, risk estimates were derived for eight outcomes for childhood underweight:

- malaria mortality;
- malaria incidence;
- pneumonia (acute lower respiratory infection [ALRI]) mortality;
- pneumonia/ALRI incidence;
- diarrhoea mortality;
- diarrhoea incidence;
- measles mortality; and
- all-cause child mortality.

All of the estimates apply to children aged 0–4 years. In addition, mortality due to perinatal causes among neonates was attributed to maternal underweight status. There was insufficient evidence to evaluate relationships among older age groups. Although some individual studies might suggest sex differences, the summary risk estimates here were assumed to be the same for males and females. Further, although risk relationships might vary by setting, the risk estimates were regarded in the analysis as constant across all subregions of the world.

Other outcomes such as cognitive impairment and additional pregnancy effects were reviewed below, but were not included toward the burden of disease estimate. The lack of current epidemiological evidence suitable to calculate a burden estimate does not necessarily imply the lack of an effect. For example, there is a large body of research into the influence of undernutrition on cognitive function. However, it was felt that there was too much heterogeneity in the types of studies and interventions, exposure variables, and outcome measurements to adequately quantify the undernutrition relationship through meta-analysis. There is also ample evidence describing the role of insufficient weight gain during pregnancy on the risk of IUGR, but prevalence data on pregnancy weight gain in developing countries are scarce.

4.1 Risk of mortality due to childhood infections

It has been demonstrated that a child's risk of dying due to undernutrition is not limited to only those children with the most severe undernutrition (Pelletier et al. 1994). Rather, there exists a spectrum of risk

associated with all degrees of undernutrition—mild, moderate and severe. Although the risk of dying is highest among those most undernourished, when one considers the small but significantly elevated risk of mortality associated with mild and moderate undernutrition and the high prevalence of mild undernutrition worldwide, much of the burden of childhood deaths due to undernutrition may be attributable to mild and moderate, rather than to severe undernutrition.

Pelletier et al. (1994) estimated the relations between weight-for-age and risk of mortality from all causes, and used this information to calculate the burden of child deaths attributable to undernutrition. These relations however are likely to vary depending on specific causes of death. For example, the relative risk of dying from malaria associated with varying degrees of undernutrition may not be similar to the risk for diarrhoea. Despite problems in defining cause of death, particularly in developing countries, in which one may often need to rely on verbal autopsy methods, it is worthwhile to consolidate the evidence to-date and consider the implications of analyses relating variation in anthropometric status and risk of dying across the principal causes of death for children in developing countries: diarrhoea, pneumonia, measles and malaria.

Methods for estimating risk of mortality

Initially, we surveyed the published literature to gather data to estimate the relationship between anthropometric status and cause-specific mortality (Rice et al. 2000). Because insufficient data were available, we contacted investigators with relevant data (published or unpublished) and asked them to contribute specific study results for this analysis. We sought community-based prospective cohort studies in which anthropometric status was assessed to determine weight-for-age, vital status monitored and cause of death determined by documented methods. Data sets ultimately contributing to the mortality analysis are listed in Table 2.3.

Each investigator was asked to provide the following information: (i) a description of their study; (ii) the number of children in the study or child-years of study with WAZ <–3, –2 to –3, –1 to –2, 0 to –1 and >0; and (iii) deaths in each category attributable to diarrhoea, pneumonia, measles, malaria, or other cause and total (all-cause). During analysis, we collapsed the last two categories of anthropometric status, so that the reference group would be composed of those children with WAZ >–1.

Analytic methods used to combine mortality data

We followed the procedures of Pelletier et al. (1993, 1994, 1995) and used the SAS Proc Mixed program for all procedures. Because this has been described elsewhere, we describe the steps only briefly here. First, we calculated the mortality rate (per 1000) by anthropometric status and each cause of death for each study. These rates are listed in Table 2.4

Table 2.3 Data sets with information contributing to the childhood mortality analysis

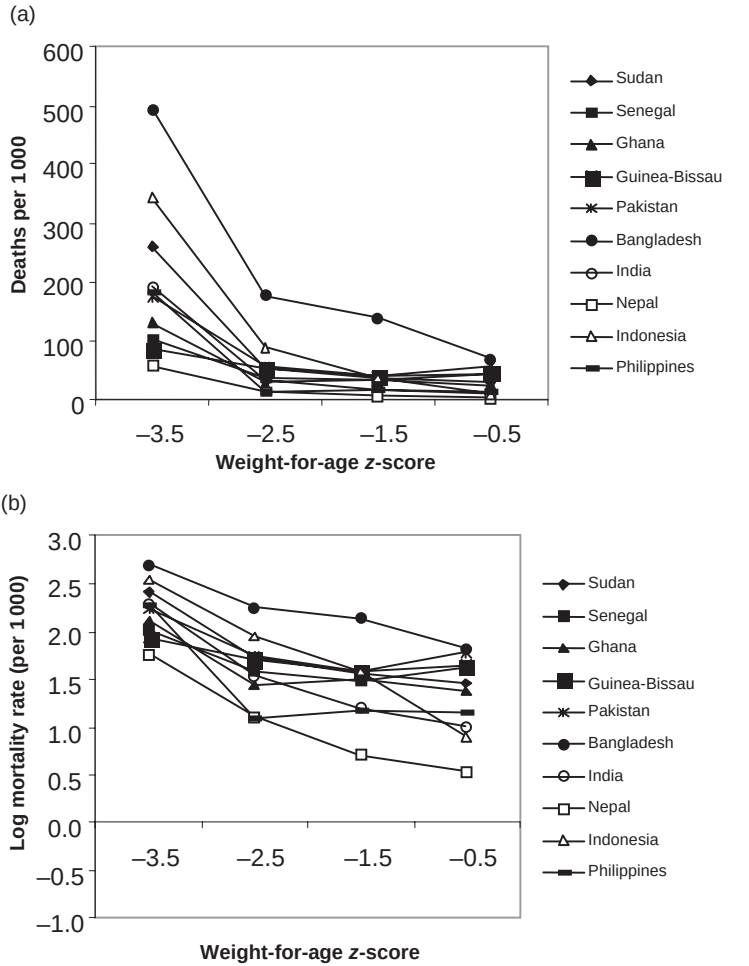
				Number of children			
Country	*Study*	*Age range (months)*	*Follow-up (months)*	*<–3 SDs*	*>–3 to <–2 SDs*	*>–2 to <–1 SD*	*>–1 SD*
Sudan	Fawzi et al. (1997)	6–72	6	365	985	1 123	592
Senegal	Garenne et al. (1987)	0–59	6	1 663	2 186	2035	1 249
Guinea-Bissau	Andersen (1997)	0–59	6–12	1 155	4366	7341	2731
Ghana	WHO/CHD (1998)	0–12	12	46	183	506	1 410
Nepal	West et al. (1991, 1997)	0–72	12	1 030	2082	2002	892
Bangladesh	Arifeen et al. (2001)	0–11	3	79	250	475	478
Pakistan	Khan et al. (1993); Jalil et al. (1993)	0–24	6	309	778	1 182	1 165
India	WHO/CHD (1998)	0–12	12	172	639	1 259	1 295
Indonesia	Sutrisna et al. (1993)	0–60	18	207	240	797	4856
Philippines	Ricci and Becker (1996)	0–59	3	800	3 144	4834	5 115

Table 2.4 Mortality rate (000s) by anthropometric status and cause of death

WAZ	Sudan	Senegal	Ghana	Guinea-Bissau	Nepal	Pakistan	Bangladesh	Indonesia	India	Philippines
All-cause mortality										
<–3	260.3	102.2	130.4	86.6	57.3	146.2	493.7	343.0	191.9	182.5
–3 to –2	52.8	37.5	27.3	51.5	12.5	48.0	176.0	87.5	34.4	12.1
–2 to –1	35.6	30.5	31.6	38.7	5.0	34.6	136.8	37.6	15.9	14.9
>–1	28.7	41.6	23.5	44.1	3.4	52.4	66.9	7.8	10.0	14.1
Diarrhoea										
<–3	147.9	42.7	21.7	13.0	21.4	87.0	126.6	29.0	64.0	81.3
–3 to –2	14.2	14.6	5.5	6.0	8.2	16.0	36.0	4.2	23.5	6.4
–2 to –1	11.6	8.8	11.9	2.6	2.0	6.4	18.9	2.5	4.8	6.8
>–1	6.8	15.2	4.2	3.7	1.1	6.1	16.7	1.0	0.8	7.4
Pneumonia										
<–3	32.9	6.6	65.2	2.6	19.4	23.7	151.9	159.4	34.9	87.5
–3 to –2	7.1	4.1	10.9	2.3	4.8	2.9	52.0	37.5	4.7	4.5
–2 to –1	2.7	6.4	4.0	1.6	1.5	7.3	31.6	18.8	1.6	6.6
>–1	1.7	8.8	2.8	1.9	1.1	12.2	18.8	3.1	3.1	5.1
Malaria										
<–3	—	3.6	21.7	33.8	—	—	—	—	—	—
–3 to –2	—	5.0	0.0	19.7	—	—	—	—	—	—
–2 to –1	—	2.5	2.0	15.5	—	—	—	—	—	—
>–1	—	3.2	4.2	16.2	—	—	—	—	—	—
Measles										
<–3	—	12.6	0.0	2.6	3.9	—	—	14.5	—	13.8
–3 to –2	—	2.7	0.0	2.5	1.0	—	—	4.2	—	1.3
–2 to –1	—	3.4	4.0	1.0	1.0	—	—	1.3	—	1.4
>–1	—	2.4	0.0	1.6	0.0	—	—	1.4	—	1.6

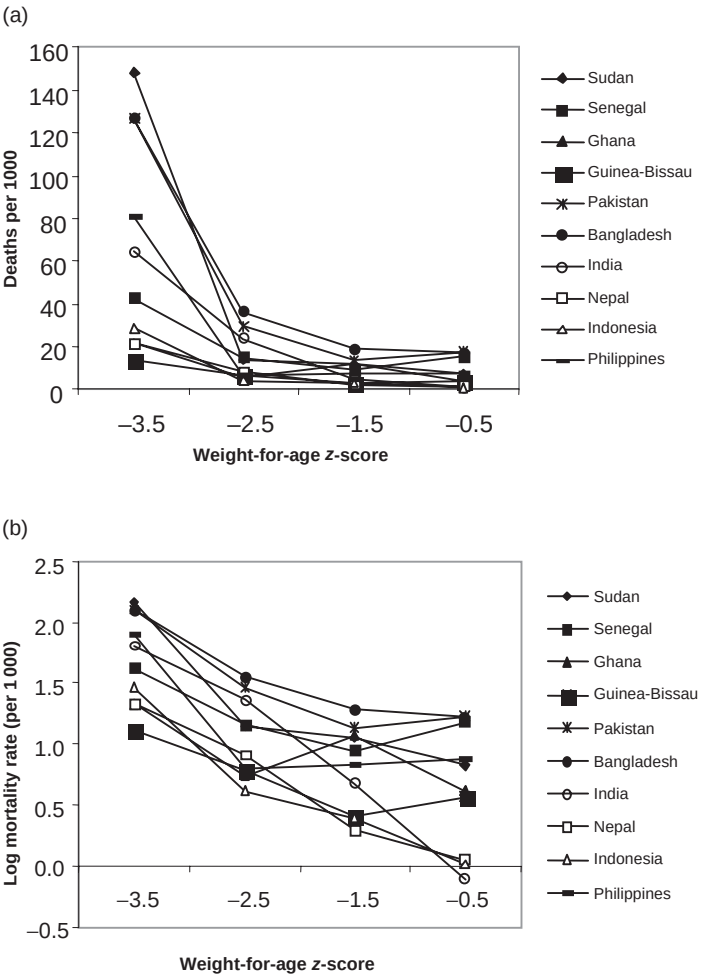
— No data.

Figure 2.1 Underweight and all-cause mortality: (a) deaths per 1000; (b) logarithm of deaths per 1000



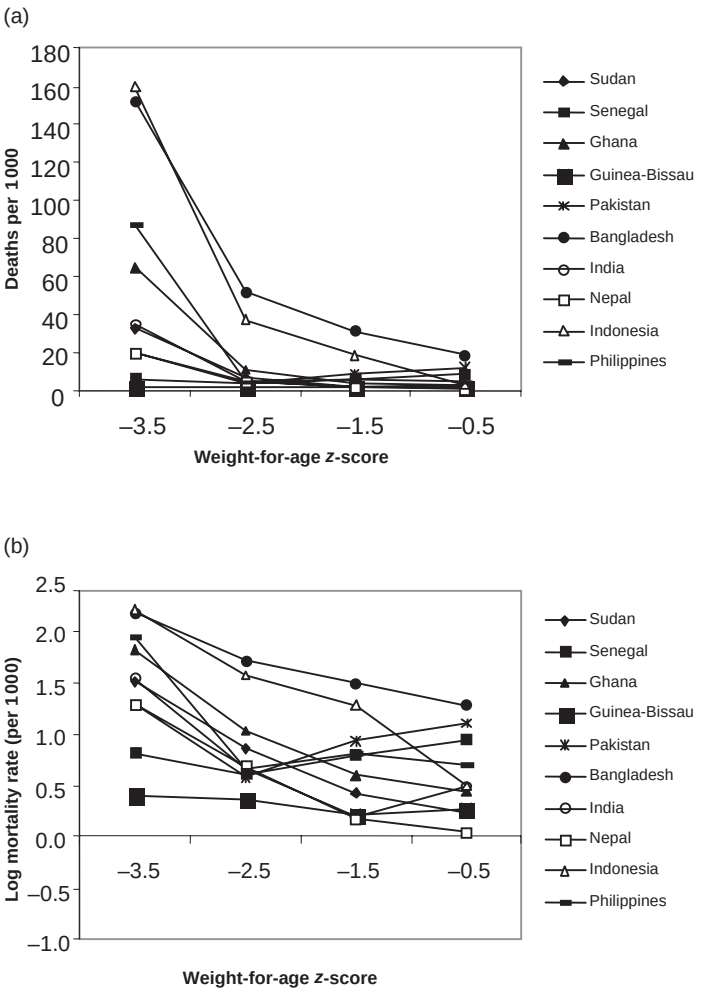
and presented graphically in Figures 2.1(a)–2.5(a). We then calculated the logarithm of the mortality rate by anthropometric status and each cause of death for each study, and re-graphed the data (Figures 2.1[b]–2.5[b]). Second, we regressed the logarithm of mortality on WAZ and compared these results with regressions of the simple mortality rates by WAZ. Third, we compared the goodness-of-fit characteristics for the two models (R^2 and MSE). The models with log mortality rate as the outcome had better goodness-of-fit. For these analyses, we utilized a weighted regression with the weighting scheme of Pelletier and col-

Figure 2.2 Underweight and diarrhoea mortality: (a) deaths per 1000; (b) logarithm of deaths per 1000



leagues: (1/deaths) + (1/children). Fourth, we utilized weighted random effects models (Proc Mixed in SAS—see section 2.2 under subregional estimates), to provide combined estimates of the relation between weight-for-age and risk of mortality. The midpoint of the anthropometric category was used for estimation, and –0.5 SD was considered the value of the reference category. The results of the regression analyses are provided in Table 2.5. From these coefficients, estimated relative risk and 95% CIs were calculated. These steps were performed for all-cause mortality as well as by cause of death.

Figure 2.3 Underweight and pneumonia mortality: (a) deaths per 1000; (b) logarithm of deaths per 1000

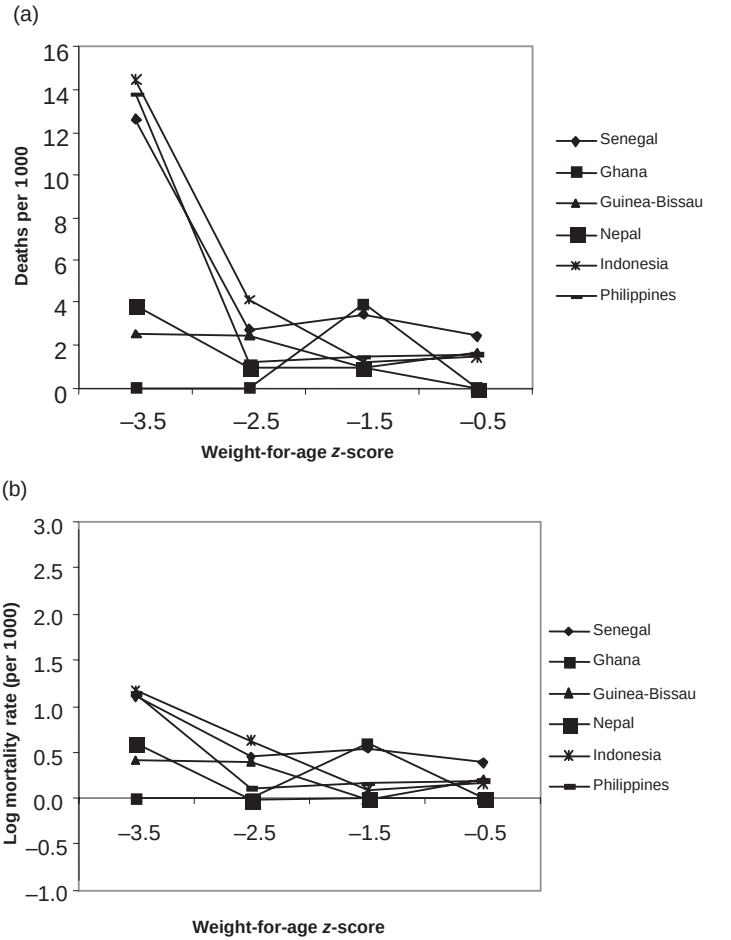


Results

In all, we identified 12 potential studies, and have utilized data from 10 studies in the current analysis. We excluded two studies from the analysis: data from Peru were excluded because the study was too small and provided insufficient deaths for the analysis; data from Brazil were excluded because they resulted from a case–control study and were therefore not appropriate for our analysis.

The 10 studies were conducted in sub-Saharan Africa and Asia (Table 2.3). Each study contributed data on deaths due to diarrhoea and pneu-

Figure 2.4 Underweight and measles mortality: (a) deaths per 1000; (b) logarithm of deaths per 1000



monia (see Figures 2.2 and 2.3); however, exposure to infectious diseases such as malaria and measles depends on the ecology of the study setting and health care utilization (i.e. measles vaccination rates), and thus, not all studies contributed data on these causes of death. In all, six studies from Ghana, Guinea-Bissau, Indonesia, Nepal, the Philippines and Senegal contributed data on deaths due to measles (Figure 2.4). Three studies, from Ghana, Guinea-Bissau and Senegal contributed data on malaria-related deaths (Figure 2.5).

From the regression analyses we calculated the relative risk (95% CI) of death by cause of death for each category of weight-for-age as

Figure 2.5 Underweight and malaria mortality: (a) deaths per 1000; (b) logarithm of deaths per 1000

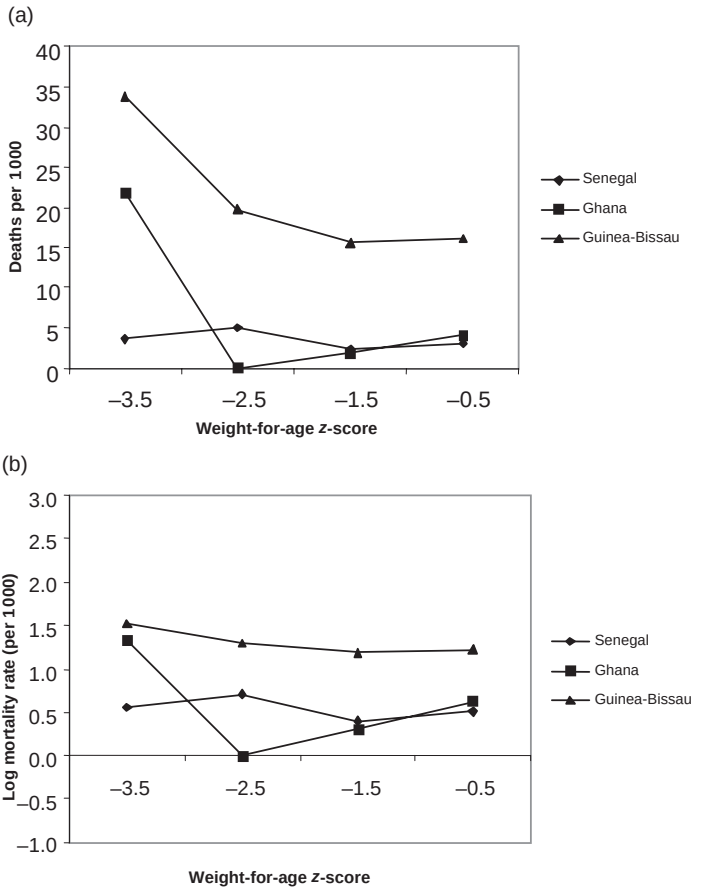


Table 2.5 Regression coefficients for models relating low weight-for-age with mortality, by cause

Outcome	*Intercept (SE)*	*Weight-for-age (SE)*
All-cause mortality	+2.26[a] (0.30)	–0.722[a] (0.077)
Diarrhoea mortality	+0.490 (0.338)	–0.842[a] (0.094)
Pneumonia mortality	+0.459 (0.361)	–0.697[a] (0.105)
Malaria mortality	+0.058 (0.454)	–0.750[a] (0.182)
Measles mortality	–0.263 (0.370)	–0.551[a] (0.140)

[a] $P < 0.05$.

Table 2.6 RR of mortality associated with low weight-for-age estimated from regression analysis, by cause of death[a]

Cause of death	*<–3 SDs (95% CI)*	*–2 to –3 SDs (95% CI)*	*–1 to –2 SDs (95% CI)*	*>–1 SD*
Diarrhoea	12.50 (7.19–21.73)	5.39 (3.73–7.79)	2.32 (1.93–2.79)	1.0
Pneumonia	8.09 (4.36–15.01)	4.03 (2.67–6.08)	2.01 (1.63–2.47)	1.0
Malaria	9.49 (3.25–27.66)	4.48 (2.20–9.15)	2.12 (1.48–3.02)	1.0
Measles	5.22 (2.29–11.88)	3.01 (1.74–5.21)	1.73 (1.32–2.28)	1.0
All-cause	8.72 (5.55–13.72)	4.24 (3.13–5.73)	2.06 (1.77–2.39)	1.0

[a] Calculated at –3.5, –2.5, –1.5 vs 0.5 SD weight-for-age.

compared to the reference category of weight-for-age >–1 SD (Table 2.6). As shown, there are significant risks of death associated with low weight-for-age for overall mortality as well as for each cause of death examined.

Several results on the relationships between anthropometric status and specific causes of mortality should be interpreted with caution. First, studies on the influence of low weight-for-age on measles mortality have yielded equivocal results. For example, a community-based longitudinal study by Chen et al. (1980) in Bangladesh found that underweight children were at over twice the risk for measles mortality (risk ratio 2.37, 95% CI 0.96–5.86), while Aaby et al. (1988) observed little effect attributable to pre-existing nutritional status in Guinea-Bissau (estimated risk ratio 0.83, 95% CI 0.25–2.78). Other factors, such as intra-household crowding and the different levels of exposure experienced by primary and secondary cases, appeared to have greater influence on clinical outcome. Second, in the study by Andersen (1997) in Guinea-Bissau, deaths due to malaria were reported as due to fever, and thus deaths due to febrile illnesses other than malaria were necessarily included. However, as shown in Figure 2.5 (b), the results are quite consistent with those from Senegal. The results from Ghana suggest a different pattern of relationship with mortality risk, but it should be noted that the number of deaths due to malaria is quite small ($n=8$). Further research is needed to refine these estimates. Finally, as described earlier, poor nutritional status is associated with poverty and poor environment. Some of the effects of such factors on child health are mediated through modifying anthropometry and some through other mechanisms. Therefore, it is likely that the hazard estimates presented here are affected by confounding due to a number of such factors.

4.2 Risk of morbidity from childhood infections

The incidence of infection and the risk of other morbidities associated with underweight status were estimated through a literature review and meta-analysis of published data.

Search strategy for identifying studies

Articles relating to undernutrition were identified for review based upon database searches of literature published between 1966 and 2001 in English, or having an English abstract. Searches of Medline, Popline and PsychInfo databases were conducted through PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) and Internet Grateful Med (http://igm.nlm.nih.gov, now discontinued) using numerous keywords, author names and "related articles" links. After reviewing the abstracts, English-language articles that examined the relationship between anthropometric status and health outcomes among human populations were selected.

Once copies of articles were obtained, additional publications were identified from the reference lists of those articles. Several nutrition researchers were consulted as to their awareness of any ongoing studies or additional published or unpublished data. However, beyond this and the search strategy described above, there was no systematic attempt to identify unpublished studies or dissertations.

Inclusion/exclusion criteria

The studies considered for review were restricted to: (i) original research reports of community-based or facility-based controlled trials, cohort studies, case–control studies, cross-sectional studies and retrospective analyses of records; (ii) critical review articles that contained original research results not available elsewhere; and (iii) meta-analyses of original research results. Studies that were excluded from the review and analysis were: (i) animal studies; (ii) case reports; (iii) ecological analyses; (iv) studies of special populations (e.g. dialysis patients, acquired immunodeficiency syndrome [AIDS] patients); (v) studies without a control or comparison group; (vi) studies where nutritional status was defined only by birth weight; (vii) studies where the term "malnutrition" was used without further descriptive information or reference to a source providing such information; and (viii) studies where clear risk estimates were not presented or could not be calculated from the reported data.

The analysis was limited to studies conducted among populations in developing countries, among whom poor anthropometric status was considered more likely to reflect undernutrition. Studies of protein/energy supplementation or fortification were excluded from the analysis because the exposure variable (i.e. supplemented vs not supplemented) was not compatible with the anthropometric definition of undernutrition used here. The analysis of studies was limited to those reporting weight-for-age according to either *z*-score or percentage of median relative to the Harvard (Jelliffe 1966) or NCHS/WHO (Hamill 1977; WHO 1978) references.

Analytic methods used to combine individual study risk estimates

Meta-analyses were performed using unadjusted data from studies that satisfied all of the inclusion/exclusion criteria and provided sufficient statistical information (e.g. sample sizes per group, means and SDs or significance test values). Original source data were not obtained for these meta-analyses. Each meta-analysis was based on data exactly as reported in the publication, whenever possible. In some cases, the data had to be adapted from reported rates and statistical information in order to convert them into comparable units of measurement or to conform to comparable nutritional categories. For example, a multiplier would be used to convert diarrhoea episodes per month into diarrhoea episodes per year, or categorical data corresponding to two or more degrees of malnutrition would be collapsed into a single category. Estimates were made of data plotted in figure form if the figure provided sufficient clarity and precision.

All modelling and testing was conducted using Intercooled STATA 6.0. Studies reviewing malaria risk associated with underweight status were combined using Mantel-Haenszel fixed-effect models and tests of heterogeneity. Relative risk of diarrhoea associated with low weight-for-age was calculated from summary data and estimates of lower and upper confidence limits were calculated using the incidence-density binomial approximation to the normal distribution. Individual study estimates were then combined using Mantel-Haenszel combination techniques and tests of heterogeneity. Random effects models were used to combine individual study estimates for risk of pneumonia associated with low weight-for-age. For each outcome, sensitivity analyses were conducted to determine if any studies were significantly driving the estimate.

Although *z*-score is now preferable, most studies reported anthropometric status in terms of percentage of median, and cut-off points to classify malnutrition varied among different studies. As a result, the definition of underweight was not absolutely consistent among the studies combined in each summary estimate. The differences in definition in such cases were distinguished in this review through the use of multiple analysis "levels", wherein studies were separated by their nutritional categorization scheme during the analysis process in order to compare and contrast the results. Analysis levels are described further in the sections on pneumonia and diarrhoea results.

Weight-for-age was analysed according to multiple categories of severity, when possible, in order to describe any potential dose–response effect and better characterize possible health risks among the large proportion of mild-to-moderate malnutrition cases. The ability to examine multiple weight-for-age levels, however, was highly limited by the available published data; the majority of studies analysed anthropometric status as a dichotomous variable only. Therefore, for all health outcomes, underweight was analysed as a dichotomous variable, comparing individuals

falling below the designated weight-for-age cut-off point to those above the cut-off point (the reference group). A drawback to the dichotomous approach is that if a dose–response trend exists, combining intermediate-risk and low-risk groups into a single category for a dichotomous analysis could have the effect of underestimating the true risk. An additional analysis was conducted when data on multiple weight-for-age categories were available, in which case data were conflated into three anthropometric categories: moderately to severely underweight (e.g. weight-for-age below –2 SDs), mildly underweight (e.g. weight-for-age between –1 and –2 SDs) and normal (e.g. weight-for-age greater than –1 SD). Risk ratios were then estimated for both categories in relation to the reference category of weight-for-age >–1 SD. When weight-for-age was defined by percentage of median, the overall analysis was subdivided into separate analysis levels according to the cut-off points used.

Measles results

There were an inadequate number of eligible studies for a summary risk analysis of weight-for-age and measles incidence. Evidence from an observational study in the Gambia (Lamb 1988) and a controlled supplementation trial in India (Gopalan et al. 1973) suggest, however, that pre-morbid underweight status has no significant effect on the incidence of measles infection. In India, Sinha et al. (1977) observed a reduced incidence of measles rash among children in the lowest weight percentiles, but this may represent a lowered immune response rather than a reduced incidence of infection. Beau et al. (1987) in Senegal noted a higher prevalence of measles among hospitalized children who were wasted at admission, but reverse causality would explain this observation.

Malaria results

Research and clinical observation over the past several decades have generated debate as to how undernutrition may influence susceptibility to malaria. Conflicting results occur, in part, because susceptibility to malaria attack and/or infection is highly dependent on the individual's immune status, which, in turn, is influenced by factors such as age, pregnancy status and the level of endemicity within a population (Shankar 2000). The relationship between malaria and undernutrition has been examined according to several outcome variables, including presence or density of malaria parasites in the blood, episodes of malarial illness, incidence of complicated malaria (cerebral malaria or severe malarial anaemia) among malaria cases and case-fatality. This comparative risk analysis focused only on the incidence of malaria attacks, defined clinically as episodes of fever with slide-confirmation of parasites in the blood, or, in some studies, less specifically as fever with chills. Most of the data related to infection by *Plasmodium falciparum*, although some studies included data on *Plasmodium vivax*, as well.

Table 2.7 Risk of malaria attack associated with low weight-for-age from five studies

Location	*Study*	*Study type*	*Cut-off point*	*Sample size*	*Risk estimate (95% CI)*
Congo	Tonglet et al. (1999)	Community-based cohort	WA <25th percentile	842	RR = 0.92 (0.72–1.17)
Gambia	Snow et al. (1991)	Community-based cohort	WA <70%	138	RR = 1.52 (0.59–3.93)
Nigeria	Adelekan et al. (1997)	Facility-based case–control	WAZ <–2	65	OR = 1.50 (0.51–4.41)
Sudan	el Samani et al. (1987)	Community-based cross-sectional	WA <75%	445	RR = 1.63 (1.18–2.27)
Vanuatu	Williams et al. (1997)	Community-based cohort	WAZ <–2	911	RR = 1.28 (0.87–1.89)

WA Weight-for-age.

It is difficult to adequately estimate any effect of low weight-for-age on risk of malaria morbidity given the scarcity of studies reporting both weight-for-age and malaria data. Five studies were identified that fulfilled that initial requirement (Table 2.7). These studies examined nutritional status as a dichotomous variable, comparing underweight children (defined as WAZ <–2, weight-for-age <70%, or weight-for-age <75% of the NCHS reference median) to adequate-weight children; there were insufficient data from eligible prospective studies to examine any potential risk associated with milder degrees of malnutrition (i.e. WAZ between –1 and –2). Of the five studies, cohort studies from the Gambia (Snow et al. 1991), the Congo (Tonglet et al. 1999) and Vanuatu (Williams et al. 1997) among children aged 1–4 years, <2 years and <10 years, respectively, reported statistically non-significant differences in malaria morbidity between underweight and normal children. In a facility-based case–control study in Nigeria (Adelekan et al. 1997) malaria cases in children aged <8 years had slightly, albeit not significantly, lower weight-for-age than non-infected controls, but this study was dropped from the final analysis because nutritional status was assessed after the onset of illness, leaving causality ambiguous. A cross-sectional study in the Sudan (el Samani et al. 1987) observed significantly greater history of malaria attacks (defined as fever with rigors and joint pain) among underweight children aged <5 years, but the causality was unclear in this case, as well.

Of the remaining three prospective studies, the Congo study (Tonglet et al. 1999), which reported a relative risk of 0.92 (95% CI 0.72–1.17) for a malaria episode, was dropped from the summary analysis because nutritional categories were defined according to local reference data. Following meta-analysis of the two remaining cohort studies, the most

Table 2.8 Combined estimate of risk for malaria attack associated with low weight-for-age from two cohort studies

Location	*Study*	*Risk estimate (95% CI)*
Gambia	Snow et al. (1991)	1.52 (0.59–3.93)
Vanuatu	Williams et al. (1997)	1.28 (0.87–1.89)
Combined estimate		1.31 (0.92–1.88)

appropriate for this assessment, the combined relative risk for malaria among children having weight-for-age <–2 SDs was statistically non-significant (RR 1.31, 95% CI 0.92–1.88) (Table 2.8). This overall estimate was more heavily influenced by the Vanuatu cohort study, which reported a slightly but not significantly higher incidence of *P. falciparum* malaria (defined as fever with parasitaemia >1000/µl) among children who were classified as underweight prior to the period of morbidity follow-up.

Pneumonia/ALRI results

Undernutrition may increase the risk of pneumonia through a number of potential mechanisms. In general, cell-mediated immunity is depressed in undernourished children (Rivera and Martorell 1988; Scrimshaw and SanGiovanni 1997). Respiratory muscles weaken, impairing the cough reflex and reducing a child's ability to adequately clear secretions from the respiratory tract or respond to hypoxia through tachypnea (Wilson 1985). Salivary IgA is decreased, compromising the integrity of the respiratory tract mucosa and leaving the mucosa susceptible to invasion by microorganisms (Lehmann et al. 1988).

Over 60 studies evaluating the relationship between acute respiratory infections and malnutrition were initially identified. These included a collaborative data group from the United States National Academy of Sciences Research Program of the Board on Science and Technology for International Development (BOSTID). We immediately excluded studies that examined upper respiratory tract infections only; did not distinguish between upper and lower respiratory tract infections in their data collection and/or analysis; limited the report to single etiological agents (e.g. only pneumococcus); or did not report anthropometric status in terms of weight-for-age. The remaining studies are briefly described below, although not all fulfilled the criteria for inclusion in a summary analysis, usually for reasons of insufficient data or statistical information. Studies that provided estimates of risk are listed in Tables 2.9 and 2.10.

Studies varied in their case definitions of ALRI and pneumonia, classifying them on the basis of mothers' recall of the physician's diagnosis (Victora et al. 1990); radiologically confirmed pneumonia (Alam et al. 1984; Fonseca et al. 1996; Victora et al. 1994); or cough and fever with

Table 2.9 Risk of pneumonia/ALRI incidence associated with low weight-for-age from studies included in summary estimate

Analysis level	*Study*	*Location*	*Cut-off point*	*Sample size*	*Crude RR (95% CI)*	*Adjusted RR*[a] *(95% CI)*
1	Victora et al. (1990)	Brazil	WAZ <–2	4 486	1.32 (0.70–2.47)	1.75[b]
1	Zaman et al. (1996)	Bangladesh	WAZ <–2	696	1.25 (0.76–2.05)	—
3	James (1972)	Costa Rica	WA <75%	137	12.37 (3.11–49.25)	—
4	Ballard and Neumann (1995)	Kenya	WA <80%	109	0.90 (0.37–2.17)	1.8[c] (0.52–6.4)
4	Deb (1998)	India	Unclear	800	2.53 (1.72–3.73)	—

— No data.

[a] All crude relative risks reported in Table 2.9 represent risk associated with weight-for-age below the cut-off point compared to risk associated with weight-for-age above the cut-off point. Adjusted relative risks, however, varied in their referent group and in the variables adjusted as indicated in the table footnotes.

[b] Adjusted for income. Adjusted risk ratio was based on WAZ <–2 relative to WAZ ≥0. Crude risk estimate of 1.32 was based on WAZ <–2 relative to WAZ >–2. (Crude risk estimate based on WAZ <–2 relative to WAZ ≥0 is 2.38 [95% CI 1.18–4.78].)

[c] Adjusted for season, socioeconomic status and geographic region. Adjusted RR was based on weight-for-age <80% relative to weight-for-age >90%; crude RR was based on weight-for-age <80% relative to weight-for-age >80%. (Crude RR based on weight-for-age <80% relative to weight-for-age >90% is 2.03 [95% CI 0.44–9.25].)

rapid respiratory rate (Cunha 2000; Deb 1998; Smith et al. 1991) and/or chest indrawing (Ballard and Neumann 1995; Spooner et al. 1989; Zaman et al. 1996). The case definition for pneumonia recommended by WHO is cough or difficult breathing with rapid respiration (>50 breaths/min for infants aged 2 months to under 1 year; >40 breaths/min for children aged 1 to 5 years) or chest indrawing, stridor or general danger signs such as vomiting, convulsions, lethargy, unconsciousness or inability to drink/breastfeed (WHO 1999b). The coordinated BOSTID data group defined ALRI as the presence of at least one of the following: rales or crepitations, wheezing, stridor, cyanosis, rapid respiratory rate (>50 breaths/min), or chest indrawing (Selwyn 1990). Studies were considered for our summary analysis if the case definition for ALRI was consistent with the recommended WHO definition. With the exception of a Bangladesh study among diarrhoea patients aged <12 years (Alam et al. 1984), all of the studies examined children aged ≤5 years. Incidence was reported predominantly as the number of ALRI episodes over a given follow-up period (i.e. multiple episodes per individual child counted as separate events), although a few studies reported the proportion of children with one or more ALRI episodes (i.e. multiple episodes per individual child counted as a single event).

Table 2.10 Risk of pneumonia/ALRI incidence associated with low weight-for-age from excluded studies

Location	*Study*	*Study type*	*Cut-off point*	*Crude risk estimate (95% CI)*	*Adjusted risk estimate[a] (95% CI)*	*Reason for exclusion*
Brazil	Cunha et al. (2000)	Community-based cohort	WAZ –3 to –2	—	OR = 1.59[b] (1.09–2.33)	Insufficient incidence data
Brazil	Fonseca et al. (1996)	Community-based cohort	WAZ <–2	—	OR = 4.57[c] (2.93–7.13)	Reverse causality
Brazil	Victora et al. (1994)	Facility-based case–control	WAZ <–2	OR = 5.87 (3.30–10.44)	OR = 4.77[d] (2.46–9.06)	Reverse causality
China	Liu et al. (1991)	Community-based case–control	Not reported	OR = 5.79 (3.70–9.14)	—	Reverse causality; no PEM definition
India	Shah et al. (1994)	Facility-based case–control	WA <75%	OR = 2.36 (1.53–3.65)	—	Reverse causality
Papua New Guinea	Binns (1976)	Community-based cohort	WA <80%	RR = 1.59	—	No categorical sample size data
Papua New Guinea	Smith et al. (1991)	Community-based cohort	WAZ <–2	—	RR = 2.1[e] (1.3–3.4)	Data reported in figure form
South Africa	Wesley and Loening (1996)	Community-based case–control	WA <10th percentile	OR = 1.47 (0.38–5.88)	—	Reverse causality; cut-off point

— No data.

PEM Protein–energy malnutrition.

[a] All crude relative risks reported in Table 2.10 represent risk associated with weight-for-age below the cut-off point compared to risk associated with weight-for-age above the cut-off point. Adjusted relative risks, however, varied in their referent group and in the variables adjusted as indicated in the table footnotes.

[b] Adjusted for age, sex, household air pollution and crowding. Adjusted OR is based on WAZ between –2 and –3 relative to WAZ >–1.

[c] Adjusted for income, parents' education and previous episode of pneumonia. Adjusted OR is based on WAZ <–2 relative to WAZ ≥0.

[d] Adjusted for age, sex, father's education, household crowding and other factors. Crude and adjusted ORs are based on WAZ <–2 relative to WAZ >–1.

[e] Adjusted for age. Adjusted risk ratio is based on WAZ <–2 relative to WAZ ≥0.

Excluded studies

The collaborative BOSTID study reported community-based longitudinal data from Guatemala, Papua New Guinea, the Philippines and Uruguay (Selwyn 1990). In each population, researchers observed higher incidence of ALRI among underweight children aged 18–59 months, with relative risks ranging between 1.2 (Guatemala) and 2.7 (Uruguay). An increased risk was observed among the younger group of 0–17-month-old children only in the Philippines (RR = 1.3). While the methodology used in these four countries was standardized for better internal comparability among study sites, the results were not included in our summary analysis because nutritional status was evaluated using an anthropometric cut-off point (10th percentile) higher than WAZ of –2 (equivalent to approximately the third percentile—Pelletier 1994) and the case definitions used in Guatemala and Uruguay could have classified asthma as ALRI.

Ten ALRI investigations were case–control studies or record reviews and were excluded because of the possibility of reverse-causality. In Colombia (Berman et al. 1983) and India (Shah et al. 1994), children with pneumonia were significantly more likely to be moderately or severely malnourished than were non-ALRI paediatric patients or outpatients. In South Africa, in contrast, odds of being malnourished were not significantly different between pneumonia patients and a control group of upper respiratory infection patients (Wesley and Loening 1996). In a case history review in Bangladesh, malnourished diarrhoea patients aged 1–5 years had a higher incidence of pneumonia during hospitalization than diarrhoea patients considered well-nourished, although the relationship was not observed in infants (Alam et al. 1984).

Case–control studies in Brazil, China and Papua New Guinea (Fonseca et al. 1996; Victora et al. 1994) compared cases to healthy controls from the surrounding community. Children having lower respiratory infections in China (Liu et al. 1991) and Papua New Guinea (Spooner et al. 1989) were at significantly greater odds of being underweight compared to healthy controls, and underweight children in Papua New Guinea were four times as likely to be admitted to the hospital with pneumonia as non-malnourished children (Barker et al. as cited in Lehmann et al. 1988). Similarly, in an urban area of southern Brazil, children aged <2 years hospitalized with pneumonia had a reported OR of 5.87 (95% CI 3.30–10.44) for weight-for-age <–2 SDs compared to healthy, age-matched neighbourhood controls; adjusted for age, sex, crowding and socioeconomic factors, the odds ratio decreased slightly to 4.77 (95% CI 2.46–9.06) (Victora et al. 1994). Fonseca et al. (1996) conducted a similarly designed study in northern Brazil and found undernutrition to be the most important risk factor for pneumonia among children aged <2 years attending an outpatient clinic; the odds ratio for weight-for-age <–2 SDs among cases was 4.57 (95% CI 2.93–7.13) adjusted for income, parents' education and previous pneumonia.

In a community-based survey in Brazil, Cunha et al. (2000) compared anthropometric status of children aged <5 years according to mothers' report of respiratory illness in the previous week (Cunha et al. 2000). Adjusted for age, sex and household crowding, children with weight-for-age below –2 SDs had significantly greater odds for an ALRI episode compared to children with weight-for-age >–1 SD.

Prospective cohort studies that assessed anthropometric status prior to illness were more appropriate for evaluating malnutrition as a causal factor in ALRI incidence. In rural Papua New Guinea, Smith et al. (1991) assessed nutritional status and subsequent incidence of ALRI through twice-weekly home visits, reporting an age-adjusted incidence rate ratio of approximately 2.1 (95% CI 1.25–3.4) associated with WAZ <–2 relative to weight-for-age >0 SD. There was no evidence of confounding by socioeconomic status (defined by education, income and household crowding) or previous episodes of illness. The data, however, were reported only in figure form and lacked sufficient statistical information for inclusion in the meta-analysis. An earlier cohort study in Papua New Guinea by Binns (1976) observed a relative risk of 1.59 for pneumonia among children having weight-for-age <80%, but, likewise, did not report sufficient statistical data for inclusion (such as sample sizes per weight-for-age category).

Studies included in the risk estimate

James (1972) in urban Costa Rica reported the highest risk estimate among cohort studies. Based on weekly physician visits and mothers' recall, underweight children aged <5 years had a similar number of overall respiratory tract infections as normal-weight children, but experienced a relative risk of 12.4 (95% CI 3.11–49.25) for bronchopneumonia, with no apparent differences between groups in breastfeeding duration, age distribution, levels of household crowding, incomes or sanitation. In urban Brazil, Victora et al. (1990) followed a cohort of infants for subsequent hospital admissions, reporting a significant relative risk (adjusted for family income) of 1.75 for pneumonia among children with pre-morbid WAZ <–2 compared to ≥0. The risk estimate remained statistically significant after adjusting for previous pneumonia hospitalizations (data not reported). Incidence referred to hospital admissions, which represented only the more severe cases of ALRI, and there is potential bias if underweight ALRI cases are more likely to be admitted than the normal weight cases. In a community-based cohort study in Bangladesh, Zaman et al. (1996) followed up morbidity every four days and observed an increased, but not statistically significant, risk of 1.25 between low weight-for-age and subsequent incidence of ALRI among children aged ≤5 years; adjusted for age, sex and socio-demographic variables, the relative risk became statistically significant, with a one-unit decrease in WAZ being associated with a 55% increase in the incidence of ALRI. A smaller cohort study in Kenya reported a slightly higher,

but statistically non-significant, relative risk for ALRI of 1.8 (95% CI 0.52–6.4) among children aged 18–25 months with weight-for-age <80% relative to weight-for-age >90%, adjusted for season, socioeconomic status and geographic region (Ballard and Neumann 1995). In an urban and rural community-based cohort study in India (Deb 1998), underweight children aged <5 years experienced a significantly higher rate of pneumonia over the course of 18 months relative to normal-weight children (RR=2.53), although it was not reported how comparable malnourished and normal groups were in relation to potentially confounding variables.

Relative risk estimate

There were an insufficient number of studies reporting multiple categories of weight to compare the risk of ALRI associated with mild-to-moderate degrees of underweight, and, therefore, only a dichotomous analysis was performed. Two cohort studies reported anthropometric status in terms of *z*-score and were treated as "analysis level one" (Table 2.11). Analysis levels three and four used cut-off points in terms of percentage of median. (Analysis level two was reserved for studies using a cut-off point of 70%, but no eligible studies using that cut-off point were included here.)

Relative risks according to cut-off point are represented graphically in Figure 2.6 and summary risk estimates are listed in Table 2.12 according to analysis level. Overall, community-based cohort studies that

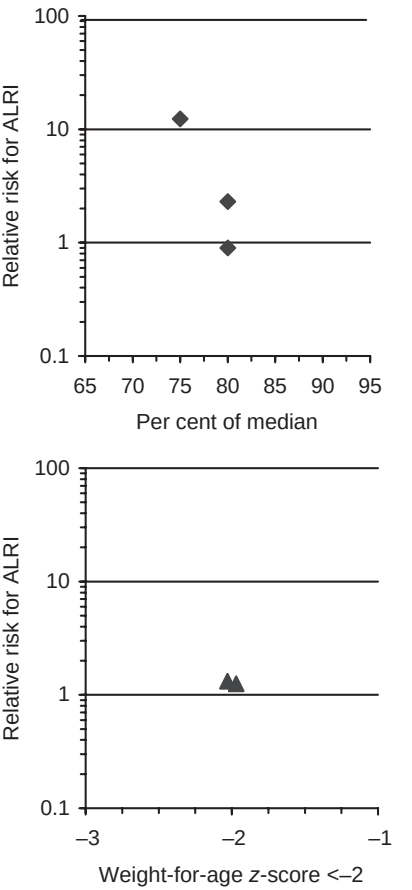
Table 2.11 Analysis levels according to anthropometric classification used

Analysis level	*Comparison*
1	WAZ <–2 vs WAZ >–2
2	WA <70% vs WA >70%
3	WA <75% vs WA >75%
4	WA <80% vs WA >80%

Table 2.12 Combined estimate of risk for pneumonia/ALRI incidence associated with low weight-for-age

Study type	*Analysis level*	*Number of studies*	*Combined risk estimate (95% CI)*
Cohort	1	2	1.28 (0.86–1.89)
Cohort	3	1	12.37 (2.98–51.31)
Cohort	4	2	2.22 (1.55–3.18)
Cohort	1+4	4	1.72 (1.32–2.25)
Combined estimate	1+3+4	5	1.86 (1.06–3.28)

Figure 2.6 Relative risk of pneumonia/ALRI according to weight-for-age cut-off point used in study



provided sufficient results and statistical data yielded a combined risk estimate for ALRI of 1.86 associated with low weight-for-age (Table 2.12). Even excluding the high estimate observed in the study by James (1972), the risk (RR=1.72) remained statistically significant.

Diarrhoea results

There is a large body of literature examining the relationship between malnutrition and diarrhoea, and cross-sectional studies among children have consistently shown a trend of increasing diarrhoea prevalence associated with decreases in anthropometric status. Malnutrition and concomitant growth faltering and weight decline are not uncommon following severe bouts of diarrhoea among children in developing coun-

tries, but the reverse relationship—that pre-morbid undernutrition increases susceptibility to subsequent diarrhoea attack—is more uncertain. We selected prospective studies that specifically examined pre-morbid anthropometric status as a risk factor for subsequent diarrhoea, rather than the reverse relationship. Studies that simultaneously assessed weight-for-age and diarrhoea were not considered because the direction of the relationship could not be determined—i.e. there was potential reverse causality with regard to the risk relationship. All of the studies related to children aged ≤5 years; little if any data were available for older age groups. In some studies, morbidity was compared to the initial assessment of nutritional status only, whereas other studies reclassified children, as necessary, according to periodic follow-up measurements. An episode of diarrhoea was typically defined as three or more loose, liquid or watery stools, or at least one bloody stool in a 24-hour period. An episode was generally considered terminated when normal stool patterns returned for at least three days. Some of the outcome variables relating to diarrhoea included incidence of general diarrhoea, incidence of dysentery and incidence of persistent diarrhoea, defined as diarrhoea lasting 14 days or longer. We restricted our analysis to the incidence of general diarrhoea, and excluded studies that focused solely on a single pathogenic agent (e.g. *Cryptosporidium, Vibrio cholerae*), watery diarrhoea alone or bloody diarrhoea alone.

Literature supports an increased risk of diarrhoea mortality associated with low weight-for-age (Bhan et al. 1986; Chen et al. 1980; Fawzi et al. 1997; Rice et al. 2000; Yoon et al. 1997), but the effect on diarrhoea incidence has been less clear. Cohort studies in Bangladesh (Baqui et al. 1993; Chowdhury et al. 1990), Brazil (Schorling et al. 1990), Costa Rica (James 1972), the Congo (Tonglet et al. 1999), Ethiopia (Lindtjorn et al. 1993), the Gambia (Tomkins et al. 1989), Ghana (Biritwum et al. 1986), Guatemala (Gordon et al. 1964), India (Ghai and Jaiswal 1970; Walia et al. 1989), Mexico (Sepulveda et al. 1988), Papua New Guinea (Binns 1976) and the Sudan (el Samani et al. 1988; Kossman et al. 2000), reported higher diarrhoea incidence rates among underweight children (rate ratios of 1.1 to 2.4), while other studies observed no statistically significant effect (Anand et al. 1994; Bairagi et al. 1987; Bhan et al. 1986; Black et al. 1984; Chen et al. 1981; Henry et al. 1987; Khan and Yunus 1990; Mathur et al. 1985; Molbak et al. 1997b; Thongkrajai et al. 1990; Tomkins 1981; Victora et al. 1990). Factors such as age, socioeconomic status, season, breastfeeding and recent history of diarrhoea, among others, can be important confounders in the relationship between anthropometric status and diarrhoeal illness. When statistical adjustment had been made for such variables, several studies (e.g. el Samani et al. 1988; Kossman et al. 2000; Schorling et al. 1990; Sepulveda et al. 1988; Tonglet et al. 1999; Wierzba et al. 2001) continued to show a significant relationship, while others (Chowdhury et al. 1990; Lindtjorn et al. 1993) did not.

Table 2.13 Diarrhoea cohort studies included in dichotomous analysis

Analysis level	*Study*	*Location*	*Cut-off point*	*Sample size*	*Crude RR (95% CI)*	*Adjusted RR*[a] *(95% CI)*
1	Wierzba et al. (2001)	Egypt	WAZ <–2	143	1.83 (1.36–2.47)	1.7 (1.2–2.3)[b]
1	Baqui et al. (1993)	Bangladesh	WAZ <–2	512	1.11 (1.00–1.23)	1.22 (1.09–1.35)[c]
1	Schorling et al. (1990)	Brazil	WAZ <–2	61	1.18 (1.06–1.34)	OR = 3.4 (1.0–11.9)[d]
1	Victora et al. (1990)	Brazil	WAZ <–2	4 486	0.78 (–0.26–1.95)	0.58[e]
2	Bhan et al. (1986)	India	WA <70%	1 467	0.90 (0.80–1.01)	—
2	Walia et al. (1989)	India	WA <70%	838	1.33 (1.07–1.62)	—
2	Anand et al. (1994)	India	WA <70%	250	1.08 (0.92–1.26)	—
2	Sepulveda et al. (1988)	Mexico	WA <70%	284	1.86 (1.54–2.21)	1.7[f]
3	Mathur et al. (1985)	India	WA <75%	687	1.40 (1.24–1.58)	—
3	Chen et al. (1981)	Bangladesh	WA <75%	207	1.04 (0.91–1.20)	—
3	Black et al. (1984)	Bangladesh	WA <75%	125	1.10 (0.88–1.33)	—
3	Bairagi et al. (1987)	Bangladesh	WA <75%	1 454	1.10 (0.96–1.26)	—
3	Henry et al. (1987)	Bangladesh	WA <75%	300	0.93 (0.82–1.06)	—
3	James (1972)	Costa Rica	WA <75%	137	1.08 (0.93–1.26)	—
3	Gordon et al. (1964)	Guatemala	WA <75%	179	1.73 (1.45–2.07)	—
3	Tomkins et al. (1981)	Nigeria	WA <75%	343	1.22 (1.00–1.45)	—
3	el Samani et al. (1988)	Sudan	WA <75%	403	1.22 (1.00–1.42)	OR = 1.3 (1.0–1.7)[g]
4	Khan and Yunus (1990)	India	WA <80%	183	1.39 (0.75–2.58)	—
4	Biritwum et al. (1986)	Ghana	WA <80%	250	1.53 (1.1– 2.01)	—
5	Chowdhury et al. (1990)	Bangladesh	WA <85%	753	1.54 (0.87–2.72)	—

— No data.

[a] All crude risk estimates in Table 2.13 represent incidence below cut-off relative to incidence above cut-off. Adjusted risk estimates, however, vary in their referent category and adjusted variables as shown in the following table footnotes.

[b] Estimate adjusted for age, sex, socioeconomic status, breastfeeding and previous morbidity. WAZ <–2 vs WAZ >–2.

[c] Estimate adjusted for age. WAZ <–2 vs WAZ >–2. When stratified by previous diarrhoea experience, age-adjusted rate ratios were 1.00 (0.75–1.33) and 1.26 (1.07–1.49) for underweight children without recent morbidity and with recent morbidity, respectively.

[d] Estimate adjusted for previous diarrhoea morbidity, age, sex and household crowding. Estimate is an OR comparing WAZ <–3 to WAZ >–3.

[e] Estimate adjusted for income. WAZ <–2 vs WAZ ≥0.

[f] Estimate adjusted for age. Weight-for-age <75% vs weight-for-age ≥90%.

[g] Estimate adjusted for age, sex, season, socioeconomic status and previous morbidity. Weight-for-age <90% vs weight-for-age ≥90%.

Table 2.14 Analysis levels for dichotomous analysis according to anthropometric definition used in study

Analysis level	*Comparison*
1	WAZ <–2 vs WAZ >–2
2	WA <70% vs WA >70%
3	WA <75% vs WA >75%
4	WA <80% vs WA >80%
5	WA <85% vs WA >85%

Table 2.13 summarizes prospective studies used to estimate diarrhoea incidence according to weight-for-age. The majority of diarrhoea studies reported anthropometric status in terms of percentage of median rather than *z*-score and the cut-off points varied by study. In India, for example, most studies conformed to the Indian Academy of Pediatrics classification in which weight-for-age >80% represents normal status and weight-for-age <70% represents second-degree, third-degree or fourth-degree malnutrition (Indian Academy of Pediatrics 1972). Many others used the Gomez classification, defining second-degree malnutrition and worse as weight-for-age <75% (Gomez et al. 1956). For comparison, studies were grouped into different analysis levels according to the cut-off points used to classify malnutrition (Table 2.14).

Dichotomous estimate

In developing a summary risk estimate, nutritional status was first examined as a dichotomous variable comparing all children below the cut-off point ("malnourished") to children above that point (reference group). The dichotomous approach allowed for the inclusion of the greatest number of studies, since many studies did not further subdivide the malnourished group into discrete anthropometric categories.

Excluded studies

Ten studies that were identified were excluded from the risk analysis (Table 2.15). Seven prospective studies were excluded due to insufficient statistical data (e.g. sample sizes per anthropometric category), data presented as a figure only, or the use of a different growth reference. Six of the seven reported an increased incidence of diarrhoea episodes associated with low weight-for-age, including studies in the Sudan (Kossman et al. 2000) and the Congo (Tonglet et al. 1999) that adjusted for previous diarrhoea morbidity. An additional three cross-sectional studies in Ecuador (Brussow et al. 1993), India (Luwang and Datta 1982) and El Salvador (Stetler et al. 1981) reported risk estimates on the order of 1.45 to 1.57, but reverse causality disqualified the studies.

Studies included in the risk estimate

Figure 2.7 illustrates the distribution of individual study risk estimates according to the cut-off point used. Twenty cohort studies provided sufficient results and statistical data for inclusion in a summary estimate (Table 2.13). The evidence regarding risk of diarrhoea was equivocal

Figure 2.7 Relative risk for diarrhoea according to weight-for-age cut-off point used in study

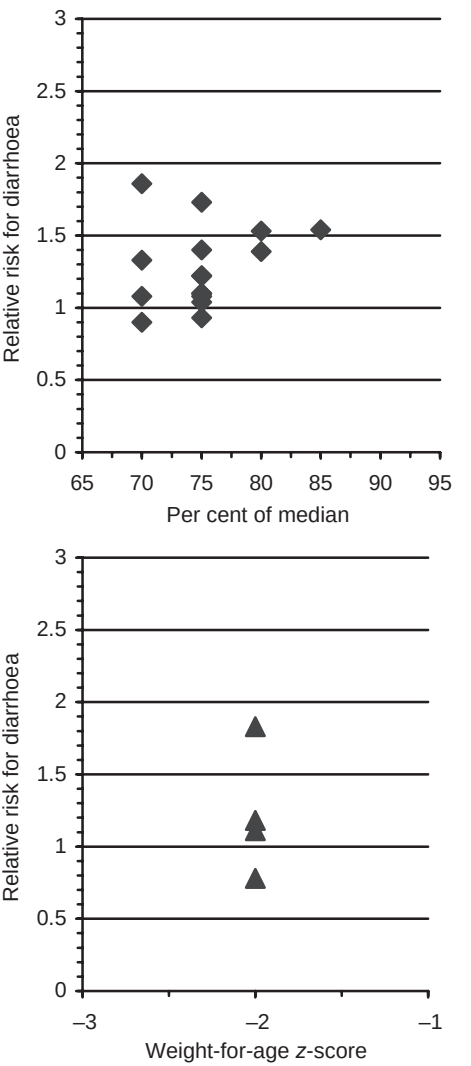


Table 2.15 Diarrhoea studies excluded from dichotomous analysis

Location	*Study*	*Cut-off point*	*Sample size*	*Crude RR (95% CI)*[a]	*Adjusted RR (95% CI)*	*Cause for exclusion*
Congo	Tonglet et al. (1999)	WA <25th percentile	842	1.22[b] (1.02–1.46)	OR= 1.49 (0.94–2.05); 1.50 (1.10–1.89)	Local growth reference
Ecuador	Brussow et al. (1993)	WAZ <–2	321	1.45 (0.99– 2.12)	—	Cross-sectional; reverse causality
El Salvador	Stetler et al. (1981)	WA <75%	3 705	1.46 (1.24–1.71)	—	Cross-sectional; reverse causality
Ethiopia	Lindtjorn et al. (1993)	WAZ <–2	425	2.2[c]	—	Data reported in figure form; no categorical sample size data
Gambia	Tomkins et al. (1989)	WAZ <–2	211	1.18; 1.33[d]	—	Data reported in figure form; no categorical sample size data
India	Ghai and Jaiswal (1970)	WA <85%	925	2.35 (1.97–2.81)	—	Uncertain growth reference
India	Luwang and Datta (1982)	WA <70%	508	1.57 (1.26–1.94)	—	Cross-sectional; reverse causality
Papua New Guinea	Binns (1976)	WA <80%	630	1.75	—	No categorical sample size data
Sudan	Kossman et al. (2000)	WAZ <–2	28 753	1.32; 1.84[e]	OR= 1.13 (1.21–1.45); 1.75 (1.56–1.96)	No categorical sample size data
Thailand	Thongkrajai et al. (1990)	WA <75%	1 339	0.18 (0.06–0.43)	—	Local growth reference

— No data.

[a] Crude risk estimates represent incidence below cut-off point relative to incidence above cut-off point except where indicated as follows.

[b] Weight-for-age <25th percentile vs weight-for-age >75th percentile. Crude RR is a Mantel-Haenszel weighted risk ratio. Adjusted ORs are among children aged <9 months and ≥9 months, respectively. Adjusted for age, sex and previous morbidity.

[c] WAZ <–2 vs WAZ –1 to 0. Estimate of data reported in figure form.

[d] WAZ<–2 vs WAZ –1 to 0. Relative risks of diarrhoea on day of monthly visit during the dry and rainy seasons, respectively. Estimates of data reported in figure form.

[e] WAZ –3 to –2 vs WAZ ≥–1, and WAZ –4 to –3 vs WAZ ≥–1, respectively. OR was adjusted for age, sex, socioeconomic status, season, breastfeeding, vitamin A intake and previous morbidity.

Table 2.16 Combined estimate for diarrhoea incidence from dichotomous analysis

Study type	*Analysis level*	*Number of studies*	*Combined risk estimate (95% CI)*
Cohort	1	4	1.25 (1.04–1.50)
Cohort	2	4	1.24 (0.90–1.70)
Cohort	3	9	1.18 (1.05–1.33)
Cohort	4+5	3	1.51 (1.20–1.90)
Combined estimate	1+2+3+4+5	20	1.23 (1.12–1.35)

among these studies, with half reporting no significant effect. Individual studies reported crude risk estimates ranging between 0.78 in Brazil (Victora et al. 1990) and 1.86 in Mexico (Sepulveda et al. 1988). Three of four studies that adjusted for previous diarrhoea morbidity found a significantly increased risk of diarrhoea incidence associated with low weight-for-age (el Samani et al. 1988; Schorling et al. 1990; Wierzba et al. 2001). The fourth, in Bangladesh, observed an increased risk of diarrhoea among underweight children (RR=1.26) who had already suffered diarrhoea within the preceding three months, but the risk was not significant for those children without recent diarrhoea experience (RR=1.00) (Baqui et al. 1993). In the most recently published investigation, Wierzba et al. (2001) in Egypt observed that WAZ <–2 predisposed toward increased incidence of diarrhoea among children aged <3 years, yielding a relative risk of 1.7 (95% CI 1.2–2.3) compared to *z*-score >–2, after adjusting for age, sex, socioeconomic status, breastfeeding and previous episodes of diarrhoea.

Dichotomous relative risk estimate

Based on all cohort studies, a combined estimate suggested underweight children were at a significantly increased relative risk of 1.23 (95% CI 1.12–1.35) for developing an episode of diarrhoea (Table 2.16). The estimate based on a cut-off point of *z*-score <–2 (RR=1.25) was similar to the estimate using percentage of median <70% (RR=1.24) and percentage of median <75% (RR=1.18). Higher cut-off points of 80% or 85% yielded a higher relative risk of 1.51, possibly due to the small number of studies or the comparatively better nutritional status of the referent group.

Multi-categorical estimate

We also attempted to examine the risk of diarrhoea incidence according to multiple anthropometric categories, comparing incidence among moderately to severely underweight (e.g. WAZ <–2), mildly underweight (e.g. WAZ between –2 and –1) and "normal"(e.g. WAZ >–1) children. The

Table 2.17 Analysis levels for multiple categorical analysis according to anthropometric classification used in study

Analysis level	*Underweight categories*	*Cut-off point*
1	Moderate–severe	WAZ <–2
	Mild	WAZ –2 to –1
	Normal (referent)	WAZ >–1
2	Moderate–severe	WA <70%
	Mild	WA 70–80%
	Normal (referent)	WA >80%
3	Moderate–severe	WA <75%
	Mild	WA 75–90%
	Normal (referent)	WA >90%
4	Moderate–severe	WA <60
	Mild	WA 60–85%
	Normal (referent)	WA >85%

studies used different cut-off points based on percentage of median and *z*-score and were subdivided into analysis levels according to the anthropometric classification scheme used (Table 2.17). A subset of 10 cohort studies reporting multiple anthropometric categories provided sufficient statistical data for inclusion in a summary analysis (Table 2.18).

The different classification schemes complicated combining studies to a greater extent than in the dichotomous analysis. Eight of 10 studies, however, fell into the second or third analysis levels, which produced relative risks of 1.23 and 1.28, respectively, associated with moderate to severely low weight-for-age (Table 2.19). The corresponding risk estimates associated with mildly low weight-for-age were 1.17 and 0.95 for these analysis levels (Table 2.20). The overall risk estimates for diarrhoea based on all analysis levels were 1.25 (statistically significant) for moderate and severe underweight and 1.12 (not statistically significant) for mild underweight. Since the risk relationship was not significant for mild underweight, only the risk for moderate–severe underweight was considered toward the burden of disease estimate. This value (1.25) was similar to the value calculated in the dichotomous analysis (1.23). As there was no significant difference between the two estimates and the dichotomous value was based on a larger number of studies, the dichotomous value of 1.23 was selected for calculating burden of disease.

Summary of morbidity risk estimates

Three morbidity outcomes contributed to the overall calculation of disease burden: diarrhoea incidence, pneumonia/ALRI incidence and malaria incidence. Table 2.21 summarizes the risk of disease incidence associated with low weight-for-age for each outcome. There was no evidence that undernutrition contributed to incidence of measles and other disease relationships cannot be adequately quantified at this time.

Table 2.18 Cohort studies of diarrhoea incidence included in categorical analysis

Analysis level	*Study*	*Location*	*Sample size*	*Crude risk estimate (95% CI)*	
1	Victora et al. (1990)	Brazil	4 486	Severe–moderate Mild	0.94 (0.22–3.94) 1.93 (1.05–3.56)
2	Walia et al. (1989)	India	838	Severe–moderate Mild	1.37 (1.01–1.85) 1.05 (0.84–1.32)
2	Anand et al. (1994)	India	250	Severe–moderate Mild	1.07 (0.74–1.54) 0.98 (0.69–1.40)
2	Bhan et al. (1986)	India	1 399	Severe–moderate Mild	0.996 (0.85–1.17) 1.27 (1.10–1.48)
2	Sepulveda et al. (1988)	Mexico	239	Severe–moderate Mild	1.96 (1.20–3.21) 1.18 (0.85–1.64)
3	Mathur et al. (1985)	India	687	Severe–moderate Mild	1.10 (0.81–1.49) 0.72 (0.53–0.99)
3	Chen et al. (1981)	Bangladesh	207	Severe–moderate Mild	0.79 (0.44–1.42) 0.71 (0.38–1.32)
3	Gordon et al. (1964)	Guatemala	179	Severe–moderate Mild	2.56 (1.53–4.29) 1.64 (0.97–2.78)
3	el Samani et al. (1988)	Sudan	445	Severe–moderate Mild	1.22 (0.80–1.87) 1.03 (0.75–1.39)
4	Chowdhury et al. (1990)	Bangladesh	753	Severe–moderate Mild	1.47 (0.65–3.34) 2.15 (0.99–4.64)

Table 2.19 Combined estimates of diarrhoea incidence associated with severe to moderate underweight status relative to WAZ >–1

Analysis level	*Category*	*Number of studies*	*Combined risk estimate (95% CI)*
1	WAZ <–2	1	0.94 (0.22–3.94)
2	WA <70%	4	1.23 (0.95–1.60)
3	WA <75%	4	1.28 (0.85–1.94)
4	WA <60%	1	1.47 (0.65–3.34)
1+2+3		9	1.25 (1.02–1.53)
1+2+3+4		10	1.25 (1.03–1.52)

4.3 Risk of mortality due to perinatal conditions

"Perinatal conditions" are responsible for approximately 18% of all deaths among children aged <5 years in developing countries (de Onis et al. 1998). These deaths, concentrated in the neonatal period (≤28 days postpartum), result mostly from low birth weight, birth asphyxia and trauma, neonatal infections (e.g. tetanus and syphilis) and congenital

Table 2.20 Combined estimates of diarrhoea incidence associated with mild underweight status relative to WAZ >–1

Analysis level	*Category*	*Number of studies*	*Combined risk estimate (95% CI)*
1	WAZ –2 to –1	1	1.93 (1.05–3.56)
2	WA 70–80%	4	1.17 (1.05–1.31)
3	WA 75–90%	4	0.95 (0.68–1.34)
4	WA 60–85%	1	2.15 (0.99–4.64)
1+2+3		9	1.09 (0.92–1.29)
1+2+3+4		10	1.12 (0.95–1.32)

Table 2.21 Relative risk of morbidity associated with weight-for-age <–2 SDs

Morbidity outcome	*Relative risk (95% CI)*
Diarrhoea incidence	1.23 (1.12–1.35)
Pneumonia incidence	1.86 (1.06–3.28)
Malaria incidence	1.31 (0.92–1.88)

anomalies (Anonymous 1999). In developed regions such as North America and western Europe, 23% of neonatal deaths are due to congenital anomalies and an additional 65% are the result of other perinatal conditions (C. Stein, personal communication, 2001). Of the deaths from perinatal conditions, the largest share (32–65%) is attributed to low birth weight.

The Global Burden of Disease (GBD) study categorizes low birth weight, birth asphyxia, birth trauma and other conditions (such as neonatal sepsis, maternal and placental complications, respiratory distress, fetal blood loss, fetal haematological disorders, anaemia, perinatal infections and maternal diabetes) as "perinatal conditions", while deaths due to congenital anomalies, neonatal tetanus and syphilis are addressed separately (WHO 1992a). Among these conditions, low birth weight—specifically that due to IUGR—is the most strongly linked to undernutrition and is the only perinatal condition considered in our analysis.

Low birth weight is defined as birth weight below 2500 grams. It is a product of IUGR, preterm birth, or both in combination (Kramer 1987). In developing countries, the majority of low-birth-weight births are due to IUGR (usually defined as birth weight less than the tenth percentile of weight-for-gestational-age) whereas preterm birth (<37 weeks gestation) is the predominant cause in most developed countries (Ashworth 1998). Preterm low-birth-weight infants tend to have higher neonatal mortality rates than full-term, growth-retarded infants; at

highest risk are low-birth-weight infants who are both growth-retarded and preterm (Barros et al. 1992; Behrman et al. 1971; Cogswell and Yip 1995; Gray et al. 1991; Sappenfield et al. 1987).

The etiology of IUGR is complex and multifactorial. In developing countries maternal undernutrition is the major determinant of IUGR, and evidence across populations has demonstrated a greater incidence of IUGR births among women who are underweight or stunted prior to conceiving, or who fail to gain sufficient weight during pregnancy (Bakketeig et al. 1998; King and Weininger 1989; Kramer 1987; WHO 1997). Poor maternal nutrition during pregnancy is thought to account for 14% of IUGR in developing countries; maternal stunting may account for 18.5% (ACC/SCN 2000b). Malaria, other acute and chronic infections and cigarette smoking are also important etiologic factors for IUGR in developing countries. In developed countries, smoking is the most important determinant of IUGR, followed by factors such as maternal nutrition, pre-eclampsia, genetic factors and alcohol or drug use (Bakketeig et al. 1998). IUGR is also associated with multiple births and primiparity (Cogswell and Yip 1995).

Fetal growth retardation takes different forms, which may have different implications for neonatal and infant health. IUGR can be subdivided into asymmetric (wasted) IUGR, characterized by adequate length and head circumference, but reduced weight and low ponderal index; and symmetric (stunted) IUGR, in which the ponderal index is normal but weight, length and head circumference are all reduced (Bakketeig 1998). Symmetric IUGR generally reflects early onset or chronic undernutrition *in utero*, while asymmetric IUGR is thought to result from undernutrition of later onset (Ashworth 1998). The difference may be clinically important, as asymmetrically growth-retarded infants have demonstrated higher risks of asphyxia, hypoglycaemia and other morbidities, and higher mortality rates in the early neonatal period (Ashworth 1998; Caulfield et al. 1991; Villar et al. 1990). Stunted infants, on the other hand, have greater risks of mortality in later infancy (Ashworth 1998; Balcazar and Haas 1990; Cheung et al. 2001).

The evidence relating low maternal BMI to preterm birth is more ambiguous. A 1995 WHO meta-analysis based on data sets from 20 developed and developing countries calculated a combined OR of 1.3 (95% CI 1.1–1.4) for preterm birth associated with pre-pregnancy BMI $<20\,kg/m^2$ (WHO 1995b). Individual studies, however, have been inconsistent. In Papua New Guinea, BMI was found to be a significant predictor of preterm delivery; a one-unit increase in BMI was associated with a reduced risk of preterm delivery (OR=0.79, 95% CI 0.66–0.94), and remained significant after being adjusted for haemoglobin concentration, smoking, gravidity and anti-malarial use (Allen et al. 1998). A case–control study in India observed an increased risk of preterm birth with underweight status as well (Mavalankar et al. 1994). Other studies in Malawi (Pelletier et al. 1995) and Indonesia (Husaini et al. 1995)

reported little or no association between pre-pregnancy BMI and preterm delivery. In developed settings, studies from Canada (Kramer et al. 1995), Italy (Spinillo et al. 1998), the United Kingdom (Sebire et al. 2001) and the United States (Edwards et al. 1979; Naeye 1990; Siega-Riz et al. 1996) observed higher rates of preterm labour or delivery among underweight women, while other studies in Canada (Kramer et al. 1992), Finland (Rantakallio et al. 1995) and Sweden (Cnattingius et al. 1998) did not. Recently, in a study in the United States of America based on the National Maternal and Infant Health Survey found that underweight women had an increased risk for preterm delivery only when their pregnancy weight gain was inadequate (Schieve et al. 2000). Because of the uncertain risk relationship, low birth weight due to preterm birth was excluded from our analysis.

Although many studies conducted in developing countries examined the influence of maternal body size on infant birth weight and others compared neonatal mortality rates according to birth weight, few studies directly compared maternal weight to neonatal or perinatal mortality. These studies used postpartum weight as a proxy for pre-pregnant weight, and therefore, possible effects of pregnancy weight gain cannot be excluded. Among these, a slightly elevated risk of early neonatal death (adjusted OR=1.4, 95% CI 1.0–1.9) was associated with maternal weight below 50 kg in a nested case–control study in Brazil (Gray et al. 1991). The authors adjusted for low birth weight in one regression model to distinguish between risk factors that might operate in part through low birth weight and factors that might influence neonatal death independently. Low maternal weight remained significantly associated with neonatal death only when low birth weight was excluded from the model, suggesting maternal weight influences neonatal death through low birth weight.

In other studies, maternal weight <40 kg and low weight-to-height ratio were significantly associated with perinatal death in Ahmedabad, India (OR = 2.9, 95% CI 1.8–4.7 and OR=3.0, 95% 1.9–4.4, respectively), adjusted for maternal age, parity, obstetric history and antenatal care (Mavalankar et al. 1994). In the Sudan, maternal weight below 50 kg was significantly associated with perinatal death, after adjustment for birth interval, prior fetal loss and antenatal care, among other factors (adjusted OR=2.3, 95% CI 1.1–4.8) (Taha et al. 1994). In a community-based case–control study in Punjab, perinatal death was significantly associated with weight <40 kg and height <152 cm, but not BMI <20 kg/m^2, after controlling for factors such as birth interval and length of gestation (Sachar and Soni 2000).

In developed countries, there is a consistent association between maternal underweight status and low birth weight, but the evidence relating maternal underweight status to perinatal death has been mixed. In New York City, low BMI prior to pregnancy was associated with slightly, but not significantly, higher perinatal mortality rates in one hospital-

based study (Bracero and Byrne 1998). Another analysis using data from the USA Collaborative Perinatal Study reported reduced perinatal mortality for infants of underweight mothers; among mothers with low pregnancy weight gain (<0.8 kg/month), however, underweight status was associated with higher perinatal mortality (Naeye 1990). In Australia, the odds ratios for stillbirth/neonatal death (adjusted for gestational age, parity, smoking and maternal age) were 1.65 and 2.64 among women with low postpartum BMI (defined for postpartum women as 20–24.4 kg/m^2) and very low postpartum BMI (<20 kg/m^2), respectively (Cattanach et al. 1993). In Finland, perinatal and childhood mortality rates were similar between women having low and normal BMI (Rantakallio et al. 1995), and in Sweden low maternal BMI was associated with reduced risk of late fetal death and a slightly, but not significantly, reduced risk of early neonatal death relative to maternal BMI of 20–25 kg/m^2 (Cnattingius et al. 1998).

Such studies have generated uncertainty about the significance of low birth weight, *per se*, as an intermediate variable in the causal pathway between prenatal factors and perinatal mortality (Rush 2001; Wilcox 2001). As with other anthropometric indicators, birth weight is regarded as a proxy for underlying biological processes that must be inferred. All prenatal factors that influence birth weight may not affect infant health equally. For example, high altitude is associated with lower birth weight, but not necessarily higher mortality (Cogswell and Yip 1995; Wilcox 2001). Therefore, caution must be taken when generalizing across populations.

Estimate of mortality due to perinatal conditions

The relationship between maternal underweight status and neonatal mortality was estimated by considering two stages of the conceptual pathway mediated through IUGR. First, what is the proportion of IUGR attributable to poor maternal pre-pregnancy anthropometric status? And second, what proportion of neonatal mortality can be attributed to IUGR? There are four components to this equation: the proportion of IUGR births among live births in each subregion, an estimate of infant mortality risk associated with IUGR, subregional prevalence of underweight status among women of reproductive age and an estimate of the risk of IUGR associated with pre-pregnant underweight status.

By estimating the risk of IUGR in relation to pre-pregnancy BMI only, we are not considering the fraction of IUGR attributable to inadequate weight gain during pregnancy, and are potentially underestimating the overall influence of maternal weight on infant birth weight. Gains in pre-pregnancy and pregnancy weight have independent, additive effects on birth weight (Krasovec and Anderson 1991). Across diverse populations, low pregnancy weight gain, particularly in the second and third trimesters, has been associated with risk ratios of 1.7 to 2.0 for IUGR; among mothers who are below average height or weight before preg-

nancy, the risk ratios are 3.1 and 5.5, respectively (Strauss and Dietz 1999; WHO 1997). The prevalence data on pregnancy weight gain in developing countries is scarce, but there is evidence that poor weight gain is common, especially among women who have low pre-pregnancy BMI and must gain more to compensate. In rural Indonesia, for example, 79% of women in a cohort study failed to reach their recommended total weight gain, including 82.4% of the women with a pre-pregnancy BMI below 20 kg/m^2 (Winkvist et al. 2002).

Methods

The overall attributable fraction of neonatal mortality due to maternal underweight status was calculated as the product of the attributable fraction of neonatal mortality due to IUGR and the attributable fraction of IUGR due to maternal underweight status. Attributable fractions were calculated according to the formula $[(P)(RR-1)]/[1+(P)(RR-1)]$, where P is the prevalence of the risk factor and RR is the associated risk ratio. Prevalence and risk ratio estimates were derived from available published and unpublished sources.

Incidence of IUGR

Classification of IUGR in developing countries can be problematic because gestational age cannot be accurately determined in most cases, and reference curves that are adjusted for gestational age are not widely used (ACC/SCN 2000b). Therefore, the incidence of low birth weight at term (referred to as "term-LBW" or "IUGR-LBW") is used as the best proxy for IUGR incidence, although this will underestimate the actual incidence of IUGR because it excludes growth-retarded infants born preterm and those born over 2500 grams but below the tenth percentile for their gestational age (de Onis et al. 1998).

Incidence rates of IUGR-LBW for most developing countries were previously estimated by de Onis et al. (1998) using low birth weight estimates from the WHO database on Low Birth Weight, compiled by the Maternal Health and Safe Motherhood Programme (WHO 1992b). The authors applied a linear regression model $[Y=-3.2452+0.8528X]$ derived from numerous studies in developing countries where birth weight and valid gestational age assessments were recorded. The dependent variable in the model was IUGR-LBW and the independent variable was the total incidence rate of low birth weight ($\beta=0.8528$; SE $=0.0282$; $P=0.0001$; $r=0.96$) (de Onis et al. 1998; Villar et al. 1994). The linear regression model was found to be unsuitable as a predictor of IUGR-LBW in developed countries, however.

Incidence rates of IUGR-LBW in developed countries were based on Medline (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi), Popline (http://db.jhuccp.org/popinform/index.stm) and Google (http://www.google.com/) searches for country-level data sets and nationally-representative study samples that reported rates of IUGR-

LBW or sufficient statistical information (including numbers of births, mean birth weights and SDs or percentiles according to week of gestation) for calculating the rate of IUGR-LBW among total live births. The studies used in estimating rates were published between 1993 and 2001. The data reported in most studies were collected between 1992 and 2001, although in a few instances the data reflect populations from as early as 1984. In general, the reported data were limited to singleton births and excluded births having major congenital anomalies. Where data were unavailable—as was the case for the majority of European countries—the rate of IUGR-LBW was assumed for these purposes to be equivalent to the rate in AMR-A, or 2.5% of total live births (Kramer et al. 2001; Ventura et al. 1999). Estimates of small-for-gestational-age incidence were not appropriate for this analysis because they can include births weighing over 2500 grams. The estimated incidence rate of IUGR-LBW for each country was multiplied by the estimated total number of live births in that country for the year 2000; the country estimates were then collapsed into the 14 subregions in order to calculate subregional rates (Table 2.22). Estimates of live births per year for each country were taken from the United Nations Population Division (UN 2001).

IUGR and risk of neonatal mortality

Rice et al. (unpublished) calculated the risk of neonatal mortality associated with IUGR-LBW in an initial review and meta-analysis of the rela-

Table 2.22 Incidence of IUGR-LBW, by subregion

Subregion	*Total live births per year (000s)*	*IUGR-LBW births as percentage of total live births*	*Estimated number of IUGR-LBW births per year (000s)*
AFR-D	11 185	10.5	1 176
AFR-E	13 240	9.3	1 229
AMR-A	4 426	2.5	112
AMR-B	9 303	6.7	621
AMR-D	2 011	6.6	133
EMR-B	3 410	4.1	141
EMR-D	12 003	12.1	1 455
EUR-A	4 233	2.5	107
EUR-B	3 743	2.6	96
EUR-C	2 527	2.5	63
SEAR-B	5 933	4.2	250
SEAR-D	42 147	22.7	6 866
WPR-A	358	2.3	8
WPR-B	26 840	2.9	769
World	129 493	10.1	13 027

tionship between malnutrition and cause-specific mortality. The authors conducted a Medline search for English-language research reports published between 1966 and 1999 on child mortality, nutritional status, low birth weight, perinatal causes of death and neonatal mortality, excluding studies conducted in developed countries. They selected community and hospital-based studies that reported sufficient statistical and follow-up data on infants who were low birth weight at term, excluding data on very low birth weight (<1000 g) infants. Follow-up times and cut-off points varied among the studies as summarized in Table 2.23. Unadjusted data from studies were combined according to the random-effects method described by Morris (Everson and Morris 1983; Morris 1983). The combined risk estimate from all studies was 5.53 (3.74–8.17) and the risk estimate from the subset of studies using a 2500 g cut-off was 6.00 (3.63–9.90). Because the overall combined estimate of 5.53 was heavily weighted toward studies with short post-natal follow-up periods and higher birth weight cut-off points, we selected the 6.00 risk estimate for our calculations.

An elevated mortality risk has been observed among IUGR-LBW infants in developed countries, as well. Ashworth (1998) estimated the risk of neonatal mortality according to birth weight, combining 10 data sets from developing and developed countries (predominantly weighted toward births in the United States) and excluding most preterm births. Individual studies showed a consistent dose–response effect of increasing mortality risk with decreasing birth weight. Compared to birth weight of 2500–2999 g, the overall relative risk associated with birth weight between 2000 g and 2499 g was 4.0 and the risk associated with birth weight 1500–1999 g was 18.0. An overall dichotomous risk estimate comparing birth weight <2500 g to >2500 g was not reported, but after pooling published data from four (Behrman et al. 1971; Binkin et al. 1985; Lubchenco et al. 1972; Sappenfield et al. 1987) of six United States studies included in the estimate, the combined risk for neonatal mortality associated with birth weight <2500 g at term was 10.64 (95% CI 9.94–11.38). This crude estimate is based on mostly white, singleton births between 38 and 42 weeks gestation and excludes births below 1000 g.

Prevalence of low maternal BMI

Refer to section 3: prevalence of underweight among women of reproductive age.

Maternal pre-pregnancy BMI and risk of IUGR

In 1995, WHO published a meta-analysis based on data sets from 25 studies that related maternal anthropometry to pregnancy outcomes (WHO 1995b). These sets represented over 111 000 births in 20 developing and developed countries throughout the world. Countries were grouped together for analysis according to similarities in the population

Table 2.23 Risk of neonatal (≤28 days) or early neonatal (≤7 days) death among term infants according to birth weight[a]

Location	*Study*	*Study type*	*Neonatal period studied*	*Sample size*	*Birth weight comparison*	*Crude relative risk (95% CI)*
Bolivia	Haas et al. (1987)	Retrospective cohort	≤2 days	12 280	<2900 g vs ≥2900 g	3.63 (1.93–6.82)
Brazil	Barros et al. (1987)	Prospective cohort	≤7 days	5 356	<2500 g vs ≥2500 g	6.28 (2.57–15.33)
Brazil	de Almeida and Jorge (1998)	Retrospective cohort	≤28 days	2 014	<10th percentile vs ≥10th percentile	10.61 (3.34–33.72)
Guatemala	Mata (1978)	Community-based cohort	≤28 days	385	<2500 g vs ≥2500 g	3.41 (0.63–18.40)
India	Arora et al. (1987)	Prospective cohort	≤28 days	200	<10th percentile vs ≥10th percentile	3.03 (0.32–28.64)
India	Bhargava et al. (1985)	Prospective cohort	≤7 days	13 806	<–2 SDs vs ≥–2 SDs[b]	11.08 (7.34–16.73)
India	Ghosh et al. (1979)	Community-based cohort	≤28 days	3 650	≤2500 g vs >2500 g	6.25 (3.14–12.42)
Mexico	Balcazar and Haas (1991)	Retrospective cohort	≤3 days	8 526	<10th percentile vs ≥10th percentile	5.35 (2.69–10.65)
Mexico	Haas et al. (1987)	Retrospective cohort	≤2 days	9 228	<2900 g vs ≥2900 g	2.13 (1.12–4.06)
Combined estimate (all studies)						5.53 (3.74–8.17)
Combined estimate (Barros et al. 1987; Mata et al. 1978; Ghosh et al. 1979)						6.00 (3.63–9.90)

[a] Table adapted from Rice et al. (unpublished).

[b] SD according to North Indian reference.

Table 2.24 Analysis groups used by WHO Collaborative Study on Maternal Anthropometry and Pregnancy Outcomes

Group	*Countries/data sets included in group*	*25th quartile cut-off (BMI)*	*75th quartile cut-off (BMI)*
1	India (Pune), Sri Lanka	17.3	20.1
2	China, Gambia, India (Hyderabad), Indonesia, Myanmar, Nepal (Rural), Viet Nam	18.4	21.0
3	Guatemala, Malawi, Thailand	19.4	22.7
4	Argentina, Cuba, United Kingdom, USA	20.1	25.0
5	Colombia, Ireland, USA	21.0	26.7

Source: WHO 1995a.

Table 2.25 Odds ratio for IUGR according to pre-pregnancy BMI

Group	*BMI cut-off*	*BMI referent*	*OR for IUGR (95% CI)*
1	≤17.3	≥20.1	0.7 (0.1–2.6)
2	≤18.4	≥21.0	1.8 (1.5–2.3)
3	≤19.4	≥22.7	1.8 (1.3–2.5)
4	≤20.1	≥25.0	2.0 (1.8–2.2)
5	≤21.0	≥26.7	1.5 (1.3–1.7)
Combined	≤19.7[a]	≥24.2[a]	1.8 (1.7–2.0)

[a] Combined BMI cut-offs were not reported. Values here are the weighted means of the 25th and 75th quartile values from each data set.

Source: WHO 1995a.

distributions for various anthropometric indicators, including pre-pregnancy weight, height, BMI and arm circumference. Table 2.24 describes the composition of analysis groups and the corresponding BMI cut-offs. Unadjusted odds ratios for pregnancy outcomes were then calculated by comparing the lowest quartile to the highest quartile within each analysis group.

Results are presented in Table 2.25. The meta-analysis reported significantly greater risk for IUGR associated with pre-pregnancy BMI below 19.7 kg/m^2 relative to BMI above 24.2 kg/m^2, with an overall OR of 1.8 (95% CI 1.7–2.0). This estimate was consistent across the analysis groups (with the exception of group one studies) despite the differences in their cut-off and reference points.

Results

Subregional estimates of the attributable fraction of IUGR due to low pre-pregnancy BMI are listed in Table 2.26 for women aged 15–29 and

Table 2.26 Attributable fraction of IUGR due to low BMI among women aged 15–44 years, by subregion

	Prevalence of BMI ≤20 kg/m² (%)		*Fraction of IUGR attributable to BMI ≤20 kg/m² (%)*	
Subregion	*15–29 years*	*30–44 years*	*15–29 years*	*30–44 years*
AFR-D	43.3	29.5	25.7	19.1
AFR-E	37.8	27.4	23.2	18.0
AMR-A	25.1	19.5	16.7	13.5
AMR-B	22.7	11.1	15.4	8.2
AMR-D	11.7	9.3	8.6	6.9
EMR-B	28.4	12.7	18.5	9.2
EMR-D	40.1	32.6	24.3	20.7
EUR-A	20.9	13.8	14.3	9.9
EUR-B	24.5	14.0	16.4	10.1
EUR-C	24.5	9.7	16.4	7.2
SEAR-B	44.4	12.1	26.2	8.8
SEAR-D	56.7	42.1	31.2	25.2
WPR-A	40.9	27.1	24.7	17.8
WPR-B	32.6	24.8	20.7	16.6

30–44 years based on the prevalence of low BMI and the risk ratio of 1.8 reported by the WHO meta-analysis. Table 2.27 lists the attributable fraction of neonatal deaths due to IUGR-LBW for each subregion based on the prevalence of IUGR-LBW and the risk ratio of 6.0 calculated by Rice et al. (unpublished). The results of both tables are summarized in Table 2.28 with the overall attributable fraction of neonatal deaths due to low pre-pregnancy BMI. The fraction of neonatal deaths attributed to maternal BMI ranged between 0.8% (women aged 30–44 years in EUR-C) and 16.6% (women aged 15–29 years in SEAR-D).

4.4 Other health outcomes

Other important health outcomes related to underweight status were reviewed, but ultimately not used for burden of disease estimates. The adverse effects of undernutrition on risk of dysentery and persistent diarrhoea, pregnancy outcome, cognitive function and chronic diseases in later life are described below.

Dysentery and persistent diarrhoea

Dysentery, defined by diarrhoea with blood, was specifically examined in two community-based prospective studies, both among children aged <24 months in Bangladesh. Henry et al. (1987) observed no significant difference in incidence of dysentery between children having weight-for-

Table 2.27 Attributable fraction of neonatal mortality due to IUGR-LBW, by subregion

Subregion	*Incidence of IUGR-LBW (% of total live births per year)*	*Attributable fraction of neonatal deaths due to IUGR-LBW (%)*
AFR-D	10.5	34.4
AFR-E	9.3	31.7
AMR-A	2.5	11.1
AMR-B	6.7	25.1
AMR-D	6.6	24.8
EMR-B	4.1	17.0
EMR-D	12.1	37.7
EUR-A	2.5	11.1
EUR-B	2.6	11.5
EUR-C	2.5	11.1
SEAR-B	4.2	17.4
SEAR-D	22.7	53.2
WPR-A	2.3	10.3
WPR-B	2.9	12.7

Table 2.28 Attributable fraction of neonatal mortality due to low maternal BMI, by subregion

	Attributable fraction of IUGR due to BMI ≤20 kg/m^2 (%)		*Attributable fraction of neonatal deaths due to IUGR (%)*	*Attributable fraction of neonatal deaths due to low BMI (%)*	
Subregion	*15–29 years*	*30–44 years*		*15–29 years*	*30–44 years*
AFR-D	25.7	19.1	34.4	8.9	6.6
AFR-E	23.2	18.0	31.7	7.4	5.7
AMR-A	16.7	13.5	11.1	1.9	1.5
AMR-B	15.4	8.2	25.1	3.9	2.1
AMR-D	8.6	6.9	24.8	2.1	1.7
EMR-B	18.5	9.2	17.0	3.2	1.6
EMR-D	24.3	20.7	37.7	9.2	7.8
EUR-A	14.3	9.9	11.1	1.6	1.1
EUR-B	16.4	10.1	11.5	1.9	1.2
EUR-C	16.4	7.2	11.1	1.8	0.8
SEAR-B	26.2	8.8	17.4	4.6	1.5
SEAR-D	31.2	25.2	53.2	16.6	13.4
WPR-A	24.7	17.8	10.3	2.5	1.8
WPR-B	20.7	16.6	12.7	2.6	2.1

age <75% and those above 75%. Black et al. (1984) found that incidence of *Shigella* diarrhoea, specifically, did not vary significantly according to weight-for-age.

The incidence of persistent diarrhoea, defined as an episode lasting 14 or more days, was greater among underweight children in community-based studies in Brazil (Guerrant et al. 1992; Schorling et al. 1990), India (Bhandari et al. 1989) and Bangladesh (Baqui 1990). Children aged <5 years having weight-for-age at or below 75% in the Brazil cohort study were at a relative risk of 1.59 for persistent diarrhoea. In Bangladesh, the relative risk for persistent diarrhoea among children having *z*-score <–2 was 1.29. Combining unadjusted figures from the two cohort studies yielded an overall relative risk of 1.35 (95% CI 0.97–1.90). In a case–control study in India, pre-morbid weight-for-age below 70% was significantly more common among persistent diarrhoea cases compared to healthy age-matched controls, producing an OR of 3.25 (95% CI 1.46–7.29). A community-based cohort study in Guinea-Bissau (Molbak et al. 1997) assessed risk according to stature and observed a statistically non-significant relative risk of 1.17 (95% CI 0.68–2.01) associated with height-for-age *z*-score <–2.

Other pregnancy outcomes

There is extensive literature supporting the influence of maternal undernutrition on fetal growth and risk of low birth weight as described in previous sections, but the relationship between low pre-pregnancy BMI and other adverse reproductive outcomes such as fetal death and maternal mortality is less clear. Research on maternal undernutrition as a risk factor for congenital anomalies, other than those attributable to micronutrient deficiencies (e.g. folic acid) is lacking.

Obstructed labour and maternal mortality

Few studies from developing countries have been published relating low BMI to maternal mortality, although studies have described an increased risk of obstructed or prolonged labour associated with maternal height of 160 cm and below (Adadevoh et al. 1989; Anonymous 1984; Bhatt et al. 1967; Essex and Everett 1977; Konje and Ladipo 2000; Kwawukume et al. 1993; Mati 1983; Sokal et al. 1991; Tsu 1992), and one study in India reported an increased risk of caesarean section associated with low weight–height product index (weight times height over weight times height of reference population median) (Thilothammal et al. 1992). This risk may result from cephalopelvic disproportion (CPD) between mother and fetus (Rush 2000), increasing the likelihood of intrapartum caesarean delivery (Adadevoh et al. 1989; Merchant et al. 2001; Sokal et al. 1991; Tsu 1992) and perinatal distress (Merchant et al. 2001). In Nigeria, primigravida women below 150 cm were at a relative risk of 10.34 for CPD relative to women 160 cm or taller (Harrison et al. 1985). In Malawi, the odds ratio for CPD associated

Table 2.29 Study of early fetal death (<28 weeks)

Study	*Location*	*Study type*	*Comparison*	*Crude risk estimate (95% CI)*	*Adjusted risk estimate (95% CI)*
Agarwal et al. (1998)	India	Community-based cohort	Weight <42.5 kg vs >42.5 kg	RR = 1.21 (1.05–1.38)	—
Same as above	Same as above	Same as above	Height <147.5 cm vs >147.5 cm	RR = 1.21 (1.06–1.38)	—

— No data.

with height at or below 154 cm was 3.8, adjusted for birth weight and parity (Brabin et al. 2002).

The 1995 WHO meta-analysis examined assisted delivery, defined as non-spontaneous delivery covering a range of complications (but not prolonged labour), and estimated an odds ratio between 1.0 and 2.1 (1.6, overall) associated with maternal height below the 25th percentile (WHO 1995b). The odds ratio for assisted delivery according to pre-pregnancy BMI was 0.7, explained as the result of constrained fetal growth reducing the risk of CPD; however, numerous studies have found that an association between maternal anthropometric status and assisted delivery remains after adjusting for multiple parameters of fetal size (Witter et al. 1995).

Fetal death

Fetal death may be more common among underweight mothers (Tables 2.29 and 2.30). A community-based cohort study in India reported significant risks of spontaneous abortion (defined in the study as death <28 weeks' gestation) and late fetal death (>28 weeks) associated with both short stature and low absolute weight (Agarwal et al. 1998). A case–control study in the Sudan reported an adjusted odds ratio for stillbirth of 2.3 associated with absolute weight below 50 kg (Taha et al. 1994). On the other hand, Conde-Agudelo et al. (2000) analysed over 800 000 births recorded in the Perinatal Information System database, a system used by over 700 hospitals throughout Latin American and the Caribbean, and found no significant risk of fetal death associated with BMI <19.8 kg/m^2 relative to BMI between 19.8 and 26.0 kg/m^2.

Post-neonatal consequences of IUGR

Growth-retarded neonates may experience partial catch-up growth in the first two years of life relative to non-IUGR controls, but they remain shorter and lighter than controls and are more likely to be classified as underweight (Martorell et al. 1998). They are at increased risk of infection in infancy as a result of multiple immunological abnormalities, including reduced T- and B-lymphocyte numbers and activity, lower

Table 2.30 Studies of stillbirth

Study	*Location*	*Study type*	*Comparison*	*Crude risk estimate (95% CI)*	*Adjusted risk estimate (95% CI)*
Agarwal et al. (1998)	India	Community-based cohort	Weight <45 kg vs >45 kg	RR = 5.07 (2.94–8.73)	—
Same as above	Same as above	Same as above	Height <147.5 cm vs >147.5 cm	RR = 4.18 (2.88–6.05)	—
Taha et al. (1994)	Sudan	Facility-based case–control	Weight <50 kg vs ≥70 kg	OR = 2.0 (1.0–4.1)	OR = 2.3 (1.1–4.8)[a]
Conde-Agudelo et al. (2000)	Latin America, Caribbean	Facility-based cohort	BMI <19.8 kg/m^2 vs 19.8–26.0 kg/m^2	—	RR = 0.98 (0.88–1.08)[b]

— No data.

[a] OR adjusted for prior fetal loss, number of antenatal care visits and malaria in early pregnancy. Several socioeconomic status indicators were assessed, but none was significantly associated with stillbirth and therefore were not included in the final regression model.

[b] Relative risk adjusted for antenatal care, age, literacy, cigarette smoking and prior fetal loss. Study addressed fetal death, defined as death >20 weeks' gestation.

levels of IgG and impaired bactericidal polymorphonuclear neutrophil function (Ferro-Luzzi et al. 1998; Xanthou 1985). Depending on the severity of the growth retardation, this immune deficiency may persist into later childhood (Chandra 1977). In addition to higher neonatal mortality rates, IUGR infants are at increased risk of mortality in the post-neonatal period, including an increased risk of sudden infant death syndrome (Ferro-Luzzi et al. 1998).

IUGR may increase the risk of neurological dysfunction and mild cognitive impairment. IUGR infants show higher rates of hyperactivity, attention deficit and impaired motor coordination, depending on the degree of growth retardation, but the association of IUGR with low socioeconomic status and hypoxia makes it difficult to interpret the impact of IUGR (Goldenberg et al. 1998). Similarly, IUGR children have manifested small, but statistically significant IQ and developmental deficits, aggravated by impoverished environmental surroundings and poor psychosocial stimulation, but few studies have been conducted in developing countries, and socioeconomic factors may be confounding the relationship (Grantham-McGregor et al. 1998).

IUGR has been associated with increased susceptibility to chronic diseases in later life. The "fetal origins of disease" hypothesis posits that fetal undernutrition causes permanent structural and metabolic changes that potentiate subsequent risk of cardiovascular and endocrine disease (Barker 1995). IUGR infants have demonstrated insulin resistance and

higher blood pressure in childhood, and increased rates of ischaemic heart disease and non-insulin-dependent diabetes mellitus have been observed among adults who were born growth-retarded (Barker 1995; Chatelain et al. 1998; Law et al. 2001; Stein et al. 1996). Studies are inconsistent and causality is uncertain, but the possible risk relationship has important health implications for developing countries as they undergo epidemiological transition.

Cognitive function

Cognitive function has been studied in terms of global measures of development and intelligence such as IQ, along with school performance and more narrowly defined intellectual, psychomotor, and behavioural skills such as attention, memory, verbal reasoning, motivation, visual–spatial abilities and social interaction. An array of psychometric tests and scales have been used to evaluate these functions, including modified versions of Stanford-Binet, Weschler Intelligence Scale for Children (WISC), Bayley Scales of Infant Development, Griffiths Mental Development Scale, Goodenough Drawing Test, Raven's Progressive Matrices, Piagetian tests of conservation and the Bender Visual Motor Gestalt Test. A major portion of research into malnutrition and cognition has addressed whether early childhood presents a critical period of vulnerability during which severe undernutrition causes lasting cognitive deficits in later life, and if potential deficits are amenable to subsequent nutritional and psychosocial interventions.

The immediate response to acute malnutrition is irritability, lethargy and apathy (Grantham-McGregor 1984). During this stage, children demonstrate lower activity levels and reduced exploratory behaviour and developmental quotients tend to be extremely low (Grantham-McGregor 1984). Electroencephalograms performed on children with acute malnutrition show nonspecific abnormalities (e.g. diffuse slowing of background rhythm) that improve with recovery (Chopra and Sharma 1992). During recovery and rehabilitation, behaviour improves to normal or near-normal levels and developmental quotients generally improve, but the long-term developmental implications remain uncertain (Grantham-McGregor 1995).

Numerous short-term and long-term follow-up studies have reported lasting developmental deficits associated with an early history of marasmus and/or kwashiorkor. Persistent deficits have been described in short-term memory (Nwuga 1977), visual-spatial perception (Champakam et al. 1968; Cravioto et al. 1971; Ghai 1975; Hoorweg and Stanfield 1976; Reyes et al. 1990; Stoch and Smythe 1976), motivation (Stoch and Smythe 1967), Piagetian conservation tasks (Galler and Ramsey 1987) and perceptual-motor function (Grantham-McGregor et al. 1997). Poor academic performance and behavioural learning disabilities have also been recognized (Galler et al. 1984, 1990; Richardson et al. 1973).

Studies that assessed general measures of cognitive function among school-age children have observed significantly lower overall developmental and intelligence scores associated with early malnutrition (Berkman et al. 2002; Bhat et al. 1973; Birch et al. 1971; Botha-Antoun et al. 1968; Cabak and Najdanvic 1965; Cravioto et al. 1971; Fisher 1972; Galler et al. 1983, 1987a, 1987b; Hertzig et al. 1972; Ivanovic et al. 2000; McLaren et al. 1973; Mehta et al. 1975; Mendez and Adair 1999; Parekh et al. 1974; Pek et al. 1967; Sigman et al. 1991; Srikantia and Sastri 1971; Stoch and Smythe 1967, 1976; Udani et al. 1976). IQ differentials among these studies were predominantly in the order of 8 to 18 points. Studies in South Africa (Evans et al. 1971, 1980), however, observed no significant IQ difference between early kwashiorkor cases and non-hospitalized siblings. In Jamaica, Richardson et al. (1978) observed that height-for-age or weight-for-height among severely malnourished infants had no significant effect on IQ scores at school age after adjusting for social and environmental factors.

Among most of the studies showing long-term deficits, it could not be distinguished whether the observed impairment was related to the severe episode of acute malnutrition or to underlying or subsequent chronic undernutrition. In Jamaica, Grantham-McGregor (1982) reported that initial height-for-age, but not weight-for-height or presence of oedema, significantly predicted developmental quotients one month after hospitalization, suggesting the presence of chronic malnutrition was more closely associated with cognitive function than acute malnutrition (Grantham-McGregor 1982; Grantham-McGregor et al. 1989a, 1989b). In a long-term longitudinal study by Walker et al. (2000) height and head circumference in the first 24 months of life were found to be more significantly predictive of IQ at age 11 years than were anthropometric measurements taken at or near the time of cognitive testing, even after controlling for age, sex and socioeconomic factors, suggesting chronic malnutrition at an early age could have enduring effects on intelligence despite subsequent improvements in growth (Grantham-McGregor et al. 2000). In Peru, school-age children who were severely stunted in the second year of life scored 10.0 points lower than those moderately stunted or not stunted in the second year of life, after adjusting for socioeconomic status and schooling (Berkman et al. 2002). In the Philippines, severe stunting at 2 years of age was significantly associated with cognitive deficits at age 8 years, adjusting for schooling, socioeconomic status, sex and other covariates, but the differences were not significant by age 11 years (Mendez and Adair 1999). In Jamaica, Richardson (1976), observed that the long-term cognitive effect of early acute malnutrition was more heavily determined by chronic undernutrition and social background factors such as caretaker capability, presence of electricity and appliances, and child's access to toys, radio or stories. For the children having adequate growth and an advantageous social back-

ground, malnutrition during infancy was associated with an average IQ only 2 points lower than those not malnourished during infancy; for those experiencing both an unfavourable background and inadequate growth, the difference in IQ between children with and without malnutrition during infancy was 9 points by age 6–10 years (Richardson 1976).

A large number of correlational studies have examined the association between current anthropometric status and cognitive function. Low height-for-age was significantly associated with low IQ or poor school achievement in Brazil (Paine et al. 1992), China (Jamison 1977), Guatemala (Johnston et al. 1987), India (Agarwal et al. 1987), Nepal (Moock and Leslie 1986) and the Philippines (Florencio 1988), but not Chile (Colombo et al. 1988). Deficits in other developmental scores were observed among stunted children in Chile (Monckeberg 1972), Guatemala (Lasky et al. 1981), India (Agarwal et al. 1989), Jamaica (Powell and Grantham-McGregor 1985) and Nigeria (Ashem and Janes 1978). Low weight-for-age has been associated with delayed motor development (Agarwal et al. 1992; Groos 1991; Heywood et al. 1991; Sathy et al. 1991; Vazir et al. 1998), delayed language development (Agarwal et al. 1992; Vazir et al. 1998) and poor performance on conservation tasks (Agarwal et al. 1989). Lower scores on aggregate measures such as IQ have been observed among underweight children in Ethiopia (Aboud and Alemu 1995), India (Agarwal et al. 1992; Gupta et al. 1975; Kalra et al. 1980; Lahiri et al. 1994; Sathy et al. 1991; Singh and Sidhu 1987; Upadhyay et al. 1989), Indonesia (Pek 1967), Kenya (Sigman et al. 1989) and Thailand (Rajatasilpin et al. 1970), with evidence of progressively increasing cognitive impairment associated with decreasing weight-for-age (Agarwal et al. 1992; Kalra et al. 1980; Lahiri et al. 1994; Sathy et al. 1991; Singh et al. 1976; Upadhyay et al. 1989). The differences in mean IQ between normal and underweight children in these correlational studies ranged between 7 and 31 points.

Among the more recent of these studies to report IQ, Agarwal et al. (1992) found Indian children aged 36 months with weight-for-age below 70% had a mean IQ approximately 8.7 points lower than adequately nourished children with weight-for-age of 80% or above; the relative risk for IQ below 80 points associated with underweight status (weight-for-age <80%) was 2.33 (95% CI 1.46–3.74). Upadhyay et al. (1989) reported a difference of 7.2 points between children below 75% and those above 90%. Lahiri et al. (1994) observed a significant trend toward lower IQ scores with decreasing weight-for-age (chi-square = 6.78, $P < 0.05$) among children aged 3–6 years from low socioeconomic levels in rural India, but the effect was not statistically significant when adjusted for age and educational exposure.

Neuroanatomical changes observed in animal models of PEM offer a theoretical foundation for the possibility that severe early malnutrition, particularly during the period of rapid brain growth and myelination in the first two years of life, presents a permanent structural insult to

brain function, leading to irreversible intellectual impairment (Strupp and Levitsky 1995). PEM has also generated abnormalities in neurotransmitter activity and receptor number (Levitsky and Strupp 1995). However, it is widely held now that neurobiological changes, on their own, are not sufficient to explain the complicated, multifactorial relationship between undernutrition and cognition, particularly among mild-to-moderately undernourished cases (Pollitt 1987). Increasing attention has been paid to environment, social context and experiential factors as potential modifiers or confounders of the nutrition–cognition relationship. Lack of energy, impaired psychomotor function and poor social interaction may prevent a child from exploring her surroundings as fully as other children, leading to less stimulation and slower acquisition of skills (Grantham-McGregor et al. 1989a, 1989b). The poverty associated with malnutrition is an environment of scarce resources, overcrowding, poor sanitation, illiteracy, few adequate educational opportunities and high morbidity, lacking in constructive forms of cognitive stimulation. Households tend to have few toys or books, social contacts are limited, and parents may offer less care and attention because of poor health, low income, low intelligence and education levels or large family sizes (Grantham-McGregor 1995). Returning to such an environment following severe malnutrition in infancy, for example, may explain persisting cognitive deficits observed in follow-up studies of infant malnutrition. Saco-Pollitt et al. (1985) offered a *cumulative deficit hypothesis* that suggests cognitive deficits increase as children are continuously exposed to environments that fail to meet their physiological, emotional and educational requirements (Pollitt 1987). Experimental studies have utilized interventions based on some of these neurobiological and psychosocial concepts.

Intervention studies to prevent or remedy impairments have focused on two general types of treatment: nutritional supplements provided to very young children and, in some cases, pregnant women; and psychosocial stimulation with or without nutritional supplementation provided to very young children. Evidence from nutritional interventions among high-risk or undernourished children has suggested early (<2 years of age) supplementary feeding improves their developmental scores, with some indication of long-term benefits. Short-term (90 days) and long-term (2–3 years) supplementation programmes in Colombia (Waber et al. 1981), Guatemala (Pollitt et al. 1993), Indonesia (Hussaini et al. 1991) and Jamaica (Grantham-McGregor et al. 1991) have improved motor development among infants. Concurrent improvements in other developmental outcomes have been less consistent, but Waber et al. (1981) in Colombia observed significantly higher scores in personal–social, speech and language, and performance subscales in addition to locomotor and eye–hand coordination subscales among infants supplemented until 3 years of age. Long-term follow-up identified improvements in certain achievement-related abilities, but not basic cog-

nitive skills by 6 years of age (Gorman et al. 1995). In India, Elizabeth and Sathy (1997) reported larger gains in developmental quotient and higher overall IQ (+2.6 points) among malnourished infants by the end of a two-year nutritional management and supplementation intervention. In Guatemala, children exposed to prenatal and early postnatal supplementation demonstrated long-term cognitive benefits, performing significantly better at ages 13–19 years on general intelligence tests and achievement-related subtests of numeracy, general knowledge, reading and vocabulary, even after adjusting for socioeconomic factors and educational experience; some information-processing tasks showed improvement as well (Pollitt et al. 1995). In Indonesia, infants who began 90 days of supplementation before 18 weeks of age demonstrated a positive effect on memory skills at 8 years of age, but differences in other cognitive processes were not significant (Pollitt et al. 1997).

Intervention programmes based on early psychosocial stimulation have improved developmental scores among moderately to severely malnourished infants and preschool-age children. Various studies have employed educational day care programmes (McKay et al. 1978), clinic-based therapy and education (Elizabeth and Sathy 1997) and weekly home visits with mothers and infants (Grantham-McGregor et al. 1994; Waber et al. 1981). In Jamaica, demonstrating play techniques to mothers and severely malnourished infants at home over three years was associated with both immediate and long-term improvements in global intelligence and development scores relative to a non-intervened control group (Grantham-McGregor et al. 1994). At 14 years follow up, mean scores on WISC for the intervened group were 8.6 points higher than the non-intervened group, but both intervened and non-intervened groups still performed significantly worse than an adequately nourished, generally higher socioeconomic status control group (9.7 and 18.3 IQ points below, respectively). Similar results were observed in a facility-based study in India among malnourished infants provided nutritional management with or without cognitive stimulation (Elizabeth and Sathy 1997). At the end of two years, both interventions were associated with significant improvements in developmental quotients, with the final IQ of stimulated infants 8.3 points higher than those receiving nutritional management alone, but both treatment groups ultimately performed below an adequately nourished/higher mean socioeconomic status control group by 5.4 to 13.7 IQ points. In a community-based component of the study, stimulated infants achieved IQ scores 6.5 points higher than an untreated, comparable control group and 3.8 points higher than infants receiving nutritional management alone; it is too early to know long-term effects in this case.

In Colombia, McKay et al. (1978) assigned underweight children aged 3 years to varying durations of an integrated health, nutrition and education programme and found that earlier initiation and longer duration of intervention were associated with higher general cognitive scores.

However, by school age, the intervened groups continued to score below an adequately nourished, higher socioeconomic status control group, and the absence of a comparable malnourished/low socioeconomic status control group made the absolute effect of the intervention unclear. Waber et al. (1981) evaluated cognitive development of nutritionally at-risk Colombian infants according to their exposure to prenatal and postnatal nutritional supplementation and a maternal-and-child educational programme. Nutritional supplementation was associated with higher scores on tests of primarily motor skills, and maternal–child education was associated with better language performance.

In a randomized controlled trial among stunted infants in Jamaica, Grantham-McGregor et al. (1991, 1997) assessed the immediate and long-term developmental effects of nutritional supplementation with or without psychosocial stimulation. By the end of the two-year intervention, supplementation and stimulation each had a significant benefit on developmental quotients (by 7 and 8 points, respectively), with the combination of treatments having an additive effect. Follow-up at ages 7–8 years (Grantham-McGregor et al. 1997) and 11–12 years (Walker et al. 2000), indicated persistent benefits in overall IQ, vocabulary and reasoning ability associated with the early psychosocial stimulation, but less of an effect from nutritional supplementation. Supplementation alone was associated with a benefit of 4.2 IQ points (not statistically significant), stimulation alone was associated with 6.3 points, and both treatments combined were associated with 6.1 points relative to a control group of untreated, stunted children; all three groups performed below a non-stunted, untreated control group.

Unfortunately, few studies (and no individually randomized controlled trials) assessed the cognitive benefit of sustained nutritional supplementation among school-age children in developing countries. In Guatemala, a year of supplementation had no consistent effect on children aged 5–7 years (Pollitt et al. 1993). A two-year school-based supplementation programme in India observed marginal but significant effects on IQ scores and Piagetian tasks, but treatment-related differences in school attendance may have influenced the results (Agarwal et al. 1989). Several studies have examined the short-term effects of breakfast programmes (Chandler et al. 1995) or breakfast omission (Lopez et al. 1993; Simeon and Grantham-McGregor 1989) on cognitive performance among schoolchildren. In Jamaica, controlled breakfast omission was associated with impaired performances in short-term memory, idea generation and problem-solving ability among stunted or previously malnourished children, but not among adequately nourished children (Simeon and Grantham-McGregor 1989). A subsequent randomized controlled trial found that only the undernourished children responded to breakfast supplementation, showing improvement in idea generation capacity but not memory or problem-solving skills (Chandler et al. 1995). In Chile, controlled breakfast omission had no significant effect on short-term visual

memory, problem-solving capacity, or attention, regardless of pre-existing nutritional status (Lopez et al. 1993).

As with other health outcomes, the close relationship between poverty and malnutrition raises the possibility of confounding. While many of the correlational and matched case–control studies attempted to control or adjust for potential socioeconomic and environmental differences, those variables were frequently defined in broad terms and may have overlooked subtler, as-yet-unidentified, non-nutritional determinants of cognitive function. Educational status could have played a role in some findings, as well; for example, initial school enrolment may be delayed among stunted children because they appear or act younger than their chronological age (Brown and Pollitt 1996). Undernutrition could influence cognition indirectly through higher morbidity; illness could reduce activity and social interaction, or contribute to higher school absentee and drop-out rates (Mendez and Adair 1999; Neumann et al. 1991; Pollitt 1983).

Another important consideration in estimating the effect of low weight-for-age on cognitive function is possible confounding by deficiencies of iron and other micronutrients (Pollitt 1995). Iron deficiency has been associated with developmental delays (Lozoff et al. 1991; Soewondo et al. 1989; Walter 1993) and iron supplementation studies have demonstrated improvements in cognitive function among iron-deficient subjects (Pollitt 1995; Pollitt and Metallinos-Katsaras 1990; Seshadri and Gopaldas 1989). Further, studies of iron deficiency and growth have observed significant covariance between the two (Peragallo-Guarda 1984; Pollitt 1995), with evidence that iron supplementation improves both growth velocity (Chwang et al. 1988) and weight (Lawless et al. 1994) among anaemic children. Zinc deficiency may also play a role in cognitive ability (Golub et al. 1995). Several intervention studies described above (Elizabeth and Sathy 1997; Husaini et al. 1991; McKay et al. 1978; Waber et al. 1981) provided micronutrient-rich indigenous foods or supplements between experimental groups differentially and most observational studies did not control for other nutritional factors.

4.5 Risk reversibility

Risk reversibility refers to the extent to which an increased relative risk persists among a previously exposed group after that exposure is removed. There has been some investigation of the lasting effect of fetal malnutrition on immune function of children and adults in Africa (Moore et al. 1999, 2001). However, there is insufficient evidence at this time to state that past underweight status during childhood increases the mortality or morbidity risk of malaria, measles, pneumonia or diarrhoea among those no longer underweight. Therefore, the increased risk of mortality and morbidity associated with low weight-for-age is considered completely reversible. Likewise, the risk of neonatal death attribut-

able to low maternal BMI is considered completely reversible once underweight status is corrected.

5. Estimates of attributable burden

Estimates of the attributable fraction, attributable mortality and attributable burden of underweight status in the age group 0–4 years were calculated for mortality due to measles, malaria, diarrhoea, pneumonia and perinatal causes based upon the above estimates of underweight prevalence, relative risk and reversibility. Attributable fractions and attributable burdens were also calculated for morbidity due to malaria, pneumonia and diarrhoea. Because we were unable to calculate relative risks of morbidity for the proportion of children falling in the weight-for-age category of –1 SD to –2 SDs, the mortality and morbidity estimates are based on different anthropometric thresholds. The mortality estimates represent the cause-specific deaths that are attributable to weight-for-age less than –1 SD, and the morbidity estimates refer to the cause-specific episodes of illness attributable to weight-for-age less than –2 SDs. The burden estimates for mortality from perinatal causes are based on maternal pre-pregnancy BMI ≤20 kg/m^2 and infant deaths attributed to low birth weight. Results are listed in Tables 2.31 through 2.35

Table 2.31 Attributable burden of low weight-for-age on measles infection among children aged 0–4 years, by subregion

	Mortality (WA <–1 SD)			*Incidence (WA <–2 SDs)*	
Subregion	*Attributable fraction (%)*	*Attributable mortality (000s)*	*Attributable burden DALYs (000s)*	*Attributable fraction (%)*	*Attributable burden DALYs (000s)*
AFR-D	45.2	94.7	3 302.1	0.0	0.0
AFR-E	44.2	64.2	2 238.0	0.0	0.0
AMR-A	0.0	0.0	0.0	0.0	0.0
AMR-B	9.3	0.0	0.0	0.0	0.0
AMR-D	24.3	0.0	0.0	0.0	0.0
EMR-B	16.5	0.0	0.6	0.0	0.0
EMR-D	39.2	26.3	915.8	0.0	0.0
EUR-A	0.0	0.0	0.0	0.0	0.0
EUR-B	15.5	0.7	25.4	0.0	0.0
EUR-C	1.5	0.0	0.0	0.0	0.0
SEAR-B	39.9	9.2	320.4	0.0	0.0
SEAR-D	53.8	59.6	2 073.9	0.0	0.0
WPR-A	5.7	0.0	0.1	0.0	0.0
WPR-B	29.3	6.5	226.0	0.0	0.0
World	44.8	261.3	9 102.1	0.0	0.0

Table 2.32 Attributable burden of low weight-for-age on malaria infection among children aged 0–4 years, by subregion

	Mortality (WA <–1 SD)			*Morbidity/incidence (WA <–2 SDs)*	
Subregion	*Attributable fraction (%)*	*Attributable mortality (000s)*	*Attributable burden DALYs (000s)*	*Attributable fraction (%)*	*Attributable burden DALYs (000s)*
AFR-D	57.7	251.5	8480.9	8.4	115.9
AFR-E	56.7	235.6	7982.9	8.1	115.6
AMR-A	0.0	0.0	0.0	0.0	0.0
AMR-B	13.8	0.1	1.7	0.8	0.1
AMR-D	33.7	0.0	0.9	3.0	0.1
EMR-B	23.7	0.0	0.0	1.8	0.1
EMR-D	51.3	23.3	787.3	6.6	7.4
EUR-A	0.0	0.0	0.0	0.0	0.0
EUR-B	22.3	0.0	0.0	1.6	0.0
EUR-C	2.3	0.0	0.0	0.1	0.0
SEAR-B	52.0	1.7	56.0	6.8	1.8
SEAR-D	66.4	35.9	1223.1	11.8	11.4
WPR-A	8.5	0.0	0.0	0.5	0.0
WPR-B	39.8	1.2	40.1	4.1	0.5
World	57.3	549.2	18572.7	8.2	253.0

Table 2.33 Attributable burden of low weight-for-age on pneumonia/ALRI among children aged 0–4 years, by subregion

	Mortality (WA <–1 SD)			*Morbidity/incidence (WA <–2 SDs)*	
Subregion	*Attributable fraction (%)*	*Attributable mortality (000s)*	*Attributable burden DALYs (000s)*	*Attributable fraction (%)*	*Attributable burden DALYs (000s)*
AFR-D	54.6	171.1	5729.9	20.1	38.2
AFR-E	53.6	200.9	6739.8	19.5	42.4
AMR-A	0.0	0.0	0.0	0.0	0.0
AMR-B	12.6	3.4	113.6	2.2	6.7
AMR-D	31.2	6.6	221.5	7.9	4.8
EMR-B	21.7	4.5	151.2	4.7	5.0
EMR-D	48.2	108.2	3661.4	16.1	51.6
EUR-A	0.0	0.0	0.0	0.0	0.0
EUR-B	20.4	9.8	328.2	4.3	1.9
EUR-C	2.1	0.2	5.2	0.3	0.0
SEAR-B	49.0	20.5	692.7	16.5	37.7
SEAR-D	63.4	432.0	14606.4	26.9	262.3
WPR-A	7.7	0.0	0.9	1.3	0.0
WPR-B	37.1	85.9	2884.4	10.4	77.8
World	52.3	1042.9	35135.0	16.5	528.3

Table 2.34 Attributable burden of low weight-for-age on diarrhoea infection among children aged 0–4 years, by subregion

	Mortality (WA <–1 SD)			*Morbidity/incidence (WA <–2 SDs)*	
Subregion	*Attributable fraction (%)*	*Attributable mortality (000s)*	*Attributable burden DALYs (000s)*	*Attributable fraction (%)*	*Attributable burden DALYs (000s)*
AFR-D	62.7	118.0	3 960.1	6.4	12.4
AFR-E	61.7	198.6	6 698.3	6.2	14.0
AMR-A	0.0	0.0	0.0	0.0	0.0
AMR-B	16.1	4.2	140.0	0.6	0.9
AMR-D	38.1	7.3	247.1	2.3	0.7
EMR-B	27.1	4.0	133.8	1.3	0.7
EMR-D	56.3	138.1	4 657.9	5.0	9.0
EUR-A	0.0	0.0	0.0	0.0	0.0
EUR-B	25.5	3.8	128.0	1.2	0.5
EUR-C	2.8	0.1	1.7	0.1	0.0
SEAR-B	57.1	15.2	507.2	5.1	4.8
SEAR-D	71.1	295.5	9 975.4	9.1	47.6
WPR-A	10.0	0.0	0.1	0.3	0.0
WPR-B	44.5	31.3	1 050.5	3.0	8.0
World	60.7	815.9	27 500.1	5.3	98.6

Table 2.35 Attributable burden of low pre-pregnancy BMI on mortality due perinatal conditions, by subregion

	Mortality (BMI ≤20 kg/m²)		
Subregion	*Attributable fraction (%)*	*Attributable mortality (000s)*	*Attributable burden DALYs (000s)*
AFR-D	8.0	10.1	358.5
AFR-E	6.7	9.0	318.2
AMR-A	1.7	0.1	4.8
AMR-B	3.2	2.5	87.6
AMR-D	1.9	0.3	10.0
EMR-B	2.6	0.3	11.9
EMR-D	8.7	17.5	637.8
EUR-A	1.4	0.1	2.7
EUR-B	1.6	0.3	10.6
EUR-C	1.5	0.1	3.3
SEAR-B	3.5	1.3	46.2
SEAR-D	15.5	104.5	3 792.0
WPR-A	2.5	0.0	0.9
WPR-B	2.4	2.4	85.8
World	10.5	148.4	5 370.1

Table 2.36 Total burden of underweight status among children aged 0–4 years

	Mortality (WA <–1 SD)			*Morbidity/incidence (WA <–2 SDs)*	
Disease	*Attributable fraction (%)*	*Attributable mortality (000s)*	*Attributable burden DALYs (000s)*	*Attributable fraction (%)*	*Attributable burden DALYs (000s)*
Protein–energy malnutrition	100.0	153.6	5 252.7	100	9 632.5
Perinatal conditions[a]	10.5	148.4	4 967.0	0.0	0.0
Pneumonia/ ALRI	52.3	1 042.9	35 135.0	16.5	528.3
Diarrhoea	60.7	815.9	27 500.1	5.3	98.6
Malaria	57.3	549.2	18 572.7	8.2	253.0
Measles	44.8	261.3	9 102.1	0.0	0.0
Other	53.1	776.9	26 355.8	—	—
Total	34.7	3 748.2	126 885.4	—	10 512.2

— No data.

[a] "Perinatal conditions" include low birth weight, birth asphyxia and trauma, neonatal sepsis, maternal and placental complications, respiratory distress, fetal blood loss, fetal haematological disorders, anaemia, perinatal infections, maternal diabetes and various other conditions. The category does not include congenital anomalies, neonatal tetanus or syphilis. The burden estimates represent infant deaths due to low birth weight only.

for both sexes combined according to outcome and subregion. Table 2.36 summarizes the total burden estimates associated with underweight status, including estimates of mortality directly attributable to PEM and "other" indeterminate deaths in the residual category. The total attributable fraction of mortality among children aged <5 years due to maternal and child undernutrition was 34.7% (Table 2.36). This was calculated from the sum of the cause-specific attributable mortality estimates divided by the estimate of total deaths among children aged 0–59 months. This fraction includes deaths directly and indirectly attributable to undernutrition. In determining the fraction of deaths indirectly caused by undernutrition, the analysis differentiated postneonatal from neonatal deaths, with maternal undernutrition considered as the risk factor for neonatal deaths.

6. Discussion

The results of these analyses indicate that undernutrition in young children contributes significantly toward the global burden of disease. We

estimate that undernutrition in children aged <5 years, as reflected in underweight or low weight-for-age, causes 3 599 800 deaths, including 815 900 diarrhoea deaths, 1 042 900 pneumonia deaths, 261 300 measles deaths and 549 200 malaria deaths. The estimates also illustrate that the burden of undernutrition in children begins *in utero*, with approximately 148 400 neonatal deaths from low birth weight attributable to maternal underweight status. The 3 748 200 total deaths attributable to maternal and child undernutrition constitute 34.7% of all deaths among children aged <5 years. The loss in DALYs associated with these deaths is staggering—over 126 million. Among the principal causes of death in young children, 60.7% of deaths due to diarrhoea, 52.3% of deaths due to pneumonia, 44.8% of deaths due to measles and 57.3% of deaths due to malaria are attributable to undernutrition. These attributable fractions are large because undernutrition substantially increases a child's risk of dying from common childhood illnesses, and because undernutrition is still highly prevalent in many regions of the world. In particular, the subregions SEAR-D, AFR-D and AFR-E respectively account for 32%, 22% and 24% of the total DALYs lost from undernutrition, followed by EMR-D (12%) and WPR-B (6%).

Undernutrition contributes to the morbidity burden among children as well. Our analyses indicate that having a weight-for-age less than –2 SDs places a child at increased risk of developing pneumonia, diarrhoea or malaria. We estimate that 16.5% of pneumonia, 5.3% of diarrhoea illness and 8.2% of malarial attacks are attributable to low weight-for-age, with an associated loss of DALYs amounting to 528 300 for pneumonia, 98 600 for diarrhoea and 253 000 for malaria. Available evidence suggests that undernutrition does not influence a child's risk of contracting measles and thus none of the measles morbidity burden is attributed to this risk factor.

The relatively greater burden of death as compared to illness attributable to undernutrition is understandable, given the known synergy between illness and malnutrition. This synergy was first described by Scrimshaw et al. (1968): "The simultaneous presence of malnutrition and infection results in an interaction that is more serious for the host than would be expected from the combined effect of the two working independently". Undernutrition potentiates the risk of mortality by increasing the likelihood that the illness will be prolonged or become severe; and more prolonged or severe illness is more likely to negatively affect the nutritional status of the child, placing her at ever-increasing risk of future and more prolonged or severe illness episodes. This has been most clearly demonstrated in the literature for diarrhoeal illnesses (Black et al. 1984), and our analysis makes the extension to three other principal causes of death among young children: pneumonia, malaria and measles. Such findings underscore the need to prioritize the improvement of the nutritional status of children, including within disease control programmes (Becker et al. 1991).

In attempting to quantify the relationship between underweight status and disease, it is important to consider that undernutrition, as assessed by the underweight indicator (or a stunting indicator), is commonly associated with deficiencies of micronutrients (Bhan et al. 2001). In fact, some of these deficiencies, such as zinc, may themselves contribute to poor growth (Brown 2002). These deficiency conditions, especially of vitamin A, iron and zinc, put the child at risk of adverse outcomes, including morbidity and mortality from infectious disease and cognitive impairment. The consequences of these deficiency states can be estimated separately, as has been done in other chapters in this book. The association of underweight condition with these deficiencies means that some of the risk attributed to being underweight may be, in fact, due to specific micronutrient deficiencies. On the other hand, these other deficiencies can occur in children who are not considered underweight, so the risk of adverse outcomes is not entirely encompassed in the subset of the population who are underweight. In fact, the effect of vitamin A supplementation on reducing mortality in vitamin A-deficient populations has been found to be similar in children who were more or less well nourished at the beginning of the trial (Sommer 1986; West 1991). Likewise, zinc supplementation in populations that are presumably zinc deficient has had similar effects on reducing infectious disease morbidity in children who were classified as both "wasted" or "not wasted" (Zinc Investigators' Collaborative Group 1999). Therefore, the effects of undernutrition as identified by being underweight and those of deficiencies of vitamin A, iron and zinc cannot be simply added to determine the overall burden of disease due to nutritional risk factors, nor is it appropriate to assume that all of the consequences of micronutrient deficiencies are subsumed in the underweight calculation. Additional work is needed to determine the joint prevalence distributions of being underweight and being deficient in each of these micronutrients and to assess the joint effects of these aspects of undernutrition.

The outcomes described here represent some of the fundamental global health challenges facing populations at greatest risk for undernutrition. However, the burden of undernutrition on human health and well-being no doubt extends beyond the relatively narrow focus of this analysis. We presented findings to suggest a role for maternal malnutrition as a risk factor for maternal mortality, as well as a role for undernutrition in disability due to poor cognitive development, but the research base thus far does not allow for the calculation of burden estimates. Other considerations relating to undernutrition may include the short-term or long-term effects of underweight status on work capacity or the effect of IUGR on childhood development and morbidity. Many areas are still largely unknown or speculative, such as the role of early or ongoing undernutrition in potentiating chronic disease (Barker 1995;

Law et al. 2001; Stein et al. 1996) or the effect of undernutrition on susceptibility to infection among adult and elderly populations—questions that will only gain in importance as developing countries continue to go through demographic and epidemiological transitions.

Several reports suggest that through current programmatic efforts, rates of undernutrition among children are declining at 1% per year. In contrast, our projections indicate that over the coming decades we can expect variable changes in these prevalences. Because our analyses clearly indicate the overwhelming magnitude of the disease burden associated with child malnutrition, effective strategies to reduce child undernutrition are urgently needed. Energy supplementation for pregnant women, counselling and promotion of breastfeeding and adequate complementary food intake, and child growth monitoring are some of the more effective and affordable interventions for preventing low birth weight and improving child growth (ACC/SCN 2001; WHO 2002). Micronutrient supplementation or fortification, the use of oral rehydration therapy and childhood immunizations, have also been key elements to improving nutritional status and preventing severe childhood disease. Further innovations will be necessary in order to meet the challenge of undernutrition in all populations.

7. Projections of exposure: trends in child underweight status from 2000 to 2030

The estimates for 2010 and 2020 are directly derived from the model as outlined in section 2.2, based on estimates of underweight prevalence in individual countries at multiple points in time. To extend these model estimates to 2030, we applied the lowest delta between last available trend intervals, i.e. for AFR-D and AFR-E, we used 2010–2015 and for the other subregions the deltas 2015–2020; the respective difference was multiplied by 2 (as they refer to a five-year interval) and then subtracted from or added to the estimate of 2020 to derive the value for 2030 (Table 2.37).

Table 2.37 Estimated prevalence of underweight among children aged 0–4 years from 2000 to 2030, by subregion

	% having weight-for-age below –2 SDs			
Subregion	*2000*	*2010*	*2020*	*2030*
AFR-D	32.2	34.2	36.2	38.2
AFR-E	31.0	37.3	44.1	50.7
AMR-A	2.3	1.5	0.7	0.0[a]
AMR-B	5.0	3.3	2.2	1.1
AMR-D	12.4	9.5	7.2	5.0
EMR-B	8.1	4.3	2.3	0.5
EMR-D	25.1	20.4	16.4	12.6
EUR-A	2.3	1.5	0.7	0.0[a]
EUR-B	7.6		Overall stagnation[b]	
EUR-C	2.6		Overall declining trend[b]	
SEAR-B	25.8	18.7	13.2	8.0
SEAR-D	45.9	37.6	30.0	22.6
WPR-A	3.8	2.5	1.2	0.0[a]
WPR-B	16.0	11.8	8.6	5.6

[a] AMR-A, EUR-A and WPR-A, comprising the developed countries, are estimated to move further towards overweight and thus the underweight levels are forecasted to decrease stepwise to reach 0% by 2030. In WPR-A the estimated trend is driven by Japan (comprising 77% of the population aged 0–4 years in this subregion) and a national survey from 1978–81 already resulted with a low prevalence of underweight (3.7%). Similarly the 1996 national survey in Australia (contributing 16% of the population aged 0–4 years in this subregion) reported 0% underweight. Appendix C lists by country in alphabetical order publications backing the estimated trend towards overweight in AMR-A, EMR-A and WPR-A.

[b] There are very scarce empirical data on the nutritional status of children aged <5 years in EUR-B and EUR-C. Based on the little information available to date (see Appendix D) the estimated trends of underweight until 2030 for these two subregions are expected to stagnate and decline, respectively. These overall trend estimations for EUR-B and EUR-C, however, are to be taken with caution.

(i) EUR-B

The available data for this subregion show a diverse pattern. There are countries with decreasing rates in child underweight and parallel there are others where increase in the national prevalence of child underweight can be observed. With the information available to date it is very difficult to estimate a trend in child underweight from 2000 to 2030. The trend pattern is expected to be driven by Turkey, which has 40% of the total <5 population in this subregion. However, given the available trend data for other countries in this subregion and the unfavourable conditions (demographic and economic transition associated in parts with political instability) in some of them an overall stagnation of the underweight prevalence from 2000 to 2030 is to be expected. Appendix E(a) lists references by country in alphabetical order to document the forecasted trend in this subregion.

(ii) EUR-C

Given that any trend in this subregion is likely to be dominated by Russia (which has 56% of the total population of children aged <5 years in this subregion) and that current evidence shows raising rates in overweight in this country we would estimate an overall declining trend of underweight. However, given the enduring unstable situation in some of the countries in EUR-C and the uncertainty about support and investments from developed countries, a quantification of the expected decline cannot be made. Appendix E(b) lists references by country in alphabetical order derived from the WHO Global Database, Medline and the Internet which contain additional information to document the forecasted trend in this subregion.

Acknowledgements

We thank Majid Ezzati for guidance in global burden of disease comparative risk assessment methodology; Steve Vander Hoorn for comparative risk assessment analysis and burden of disease calculations; Amy Rice, Lisa Sacco and Constantine Frangakis for their analysis of malnutrition and perinatal causes of death; Andres Lescano for additional statistical analysis of morbidity data; Jeffrey McGuckin for his assistance in coordinating comparative risk assessment efforts; and Julie West and Seema Rai for their assistance with the literature search and compilation of risk data.

We are grateful to Wafaie Fawzi, Michel Garenne, Marc Andersen, Keith West, Shams el Arifeen, Fehmida Jalil, S.R. Khan, Bambang Sutrisna, and Stan Becker, for providing original data on cause-specific mortality; and K. Zaman, for providing data on pneumonia morbidity.

We are grateful for the statistical support received from Allen Shoemaker for conducting primary data analysis of raw data sets relating to underweight prevalence; Richard Morris for the modelling of the subregional estimates; and Gilda Piaggio for transforming the categorical underweight prevalences into continuous categories.

This manuscript was supported in part by the Family Health and Child Survival (FHACS) Cooperative Agreement between the United States Agency for International Development, Office of Health and Nutrition and the Johns Hopkins Bloomberg School of Public Health, Department of International Health; and by the World Health Organization, Evidence and Information for Policy Department, Department of Child and Adolescent Health and Development, and Department of Nutrition for Health and Development.

Notes

1 See preface for an explanation of this term.

References

Aaby P, Bukh J, Lisse IM, da Silva MC (1988) Decline in measles mortality: nutrition, age at infection, or exposure? *British Medical Journal*, **296**:1225–1228.

Aboud FE, Alemu T (1995) Nutrition, maternal responsiveness and mental development of Ethiopian children. *Social Science and Medicine*, **41**:725–732.

ACC/SCN (2000a) Ending malnutrition by 2020: An agenda for change in the millennium. *Food and Nutrition Bulletin,* **21**:S3–88.

ACC/SCN (2000b) *Fourth report on the world nutrition situation.* United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition, Geneva.

ACC/SCN (2001) *What works? A review of the efficacy and effectiveness of nutrition interventions*. Allen LH, Gillespie SR, eds. United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition, Geneva in collaboration with the Asian Development Bank, Manila.

Adadevoh SW, Hobbs C, Elkins TE (1989) The relation of the true conjugate to maternal height and obstetric performance in Ghanaians. *International Journal of Gynaecology and Obstetrics*, **28**:243–251.

Adelekan DA, Adeodu OO, Thurnham DI (1997) Comparative effects of malaria and malnutrition on plasma concentrations of antioxidant micronutrients in children. *Annals of Tropical Paediatrics*, **17**:223–227.

Agarwal DK, Agarwal A, Singh M, Satya K, Agarwal S, Agarwal KN (1998) Pregnancy wastage in rural Varanasi: relationship with maternal nutrition and sociodemographic characteristics. *Indian Pediatrics*, **35**:1071–1079.

Agarwal DK, Agarwal KN, Upadhyay SK (1989) Effect of mid-day meal programme on physical growth and mental function. *Indian Journal of Medical Research*, **90**:163–174.

Agarwal DK, Awasthy A, Upadhyay SK, Singh P, Kumar J, Agarwal KN (1992) Growth, behavior, development and intelligence in rural children between 1–3 years of life. *Indian Pediatrics*, **29**:467–480.

Agarwal DK, Upadhyay SK, Agarwal KN (1989) Influence of malnutrition on cognitive development assessed by Piagetian tasks. *Acta Paediatrica Scandinavica*, **78**:115–122.

Agarwal DK, Upadhyay SK, Tripathi AM, Agarwal KN (1987) *Nutritional status, physical work capacity and mental function in school children*. (Scientific Report No. 6.) Nutritional Foundation of India, New Delhi.

Alam AN, Chowdhury AA, Kabir IA, Sarker SA, Rahaman MM (1984) Association of pneumonia with undernutrition and shigellosis. *Indian Pediatrics*, **21**:609–613.

Allen SJ, Raiko A, O'Donnell A, Alexander ND, Clegg JB (1998) Causes of preterm delivery and intrauterine growth retardation in a malaria endemic region of Papua New Guinea. *Archives of Disease in Childhood, Fetal and Neonatal Edition*, **79**:F135–140.

Anand K, Sundaram KR, Lobo J, Kapoor SK (1994) Are diarrheal incidence and malnutrition related in under five children? A longitudinal study in an area of poor sanitary conditions. *Indian Pediatrics*, **31**:943–948.

Andersen M (1997) *Anthropometric measurements in health programmes: Epidemiological and statistical aspects* [Dissertation]. University of Copenhagen, Copenhagen.

Anonymous (1984) Antenatal screening for fetopelvic dystocias. A cost-effectiveness approach to the choice of simple indicators for use by auxiliary personnel. The Kasongo Project Team. *Journal of Tropical Medicine and Hygiene*, **87**:173–183.

Anonymous (1999) *Reducing perinatal and neonatal mortality*. (Child Health Research Project Special Report. Vol. 3, No. 1.) Johns Hopkins University, Baltimore, MD.

Arifeen S, Black RE, Antelman G, Baqui A, Caulfield L, Becker S (2001) Exclusive breastfeeding reduces acute respiratory infection. *Pediatrics*, **108**:E67.

Armitage P, Berry G (1994) *Statistical methods in medical research*. 3rd edn. Blackwell Science, Oxford.

Arora NK, Paul VK, Singh M (1987) Morbidity and mortality in term infants with intrauterine growth retardation. *Journal of Tropical Pediatrics*, **33**: 186–189.

Ashem B, Janes MD (1978) Deleterious effects of chronic undernutrition on cognitive abilities. *Journal of Child Psychology and Psychiatry*, **19**:23–31.

Ashworth A (1998) Effects of intrauterine growth retardation on mortality and morbidity in infants and young children. *European Journal of Clinical Nutrition*, **52**:S34–41.

Bairagi R, Chowdhury MK, Kim YJ, Curlin GT, Gray RH (1987) The association between malnutrition and diarrhoea in rural Bangladesh. *International Journal of Epidemiology*, **16**:477–481.

Bakketeig LS (1998) Current growth standards, definitions, diagnosis and classification of fetal growth retardation. *European Journal of Clinical Nutrition*, **52**:S1–4.

Bakketeig LS, Butte N, de Onis M, et al. (1998) Report of the IDECG Working Group on definitions, classifications, causes, mechanisms and prevention of IUGR. *European Journal of Clinical Nutrition*, **52**:S94–96.

Balcazar H, Haas J (1990) Classification schemes of small-for-gestational age and type of intrauterine growth retardation and its implications to early neonatal mortality. *Early Human Development*, **24**:219–230.

Balcazar H, Haas JD (1991) Retarded fetal growth patterns and early neonatal mortality in a Mexico City population. *Bulletin of the Pan American Health Organization*, **25**:55–63.

Ballard TJ, Neumann CG (1995) The effects of malnutrition, parental literacy and household crowding on acute lower respiratory infections in young Kenyan children. *Journal of Tropical Pediatrics*, **41**:8–13.

Baqui AH (1990) *Epidemiology of persistent diarrhea in Bangladeshi children*. [Dissertation]. Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD.

Baqui AH, Black RE (2002) Childhood infectious diseases and their contribution to undernutrition. In: *Public health issues in infant and child nutrition*. Black RE, Michaelson KF, eds. (Nestlé Nutrition Workshop Series, Pediatric Program, Volume 48.) Lippincott Williams & Wilkins, Philadelphia, PA.

Baqui AH, Black RE, Sack RB, Chowdhury HR, Yunus M, Siddique AK (1993) Malnutrition, cell-mediated immune deficiency, and diarrhea: a community-based longitudinal study in rural Bangladeshi children. *American Journal of Epidemiology*, **137**:355–365.

Barker DJ (1995) The fetal and infant origins of disease. *European Journal of Clinical Investigation*, **25**:457–463.

Barros FC, Huttly SR, Victora CG, Kirkwood BR, Vaughan JP (1992) Comparison of the causes and consequences of prematurity and intrauterine growth retardation: a longitudinal study in southern Brazil. *Pediatrics,* **90**:238–244.

Barros FC, Victora CG, Vaughan JP, Estanislau HJ (1987) Perinatal mortality in southern Brazil: a population-based study of 7392 births. *Bulletin of the World Health Organization*, **65**:95–104.

Beau JP, Garenne M, Diop B, Briend A, Diop MI (1987) Diarrhoea and nutritional status as risk factors of child mortality in a Dakar hospital (Senegal). *Journal of Tropical Pediatrics*, **33**:4–9.

Becker S, Black RE, Brown KH (1991) Relative effects of diarrhea, fever, and dietary energy intake on weight gain in rural Bangladeshi children. *American Journal of Clinical Nutrition*, **53**:1499–1503.

Behrman RE, Babson GS, Lessel R (1971) Fetal and neonatal mortality in white middle class infants. Mortality risks by gestational age and weight. *American Journal of Diseases of Children*, **121**:486–489.

Berkman DS, Lescano AG, Gilman RH, Lopez SL, Black MM (2002) Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study. *The Lancet*, **359**:564–571.

Berman S, Duenas A, Bedoya A, et al. (1983) Acute lower respiratory tract illnesses in Cali, Colombia: a two-year ambulatory study. *Pediatrics*, **71**: 210–218.

Bhan MK, Arora NK, Ghai OP, Ramachandran K, Khoshoo V, Bhandari N (1986) Major factors in diarrhoea related mortality among rural children. *Indian Journal of Medical Research*, **83**:9–12.

Bhan MK, Sommerfelt H, Strand T (2001) Micronutrient deficiency in children. *British Journal of Nutrition*, **85**:S199–203.

Bhandari N, Bahl R, Nayyar B, Khokhar P, Rohde JE, Bhan MK (2001) Food supplementation with encouragement to feed it to infants from 4 to 12 months of age has a small impact on weight gain. *Journal of Nutrition*, **131**:1946–1951.

Bhandari N, Bhan MK, Sazawal S, Clemens JD, Bhatnagar S, Khoshoo V (1989) Association of antecedent malnutrition with persistent diarrhoea: a case-control study. *British Medical Journal*, **298**:1284–1287.

Bhat US, Udani PM, Shah BP, Naik PA, Ezhuthachan SG (1973) Nutritional growth failure and mental development. *Indian Pediatrics*, **10**:657–660.

Bhargava SK, Sachdev HP, Ghosh S (1985) Distribution of live births and early neonatal mortality in relation to gestation and intrauterine growth. *Indian Journal of Medical Research*, **82**:95–97.

Bhatt RV, Modi NS, Acharya PT (1967) Height and reproductive performance. *Journal of Obstetrics and Gynaecology of India*, **17**:75–79.

Binkin NJ, Williams RL, Hogue CJ, Chen PM (1985) Reducing black neonatal mortality. Will improvement in birth weight be enough? *Journal of the American Medical Association*, **253**:372–375.

Binns CW (1976) Food, sickness and death in children of the highlands of Papua New Guinea. *Journal of Tropical Pediatrics and Environmental Child Health*, **22**:9–11.

Birch HG, Pineiro E, Alcalde E, Toca T, Cravioto J (1971) Relation of kwashiorkor in early childhood and intelligence at school age. *Pediatric Research*, **5**:579–585.

Biritwum RB, Isomura S, Assoku A, Torigoe S (1986) Growth and diarrhoeal disease surveillance in a rural Ghanaian pre-school child population. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **80**:208–213.

Black RE (1991) Would control of childhood infectious diseases reduce malnutrition? *Acta Paediatrica Scandinavica*, **374**:S133–140.

Black RE, Brown KH, Becker S (1984) Malnutrition is a determining factor in diarrheal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh. *American Journal of Clinical Nutrition*, **39**:87–94.

Botha-Antoun E, Babayan S, Harfouche JK (1968) Intellectual development related to nutritional status. *Journal of Tropical Pediatrics*, **14**:112–115.

Brabin L, Verhoeff F, Brabin BJ (2002) Maternal height, birthweight and cephalo pelvic disproportion in urban Nigeria and rural Malawi. *Acta Obstetricia et Gynecologica Scandinavica*, **81**:502–507.

Bracero LA, Byrne DW (1998) Optimal maternal weight gain during singleton pregnancy. *Gynecologic and Obstetric Investigation*, **46**:9–16.

Brown JL, Pollitt E (1996) Malnutrition, poverty and intellectual development. *Scientific American*, **274**:38–43.

Brown KH, Peerson JM, Rivera JA, Allen LH (2002) Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition*, **75**:1062–1071.

Brussow H, Rahim H, Barclay D, Freire WB, Dirren H (1993) Nutritional and environmental risk factors for diarrhoeal diseases in Ecuadorian children. *Journal of Diarrhoeal Diseases Research*, **11**:137–142.

Cabak V, Najdanvic R (1965) Effect of undernutrition in early life on physical and mental development. *Archives of Disease in Childhood*, **40**:532–534.

Cattanach S, Morrison J, Andersen MJ, Williams GM, Sheahan T (1993) Pregnancy hazards associated with low maternal body mass indices. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **33**: 45–47.

Caulfield LE, Haas JD, Belizan JM, Rasmussen KM, Edmonston B (1991) Differences in early postnatal morbidity risk by pattern of fetal growth in Argentina. *Paediatric and Perinatal Epidemiology*, **5**:263–275.

Champakam S, Srikantia SG, Gopalan C (1968) Kwashiorkor and mental development. *American Journal of Clinical Nutrition*, **21**:844–852.

Chandler AM, Walker SP, Connolly K, Grantham-McGregor SM (1995) School breakfast improves verbal fluency in undernourished Jamaican children. *Journal of Nutrition*, **125**:894–900.

Chandra RK (1977) Lymphocyte subpopulations in human malnutrition: cytotoxic and suppressor cells. *Pediatrics*, **59**:423–427.

Chatelain PG, Nicolino M, Claris O, Salle B, Chaussain J (1998) Multiple hormone resistance in short children born with intrauterine growth retardation? *Hormone Research*, **49**:S20–22.

Chen LC, Chowdhury A, Huffman SL (1980) Anthropometric assessment of energy-protein malnutrition and subsequent risk of mortality among preschool aged children. *American Journal of Clinical Nutrition*, **33**: 1836–1845.

Chen LC, Huq E, Huffman SL (1981) A prospective study of the risk of diarrheal diseases according to the nutritional status of children. *American Journal of Epidemiology*, **114**:284–292.

Cheung YB, Yip PS, Karlberg JP (2001) Parametric modelling of neonatal mortality in relation to size at birth. *Statistics in Medicine*, **20**:2455–2466.

Chopra JS, Sharma A (1992) Protein energy malnutrition and the nervous system. *Journal of the Neurological Sciences*, **110**:8–20.

Chowdhury MK, Gupta VM, Bairagi R, Bhattacharya BN (1990) Does malnutrition predispose to diarrhoea during childhood? Evidence from a longitudinal study in Matlab, Bangladesh. *European Journal of Clinical Nutrition*, **44**:515–525.

Chwang LC, Soemantri AG, Pollitt E (1988) Iron supplementation and physical growth of rural Indonesian children. *American Journal of Clinical Nutrition*, **47**:496–501.

Cnattingius S, Bergstrom R, Lipworth L, Kramer MS (1998) Prepregnancy weight and the risk of adverse pregnancy outcomes. *New England Journal of Medicine*, **338**:147–152.

Cogswell ME, Yip R (1995) The influence of fetal and maternal factors on the distribution of birthweight. *Seminars in Perinatology*, **19**:222–240.

Colombo M, de Andraca I, Lopez I (1988) Mental development and stunting. In: *Linear growth retardation in less developed countries*. Nestlé Nutrition Workshop. Waterlow JC, ed. Raven Press, New York.

Conde-Agudelo A, Belizan JM, Diaz-Rossello JL (2000) Epidemiology of fetal death in Latin America. *Acta Obstetricia et Gynecologica Scandinavica*, **79**:371–378.

Cravioto J, DeLicardie ER, Pinero C, Lindoro M, Arroyo M, Alcade E (1971) Mental development and malnutrition. Neurointegrative development and intelligence in school children recovered from malnutrition in infancy. *Indian Journal of Medical Research*, **59**:S195–215.

Cunha AL (2000) Relationship between acute respiratory infection and malnutrition in children under 5 years of age. *Acta Paediatrica*, **89**:608–609.

de Almeida MF, Jorge MH (1998) [Small for gestational age: risk factor for neonatal mortality]. *Revista de Saude Publica*, **32**:217–224.

de Onis M (2000) Measuring nutritional status in relation to mortality. *Bulletin of the World Health Organization*, **78**:1271–1274.

de Onis M (2001) Child growth and development. In: *Nutrition and health in developing countries*. Semba RD, Bloem MW, eds. Humana Press, Totowa, NJ.

de Onis M, Blössner M (1997) *WHO Global Database on Child Growth and Malnutrition*. Available at http://www.who.int/nutgrowthdb.

de Onis M, Blössner M (2000) Prevalence and trends of overweight among preschool children in developing countries. *American Journal of Clinical Nutrition*, **72**:1032–1039.

de Onis M, Blössner M, Villar J (1998) Levels and patterns of intrauterine growth retardation in developing countries. *European Journal of Clinical Nutrition*, **52**:S5–15.

de Onis M, Frongillo EA, Blössner M (2000) Is malnutrition declining? An analysis of changes in levels of child malnutrition since 1980. *Bulletin of the World Health Organization*, **78**:1222–1233.

de Onis M, Garza C, Habicht JP (1997) Time for a new growth reference. *Pediatrics*, **100**:E8.

de Onis M, Habicht JP (1996) Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. *American Journal of Clinical Nutrition*, **64**:650–658.

de Onis M, Monteiro C, Akre J, Glugston G (1993) The worldwide magnitude of protein-energy malnutrition: an overview from the WHO global database on child growth. *Bulletin of the World Health Organization*, **71**:703–712.

de Onis M, Victora CG, Garza C, Frongillo EA, Cole TJ, for the WHO Working Group on the Growth Reference Protocol (2001) A new international growth reference for young children. In: *Perspectives in human growth, development and maturation*. Dasgupta P, Hauspie R, eds. Kluwer Academic Publishers, Dordrecht.

de Onis M, Yip R (1996) The WHO growth chart: historical considerations and current scientific issues. *Bibliotheca Nutritio et Dieta*, **53**:74–89.

Deb SK (1998) Acute respiratory disease survey in Tripura in case of children below five years of age. *Journal of the Indian Medical Association*, **96**: 111–116.

Edwards LE, Alton IR, Barrada MI, Hakanson EY (1979) Pregnancy in the underweight woman. Course, outcome, and growth patterns of the infant. *American Journal of Obstetrics and Gynecology*, **135**:297–302.

el Samani EF, Willett WC, Ware JH (1988) Association of malnutrition and diarrhea in children aged under five years. A prospective follow-up study in a rural Sudanese community. *American Journal of Epidemiology*, **128**: 93–105.

el Samani FZ, Willett WC, Ware JH (1987) Nutritional and socio-demographic risk indicators of malaria in children under five: a cross-sectional study in a Sudanese rural community. *Journal of Tropical Medicine and Hygiene*, **90**:69–78.

Elizabeth KE, Sathy N (1997) The role of developmental stimulation in nutritional rehabilitation. *Indian Pediatrics*, **34**:681–695.

Essex BJ, Everett VJ (1977) Use of an action-orientated record for antenatal screening. *Tropical Doctor*, **7**:134–138.

Evans D, Hansen JD, Moodie AD, van der Spuy HI (1980) Intellectual development and nutrition. *Journal of Pediatrics*, **97**:358–363.

Evans DE, Moodie AD, Hansen JD (1971) Kwashiorkor and intellectual development. *South African Medical Journal*, **45**:1413–1426.

Everson PJ, Morris CN (1983) *Hierarchical normal regression model.* (Technical Report.) Harvard University, Boston, MA.

FAO (2001) *The state of food insecurity in the world*. The Food and Agriculture Organization of the United Nations, Rome.

Fawzi WW, Herrera MG, Spiegelman DL, el Amin A, Nestel P, Mohamed KA (1997) A prospective study of malnutrition in relation to child mortality in the Sudan. *American Journal of Clinical Nutrition*, **65**:1062–1069.

Ferro-Luzzi A, Ashworth A, Martorell R, Scrimshaw NS (1998) Report of the IDECG Working Group on effects of IUGR on infants, children and adolescents: immunocompetence, mortality, morbidity, body size, body composition, and physical performance. *European Journal of Clinical Nutrition*, **52**:S97–99.

Fisher MM (1972) Malnutrition and reasoning ability in Zambian schoolchildren. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **66**:471–478.

Florencio CA (1988) *Nutrition, health and other determinants of academic achievement and school related behavior of grade one to grade six pupils*. University of the Philippines, Quezon City.

Fonseca W, Kirkwood BR, Victora CG, Fuchs SR, Flores JA, Misago C (1996) Risk factors for childhood pneumonia among the urban poor in Fortaleza, Brazil: a case–control study. *Bulletin of the World Health Organization*, **74**:199–208.

Galler JR, Ramsey F (1987) A follow-up study of the influence of early malnutrition on development: V. Delayed development of conservation (Piaget). *Journal of the American Academy of Child and Adolescent Psychiatry*, **26**:23–27.

Galler JR, Ramsey F, Solimano G (1984) The influence of early malnutrition on subsequent behavioral development III. Learning disabilities as a sequel to malnutrition. *Pediatric Research*, **18**:309–313.

Galler JR, Ramsey F, Solimano G, Lowell WE, Mason E (1983) The influence of early malnutrition on subsequent behavioral development. I. Degree of impairment in intellectual performance. *Journal of the American Academy of Child Psychiatry*, **22**:8–15.

Galler JR, Ramsey FC, Forde V, Salt P, Archer E (1987a) Long-term effects of early kwashiorkor compared with marasmus. II. Intellectual performance. *Journal of Pediatric Gastroenterology and Nutrition*, **6**:847–854.

Galler JR, Ramsey FC, Morley DS, Archer E, Salt P (1990) The long-term effects of early kwashiorkor compared with marasmus. IV. Performance on the national high school entrance examination. *Pediatric Research*, **28**: 235–239.

Galler JR, Ramsey FC, Salt P, Archer E (1987b) Long-term effects of early kwashiorkor compared with marasmus. III. Fine motor skills. *Journal of Pediatric Gastroenterology and Nutrition*, **6**:855–859.

Garenne M, Maire B, Fontaine O, Dieng K, Briend A (1987) *Risques de décès associés à différents états nutritionnels chez l'enfant d'âge préscolaire [Risks of dying associated with different nutritional status in pre-school aged children]*. Rapport final. ORSTOM, Dakar, September 1987. Reprinted 2000 by the Centre Population et Développement (CEPED), Paris.

Ghai OP (1975) Effect of early marasmic malnutrition on subsequent mental development. *Indian Pediatrics*, **12**:85.

Ghai OP, Jaiswal VN (1970) Relationship of undernutrition to diarrhoea in infants and children. *Indian Journal of Medical Research*, **58**:789–795.

Ghosh S, Ramanujacharyulu TK, Hooja V, Madhavan S (1979) Mortality pattern in an urban birth cohort. *Indian Journal of Medical Research*, **69**:616–623.

Goldenberg R, Hack M, Grantham M, Schurch B (1998) Report of the IDECG/IUNS Working Group on IUGR effects on neurological, sensory, cognitive, and behavioral function. *European Journal of Clinical Nutrition*, **52**:S100–101.

Golub MS, Keen CL, Gershwin ME, Hendrickx AG (1995) Developmental zinc deficiency and behavior. *Journal of Nutrition*, **125**:S2263–2271.

Gomez F, Galvan R, Frenk S, Cravioto Munoz J, Chavez R, Vazquez L (1956) Mortality in second and third degree malnutrition. *Journal of Tropical Pediatrics*, **2**:77–83.

Gopalan C, Swaninathan MC, Kumari VK, Rao DH, Vijayaraghavan K (1973) Effect of calorie supplementation on growth of undernourished children. *American Journal of Clinical Nutrition*, **26**:563–566.

Gordon JE, Guzman MA, Ascoli W, Scrimshaw NS (1964) Acute diarrhoeal disease in less developed countries. 2. Patterns of epidemiological behaviour in rural Guatemalan villages. *Bulletin of the World Health Organization*, **31**:9–20.

Gorman KS (1995) Malnutrition and cognitive development: evidence from experimental/quasi-experimental studies among the mild-to-moderately malnourished. *Journal of Nutrition*, **12**:S2239–2244.

Grantham-McGregor S (1982) The relationship between developmental level and different types of malnutrition in children. *Human Nutrition: Clinical Nutrition*, **36**:319–320.

Grantham-McGregor S (1984) Chronic undernutrition and cognitive abilities. *Human Nutrition. Clinical Nutrition*, **38**:83–94.

Grantham-McGregor S (1995) A review of studies of the effect of severe malnutrition on mental development. *Journal of Nutrition*, **125**:S2233–2238.

Grantham-McGregor S, Meeks Gardner JM, Walker S, Powell C (1989a) The relationship between undernutrition, activity levels and development in young children. In: *Activity, energy expenditure and energy requirements of infants and children*. (Proceedings of an IDECG workshop held in Cambridge, Massachusetts, USA, November 14 to 17, 1989.) Schurch B, Scrimshaw NS, eds. United Nations University Press, New York.

Grantham-McGregor S, Powell C, Fletcher P (1989b) Stunting, severe malnutrition and mental development in young children. *European Journal of Clinical Nutrition*, **43**:403–409.

Grantham-McGregor S, Powell C, Walker S, Chang S, Fletcher P (1994) The long-term follow-up of severely malnourished children who participated in an intervention program. *Child Development*, **65**:428–439.

Grantham-McGregor SM, Lira PI, Ashworth A, Morris SS, Assuncao AM (1998) The development of low birth weight term infants and the effects of the environment in northeast Brazil. *Journal of Pediatrics*, **132**:661–666.

Grantham-McGregor SM, Powell CA, Walker SP, Himes JH (1991) Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. *The Lancet*, **338**:1–5.

Grantham-McGregor SM, Walker SP, Chang S (2000) Nutritional deficiencies and later behavioural development. *Proceedings of the Nutrition Society*, **59**:47–54.

Grantham-McGregor SM, Walker SP, Chang SM, Powell CA (1997) Effects of early childhood supplementation with and without stimulation on later development in stunted Jamaican children. *American Journal of Clinical Nutrition*, **66**:247–253.

Gray RH, Ferraz EM, Amorim MS, de Melo LF (1991) Levels and determinants of early neonatal mortality in Natal, northeastern Brazil: results of a surveillance and case-control study. *International Journal of Epidemiology*, **20**:467–473.

Groos AD (1991) Delayed motor development in relation to nutritional status among children under two years of age in two districts of Simbu Province. *Papua New Guinea Medical Journal*, **34**:238–245.

Guerrant RL, Schorling JB, McAuliffe JF, de Souza MA (1992) Diarrhea as a cause and an effect of malnutrition: diarrhea prevents catch-up growth and malnutrition increases diarrhea frequency and duration. *American Journal of Tropical Medicine and Hygiene*, **47**:28–35.

Gupta S, Dhingra DC, Singh MV, Anand NK (1975) Impact of nutrition on intelligence. *Indian Pediatrics*, **12**:1079–1082.

Haas JD, Balcazar H, Caulfield L (1987) Variation in early neonatal mortality for different types of fetal growth retardation. *American Journal of Physical Anthropology*, **73**:467–473.

Hamill PV, Drizd TA, Johnson CL, Reed RB, Roche AF (1977) NCHS growth curves for children birth-18 years. United States. *Vital Health Statistics*, **11**:i–iv, 1–74.

Harrison KA, Rossiter CE, Chong H (1985) Relations between maternal height, fetal birth weight and cephalopelvic disproportion suggest that young Nigerian primigravidae grow during pregnancy. *British Journal of Obstetrics and Gynaecology*, **92**:S40–48.

Henry FJ, Alam N, Aziz KM, Rahaman MM (1987) Dysentery, not watery diarrhoea, is associated with stunting in Bangladeshi children. *Human Nutrition. Clinical Nutrition*, **41**:243–249.

Hertzig ME, Birch HG, Richardson SA, Tizard J (1972) Intellectual levels of school children severely malnourished during the first two years of life. *Pediatrics*, **49**:814–824.

Heywood AH, Marshall T, Heywood PF (1991) Motor development and nutritional status of young children in Madang, Papua New Guinea. *Papua New Guinea Medical Journal*, **34**:109–116.

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, **58**:295–300.

Hoorweg J, Stanfield JP (1976) The effects of protein energy malnutrition in early childhood on intellectual and motor abilities in later childhood and adolescence. *Developmental Medicine and Child Neurology*, **18**:330–350.

Husaini MA, Husaini YK, Sandjaja S et al. (1995) Maternal anthropometry and pregnancy outcomes in Indonesia. *Bulletin of the World Health Organization*, **73**:77–79.

Husaini MA, Karyadi L, Husaini YK, Sandjaja S, Karyadi D, Pollitt E (1991) Developmental effects of short-term supplementary feeding in nutritionally-at-risk Indonesian infants. *American Journal of Clinical Nutrition*, **54**:799–804.

IDECG Working Group (1987) Pregnancy, lactation and childhood: report of working group 1. In: *Chronic energy deficiency: consequences and related issues*. Schurch B, Scrimshaw NS, eds. International Dietary Energy Consultancy Group, Lausanne.

Indian Academy of Pediatrics (1972) Nutrition sub committee of IAP: report of the convenor. *Indian Pediatrics*, **9**:360

Institute of Medicine (1990) *Nutrition during pregnancy.* National Academy Press, Washington, DC.

Ivanovic DM, Leiva BP, Perez HT et al. (2000) Long-term effects of severe undernutrition during the first year of life on brain development and learning in Chilean high-school graduates. *Nutrition*, **16**:1056–1063.

Jalil F, Lindblad BS, Hanson LA et al. (1993) Early child health in Lahore, Pakistan: I. Study design. *Acta Paediatrica*, *Supplement,* **82**:S3–16.

James JW (1972) Longitudinal study of the morbidity of diarrheal and respiratory infections in malnourished children. *American Journal of Clinical Nutrition*, **25**:690–694.

Jamison DT (1977) Child malnutrition and school performance in China. *Journal of Development Economics*, **20**:299–309.

Jelliffe DB (1966) *The assessment of the nutritional status of the community*. (WHO Monograph 53). World Health Organization, Geneva.

Johnson FE, Low SM, de Baessa Y, MacVean RB (1987) Interaction of nutritional and socioeconomic status as determinants of cognitive development in disadvantaged urban Guatemalan children. *American Journal of Physical Anthropology*, **73**:501–506.

Kalra A, Mishra MN, Kumar R, Prasad R, Dayal RS (1980) The impact of malnutrition on intelligence. *Indian Pediatrics*, **17**:109–116.

Khan MA, Yunus M (1990) Host factors in childhood diarrhoea. *Journal of the Royal Society of Health*, **110**:94–95.

Khan SR, Jalil F, Zaman S, Lindblad BS, Karlberg J (1993) Early child health in Lahore, Pakistan: X. Mortality. *Acta Paediatrica*, *Supplement,* **82**: S109–117.

King JC, Weininger J (1989) Nutrition during pregnancy. *Seminars in Perinatology*, **13**:162–168.

Konje JC, Ladipo OA (2000) Nutrition and obstructed labor. *American Journal of Clinical Nutrition*, **72**:S291–297.

Kossmann J, Nestel P, Herrera MG, el Amin A, Fawzi WW (2000) Undernutrition in relation to childhood infections: a prospective study in the Sudan. *European Journal of Clinical Nutrition*, **54**:463–472.

Kramer MS (1987) Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the World Health Organization*, **65**:663–737.

Kramer MS, Coates AL, Michoud MC, Dagenais S, Hamilton EF, Papageorgiou A (1995) Maternal anthropometry and idiopathic preterm labor. *Obstetrics and Gynecology*, **86**:744–748.

Kramer MS, Kakuma R (2002) Optimal duration of exclusive breastfeeding. *Cochrane Database of Systematic Reviews*, 1:CD003517

Kramer MS, McLean FH, Eason EL, Usher RH (1992) Maternal nutrition and spontaneous preterm birth. *American Journal of Epidemiology*, **136**:574–583.

Kramer MS, Platt RW, Wen SW et al. (2001) A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*, **108**:E35.

Krasovec K, Anderson MA (1991) Maternal anthropometry for prediction of pregnancy outcomes. (Memorandum from a USAID/WHO/PAHO/MotherCare meeting.) *Bulletin of the World Health Organization*, **69**: 523–532.

Kwawukume EY, Ghosh TS, Wilson JB (1993) Maternal height as a predictor of vaginal delivery. *International Journal of Gynaecology and Obstetrics*, **41**:27–30.

Lahiri SK, Mukhopadhyay SP, Das KK, Ray SK, Biswas D (1994) Study of the impact of epidemiological factors on intelligence of rural children of 3 to 6 years age group belonging to low socioeconomic status. *Indian Journal of Public Health*, **38**:133–142.

Lamb WH (1988) Epidemic measles in a highly immunized rural West African (Gambian) village. *Reviews of Infectious Diseases*, **10**:457–462.

Lasky RE, Klein RE, Yarbrough C, Engle PL, Lechtig A, Martorell R (1981) The relationship between physical growth and infant behavioral development in rural Guatemala. *Child Development*, **52**:219–226.

Law CM, Egger P, Dada O et al. (2001) Body size at birth and blood pressure among children in developing countries. *International Journal of Epidemiology*, **30**:52–57.

Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM (1994) Iron supplementation improves appetite and growth in anemic Kenyan primary school children. *Journal of Nutrition*, **124**:645–654.

Lehmann D, Howard P, Heywood P (1988) Nutrition and morbidity: acute lower respiratory tract infections, diarrhoea and malaria. *Papua New Guinea Medical Journal*, **31**:109–116.

Levitsky DA, Strupp BJ (1995) Malnutrition and the brain: changing concepts, changing concerns. *Journal of Nutrition*, **125**:S2212–2220.

Lindtjorn B, Alemu T, Bjorvatn B (1993) Nutritional status and risk of infection among Ethiopian children. *Journal of Tropical Pediatrics*, **39**: 76–82.

Liu YL, Lin LM, Zhu J, Zhang ZJ, Li Z (1991) Case-control study on pathogenesis of pneumonia in children aged 0–2 years. *Chinese Medical Journal (Engl.)*, **104**:22–26.

Lopez I, de Andraca I, Perales CG, Heresi E, Castillo M, Colombo M (1993) Breakfast omission and cognitive performance of normal, wasted and stunted schoolchildren. *European Journal of Clinical Nutrition*, **47**:533–542.

Lozoff B, Jimenez E, Wolf AW (1991) Long-term developmental outcome of infants with iron deficiency. *New England Journal of Medicine*, **325**:687–694.

Lubchenco LO, Searls DT, Brazie JV (1972) Neonatal mortality rate: relationship to birth weight and gestational age. *Journal of Pediatrics*, **81**:814–822.

Lutter C (2000) Length of exclusive breastfeeding: linking biology and scientific evidence to a public health recommendation. *Journal of Nutrition*, **130**:1335–1338.

Lutter CK, Mora JO, Habicht JP et al. (1989) Nutritional supplementation: effects on child stunting because of diarrhea. *American Journal of Clinical Nutrition*, **50**:1–8.

Luwang NC, Datta SN (1982) Association between diarrhoeal disease and undernutrition in pre-school children. *Indian Journal of Medical Sciences*, **36**:29–30.

Man WD, Weber M, Palmer A et al. (1998) Nutritional status of children admitted to hospital with different diseases and its relationship to outcome in the Gambia, West Africa. *Tropical Medicine and International Health*, **3**: 678–686.

Martorell R, Ramakrishnan U, Schroeder DG, Melgar P, Neufeld L (1998) Intrauterine growth retardation, body size, body composition and physical performance in adolescence. *European Journal of Clinical Nutrition*, **52**:S43–52.

Martorell R, Rivera JA, Kaplowitz H, Pollitt E (1992) Longterm consequences of growth retardation during early childhood. In: *Human growth: basic and clinical aspects*. Hernandez M, Argente J, eds. Elsevier Science Publishers B.V., Amsterdam.

Mata LJ (1978) *The children of Santa Maria Cauque: a prospective field study of health and growth*. MIT Press, Cambridge, MA.

Mathur R, Reddy V, Naidu AN, Ravikumar, Krishnamachari KA (1985) Nutritional status and diarrhoeal morbidity: a longitudinal study in rural Indian preschool children. *Human Nutrition. Clinical Nutrition*, **39**:447–454.

Mati JK (1983) The Nairobi birth survey III. Labor and delivery. *Journal of Obstetrics and Gynaecology of Eastern and Central Africa*, **2**:47–56.

Mavalankar DV, Trivedi CC, Gray RH (1994) Maternal weight, height and risk of poor pregnancy outcome in Ahmedabad, India. *Indian Pediatrics*, **31**: 1205–1212.

McKay H, Sinisterra L, McKay A, Gomez H, Lloreda P (1978) Improving cognitive ability in chronically deprived children. *Science*, **200**:270–278.

McLaren DS, Yaktin US, Kanawati AA, Sabbagh S, Kadi Z (1973) The subsequent mental and physical development of rehabilitated marasmic infants. *Journal of Mental Deficiency Research*, **17**:273–281.

Mehta S, Teja JS, Wig NN, Thukral S, Pasricha S (1975) Protein calorie malnutrition—a follow-up study. *Indian Journal of Medical Research*, **63**: 576–582.

Mendez MA, Adair LS (1999) Severity and timing of stunting in the first two years of life affect performance on cognitive tests in late childhood. *Journal of Nutrition*, **129**:1555–1562.

Merchant KM, Villar J, Kestler E (2001) Maternal height and newborn size relative to risk of intrapartum caesarean delivery and perinatal distress. *British Journal of Obstetrics and Gynaecology*, **108**:689–696.

Molbak K, Jensen H, Ingholt L, Aaby P (1997) Risk factors for diarrheal disease incidence in early childhood: a community cohort study from Guinea-Bissau. *American Journal of Epidemiology*, **146**:273–282.

Monckeberg F (1972) Malnutrition and mental capacity. In: *Nutrition, the nervous system and behaviour.* (PAHO Scientific Publication, No. 251.) Pan American Health Organization, Washington, DC.

Moock PR, Leslie J (1986) Childhood malnutrition and schooling in the Teri region of Nepal. *Journal of Development Economics*, **20**:33–52.

Moore SE, Cole TJ, Collinson AC, Poskitt EM, McGregor IA, Prentice AM (1999) Prenatal or early postnatal events predict infectious deaths in young adulthood in rural Africa. *International Journal of Epidemiology*, **28**: 1088–1095.

Moore SE, Collinson AC, Prentice AM (2001) Immune function in rural Gambian children is not related to season of birth, birth size, or maternal supplementation status. *American Journal of Clinical Nutrition*, **74**: 840–847.

Morris CN (1983) Parametric empirical Bayes inference: theory and applications. *Journal of the American Statistical Association,* **78**:47–65.

Naeye RL (1990) Maternal body weight and pregnancy outcome. *American Journal of Clinical Nutrition*, **52**:273–279.

Neumann C, McDonald MA, Sigman M, Bwibo N, Marquardt M (1991) Relationships between morbidity and development in mildly to moderately malnourished Kenyan toddlers. *Pediatrics,* **88**:934–942.

Nwuga VC (1977) Effect of severe kwashiorkor on intellectual development among Nigerian children. *American Journal of Clinical Nutrition*, **30**: 1423–1430.

PAHO (1998) *Nutrition, health and child development*. (Scientific Publication No. 566.) Pan American Health Organization, Washington, DC.

Paine P, Dorea JG, Pasquali J, Monteior AM (1992) Growth and cognition in Brazilian school children: a spontaneously occurring intervention study. *International Journal of Behavioral Development*, **15**:160–183.

Parekh UC, Udani PM, Naik PA, Shah BP (1974) Mental development of children with severe protein calorie malnutrition in the past and present. *Indian Pediatrics*, **11**:465–469.

Patwari AK (1999) Diarrhoea and malnutrition interaction. *Indian Journal of Pediatrics*, **66**: S124–134.

Pek HL, Tjiook TH, Oey HJ, Lauw TG (1967) Evaluation of mental development in relation to early malnutrition. *American Journal of Clinical Nutrition,* **20**:1290–1294.

Pelletier DL (1994) The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research. *Journal of Nutrition*, **124**:S2047–2081.

Pelletier DL, Arimond M, Johnson FC, et al. (1995) Maternal anthropometry predictors of intrauterine growth retardation and prematurity in the Malawi Maternal and Child Nutrition Study. *Bulletin of the World Health Organization*, **73**:80–81.

Pelletier DL, Frongillo EA, Jr, Habicht JP (1993) Epidemiologic evidence for a potentiating effect of malnutrition on child mortality. *American Journal of Public Health*, **83**:1130–1133.

Pelletier DL, Frongillo EA, Jr, Schroeder DG, Habicht JP (1994) A methodology for estimating the contribution of malnutrition to child mortality in developing countries. *Journal of Nutrition*, **124**:S2106–2122.

Pelletier DL, Frongillo EA, Jr, Schroeder DG, Habicht JP (1995) The effects of malnutrition on child mortality in developing countries. *Bulletin of the World Health Organization*, **73**:443–448.

Peragallo-Guarda N (1984) *Severity of iron deficiency anemia and its relationship to growth and morbidity in a population of pre-schoolers in rural Guatemala* [Dissertation]. University of Texas, Houston, TX.

Pollitt E (1983) Morbidity and infant development. *International Journal of Behavioral Development*, **6**:461–475.

Pollitt E (1987) A critical view of three decades of research on the effects of chronic energy malnutrition on behavioral development. In: *Chronic energy deficiency: consequences and related issues*. Schurch B, Scrimshaw NS, eds. International Dietary Energy Consultancy Group, Lausanne.

Pollitt E (1995) Functional significance of the covariance between protein energy malnutrition and iron deficiency anemia. *Journal of Nutrition*, **125**:S2272–2277.

Pollitt E, Gorman KS, Engle PL, Martorell R, Rivera JA (1993) Early supplementary feeding and cognition: effects over two decades. *Monographs of the Society for Research in Child Development*, **58**:1–99.

Pollitt E, Gorman KS, Engle PL, Rivera JA, Martorell R (1995) Nutrition in early life and the fulfillment of intellectual potential. *Journal of Nutrition*, **125**:S1111–1118.

Pollitt E, Metallinos-Katsaras E (1990) Iron deficiency and behavior: constructs, methods, and validity of the findings. In: *Nutrition and the brain*. Wurtman RJ, Wurtman JJ, eds. Raven Press, New York.

Pollitt E, Oh S (1994) Early supplementary feeding, child development, and health policy. *Food and Nutrition Bulletin*, **15**(3).

Pollitt E, Watkins WE, Husaini MA (1997) Three-month nutritional supplementation in Indonesian infants and toddlers benefits memory function 8 years later. *American Journal of Clinical Nutrition*, **66**:1357–1363.

Powell CA, Grantham-McGregor S (1985) The ecology of nutritional status and development in young children in Kingston, Jamaica. *American Journal of Clinical Nutrition*, **41**:1322–1331.

Rajatasilpin A, Suepsaman B, Yamarat V (1970) Intellectual development and its relationship to the nutritional status among school children. *Journal of the Medical Association of Thailand*, **53**:788–793.

Rantakallio P, Laara E, Koiranen M, Sarpola A (1995) Maternal build and pregnancy outcome. *Journal of Clinical Epidemiology*, **48**:199–207.

Reyes MR, Valdecanas CM, Reyes OL, Reyes TM (1990) The effects of malnutrition on the motor, perceptual, and cognitive functions of Filipino children. *International Disability Studies*, **12**:131–136.

Ricci JA, Becker S (1996) Risk factors for wasting and stunting among children in Metro Cebu, Philippines. *American Journal of Clinical Nutrition*, **63**:966–975.

Rice AL, Sacco L, Hyder A, Black RE (2000) Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. *Bulletin of the World Health Organization*, **78**:1207–1221.

Rice AL, Sacco L, Hyder A, Frangakis C, Black RE (2001) *Malnutrition as an associated cause of death in children: evidence for an impact on cause-*

specific mortality. Report by the Department of International Health, Bloomberg School of Public Health, Johns Hopkins University [unpublished].

Richardson SA (1976) The relation of severe malnutrition in infancy to the intelligence of school children with differing life histories. *Pediatric Research*, **10**:57–61.

Richardson SA, Birch HG (1973) School performance of children who were severely malnourished in infancy. *American Journal of Mental Deficiency*, **77**:623–632.

Richardson SA, Koller H, Katz M, Albert K (1978) The contributions of differing degrees of acute and chronic malnutrition to the intellectual development of Jamaican boys. *Early Human Development*, **2**:163–170.

Rivera JA, Martorell R (1988) Nutrition, infection and growth. Part II: effects of malnutrition on infection and general conclusions. *Clinical Nutrition*, **7**:163–167.

Rose G (1985) Sick individuals and sick populations. *International Journal of Epidemiology*, **14**:32–38.

Rotimi C, Okosun I, Johnson L et al. (1999) The distribution and mortality impact of chronic energy deficiency among adult Nigerian men and women. *European Journal of Clinical Nutrition*, **53**:734–739.

Rush D (2000) Nutrition and maternal mortality in the developing world. *American Journal of Clinical Nutrition*, **72**:S212–240.

Rush D (2001) Maternal nutrition and perinatal survival. *Journal of Health, Population, and Nutrition*, **19**:S217–264.

Sachar RK, Soni RK (2000) Perinatal mortality in rural Punjab—a population-based study. *Journal of Tropical Pediatrics*, **46**:43–45.

Saco-Pollitt C, Pollitt E, Greenfield D (1985) The cumulative deficit hypothesis in the light of cross-cultural evidence. *International Journal of Behavioral Development*, **8**:75–97.

Sappenfield WM, Buehler JW, Binkin NJ, Hogue CJ, Strauss LT, Smith JC (1987) Differences in neonatal and postneonatal mortality by race, birth weight, and gestational age. *Public Health Reports*, **102**:182–192.

Sathy N, Elizabeth KE, Nair MK, Bai NS (1991) Growth faltering and developmental delay in children with PEM. *Indian Pediatrics*, **28**:255–258.

Schieve LA, Cogswell ME, Scanlon KS et al. (2000) Prepregnancy body mass index and pregnancy weight gain: associations with preterm delivery. *Obstetrics and Gynecology*, **96**:194–200.

Schorling JB, McAuliffe JF, de Souza MA, Guerrant RL (1990) Malnutrition is associated with increased diarrhoea incidence and duration among children in an urban Brazilian slum. *International Journal of Epidemiology*, **19**: 728–735.

Schroeder DG, Brown KH (1994) Nutritional status as a predictor of child survival: summarizing the association and quantifying its global impact. *Bulletin of the World Health Organization*, **72**:569–579.

Scrimshaw NS, SanGiovanni JP (1997) Synergism of nutrition, infection, and immunity: an overview. *American Journal of Clinical Nutrition*, **66**: S464–477.

Scrimshaw NS, Taylor CE, Gordon JE (1968) *Interaction of nutrition and infection*. (Monograph Series 57.) World Health Organization, Geneva.

Sebire NJ, Jolly M, Harris J, Regan L, Robinson S (2001) Is maternal underweight really a risk factor for adverse pregnancy outcome? A population-based study in London. *British Journal of Obstetrics and Gynaecology*, **108**:61–66.

Selwyn BJ (1990) The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Coordinated Data Group of BOSTID Researchers. *Reviews of Infectious Diseases*, **12**:S870–888.

Sepulveda J, Willett W, Munoz A (1988) Malnutrition and diarrhea. A longitudinal study among urban Mexican children. *American Journal of Epidemiology*, **127**:365–376.

Seshadri S, Gopaldas T (1989) Impact of iron supplementation on cognitive functions in preschool and school-aged children: the Indian experience. *American Journal of Clinical Nutrition*, **50**:S675–684.

Shah N, Ramankutty V, Premila PG, Sathy N (1994) Risk factors for severe pneumonia in children in south Kerala: a hospital-based case-control study. *Journal of Tropical Pediatrics*, **40**:201–206.

Shankar AH (2000) Nutritional modulation of malaria morbidity and mortality. *Journal of Infectious Diseases*, **182**:S37–53.

Shetty PS, James WP (1994) Body mass index. A measure of chronic energy deficiency in adults. *FAO Food and Nutrition Paper*, **56**:1–57.

Siega-Riz AM, Adair LS, Hobel CJ (1996) Maternal underweight status and inadequate rate of weight gain during the third trimester of pregnancy increases the risk of preterm delivery. *Journal of Nutrition*, **126**:146–153.

Sigman M, McDonald MA, Neumann C, Bwibo N (1991) Prediction of cognitive competence in Kenyan children from Toddler nutrition, family characteristics and abilities. *Journal of Child Psychology and Psychiatry*, **32**:307–320.

Sigman M, Neumann C, Baksh M, Bwibo N, McDonald MA (1989) Relationship between nutrition and development in Kenyan toddlers. *Journal of Pediatrics*, **115**:357–364.

Simeon DT, Grantham-McGregor S (1989) Effects of missing breakfast on the cognitive functions of school children of differing nutritional status. *American Journal of Clinical Nutrition*, **49**:646–653.

Singh MB, Sidhu K (1987) Effect of age, sex and birth order on the intelligence of well-nourished and malnourished slum children. *Indian Pediatrics*, **24**:713–718.

Singh MV, Anand NK, Gupta S, Dhingra DC (1976) Intelligence in relation to degree of malnutrition. *Indian Journal of Clinical Psychology,* **3**:117–120.

Sinha DP (1977) Measles and malnutrition in a West Bengal village. *Tropical and Geographical Medicine*, **29**:125–134.

Smith TA, Lehmann D, Coakley C, Spooner V, Alpers MP (1991) Relationships between growth and acute lower-respiratory infections in children aged less than 5 years in a highland population of Papua New Guinea. *American Journal of Clinical Nutrition*, **53**:963–970.

Snow RW, Byass P, Shenton FC, Greenwood BM (1991) The relationship between anthropometric measurements and measurements of iron status and susceptibility to malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **85**:584–589.

Soewondo S, Husaini M, Pollitt E (1989) Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. *American Journal of Clinical Nutrition*, **50**:S667–673.

Sokal D, Sawadogo L, Adjibade A (1991) Short stature and cephalopelvic disproportion in Burkina Faso, West Africa. Operations Research Team. *International Journal of Gynaecology and Obstetrics*, **35**:347–350.

Sommer A, Tarwotjo I, Djunaedi E et al. (1986) Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. *The Lancet* **1**:1169–1173.

Spinillo A, Capuzzo E, Piazzi G, Ferrari A, Morales V, Di Mario M (1998) Risk for spontaneous preterm delivery by combined body mass index and gestational weight gain patterns. *Acta Obstetricia et Gynecologica Scandinavica*, **77**:32–36.

Spooner V, Barker J, Tulloch S et al. (1989) Clinical signs and risk factors associated with pneumonia in children admitted to Goroka Hospital, Papua New Guinea. *Journal of Tropical Pediatrics*, **35**:295–300.

Spurr GB, Barac-Nieto M, Maksud MG (1977) Productivity and maximal oxygen consumption in sugar cane cutters. *American Journal of Clinical Nutrition*, **30**:316–321.

Srikantia SG, Sastri CY (1971) Observations on malnutrition and mental development. *Indian Journal of Medical Research*, **59**:S216–220.

Stein CE, Fall CH, Kumaran K, Osmond C, Cox V, Barker DJ (1996) Fetal growth and coronary heart disease in South India. *The Lancet*, **348**: 1269–1273.

Stetler HC, Trowbridge FL, Huong AY (1981) Anthropometric nutrition status and diarrhea prevalence in children in El Salvador. *American Journal of Tropical Medicine and Hygiene*, **30**:888–893.

Stoch MB, Smythe PM (1967) The effect of undernutrition during infancy on subsequent brain growth and intellectual development. *South Africa Medical Journal*, **41**:1027–1030.

Stoch MB, Smythe PM (1976) 15-year developmental study on effects of severe undernutrition during infancy on subsequent physical growth and intellectual functioning. *Archives of Disease in Childhood*, **51**:327–336.

Strauss RS, Dietz WH (1999) Low maternal weight gain in the second or third trimester increases the risk for intrauterine growth retardation. *Journal of Nutrition*, **129**:988–993.

Strupp BJ, Levitsky DA (1995) Enduring cognitive effects of early malnutrition: a theoretical reappraisal. *Journal of Nutrition*, **125**:S2221–2232.

Taha TE, Gray RH, Abdelwahab MM, Abdelhafeez AR, Abdelsalam AB (1994) Levels and determinants of perinatal mortality in central Sudan. *International Journal of Gynaecology and Obstetrics*, **45**:109–115.

Thilothammal N, Kamala KG, Ashok TP et al. (1992) Influence of maternal nutritional status on mode of delivery and asphyxia neonatorum. *Indian Journal of Pediatrics*, **59**:325–329.

Thongkrajai E, Stoeckel J, Thongkrajai P (1990) Nutritional status and the incidence and duration of diarrhoeal disease among children in northeast Thailand. *Social Science and Medicine*, **30**:773–776.

Tomkins A (1981) Nutritional status and severity of diarrhoea among pre-school children in rural Nigeria. *The Lancet*, **1**:860–862.

Tomkins A, Watson F (1989) *Malnutrition and infection: a review.* (ACC/SCN State-of-the-Art Series, Nutrition Policy Discussion Paper No. 5.) United Nations Administrative Committee on Coordination/Subcommittee on Nutrition, Geneva.

Tomkins AM, Dunn DT, Hayes RJ (1989) Nutritional status and risk of morbidity among young Gambian children allowing for social and environmental factors. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **83**:282–287.

Tonglet R, Mahangaiko LE, Zihindula PM, Wodon A, Dramaix M, Hennart P (1999) How useful are anthropometric, clinical and dietary measurements of nutritional status as predictors of morbidity of young children in central Africa? *Tropical Medicine and International Health*, **4**: 120–130.

Tsu VD (1992) Maternal height and age: risk factors for cephalopelvic disproportion in Zimbabwe. *International Journal of Epidemiology*, **21**: 941–946.

Udani PM, Bhat US, Shah BP (1976) Mental development in severe protein calorie malnutrition (a study of 252 children and 25 mothers). *Indian Pediatrics*, **13**:507–516.

UN (1999) *UN world population prospects. The 1998 revision.* United Nations, Department of International Economic and Social Affairs, New York.

UN (2001) *UN world population prospects. The 2000 revision.* United Nations, Department of International Economic and Social Affairs, New York.

Upadhyay SK, Agarwal DK, Agarwal KN (1989) Influence of malnutrition on intellectual development. *Indian Journal of Medical Research*, **90**:430–441.

Vazir S, Naidu AN, Vidyasagar P (1998) Nutritional status, psychosocial development and the home environment of Indian rural children. *Indian Pediatrics*, **35**:959–966.

Ventura SJ, Martin JA, Curtin SC, Mathews TJ (1999) Births: final data for 1997. *National Vital Statistics Report*, **47**:1–96.

Victora CG, Barros FC, Kirkwood BR, Vaughan JP (1990) Pneumonia, diarrhea, and growth in the first 4 years of life: a longitudinal study of 5914 urban Brazilian children. *American Journal of Clinical Nutrition*, **52**:391–396.

Victora CG, Fuchs SC, Flores JA, Fonseca W, Kirkwood B (1994) Risk factors for pneumonia among children in a Brazilian metropolitan area. *Pediatrics,* **93**:977–985.

Villar J, Belizan JM (1982) The relative contribution of prematurity and fetal growth retardation to low birth weight in developing and developed societies. *American Journal of Obstetrics and Gynecology*, **143**:793–798.

Villar J, de Onis M, Kestler E, Bolanos F, Cerezo R, Bernedes H (1990) The differential neonatal morbidity of the intrauterine growth retardation syndrome. *American Journal of Obstetrics and Gynecology*, **163**:151–157.

Villar J, Ezcurra EJ, Gurtner de la Fuente V, Campodonico L (1994) Preterm delivery syndrome: the unmet need. *Research and Clinical Forums,* **16**:9–38.

Waber DP, Vuori-Christiansen L, Ortiz N et al. (1981) Nutritional supplementation, maternal education, and cognitive development of infants at risk of malnutrition. *American Journal of Clinical Nutrition*, **34**:S807–813.

Walia BN, Singhi S, Gambhir SK, Sroa SR (1989) Impact of acute diarrhoea and oral rehydration solution on nutritional status of preschool children. *Indian Journal of Medical Research*, **90**:415–425.

Walker SP, Grantham-McGregor SM, Powell CA, Chang SM (2000) Effects of growth restriction in early childhood on growth, IQ, and cognition at age 11 to 12 years and the benefits of nutritional supplementation and psychosocial stimulation. *Journal of Pediatrics*, **137**:36–41.

Walter T (1993) Impact of iron deficiency on cognition in infancy and childhood. *European Journal of Clinical Nutrition*, **47**:307–316.

Waterlow JC, Buzina R, Keller W, Lane JM, Nichaman MZ, Tanner JM (1977) The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. *Bulletin of the World Health Organization*, **55**:489–498.

Wesley AG, Loening WE (1996) Assessment and 2-year follow-up of some factors associated with severity of respiratory infections in early childhood. *South Africa Medical Journal*, **86**:365–368.

West KP, LeClerq SC, Shrestha SR et al. (1997) Effects of vitamin A on growth of vitamin A-deficient children: field studies in Nepal. *Journal of Nutrition*, **127**:1957–1965.

West KP, Jr, Pokhrel RP, Katz J et al. (1991) Efficacy of vitamin A in reducing preschool child mortality in Nepal. *The Lancet*, **338**:67–71.

WHO (1978) *A growth chart for international use in maternal and child health care: guidelines for primary health care personnel.* World Health Organization, Geneva.

WHO (1992a) *International statistical classification of diseases and related health problems, 10th revision (ICD-10)*. World Health Organization, Geneva.

WHO (1992b) *Low birth weight: a tabulation of available information*. Maternal Health and Safe Motherhood Programme. World Health Organization, Geneva.

WHO (1995a) An evaluation of infant growth: the use and interpretation of anthropometry in infants. WHO Working Group on Infant Growth. *Bulletin of the World Health Organization,* **73**:165–174.

WHO (1995b) Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organization Technical Report Series,* **854**:1–452.

WHO (1997) *WHO Global Database on Child Growth and Malnutrition*. World Health Organization, Geneva.

WHO (1998) *Complementary feeding of young children in developing countries: a review of current scientific knowledge*. World Health Organization, Geneva.

WHO (1999a) *A critical link. Interventions for physical growth and psychological development. A review.* (WHO/CHS/CAH/99.3.) World Health Organization, Geneva.

WHO (1999b) *WHO recommended surveillance standards*. 2nd edn. (WHO/CDS/CSR/ISR/99.2.) World Health Organization, Geneva.

WHO (2002) *The world health report 2002: Reducing risks, promoting healthy life*. World Health Organization, Geneva.

WHO/CHD Immunisation-linked Vitamin A Supplementation Study Group (1998) Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. *The Lancet*, **352**:1257–1263.

Wierzba TF, el Yazeed RA, Savarino SJ et al. (2001) The interrelationship of malnutrition and diarrhea in a periurban area outside Alexandria, Egypt. *Journal of Pediatric Gastroenterology and Nutrition*, **32**:189–196.

Wilcox AJ (2001) On the importance—and the unimportance—of birthweight. *International Journal of Epidemiology*, **30**:1233–1241.

Williams TN, Maitland K, Phelps L et al. (1997) *Plasmodium vivax*: a cause of malnutrition in young children. *Quarterly Journal of Medicine*, **90**: 751–757.

Wilson DO, Rogers RM, Hoffman RM (1985) Nutrition and chronic lung disease. *American Review of Respiratory Disease*, **132**:1347–1365.

Winkvist A, Stenlund H, Hakimi M, Nurdiati DS, Dibley MJ (2002) Weight-gain patterns from prepregnancy until delivery among women in Central Java, Indonesia. *American Journal of Clinical Nutrition*, **75**:1072–1077.

Witter FR, Caulfield LE, Stoltzfus RJ (1995) Influence of maternal anthropometric status and birth weight on the risk of cesarean delivery. *Obstetrics and Gynecology*, **85**:947–951.

Xanthou M (1985) Immunologic deficiencies in small-for-dates neonates. *Acta Paediatrica Scandinavica*, *Supplement*, **319**:143–149.

Yoon PW, Black RE, Moulton LH, Becker S (1997) The effect of malnutrition on the risk of diarrheal and respiratory mortality in children <2 years of age in Cebu, Philippines. *American Journal of Clinical Nutrition*, **65**: 1070–1077.

Zaman K, Baqui AH, Yunus M et al. (1996) Association between nutritional status, cell-mediated immune status and acute lower respiratory infections in Bangladeshi children. *European Journal of Clinical Nutrition*, **50**:309–314.

Zinc Investigators' Collaborative Group (1999) Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *Journal of Pediatrics* **135**:689–697.

Appendix A

National surveys included in prevalence estimates

Country	*Author(s)*[a]	*Reference*
Afghanistan		(1998) *Afghanistan 1997 multiple indicator baseline (MICS). Report to UNICEF*. Centro de Investigacion de Enfermedades Tropicales (CIET), Acapulco.[b]
Algeria	Kellou K	(1987) Etat nutritionnel des enfants algériens de 0 à 10 ans et niveaux d'urbanisation d'après les résultats préliminaires de l'enquête épidémiologique sur la malnutrition protéino-énérgétique en 1987. Institut National de Santé Publique, Algiers.
Algeria	République Algérienne Démocratique et Populaire	(1992) *Enquête algérienne sur la santé de la mère et de l'enfant*. Office national des statistiques. (PAPCHILD Surveys.) The League of Arab States, Cairo.
Algeria	Ministère de la Santé et de la Population	(1996) *Enquête nationale sur les objectifs de la mi-décennie, "MDG Algérie", 1995*. Algiers.[b]
Angola		(1999) *Inquerito de indicadores multiplos (MICS) 1996*. Instituto Nacional de Estatistica, Gabinete de Monitorização das Condições de Vida da População. Luanda.[b]
Argentina	Lejarraga H, Krupitzky S, Gimenez E et al.	(1997) The organisation of a national survey for evaluating child psychomotor development in Argentina. *Paediatric and Perinatal Epidemiology*, **11**:359–373.[b]
Armenia		(1998) *The health and nutritional status of children and women in Armenia*. National Institute of Nutrition, Italy.[b]
Azerbaijan	Branca F, Burkholder B, Hamel M, Parvanta I, Robertson A	(1996) *Health and nutrition survey of internally displaced and resident population of Azerbaijan—April 1996*. Baku.[b]
Bahrain	Ministry of Health	(1992) *Bahrain child health survey 1989*. Manama.
Bangladesh	Helen Keller International, Institute of Public Health	(1985) *Bangladesh nutritional blindness study, 1982–83: nutritional findings*. Dhaka.[b]
Bangladesh	Government of the People's Republic of Bangladesh	(1987) *Report of the child nutrition status module, Bangladesh household expenditure survey 1985–86*. Bangladesh Bureau of Statistics, Dhaka.

Bangladesh	Government of the People's Republic of Bangladesh	(1991) *Report of the child nutrition status survey 1989–90*. Bangladesh Bureau of Statistics, Dhaka.
Bangladesh	Ministry of Planning	(1994) *Child nutrition survey of Bangladesh 1992*. Bangladesh Bureau of Statistics, Dhaka.
Bangladesh		(1997) *Bangladesh demographic and health survey 1996–97*. (Demographic and Health Surveys.) National Institute for Population Research and Training, Dhaka.[b]
Barbados		(1986) *National nutrition survey of Barbados, 1981*. Caribbean Food and Nutrition Institute, Jamaica.[b]
Belize	Ministry of Health	(1992) *Assessment of the food, nutrition and health situation of Belize*. (INCAP Publication DC1/002.) Institute of Nutrition of Central America and Panama, Kingston.
Benin	Kodjogbé N, Mboup G, Tossou J et al.	(1997) *Enquête démographique et de santé 1996*. (Demographic and Health Surveys.) Ministère du Plan, de la Restructuration Economique et de la Promotion de l'Emploi, Cotonou.
Bhutan		(1989) *Bhutan Directorate of Health Services. Report on the national nutrition survey*. Bhutan.
Bhutan	Ministry of Health and Education	(1999) *National anthropometric survey of under five children in Bhutan*. Division of Health Services, Thimphu.[b]
Bolivia	Government of Bolivia	(1982) *Bolivia national nutritional status survey, 1981: summary report*. National Institute for Food and Nutrition, La Paz.
Bolivia	Ministerio de Planeamiento y Coordinacion	(1990) *Encuesta nacional de demografia y salud 1989*. (Demographic and Health Surveys.) La Paz.[b]
Bolivia	Ministerio de Planeamiento y Coordinacion	(1992) *Situacion alimentaria y nutricional de Bolivia 1992*. Instituto Nacional de Alimentacion y Nutricion, La Paz.
Bolivia	Ministerio de Desarrollo Sostenible y Medio Ambiente	(1994) *Encuesta nacional de demografia y salud 1994*. (Demographic and Health Surveys.) La Paz.[b]
Bolivia	Ministerio de Desarrollo Humano	(1994) *Bolivia: mapa de la desnutricion 1990–1992*. La Paz.
Bolivia	Gutierrez Sardan M	(1997) *Encuesta nacional de multiples indicadores 1996 (MICS)*. Ministerio de Desarrollo Humano, La Paz.[b]

continued

NATIONAL SURVEYS INCLUDED IN PREVALENCE ESTIMATES (*continued*)

Country	*Author(s)*[a]	*Reference*
Bolivia	Ministerio de Haciendo, Instituto Nacional de Estadistica	(1998) *Encuesta nacional de demografia y salud 1998*. (Demographic and Health Surveys.) La Paz.[b]
Botswana		(1999) *The 1996 Botswana family health survey III*. Central Statistics Office, Gaborone.
Brazil	Monteiro CA, Benicio MH, Gouveia NC	(1991) *Growth and nutritional status of the Brazilian children: findings from the 1989 National Health and Nutrition Survey*. Country Studies on Nutritional Anthropometry (NUT/ANTREF/1/91.) World Health Organization, Geneva.[b]
Brazil	Monteiro CA, Benicio MH, Iunes R, Gouveia NC, Taddei JA, Cardoso MA	(1992) Nutritional status of Brazilian children: trends from 1975 to 1989. *Bulletin of the World Health Organization*, **70**:657–666.[b]
Brazil	Ministry of Health	(1996) *Pesquisa nacional sobre demografia e saùde 1996 (relatorio preliminar)*. (Demographic and Health Surveys.) Rio de Janeiro.[b]
Burkina Faso	Konaté DL, Sinaré T, Seroussi M	(1994) *Enquête démographique et de santé, Burkina Faso 1993*. (Demographic and Health Surveys.) Ouagadougou.[b]
Burundi	Segamba L, Ndikumasabo V, Makinson C, Ayad M	(1988) *Enquête démographique et de la santé au Burundi, 1987*. (Demographic and Health Surveys.) Gsitega.[b]
Cambodia	Ministry of Planning	(1997) *Socioeconomic survey of Cambodia 1996. Volume 1. Summary results*. National Institute of Statistics, Phnom Penh.[b]
Cameroon	The Government of Cameroon	(1978) *United Republic of Cameroon national nutrition survey*. USAID, Washington, DC.
Cameroon	Balépa M, Fotso M, Barrère B	(1992) *Enquête démographique et de santé Cameroun, 1991*. (Demographic and Health Surveys.) Yaoundé.[b]
Cameroon	Fotso M, Ndonou R, Libité PR et al.	(1999) *Enquête démographique et de santé, Cameroun 1998 (DHS)*. Bureau Central des Recensements et des Etudes de Population, Ministère des Investissements Publics et de l'Aménagement du Territoire, Yaoundé.[b]
Cape Verde	Reitmaier P, Dupret A, Cutting WAM	(1987) Better health data with a portable microcomputer at the periphery: an anthropometric survey in Cape Verde. *Bulletin of the World Health Organization*, **65**:651–657.[b]

Cape Verde	Wennberg A	(1988) Anthropometric assessment of the nutritional status of preschool children in Cape Verde. *Bulletin of the World Health Organization*, **66**:375–386.
Cape Verde	Ferreira Medina JB, Skard T, Sobhy S, America Ungaretti M	(1996) *A saúde das crianças menores de cinco anos em Cabo Verde*. Ministério de Saúde e Promoção Social and UNICEF, Cape Verde.
Central African Republic	Ministère de la Santé Publique et de la Population	(1995) *Etat nutritionnel de la population. Rapport préliminaire de l'enquête de nutrition mai–juillet 1995*. Bangui.
Central African Republic	Ndamobissi R, Mboup G, Nguélébé EO	(1995) *Enquête démographique et de santé, République Centrafricaine 1994–95*. (Demographic and Health Surveys.) Bangui.[b]
Chad		(1998) *Enquête démographique et de santé, Tchad 1996–97*. (Demographic and Health Surveys.) Bureau Central du Recensement, Direction de la Statistique, des Etudes Economiques et Démographiques, N'Djamena.[b]
Chile	Ministerio de Salud	(1986) *Estado nutricional de la poblacion en control de salud. Sistema de vigilancia alimentaria y nutricional*. Departamento de Control y Evaluacion, Santiago.
Chile	Avila B, Garcia F, Vera G	(1988) *Situacion alimentaria nutricional de Chile, periodo 1984–87*. Universidad de Chile, Santiago.
Chile	Ministerio de Salud, SISVAN	(1987) *Estado nutricional de la poblacion infantil, 1986*. Santiago.
Chile	Monckeberg F, Valienta S, Mardones F	(1987) Infant and pre-school nutrition: economical development versus intervention strategies—the case of Chile. *Nutrition Research*, **7**:327–342.
Chile	Ministerio de Salud	(1994) *National health service system*. Nutrition Unit, Santiago.
Chile	Castillo CL, Atalah E, Castro R	(1996) Alimentacion del menor de 18 meses: relacion con el estado nutricional. *Revista Chilena de Pediatria*, **67**:22–28.
Chile	Ministerio de Salud	(1995) *National health service system*. Santiago.
Chile	Ministerio de Salud	(1997) *National health service system*. Santiago.
Chile	Ministerio de Salud	(1999) *Boletin anual de vigilancia nutricional, año 1998*. Departamento Coordinacion e Informatica, Santiago.
China	Ge K	(1995) *The dietary and nutritional status of Chinese population (1992 national nutrition survey)*. Institute of Nutrition and Food Hygiene, Beijing.[b]

continued

NATIONAL SURVEYS INCLUDED IN PREVALENCE ESTIMATES (*continued*)

Country	*Author(s)*[a]	*Reference*
Colombia	Mora JO	(1982) *Situacion nutricional de la poblacion Colombiana en 1977–80. Volumen I: Resultados antropometricos y de laboratorio; Comparacion con 1965/66*, Ministerio de Salud, Instituto Nacional de Salud, Bogota.
Colombia	Mora JO, de Paredes B, de Navarro L, Rodriguez E	(1992) Consistent improvement in the nutritional status of Colombian children between 1965 and 1989. *Bulletin of PAHO*, **26**:1–13.
Colombia	Ministerio de Salud	(1988) *Tercera encuesta nacional de prevalencia del uso de anticonceptivos y primera de demografia y salud, 1986.* (Demographic and Health Surveys.) Institute for Resource Development, Bogota.[b]
Colombia		(1995) *Encuesta nacional de demografia y salud 1995*. (Demographic and Health Surveys.) Bogota.[b]
Comoros	Ministère de la Santé Publique et de la Population	(1995) *Rapport sur l'état nutritionnel et les facteurs impliqués chez les enfants de moins de deux ans en République Fédérale Islamique des Comores 1991*. Direction de la Santé Familiale, Comoros.
Comoros	Mondoha KA, Schoemaker J, Barrère M	(1997) *Enquête démographique et de santé, Comores 1996*. (Demographic and Health Surveys.) Centre National de Documentation et de Recherche Scientifique, Moroni.
Congo	Cornu A, Delpeuch F, Simondon F et al.	(1990) *Enquête nationale sur l'état nutritionnel des enfants d'age préscolaire au Congo*. (Collection Etudes et Thèses.) ORSTOM, Institut Francais de Recherche Scientifique pour le Développement en Coopération, Paris.
Costa Rica	Ministerio de Salud	(1982) *Encuesta nacional de nutrition 1982*. Departamento de Nutricion, San José.
Costa Rica	Ministerio de Salud	(1994) *Analisis del estado nutricional de la poblacion Costarricense 1992*. Departamento de Nutricion y Atencion Integral, Seccion Vigilancia Nutricional, San José.
Costa Rica	Ministerio de Salud	(1996) *Estado nutricional de preescolares atendidos por el programa de atencion primaria*. Departamento de Nutricion, Seccion de Vigilancia Nutricional, San José.
Costa Rica	Ministerio de Salud	(1996) *Encuesta nacional de nutricion: I fasciculo antropometria*. San José.
Côte d'Ivoire	Sahn DE	(1990) *Malnutrition in Côte d'Ivoire, prevalence and determinants*. (Working Paper No. 4.) World Bank, Washington, DC.[b]
Côte d'Ivoire	Sombo N'Cho, Kouassi L, Kouamé Koffi A et al.	(1995) *Enquête démographique et de santé, Côte d'Ivoire 1994*. (Demographic and Health Surveys.) Abidjan.[b]

Democratic Republic of the Congo	Ministère du Plan et Reconstruction Nationale	(1996) *Enquête nationale sur la situation des enfants et des femmes au Zaire en 1995*. Kinshasa.
Djibouti	Ministère de la Santé Publique et des Affaires Sociales	(1990) *Enquête couverture vaccinale malnutrition. République de Djibouti*. Djibouti.
Djibouti		(1997) *Enquête djiboutienne auprès des ménages indicateurs sociaux (EDAM-IS 1996)*. Ministère du Commerce et du Tourisme, Direction Nationale de la Statistique, Djibouti.
Dominican Republic		(1987) *Encuesta demografica y de salud 1986*. (Demographic and Health Surveys.) Consejo Nacional de Poblacion y Familia, Santo Domingo.[b]
Dominican Republic		(1992) *Encuesta demografica y de salud 1991*. (Demographic and Health Surveys.) Santo Domingo.[b]
Dominican Republic		(1997) *Encuesta demografica y de salud 1996*. (Demographic and Health Surveys.) Centro de Estudios Sociales y Demograficos, Asociacion Dominicana Pro Bienestar de la Familia, Oficina Nacional de Planificacion, Santo Domingo.[b]
Ecuador	Freire W, Dirren H, Mora J et al.	(1988) *Diagnostico de la situacion alimentaria, nutricional y de salud de la poblacion ecuatoriana menor de cinco años*. Ministerio de Salud Publica y Consejo Nacional de Desarrollo, Quito.
Egypt	Ministry of Health[a]	(1978) *National nutrition survey, 1978*. Cairo.[b]
Egypt	Abdel-Sayed H, Osman M, El-Zanaty F, Way A	(1989) *Egypt demographic and health survey 1988*. (Demographic and Health Surveys.) Egypt National Population Council, Cairo.[b]
Egypt		(1992) *Egyptian maternal and child health survey*. (PAPCHILD Surveys.) Agency for Public Mobilisation and Statistics, Cairo.[b]
Egypt	El-Zanaty FH, Sayed HAA, Zaky HHM, Way AA	(1993) *Egypt demographic and health survey 1992*. (Demographic and Health Surveys.) Cairo.[b]
Egypt		(1995) *National survey for assessment of vitamin "A" status in Egypt*. Nutrition Institute, Cairo.
Egypt	El-Zanaty F, Hussein EM, Shawsky GA, Way AA, Kishor S	(1996) *Egypt demographic and health survey 1995*. (Demographic and Health Surveys.) National Population Council, Cairo.[b]

continued

NATIONAL SURVEYS INCLUDED IN PREVALENCE ESTIMATES (*continued*)

Country	*Author(s)*[a]	*Reference*
Egypt		(1998) *Egypt demographic and health survey 1997*. (Demographic and Health Surveys.) El-Zanaty and Associates, Cairo.
El Salvador	Trowbridge FL	(1984) *Center for Disease Control Survey (CDC): Data on El Salvador, 1975*. Atlanta, GA.
El Salvador		(1990) *Evaluacion de la situacion alimentaria nutricional en El Salvador (ESANES-88)*. Ministerio de Salud Publica y Asistencia Social, San Salvador.
El Salvador	Salvadoran Demographic Association	(1994) *National family health survey 1993 (FESAL-93)*. Government of El Salvador, San Salvador.[b]
Eritrea	Ministry of Finance and Development	(1994) *Children and women in Eritrea: situation analysis, 1994*. Government of the State of Eritrea and UNICEF, Asmara.
Eritrea		(1997) *Eritrea demographic and health survey 1995*. (Demographic and Health Surveys.) Asmara.
Ethiopia		(1993) *Report on the national rural nutrition survey, core module*. (Statistical Bulletin No 113.) Transitional Government of Ethiopia, Central Statistical Authority, Addis Ababa.
Fiji		(1995) *1993 National nutrition survey—main report*. National Food and Nutrition Committee, Suva.
Gambia		(1997) *Report of the progress of the mid-decade goals in the Gambia (MICS), 1996 (draft)*. Central Statistics Department, Banjul.
Ghana	Alderman H	(1989) *Nutritional status in Ghana and its determinants*. (Working Paper No. 3.) World Bank, Washington, DC. (And additional analysis on the Living Standards Survey, Ghana 1987–88.)
Ghana		(1989) *Ghana demographic and health survey 1988*. (Demographic and Health Surveys.) Ghana Statistical Service, Accra.[b]
Ghana		(1994) *Ghana demographic and health survey 1993*. (Demographic and Health Surveys.) Ghana Statistical Service, Accra.[b]
Ghana		(1999) *Ghana demographic and health survey 1998*. (Demographic and Health Surveys.) Ghana Statistical Service, Accra.[b]
Guatemala	Delgado H, Hidalgo E, Giron EM, Pareja G	(1989) *Encuesta nacional de salud materno infantil 1987*. (Demographic and Health Surveys.) Ministerio de Salud Publica y Asistencia Social, Guatemala.[b]

Guatemala		(1996) *Encuesta nacional de salud materno infantil 1995*. (Demographic and Health Surveys.) Guatemala City.[b]
Guatemala		(1999) *Encuesta nacional de salud materno infantil 1998–1999*. (Demographic and Health Surveys.) Guatemala City.[b]
Guyana	Government of Guyana	(1979) *The national food and nutrition survey of Guyana 1971*. (Scientific Publication No. 323.) Georgetown.
Guyana	Caribbean Food and Nutrition Institute	(1981) *Guyana nutritional status survey 1981*. Caribbean Food and Nutrition Institute, Kingston.[b]
Guyana	Guyana Bureau of Statistics	(1994) Household income and expenditure survey 1993 and Guyana living standards measurement survey. In: *Guyana strategies for reducing poverty*. (Report No. 12861-GUA, pp. 50–67) World Bank, Washington, DC.
Haiti	Graitcer PL, Gedeon MA, de Beausset I, Duckett EM	(1980) Haiti nutrition status survey, 1978. *Bulletin of the World Health Organization*, **58**:757–765.[b]
Haiti	Ministry of Public Health and Population	(1993) *Haiti's nutrition situation in 1990: A report based on anthropometric data of the 1990 nutrition surveys*. Port-au-Prince.
Haiti	Cayemittes M, Rival A, Barrère B, Lerebours G, Gédéon MA	(1995) *Enquête mortalité, morbidité et utilisation des services (EMMUS-II) Haiti 1994/95*. (Demographic and Health Surveys.) Pétionville.[b]
Honduras	Barahona F, Soto RJ, Tronconi E, Maradiaga A, O'Connor G, Corrales G	(1988) *Encuesta nacional de nutricion, Honduras, 1987. Cuadros de frequencias por regiones de salud y nacionales*. Ministerio de Salud Publica, Tegucigalpa.[b]
Honduras	Ministerio de Salud Publica	(1993) *Encuesta nacional de epidemiologia y salud familiar (ENESF), 1991/92*. Tegucigalpa.[b]
Honduras		(1996) *National survey of socioeconomic indicators 1993/94*. Tegucigalpa.[b]
Honduras	Ministry of Health	(1997) *National micronutrient survey Honduras 1996*. Tegucigalpa.[b]
India	National Institute of Nutrition	(1993) *National Nutrition Monitoring Bureau, 1991–92 (8 States pooled data)*. Hyderabad.[b]
India	National Institute of Nutrition	(1993) *National Nutrition Monitoring Bureau, 1974–79 (8 States pooled data)*. Hyderabad.[b]
India	National Institute of Nutrition	(1993) *National Nutrition Monitoring Bureau, 1988–90 (8 States pooled data)*. Hyderabad.[b]

continued

NATIONAL SURVEYS INCLUDED IN PREVALENCE ESTIMATES (*continued*)

Country	*Author(s)*[a]	*Reference*
India	Vijayaraghavan K, Hanumantha Rao D	(1998) Diet and nutrition situation in rural India. *Indian Journal of Medical Research*, **108**:243–253.[b]
India	International Institute for Population Sciences	(1995) *National family health survey, India 1992–93*. (Demographic and Health Surveys.) Bombay.[b]
Indonesia		(1992) *National socioeconomic survey 1987 (SUSENAS-1987)*. Central Bureau of Statistics, Jakarta.[b]
Indonesia		(1997) *Indonesia multiple indicator cluster survey (MICS) 1995*. UNICEF, Jakarta. (Preliminary results provided by the Centers for Disease Control and Prevention.)
Iran (Islamic Republic of)	Undersecretary for Public Affairs, Ministry of Health and Medical Education	(1996) *Cluster survey for evaluation of mid decade goal indicators (MICS)*. Teheran.[b]
Iran (Islamic Republic of)		(2000) *The nutritional status of children, October–November 1998 (ANIS)*. Ministry of Health and Medical Education and UNICEF, Teheran.
Iraq	International Study Team	(1992) *Infant and child mortality and nutritional status of Iraqi children after the Gulf conflict: results of a community-based study*. Center for Population and Development Studies, Harvard University, Cambridge, MA.
Jamaica	Ministry of Health and Environmental Control	(1978) *Unpublished data*. The Nutrition Unit, Kingston.[b]
Jamaica		(1990) *Jamaica living standards and measurement survey 1989*. World Bank, Kingston.[b]
Jamaica		(1992) *Jamaica survey of living conditions—report 1991*. The Planning Institute and the Statistical Institute of Jamaica, Kingston.[b]
Jamaica		(1994) *Jamaica survey of living conditions 1992*. The Planning Institute and the Statistical Institute of Jamaica, Kingston.[b]
Jamaica		(1995) *Jamaica survey of living conditions 1993*. The Planning Institute and the Statistical Institute of Jamaica, Kingston.[b]
Jamaica		(1996) *Jamaica survey of living conditions, 1994*. The Planning Institute and the Statistical Institute of Jamaica, Kingston.[b]
Jamaica		(1997) *Jamaica survey of living conditions, 1995*. The Planning Institute and the Statistical Institute of Jamaica, Kingston.[b]
Jamaica		(1997) *Jamaica survey of living conditions, 1996*. The Planning Institute and the Statistical Institute of Jamaica, Kingston.[b]

Jamaica		(1998) *Jamaica survey of living conditions, 1997*. The Planning Institute and the Statistical Institute of Jamaica, Kingston.[b]
Jordan	Zou'bi A, Poedjastoeti S, Ayad M	(1992) *Jordan population and family health survey 1990*. (Demographic and Health Surveys.) Ministry of Health, Amman.[b]
Jordan		(1998) *Jordan population and family health survey 1997*. (Demographic and Health Surveys.) Department of Statistics, Amman.[b]
Kazakhstan	National Institute of Nutrition	(1996) *Kazakhstan demographic and health survey 1995*. (Demographic and Health Surveys.) Almaty.[b]
Kenya		(1991) *Fourth rural child nutrition survey, 1987*. Central Bureau of Statistics, Ministry of Planning and National Development, Nairobi.
Kenya		(1994) *Kenya demographic and health survey 1993*. (Demographic and Health Surveys.) Central Bureau of Statistics, Nairobi.[b]
Kenya	Central Bureau of Statistics	(1995) *Fifth child nutrition survey, 1994. Welfare monitoring survey*. Nairobi.
Kenya	National Council for Population and Development	(1999) *Kenya demographic and health survey 1998*. (Demographic and Health Surveys.) Central Bureau of Statistics, Nairobi.
Kiribati	Ministry of Health and Family Planning	(1990) *National nutrition survey, 1985* (draft version). Government of Kiribati, South Tarawa.
Kuwait	Bayoumi A, Moussa MAA	(1985) Kuwait nutritional survey: comparison of the nutritional status of Kuwaiti children, 0–5 years with the NCHS/CDC reference. *World Health Organization Bulletin,* **63**:521–526.
Kuwait	Amine EK, Al-Awadi FA	(1996) Nutritional status survey of preschool children in Kuwait. *Eastern Mediterranean Health Journal*, **2**:386–394.
Kyrgyzstan		(1998) *Kyrgyz Republic demographic and health survey 1997*. (Demographic and Health Surveys.) Bishkek City.[b]
Lao People's Democratic Republic		(1995) *Diagnostic de la situation nutritionnelle et consommation alimentaire au Laos. Rapport complet de l'étude sur l'état nutritionnel de la population laotienne*. (ESNA: TCP/LAO/2354.) Food and Agriculture Organization of the United Nations, Rome.
Lao People's Democratic Republic	Ministry of Public Health	(1994) *Women and children in the Lao People's Democratic Republic. Results from the Lao social indicator survey (LSIS)*. Mother and Child Institute, Vientiane.

continued

National surveys included in prevalence estimates (*continued*)

Country	*Author(s)*[a]	*Reference*
Lebanon		(1996) *Lebanon maternal and child health survey (preliminary report)*. (PAPCHILD Surveys.) The League of Arab States, Cairo.
Lesotho		(1977) *Lesotho national nutrition survey*. The Government of Lesotho, Maseru.
Lesotho	Ministries of Health and Agriculture	(1992) *National nutrition survey report, May–June 1992*. Maseru.
Lesotho	Ministry of Health	(1994) *National survey on iodine, vitamin A and iron status of women and children in Lesotho*. Maseru.
Lesotho	Spring CA	(1996) *Mid-decade goals: progress towards the world summit, May 1996 (MICS)*. Bureau of Statistics and UNICEF, Maseru.
Liberia	Ministry of Health and Social Welfare	(1978) *Liberia national nutrition survey 1975–1976*. Monrovia.
Libyan Arab Jamahiriya		(1997) *Libyan maternal and child health survey*. (PAPCHILD Surveys.) The League of Arab States, Cairo.
Madagascar	Adrianasolo R	(1986) *Etude des aspects épidémiologiques de l'allaitement maternel à Madagascar*. Laboratoire Central de Nutrition MINSAN, Antananarivo.
Madagascar	Refeno G, Rabeza V, Mboup G, Schoemaker J	(1994) *Enquête nationale démographique et sanitaire 1992*. (Demographic and Health Surveys.) Centre National de Recherches sur l'Environnement, Antananarivo.[b]
Madagascar	Institut National de la Statistique	(1995) *Enquête permanente auprès des ménages—rapport principal, décembre 1995*. Antananarivo.
Madagascar	Institut National de la Statistique	(1996) *Enquête par grappes à indicateurs multiples (résultats préliminaires). Multiple Indicators Cluster Survey*. Antananarivo.
Madagascar		(1998) *Enquête démographique et de santé, Madagascar 1997*. (Demographic and Health Surveys.) Institut National de la Statistique, Antananarivo.[b]
Malawi	Malawi Government	(1984) *National sample survey of Agriculture 1980/81. Vol. III*. National Statistics Office, Zomba.
Malawi		(1993) *Malawi demographic and health survey 1992*. (Demographic and Health Surveys.) National Statistics Office, Zomba.[b]

Malawi	Ministry of Economic Planning and Development	(1996) *Malawi social indicators survey 1995. MICS surveys.* National Statistical Office and the Centre for Social Research, Lilongwe.
Malaysia	Ministry of Health	(1994) *Annual reports, 1990–1993. Family Health Information System*. Information and Documentation Unit, Kuala Lumpur.
Malaysia	Ministry of Health	(1996) *Annual reports, 1994 and 1995. Family Health Information System*. Division of Family Health Development, Kuala Lumpur.
Maldives	Ministry of Health and Welfare	(1994) *Nutritional status and child feeding practices of Maldivian children*. Department of Public Health, Male.
Maldives		(1996) *Maldives multiple indicator survey report (MICS).* United Nations Children's Fund, Male.[b]
Maldives	Ministry of Planning and National Development, United Nations Development Programme	(1999) *Vulnerability and poverty assessment 1998*. Male.[b]
Mali	Traoré B, Konaté M, Stanton C	(1989) *Enquête démographique et de santé au Mali, 1987*. (Demographic and Health Surveys.) Bamako.[b]
Mali	Coulibaly S, Dicko F, Traoré SM, Sidibé O, Seroussi M, Barrère B	(1996) *Enquête démographique et de santé Mali 1995–1996*. (Demographic and Health Surveys.) Cellule de Planification et de Statistique, Bamako.[b]
Mali		(1996) *Enquête à indicateurs multiples au Mali (EIM) 1996 (MICS). Rapport d'analyse*. Direction Nationale de la Statistique et de l'Informatique (DNSI), Bamako.
Mauritania	Elder JA	(1990) *The socioeconomic determinants of nutritional status among children under five in Mauritania.* (Social dimensions of adjustment surveys.) World Bank, Washington, DC.
Mauritania	Ministry of Planning	(1992) *Mauritania maternal and child health survey 1990–91*. (PAPCHILD surveys.) Nouakchott.[b]
Mauritania	Ministère du Plan, Direction des Ressources Humaines	(1996) *Enquête nationale sur les indicateurs des objectifs à mi-terme en Mauritanie (MICS).* Nouakchott.
Mauritius	Ministry of Health	(1988) *Mauritius national nutrition survey 1985: summary report.* Evaluation and Nutrition Unit, Port Louis.
Mauritius	Ministry of Health	(1996) *A survey on nutrition in Mauritius and Rodrigues, 1995 (final report)*. Port Louis.

continued

NATIONAL SURVEYS INCLUDED IN PREVALENCE ESTIMATES (*continued*)

Country	*Author(s)*[a]	*Reference*
Mexico		(1990) *Encuesta nacional de alimentacion en el medio rural, 1974*. Instituto de la Nutricion 'Salvador Zubiran', Comision Nacional de Alimentacion, Division de Nutricion, INNSZ, Tlalpan, Mexico City.
Mexico		(1990) *Encuesta nacional de alimentacion en el medio rural, 1979*. Instituto de la Nutricion 'Salvador Zubiran', Comision Nacional de Alimentacion, Division de Nutricion, INNSZ, Tlalpan, Mexico City.
Mexico	Sepulveda AJ, Lezana MA, Tapia Conyer R, Valdespino IL, Madrigal H, Kumate J	(1990) Estado nutricional de preescolares y las mujeres en Mexico: resultados de una encuesta probabilistica nacional. *Gaceta Medica de Mexico*, **126**:207–226.[b]
Mexico		(1990) *Encuesta nacional de alimentacion en el medio rural, 1989 (ENAL)*. Instituto de la Nutricion 'Salvador Zubiran', Comision Nacional de Alimentacion, Division de Nutricion, INNSZ, Tlalpan, Mexico City.[b]
Mongolia	Kachondham Y	(1992) *Report of a consultancy on the Mongolian child nutrition survey*. Institute of Nutrition, Nakornpathom.
Mongolia	Kachondham Y	(2000) *Report on the 2nd national child and nutrition survey, Mongolia 1999*. Institute of Nutrition and Faculty of Medicine, Ramathibodi Hospital, Mahidol University.[b]
Morocco	Azelmat M, Ayad M, Belhachmi H	(1989) *Enquête nationale sur la planification familiale, la fécondité et la santé de la population au Maroc (ENPS) 1987*. (Demographic and Health Surveys.) Ministère de la Santé Publique, Rabat.[b]
Morocco	Azelmat M, Ayad M, Housni El A	(1993) *Enquête nationale sur la population et la santé (ENPS-II) 1992*. (Demographic and Health Surveys.) Rabat.[b]
Mozambique	Government of Mozambique, UNICEF	(1996) *Multiple indicator cluster survey Mozambique—1995. MICS surveys*. Ministry of Planning and Finance, Maputo.
Mozambique		(1998) *Moçambique inquérito demográfico e de saúde 1997*. (Demographic and Health Surveys.) Instituto Nacional de Estatística, Maputo.[b]
Myanmar	Daw Cho Nwe Oo	(1981) *Feeding practices in infants and young children in Rangoon Division. 1980–1981*. Rangoon.
Myanmar	Daw Cho Nwe Oo	(1986) *Feeding practices in young children and infants*. Department of Medical Research, Rangoon.
Myanmar	Ministry of Health	(1991) *Nutrition situation of Myanmar children. Preliminary report of the national nutrition survey 1990*. Rangoon.

Myanmar	Ministry of Health	(1994) *Nutrition situation of Myanmar children. Report of the national nutrition nurvey 1991*. Rangoon.
Myanmar	Department of Health	(1995) *National nutrition survey, 1994*. National Nutrition Centre, Yangon.
Myanmar	Ministry of Health	(1995) *Monitoring progress toward the goals of the World Summit for Children through multiple indicator cluster survey (MICS)*. Yangon.
Myanmar	Ministry of Health	(2000) *National nutrition survey 1997*. National Nutrition Centre, Yangon.[b]
Namibia	Katjiuanjo P, Titus S, Zauana M, Boerma T	(1993) *Namibia demographic and health survey 1992*. (Demographic and Health Surveys.) Windhoek.[b]
Nepal	His Majesty's Government of Nepal	(1975) *Nepal nutrition status survey, January–May 1975*. Kathmandu.[b]
Nepal	National Planning Commission	(1996) *Nepal multiple indicator surveillance: cycle I, January–March 1995 health and nutrition—final report (MICS)*. Kathmandu.[b]
Nepal	Ajit Pradhan, Ram Hari Aryal, Gokarna Regmi, Bharat Baan, Pavalavalli Govindasamy	(1997) *Nepal family health survey, 1996*. (Demographic and Health Surveys.) Ministry of Health, Kathmandu.[b]
Nicaragua	Ministerio de Salud	(1988) *Enfoque de riesgo y estado nutricional de los ninos menores de 5 anos en la region III, 1988*. Centro de investigaciones y estudios de la salud, Managua.
Nicaragua	Ministry of Health	(1982) *Unpublished data*. Managua.
Nicaragua		(1997) *Nicaragua 1993 living standards measurement survey (LSMS)*. World Bank, Washington, DC.[b]
Nicaragua	Ministerio de Salud	(1999) *Encuesta nicaraguense de demografia y salud 1998*. (Demographic and Health Surveys.) Instituto Nacional de Estadisticas y Censos, Managua.[b]
Niger	Ministère de la Santé Publique et des Affaires Sociales	(1985) *Enquête nationale sur la morbidité et la mortalité, rapport No 1*. Cellule de Planification, Niamey.
Niger	Kourguéni IA, Garba B, Barrère B	(1993) *Enquête démographique et de santé, Niger 1992*. (Demographic and Health Surveys.) Niamey.[b]

continued

NATIONAL SURVEYS INCLUDED IN PREVALENCE ESTIMATES (*continued*)

Country	*Author(s)*[a]	*Reference*
Niger	Attama S, Seroussi M, Kourguéni AI, Koché H, Barrère B	(1998) *Enquête démographique et de santé, Niger 1998*. (Demographic and Health Surveys.) Care International, Niger and Macro International Inc., Calverton, MD.[b]
Nigeria		(1992) *Nigerian demographic and health survey 1990*. (Demographic and Health Surveys.) Federal Office of Statistics, Lagos.[b]
Nigeria	Federal Ministry of Health and Social Services	(1996) *National micronutrient survey, 1993*. Ibadan.[b]
Oman	Musaiger OA (On behalf of the Ministry of Health)	(1993) *National nutrition survey of the Sultanate of Oman*. On behalf of the Ministry of Health. UNICEF, Muscat.[b]
Oman	Ministry of Health	(1995) *National study on the prevalence of vitamin A deficiency (VAD) among children 6 months to 7 years*. Muscat.[b]
Pakistan		(1992) *Pakistan demographic and health survey 1990/91*. (Demographic and Health Surveys.) National Institute of Population Studies, Islamabad.[b]
Pakistan	Government of Pakistan	(1978) *Micronutrient survey of Pakistan*. Nutrition Cell, Planning and Development Division, Islamabad.[b]
Pakistan	Government of Pakistan	(1988) *National nutrition survey 1985–87 report*. National Institute of Health, Nutrition Division, Islamabad.[b]
Pakistan	Ministry of Health	(1996) *Multiple indicator cluster survey of Pakistan, 1995. MICS surveys*. Government of Pakistan, Islamabad.
Pakistan	Pakistan Medical Research Council	(1998) *National health survey of Pakistan (NHSP, 1990–94): Health profile of the people of Pakistan*. Islamabad.
Panama	Franklin DL, Harrell M, Tamaro J, Frazao B, Vial I, Parillon C	(1982) *Nutrition evaluation project: second annual report*. Research Triangle Institute, North Carolina.
Panama	Ministerio de Salud	(1992) *Encuesta nacional de Vitamina A, 1992*. Departamento de Nutricion y Dietetica, Panama.
Papua New Guinea	Smith T, Keig G, Marks J, Grau R	(1992) *Summary results by environmental zone from the 1982/83 National Nutrition Survey of Papua New Guinea*. Papua New Guinea Institute of Medical Research, Goroka.[b]

Papua New Guinea	Jenkins C, Zemel B	(1990) *Ancient diversity and contemporary change in the growth patterns of Papua New Guinea children*. (59th Annual Meeting of the American Association of Physical Anthropologists.) Miami, FL.
Paraguay	Carron JM, Loaiza E, Ochoa LH	(1991) *Encuesta nacional de demografia y salud 1990*. (Demographic and Health Surveys.) Asuncion.[b]
Peru	Ministerio de Salud	(1988) *Situacion nutricional en el Peru. Encuesta nacional de nutricion y salud (ENSSA), 1984*; and *Evaluacion nacional de nutricion por antropometria (ENPPE), 1975*. Ministerio de Salud, Lima.
Peru	Padilla A, Ochoa LH, Marckwardt AM	(1992) *Encuesta demografica y de salud familiar 1991/1992*. (Demographic and Health Surveys.) Lima.[b]
Peru		(1997) *Peru demographic and health survey 1996*. (Demographic and Health Surveys.) Instituto Nacional de Estadistica e Informacion, Lima.[b]
Philippines		(1975) *1971–75 unpublished data*. Department of Physiological Hygiene and Nutrition, Institute of Public Health, Manila.
Philippines	Food and Nutrition Research Institute	(1982) *Second nationwide nutrition survey, Philippines, 1982*. National Science and Technology Authority, Manila.
Philippines	National Economics and Statistics Section	(1991) *Regional updating of nutritional status of Filipino children, 1989–90*. Food and Nutrition Research Institute, Manila.[b]
Philippines	Department of Science and Technology	(1991) *Third national nutrition survey Philippines, 1987*. Food and Nutrition Research Institute. Manila.[b]
Philippines	Department of Science and Technology	(1994) *The 1992 regional nutrition survey*. Food and Nutrition Research Institute, Manila.[b]
Philippines	Department of Science and Technology	(1995) *The fourth national nutrition survey: Philippines 1993*. Food and Nutrition Institute, Manila.[b]
Qatar	Amine EK	(1996) *Nutritional assessment in Qatar*. (Assignment report EM/NUT169/E/R/01.96/27.) World Health Organization Regional Office, Alexandria.
Rwanda	Meheus A, Butera S, Dindinian O, Eylenbosch W	(1977) *Evaluation de l'état nutritionnel des enfants de 0 à 5 ans dans la République Rwandaise, 1976*. Université Instelling, Antwerpen.[b]

continued

National surveys included in prevalence estimates (*continued*)

Country	*Author(s)*[a]	*Reference*
Rwanda	Barrère B, Schoemaker J, Barrère M, Habiyakare T, Kabagwira A, Ngendakumana M	(1994) *Enquête démographique et de santé, Rwanda 1992*. (Demographic and Health Surveys.) Kigali.[b]
Rwanda	Ministère de la Santé	(1997) *National nutrition survey of women and children in Rwanda in 1996*. Kigali.
Saint Lucia	The Government of St Lucia	(1976) *The national food and nutrition survey of St. Lucia, 1974*. The Caribbean Food and Nutrition Institute, Kingston.[b]
Sao Tome and Principe	Ministerio de Saude	(1986) *Estado nutricional e cobertura vacinal des crianças menoras de 5 anos na*. Secçao de Nutriçao. Sao Tome.
Senegal	Ndiaye S, Sarr I, Ayad M	(1987) *Enquête démographique et de santé au Sénégal, 1986*. (Demographic and Health Surveys.) Dakar.[b]
Senegal	Senegal Bureau of Statistics	(1993) *Social dimensions of adjustment. Household priority survey 1991–92*. World Bank, New York.
Senegal	Ndiaye S, Papa Demba Diouf, Ayad M	(1994) *Enquête démographique et de santé au Sénégal (EDS-II) 1992/93*. (Demographic and Health Surveys.) Dakar.[b]
Senegal		(1996) *Evaluation des objectifs intermédiaires (MICS)*. UNICEF, Dakar.
Seychelles	Ministry of Health	(1989) *Nutritional status of Seychellois children* (unpublished data). Victoria.
Sierra Leone	Ministry of Health	(1975) *WHO global epidemiological surveys*. World Health Organization, Health Situation Unit, Geneva.
Sierra Leone	Government of Sierra Leone, USAID	(1978) *Sierra Leone national nutrition survey 1977–78*. USAID, Washington, DC.
Sierra Leone	Ministry of Health	(1990) *The Republic of Sierra Leone national nutrition survey*. Freetown.
Solomon Islands	Solomon Islands Government	(1970) *National nutrition survey* (unpublished data). South Pacific Health Service, Honiara.
Solomon Islands	Ministry of Health and Medical Services	(1990) *Solomon Islands national nutrition survey 1989*. Honiara.[b]
South Africa	The South African Vitamin A Consultative Group	(1995) *Children aged 6 to 71 months in South Africa, 1994: their anthropometric, vitamin A, iron and immunisation coverage status*. Johannesburg.[b]

Sri Lanka	Ministry of Health	(1976) *Sri Lanka nutrition status survey, 1976*. Colombo.[b]
Sri Lanka	Ministry of Plan Implementation	(1987) *Sri Lanka demographic and health survey 1987*. (Demographic and Health Surveys.) Colombo.[b]
Sri Lanka	Ministry of Plan Implementation	(1979) *National nutritional survey 1977–78 (resurvey)*. Colombo.[b]
Sri Lanka	Department of Census and Statistics	(1995) *Sri Lanka demographic and health survey 1993*. (Demographic and Health Surveys.) Colombo.
Sri Lanka	Ramanujam P, Nestel P	(1997) Preliminary report on the fourth national nutrition and health survey July–August, 1995. *The Ceylon Journal of Medical Science*, **40**:13–24.
Sudan		(1994) *Sudanese maternal and child health survey, 1993*. (PAPCHILD surveys.) The League of Arab States, Cairo.
Swaziland	Serdula MK, Aphane JM, Kuene PF et al.	(1987) Acute and chronic undernutrition in Swaziland. *Journal of Tropical Pediatrics*, **33**:35–42.[b]
Syrian Arab Republic		(1994) *Syrian maternal and child health survey*. (PAPCHILD surveys.) The League of Arab States, Cairo.
Syrian Arab Republic	Prime Minister's Council	(1996) *Multiple indicator cluster survey in the Syrian Arab Republic (MICS)*. Central Bureau of Statistics, Damascus.
Thailand	Chayovan N, Kamnuansilpa P, Knodel J	(1988) *Thailand demographic and health survey 1987*. (Demographic and Health Surveys.) Institute of Population Studies, Chulalongkorn University, Bangkok.[b]
Thailand	Kitvorapat W, Chaotilittakul N, Sinawat S, Wanaratana L	(1996) Random survey on nutritional status of children of ages under five. *Thailand Journal of Health Promotion and Environmental Health*, **19**:57–66.[b]
Togo	Togo Ministry of Rural Development	(1978) *Togo nutrition status survey, 1977*. Lomé.[b]
Togo	Agounké A, Assogba M, Anipah K	(1989) *Enquête démographique et de santé au Togo 1988*. (Demographic and Health Surveys.) Direction Générale de la Santé, Lomé.[b]
Togo	Kotokou K, Anipah K, Jondoh C	(1996) *Enquête nationale sur la situation des enfants au Togo en 1995 (MICS) (version préliminaire)*. Ministère du Plan et de l'Aménagement du Territoire, Lomé.

continued

National surveys included in prevalence estimates (*continued*)

Country	*Author(s)*[a]	*Reference*
Togo	Anipah K, Mboup G, Ouro-Gnao AM, Boukpessi B, Messan PA, Salami-Odjo R	(1999) *Enquête démographique et de santé, Togo 1998*. (Demographic and Health Surveys.) Ministère de la Planification et du Développement Economique, Direction de la Statistique, Lomé.[b]
Trinidad and Tobago	Gueri M, Andrews N, Jutsum P, Rawlins R	(1980) Nutritional status of young children in Trinidad and Tobago. *Journal of Tropical Pediatrics,* **26**:11–15.[b]
Trinidad and Tobago	Heath K, Da Costa-Martinez D, Sheon AR	(1988) *Trinidad and Tobago demographic and health survey 1987*. (Demographic and Health Surveys.) Family Planning Association of Trinidad and Tobago, Port-of-Spain.[b]
Tunisia	Forbes AL, Pelletier O, Lowenstein FW, Lane M, Keller W	(1976) *Preliminary report of the 1973–1975 Tunisian national nutrition survey*. Tunisian National Institute of Nutrition and Food Technology, Tunis.[b]
Tunisia	Aloui T, Ayad M, Fourati H	(1989) *Enquête démographique et de santé en Tunisie 1988*. (Demographic and Health Surveys.) Office National de la Famille et de la Population, Tunis.[b]
Tunisia	Ministère de la Santé Publique, Institut National de Nutrition et de Technologie Alimentaire	(1998) *Enquête nationale 1996–1997. Evaluation de l'état nutritionnel de la population Tunisienne: Rapport national.* Sotepa Grafic, Tunis.[b]
Turkey		(1994) *Turkey demographic and health survey, 1993*. (Demographic and Health Surveys.) Ankara.[b]
Turkey	Ministry of Health	(1996) *Multiple indicator cluster survey in Turkey 1995*. National Bureau of Statistics, Ankara.
Turkey		(1999) *Turkish demographic and health survey 1998*. (Demographic and Health Surveys.) Hacettepe University, Institute of Population Studies, Ankara.[b]
Uganda	Kaijuka EM, Kaija EZA, Cross AR, Loaiza E	(1989) *Uganda demographic and health survey 1988/89*. (Demographic and Health Surveys.) Ministry of Health, Entebbe.[b]
Uganda		(1996) *Uganda demographic and health survey 1995*. (Demographic and Health Surveys.) Entebbe.[b]

United Republic of Tanzania	Ngallaba S, Kapiga SH, Ruyobya I, Boerma JT	(1992) *Tanzania demographic and health survey 1991/92*. (Demographic and Health Surveys.) Dar es Salaam.[b]
United Republic of Tanzania	Bureau of Statistics	(1997) *Tanzania demographic and health survey 1996*. (Demographic and Health Surveys.) Dar es Salaam.[b]
Uruguay	Bove MI	(1987) *Uruguay: Situacion alimentario-nutricional, algunos factores condicionantes 1970–87*. (Document prepared for the ACC/SCN.) Montevideo.
Uruguay	Ministerio de Salud Publica	(1996) *Sistema de vigilancia epidemiologica nutricional (SISVEN)*. Departamento de nutricion, Montevideo
Uzbekistan	Ministry of Health	(1997) *Uzbekistan demographic and health survey 1996*. (Demographic and Health Surveys.) Institute of Obstetrics and Gynecology, Tashkent City.[b]
Vanuatu	Hung MM	(1983) *National nutrition survey report*. Department of Health, Port Vila.
Venezuela	Instituto Nacional de Nutricion	(1986) *Encuesta nacional de nutricion 1981–82*. Caracas.
Venezuela		(1995) *Proyecto Venezuela 1987*. Centro de estudios sobre crecimiento y desarrollo de la poblacion venezolana, Caracas.[b]
Venezuela	Oficina SISVAN	(1996) *Resultados de la evalucion antropometrica del componente menores de 5 años del Sistema de Vigilancia Alimentaria y Nutricional (SISVAN) segun los puntos de corte de la OMS: Venezuela 1990–1993*. Instituto Nacional de Nutricion, Caracas.
Venezuela	Oficina SISVAN	(1996) *Clasificacion antropometrica nutricional, Venezuela 1994. INN-SISVAN componente menores de 15 años*. Instituto Nacional de Nutricion, Caracas.
Venezuela	Oficina SISVAN	(1998) *Evaluacion antropometrica nutricional de los menores de cinco años, para comparacion internacional: Venezuela 1995–1997*. Instituto Nacional de Nutricion, Caracas.
Venezuela	Oficina SISVAN	(1999) *Evaluacion antropometrica nutricional de los menores de cinco años, para comparacion internacional. Venezuela 1990–1998*. Instituto Nacional de Nutricion, Caracas.
Viet Nam	Tu Giay, Ha Huy Khoi, Luong Tan Thanh	(1986) Some characteristics about protein energy nutritional status in Vietnamese children. In: *Applied nutrition, proceedings of the international conference on applied nutrition, Hanoi 25/26 April 1986*:201–208.
Viet Nam	Ministry of Health	(1991) *Report on reanalysed data collected by the General Nutrition Survey 1987–89*. Department of Planning, Hanoi.
Viet Nam	Bloem MW, Gorstein J	(1995) *Viet Nam: Xerophthalmia free; 1994 national Vitamin A deficiency and protein-energy malnutrition prevalence survey. Consultancy report 5–17 March 1995*. National Institute of Nutrition, Hanoi.

continued

National surveys included in prevalence estimates (*continued*)

Country	*Author(s)*[a]	*Reference*
Viet Nam		(1998) *Viet Nam living standards survey 1992–93 (VNLSS)*. World Bank, Washington, DC.[b]
Viet Nam	Dibley MJ, Khoi HH, Khan NC et al.	(1999) *National protein energy malnutrition survey, Viet Nam 1998*. National Institute of Nutrition, Hanoi; and Centre for Clinical Epidemiology and Biostatistics, Newcastle, Australia.[b]
Viet Nam	Khoi HH, Khan NC, Tuyen LD, Ngu T, Xuan TT	(2000) *1999 Viet Nam—child nutrition situation. The national goal for child malnutrition control*. Medical Publishing House, Hanoi.[b]
Yemen	Ministry of Health	(1992) *Yemen maternal and child health survey*. (PAPCHILD Surveys.) Sana'a.[b]
Yemen		(1996) *Yemen multiple indicator cluster survey (March 1996): Final results*. Ministry of Planning and Development, Sana'a.[b]
Yemen		(1998) *Yemen democratic and maternal and child health survey 1997*. (Demographic and Health Surveys.) Central Statistical Organization, Sana'a.
Zambia	Wenlock RW	(1980) Nutritional risk and the family environment in Zambia. *Ecology of Food and Nutrition*, **10**:79–86.[b]
Zambia	Gaisie K, Cross AR, Nsemukila G	(1993) *Zambia demographic and health survey 1992*. (Demographic and Health Surveys.) Central Statistical Office, Lusaka.[b]
Zambia	Cogill B, Zaza M	(1990) *Report of the nutrition module as part of the crop forecasting survey—Rural Zambia 1990*. Ministry of Health, Lusaka.
Zambia		(1997) *Zambia demographic and health survey 1996*. (Demographic and Health Surveys.) Central Statistical Office, Lusaka.[b]
Zimbabwe	Ministry of Health	(1987) *Report of the nutrition component of the national health information system*. Harare.
Zimbabwe	Ministry of Finance, Economic Planning and Development	(1989) *Zimbabwe demographic and health survey, 1988*. (Demographic and Health Surveys.) Harare.[b]
Zimbabwe		(1995) *Zimbabwe demographic and health survey 1994*. (Demographic and Health Surveys.) Harare.[b]

[a] Where no authors are listed, documents have been written by multiple authors such as organizations, institutions and governments.

[b] Survey data have been reanalysed either by responsible national authorities or by WHO.

Appendix B

Numbers of countries and population coverage of children aged <5 years for underweight, by subregion

Subregion	*No. of countries/total*	*% population aged <5 years covered*
AFR-D	23/26	99.1
AFR-E	20/20	100
AMR-A	1/3	87.9
AMR-B	19/26	99.8
AMR-D	6/6	100
EMR-B	10/13	81.6
EMR-D	8/9	96.7
EUR-A	2/26	20.5
EUR-B	5/16	58.9
EUR-C	3/9	69.8
SEAR-B	3/3	100
SEAR-D	6/7	98.4
WPR-A	2/5	92.3
WPR-B	13/22	97.4

Appendix C

Trends in underweight status; references for AMR-A, EUR-A, and WPR-A

Country	*Author(s)*	*Reference*
Australia	Margarey AM, Daniels LA, Boulton TJ	(2001) Prevalence of overweight and obesity in Australian children and adolescents: reassessment of 1985 and 1995 data against new standard international definitions. *Medical Journal of Australia*, **174**:561–564.
Australia	Booth ML, Wake M, Amstrong T, Chey T, Hesketh K, Mathur S	(2001) The epidemiology of overweight and obesity among Australian children and adolescents, 1995–97. *Australian and New Zealand Journal of Public Health*, **25**:162–169.
Canada	Hanley AJG, Harris SB, Gittelsohn J, Wolever TMS, Saksvig, Zinman B	(2000) Overweight among children and adolescents in a native Canadian community: prevalence and associated factors. *American Journal of Clinical Nutrition*, **71**:693–700.
France	Deheeger M, Rolland-Cachera MF, Labadie MD, Rossignol C	(1994) Etude longitudinale de la croissance et de l'alimentation d'enfants examinés de l'âge de 10 mois à 8 ans. *Cahiers de Nutrition et de Diététique*, **XXIX**:16–23
France	Lehingue Y, Miginiac M, Locard E, Mamelle N	(1993) Birth weight and obesity at the age of 6. Study from the growth curves of a population of schoolchildren. *Pediatrie*, **48**:623–632.
Germany	Schaefer F, Georgi M, Wuhl E, Scharer K	(1998) Body mass index and percentage fat mass in healthy German school children and adolescents. *International Journal of Obesity Related Disorders*, **22**:461–469.
Germany	Kromeyer-Hauschild K, Zellner K, Jaeger U, Hoyer H	(1999) Prevalence of overweight and obesity among school children in Jena (Germany). *International Journal of Obesity Related Disorders*, **23**:1143–1150.
Greece	Mamalakis G, Kafatos A, Manios Y, Anagnosto-poulou T, Apostolaki I,	(2000) Obesity indices in a cohort of primary school children in Crete: a six year prospective study. *International Journal of Obesity & Related Metabolic Disorders*, **24**:765–771.
Japan	Mitsunori Murata	(2000) Secular trends in growth and changes in eating patterns of Japanese children. *American Journal of Clinical Nutrition*, **72**:S1379–1383.
Netherlands	Cole TJ, Roede MJ	(1999) Centiles of body mass index for Dutch children aged 0–20 years in 1980—a baseline to assess recent trends in obesity. *Annals of Human Biology*, **26**:303–308.
Netherlands	Fredriks AM, van Buuren S, Burgmeijer RJF et al.	(2000) Continuing positive secular growth change in the Netherlands 1955–1997. *Pediatric Research*, **47**:316–323.

Netherlands	Hirasing RA, Fredriks AM, van Buuren S, Verloove-Vanhorick SP, Wit JM	(2001) Increased prevalence of overweight and obesity in Dutch children and the detection of overweight and obesity using international criteria and new reference diagrams. *Nederlands Tijdschrift voor Geneeskunde*, **145**:1303–1308.
Spain	Proyecto Universitario	(1984) *Paidos'84, estudio epidemiologico sobre nutricion y obesidad infantil.* Graficas Jomagar, Mostoles, Madrid.
Spain	Moreno LA, Sarria A, Fleta J, Rodriguez G, Bueno M	(2000) Trends in body mass index and overweight prevalence among children and adolescents in the region of Aragon (Spain) from 1985 to 1995. *International Journal of Obesity and Related Metabolic Disorders*, **24**:925–931.
Spain	Rios M, Fluiters E, Perez Mendez LF, Garcia-Mayor EG, Garcia-Mayor RV	(1999) Prevalence of childhood overweight in northwestern Spain: a comparative study of two periods with a ten year interval. *International Journal of Obesity and Related Metabolic Disorders*, **23**:1095–1098.
Spain	Moreno LA, Sarria A, Fleta J, Rodriguez G, Gonzalez JM, Bueno M	(2001) Sociodemographic factors and trends on overweight prevalence in children and adolescents in Aragon (Spain) from 1985 to 1995. *Journal of Clinical Epidemiology*, **54**:921–927.
United Kingdom	Chinn S, Hughes JM, Rona RJ	(1998) Trends in growth and obesity in ethnic groups in Britain. *Archives of Disease in Childhood*, **78**:513–517.
United Kingdom	Reilly JJ, Dorosty AR.	(1999) Epidemic of obesity in UK children. *The Lancet*, **354**:1874–1875.
United Kingdom	Reilly JJ, Dorosty AR, Emmett PM	(1999) Prevalence of overweight and obesity in British children: cohort study. *British Medical Journal,* **319**:1039.
United Kingdom	Chinn S, Rona RJ	(2001) Prevalence and trends in overweight and obesity in three cross-sectional studies of British children, 1974–94. *British Medical Journal*, **322**:24–26.
United Kingdom	Bundred P, Kitchiner D, Buchan I	(2001) Prevalence of overweight and obese children between 1989 and 1998: population based series of cross-sectional studies. *British Medical Journal*, **322**:313–314.
United Kingdom	Rudolf MC, Sahota P, Barth JH, Walker J.	(2001) Increasing prevalence of obesity in primary school children: cohort study. *British Medical Journal*, **322**:1094–1095.
USA	Overpeck MD, Hediger ML, Ruan WJ et al.	(2000) Stature, weight, and body mass among young US children born at term with appropriate birth weights. *Journal of Pediatrics*, **137**:205–213.
USA	Park MK, Menard SW, Schoolfield J	(2001) Prevalences of overweight in a triethnic pediatric population of San Antonio, Texas. *International Journal of Obesity and Related Metabolic Disorders*, **25**:409–416.
USA	Mei Z, Scanlon KS, Grummer-Strawn LM, Freedman DS, Yip R, Trowbridge FL	(1998) Increasing prevalence of overweight among US low-income preschool children: the Centers for Disease Control and Prevention pediatric nutrition surveillance, 1983 to 1995. *Pediatrics*, **101**:E12.

Appendix D

National survey data on trends of underweight (<–2 SD weight-for-age) in children aged <5 years in EUR-B and EUR-C countries

Country	*Year of survey*	*% <–2 SD weight-for-age*	*Overall trend*[a]	*pp/yr*[b]	*Pop. estimate*[c]
EUR-B					
Albania	1996–1998, 2000[d]	8.1, 14.3[d]	↑	2.07	309
Armenia	1998	3.3			207
Azerbaijan	1996, 2000[d]	10.1, 16.8[d]	↑	1.68	609
Bosnia and Herzegovina	2000[d]	4.1[d]			205
Bulgaria	—	—			317
Georgia	1999	3.1			299
Kyrgyzstan	1997	11.0			524
Poland	—	—			1 994
Romania	1991	5.7			1 137
Slovakia	—	—			289
Tajikistan	—	—			773
The former Yugoslav Republic of Macedonia	1999	5.9			145
Turkey	1993, 1995, 1998	10.4, 10.3, 8.3	↓	–0.42	7 108
Turkmenistan	—	—			602
Uzbekistan	1996	18.8			2 761
Former Yugoslavia	1996, 2000	1.6, 1.9	↔	–0.08	640
EUR-C					
Belarus	—	—			468
Estonia	—	—			61
Hungary	1980–1988	2.2			490
Kazakhstan	1995, 1999	8.3, 4.2	↓	–1.03	1 273
Latvia	—	—			93
Lithuania	—	—			186
Republic of Moldova	—	—			258
Russian Federation	1993, 1995	4.2, 3.0	↓	–0.60	6 362
Ukraine	2000[d]	3.0[d]			2 190

Key: ↑, Rising: ≥0.30 percentage points per year; ↔, Static: <0.30 or >–0.30 percentage points per year; ↓, Falling; ≥–0.30 percentage points per year.

— No data.

[a] For countries with no arrow, a trend could not be established.

[b] Percentage point change per year calculated by dividing the difference between the earliest and the last data points by the number of years between the two surveys. Trends are classified as rising, static or falling according to the cut-offs listed above.

[c] *World population prospects: the 2000 revision*; estimates refer to total number (000s) of children aged <5 years in 2000, sexes combined.

[d] MICS end-decade draft results.

Appendix E

Trends in underweight status; references for EUR-B and EUR-C

(a) References for EUR-B

Country	*Author(s)*[a]	*Reference*
Georgia		(2000) *Georgia multiple indicator cluster survey 1999 (MICS)*. Tibilisi.[b]
Hungary	Nemeth A, Eiben OG	(1997) Secular growth changes in Budapest in the 20th century. *Acta Medica Auxologica*, **29**:5–12.

[a] Where no authors are listed, documents have been written by multiple authors such as organizations, institutions and governments.

[b] Survey data have been reanalysed either by responsible national authorities or by WHO.

(b) References for EUR-C

Country	*Author(s)*	*Reference*
Russian Federation	Popkin BM, Richards MK, Monteiro CA	(1996) Stunting is associated with overweight in children of four nations that are undergoing the nutrition transition. *Journal of Nutition*, **126**:3009–3016.
Russian Federation	Popkin BM et al.	Russia longitudinal monitoring survey, http://www.cpc.unc.edu/projects/rlms/
Russian Federation	Khandy MV	(1997) Dynamics of growth and development of rural children in the Republic of Sakha (Yakutia) over a 70 year period. *Gigiena i Sanitariia*, **4**:30–31.
Russian Federation	Beliaev EN, Chiburaev VI, Ivanov AA, Plantonova AG, Markelova SV	(2000) Characteristics of actual nutrition and health of children in regions of the Russian Federation. *Voprosy Pitaniia*, **69**:3–7.

Chapter 3

Iron deficiency anaemia

Rebecca J. Stoltzfus, Luke Mullany and
Robert E. Black

Summary

Iron deficiency is a highly prevalent form of undernutrition, affecting around one-fourth of the world's women and children, and is one of the most common causes of anaemia.

We conducted comprehensive reviews of published literature linking iron deficiency to disability and death for four potential outcomes: child mortality, perinatal mortality, maternal mortality and mild mental retardation. For all of these outcomes, the best available data were prospective observational studies in which anaemia or haemoglobin concentration was the risk factor. Data on child mortality were not adequate for this task, although a true risk cannot be precluded by the data. Summary relative risks for perinatal mortality (10 studies), maternal mortality (six studies) and mental retardation (five studies) were estimated using random effects models (both mortality outcomes) or a fixed-effects model (retardation) and weighting individual estimates by the inverse of their within-study variance. For mortality outcomes, the bivariate relations between haemoglobin and death were used. In two studies of perinatal mortality, unadjusted and multivariate adjusted odds ratios were compared to assess the potential degree of bias in the unadjusted associations. For mental retardation, published multivariate adjusted relations between haemoglobin and IQ were used. Global anaemia prevalence data were supplied by the World Health Organization (WHO), and converted to mean haemoglobin concentrations, assuming normal distribution and observed standard deviations from a large number of studies. To estimate the haemoglobin distribution if iron deficiency were corrected, we assumed the prevalence of anaemia in women and children would be reduced by 50%. On average, for the world, this would increase haemoglobin concentration by about 0.45 g/dl (range: 0.0 g/dl to 1.28 g/dl).

The relative risks associated with a 1 g/dl increase in population mean haemoglobin were 0.75 (95% CI 0.62–0.89) for maternal mortality, 0.72 (0.65–0.81) for perinatal mortality and 0.78 (0.70–0.86) for mental retardation. Subgroup analyses suggested that the relative risk for perinatal mortality in malaria-endemic regions, 0.65 (0.56–0.75), was lower than that in regions without endemic *Plasmodium falciparum* malaria, 0.80 (0.73–0.87). These estimates were attenuated by 20% to account for probable bias leading to overestimation of the true relationship. Based on these estimates of iron deficiency anaemia as a risk factor for mortality, iron deficiency is estimated to cause 591 000 perinatal deaths and 115 000 maternal deaths globally. The associated loss of healthy life years amounts to more than 19 million disability-adjusted life years (DALYs) from perinatal causes and more than 3 million from maternal causes. When the direct sequelae of iron deficiency anaemia are added, the total global burden attributed to iron deficiency anaemia amounts to 841 000 deaths and 35 057 000 DALYs.

The available evidence suggests that iron deficiency anaemia contributes substantially to death and disability in the world. The great majority of this disease burden derives from anaemia in pregnancy and early childhood and is borne by women and children in Asia and Africa. The high global prevalence of anaemia and its potentially associated disease burden, as reflected in these estimates, constitute an urgent research agenda. Because these estimates are uncertain in many respects, their most important use may be to motivate public health scientists to provide definitive evidence.

1. Introduction

Iron deficiency is one of the most prevalent nutrient deficiencies in the world, affecting an estimated two billion people (Stoltzfus and Dreyfuss 1998). Young children and pregnant and postpartum women are the most commonly and severely affected because of the high iron demands of infant growth and pregnancy. However, where diets are based mostly on staple foods with little meat intake, or people are exposed to infections that cause blood loss (primarily hookworms and urinary schistosomiasis), iron deficiency may occur throughout the life span. Current WHO/International Nutritional Anemia Consultative Group/United Nations Children's fund/United Nations Children's fund (WHO/INACG/UNICEF) guidelines recommend universal iron and folic acid supplementation of young children and pregnant women where anaemia is highly prevalent (Stoltzfus and Dreyfuss 1998).

Although much is known about iron metabolism, the health consequences of iron deficiency continue to be a subject of research and debate. This is partly because in many regions of the world iron supplements are the standard of care for individuals with anaemia. Most trials of iron supplementation have measured haemoglobin concentra-

tion as the primary outcome. There is a relatively small body of clinical trials of iron repletion to humans with functional iron deficiency (i.e. iron deficiency severe enough to affect erythropoiesis) with pregnancy outcomes or mortality as primary objectives. There is surprisingly little evidence to either support or refute a causal link between iron deficiency and these important adverse health outcomes. As processes like this comparative risk assessment (CRA) bring to light the overall weakness of evidence either supporting or refuting the relationship, new research priorities may emerge.

2. Health outcomes considered

In May 2000, a meeting commissioned by WHO, INACG and the Edna McConnell Clark Foundation systematically reviewed the evidence of a causal relationship between iron deficiency or anaemia and six health outcomes: child mortality, maternal mortality, birth outcomes, morbidity, work productivity and child development. These papers were subsequently published in a supplement to the *Journal of Nutrition* (Beard and Stoltzfus 2001). We began by considering those six outcomes.

Malnutrition (in this case, iron deficiency) may contribute to death and disability through direct sequelae or as a risk factor for death and disability from other causes. The total death and disability attributed to iron deficiency is therefore the sum of its actions as a risk factor and its direct sequelae. The objective of the present paper is to consider iron deficiency as a risk factor for death and disability from other causes.

Of the six outcomes considered above, child mortality, maternal mortality, birth outcomes and morbidity were considered in the framework of iron deficiency as a risk factor. For example, women do not die in childbirth as a direct effect of iron deficiency, but rather die of heart failure due to blood loss, which is made more precipitous by iron deficiency anaemia. Similarly, babies do not die in the perinatal period from iron deficiency, but rather die of other causes, some of which are related to preterm birth, for which maternal iron deficiency is a risk factor. In contrast, decreased work productivity and altered child development (or intelligence) were considered to be direct sequelae of iron deficiency, the assumption being that iron deficiency directly causes decreased oxygen delivery to muscles and the brain.

2.1 Outcomes considered

Child mortality

There is a body of observational evidence linking child mortality to anaemia. However, we could find no published or unpublished studies of reasonably large size that described the relationship between anaemia and cause-specific mortality. Furthermore, nearly all the evidence linking anaemia to overall mortality comes from sub-Saharan Africa or Papua New Guinea, where *P. falciparum* malaria is a major cause of anaemia,

especially severe anaemia, and malaria is also a major cause of mortality. Thus it seemed unjustified to attribute the observed relationship between anaemia and mortality to iron deficiency in this context, or to generalize to other regions of the world. Brabin et al. (2001a) summarized these data and their interpretation. There are no observational studies linking iron deficiency *per se* to child mortality, nor any iron supplementation trials with child mortality as outcome. For these reasons, we were unable to estimate the relationship between iron deficiency and cause-specific child mortality. However, it is important to note that the available evidence does not preclude that relationship.

Maternal mortality

There are a number of observational studies of anaemia and maternal mortality from both Africa and Asia. None of these studies attempted to distinguish iron deficiency anaemia from other causes of anaemia, although several discussed the multiple causes of anaemia within their study population. Where *P. falciparum* malaria is endemic, it is an important cause of anaemia, especially in first pregnancies (Brabin 1983). However, there is no evidence that malarial infection contributes directly to maternal mortality, even in areas where *P. falciparum* is endemic (Brabin et al. 2001b). Thus in contrast to the situation with child mortality, it is less plausible that malaria would confound the observed relationship between anaemia and maternal mortality (as it likely does with anaemia and child mortality). There are no observational studies linking iron deficiency *per se* to maternal mortality, nor are there any iron intervention trials with maternal mortality as outcome. Thus we used the available observational data to estimate the relationship between anaemia and maternal mortality.

Perinatal mortality

There are several observational studies of maternal anaemia and stillbirths, neonatal or perinatal mortality from Africa, Asia, North America, and the United Kingdom of Great Britain and Northern Ireland. None of these studies attempted to distinguish iron deficiency anaemia from other causes linking anaemia. There are no observational studies linking maternal iron deficiency *per se* to perinatal mortality, and the few published iron intervention trials with perinatal morality as outcome are small or poorly designed. As with maternal mortality, we used the available observational data to estimate the anaemia–perinatal mortality relationship.

Low birth weight

We did not consider low birth weight as a separate outcome in these analyses, but rather assumed that the mortality risk and morbidity burden of anaemia-associated low birth weight was subsumed in our estimate of perinatal mortality as outcome. The relationship between iron status and

low birth weight has been examined in several clinical trials, and it has been the subject of two recent systematic reviews (Mahomed 2000a; Rasmussen 2001). Both concluded that causal evidence from trials is lacking. Rasmussen (2001) noted that there was insufficient evidence from these trials either to support or refute the relationship, because most trials conducted in populations with a significant burden of anaemia have suffered from poor research designs. There is however a substantial body of observational data relating pregnancy anaemia to low birth weight, similar to the observational data relating pregnancy anaemia to maternal and perinatal mortality. Scott Poe and Mary Cogswell (personal communication) have recently completed a meta-analysis of these observational studies. They found that pregnancy anaemia assessed in the first two trimesters of pregnancy was significantly associated with preterm birth (but not intrauterine growth retardation), and that the risk of preterm birth increased with increasing severity of anaemia.

2.2 Outcomes considered to be direct sequelae of iron deficiency

Work productivity

There is a substantial body of evidence in animals and humans demonstrating that iron deficiency decreases fitness and aerobic work capacity through mechanisms that include oxygen transport and respiratory efficiency within the muscle (Beard 2001; Haas and Brownlie 2001). This relationship is directly and linearly related to the severity of iron deficiency anaemia. The personal and socioeconomic consequences of this relationship are likely to be real and measurable (Horton and Levin 2001). This consequence of iron deficiency is estimated as a direct sequela of iron deficiency, and is not presented here as a risk factor.

Intelligence or cognitive capacity

There is a growing body of evidence from animal and human studies that supports a causal relationship between iron deficiency anaemia in early childhood and intelligence in mid-childhood (Beard 2001; Grantham-McGregor and Ani 2001). Although this effect of iron deficiency will be considered as a direct sequela of iron deficiency, we used the observational studies of iron deficiency anaemia in early childhood and measures of intelligence in mid-childhood to obtain a quantitative estimate of this relationship. Different investigators used different measures of cognition, learning or intelligence, making it impossible to summarize all the results. We therefore limited the outcome to global measures of intelligence that were either IQ or on the same scale as IQ (i.e. mean of 100 with standard deviation of 15 points). However, all of these studies measured deviations in intelligence within the clinically normal range (i.e. ≥70 points). In terms of the International Statistical Classification of Diseases and Related Health Problems, ninth revision

(ICD-9) classification, disability in this domain is limited to mental retardation, which these studies do not directly address. We have therefore provided an estimate of the effect of early iron deficiency on mental retardation in mid-childhood, making the controversial assumption that the reported association of iron deficiency anaemia and mean IQ does not affect the variance of IQ. Based on this assumption we can estimate the expected increased risk of IQ <70 (i.e. mild mental retardation) associated with shifts in mean IQ.

Morbidity

The bulk of experimental evidence from iron supplementation trials regards morbidity. There is evidence that sufficient iron is essential for immune function (Beard 2001), and also that excess iron may exacerbate some diseases. The evidence from experimental trials does not suggest that iron supplementation reduces morbidity; in some cases it has been associated with increased morbidity, most notably malaria and respiratory infections in malarious areas (Oppenheimer 2001). However, it is most plausible that this excess risk is associated with therapeutic iron supplementation intended to treat iron deficiency; not that iron deficiency itself is beneficial. Those trials that used low-dose oral supplementation in currently recommended dosages found no adverse effect (INACG 1999). Therefore, we did not estimate a morbidity risk associated with iron deficiency; nor does the available evidence support a risk associated with the correction of iron deficiency by currently recommended public health strategies.

To summarize, we have presented estimates of risk relationships for maternal mortality and perinatal mortality. These were based on anaemia as the indicator of iron deficiency, and only a proportion of that risk is therefore attributed to iron deficiency. We have also presented an estimate of the relationship between iron deficiency anaemia, decreased IQ and mental retardation, although we believe it should be interpreted with extreme caution.

3. Nature and definition of the risk factor

Iron is required in all tissues of the body for cellular respiration and many other reduction-oxidation enzyme systems, and has particular functions in muscle, brain and red cells. Critical metabolic functions in these three organs become perturbed at about the same time as animals are depleted of iron (Beard 2001). Anaemia has been used as the hallmark of iron deficiency severe enough to affect tissue function, because red cells are the tissue most amenable to sampling. Although more specific indicators of functional iron deficiency are available, notably erythrocyte protoporphyrin and serum transferrin receptor, there is insufficient data to link those indicators to the health outcomes that fit the construct of this project, namely maternal and perinatal mortality.

It is problematic that all of the available data on maternal and perinatal mortality use anaemia as the indicator, because iron deficiency is not the sole cause of anaemia in most populations. Even within individuals, anaemia may be caused by multiple factors. The available studies do not attempt to separate iron deficiency from anaemia, and there are no good regional estimates of the proportion of anaemia attributable to iron deficiency, although the topic has been discussed and debated (Gillespie and Johnston 1998).

We therefore took the approach of estimating the risk function associated with low haemoglobin, using haemoglobin as a continuous variable. Where studies reported haematocrit instead of haemoglobin, we converted to haemoglobin by dividing haematocrit by 3.

Because our task was to estimate the burden due to iron deficiency, the counterfactual (i.e. theoretical minimum) distribution should therefore represent the haemoglobin distribution if iron deficiency were eliminated. We assumed that the change in haemoglobin distribution following a supervised period of iron supplementation was a conservative approximation of the virtual elimination of iron deficiency.[1] By conservative we mean that it is more likely to underestimate the contribution of iron deficiency than to overestimate it, due to problems of noncompliance with supplementation, insufficient dosage, or insufficient duration.

We approached this calculation from two angles. The first approach was to estimate the percentage of anaemia attributable to iron deficiency. Knowing this, we could estimate the shift in the haemoglobin distribution needed to reduce anaemia by that proportion. Beaton recently summarized the per cent reduction in anaemia observed in nine controlled supplementation trials, all conducted in children (Table 3.1). The range of values was wide, 21–85%. Although there is regional diversity in the studies, these data are not sufficient to generate regional estimates. They provide a global average of 51%.

A second and complementary approach was to examine mean changes in haemoglobin attributable to iron supplementation in iron supplementation trials. Sloan et al. (2002) conducted a meta-analysis of haemoglobin response to iron supplementation to pregnant women in randomized controlled trials. Of 70 trials in the literature, 23 met their inclusion criteria, and 15 of those were from developing countries. In studies from developing countries, haemoglobin response was smaller in study samples with higher initial haemoglobin (summarized mean change of 1.13 g/dl in those with initial mean haemoglobin <10.0 g/dl compared to 0.85 g/dl in those with haemoglobin 11.0–11.9 g/dl). However, in studies from developed countries, the initial haemoglobin concentrations were uniformly ≥11.0 g/dl, and the effect size was large (1.17 g/dl). The response to iron supplementation was strongly related to iron dose, with maximum effects observed in the eight studies that provided a daily dose ≥91 mg. In these studies the mean haemoglobin response was around

Table 3.1 Estimated proportion of anaemia attributable to iron deficiency

Site	*Age group*	*Estimated attribution to iron*[a]
Bolivia	School children	84
India (Baroda)	Adolescents	26
India (Bombay)	Adolescents	55
India (Delhi)	Adolescents	41
Indonesia	Adolescents	63
Mali	Adolescents	21
Peru	School children	52
Sri Lanka	Adolescents	36
Viet Nam	Preschool children	85
Average		51

[a] Percentage reduction in anaemia in supplemented group minus per cent age reduction in control group.

Source: Beaton (2002).

1.8 g/dl. This maximal response might be considered the best theoretical basis for predicting the effect of eradicating iron deficiency. However, it is likely that the highest doses were also used in studies of more severely anaemic populations. A case can also be made for using 1.17 as the predicted effect size, as this was the average effect seen in women from developed countries, and very similar to that seen in women from developing countries with initially low haemoglobin (1.10–1.13 g/dl).

An important question for the present exercise is whether the predicted haemoglobin shift should vary by region. Sloan et al. (2002) did not disaggregate their data by global region, and the studies examined by Beaton are too few to disaggregate (see Table 3.1). If significant regional differences exist in the percentage of anaemia attributed to iron deficiency, the iron-attributable portion might be smaller in Africa, where malaria contributes greatly to the burden of anaemia. Therefore iron would logically claim a smaller portion of total anaemia. Shankar recently summarized data from controlled iron supplementation trials conducted in *P. falciparum* malaria-endemic populations, including the haemoglobin response attributable to iron (INACG 1999). Eleven studies were included, nine of them from sub-Saharan Africa (Adam 1997; Fleming et al. 1986; Harvey et al. 1989; Lawless et al. 1994; Menendez et al. 1994, 1997; Murray et al. 1978; Oppenheimer et al. 1986; Smith et al. 1989). The studies included younger and older children, and adults, including pregnant women. The change in haemoglobin attributable to iron supplementation in individual studies ranged from 0.3 to 3.6 g/dl, yielding a weighted average of 1.24 (95% CI 1.16–1.33). Although malaria certainly contributed to anaemia in these populations, it is

remarkable that the haemoglobin response to iron supplementation was similar to that reported by Sloan et al. (2002). Two of the 11 studies in the Shankar analysis were in pregnant women—the subject of analysis by Sloan et al. and the group at risk for the outcomes estimated in this chapter. These two studies from the Shankar analysis both used an iron dose of 60 mg/day, and yield a weighted average haemoglobin response of 0.83 g/dl. These studies were excluded from the analysis by Sloan et al., but are consistent with the haemoglobin responses at the dosage reported by them: 0.41 in studies of doses ≤60 mg/day, and 0.86 in studies of doses 61–90 mg/day.

Thus, the data suggest that iron deficiency is responsible for about 50% of anaemia, and that, where anaemia is prevalent, elimination of iron deficiency results in a change in mean haemoglobin of about 1.17 g/dl or perhaps even higher. The data are lacking in several respects: notably, the studies included in these three meta-analyses did not include non-pregnant adults outside of Africa. From the data at hand, there is no strong basis for altering these values by region. We used both of these lines of evidence to estimate the proportion of the risk associated with anaemia that is attributable to iron deficiency (see section 8).

4. Search strategy

4.1 Maternal mortality

We based our work on the recent systematic review by Brabin et al. (2001b). Because there are no experimental trials of iron deficiency and maternal mortality, we estimated the risk relationship from observational data. As described by Brabin et al. (2001b), several studies from Nigeria have documented extremely high risks of maternal mortality at haemoglobin concentrations <5 g/dl. We decided to limit our description of the haemoglobin-mortality risk relationship to the haemoglobin range of 5–12 g/dl. Values <5 g/dl are rare on a population basis, being more than 2 standard deviations below the mean in even the most severely anaemic communities, and we did not want those data to influence our risk estimates for the common population ranges. Pregnancy haemoglobin values >12 g/dl were excluded because we judged that variation in this high range is mostly unrelated to iron status, and our ultimate objective was to estimate risk associated with iron deficiency. We thus included those studies that reported mortality rates in at least two haemoglobin groups in the range of 5–12 g/dl rates. This excluded three studies: Fullerton and Turner (1962), Johnson and Ojo (1967) and Tasker (1958). We further excluded the study of Chi et al. (1981) from Indonesia, because the haemoglobin categories presented in their Table 5 disagreed with that in the text and we had no basis for determining which was correct. In summary, 10 studies were identified, and six of these were included in the meta-analysis (see Table 3.2 for study descriptions).

Table 3.2 Observational studies of anaemia and maternal mortality

Country (reference)	*Site*	*Period of data collection*	*Selection criteria*	*Time in pregnancy of anaemia assessment*	*Etiologies of anaemia at population level*
India (Konar et al. 1980)	Calcutta	1964–1973	Anaemic and nonanaemic 20–32 weeks pregnant women	Mid-pregnancy	Not discussed
India (Sarin 1995)	Punjab	1990–1994	Population-based survey of pregnant women	Different stages during pregnancies	Iron deficiency anaemia
Indonesia (Chi et al. 1981)	Java (multicentre)	1977–1980	Women admitted for delivery to 12 hospitals	At delivery, upon admission	Not discussed
Malaysia (Llewellyn-Jones 1965)	Kuala Lumpur	1953–1962	Women treated at Maternity Hospital in given time period	Not stated	Iron deficiency anaemia: (i) hookworm; (ii) diet. Megaloblastic anaemia: (i) liver damage in malnutrition (ii) diet-amount of folic acid, haemolytic, normoblastic anaemia
Malaysia (Tasker 1958)	Kuala Lumpur	1952–1958	Women admitted to obstetric unit at General Hospital in Kuala Lumpur	At delivery, upon admission	Iron deficiency and some megaloblastic anaemia
Nigeria (Fullerton and Turner 1962)	Ibadan	1957–1958	Pregnant women with severe anaemia (haematocrit ≤13%) not treated by exchange transfusion	At delivery, upon admission	Haemolytic anaemia—due to malaria
Nigeria (Johnson and Ojo 1967)	Ibadan	1961	20–32 weeks pregnant, anaemic (haematocrit ≤24%) women	20–32 weeks	Haemolysis; folic acid deficiency
Nigeria (Harrison 1975)	Ibadan	1965–1967	Pregnant women with haematocrit ≤26%	Pregnant and puerperal women in hospital	Red cell haemolysis due to malaria, dietary deficiency of folates and haemoglobinopathies
Nigeria (Harrison 1982)	Zaria	1976	Pregnant women who develop anaemia	Mid-pregnancy	Nutritional deficiency of iron and folates, malaria, haemoglobinopathies, blood loss, bacterial infections, and socioeconomic deprivation
Nigeria (Harrison and Rossiter 1985)	Zaria	—	Zaria area pregnant women	At delivery and interval between admission and death	Combined effects of malaria, dietary deficiency of iron and folic acid, sometime blood loss

Country (reference)	*Method of anaemia assessment*	*Maternal mortality definition*	*Level of care*	*Number of deaths/ total sample*	*Reasons for exclusion (see text for details)*
India (Konar et al. 1980)	Haemoglobin level at time of admission, method not stated	Death of any woman dying of any cause while pregnant or within 42 days of term of pregnancy	Eden Hospital, Calcutta (referral hospital for urban and rural population)	637/114 698	
India (Sarin 1995)	Haemoglobin determined by Tallqvist screen for anaemia followed by Sahli acid haematin method for anaemics	Death of pregnant women at delivery according to hospital records (1982–1994)	Referral hospital in area	339/38 565	
Indonesia (Chi et al. 1981)	Haemoglobin at time of admission	Hospital puerperal mortality rate	12 teaching hospitals (urban and rural)	135/36 062	Haemoglobin categories difficult to interpret
Malaysia (Llewellyn-Jones 1965)	Haemoglobin, method not stated	Death at childbirth	Maternity Hospital, Kuala Lumpur	283/73 048	
Malaysia (Tasker 1958)	Haemoglobin determined by Tallqvist screen for anaemia followed by Sahli acid haematin method for anaemics	Death at childbirth	Institute of Medical Research, Kuala Lumpur	132/28 720	Less than two groups with haemoglobin midpoint >5 g/dl

continued

Table 3.2 Observational studies of anaemia and maternal mortality (*continued*)

Country (reference)	*Method of anaemia assessment*	*Maternal mortality definition*	*Level of care*	*Number of deaths/ total sample*	*Reasons for exclusion (see text for details)*
Nigeria (Fullerton and Turner 1962)	Haematocrit	Death at childbirth	University College Hospital, Ibadan	18/92	Less than two groups with haemoglobin midpoint >5 g/dl
Nigeria (Johnson and Ojo 1967)	Microhaematocrit prior to amniocentesis, bone marrow at delivery	Deaths in anaemic and non-anaemic women 20–32 weeks pregnant	University College Hospital, Ibadan	9/234	Less than two groups with haemoglobin midpoint >5 g/dl
Nigeria (Harrison 1975)	Haematocrit	Death in pregnancy, labour or puerperium	University College Hospital, Ibadan	10/401 (excluding group with haematocrit <14%)	
Nigeria (Harrison 1982)	Haemoglobin from capillary sample, method not stated	Death in pregnancy, labour or puerperium	Hospital, Zaria	8/258	
Nigeria (Harrison 1985)	Haematocrit	Deaths during pregnancy and up to 42 days afterward	Hospital access but many home deliveries	121/1 777	

— No data.

Note: Shaded rows indicate excluded studies.

4.2 Perinatal mortality

As with maternal mortality, we estimated the risk relationship from observational studies, using pregnancy or delivery maternal haemoglobin concentration as the risk factor. Published trials of iron supplementation that reported perinatal or neonatal mortality as an outcome were not used as a basis for our risk estimate because the women in the trial were not anaemic (Hemminki and Rimpelä 1991) or because they were small or poorly designed to test the effect of iron (Agarwal et al. 1991; Fleming et al. 1986).

We based our search on the recent systematic reviews of Brabin et al. (2001b), Rasmussen (2001) and Xiong et al. (2000). We added to this one unpublished study by Dreyfuss et al. in which one of us was involved. Xiong et al. described the relationship between pregnancy anaemia and perinatal outcomes in 16 936 women in China. This study is published only as an abstract (Xiong et al. 1996); however, the authors provided the data we needed to include here. In summary, 13 studies were identified and 10 were included in the meta-analysis (see Table 3.3 for study descriptions).

4.3 Child development

We based our work on the recent systematic review by Grantham-McGregor and Ani (2001). We were interested in estimating the risk of continuous decrement in cognitive function or capacity in children who were iron-deficient anaemic in early childhood. Thus we limited our meta-analysis to those studies that identified iron-deficient anaemic and non-anaemic infants and toddlers and then compared their intelligence at age 2–7 years. We further limited the meta-analysis to studies that used standardized tests on a scale of 100 with standard deviation 15 (i.e. IQ tests and the Bayley Mental Development Index). Seven different longitudinal studies were described by Grantham-McGregor and Ani (Table 3.4). The study by Hurtado et al. (1999) was excluded because the outcome measure was placement in special education, rather than a measure of intelligence. Similarly, the study by Dommergues et al. (1989) was excluded because the outcome measure (Brunet-Lezine test) did not meet our criterion for a summarizable outcome. The two longitudinal studies by Lozoff et al. followed the same cohort of children; the data from the 1991 publication were used in this analysis. The two studies of Wasserman et al. also followed the same cohort of children. The data from the 1992 publication were used in this analysis because nearly 40% of the cohort was lost to follow-up by the time of the evaluation of the children at four years of age in the 1994 publication. The five studies that were included in our meta-analysis are described in Table 3.4.

Table 3.3 Observational studies of anaemia and perinatal mortality

Country (reference)	*Site*	*Period of data collection*	*Selection criteria*	*Time in pregnancy of anaemia assessment*	*Etiologies of anaemia*
China (Xiong 1996)	Suzhou	1989–1990	Perinatal care monitoring records	At entry into prental care; about 12 gestational weeks, and again at 32 weeks	Not described
India (Sarin 1995)	Punjab	1990–1994	Population-based survey of pregnant women	Different stages during pregnancies	Iron deficiency anaemia
Kenya (Macgregor 1963)	Mombasa	1957–1961	Patients at Lady Grigg Maternity Hospital	Within 48 hours of onset of labour	Malaria and iron deficiency are discussed
Malaysia (Llewellyn-Jones 1965)	Kuala Lumpur	1953–1962	Women treated in maternity hospital in given time period	Not stated	Iron deficiency anaemia: (i) hookworm; (ii) diet. Megaloblastic anaemia: (i) liver damage in malnutrition; (ii) diet-amount of folic acid, haemolytic, normoblastic anaemia
Malaysia (Tasker 1958)	Kuala Lumpur	1952–1958	Pregnant women with haemoglobin levels <45%	At delivery, upon admission	Iron deficiency and some megaloblastic anaemia
Nepal (Dreyfuss and West 2001)	Sarlahi	1994–1996	Community-based sample of pregnant women enrolled in vitamin A trial	Mid-pregnancy	Iron deficiency, other micronutrient deficiencies, *Plasmodium vivax* malaria, hookworms
Nigeria (Harrison 1975)	Ibadan	1957–1968	Pregnant women with haematocrit ≤26%	At delivery, upon admission	Red cell haemolysis due to malaria, dietary deficiency of folates, and haemoglobinopathies

Nigeria (Johnson and Ojo 1967)	Ibadan	1961	20–32 weeks pregnant, anaemic (haematocrit ≤24%) women	20–32 weeks	Haemolysis; folic acid deficiency
Nigeria (Harrison 1982)	Zaria	1976	Pregnant women who develop anaemia	Mid-pregnancy	Nutritional deficiency of iron and folates, malaria, haemoglobinopathies, blood loss, bacterial infections, and socioeconomic deprivation
Nigeria (Harrison et al. 1985)	Zaria	—	Pregnant women in Zaria area	First attendance at hospital to book for antenatal care or seek emergency care	Malaria, iron deficiency, haemoglobinopathies
Papua New Guinea (Mola et al. 1999)	Port Moresby	1987–1992	Pregnant women booked at antenatal clinics in or around Port Moresby and delivered in Port Moresby General Hospital	Lowest haemoglobin concentration from multiple values, mostly in second half of pregnancy	Malaria, alpha thallasemia, hookworm infection, iron and folate deficiencies
United Kingdom (Murphy et al. 1986)	Cardiff, Wales	1970–1982	All singleton births to South Glamorgan residents (Cardiff Births Study)	At first booking; 70% within first 13 weeks, 24% at 13–19 weeks, 5% at 20–24 weeks	Social disadvantage
USA (Garn et al. 1981)	multicentre	—	National Collaborative Perinatal Project	Lowest haemoglobin concentration in pregnancy from multiple antenatal values	Not described

continued

Table 3.3 Observational studies of anaemia and perinatal mortality (*continued*)

Country (reference)	*Method of anaemia assessment*	*Perinatal mortality definition*	*Level of care*	*Number of events/total sample*	*Reason for exclusion*
China (Xiong 1996)	Not stated	Perinatal mortality	Hospital	209/16 936	
India (Sarin 1995)	Haemoglobin by Sahli acid haematin method	Perinatal mortality	Referral hospital in area	1 529/33 160	
Kenya (Macgregor 1963)	Tallqvist method, confirmed by lab method if <6 g/dl	Stillbirths and neonatal deaths	Maternity hospital	339/3 950	
Malaysia (Llewellyn-Jones 1965)	Haemoglobin, method not stated	"Perinatal loss" (premature and mature stillbirth + neonatal)	Maternity Hospital, Kuala Lumpur	5 109/73 048	
Malaysia (Tasker 1958)	Haemoglobin determined by Tallqvist screen for anaemia followed by Sahli acid haematin method for anaemics	Fetal loss (premature and mature)	Institute of Medical Research, Kuala Lumpur	1 676/26 442	Less than two groups with haemoglobin midpoint >5 g/dl
Nepal (Dreyfuss and West 2001)	Haemoglobin from venous sample, by Hemocue	Neonatal death, i.e. death in first 28 post-natal days	Rural with little access to obstetric care; nearly all deliveries occurred at home	59/1 081	
Nigeria (Harrison 1975)	Haematocrit	Fetal loss	University College Hospital, Ibadan	17/301	

Nigeria (Johnson and Ojo 1967)	Microhaematocrit prior to amniocentesis, bone marrow at delivery	Abortions/immature deliveries, stillbirths and neonatal deaths ("total pregnancy wastage")	University College Hospital, Ibadan	19/145	Less than two groups with haemoglobin midpoint >5 g/dl
Nigeria (Harrison 1982)	Haemoglobin from capillary sample, method not stated	Fetal loss	Hospital, Zaria	36/221	
Nigeria (Harrison et al. 1985)	Haematocrit	Stillbirth and neonatal deaths	General hospital	1 834/18 116 (excluding groups with haemoglobin midpoints <5 g/dl)	
Papua New Guinea (Mola et al. 1999)	Haemoglobin, method not stated	Stillbirths	General hospital	246/13 311 (excluding groups with haemoglobin midpoints >12 g/dl)	
United Kingdom (Murphy et al. 1986)	Haemoglobin, method not stated	Perinatal mortality	Modern United Kingdom health system	4 195/36 466 (excluding group with haemoglobin midpoint >12 g/dl)	
USA (Garn et al. 1981)	Haemoglobin or haematocrit	Fetal death	Modern USA health system	1 196/ >50 000	Numerators and denominators not tabulated for haemoglobin groups

— No data.

Note: Shaded rows indicate excluded studies.

Table 3.4 Longitudinal observational studies of iron deficiency anaemia and child intelligence[a]

Country (reference)	*Sample size*	*Period of follow-up*	*Exclusions*	*Study design*
Chile (de Andraca et al. 1990)	Total = 77. Formerly anaemic = 41. Formerly non-anaemic = 29. All anaemic treated at 12 months	Birth to 5–6 years	BW <2 500 g, chronic ill health, intermediate levels of anaemia	Part of a randomized trial of iron fortification in early infancy, at one year, 25% of the non-fortified group had anaemia. The anaemic children all received 3 months of iron treatment. Selected children re-examined at 5 to 6 years of age
Costa Rica (Lozoff et al. 1991)	163 of 191 children originally evaluated at 12–24 months. 30 had moderate anaemia = Hb ≤10.0 g/dl, ferritin ≤12 mcg, EP >1.77 mcgmol or transferrin ≤10%. 133 comparison group	12 months to 5 years	BW <2.5 kg, multiple pregnancy, complicated births, acute or chronic medical problem	Follow-up at 5 years of Lozoff et al. (1987). The IDA group was initially treated for 3 months to to correct their anaemia. Current evaluators blind to original iron status. All now free of anaemia
Former Yugoslavia (Wasserman et al. 1992)	Children whose mothers were followed up from pregnancy in two areas of Kosovo. Mitrovica = lead exposed. Pristina = nonlead exposed. 541 agreed to participate. 392 (208 + 184) seen at 24 months	Birth to 24 months	Major CNS defects, chromosomal abnormalities, multiple pregnancy	Follow-up two cohorts from birth measuring serum lead, iron status and developmental indices. Related Hb at each age with DQ at 24 months. Anaemic children treated
Israel (Palti et al. 1983)	Routine health service screen for Hb at 9 months. Tested at 2 years = 873. At 3 years = 388. At 5 years = 239. Hb only measure of iron status	9–10 months to 5 years	Not given	Follow–up of all children from 9–10 months to 2, 3 and 5 years. All with Hb<11 g/dl treated with iron at 9 months for 3 months. At 5 years took a random sample of remaining children
USA (Cantwell 1974)	61 full-term neonates from comparable socioeconomic groups: 29 given IM iron in neonatal period 32 infants developed Fe deficiency anaemia between 6–18 months. (Hb 6.1–9.5g%) without PEM. No details of iron status	Birth to 7 years	Preterm	29 of 61 infants received iron injections (method of assignment not given) and were not anaemic (Hb 11.5–12.9). 32 infants developed IDA. Examined at 6–7 years by examiners blind to the groups

Country (reference)	*Outcome measures*	*Covariates adjusted for*	*Findings*	*Remarks*
Chile (de Andraca et al. 1990)	Stanford-Binet IQ, Illinois psycholinguistic abilities test, psychoeducational abilities test, Bruininks-Osteretsky test of motor proficiency, VMI, neurological exam	Home, maternal depression and stress. Not clear if used in analysis	Hb at 1 year = 10.1±0.7 vs 13.0±0.8. Hb a 15 months = 12.8±0.7 vs 13.0±0.8. Current Hb level not given. Formerly anaemic children performed significantly worse in IQ ($P = 0.02$), psychoeducational abilities ($P < 0.01$), VMI ($P < 0.01$), motor proficiency ($P < 0.01$), language abilities ($P < 0.01$). They were more neurologically immature ($P < 0.01$). Their homes were significantly less stimulating and their mothers were more depressed and less affectionate	
Costa Rica (Lozoff et al. 1991)	Current iron status. WISC test, Woodcock Johnson psychoeducational battery, Goodenough-Harris draw-a-man test, Beery developmental test of VMI, Bruininks-Oseretsky test of motor proficiency	Sex, birth weight, mother's IQ, height and education, breastfeeding, absence of father, home	No current difference in Hb and other measures of iron status. After controlling for covariates, previously anaemic group had lower scores on performance IQ, quantitative and visual matching subtests of the Woodcock Johnson battery, the VMI and the Bruininks-Oseretsky test of motor proficiency. In post hoc analyses, children who were non-anaemic but continued to have iron deficiency after treatment also had significantly lower scores	Good covariate control. Verbal skills less affected
Former Yugoslavia (Wasserman et al. 1992)	Bayley MDI at 6, 12, 18, 24 months with iron and lead status	Ethnic group, home, birth order, BW, sex, maternal IQ, education and age, lead levels	Hb at 6, 12 and 24 months was not significantly associated with MDI at 24 months but Hb at 18 months was significant. Controlling for all covariates, in both	At all ages mothers' education had the most significant effect on DQ

continued

Table 3.4 Longitudinal observational studies of iron deficiency anaemia and child intelligence[a] (*continued*)

Country (reference)	*Outcome measures*	*Covariates adjusted for*	*Findings*	*Remarks*
			Mitrovica and Pristina a change in Hb at 18 months of 2.0 g/dl was associated with a change of 3.4 MDI points ($P = 0.02$). Other indices of iron deficiency not associated with development	
Israel (Palti et al. 1983)	Brunet-Lezine test at 2 years. MILI test (an Israeli intelligence test) at 3 years. Wechsler with Israeli adaptation (WPSSI) at 5 years	Maternal education, father's occupation, BW, sex	When controlling for covariates: Hb at 9 months not significantly associated with DQ at 2 years ($P = 0.105$) and at 3 years ($P = 0.07$) but at 5 years had a significant effect on IQ ($P = 0.02$). At 5 years an increase of 1.0 g/dl of Hb associated with 1.75 change in IQ points	A large number of cognitive tests. Previously anaemic not reported alone
USA (Cantwell 1974)	Neurological examination and Stanford-Binet IQ	None reported	The formerly anaemic group had a higher incidence of "soft signs" e.g. clumsiness with balancing on one foot, in tandem walking, and repetitive hand and foot movement and were more inattentive and hyperactive than the non-anaemic group. IQ scores averaged 98 in the non-anaemic and 92 in the anaemic. No significance levels levels reported	

Key: Hb, haemoglobin; EP, erythrocyte protopophyrin; BW, birth weight; IDA, iron deficiency anaemia; CNS, central nervous system; DQ, developmental quotient; IM, intramuscular; PEM protein–energy malnutrition; VMI, visual-motor integration; MDI, Mental Development Index.

[a] Inclusion criteria: IQ/MDI/General Cognitive Index (GCI) as outcome measure.

Source: Table adapted from Grantham-McGregor and Ani (2001), with permission.

5. Methods for combining risk estimates from individual studies

5.1 Anaemia and maternal mortality

In each study, maternal mortality data were given in aggregate for each of the ranges. All ranges were converted to haemoglobin by dividing haematocrit values by 3. The midpoint of each range was used as the independent variable. The midpoints were estimated from the information provided in the articles. A logistic regression model was then used to fit the observed data, weighting each haemoglobin midpoint-mortality point by the total number of women in that range. Within each study, an estimate of the risk ratio associated with a one-unit difference in haemoglobin was calculated. These individual estimates were initially combined in a fixed-effects model, weighting individual estimates by the inverse of their within-study variance, to estimate an overall risk ratio. The heterogeneity statistic indicated that individually observed effect sizes varied significantly around the overall fixed-effects model estimate. Dropping the assumption of a fixed-treatment effect, the individual effect sizes were then assumed to be normally distributed and a random-effects combined estimate was calculated using the method of DerSimonian and Laird (1986).

5.2 Anaemia and perinatal mortality

Analyses for perinatal mortality were conducted in a similar manner as that for maternal mortality. The nine studies included in the meta-analysis were sufficiently heterogeneous that a random-effects model was used to generate combined estimates (DerSimonian and Laird 1986).

5.3 Iron deficiency anaemia and child intelligence

The beta coefficients from multivariate regression models associated with a 1 g/dl change in haemoglobin were obtained directly from the original published paper (Palti et al. 1983; Wasserman et al. 1992) or estimated indirectly from means and *P*-values (Cantwell 1974; de Andraca et al. 1990; Lozoff et al. 1991). Standard deviations were obtained directly from the original paper (Wasserman et al. 1992), estimated from *P*-values and beta coefficients (de Andraca et al. 1990; Lozoff et al. 1991; Palti et al. 1983), or estimated by assuming a significance level of 0.05 (Cantwell et al. 1974). As original data were not available, variability in baseline anaemia levels was not considered; rather, baseline mean haemoglobin levels were compared to follow-up IQ scores with standard deviations to estimate individual study regression coefficients. The estimates were combined in a fixed-effects model, weighting studies according to the reciprocal of their within-study variance. A chi-squared test for heterogeneity found no significant between-study variance; thus a random-effects model was not necessary.

6. Results

6.1 Maternal mortality

We computed odd ratios for maternal mortality associated with a 1 g/dl increase in pregnancy haemoglobin. Of the six studies included in our meta-analysis, all had individual study ORs <1.0, and three of those were statistically significant (Table 3.5 and Figure 3.1). The estimated OR from combining data points from all the studies was 0.75, with a CI that clearly excluded unity (0.62–0.89). The studies were not geographically diverse, coming from only three countries (India, Malaysia and Nigeria). However there was not a systematic difference between the risk estimates from the Nigerian vs the Asian studies. Two Nigerian studies had markedly lower ORs than the other four studies; however these two studies carried little weight in the combined OR.

6.2 Perinatal mortality

Ten studies were included in our meta-analysis. The individual ORs for perinatal mortality associated with a 1 g/dl increase in haemoglobin ranged from 0.55 to 0.87 (Table 3.6 and Figure 3.2). Nine of the 10 individual study estimates were statistically different from unity. The estimated OR from the 10 studies combined was 0.72 (95% CI 0.65–0.81).

The nine studies included in the meta-analysis were sufficiently heterogeneous that a random-effects model was used to generate combined estimates. We explored three factors that might explain this heterogeneity; these subgroup analyses are presented in Table 3.7. First, we were liberal in accepting various outcome definitions related to perinatal mortality. Only three of the 10 studies used the correct definition, which includes fetal death after 22 (or 28) weeks' gestation and neonatal mortality in the first seven days of life. Use of the correct definition of

Table 3.5 Individual and combined estimates of odds ratio of maternal death

Country (study)	*Point estimate (OR)*[a]	*95% CI*
India (Konar et al. 1980)	0.61	0.57–0.64
India (Sarin 1995)	0.84	0.81–0.88
Malaysia (Llewellyn-Jones 1965)	0.74	0.69–0.80
Nigeria (Harrison 1975)	0.46	0.15–1.42
Nigeria (Harrison 1982)	0.38	0.14–1.03
Nigeria (Harrison and Rossiter 1985)	0.95	0.83–1.09
Combined	0.75	0.62–0.89

[a] Odds ratio for maternal mortality associated with a 1 g/dl improvement in haemoglobin concentration, in the range of 5–12 g/dl haemoglobin.

Figure 3.1 Individual and combined estimates of odds ratio of maternal death

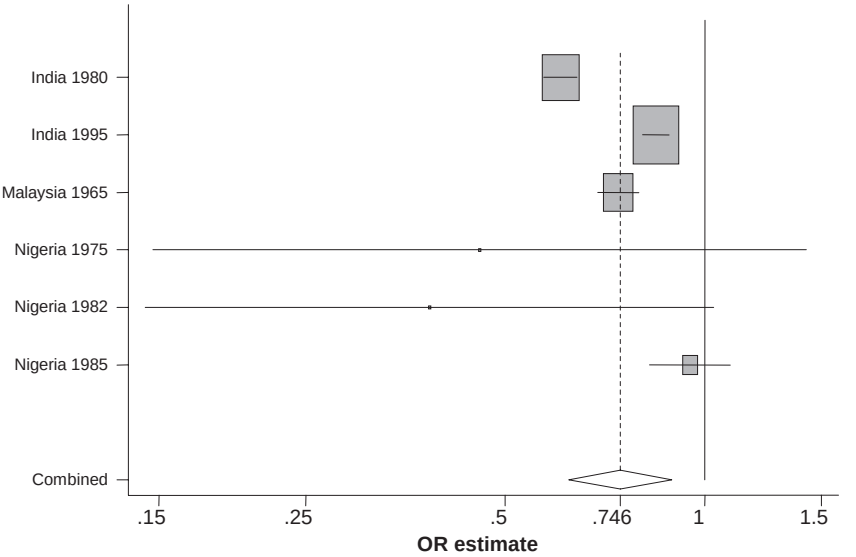


Table 3.6 Individual and combined estimates of odds ratio of perinatal death

Country (study)	*Point estimate (OR)*[a]	*95% CI*
China (Xiong et al. 1996)	0.82	0.66–1.03
India (Sarin 1995)	0.87	0.85–0.89
Kenya (Macgregor 1963)	0.66	0.60–0.73
Malaysia (Llewellyn-Jones 1965)	0.86	0.84–0.89
Nepal (Dreyfuss and West 2001)	0.82	0.70–0.97
Nigeria (Harrison 1975)	0.55	0.33–0.92
Nigeria (Harrison 1982)	0.59	0.45–0.78
Nigeria (Harrison et al. 1985)	0.58	0.55–0.61
Papua New Guinea (Mola et al. 1999)	0.77	0.70–0.85
United Kingdom (Murphy et al. 1986)	0.62	0.57–0.68
Combined[b]	0.72	0.65–0.81

[a] Odds ratio for perinatal mortality associated with a 1 g/dl improvement in haemoglobin concentration, in the range of 5–12 g/dl haemoglobin.

[b] Random effects estimate.

Figure 3.2 Individual and combined estimates of odds ratio of perinatal death

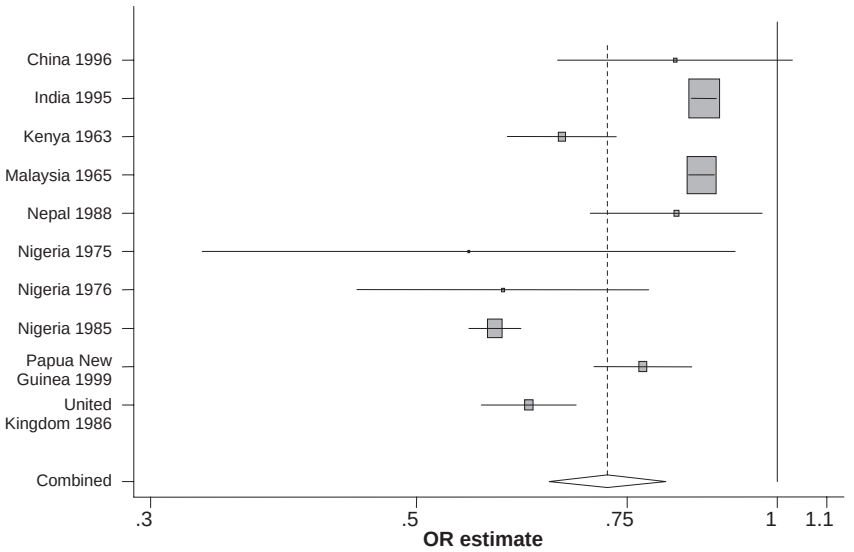


Table 3.7 Subgroup analyses for perinatal mortality

Group of studies (n)	*Point estimate (OR)*	*95% CI*	*% change from overall estimate*
All (10)[a]	0.72	0.65–0.81	
True definition of perinatal mortality (3)[b]	0.76	0.59–0.98	+5.5
Outcome includes some components of perinatal mortality (7)[c]	0.70	0.58–0.84	–2.9
P. falciparum endemic (5)[d]	0.65	0.56–0.75	–10.3
P. falciparum not endemic (5)[e]	0.80	0.73–0.87	+10.8
Haemoglobin assessed at delivery (2)[f]	0.66	0.59–0.73	–8.7
Haemoglobin assessed in early-mid pregnancy (8)[g]	0.74	0.65–0.83	+2.5

[a] Includes all 10 studies in Table 3.6.

[b] China 1996; India 1995; United Kingdom 1986.

[c] Kenya 1963; Malaysia 1965; Nepal 1998, Nigeria 1975, 1976, 1985; Papua New Guinea 1999.

[d] Kenya 1963; Nigeria 1975, 1976, 1985; Papua New Guinea 1999.

[e] China 1996; India 1995; Malaysia 1965; Nepal 1998; United Kingdom 1986.

[f] Kenya 1963; Nigeria 1975.

[g] China 1996; India 1995; Malaysia 1965; Nepal 1998; Nigeria 1976, 1985; Papua New Guinea 1999; United Kingdom 1986.

Table 3.8 Comparison of adjusted and unadjusted odds ratios in two studies of pregnancy anaemia and perinatal mortality

Hb category	*Live births*	*Neonatal deaths*	*Death rate (000s)*	*OR*	*Adjusted OR*
Study: Nepal 1998[a]					
≥11.0 g/dl	330	12	36.4	1.00	1.00
9.0–10.9	534	32	60.6	1.69	1.57
7.0–8.9	176	9	51.1	1.43	1.40
<7.0	41	6	146.3	4.54	4.61
Study: China 1996[b]					
≥10.0 g/dl	15 236	184	12	1.00	1.00
7.0–9.9	1 332	21	16	1.31	1.21
<7.0	159	4	25	2.08	1.81

[a] Adjusted ORs were adjusted for randomized supplement group (i.e. maternal supplementation with vitamin A or beta-carotene during pregnancy; this treatment did not affect neonatal death), primiparity, gestational age at Hb assessment, reported severe illness in late pregnancy, contribution of ≥1 pregnancy to the data set, preterm birth. Source: M. Dreyfuss, personal communication.

[b] Adjusted for maternal age, gestational age, parity, hypertensive disorders of pregnancy, gestational age at enrolment into prenatal care, hospital and maternal education. Source: X. Xiong, personal communication.

perinatal mortality did not significantly change the effect estimate. Second, *P. falciparum* malaria contributes to anaemia in pregnancy and may also affect perinatal mortality. Five of the studies were conducted in populations with endemic *P. falciparum* malaria, and these studies had a combined risk estimate that was substantially further from unity than those studies conducted in populations not heavily exposed to this form of malaria. We concluded that the risk relationship with anaemia is greater in *P. falciparum* malaria-endemic regions. Third, two studies assessed haemoglobin at delivery whereas the other eight assessed haemoglobin earlier in gestation. Xiong et al. (2000) have suggested that anaemia early in pregnancy carries a greater risk of adverse perinatal outcomes; however this inference was based on low birth weight as outcome. We did not find this in our data. In fact, the risk relationship was slightly stronger in the two studies that assessed haemoglobin at delivery. However, those two studies were also in *P. falciparum* malaria-endemic populations, which could bias the analysis.

The ORs presented in Table 3.6 and Figure 3.2 are unadjusted for potential confounding factors. Two of the 10 studies, Nepal 1998 and China 1996, could provide us with both unadjusted and adjusted ORs by haemoglobin category. These are displayed in Table 3.8. In the Nepal study, multivariate adjustment for a number of variables had no effect on the estimated ORs. However, in the China study, in which more

Table 3.9 Final odds ratios and confidence intervals used to generate burden of disease estimates

Outcome	*OR estimate*	*95% CI*
Maternal mortality	0.80	0.70–0.91
Perinatal mortality, Africa	0.72	0.65–0.80
Perinatal mortality, other regions	0.84	0.78–0.90

covariates were measured, multivariate adjustment attenuated the ORs by about 20%.

We have therefore attenuated the ORs for both perinatal and maternal mortality by 20%, as the evidence at hand suggests that the unadjusted estimates may be overestimated to about that degree. The final ORs and confidence intervals used to generate the burden of disease estimates are shown in Table 3.9.

6.3 Child intelligence

Five studies were included in our meta-analysis. The studies were geographically diverse, including Europe, Latin America, the Middle East and North America (the United States of America). However, there were no studies included from Africa or Asia. We estimated the expected change in IQ points associated with a 1 g/dl change in haemoglobin. The individual study estimates ranged from 1.36 to 2.52, and all were statistically different from zero (Table 3.10 and Figure 3.3). The combined estimate was 1.73 points, with a 95% CI of 1.04–2.41. The quality of the studies was high, and all of them provided estimates that were adjusted for multiple covariates.

The relevant disease outcome for this analysis would be mild mental retardation, defined as IQ <70, or more than 2 standard deviations below the expected population mean of 100. The increase in risk of mental retardation can be estimated from the expected mean change in IQ if one assumes that the mean change represents a shift in the entire distribution of values with no change in variance of the distribution. These calculations are displayed in Table 3.10. The resultant relative risk associated with a 1 g/dl increment in haemoglobin concentration is 0.78. The relative risk estimates associated with the upper and lower confidence limits of the estimated change in IQ are 0.70 and 0.86, respectively (Table 3.11).

7. Description of malnutrition tables

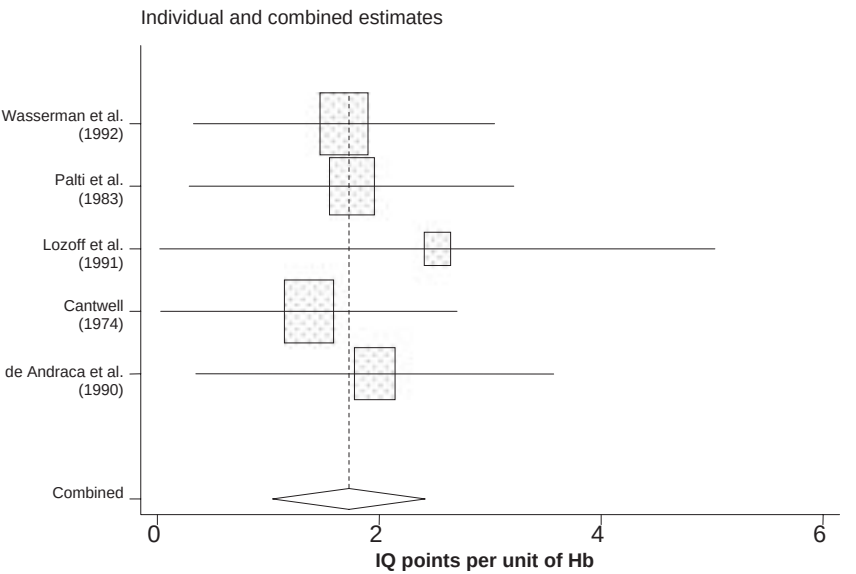
To describe the distribution of low haemoglobin by region we used the anaemia prevalence data that were published in the 1990 Global Burden

Table 3.10 Individual and combined estimates of the expected difference in IQ points per unit (g/dl) of haemoglobin

Study	*Point estimate (IQ points)*[a]	*95% CI*
Wasserman et al. (1992)	1.68	0.32–3.04
Palti et al. (1983)	1.75	0.29–3.21
Lozoff et al. (1991)	2.52	0.02–5.02
Cantwell (1974)	1.36	0.03–2.70
de Andraca et al. (1990)	1.96	0.35–3.57
Combined	1.73	1.04–2.41

[a] Estimated increase in IQ associated with a 1 g/dl increase in haemoglobin concentration.

Figure 3.3 Individual and combined estimates of IQ point difference associated with haemoglobin levels in infancy



of Disease (GBD) books (Murray and Lopez 1996a, 1996b). This database is currently being revised and updated, but the complete new data will not be available within the time frame of this project. We applied the following steps: (i) converted the prevalence data from the GBD 1990 regions to the subregions[2] used currently; (ii) converted data on prevalence of anaemia into mean haemoglobin values; and (iii) estimated the

Table 3.11 Predicted risks and relative risks of mental retardation, based on combined estimate of difference in mean IQ points in Table 3.10

	Point estimate	*Lower bound*	*Upper bound*
Expected rate of mental retardation in a healthy population[a]	2.3%		
Estimated average decrement in IQ per 1 g/dl decrement in haemoglobin[b]	1.73 points	1.04 points	2.41 points
Predicted rate of mental retardation in population with haemoglobin distribution shifted 1 g/dl downward due to iron deficiency[c]	2.94%	2.68%	3.29%
Predicted relative risk of mental retardation associated with 1 g/dl increment in haemoglobin[d]	0.78	0.86	0.70

[a] Assumes mean IQ of 100, with SD = 15.

[b] From Table 3.10.

[c] Assumes shift in mean given in row 2 with constant SD = 15.

[d] Point estimate in row 1 divided by percentages in row 3.

counterfactual haemoglobin distribution, representing the elimination of iron deficiency.

The anaemia database that we used was based on surveys conducted prior to 1990. Global monitoring of anaemia trends suggests that the prevalence of anaemia in the world has not decreased in the past decade (UNICEF 1998). However, the representativeness and reliability of these data (in terms of sample sizes) are less than we would hope for. Table 3.12 summarizes the numbers of country surveys included in the available data set, and the conversion from previous regions to the subregions used in the present analysis. Data for EUR-B and EUR-C are especially scarce. In the case of SEAR-D, the previous data source included only one country, India, but several surveys contributed to the country estimate.

Nationally representative anaemia data from the United States are available that are more recent than the data in the 1990 WHO database, and demonstrate lower anaemia prevalences (Looker et al. 1997). So as not to overestimate the burden of anaemia in economically developed regions, we used these data from the United States for three subregions, AMR-A, EUR-A and WPR-A. The haemoglobin cut-offs used to define anaemia globally have not changed since the 1990 database was created (Table 3.13). The resulting anaemia prevalence estimates are given in Table 3.14.

The second step was to convert the prevalence of anaemia to a mean haemoglobin value. We assumed all haemoglobin distributions to be approximately normal (Yip et al. 1996). We then needed to make

Table 3.12 Conversion of anaemia prevalence data from GBD 1990 regions to subregions

Subregion	*Previous (GBD 1990) region used as data source*	*Number of countries contributing surveys to regional estimate*
AFR-D	Sub-Saharan Africa	16
AFR-E	Sub-Saharan Africa	16
AMR-A	[a]	
AMR-B	Latin America and Caribbean	21
AMR-D	Latin America and Caribbean	21
EMR-B	Middle Eastern Crescent	6
EMR-D	Middle Eastern Crescent	6
EUR-A	[a]	
EUR-B	Former Soviet Economy	1
EUR-C	Former Soviet Economy	1
SEAR-B	Other Asia and islands	8
SEAR-D	India	1
WPR-A	[a]	
WPR-B	Other Asia and islands	8

[a] For these subregions, recent nationally representative data from the USA were used (Looker et al. 1997).

Table 3.13 Haemoglobin cut-offs to define anaemia in populations living at sea level

Population group	*Haemoglobin cut-off (g/l)*
Children 0–4 years	110
Children 6–14 years	120
Non-pregnant women	120
Pregnant women	110
Men	130

Source: Stoltzfus and Dreyfuss (1998).

assumptions about the standard deviation of the distributions. The standard deviation of haemoglobin in a population depends on at least two factors. The first factor is the proportion of individuals who are at their homeostatic haemoglobin concentration (i.e. non-anaemics). There is a certain amount of variability in haemoglobin that is set by individual characteristics, including genetics. This would be represented by the standard deviation in a population with no anaemia. Added to this "inherent" variability is the variability associated with non-physiologic states,

Table 3.14 Estimated anaemia prevalence by subregion, sex and age

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	60.0	52.0	28.0	28.0	28.0	47.0	47.0	47.0
	Female	60.0	52.0	41.0	41.0	41.0	47.0	47.0	47.0
AFR-E	Male	60.0	52.0	28.0	28.0	28.0	47.0	47.0	47.0
	Female	60.0	52.0	41.0	41.0	41.0	47.0	47.0	47.0
AMR-A	Male	6.5	5.0	5.0	5.0	5.0	6.0	7.0	7.0
	Female	6.5	5.0	8.0	8.0	8.0	7.0	7.0	7.0
AMR-B	Male	46.0	24.0	11.0	11.0	11.0	18.0	18.0	18.0
	Female	46.0	24.0	23.0	23.0	23.0	18.0	18.0	18.0
AMR-D	Male	46.0	24.0	11.0	11.0	11.0	18.0	18.0	18.0
	Female	46.0	24.0	23.0	23.0	23.0	18.0	18.0	18.0
EMR-B	Male	63.0	39.0	17.0	17.0	17.0	25.0	25.0	25.0
	Female	63.0	39.0	44.0	44.0	44.0	25.0	25.0	25.0
EMR-D	Male	63.0	39.0	17.0	17.0	17.0	25.0	25.0	25.0
	Female	63.0	39.0	44.0	44.0	44.0	25.0	25.0	25.0
EUR-A	Male	6.5	5.0	5.0	5.0	5.0	6.0	7.0	7.0
	Female	6.5	5.0	8.0	8.0	8.0	7.0	7.0	7.0
EUR-B	Male	22.0	20.0	5.0	5.0	5.0	12.0	12.0	12.0
	Female	22.0	20.0	10.0	10.0	10.0	12.0	12.0	12.0
EUR-C	Male	22.0	20.0	5.0	5.0	5.0	12.0	12.0	12.0
	Female	22.0	20.0	10.0	10.0	10.0	12.0	12.0	12.0
SEAR-B	Male	49.0	33.0	32.0	32.0	32.0	48.0	48.0	48.0
	Female	49.0	33.0	49.0	49.0	49.0	48.0	48.0	48.0
SEAR-D	Male	66.0	65.0	36.0	36.0	36.0	65.0	65.0	65.0
	Female	66.0	65.0	60.0	60.0	60.0	65.0	65.0	65.0
WPR-A	Male	6.5	5.0	5.0	5.0	5.0	6.0	7.0	7.0
	Female	6.5	5.0	8.0	8.0	8.0	7.0	7.0	7.0
WPR-B	Male	49.0	33.0	32.0	32.0	32.0	48.0	48.0	48.0
	Female	49.0	33.0	49.0	49.0	49.0	48.0	48.0	48.0

including iron deficiency. Thus it is logical to expect the standard deviation of haemoglobin to be higher in populations with more anaemia compared to those with infrequent anaemia. The second factor is the precision of the haemoglobin assay, with greater precision yielding smaller observed standard deviations.

The variation in haemoglobin standard deviations is illustrated in Table 3.15, which relates the prevalence of anaemia to the standard deviation, using data from a draft version of the updated (but still incomplete) anaemia database for the WHO African and Eastern Mediterranean Regions (B. de Benoist, personal communication) and data from the most recent national health and nutrition examination survey in the United States, after excluding iron-deficient individuals. The standard deviations from the data from the United States are significantly smaller,

Table 3.15 Standard deviations of haemoglobin values

	Africa and EMRO surveys[a]	*USA NHANES III data*[b]
Prevalence of anaemia	>50%	<5%
Standard deviation (g/dl)		
Children 0–4 years	1.45	0.75
Children 5–14 years	1.58	0.85
Non-pregnant women	1.66	0.91
Men	1.60	0.97

EMRO WHO Eastern Mediterranean Region.

[a] B. de Benoist, personal communication. Values are weighted averages from available country surveys.

[b] From Looker et al. (1997), Table 2.

Table 3.16 Standard deviations used to convert anaemia prevalence to mean haemoglobin

Anaemia prevalence	*Standard deviation of haemoglobin*
<15%	1.0 g/dl
15–30%	1.2 g/dl
>30%	1.5 g/dl

probably due to both of the factors discussed above. Namely, the proportion of anaemic individuals in this United States sample was very low, and the haemoglobin assessment method (venous blood collection, laboratory-based assay with rigorous quality control) was more precise than most field-based studies in developing countries.

Based on these considerations, we assumed certain standard deviations based on the anaemia prevalence of each population group. These are given in Table 3.16.

Knowing the proportion below a certain haemoglobin cut-off (i.e. prevalence of anaemia in a population) and the standard deviation of the normal distribution, we estimated the mean haemoglobin associated with the current prevalence of anaemia (Snedecor et al. 1980). These values are given in Table 3.17.

We then estimated the theoretical-minimum-risk distribution, representing the haemoglobin distribution if iron deficiency were eliminated. Assuming that 50% of anaemia in the world is attributable to iron deficiency (see section 3), we divided the current anaemia prevalences by 2. Because anaemia cut-offs are defined as the 5th percentile of a normative reference distribution (i.e. the distribution of individuals known to

Table 3.17 Estimated mean haemoglobin values (g/dl) by subregion, sex and age in 2000

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	10.62	11.67	13.70	13.70	13.70	13.11	13.11	13.11
	Female	10.62	11.67	12.34	12.34	12.34	12.11	12.11	12.11
AFR-E	Male	10.62	11.67	13.70	13.70	13.70	13.11	13.11	13.11
	Female	10.62	11.67	12.34	12.34	12.34	12.11	12.11	12.11
AMR-A	Male	12.51	13.39	14.64	14.64	14.64	14.55	14.55	14.55
	Female	12.51	13.39	13.41	13.41	13.41	13.48	13.48	13.48
AMR-B	Male	11.15	12.60	14.47	14.47	14.47	14.10	14.10	14.10
	Female	11.15	12.60	12.89	12.89	12.89	13.10	13.10	13.10
AMR-D	Male	11.15	12.60	14.47	14.47	14.47	14.10	14.10	14.10
	Female	11.15	12.60	12.89	12.89	12.89	13.10	13.10	13.10
EMR-B	Male	10.50	12.17	14.14	14.14	14.14	13.81	13.81	13.81
	Female	10.50	12.17	12.23	12.23	12.23	12.81	12.81	12.81
EMR-D	Male	10.50	12.17	14.14	14.14	14.14	13.81	13.81	13.81
	Female	10.50	12.17	12.23	12.23	12.23	12.81	12.81	12.81
EUR-A	Male	12.51	13.39	14.64	14.64	14.64	14.55	14.55	14.55
	Female	12.51	13.39	13.41	13.41	13.41	13.48	13.48	13.48
EUR-B	Male	11.93	12.76	14.64	14.64	14.64	14.41	14.41	14.41
	Female	11.93	12.76	13.28	13.28	13.28	13.41	13.41	13.41
EUR-C	Male	11.93	12.76	14.64	14.64	14.64	14.41	14.41	14.41
	Female	11.93	12.76	13.28	13.28	13.28	13.41	13.41	13.41
SEAR-B	Male	11.04	12.41	13.70	13.70	13.70	13.08	13.08	13.08
	Female	11.04	12.41	12.04	12.04	12.04	12.08	12.08	12.08
SEAR-D	Male	10.38	11.17	13.54	13.54	13.54	12.42	12.42	12.42
	Female	10.38	11.17	11.62	11.62	11.62	11.42	11.42	11.42
WPR-A	Male	12.51	13.39	14.64	14.64	14.64	14.55	14.55	14.55
	Female	12.51	13.39	13.41	13.41	13.41	13.48	13.48	13.48
WPR-B	Male	11.04	12.41	13.70	13.70	13.70	13.08	13.08	13.08
	Female	11.04	12.41	12.04	12.04	12.04	12.08	12.08	12.08

be free of disease), we set the minimum prevalence of anaemia in all world subregions to be 5.0%. We assumed a normal distribution, and applied the standard deviations in Table 3.15. This yields values in Table 3.18.

To check the plausibility of this theoretical minimum distribution, we examined the shift in population mean haemoglobin concentration from current reality to the theoretical minimum, representing the eradication of iron deficiency. These shifts are summarized in Table 3.19.

The predicted shifts in mean haemoglobin ranged from 0.0, in young adult men in affluent subregions, to 1.28 g/dl in children in SEAR-D. The predicted haemoglobin shift for young children in AFR was 1.17, which is consistent with the evidence from iron supplementation trials in the

Table 3.18 Estimated mean haemoglobin (g/dl) values if iron deficiency were eliminated (theoretical minimum distribution), by subregion, sex and age

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	11.79	12.52	14.08	14.08	14.08	13.87	13.87	13.87
	Female	11.79	12.52	12.99	12.99	12.99	12.87	12.87	12.87
AFR-E	Male	11.79	12.52	14.08	14.08	14.08	13.87	13.87	13.87
	Female	11.79	12.52	12.99	12.99	12.99	12.87	12.87	12.87
AMR-A	Male	12.58	13.39	14.64	14.64	14.64	14.60	14.55	14.55
	Female	12.58	13.39	13.51	13.51	13.51	13.55	13.55	13.55
AMR-B	Male	11.89	12.92	14.60	14.60	14.60	14.34	14.34	14.34
	Female	11.89	12.92	13.20	13.20	13.20	13.34	13.34	13.34
AMR-D	Male	11.89	12.92	14.60	14.60	14.60	14.34	14.34	14.34
	Female	11.89	12.92	13.20	13.20	13.20	13.34	13.34	13.34
EMR-B	Male	11.72	12.78	14.37	14.37	14.37	14.15	14.15	14.15
	Female	11.72	12.78	12.93	12.93	12.93	13.15	13.15	13.15
EMR-D	Male	11.72	12.78	14.37	14.37	14.37	14.15	14.15	14.15
	Female	11.72	12.78	12.93	12.93	12.93	13.15	13.15	13.15
EUR-A	Male	12.58	13.39	14.64	14.64	14.64	14.60	14.55	14.55
	Female	12.58	13.39	13.51	13.51	13.51	13.55	13.55	13.55
EUR-B	Male	12.23	13.03	14.96	14.96	14.96	14.55	14.55	14.55
	Female	12.23	13.03	13.64	13.64	13.64	13.55	13.55	13.55
EUR-C	Male	12.23	13.03	14.96	14.96	14.96	14.55	14.55	14.55
	Female	12.23	13.03	13.64	13.64	13.64	13.55	13.55	13.55
SEAR-B	Male	11.83	12.92	14.19	14.19	14.19	13.85	13.85	13.85
	Female	11.83	12.92	12.83	12.83	12.83	12.85	12.85	12.85
SEAR-D	Male	11.66	12.43	14.10	14.10	14.10	13.68	13.68	13.68
	Female	11.66	12.43	12.79	12.79	12.79	12.68	12.68	12.68
WPR-A	Male	12.58	13.39	14.64	14.64	14.64	14.60	14.55	14.55
	Female	12.58	13.39	13.51	13.51	13.51	13.55	13.55	13.55
WPR-B	Male	11.83	12.92	14.19	14.19	14.19	13.85	13.85	13.85
	Female	11.83	12.92	12.83	12.83	12.83	12.85	12.85	12.85

P. falciparum-endemic populations (1.24, 95% CI 1.16–1.33, see section 3). The predicted haemoglobin shifts for women of reproductive age range from 0.11 to 1.17 g/dl. These estimates were somewhat lower than the average haemoglobin response of pregnant women to iron supplementation (0.85 to 1.17 g/dl), and were substantially lower than the haemoglobin responses in women provided iron doses of ≥90 mg/day (i.e. 1.8 g/dl) estimated by Sloan et al. (2002).

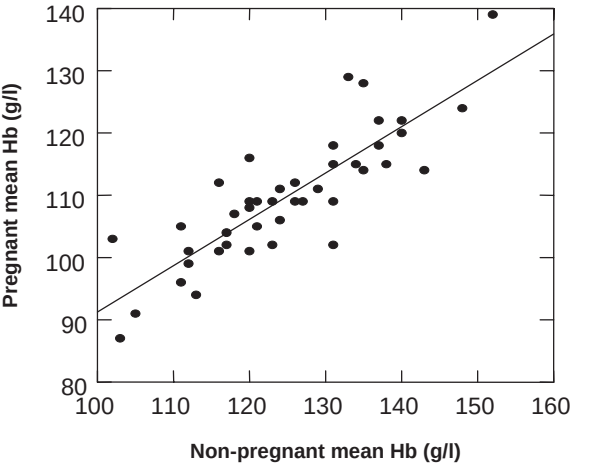
We are thus faced with some uncertainty about how to estimate the haemoglobin shift that would occur if iron deficiency were eliminated. Basing our estimates on a 50% reduction in anaemia yields a smaller shift than we would obtain if we assumed that the responses of pregnant women to maximal daily iron doses in the trials summarized by Sloan

Table 3.19 Shifts in mean haemoglobin (g/dl) from 2000 estimates (Table 3.17) if iron deficiency were eliminated (Table 3.18)

		Age group (years)								
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*Row means*
AFR-D	Male	1.17	0.85	0.38	0.38	0.38	0.75	0.75	0.75	0.68
	Female	1.17	0.85	0.65	0.65	0.65	0.75	0.75	0.75	0.78
AFR-E	Male	1.17	0.85	0.38	0.38	0.38	0.75	0.75	0.75	0.68
	Female	1.17	0.85	0.65	0.65	0.65	0.75	0.75	0.75	0.78
AMR-A	Male	0.06	0.00	0.00	0.00	0.00	0.04	0.08	0.08	0.03
	Female	0.06	0.00	0.11	0.11	0.11	0.08	0.08	0.08	0.08
AMR-B	Male	0.74	0.33	0.13	0.13	0.13	0.24	0.24	0.24	0.27
	Female	0.74	0.33	0.31	0.31	0.31	0.24	0.24	0.24	0.34
AMR-D	Male	0.74	0.33	0.13	0.13	0.13	0.24	0.24	0.24	0.27
	Female	0.74	0.33	0.31	0.31	0.31	0.24	0.24	0.24	0.34
EMR-B	Male	1.22	0.61	0.23	0.23	0.23	0.34	0.34	0.34	0.44
	Female	1.22	0.61	0.70	0.70	0.70	0.34	0.34	0.34	0.62
EMR-D	Male	1.22	0.61	0.23	0.23	0.23	0.34	0.34	0.34	0.44
	Female	1.22	0.61	0.70	0.70	0.70	0.34	0.34	0.34	0.62
EUR-A	Male	0.06	0.00	0.00	0.00	0.00	0.04	0.08	0.08	0.03
	Female	0.06	0.00	0.11	0.11	0.11	0.08	0.08	0.08	0.08
EUR-B	Male	0.30	0.27	0.32	0.32	0.32	0.14	0.14	0.14	0.24
	Female	0.30	0.27	0.36	0.36	0.36	0.14	0.14	0.14	0.26
EUR-C	Male	0.30	0.27	0.32	0.32	0.32	0.14	0.14	0.14	0.24
	Female	0.30	0.27	0.36	0.36	0.36	0.14	0.14	0.14	0.26
SEAR-B	Male	0.79	0.51	0.49	0.49	0.49	0.77	0.77	0.77	0.64
	Female	0.79	0.51	0.79	0.79	0.79	0.77	0.77	0.77	0.75
SEAR-D	Male	1.28	1.26	0.56	0.56	0.56	1.26	1.26	1.26	1.00
	Female	1.28	1.26	1.17	1.17	1.17	1.26	1.26	1.26	1.23
WPR-A	Male	0.06	0.00	0.00	0.00	0.00	0.04	0.08	0.08	0.03
	Female	0.06	0.00	0.11	0.11	0.11	0.08	0.08	0.08	0.08
WPR-B	Male	0.79	0.51	0.49	0.49	0.49	0.77	0.77	0.77	0.64
	Female	0.79	0.51	0.79	0.79	0.79	0.77	0.77	0.77	0.75
Column means		0.71	0.46	0.38	0.38	0.38	0.43	0.43	0.43	0.45

et al. (2002) represented the true effect. We used the 50% reduction in anaemia for two reasons. First, it yields more conservative estimates for the overall burden of disease attributable to iron deficiency. Second, we expect that the responses seen in iron supplementation trials are not representative of all women in the region in which they were conducted. Researchers frequently select study populations that are unusual in their potential to respond to an intervention; in this case populations that are more anaemic than the average population. Therefore it is reasonable to expect that data from randomized trials would overestimate global or regional average effects.

Figure 3.4 Relationship between mean haemoglobin values in pregnant and non-pregnant women within populations



Note: $n = 43$ surveys, $r = 0.84$, $P < 0.001$.

Source: Data from WHO (B. de Benoist, personal communication).

A final consideration is that these global tables report values for all women in the reproductive age ranges, whereas the risks of perinatal and maternal mortality apply uniquely to pregnancy anaemia. Population surveys that include both pregnant and non-pregnant women demonstrate a strong linear correlation between the haemoglobin values in these two population subgroups, as shown in Figure 3.4. Across the range of haemoglobin for women in Table 3.17, the difference between haemoglobin values in non-pregnant and pregnant states is nearly constant (range: 1.39 g/dl to 1.34 g/dl). The haemoglobin cut-off used to define anaemia is also lower in pregnancy. The WHO cut-off, for simplicity, is 1.0 g/dl lower in pregnancy. However, the physiologic haemodilution of pregnancy reduces the haemoglobin concentration by 1.5 g/dl in mid-pregnancy (Institute of Medicine 1990), when many pregnancy values are obtained in field surveys. Thus we can expect the prevalence of true anaemia to be approximately the same in pregnant and non-pregnant women. Because pregnant women are more iron-deficient than non-pregnant women, there is reason to believe that the iron-attributable fraction of anaemia would be higher in pregnancy than in other states. However, lacking firm data on this relationship, we have made the conservative assumption that the anaemia prevalence and predicted haemoglobin shift associated with the elimination of iron deficiency are the same for pregnant women as non-pregnant women.

8. Burden of disease estimates

The estimated deaths and DALYs attributable to iron deficiency are shown in Tables 3.20 and 3.21. Those attributed to iron deficiency as a risk factor for perinatal and maternal conditions are shown separately from those attributed directly to iron deficiency anaemia. For perinatal and maternal conditions, only mortality (as opposed to morbidity) from maternal conditions was attributed to iron deficiency. In the absence of any data on anaemia and morbidity related to childbirth or the puerperium, we assumed that such a relationship did not exist. As discussed earlier, the effects of iron deficiency anaemia on work productivity and child development and cognition are included in the direct attributions to iron deficiency anaemia (i.e. in the iron deficiency anaemia columns). These direct estimates are updated from the 1990 GBD (Murray et al. 1996a, 1996b), using 2000 demographic statistics, but otherwise the same methods.

The total burden of death and disability attributable to iron deficiency is higher than the 1990 estimate. This is due to differences in the risk estimates, not the prevalence estimates, which remain unchanged. The inclusion of iron deficiency anaemia as a risk factor for perinatal mortality is new, and contributes substantially to estimated deaths and DALYs lost. Furthermore, in the 1990 estimate, deaths from iron defi-

Table 3.20 Deaths from perinatal conditions, maternal conditions and iron deficiency anaemia, attributable to iron deficiency, by subregion

Subregion	*Perinatal causes (000s)*	*Maternal causes (000s)*	*Iron deficiency anaemia (000s)*	*Total (000s)*
AFR-D	97	20	8	125
AFR-E	103	29	13	145
AMR-A	1	0	3	4
AMR-B	17	2	7	26
AMR-D	3	1	3	7
EMR-B	4	1	1	6
EMR-D	56	14	9	79
EUR-A	1	0	3	4
EUR-B	4	0	2	6
EUR-C	2	0	1	3
SEAR-B	16	5	13	34
SEAR-D	222	38	66	326
WPR-A	0	0	0	0
WPR-B	63	5	5	73
World	591	115	135	841

Table 3.21 DALYs from perinatal conditions, maternal conditions and iron deficiency anaemia, attributable to iron deficiency, by subregion

Subregion	*Perinatal causes (000s)*	*Maternal causes (000s)*	*Iron deficiency anaemia (000s)*	*Total (000s)*
AFR-D	3237	614	934	4785
AFR-E	3442	881	1033	5356
AMR-A	47	2	430	479
AMR-B	561	59	291	911
AMR-D	102	36	201	339
EMR-B	149	22	344	515
EMR-D	1882	418	895	3195
EUR-A	29	1	269	299
EUR-B	145	6	286	437
EUR-C	61	4	205	675
SEAR-B	545	148	835	1528
SEAR-D	7428	1114	3955	12497
WPR-A	6	0	105	111
WPR-B	2101	145	2092	4338
World	19736	3448	11873	35057

ciency anaemia were included only as "direct" deaths due to severe and very severe anaemia. The increased maternal mortality from iron deficiency anaemia as an underlying risk factor is newly included in these estimates.

It is apparent that while the death and especially the disability *directly* attributable to iron deficiency anaemia is large, death and disability attributable to iron deficiency anaemia acting as a *risk factor* for perinatal and maternal causes is much larger. Because of the great numbers of perinatal deaths globally, perinatal causes account for 70% of the total deaths and 56% of the total DALYs attributable to iron deficiency anaemia. Numbers of maternal deaths, while very high, are much lower than perinatal deaths. Therefore the absolute contribution of maternal causes to the totals is smaller, namely 10% of DALYs and 14% of deaths. The relative contribution of maternal and perinatal causes to the total DALYs lost is largest where death rates are high (e.g. 80% in SEAR-D compared to only 25% in EUR-A). Indeed, as expected, the contribution of iron deficiency anaemia to maternal deaths is zero in AMR-A, EUR-A and WPR-A, where maternal mortality rates are very low.

When examined by region, the global burden of iron deficiency anaemia and its consequences are most heavily borne by those in South-East Asia and Africa. For maternal causes, 43% and 37% of the mater-

nal deaths (and DALYs) attributed to iron deficiency anaemia occur in Africa (AFR-D and AFR-E combined) and South-East Asia (SEAR-B and SEAR-D combined), respectively. For perinatal causes, the relative burden in the two regions is reversed, but they still suffer the greatest toll, with 34% of the iron deficiency-related perinatal deaths (and DALYs lost) in Africa and 40% in South-East Asia. WPR-B and EMR-D also bear a large burden of iron deficiency-related perinatal deaths, with approximately 10% of the global total in each of these two subregions.

9. Expected changes in the prevalence of iron deficiency anaemia

Based on the trends observed over the past 20 years there is no reason to expect anaemia or iron deficiency anaemia prevalence to decrease in the coming decade. The United Nations Subcommittee on Nutrition (ACC/SCN) reviewed trends in data from the 1970s and 1980s (ACC/SCN 1992). Iron density in the diet was decreasing during this period for every global region except the Near East and North Africa. Furthermore, trends in anaemia from 1977 to 1987 were increasing in the two regions where the problem is most severe: south Asia, and sub-Saharan Africa. In 1990, the World Summit for Children set goals for reducing malnutrition, sickness and death in children that included a goal to reduce iron deficiency anaemia by one-third by the year 2000. A progress report in 1995 (UNICEF 1995) stated:

> Very few countries have so far taken nation-scale action to eliminate iron deficiency anaemia. . . . No mid-decade target was established for progress against anaemia; but the goal . . . is unlikely to be met without a significant acceleration of effort over the next six years.

This needed acceleration of effort did not take place. A more recent progress report (WHO 2000) concluded the following:

> Unfortunately, there has been *little appreciable change* over the last two decades in the high worldwide prevalence of iron deficiency anaemia. Few active programmes in both developed and developing countries have succeeded in reducing iron deficiency and anaemia. Important factors contributing to the lack of progress include failure to recognize the causes of iron deficiency and anaemia, lack of political commitment to control it, inadequate planning of control programmes, insufficient mobilization and training of health staff, and insufficient community involvement in solving the problem.

Thus the evidence strongly suggests that under a "business-as-usual" scenario, the prevalence of iron deficiency anaemia will not decrease over the next decade. We hope that the new estimates of the burden of disease attributed to iron deficiency will result in a significant deviation from business-as-usual.

10. Discussion

Our analysis of the relationship between pregnancy anaemia and maternal mortality differed from that of the recent analysis by Brabin et al. (2001b), although we drew upon the same published studies. The salient difference is that we began by estimating the mortality–haemoglobin relationship within each study (expressed as an OR per g/dl increment in haemoglobin), and then used meta-analytic techniques to obtain a weighted average of those ORs. Restricting the analysis to observations between 5 and 12 g/dl haemoglobin, the risk increased with decreasing haemoglobin within each study.

As noted previously, there are no trials of iron supplementation with maternal mortality as outcome. Furthermore, because of cost and ethical considerations, we will likely have to continue to rely on observational data to refine these estimates. However, better observational data are badly needed. The currently available data are generally quite old, are predominantly from Asia (India and Malaysia) and are not controlled for many potentially confounding or modifying factors.

This analysis differs from most previous statements about anaemia and maternal mortality by positing a continuous relationship between haemoglobin concentration and mortality risk. INACG issued the following statement about severe anaemia and death in childbirth (1989):

> At 6.0 g/dl, evidence of circulatory decompensation becomes apparent. Women experience breathlessness and increased cardiac output at rest. At this stage, added stress from labor . . . can result in maternal death. Without effective treatment, maternal death from anemic heart failure . . . is likely with a haemoglobin concentration of 4.0 g/dl. Even a blood loss of 100 ml can cause circulatory shock and death.

A more recent summary statement (Stoltzfus 2001), based on the systematic review of Brabin et al. (2001b) also concluded that "A significant body of causal evidence exists for . . . severe anaemia and maternal mortality" but that "causal evidence is lacking or contradictory for . . . mild-moderate anaemia and maternal mortality" (Table 1). However, considering that death from cardiovascular causes is a function of blood volume, blood loss, cardiac fitness and haemoglobin concentration, it seems plausible that the relationship between haemoglobin concentration and maternal death would be continuous in nature, although not necessarily linear. Indeed the relationship as we have modelled it in this analysis is log-linear, with risk increasing exponentially with decreasing haemoglobin concentration.

We are not aware of another systematic analysis of the observational data linking pregnancy anaemia to perinatal mortality. The risk estimates from geographically diverse studies were remarkably consistent, and we believe provided the best evidence available for our purpose. Rasmussen (2001) identified four controlled iron supplementation trials that reported perinatal deaths as an outcome. All four studies had major

design concerns (low rates of follow-up or lack of anaemic individuals enrolled in the trial), and all were of insufficient sample size to draw clear conclusions. Rasmussen did not draw any firm conclusion from these data.

One relatively large trial was recently completed in rural Nepal, where the incidence of pregnancy anaemia and perinatal mortality are both high. This trial has only been reported in abstract form (Christian et al. 2002) and also was not sufficiently large to draw clear conclusions about perinatal mortality. However, it represents the strongest randomized trial evidence to date, because it was placebo-controlled and had high follow-up rates. In this trial, all women were provided anthelminthic treatment and vitamin A supplements. Women supplemented with 60 mg iron and 400 μg folic acid had 20% (95% CI 0.55–1.17) lower incidence of perinatal mortality than the placebo group (P. Christian, personal communication). This point estimate is larger than the per cent reduction we estimated in this analysis (i.e. 16%, 95% CI 10–22%). However, the trial also included several additional treatment arms, including one group that received folic acid without iron. The folic acid-supplemented group also had lower perinatal mortality rates than the placebo group, a reduction of 11% (95% CI 0.63–1.26). Micronutrient supplementation began after the first trimester of pregnancy, and therefore these reductions cannot be attributed to the demonstrated effects of folic acid in preventing neural tube defects. Although neither of these reductions is statistically significant, they are important public health findings. If we accept these point estimates as the best available estimates from trial data, we conclude that our perinatal risk estimates are in accord with the benefits seen with effective iron-folic acid supplementation, but that a large part of the benefit may in fact be attributable to the folic acid.

The biological mechanisms linking iron deficiency anaemia (or anaemia from any cause) to perinatal mortality remain to be elucidated. One possible pathway is through preterm delivery. Recent reviews of clinical trial evidence have found the evidence inconclusive in support of a role for iron supplementation in preventing preterm birth or low birth weight (Mahomed 2000b; Rasmussen 2001). However, the evidence for or against is remarkably weak, and does not rule out a causal relationship (Stoltzfus 2001). Scott Poe and Mary Cogswell (personal communication) have recently completed a meta-analysis of the observational evidence relating pregnancy anaemia to low birth weight, intrauterine growth retardation and preterm birth. They found that pregnancy anaemia assessed in the first two trimesters of pregnancy was more strongly associated with preterm birth than intrauterine growth retardation or low birth weight, and that the risk of preterm birth increased with increasing severity of anaemia. Thus, while controlled trial evidence is lacking, the observational evidence suggests that preterm birth is one plausible mechanism for the anaemia-related risk of perinatal mortality.

If we accept preterm birth as a plausible causal pathway, the question remains as to how iron deficiency anaemia causes preterm birth. Allen suggested three possible mechanisms (Allen 2001). Iron deficiency anaemia might activate a hormonal stress response, might increase oxidative stress or might increase the risk of maternal infections. Further research is needed to elucidate these mechanisms or to suggest alternative ones.

While preterm birth may be considered the leading hypothesis to explain the link between maternal anaemia and perinatal mortality, it is not the only hypothesis that should be pursued. If these above proposed mechanisms exist, it is plausible that they cause adverse effects on the fetus that go beyond preterm birth, for example by impairing the neonatal immune system, endocrine function, temperature regulation, or other systems critical to a successful transition from intra to extrauterine life. Additionally, the adverse effects of maternal anaemia on the mother's function and well-being may also increase risks to her neonate through her decreased capacity to actively care for and breastfeed the infant (Henly et al. 1995). In the extreme case, maternal death associated with anaemia would increase the neonate's risk of death.

We included here an estimate of the continuous relationship between iron deficiency anaemia in early childhood and later intelligence, even though this relationship is included in the direct disability score attributed to iron deficiency anaemia. The possible biological mechanisms underlying this relationship are the subject of a large body of ongoing research in animals and children (e.g. see Beard 2001). To date, two published placebo-controlled randomized trials have measured the effect of longer-term (i.e. >2 months) iron supplementation on cognitive development of young children in samples that included anaemic children (Idjradinata and Pollitt 1993; Stoltzfus et al. 2001). Both trials found significant benefits in the iron-supplemented group. In Indonesia (Idjradinata and Pollitt 1993), the positive effect was measured on the Bayley Scales of Infant Development, while in Zanzibar (Stoltzfus et al. 2001), parental reports of motor and language milestones were used. These trials support a causal link between iron deficiency anaemia and child development that is at least partly preventable with early treatment.

The major difficulty has been quantifying this relationship in meaningful epidemiological and socioeconomic terms, especially in the sociocultural contexts in which iron deficiency anaemia is most prevalent. Our estimated OR is an attempt to put the relationship in epidemiological terms. This estimate relies on the assumption that a mean shift in IQ can be converted into increased risk of mild mental retardation, assuming that the entire IQ distribution was shifted equally. To our knowledge there has been only one published report of the relationship between early childhood anaemia and mild mental retardation as a dichotomous outcome (as opposed to intelligence or developmental scores as continuous outcomes). Hurtado et al. (1999) assessed the association between

haemoglobin concentration of children in the United States enrolled in the Special Supplemental Program for Women, Infants, and Children, a programme of the U.S. Government that provides food supplements to low-income pregnant women and their young children (Hurtado et al. 1999). After adjusting for several important covariates, the OR for mild or moderate mental retardation at school age remained significant in their model, which treated haemoglobin concentration as a continuous risk factor (as did ours). This finding supports the plausibility of our assumption that the association between mean cognitive scores and anaemia is associated with increased risks of mild mental retardation. However, it is only a single observational study, and we believe our estimate should be interpreted with extreme caution.

In summary, the available evidence suggests that iron deficiency anaemia contributes substantially to death and disability in the world. The great majority of this disease burden is in Africa and Asia and derives from anaemia in pregnancy and early childhood. This evidence is based on critical assumptions, most importantly, that the observed prospective relationships are causal in nature, and that the relationships analysed using anaemia as the risk factor pertain equally to iron deficiency anaemia as one particular form of anaemia.

The high global prevalence of anaemia and its potentially associated disease burden, as reflected in these estimates, constitute an urgent agenda for both research and action. First, we must clarify the assumptions above, the first and foremost of these being causality, and refine these estimates with stronger evidence. Because these estimates are uncertain in many respects, their most important use may be to motivate public health scientists to provide definitive causal evidence. Second, we must establish ways to effectively reduce iron deficiency anaemia to prevent these apparent consequences. We hope these new estimates of the burden of disease due to iron deficiency will motivate these actions.

Acknowledgements

This work was supported by the Family Health and Child Survival (FHACS) Cooperative Agreement, between the United States Agency for International Development (USAID), Office of Health and Nutrition, and the Johns Hopkins Bloomberg School of Public Health, Department of International Health and by the World Health Organization Global Programme on Evidence for Health Policy. The authors are grateful to Steve Goodman for his advice on statistical issues, and to Ines Egli and Bruno de Benoist for data used in estimation of the global anaemia prevalence. We also thank Michele Dreyfuss, Parul Christian, Xu Xiong, Mary Cogswell and Scott Poe for sharing unpublished data or analyses for inclusion in this chapter. Finally, we thank Steve Fishman, Jeffrey McGuckin and Justine Kavle for their help in facilitating communication and compiling data for this project.

Notes

1 We recognize that iron supplementation is not the only means of shifting the haemoglobin distribution, but randomized trials of iron supplementation provide the best estimate of the distribution if dietary iron deficiency were nearly eliminated.

2 See preface for an explanation of this term.

References

ACC/SCN (1992) *Second report on the world nutrition situation. Vol. 1: Global and regional results*. The United Nations Subcommittee on Nutrition, ACC/SCN, Geneva.

Adam Z (1997) *Iron supplementation and malaria: a randomized, placebo-controlled field trial in rural Ethiopia* [Dissertation]. London School of Hygiene and Tropical Medicine, London.

Agarwal KN, Agarwal DK, Mishra KP (1991) Impact of anaemia prophylaxis in pregnancy on maternal haemoglobin, serum ferritin and birth weight. *Indian Journal of Medical Research*, **94**:277–280.

Allen LH (2001) Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. *Journal of Nutrition*, **131**:S581–589.

Beard JL (2001) Iron biology in immune function, muscle metabolism and neuronal functioning. *Journal of Nutrition*, **131**:S568–580.

Beard JL, Stoltzfus R, eds. (2001) Iron-deficiency anaemia: reexamining the nature and magnitude of the public health problem. Proceedings of the WHO-INACG Conference, Belmont, MD, USA, 2000. *Journal of Nutrition*, **131**:2S-II.

Beaton GH (2002) Functional outcomes of iron deficiency and iron deficiency in pregnancy and beyond. (Proceedings of the INACG Symposium, February 15–26, 2001 in Hanoi, Viet Nam) Hanoi.

Brabin BJ, Hakimi M, Pelletier D (2001b) An analysis of anaemia and pregnancy-related maternal mortality. *Journal of Nutrition*, **131**:S604–614.

Brabin BJ, Premji Z, Verhoeff F (2001a) An analysis of anaemia and child mortality. *Journal of Nutrition*, **131**:S636–645.

Brabin BJ (1983) An analysis of malaria in pregnancy in Africa. *Bulletin of World Health Organization*, **61**:1005–1016.

Cantwell RJ (1974) The long term neurological sequelae of anaemia in infancy. *Pediatric Research*, **342**:68.

Chi I-C, Agoestina T, Harbin J (1981) Maternal mortality at twelve teaching hospitals in Indonesian epidemiologic analysis. *International Journal of Gynaecology and Obstetrics*, **19**:259–266.

Christian P, West KP Jr, Khatry SK, LeClerq SC, Kimbrough-Pradhan E, Katz J (2002) The effect of maternal micronutrient supplementation on fetal loss and infant mortality in rural Nepal: a randomized trial. *FASEB Journal*, **16**:A748.

de Andraca I, Walter T, Castillo M, Pino P, Rivera P, Cobo C (1990) *Iron deficiency anaemia and its effects upon psychological development at pre-school age: a longitudinal study*. Nestlé Foundation, Lausanne.

DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Controlled Clinical Trials*, **7**:177–188.

Dommergues MP, Archambeaud B, Ducot Y et al. (1989) Carence en fer et tests de developpement psychomoteur: etude longitudinale entre l'age de 10 mois et l'age de 4 ans. [Iron deficiency and psychomotor development tests: longitudinal study between 10 months and 4 years of age.] *Archives Francaises de Pediatrie*, **46**:487–490.

Dreyfuss ML, Shrestha JB, Khatry SK et al. (1996) Relationship between iron status and helminth infection among pregnant women in Nepal. *FASEB Journal*, **10**:A730.

Fleming AF, Ghatoura GB, Harrison KA, Briggs ND, Dunn DT (1986) The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Annals of Tropical Medicine and Parasitology*, **80**:211–233.

Fullerton WT, Turner AG (1962) Exchange transfusion in treatment of severe anaemia in pregnancy. *The Lancet*, **1**:75–78.

Garn SM, Ridella SA, Petzold AS, Falkner F (1981) Maternal hematologic levels and pregnancy outcomes. *Seminars in Perinatology*, **5**:155–162.

Gillespie S, Johnston JL (1998) *Expert consultation on anaemia determinants and interventions*. Micronutrient Initiative, Ottawa, ON.

Grantham-McGregor S, Ani C (2001) A review of studies on the effect of iron deficiency on cognitive development in children. *Journal of Nutrition*, **131**:S649–666.

Haas JD, Brownlie T (2001) Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *Journal of Nutrition*, **131**:S676–690.

Harrison KA, Lister UG, Rossiter CE, Chong H (1985) Perinatal mortality. *British Journal of Obstetrics and Gynaecology*, **5**:86–99.

Harrison KA, Rossiter CE (1985) Maternal mortality. *British Journal of Obstetrics and Gynaecology*, **5**:100–115.

Harrison KA (1975) Maternal mortality in anaemia in pregnancy. *West Africa Medical Journal*, 27–31.

Harrison KA (1982) Anaemia, malaria, and sickle cell disease. *Clinics in Obstetrics and Gynaecology*, **9**:445–477.

Harvey PWJ, Heywood PF, Nesheim MC et al. (1989) The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *American Journal of Tropical Medicine and Hygiene*, **40**:12–18.

Hemminki E, Rimpelä U (1991) A randomized comparison of routine versus selective iron supplementation during pregnancy. *Journal of the American College of Nutrition*, **10**:3–10.

Henly SJ, Anderson CM, Avery MD, Hills-Bonczyk SG, Potter S, Duckett LJ (1995) Anaemia and insufficient milk in first-time mothers. *Birth*, **22**:86–92.

Horton S, Levin C (2001) Commentary on "Evidence that iron deficiency anaemia causes reduced work capacity". *Journal of Nutrition*, **131**: S691–696.

Hurtado EK, Claussen AH, Scott KG (1999) Early childhood anaemia and mild or moderate mental retardation. *American Journal of Clinical Nutrition*, **69**:115–119.

Idjradinata P, Pollitt E (1993) Reversal of developmental delays in iron-deficient anaemic infants treated with iron. *The Lancet*, **341**:1–4.

INACG (1989) *Guidelines for the control of maternal nutritional anaemia*. International Nutritional Anemia Consultative Group. International Life Sciences Institute (ILSI), Washington, DC.

INACG (1999) *Safety of iron supplementation programs in malaria-endemic regions*. ILSI, Washington, DC.

Institute of Medicine (1990) *Nutrition during pregnancy*. National Academy Press, Washington, DC.

Johnson JWC, Ojo OA (1967) Amniotic fluid oxygen tensions in severe maternal anaemia. *American Journal of Obstetrics and Gynecology*, **97**:499–506.

Konar M, Sikdar K, Basak S, Lahiri D (1980) Maternal Mortality. *Journal of the Indian Medical Association*, **75**:45–51.

Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM (1994) Iron supplementation improves appetite and growth in anaemic Kenyan primary school children. *Journal of Nutrition*, **124**:645–654.

Llewellyn-Jones D (1965) Severe anaemia in pregnancy. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **5**:191–197.

Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL (1997) Prevalence of iron deficiency in the United States. *Journal of the American Medical Association*, **277**:973–976.

Lozoff B, Jimenez E, Wolf AW (1991) Long-term developmental outcome of infants with iron deficiency. *New England Journal of Medicine*, **325**:687–694.

Macgregor MW (1963) Maternal anaemia as a factor in prematurity and perinatal mortality. *Scottish Medical Journal*, **8**:134–140.

Mahomed K (2000a) Iron supplementation in pregnancy. *Cochrane Database System Reviews*, (2):CD000117.

Mahomed K (2000b) Iron and folate supplementation in pregnancy. *Cochrane Database System Reviews*, (2):CD001135.

Menendez C, Kahigwa E, Hirt R et al. (1997) Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *The Lancet*, **350**: 844–850.

Menendez C, Todd J, Alonso PL et al. (1994) The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **88**:590–593.

Mola G, Permezel M, Amoa AB, Klufio CA (1999) Anaemia and perinatal outcome in Port Moresby. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **39**:31–34.

Murphy JF, O'Riordan J, Newcombe RG, Coles EC, Pearson JF (1986) Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *The Lancet*, **1**:992–994.

Murray CJ, Lopez AD, eds. (1996a) *The global burden of disease a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol 1. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJ, Lopez AD, eds. (1996b) *Global health statistics*: *a compendium of incidence, prevalence and mortality estimates for over 200 conditions*. Global Burden of Disease and Injury, Vol 2. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray MJ, Murray AB, Murray NJ, Murray MB (1978) The effect of iron status of Nigerian mothers on that of their infants at birth and 6 months, and on the concentration of Fe in breast milk. *British Journal of Nutrition*, **39**:627–630.

Oppenheimer SJ (2001) Iron and its relation to immunity and infectious disease. *Journal of Nutrition*, **131**:S616–635.

Oppenheimer SJ, Macfarlane SB, Moody JB, Bunari O, Hendrickse RG (1986) Effect of iron prophylaxis on morbidity due to infectious disease: report on clinical studies in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **80**:596–602.

Palti H, Pevsner B, Adler B (1983) Does anaemia in infancy affect achievement on developmental and intelligence tests? *Human Biology*, **55**:183–194.

Rasmussen KM (2001) Is there a causal relationship between iron deficiency or iron-deficiency anaemia and weight at birth, length of gestation and perinatal mortality? *Journal of Nutrition*, **131**:S590–603.

Sarin AR (1995) Severe anaemia of pregnancy, recent experience. *International Journal of Gynaecology and Obstetrics,* **50**:S45–49.

Sloan NL, Jordan E, Winikoff B (2002) Effects of iron supplementation on maternal hematologic status in pregnancy. *American Journal of Public Health*, **92**:288–293.

Smith AW, Hendrickse RG, Harrison C, Hayes RJ, Greenwood BM (1989) The effects on malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Annals of Tropical Paediatrics*, **9**:17–23.

Snedecor GW, Cochran WG (1980) *Statistical Methods*. Iowa State University Press, Ames.

Stoltzfus RJ (2001) Iron-deficiency anaemia: reexamining the nature and magnitude of the public health problem. Summary: implications for research and programs. *Journal of Nutrition*, **131**:S697–700.

Stoltzfus RJ, Dreyfuss ML (1998) *Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia*. ILSI Press, Washington, DC.

Stoltzfus RJ, Kvalsvig JD, Chwaya HM et al. (2001) Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. *British Medical Journal*, **323**:1389–1393.

Tasker PWG (1958) Anaemia in pregnancy. A five year appraisal. *Medical Journal of Malayasia*, **8**:3–8.

UNICEF (1995) *The state of the world's children 1995*. Oxford University Press, Oxford.

UNICEF (1998) *The state of the world's children 1998*. Oxford University Press, Oxford.

Wasserman G, Graziano JH, Factor-Litvak P et al. (1992) Independent effects of lead exposure and iron deficiency anaemia on developmental outcome at age 2 years. *Journal of Pediatrics*, **121**:695–703.

WHO (2000) *Nutrition for health and development. A global agenda for combating malnutrition. A progress report*. (WHO/NHD/00.6). World Health Organization, Geneva.

Xiong X (1996) *Anaemia during pregnancy and birth outcomes: new data from China & a meta-analysis* [Dissertation]. Université Libre de Bruxelles Health Science Library, Brussels.

Xiong X, Buekens P, Alexander S, Demianczuk N, Wollast E (2000) Anaemia during pregnancy and birth outcome: a meta-analysis. *American Journal of Perinatology*, **17**:137–46.

Xiong X, Buekens P, Alexander S, Wollast E (1996) The relationship between anaemia during pregnancy and birth outcomes. *Archives of Public Health*, **53**:S136.

Yip R, Stoltzfus RJ, Simmons WK (1996) Assessment of the prevalence and the nature of iron deficiency for populations: the utility of comparing haemoglobin distributions. In: *Iron nutrition in health and disease*. Hallberg L, ed. John Libby & Co., London.

Chapter 4

Vitamin A deficiency

Amy L. Rice, Keith P. West Jr. and Robert E. Black

Summary

Vitamin A deficiency is a common form of micronutrient malnutrition affecting 21.1% of preschool-age children and 5.6% of pregnant women worldwide.

The published literature linking vitamin A interventions to cause-specific child mortality due to measles, diarrhoea, malaria and other infectious diseases and to all-cause maternal mortality was comprehensively reviewed. Randomized controlled trial data of vitamin A interventions and survival were used to estimate the risk of mortality associated with vitamin A deficiency. The published relative risks were adjusted for the estimated prevalence of deficiency at study baseline. Summary relative risks were calculated from meta-analyses (for measles, diarrhoea, and other infectious disease causes of child mortality) or from single studies (malaria mortality among children and all-cause maternal mortality).

The estimated relative risks associated with vitamin A deficiency in children were 1.86 (95% CI 1.32–2.59) for measles mortality, 2.15 (95% CI 1.83–2.58) for diarrhoea mortality, 1.78 (95% CI 1.43–2.19) for malaria mortality, 1.13 (95% CI 1.01–1.32) for other infectious disease mortality and 4.51 (95% CI 2.91–6.94) for all-cause maternal mortality.

The available evidence suggests that nearly 800 000 deaths worldwide can be attributed to vitamin A deficiency among women and children. Approximately 20–24% of child mortality from measles, diarrhoea and malaria and 20% of all-cause maternal mortality can be attributed to this preventable condition. Africa and South-East Asia have the highest burden of disease.

1. Introduction

The objective of this chapter is to summarize the available evidence that can be used to *quantitatively* estimate the risk of adverse health outcomes associated with vitamin A deficiency and to calculate the associated burden of disease for different regions of the world. Vitamin A is an essential nutrient required for maintaining immune function, eye health, vision, growth and survival in human beings. Over the years, numerous studies have been conducted to identify the biological functions of vitamin A, the health consequences associated with deficiency, and the mechanisms that explain these relationships. Causal relationships have been clearly demonstrated in some instances and comprehensive reviews on the subject have been published (Sommer and West 1996).

According to World Bank estimates, vitamin A supplementation for preschool-age children is one of the most cost-effective child survival interventions (World Bank 1993). National level public health programmes to prevent and treat vitamin A deficiency are currently being implemented in countries in Asia, Africa and elsewhere. International donors and agencies including the Canadian International Development Agency (CIDA), United Nations Children's Fund (UNICEF), the United States Agency for International Development (USAID), the World Health Organization (WHO) and others have actively supported both national and global level initiatives to raise awareness about the problem of vitamin A deficiency and to promote efforts to implement effective and affordable solutions (Mason et al. 2001). Reducing the prevalence of vitamin A deficiency will lessen disease burden by improving immune function, lowering mortality rates and preventing blindness, especially among children. This chapter will contribute to ongoing efforts to assess the global problem of vitamin A deficiency by using existing data to estimate global prevalence rates, to identify and quantify the adverse health consequences associated with deficiency, and to estimate the future health benefits that could be gained by implementing even more effective control programmes.

2. Definition of malnutrition and vitamin A deficiency

Malnutrition is a complex phenomenon. Broadly defined, malnutrition refers to the condition of inappropriate nutrition. In the past, discussions of malnutrition in the context of health issues in low-income countries often used this term to refer to the condition of "undernutrition" associated with what was presumed to be protein–energy malnutrition and operationally defined as a deficit in anthropometric status or by the presence of clinical signs such as oedema or altered hair colour. In more recent years, various vitamin and mineral deficiencies, including vitamin A, iron, iodine and zinc have been recognized as discrete types of mal-

nutrition that adversely affect human health and contribute to disease and mortality. Some of these nutrients affect closely related biological systems; for example both vitamin A and zinc play important roles in maintaining different aspects of immune function (Shankar 2001) and both vitamin A and iron affect haemoglobin metabolism (Semba and Bloem 2002). Ecological-level studies have demonstrated that the prevalence of these micronutrient deficiencies are high in many of the same countries, thus many individuals may suffer from multiple micronutrient deficiencies at the same time. However, relatively few data are currently available for quantifying either the joint distribution of multiple deficiencies or the impact that multiple micronutrient deficiencies have on specific health outcomes. Therefore, the comparative risk assessment (CRA) project will estimate the separate contribution of these risk factors to the global burden of disease. Individual reviews are available for the risk factors of iron deficiency (chapter 3), zinc deficiency (chapter 5) and underweight status (chapter 2) in addition to vitamin A deficiency, which is the subject of the current chapter.

Vitamin A is an essential nutrient required for maintaining immune function, eye health, vision, growth and survival in human beings (National Research Council 1989). Although animal studies that identified vitamin A as a necessary factor for rat growth were conducted in the early 1900s and the chemical structure of the vitamin was elucidated over 20 years later, reports describing the link between xerophthalmia (signs in the eye of disease due to a severe lack of the vitamin) and successful treatment with animal liver (a rich source of the vitamin) date back to the medical writings of ancient Egypt (Olson 1996).

At present, vitamin A deficiency remains a widespread public health problem, especially in countries of South Asia and Africa. Globally, preschool-age children and women of reproductive age are the two population groups most commonly recognized to be at risk of this nutritional deficiency and its adverse health consequences. A combination of chronically lower than required dietary intakes of vitamin A-rich foods (eggs, milk, liver, deep orange fruits and dark green leafy vegetables, etc.) combined with malabsorption and increased vitamin A excretion rates associated with some common illnesses places many women and children at risk of developing vitamin A deficiency (Christian et al. 1998b; IVACG 1997; Sommer and West 1996; Stephensen 2001).

No single indicator can be reliably used to assess the full spectrum of vitamin A deficiency. Different aspects of vitamin A status are assessed using clinical indicators, biochemical indicators, functional indicators and histological indicators (WHO 1996). In humans, vitamin A is stored almost exclusively (>90%) in the liver and some investigators propose liver and/or total body stores as a primary indicator of vitamin A status. Although recent isotope dilution techniques to indirectly measure liver vitamin A stores have yielded promising results (Haskell et al. 1999;

Ribaya-Mercado et al. 1999) these techniques have not yet been used in large-scale population-based surveys.

Severe vitamin A deficiency can be identified by the presence of the classical eye signs of xerophthalmia in individuals. However, because severe vitamin A deficiency is relatively rare in most populations, a large number of individuals must be surveyed in order to generate a reliable prevalence estimate. Depending on the severity of vitamin A deficiency in a population, the sample size requirement for a xerophthalmia survey may be nearly ten times higher than what would be required to generate a reliable prevalence estimate for other indicators of vitamin A status, such as low serum retinol concentrations, which may occur more frequently in the same population (Sommer and Davidson 2002; WHO 1996).

Milder vitamin A deficiency is far more common, but the assessment of vitamin A deficiency that does not result in relatively easily observable eye signs is also more problematic. One way to identify milder forms of vitamin A deficiency is to collect blood samples and measure the concentration of circulating serum retinol in an individual. Values <0.70 μmol/l have traditionally been considered indicative of deficiency in children, based on empirical data from population-based studies that did not exclude individuals based on measurements of acute phase proteins. In adults, appropriate cut-off levels are less firmly established, but values <0.70 μmol/l and <1.05 μmol/l have been used for different purposes. Because serum retinol concentrations are transiently depressed during the acute phase response to certain infections, some investigators have questioned the validity of using this indicator to assess the vitamin A status of individuals (Stephensen 2001). However, determining the prevalence of serum retinol concentrations below a defined cut-off point remains one of the most commonly used and widely accepted approaches for assessing the vitamin A status of entire populations (Sommer and Davidson 2002).

At the population level, the prevalence of vitamin A deficiency can be determined based on the prevalence of either: (i) night blindness, usually obtained by verbal recall; (ii) other eye signs of xerophthalmia (Bitot's spots or corneal lesions); or (iii) biochemical indicator values (serum retinol, breast milk retinol, relative dose-response test, modified relative dose-response test, or serum 30-day response), or histological indicator values (conjunctival impression cytology [CIC] that fall below a defined cut-off point (WHO 1996). Until recently the majority of nationally representative, large-scale surveys related to vitamin A deficiency were conducted primarily among preschool-age children. However, in the past few years some large-scale surveys, including recent demographic and health surveys, have also attempted to estimate the prevalence of night blindness among pregnant women. More limited survey findings are available for serum and breast milk retinol concentrations among women. Surveys that included data on any or all of the indicators listed above were used

as a basis for estimating the global prevalence of vitamin A deficiency as a risk factor for the CRA project. The categorical definitions chosen to represent "vitamin A deficiency" among children (aged 0–4 years) and women (aged 15–44 years) for the CRA project are described in the following sections. A description of the data, indicators, and the process used to estimate the current prevalence of vitamin A deficiency among preschool-age children and pregnant women is presented in section 3.5.

2.1 Definitions for children (0–4 years)

Globally, the most reliable population-based survey data provide estimates of vitamin A deficiency among children aged <5 years, primarily because this is the most well-established high-risk age group for this nutritional risk factor. In the CRA project prevalence estimates have been developed only for the 0–4-year age group, although there is some evidence that slightly older children also suffer from vitamin A deficiency and its adverse health consequences.

In order to calculate the attributable fraction of an adverse health outcome that is due to a risk factor, compatible definitions must be used when estimating the relative risk of the adverse outcome associated with the risk factor and the prevalence of the risk factor itself in a population. This stringent requirement for a compatible definition greatly influenced the data that were suitable for use in the CRA project. The majority of large-scale vitamin A intervention trials involving preschool-age children have been mortality studies that assumed (but did not confirm for all participants) that the children were mildly deficient (i.e. had low serum retinol concentrations). In general, very few participants in those studies exhibited eye signs of xerophthalmia, which is consistent with the expected epidemiological pattern of vitamin A deficiency. Vitamin A receipt was associated with a lower relative risk of adverse outcomes in those trials, even among children who had no eye signs of deficiency.

After considering the availability of intervention trial data and global prevalence data for vitamin A deficiency among preschool-age children, a definition of vitamin A deficiency related to low serum retinol concentrations among children in the 0–4-year age range emerged as the most appropriate choice for use in the CRA project:

- Vitamin A deficient: serum retinol concentration <0.70 μmol/l.
- Vitamin A sufficient: serum retinol concentration ≥0.70 μmol/l.

2.2 Global prevalence estimates for children

The 1995 WHO report *Global prevalence of vitamin A deficiency* included prevalence estimates of vitamin A deficiency among preschool-age children for two classes of indicators: (i) clinical eye signs of disease (xerophthalmia); and (ii) low serum retinol concentrations. However, data were reported only for the individual countries that met the defini-

tion of a significant public health problem, which was defined as a population prevalence of low serum retinol (<0.70 μmol/l) ≥10%, of night blindness (XN) >1%, of Bitot's spots (X1B) >0.5%, of corneal xerosis and/or ulceration (X2, X3A, X3B) >0.01%, or of xerophthalmia-related corneal scars (XS) >0.05% (WHO 1995). Estimates for countries that did not meet those definitions were not incorporated into the global prevalence estimate. A global estimate for the total number of children at risk of vitamin A deficiency (~254 million) was generated by adding the estimated number of children with low serum retinol concentrations (~251 million) and the estimated number with clinical eye signs of vitamin A deficiency (~3 million).

In 1998, the Micronutrient Initiative, UNICEF and Tulane University published a joint report reviewing the recent progress of vitamin A intervention programme activities (Micronutrient Initiative/UNICEF/Tulane University 1998). To generate prevalence estimates for vitamin A deficiency among children, this group used a different approach and developed a modelling process that attempted to take into account the effects of time trends and vitamin A intervention programmes. Data from a subset of countries that had conducted prevalence surveys since the mid-1980s were used to estimate the regional and global prevalence of vitamin A deficiency among children. The number of children affected by low serum retinol concentrations was estimated to range from 75 to 140 million, while the number of children with clinical eye signs of deficiency was estimated as 3 million. The sizeable discrepancy in the estimated prevalence of vitamin A deficiency from these two sources, 254 million and 78 to 143 million children, respectively, was due in part to differences in the data and methodology used, but also to a calculation error in the WHO report (West 2002).

An updated estimate for the global prevalence of vitamin A deficiency in children appears in the 2002 publication *Extent of vitamin A deficiency among preschool children and women of reproductive age* (West 2002), hereafter referred to as the 2002 West report. A brief description of the methodology used in developing the estimate is described in this chapter in section 3.5. Those prevalence data served as the basis for calculating the global burden of disease attributable to vitamin A deficiency among children aged 0–4 years for the CRA project.

2.3 Definitions for pregnant women (15–44 years)

In recent years, women of reproductive age have increasingly been recognized as an important group at risk of vitamin A deficiency and the adverse health outcomes associated with this condition (West 2002). However, when compared to preschool-age children, far less information is available to quantitatively estimate the burden of disease among women. Current areas of active research include assessing the magnitude of the problem, investigating the causes of deficiency in women, describing the range of associated adverse health outcomes, and identifying

appropriate interventions for preventing and treating vitamin A deficiency.

Standardized indicators and definitions of vitamin A deficiency among women are only beginning to be developed. To date, relatively few large-scale surveys have been conducted to estimate the prevalence of vitamin A deficiency in women—primarily in Asia and Africa. Although many surveys used the presence of night blindness as an indicator of poor vitamin A status among women, some survey data related to low serum retinol and breast milk vitamin A concentrations are also available. However, very few studies have been conducted to date that quantitatively relate the risk of vitamin A deficiency (defined by any indicator) to adverse health outcomes in women. Despite the inherent limitations in the current data related to vitamin A deficiency in women, the evidence was considered strong enough to generate initial estimates of the related global burden of disease. Further work in this area of research will certainly lead to a refinement of these estimates.

The requirement to have a compatible definition of vitamin A deficiency for estimating the relative risk of adverse health outcomes and the global prevalence of vitamin A deficiency among women determined which data were suitable for use in the CRA project. After considering the availability of intervention trial data and global prevalence data for vitamin A deficiency in women, a definition related to low serum retinol concentrations among pregnant women in the 15–44-year age range emerged as the most appropriate choice for use in the CRA project.

Estimates for the prevalence of vitamin A deficiency have been generated only for pregnant women in the 15–44-year age range primarily because the strongest information is available for this particular group of women. Future projects that quantify the global burden of disease may include non-pregnant and older women as well, if stronger data have become available for quantitatively estimating the prevalence of deficiency and adverse health outcomes in these groups. Vitamin A deficiency in pregnant women aged 15–44 years was operationally defined as:

- Vitamin A deficient: Serum retinol concentration $<0.70\,\mu mol/l$.
- Vitamin A sufficient: Serum retinol concentration $\geq 0.70\,\mu mol/l$.

2.4 Global prevalence estimates for pregnant women

The first comprehensive estimate for the global prevalence of vitamin A deficiency among women of reproductive age appeared in the 2002 West report (West 2002). A brief description of the methodology used in developing the estimate has been described in this chapter in section 3.5. Those prevalence data will serve as the basis for calculating the global burden of disease attributable to vitamin A deficiency among pregnant women aged 15–44 years for the CRA project.

3. Adverse health outcomes considered for review

Within the framework of the larger Global Burden of Disease (GBD) project, health states (in this case vitamin A deficiency) can contribute directly or indirectly to death and disability. The total amount of death and disability attributed to vitamin A deficiency is therefore a sum of its direct and indirect effects. The direct contribution is measured by estimating the burden associated with the sequelae assigned to vitamin A deficiency as defined by the corresponding chapter in the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), whereas the indirect contribution is measured by considering vitamin A deficiency as a risk factor for other causes of death and disability.

Adverse health outcomes generally associated with micronutrient and mineral deficiencies were initially considered for review in relation to vitamin A deficiency. These included blindness; impaired cognitive function; impaired physical work capacity; morbidity (incidence and/or severity) due to diarrhoea, measles, acute respiratory infections, malaria and other infectious diseases; cause-specific mortality related to these diseases; and all-cause mortality. Outcomes potentially associated with vitamin A deficiency in pregnant women included fetal loss, low birth weight, preterm birth, all-cause infant mortality, maternal morbidity and maternal mortality.

3.1 Selection criteria for adverse health outcomes

The adverse health outcomes selected for review and inclusion in the CRA project were those that fulfilled the following criteria: (i) a health outcome included in the 2000 GBD study; (ii) a health outcome where data exist to support a probable causal relationship with vitamin A deficiency; and (iii) a health outcome where data were available to *quantitatively* estimate the relationship with vitamin A deficiency.

Blindness and an increased risk of all-cause mortality are two of the most well-established adverse outcomes associated with vitamin A deficiency in preschool-age children (Sommer 1982; Sommer and West 1996). According to recent estimates, vitamin A deficiency that leads to corneal scarring remains one of the most common preventable causes of childhood blindness in developing countries (Gilbert and Foster 2001). In the 1980s, vitamin A supplementation was shown to significantly reduce all-cause child mortality in a series of eight large-scale trials conducted in Asia and Africa. Meta-analyses of those trial data suggest a 23% to 34% reduction in all-cause mortality among children 6 months to 5 years of age (Beaton et al. 1993; Fawzi et al. 1993; Glasziou and Mackerras 1993; Tonascia 1993). Studies that provided vitamin A supplements to newborn infants immediately after birth have also demonstrated a reduction in mortality (Humphrey et al. 1996; Tielsch et al.

2001), although other trials involving vitamin A supplementation of young infants post-neonatally through five months of age have not shown a survival benefit (Anonymous 1998b; Daulaire et al. 1992; West et al. 1995).

Blindness was excluded as a health outcome from the risk factor analysis because in the GBD study, vitamin A-related blindness is considered to be a direct functional outcome of the deficiency, and the disability associated with blindness was measured in this manner (Murray et al. 1996a, 1996b). In the case of child mortality, the contribution of vitamin A deficiency to the global burden of disease was measured primarily through its contribution as a risk factor for several types of cause-specific mortality, rather than as a risk factor for all-cause mortality. However, a small number of child deaths have also been directly attributed to vitamin A deficiency in the GBD database, because vitamin A deficiency itself appears as the underlying cause of death in some vital registration data sets. For this specific cause of death, by definition, the total number of deaths in a subregion[1] was directly assigned the value obtained from the relevant child mortality statistics for that subregion (Murray et al. 2001). Thus, for the CRA project the total number of child deaths attributable to vitamin A deficiency is the sum of those that are directly and indirectly attributed to the deficiency.

Five outcomes potentially associated with maternal vitamin A deficiency during pregnancy were also excluded from the risk factor analysis because the outcomes were not assessed in the 2000 GBD study or the data were insufficient to quantitatively assess the risk of their occurrence. These were fetal loss, low birth weight, preterm birth, all-cause infant mortality and general maternal morbidity (Christian et al. 1998b, 2000, 2001; Katz et al. 2000; Semba et al. 1998). Impaired cognitive function and impaired physical work capacity were excluded from the analysis because there is little evidence to suggest a biologically plausible association with vitamin A deficiency, except for the condition of maternal night blindness, which appears to limit the time for performing household chores to daylight hours (Christian et al. 1998a). Although experimental animal data and observational human data suggest a biologically plausible role for vitamin A deficiency predisposing children to acute respiratory infections (Bloem et al. 1990; Milton et al. 1987; Sommer and West 1996; Sommer et al. 1987), morbidity and cause-specific mortality related to acute respiratory infections were excluded from the analysis because the data from controlled intervention trials in humans have not, to date, consistently revealed measurable effects of vitamin A on incidence, duration or severity of acute respiratory infections (Anonymous 1995).

After excluding those outcomes from the initial list of outcomes under consideration, the following remained for a more detailed review: (i) morbidity and mortality associated with measles in children; (ii) morbidity and mortality associated with diarrhoea in children; (iii) morbid-

ity and mortality related to malaria in children; (iv) selected other infectious disease causes of death in children (other than measles, diarrhoea, malaria or acute respiratory infections); and (v) all-cause maternal mortality. All-cause maternal mortality was a compilation of three separate conditions: maternal sepsis; maternal haemorrhage; and obstructed labour. These last three outcomes related to maternal mortality were selected from the limited number of maternal health conditions that are coded separately in the ICD-10 coding scheme.

The health outcomes selected for children aged <5 years represent the most common preventable causes of death among this age group (Murray et al. 2001). Although some studies have also explored the link between vitamin A and other specific infectious diseases coded as individual cause of death categories in the GBD study (for example helminthic infections and tuberculosis), the strength of the current evidence was considered insufficient to demonstrate a causal link and quantitatively estimate the associated risk with these specific outcomes. HIV/AIDS was also excluded as a quantifiable health outcome for the same reason. The findings relevant to the outcomes that were chosen for inclusion are presented below.

3.2 Methods for identifying relevant studies and review materials

The following sources were initially consulted to identify relevant materials for this chapter: Medline database; published books about vitamin A, international health, and nutrition; International Vitamin A Consultative Group (IVACG) statements; meeting reports; abstracts and conference proceedings; and other non-peer reviewed literature sources related to vitamin A programme implementation and cost-effectiveness analyses. The Medline database was searched for literature published between 1966 and 2001 in English or with an English language abstract. Combinations of the following keywords were used: vitamin A, vitamin A deficiency, blindness, mortality, acute respiratory infection, pneumonia, diarrhoea, measles, malaria, stillbirth, fetal loss, miscarriage, low birth weight, women.

Abstracts of articles concerning the relationship between vitamin A deficiency in humans, intervention trials, and the health outcomes of interest were reviewed and copies of relevant articles were obtained. Additional publications and reference materials were identified from the citation lists in those sources and through discussions with investigators working in the field.

3.3 Inclusion criteria for individual studies

The individual studies and reports presented in this chapter were restricted to the results of controlled intervention trials because these findings provide strong evidence for a causal relationship and the data

can be used to quantify the risk associated with either documented or suspected vitamin A deficiency (Rothman and Greenland 1998). For the outcomes where published meta-analyses or international consensus statements from IVACG exist, the results from those sources have been included in this chapter rather than a detailed presentation of data from the individual trials.

3.4 Description of excluded studies

Numerous observational cohort studies, case–control studies, and case-series investigations have been conducted over the years to explore the relationships between vitamin A and morbidity or mortality from specific diseases in children. However, the results of those studies are not presented or discussed in detail in this chapter because such designs provide weaker evidence for a causal relationship as compared to randomized controlled intervention trials. Comprehensive reviews of the numerous cohort studies, case–control studies, and case-series reports related to various adverse health outcomes can be found elsewhere (Bauernfiend 1986; Sommer and West 1996). The findings from intervention studies related to vitamin A deficiency and child morbidity have also been summarized elsewhere (Nalubola and Nestel 1999).

3.5 Estimating risk factor levels

The prevalence of vitamin A deficiency (defined as serum retinol concentrations <0.70 μmol/l) among children aged 0–4 years and pregnant women aged 15–44 years was estimated for each of the 14 subregions. This process involved several steps.

First, country-specific prevalence rates were estimated for each one of the 191 WHO Member States. Updated country-specific prevalence rates were obtained from the recent review, 2002 West report (West 2002), which includes the estimated prevalence and number of deficient children and pregnant women in countries where vitamin A deficiency is either documented or presumed to exist, based on non-population-based vitamin A status data or other indirect indicators. Since separate prevalence estimates were not reported for boys and girls, the same prevalence rate was applied to both of these groups in the CRA project analyses. Next, the prevalence of vitamin A deficiency for the countries not included in that review was assumed to be zero. A suitable database was created for analysis and the findings were summarized across the 14 subregions.

A detailed description of the methods used to compile the data for the 2002 West report appears in that document (West 2002), but a brief summary is presented here. In addition, a file that contains a complete listing of the contributing studies and technical notes associated with the 191 countries can be found at http://www.jhsph.edu/chn/GlobalVAD.html.

Data sources

A wide variety of data sources related to vitamin A deficiency were reviewed in order to obtain the most current information possible. These included: (i) the 1995 comprehensive survey report compiled by the WHO Micronutrient Deficiency Information System (MDIS) (WHO 1995); (ii) a 2001 update from the MDIS group at WHO that included national survey data published after 1995; (iii) the 1998 report published by the Micronutrient Initiative, UNICEF and Tulane University (Micronutrient Initiative/UNICEF/Tulane University 1998), which incorporated both the 1995 MDIS data and more recent country updates from 107 countries with UNICEF offices and programmes; (iv) published surveys and field studies that reported vitamin A status indicators in women or children; and (v) unpublished reports, meeting presentations and personal communication about recent field surveys and studies not included in other data sources.

Indicators

The 2002 West report presents prevalence data for xerophthalmia rates and serum retinol concentrations <0.70 μmol/l among children and for night blindness rates and serum retinol concentrations <0.70 μmol/l and <1.05 μmol/l among populations of pregnant women. Since the CRA project only utilized serum retinol data, the methodology used to generate xerophthalmia estimates is not discussed further in this chapter.

In preschool-age children the prevalence of serum retinol concentrations <0.70 μmol/l was directly estimated from survey data whenever possible. When such data were unavailable, the prevalence was assigned a value equivalent to the population prevalence of abnormal CIC results. Survey data referring to children in a narrower age than 0–4 years or surveys that included data that extended slightly beyond the fifth year of life were used as the prevalence estimate for children aged 0–4 years.

For pregnant women the prevalence of serum retinol concentrations <0.70 μmol/l was directly estimated from appropriate survey data whenever possible. When such data were lacking, the prevalence was assigned a value equivalent to the prevalence among non-pregnant or lactating women in the early postpartum period or a value equivalent to the prevalence of breast milk retinol concentrations <1.05 μmol/l. When serological or breast milk data were reported as a mean and SD, rather than as a prevalence rate, the prevalence was derived by assuming the data were normally distributed and calculating the standard normal deviate (*z*-score) and the probability associated with the area under the left tail of the normal curve.

Data extrapolation

Separate algorithms were developed for the different subregions of the world to estimate the country-specific prevalence estimates for serum retinol concentrations <0.70 μmol/l among children and pregnant

women (West 2002). In brief, nationally representative survey data, as deduced from individual reports or stated as such from aggregate WHO or other agency reports, were reported whenever possible. In the absence of national level data, results from sub-national or smaller surveys were used and adjustment factors were applied following the precedent of previous analysts (Micronutrient Initiative/UNICEF/Tulane University 1998; WHO 1995), although the subjective weight may have changed from the previous reports owing to new or reinterpreted results for a country. For countries where no data were available, estimates were generated by extrapolation in situations where cultural, dietary, demographic, health and development patterns as well as existing rates of adult and child mortality suggested that vitamin A deficiency is likely to exist. Prevalence rates were extrapolated either by assigning a value from a nearby country with comparable characteristics (primarily in the WHO Region of South-East Asia) or by assigning a median value from neighbouring country national surveys. Prevalence estimates among preschool-age children were also adjusted downwards in countries where the survey data preceded coverage reports from recent vitamin A supplementation programmes that reported coverage rates >75%. The prevalence data for women were not adjusted to account for any potential programmatic impact, because although postpartum maternal vitamin A supplementation programmes are slowly emerging, programmes to prevent vitamin A deficiency during pregnancy are virtually non-existent in the developing world at the present time.

The 2002 West report did not generate prevalence estimates for countries where there was no plausible evidence to suggest the presence of vitamin A deficiency. Therefore, those subregional prevalence estimates do not reflect the contribution of other countries in the world that were assumed to have a 0% prevalence rate of serum retinol concentrations <0.70 μmol/l. Over half of the countries assigned a 0% prevalence rate are located in the subregions classified as EUR-A, EUR-B, EUR-C or AMR-A, where child mortality rates are low (Murray et al. 2001).

The distribution of the 191 countries included in the CRA project is shown in Table 4.1 by the type of survey data used for estimating serum retinol prevalence rates <0.70 μmol/l in children. To calculate subregional prevalence rates of serum retinol concentrations <0.70 μmol/l, the number of affected individuals was totalled for the countries in each subregion and then divided by the subregional population base. For children <5 years of age, the population base was obtained from the *2001 State of the world's children report* (UNICEF 2001), which reported data for the year 1999. For pregnant women the annual number of live births was chosen to represent the population global base for pregnant women, and data were obtained from the same source (UNICEF 2001). The countries that were assigned 0% prevalence accounted for only approximately 17% of the base population of children (Table 4.2) and pregnant women (Table 4.3).

Table 4.1 Distribution of 191 WHO Member States by population group for which the prevalence of serum retinol concentrations <0.70 μmol/l was estimated by subregion and type of data used to generate subregional prevalence estimates

	Population group									
	Children (0–4 years)					*Pregnant women (15–44 years)*				
Subregion	*Total*	*National level data*	*Sub-national level data*	*Imputed prevalence estimates >0*	*No available survey data, assigned 0% prevalence estimate*	*Total*	*National level data*	*Sub-national level data*	*Imputed prevalence estimates >0*	*No available survey data, assigned 0% prevalence estimate*
AFR-D	26	5	7	14	0	26	1	5	20	0
AFR-E	20	10	7	3	0	20	3	7	10	0
AMR-A	3	0	0	0	3	3	0	0	0	3
AMR-B	26	9	2	0	15	26	0	2	9	15
AMR-D	6	4	1	1	0	6	0	1	5	0
EMR-B	13	1	1	0	11	13	0	0	0	13
EMR-D	9	2	3	4	0	9	1	3	5	0
EUR-A	26	0	0	0	26	26	0	0	0	26
EUR-B	16	1	0	0	15	16	0	0	0	16
EUR-C	9	0	0	0	9	9	0	0	0	9
SEAR-B	3	2	1	0	0	3	0	3	0	0
SEAR-D	7	3	0	3	1	7	2	2	3	0
WPR-A	5	0	0	0	5	5	0	0	0	5
WPR-B	22	5	2	9	6	22	2	2	12	6
World	191	42	24	34	91	191	9	25	64	93

Table 4.2 Global prevalence of serum retinol concentrations <0.70 μmol/l among children aged <5 years, by subregion

	Countries with assigned prevalence estimates[a]				*Countries with no assigned prevalence estimates (prevalence set to 0%)*		*Subregional and global totals*			
Subregion	*Countries*	*Children with serum retinol concentrations <0.70 μmol/l (000s)*	*Children <5 years (000s)*	*Prevalence of serum retinol concentrations <0.70 μmol/l (%)*	*Countries*	*Children <5 years (000s)*	*Countries*	*Children with serum retinol concentrations <0.70 μmol/l (000s)*	*Children <5 years (000s)*	*Prevalence of serum retinol concentrations <0.70 μmol/l (%)*
AFR-D	26	13552	47653	28.4	0	NA	26	13552	47653	28.4
AFR-E	20	19853	56281	35.3	0	NA	20	19853	56281	35.3
AMR-A	0	NA	NA	NA	3	21886	3	0	21886	0.0
AMR-B	11	7010	38256	18.3	15	6565	26	7010	44821	15.6
AMR-D	6	1209	9319	13.0	0	NA	6	1209	9319	13.0
EMR-B	2	449	7412	6.1	11	9022	13	449	16434	2.7
EMR-D	9	12215	52406	23.3	0	NA	9	12215	52406	23.3
EUR-A	0	NA	NA	NA	26	21852	26	0	21852	0.0
EUR-B	1	45	152	29.5	15	17935	16	45	18087	0.2
EUR-C	0	NA	NA	NA	9	12565	9	0	12565	0.0
SEAR-B	3	13538	28434	47.6	0	NA	3	13538	28434	47.6
SEAR-D	7	42274	140575	30.1	0	NA	7	42274	140575	30.1
WPR-A	0	NA	NA	NA	5	8019	5	0	8019	0.0
WPR-B	16	17128	122006	14.0	6	3792	22	17128	125798	13.6
World	101	127273	502494	25.3	90	101636	191	127273	604130	21.1

NA Not applicable.

[a] Country-specific data used to estimate subregional prevalence rates were based on the review article "Global prevalence of vitamin A deficiency among preschool children and women of reproductive age" (West 2002). Technical notes and data for individual countries are located at www.jhsph.edu/chn/GlobalVAD.html. In the review article, the number of children with serum retinol concentrations <0.70 μmol/l in a country was either estimated based on existing survey data or imputed for countries where vitamin A deficiency was likely to exist based on cultural, dietary, demographic, health and development patterns as well as existing rates of child mortality. In order to calculate subregional and global prevalence rates for the CRA project, the prevalence estimate was set to 0% for the remaining 90 countries where no data on preschool child vitamin A deficiency or xerophthalmia were available, but childhood vitamin A deficiency was considered unlikely to exist. These are all classified as "A" or "B" according to the WHO Comparative Risk Assessment Index (WHO 2001): **Region of the Americas** (n = 18) Antigua and Barbuda, Argentina, Bahamas, Barbados, Canada, Chile, Cuba, Grenada, Guyana, Jamaica, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States of America and Uruguay; **Eastern Mediterranean Region** (n = 11) Bahrain, Cyprus, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Qatar, Saudi Arabia, Syria, Tunisia and United Arab Emirates; **European Region** (n = 50) All countries were excluded, except The former Yugoslav Republic of Macedonia; **Western Pacific Region** (n = 11) Australia, Brunei Darussalam, Fiji, Japan, Mongolia, Nauru, New Zealand, Niue, Republic of Korea, Samoa and Singapore.

3.6 Children (0–4 years)

The subregional and global prevalence rates of serum retinol concentrations <0.70 μmol/l among children aged 0–4 years are shown in Table 4.2. The prevalence estimates from the smaller number of countries that contributed to the 2002 West report are compared to the global estimates generated for the CRA project. The results indicate that globally, approximately 21% of all children have serum retinol concentrations <0.70 μmol/l. The highest prevalence rates and the largest number of affected children live in the South-East Asian and African Regions. The estimated number of affected children is similar to what was reported by the Micronutrient Initiative, UNICEF and Tulane University group (Micronutrient Initiative/UNICEF/Tulane University 1998).

3.7 Pregnant women (15–44 years)

The subregional and global prevalence rates of serum retinol concentrations <0.70 μmol/l among pregnant women aged 15–44 years are shown in Table 4.3. The prevalence estimates from the smaller number of countries that contributed to the 2002 West report are compared to the global estimates generated for the CRA project. The results indicate that globally, approximately 5.6% of all pregnant women have serum retinol concentrations <0.70 μmol/l. Although the prevalence rates among pregnant women are approximately one-fourth those observed in children aged <5 years, a similar risk distribution emerged—with the highest prevalence rates and number of affected women being located in the South-East Asian and African Regions. Although the global prevalence is low, vitamin A deficiency may be an important contributing factor to adverse health outcomes for pregnant women in selected areas of the world.

3.8 Other groups

There is very little, if any, information available about the global prevalence of vitamin A deficiency and the associated risk in other population groups. Therefore, the prevalence of serum retinol concentrations <0.70 μmol/l among children aged ≥5 years, among non-pregnant women aged 15–44 years, among men aged 15–44 years, and among adults aged ≥45 years was not estimated.

4. Assessing causality and quantifying risk factor–disease relationships

There is often a discrepancy between the problems that motivate a study and the data available for addressing the issue. This applies to the present work, especially when identifying data to be used in estimating the relative risk of adverse health outcomes associated with vitamin A deficiency. Ideally, the results of multiple studies would be available for each outcome of interest from different countries located in different regions

Table 4.3 Global prevalence of serum retinol concentrations <0.70 µmol/l among pregnant women aged 15–44 years, by subregion

	Countries with assigned prevalence estimates[a]				*Countries with no assigned prevalence estimates (prevalence set to 0%)*		*Subregional and global totals*			
Subregion	*Countries*	*Pregnant women with serum retinol concentrations <0.70 µmol/l (000s)*	*Live births per year (000s)*	*Prevalence of serum retinol concentrations <0.70 µmol/l among pregnant women (%)*	*Countries*	*Live births per year (000s)*	*Countries*	*Pregnant women with serum retinol concentrations <0.70 µmol/l (000s)*	*Live births per year (000s)*	*Prevalence of serum retinol concentrations <0.70 µmol/l among pregnant women (%)*
AFR-D	26	1011	11185	9.0	0	NA	26	1011	11185	9.0
AFR-E	20	1441	13240	10.9	0	NA	20	1441	13240	10.9
AMR-A	0	NA	NA	NA	3	4238	3	0	4238	0.0
AMR-B	11	282	7956	3.5	15	1348	26	282	9304	3.0
AMR-D	6	93	2011	4.6	0	NA	6	93	2011	4.6
EMR-B	0	NA	NA	NA	13	3410	13	0	3410	0.0
EMR-D	9	938	12003	7.8	0	NA	9	938	12003	7.8
EUR-A	0	NA	NA	NA	26	4233	26	0	4233	0.0
EUR-B	0	NA	NA	NA	16	3743	16	0	3743	0.0
EUR-C	0	NA	NA	NA	9	2527	9	0	2527	0.0
SEAR-B	3	538	5933	9.1	0	NA	3	538	5933	9.1
SEAR-D	7	1714	30279	5.7	0	NA	7	1714	30279	5.7
WPR-A	0	NA	NA	NA	5	1629	5	0	1629	0.0
WPR-B	16	1240	24 806	5.0	6	761	22	1240	25567	4.8
World	98	7257	107413	6.8	93	21 889	191	7257	129302	5.6

NA Not applicable.

[a] Country-specific data used to estimate regional prevalence rates were based on the review article "Global prevalence of vitamin A deficiency among preschool children and women of reproductive age" (West 2002). Technical notes and data for individual countries are located at www.jhsph.edu/chn/GlobalVAD.html. In the review article the number of pregnant women aged 15–45 years with serum retinol concentrations <0.70 µmol/l in a country was either estimated based on existing survey data or imputed for countries where maternal vitamin A deficiency was likely to exist based on cultural, dietary, demographic, health and development patterns as well as existing rates of adult and child mortality. In order to calculate subregional and global prevalence rates for the CRA project, the prevalence estimate was set to 0% for the remaining 93 countries, where no prevalence data on maternal vitamin A deficiency or night blindness were available, but maternal vitamin A deficiency was considered unlikely to exist. These are all classified as "A" or "B" according to the WHO Comparative Risk Assessment Index (WHO 2001): **Region of the Americas** (n = 18) Antigua and Barbuda, Argentina, Bahamas, Barbados, Canada, Chile, Cuba, Grenada, Guyana, Jamaica, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States and Uruguay; **Eastern Mediterranean Region** (n = 13) Bahrain, Cyprus, Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syria, Tunisia and United Arab Emirates; **European Region** (n = 51) All countries were excluded; **Western Pacific Region** (n = 11) Australia, Brunei Darussalam, Fiji, Japan, Mongolia, Nauru, New Zealand, Niue, Republic of Korea, Samoa and Singapore.

of the world. This would allow the subregional estimates to be based on empirical data for each location. However, this type of data is simply not available. In the absence of such information the best data possible should be compiled and any important limitations recognized. There are several important limitations of the data and methodology used to estimate risk estimates for this project that deserve comment.

First, no definitive criteria exist for determining with certainty whether or not a particular risk factor is causally related to an adverse health outcome. However, many investigators have adopted the general principles that were originally proposed by Hill for use as guidelines when evaluating potential causal relationships (Hill 1965). A review of vitamin A studies conducted using different designs reveals that many of these general principles hold true when the entire body of evidence is considered together. However, experimental evidence—in this case the demonstration that a vitamin A-related intervention prevents an adverse health outcome—provides some of the strongest evidence for a causal relationship. Therefore, the present review has been restricted to the results of randomized placebo-controlled vitamin A intervention trials conducted in areas with either documented or suspected vitamin A deficiency. The inference commonly made from such a study is that if the vitamin A intervention prevents the occurrence of an adverse health outcome, then vitamin A deficiency is causally associated with it.

The design used for the prospective trials of vitamin A and child mortality was to assign the participants to either a vitamin A or control group, to implement the intervention, and to then follow the participants over time. Aside from observing the presence of clinical eye signs of deficiency, the vitamin A status (serum retinol concentration) of each and every participant was not assessed. The baseline vitamin A status of the populations under study was either inferred from prior survey data gathered in the same subregion or from a subset of the study participants.

Second, the risk estimates reported in the original publications of vitamin A and child mortality represent the *protective* effect of the vitamin A interventions against adverse health outcomes, rather than the relative risk of an adverse outcome associated with vitamin A deficiency *per se*. The risk of an *adverse* outcome was estimated from the original trial results as the inverse of the protective relative risk (= 1/protective relative risk). The following assumptions were made when using the intervention trial data in this manner: (i) that all children participating in the trials were vitamin A deficient at the beginning of the intervention period; and (ii) that the deficiency was corrected in all children assigned to the intervention group, while those in the placebo group remained deficient. Neither of these assumptions is likely to have been met in all of the trials. Thus the unadjusted risk estimates from the trials may underestimate the true relationship between vitamin A deficiency and an adverse health outcome.

Finally, the data from the original intervention trials were analysed on an intention-to-treat basis, rather than on the basis of achieved compliance. In reality both compliance and the biological efficacy of the particular intervention under study would influence the measured relationship between the vitamin A intervention and an adverse health outcome. Secondary analyses from one of the child mortality studies that took actual compliance into account estimated a far greater reduction in all-cause mortality than was observed in the original intention-to-treat analysis (Sommer and Zeger 1991).

On the other hand, the summary risk estimates from the meta-analyses of the individual intervention trials conducted in a variety of countries provide a certain level of built-in control for unmeasured factors that may have differed across sites. The United Nations Administrative Committee on Coordination/Subcommittee on Nutrition (ACC/SCN) meta-analysis of the child mortality trials examined the effect of age and sex on observed mortality and concluded there were no significant differences of vitamin A supplementation on all-cause mortality between males and females or by age category for children between 6 months and 5 years of age (Beaton et al. 1993). In addition, there was no detectable relationship between the effects of the vitamin A intervention and anthropometric status on child mortality.

For the purpose of the CRA project, relative risk estimates for child and maternal health outcomes used vitamin A intervention trial data as the starting point. However, the relative risk estimates were adjusted to take into account the fact that many, but not all, of the study participants had low serum retinol concentrations at the beginning of the intervention trials. The following section describes how the adjustment process was conducted. The same process was applied to data for both the child and maternal health outcomes.

The adjusted relative risks were calculated using a four-step process.

1. A quantitative estimate of the protective effect that a vitamin A intervention had in preventing an adverse health outcome was found in the published literature.

2. The prevalence of serum retinol concentrations <0.70 μmol/l was estimated among the study population at baseline.

3. An adjusted relative risk was calculated by constructing a hypothetical population of 100 000 individuals and dividing them into two strata using a serum retinol concentration cut-off of <0.70 μmol/l and the prevalence estimate obtained in the second step. The relative risk of an adverse outcome was then calculated for both strata separately by setting the background incidence rate of the adverse outcome to be equivalent among the following groups: (i) the vitamin A intervention group in the entire study population; (ii) the vitamin A intervention and control groups in the strata with serum retinol con-

centrations ≥0.70 μmol/l; and (iii) the vitamin A intervention group in the stratum with serum retinol concentrations <0.70 μmol/l. The relative risk for children in the stratum with serum retinol concentrations ≥0.70 μmol/l represents the effect of the vitamin A intervention among children who were not deficient before the trial began. In this stratum the relative risk is 1.0 because those children were not expected to benefit (in terms of reducing all-cause mortality) from the intervention. The relative risk for children in the other stratum is lower than the overall trial estimate (representing a greater protective effect) because those children were deficient when the trial began and all of the observed benefit (in terms of reducing all-cause mortality) associated with the vitamin A intervention was presumably observed among this subgroup of children.

4. The final step in the adjustment process was to calculate the relative risk of all-cause mortality associated with vitamin A deficiency by calculating the inverse of the adjusted protective effect (= 1/protective relative risk). See Table 4.4 for an example calculation based on a 23% reduction in child deaths (protective relative risk of 0.77) associated with a vitamin A intervention and a 41% baseline prevalence rate of serum retinol concentrations <0.70 μmol/l in the study population. In this example, the originally reported protective effect associated with the vitamin A intervention is a relative risk of 0.77; the adjusted protective relative risk associated with the vitamin A intervention is 0.58 (equivalent to a 42% reduction in child deaths); and the adjusted relative risk of child death associated with vitamin A deficiency is 1.72.

This adjustment process requires estimates for the baseline serum retinol concentrations <0.70 μmol/l for the populations contributing relative risk data to each adverse heath outcome. The baseline prevalence estimates are shown in Table 4.5. For some, but not all, adverse health outcomes, baseline prevalence data were directly available from the published reports that contributed relative risk estimates to the adjustment process. In other cases, the prevalence rates were extrapolated accordingly. The process used to derive prevalence rates for each included adverse health outcome is described below.

In order to derive estimates for the measles, diarrhoea, malaria and other infectious disease causes of death and disability in children attributable to vitamin A deficiency, it was necessary to estimate a single underlying prevalence of deficiency that existed in the southern Asian and African populations in which eight large community-based, vitamin A child-mortality intervention trials were conducted. Knowing a single, underlying prevalence of deficiency across these diverse trial populations reveals the background burden of vitamin A deficiency that is understood to account for the overall estimated reduction of 23% in

Table 4.4 Example of how to calculate the adjusted relative risk of child death associated with vitamin A deficiency assuming a published relative risk of 0.77 for child survival associated with the receipt of vitamin A in a controlled intervention trial and a 41% baseline prevalence rate of 'vitamin A deficiency' among the children (defined as serum retinol concentrations <0.70 μmol/l)

Study population	*Died*	*Survived*	*Total*	*Incidence of death*	*Protective relative risk*	*% reduction in deaths due to vitamin A intervention*
Entire study population						
Vitamin A group	385	49615	50000	0.0077	0.77	23
Control group	500	49500	50000	0.0100		
Total	885	99115	100000			
Children with serum retinol concentrations ≥0.70 μmol/l						
Vitamin A group	227	29273	29500	0.0077	1.00	0
Control group	227	29273	29500	0.0077		
Total	454	58456	59000			
Children with serum retinol concentrations <0.70 μmol/l						
Vitamin A group	158	20342	20500	0.0077	0.58[a]	42
Control group	273	20272	20500	0.0133		
Total	431	40569	41000			

[a] In the example above the relative risk of child death associated with vitamin A deficiency was calculated by using an overall observed relative risk of child survival associated with receipt of vitamin A (0.77) and estimating the relative risk of child survival among the 59% of children who had serum retinol concentrations ≥0.70 μmol/l (1.00) and the 41% of children with concentrations below that cut-off (0.58). The relative risk of child death associated with vitamin A deficiency was then calculated as 1.72, which equals the inverse of the protective effect among "vitamin A deficient" children who received vitamin A: 1.72 [1.00/0.58].

Table 4.5 Estimated baseline prevalence of serum retinol concentrations <0.70 μmol/l in the intervention studies used to estimate the relative risk of cause-specific mortality associated with vitamin A deficiency[a]

Cause of death	*Estimated baseline prevalence of serum retinol concentrations <0.70 μ/l in the intervention trials (%)*	*Data source*
Children		
Diarrhoea	41	See Table 4.6
Measles	41	See Table 4.6
Malaria	55	See Table 1 in Shankar et al. (1999)
Other infectious causes	41	See Table 4.6
Women		
Maternal conditions	19	See Table 2 in West et al. (1999)

[a] The cause of death outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

preschool-age child mortality achieved with vitamin A interventions (Beaton et al. 1993).

An overall background prevalence of serum retinol concentrations <0.70 μmol/l was derived by estimating the size and prevalence of vitamin A deficiency for each national or regional population judged to be represented by each intervention trial (Table 4.6). The prevalence rate for each country as available, was applied to the estimated number of preschool-age children in order to estimate the number of vitamin A deficient preschool-age children in each population represented by a trial. These steps resulted in a subjective re-weighting of the sizes of the populations at-risk in each area that were independent of sample sizes for each trial. Finally, numbers of deficient children in each population represented by a trial were summed and divided by the sum of the population estimates of children aged <5 years, resulting in a prevalence that is, roughly, weighted by the sizes of populations at risk that were represented by the trials. This exercise produced prevalence rates of serum retinol <0.70 μmol/l that ranged from 28% in the Sudan, to 72% as measured during a vitamin A child mortality trial in Ghana (Ghana VAST Study Team 1993). An estimated 19 million children, or 41%, among the estimated 46.5 million children living in areas at risk of vitamin A deficiency, representing the underlying, local populations of interest, were considered to be vitamin A deficient. In the absence of additional data, this underlying prevalence was further judged to represent the underlying pool of deficient children for whom death from severe episodes of diarrhoea, measles and other non-malarial infectious disease illnesses could be averted each year with vitamin A.

Table 4.6 Baseline prevalence estimates for serum retinol concentrations <0.70 μmol/l among populations of children aged <5 years from eight vitamin A intervention trials, by country

Host country	*Population <5 years of age*[a] *(000s)*	*Prevalence of serum retinol concentations <0.70 μmol/l*	*Number of vitamin A-deficient children (000s)*
Ghana, Kitampo	1063[b]	0.72[c]	765
India, Andra Pradhesh	8709[d]	0.31[e]	2700
India, Tamil Nadu	7143[d]	0.37[f]	2643
Indonesia	22006[g]	0.48[h]	10563
Nepal	3485[i]	0.35[j]	1220
Sudan	4162[k]	0.28[l]	1165
Total/Overall	46567	0.41[m]	19055

[a] Based on Table 1 of the *State of the world's children's report* (UNICEF 2001), unless otherwise noted.

[b] Given that the vitamin A trial in Ghana (Ghana VAST Study Team 1993) was carried out in the central part of the country, which is considered to be at higher risk than the southern, palm-oil consuming areas of the country, only one-third of the Ghanaian child population <5 years of age (3189000, UNICEF 2001) was considered to be represented by children in the trial.

[c] D Ross et al., personal communication, 1995, reported in Sommer and West (1996).

[d] Based on government of India census data for 2001 indicating 11.5% of the country's rural population was <5 years, applied to statewide census estimates for both Tamil Nadu and Andra Pradesh; statewide populations were assumed to represent the at-risk population for each trial.

[e] In the absence of serum retinol data from the trial or from representative population surveys of Andra Pradesh, a prevalence of 31% (West 2002) was applied to the state population.

[f] Rahmathullah et al. (1990).

[g] Indonesia is represented by its entire population given that the two mortality trials carried out in Aceh (Sommer et al. 1986) and West Java (Muhilal et al. 1988) were conducted in the north and central parts of the country, respectively.

[h] Prevalence based on the West Java trial (Muhilal et al. 1988) was assumed to represent Aceh and the rest of Indonesia in the early-mid-1980s, amidst evidence of higher subsequent prevalence rates (Kjolhede et al. 1995; West 2002).

[i] Because two population-based trials (Daulaire et al. 1992; West et al. 1991) were conducted in diverse and different parts of the country, the entire population of Nepalese preschool children (UNICEF 2001) was considered to be the underlying population at risk.

[j] In the absence of biochemical data from either child mortality trial in Sarlahi (West et al. 1991) or Jumla (Daulaire et al. 1992), a prevalence of 35% obtained from the 1998 National Micronutrient Survey (Anonymous 1998a) was taken to represent the prevalence during both trials and for the country.

[k] In the absence of risk differentials across different population groups of the Sudan, the entire population was assumed to be represented by children in the trial (Herrera et al. 1992).

[l] Median prevalence (28%) of distribution of 33 national prevalence estimates obtained for African and Eastern Mediterranean Regions was assumed to represent the status of Sudanese preschool children.

[m] Calculated by dividing 19055 by 46567.

A prevalence of 55% was assigned for populations of preschool-age children whose risk of death and disability due to *Plasmodium falciparum* malaria could be averted by vitamin A supplementation. This prevalence estimate was based on the data reported in Table 1 from a

single, community-based randomized trial in Papua New Guinea that measured effects of vitamin A supplementation on *P. falciparum* malaria clinic attack rates (Shankar et al. 1999). The assigned prevalence rate was calculated based on the published mean and standard deviation serum retinol concentration for the population at baseline and applying an assumption of normally distributed data.

A prevalence of 19% was assigned to represent populations of pregnant women living in areas of the world where risk of mortality may be reduced by approximately 40% with improved, regular, supplemental intakes of vitamin A, based on the data reported in Table 2 from a single, large randomized community recently conducted in rural Nepal (West et al. 1999). The same overall adjustment process was used to calculate adjusted relative risks of adverse health outcomes for each of the included child and maternal health outcomes. For the child health outcomes, the same adjusted relative risk was reported for children aged 0–4 years (boys and girls) for all regions of the world.

5. Risk factor–disease outcome relationships

The following section describes the individual studies that were used to evaluate and quantify the relative risk of an adverse health outcome associated with vitamin A deficiency. The intervention trials and results are reported separately for children aged 0–4 years and pregnant women aged 15–44 years. Insufficient data were available to quantitatively evaluate the risks of vitamin A deficiency in other population groups. Table 4.7 describes the individual studies that were used to estimate the relative risk of adverse health outcomes for the CRA project with respect to vitamin A. The studies are listed in the same order that the outcomes are discussed in the chapter. Mortality associated with measles and diarrhoeal disease in children appears first, followed by malaria incidence and malaria mortality in children, mortality associated with other infectious causes of death in children, and finally all-cause maternal mortality among pregnant women.

Unless otherwise noted, the risk estimates cited for individual studies are the findings that were originally reported in the literature and represent the *protective* effect of the vitamin A intervention against adverse health outcomes. An adjusted relative risk was calculated from these data to represent the risk of adverse health outcomes associated with vitamin A deficiency following the procedure described in section 4.

5.1 Risk estimates for preschool children (0–4 years)

Preschool-age children have traditionally been considered to be a high-risk group for vitamin A deficiency and its consequences. Most of the large-scale controlled intervention trials that have been conducted were designed to explore the relationships between vitamin A supplementation, morbidity and mortality among children aged <6 years.

Table 4.7 Studies used to estimate the relative risk of adverse health outcomes for the CRA project, by outcome[a]

Outcome (Reference)	*Study design*	*Location*	*Study population*
Children			
Measles mortality			
(Beaton et al. 1993)	Meta-analysis of randomized, placebo-controlled vitamin A supplementation trials	4 trials (Ghana; India; Sarlahi, Nepal; Jumla, Nepal)	Children 6–60 months
Original studies included in the meta-analysis:			
(Ghana VAST Study Team 1993)	Large dose vitamin A every 4 months	Ghana	Children 6–90 months
(Rahmathullah et al. 1990)	RDA of vitamin A in weekly doses	India	Children 6–60 months
(West et al. 1991)	Large dose vitamin A every 4 months	Sarlahi, Nepal	Children 6–72 months
(Daulaire et al. 1992)	Large dose vitamin A once with a 5 month follow-up	Jumla, Nepal	Children 1–59 months
Diarrhoea mortality			
(Beaton et al. 1993)	Meta-analysis of randomized, placebo-controlled vitamin A supplementation trials	5 trials (Ghana; India; Sarlahi, Nepal; Jumla, Nepal; Sudan	Children 6–60 months
Original studies included in the meta-analysis:			
(Ghana VAST Study Team 1993)	Large dose vitamin A every 4 months	Ghana	Children 6–90 months
(Rahmathullah et al. 1990)	RDA of vitamin A in weekly doses	India	Children 6–60 months
(West et al. 1991)	Large dose vitamin A every 4 months	Sarlahi, Nepal	Children 6–72 months
(Daulaire et al. 1992)	Large dose vitamin A once with a 5 month follow-up	Jumla, Nepal	Children 1–59 months
(Herrera et al. 1992)	Large dose vitamin A every 4 months	Sudan	Children 9–72 months

continued

Table 4.7 Studies used to estimate the relative risk of adverse health outcomes for the CRA project, by outcome[a] (*continued*)

Outcome (Reference)	*Study design*	*Location*	*Study population*
Malaria incidence			
(Shankar et al. 1999)	Randomized, placebo-controlled vitamin A supplementation trial	Papua New Guinea	Children 6–60 months
(Binka et al. 1995)	Large dose vitamin A every 4 months	Ghana	Children 6–90 months
(Study excluded due to non-statistically significant results)			
Malaria mortality			
(Shankar et al. 1999)	Note: A mortality effect was not assessed in the trial, but the relative risk of malaria mortality was assumed to be equivalent to the observed morbidity effect for the purpose of estimation in the CRA project	Papua New Guinea	Children 6–60 months
Other infectious causes of child mortality			
(Beaton et al. 1993)	Meta-analysis of randomized, placebo-controlled vitamin A supplementation trials	5 trials (Ghana; India; Sarlahi, Nepal; Jumla, Nepal; Sudan)	Children 6–60 months
Original studies included in the meta-analysis:			
(Ghana VAST Study Team 1993)	Large dose vitamin A every 4 months	Ghana	Children 6–90 months
(Rahmathullah et al. 1990)	RDA of vitamin A in weekly doses	India	Children 6–60 months
(West et al. 1991)	Large dose vitamin A every 4 months	Sarlahi, Nepal	Children 6–72 months
(Daulaire et al. 1992)	Large dose vitamin A once with a 5 month follow-up	Jumla, Nepal	Children 1–59 months
(Herrera et al. 1992)	Large dose vitamin A every 4 months	Sudan	Children 9–72 months
Women			
All-cause maternal mortality			
(West et al. 1999)	Randomized, placebo-controlled vitamin A/beta-carotene supplementation trial	Sarlahi, Nepal	Married women 13–45 years

RDA Recommended dietary allowance.

[a] The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

In the early 1990s the ACC/SCN commissioned a review of the existing scientific evidence to assess the effectiveness of vitamin A supplementation on child mortality and morbidity (Beaton et al. 1993). The findings from ten different community-based mortality trials conducted in Africa (Ghana and the Sudan), the Americas (Haiti) and Asia (India, Indonesia and Nepal), and 20 different morbidity trials conducted around the world were considered for inclusion in a formal meta-analysis. Sufficient data were available from five of the mortality trials (Daulaire et al. 1992; Fawzi et al. 1993; Ghana VAST Study Team 1993; Rahmathullah et al. 1990; West et al. 1991) to assess the relationship between vitamin A interventions and cause-specific mortality from measles, diarrhoea and respiratory illness. Separate relative risks were reported in the meta-analysis of these studies for all-cause mortality, mortality attributed to these three specific causes and mortality attributed to all other causes combined.

All five of those mortality trials were conducted in populations where vitamin A deficiency (both clinical and subclinical) was prevalent (assessed either as high rates of xerophthalmia or low serum retinol concentrations). In four of the trials (one in Ghana, two in Nepal and one in the Sudan), the intervention consisted of vitamin A supplementation in age appropriate doses (200 000 IU for children ≥12 months of age, 100 000 IU for children 6 to 11 months of age and, for one trial in Nepal, 100 000 IU for infants 1 to 11 months of age and 50 000 IU for infants <1 month of age) every 4–6 months. In India, the intervention was a weekly supplement that contained a weekly RDA of vitamin A. In the Ghana, India and Nepal trials, a statistically significant reduction in all-cause mortality was observed among children in the vitamin A intervention group. No statistically significant effect on all-cause mortality was observed in the Sudan.

Measles

Measles (and thus measles-related mortality) have nearly been eliminated in the Americas due to the implementation of successful measles control programmes over the past ten years (Hersh et al. 2000). At present, the highest rates of measles mortality occur among children aged <1 year in developing countries. Although unvaccinated children aged >10 years and adults are also susceptible to measles and measles mortality, estimates for the burden of disease associated with vitamin A deficiency were restricted to children aged 0–4 years for the CRA analysis.

Incidence and morbidity

Measles is a highly infectious disease caused by the measles virus (Reingold and Phares 2001). Although vitamin A is involved in different aspects of the immune defence system, there is little evidence to suggest that vitamin A status affects the incidence of measles. Therefore,

the relative risk of experiencing a measles episode associated with vitamin A deficiency was not calculated for the CRA analysis.

Mortality

Vitamin A deficiency appears to increase the risk of measles-related mortality. The ACC/SCN meta-analysis of the four prospective community-based trials with information on measles (Ghana, India and two in Nepal) suggests that vitamin A supplementation was associated with a 26% overall reduction in measles mortality (RR = 74, 95% CI 0.53–1.04) (Beaton et al. 1993). In the individual trials, the reduction in measles mortality ranged from 18% in Ghana to 75% in Sarlahi, Nepal (Sommer and West 1996). A more recent study from Ghana found no difference in the acute measles case-fatality rate between vitamin A supplemented and placebo groups (Dollimore et al. 1997). Vitamin A supplementation, however, has been found to reduce measles severity. In some (Coutsoudis et al. 1991; Ellison 1932; Hussey and Klein 1990) but not all (Rosales et al. 1996) hospital-based treatment trials, the surviving children who had received vitamin A experienced complications less frequently and recovered faster than their counterparts who received placebo treatment. These findings provide supporting evidence for a causal relationship between vitamin A deficiency and measles mortality.

The relative risk of measles (GBD code U015) mortality among children aged 0–4 years with vitamin A deficiency was estimated for the CRA project from the protective effect of vitamin A interventions (RR = 0.74, 95% CI 0.53–1.04) observed in the ACC/SCN meta-analysis of community-based trials and a 41% estimated baseline prevalence rate of serum retinol concentrations <0.70 μmol/l among those study populations. The adjusted relative risk estimate derived from those data is RR = 1.86 (95% CI 1.32–2.59). The calculations are shown in Table 4.8.

Diarrhoea

Diarrhoea and diarrhoea-related mortality are prevalent among preschool-age children, particularly in low income countries. The global burden of disease related to diarrhoea mortality is widely distributed around the world.

Incidence and morbidity

Diarrhoeal disease can be caused by a variety of bacterial, viral and parasitic agents (Reingold and Phares 2001). Although vitamin A is involved in different aspects of the immune defence system, including the maintenance of the epithelial cell border in the intestinal tract, there is little evidence from intervention trials to suggest that vitamin A status affects the incidence of diarrhoea. Therefore, the relative risk of experiencing a diarrhoea episode associated with vitamin A deficiency was not calculated. However, there is considerable evidence to link vitamin A status to the severity of diarrhoea episodes (Sommer and West 1996). Children

Table 4.8 Unadjusted and adjusted relative risks of adverse health outcomes associated with vitamin A deficiency[a]

Outcome	*Source of relative risk data*	*Original trial results (RR of protective effect due to vitamin A intervention)*		*RR associated with vitamin A deficiency*[b]		*RR associated with vitamin A deficiency (serum retinol concentrations <0.70 μmol/l)*[c]	
		RR	*95% CI*	*RR = [1.00/published protective RR]*	*95% CI = [1.00/published CI]*	*RR = [1.00/published protective RR]*	*95% CI = [1.00/published CI]*
Children (0–4 years)							
Diarrhoea mortality	Table 5.10 in Beaton et al. (1993)	0.68	0.57–0.80	1.47	1.25–1.75	2.15	1.83–2.58
Measles mortality	Table 5.10 in Beaton et al. (1993)	0.74	0.53–1.04	1.35	0.96–1.89	1.86	1.32–2.59
Malaria incidence	Table 3 in Shankar et al. (1999)	0.70	0.57–0.87	1.43	1.15–1.75	1.78	1.43–2.19
Malaria mortality	Table 3 in Shankar et al. (1999) using incidence of malaria episodes as a proxy for malaria mortality	0.70	0.57–0.87	1.43	1.15–1.75	1.78	1.43–2.19
Selected other infectious disease causes of mortality	Table 5.10 in Beaton et al. (1993)	0.95	0.81–1.06	1.05	0.94–1.23	1.13	1.01–1.32
Pregnant women (15–44 years)							
All-cause maternal mortality	Text statement about the relative risk for the maternal mortality ratio among vitamin A + beta-carotene vs placebo recipients in West et al. (1999)	0.60	0.39–0.93	1.67	1.08–2.56	4.51	2.91–6.94

[a] The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

[b] Unadjusted for baseline prevalence of serum retinol concentrations <0.70 μmol/l.

[c] Adjusted for baseline prevalence of serum retinol concentrations <0.70 μmol/l in trial populations.

with poor vitamin A status tend to suffer from more severe and more prolonged episodes of diarrhoea. These findings provide supporting evidence for a causal relationship between vitamin A deficiency and diarrhoea mortality.

Mortality

Vitamin A deficiency does appear to increase the risk of diarrhoea mortality. The ACC/SCN meta-analysis of the five community-based trials with information on diarrhoea (Ghana, India, Nepal [two trials] and the Sudan) suggest that vitamin A supplementation was associated with a 32% reduction in diarrhoea mortality (RR = 0.68, 95% CI 0.57–0.80) (Beaton et al. 1993). In the individual trials that showed a reduction (all but the Sudan), the reduction in diarrhoea mortality ranged from 34% in Ghana to 52% in India (Sommer and West 1996).

The relative risk of diarrhoea (GBD code U010) mortality among children aged 0–4 years with vitamin A deficiency was estimated from the protective effect of vitamin A interventions (RR = 0.68, 95% CI 0.57–0.80) observed in the ACC/SCN meta-analysis of community-based trials and a 41% estimated baseline prevalence rate of serum retinol concentrations <0.70 µmol/l among those study populations. The adjusted relative risk estimate derived from those data is RR = 2.15 (95% CI 1.83–2.56). The calculations are shown in Table 4.8.

Malaria

Although malaria is endemic in several areas of the world, countries in Africa have particularly high prevalence rates and children aged <5 years experience much of the associated burden of disease.

Incidence and morbidity

Malaria is caused by several species of the protozoa *Plasmodium,* which are transmitted by mosquitoes from one person to another (Reingold and Phares 2001). In humans, *P. falciparum* is the species responsible for the majority of malaria-related morbidity and mortality. Both animal and human studies have implicated specific immune mechanisms for how vitamin A could influence the incidence and severity of malarial disease (Davis et al. 1998; Krishnan et al. 1976; Serghides and Kain 2002; Stoltzfus et al. 1989). In addition, cross-sectional studies have also documented inverse associations between plasma retinol levels and *P. falciparum* parasitaemia in humans (Filteau et al. 1993; Friis et al. 1997; Galan et al. 1990; Samba et al. 1992; Tabone et al. 1992; Thurnham and Singkamani 1991), and one study has reported that low baseline vitamin A status was associated with an increased risk of parasitaemia (Sturchler et al. 1987).

Findings from more recent randomized controlled intervention trials suggest that vitamin A supplementation appears to reduce both the incidence and severity of malaria illness. In Ghana, cohorts of children

received high-dose vitamin A or a placebo every four months as part of either the Child Health (morbidity) or Child Survival (mortality) Study. Blood samples were collected on a monthly basis from different random subsamples of children in a series of cross-sectional surveys conducted over a one-year period. Based on the cross-sectional data, the authors reported no statistically significant differences in the incidence of fever, malaria parasitaemia, parasite density, or probable malaria illness between the two groups and concluded that vitamin A supplementation had no impact on malaria (Binka et al. 1995). However, given the relatively small sample sizes, these studies had limited statistical power and could only detect a statistically significant protective effect of vitamin A supplementation against probable malarial illness that exceeded 70% (Child Survival Study) or 95% (Child Health Study) (Shankar 1995).

A more definitive study of vitamin A supplementation and malaria was recently conducted in Papua New Guinea. In that study children aged 6–60 months received either high-dose vitamin A or a placebo every three months and were followed over a 13-month period. Malaria morbidity was assessed weekly using community-based case detection and surveillance of the patients who reported to the local health centre. Blood smears were prepared for children who had a fever >37.5°C at the time of the weekly home visit or for any clinic visit and for all children who participated in the three cross-sectional surveys conducted at baseline, at the midpoint, and at the end of the study. Slide-confirmed cases of malaria were followed prospectively and observed for adverse health outcomes. Children in the vitamin A group had a 30% lower frequency of *P. falciparum* febrile illnesses (RR = 0.70, 95% CI 0.57–0.87) and younger children (12–36 months) apparently benefited most from supplementation. The younger children in the vitamin A group also had less severe malaria morbidity, measured as fewer febrile episodes, fewer enlarged spleens and a lower parasite density (Shankar et al. 1999).

The study from Papua New Guinea used a stronger design, evaluated a greater number of disease variables, and had more statistical power to investigate a relationship between vitamin A and malaria morbidity as compared to the Ghana study. Therefore, the findings from Papua New Guinea were used to assess the relative risk of malaria incidence associated with vitamin A deficiency for the CRA project.

Mortality

To date, no randomized trials have demonstrated a significant reduction in malaria mortality associated with the vitamin A supplementation. However, given the recently observed relationship between vitamin A supplementation and malaria severity, an equivalent relative risk was assigned for malaria mortality for the purpose of the CRA project.

The relative risk of malaria incidence (GBD code U020) among children aged 0–4 years with vitamin A deficiency was estimated for the CRA project from the protective effect of the vitamin A intervention

(RR = 0.70, 95% CI 0.57–0.87) observed in the Papua New Guinea trial and a 55% estimated baseline prevalence rate of serum retinol concentrations <0.70 µmol/l in that study population. The adjusted relative risk estimate derived from those data is RR = 1.78 (95% CI 1.43–2.19). The calculations are shown in Table 4.8.

The relative risk of malaria mortality (GBD code U020) among children aged 0–4 years with vitamin A deficiency was estimated by extrapolation for the CRA project from the results of the vitamin A intervention on malaria incidence observed in the community-based trial in Papua New Guinea (RR = 0.70, 95% CI 0.57–0.87) and a 55% estimated baseline prevalence rate of serum retinol concentrations <0.70 µmol/l in that study population. The adjusted relative risk estimate derived from those data is RR = 1.78 (95% CI 1.43–2.19). The calculations are shown in Table 4.8.

Other infectious diseases in children

Infectious diseases are a common cause of death among preschool-age children worldwide. The global burden of disease related to the GBD category of "other infectious diseases" among children is widely distributed around the world.

Although acute respiratory infections, diarrhoeal diseases, measles and malaria represent the most common causes of childhood illness and death, many other bacterial, viral and parasitic agents cause disease among children as well. Since vitamin A is involved in a wide variety of different biological processes, vitamin A deficiency may also increase the risk of death due to other less common causes of childhood disease, although studies to date have not specifically quantified those relationships. The GBD study included a group of "other infectious diseases" (GBD code U037) in children that captured the contribution of many low-incidence causes of death under one category. Causes of infectious diseases not explicitly listed in the other GBD categories for children are included under this code (Murray et al. 2001).

Mortality

Data from intervention trials among children suggest that vitamin A deficiency increases the risk of mortality from causes other than diarrhoea, measles and malaria. The ACC/SCN meta-analysis of the five community-based trials (Ghana, India, Nepal [two trials] and the Sudan) with information on cause-specific mortality found that vitamin A supplementation was associated with a 5% reduction in mortality from unspecified causes of death (RR = 0.95, 95% CI 0.81–1.06) (Beaton et al. 1993). This risk estimate was used for the purposes of estimation. The relative risk of mortality due to other infectious diseases (GBD code U037) among children aged 0–4 years with vitamin A deficiency was estimated for the CRA project from the protective effect of vitamin A interventions (RR = 0.95, 95% CI 0.81–1.06) observed in the ACC/SCN

meta-analysis of community-based trials and a 41% estimated baseline prevalence rate of serum retinol concentrations <0.70 μmol/l among those study populations. The adjusted relative risk estimate derived from those data is RR = 1.13 (95% CI 1.01–1.32). The calculations are shown in Table 4.8.

5.2 Risk estimates for pregnant women (15–44 years)

Over half a million women around the world die each year from causes associated with pregnancy and childbirth. Most of these maternal deaths occur in the Regions of Africa and South-East Asia.

Although data from either observational or experimental studies relating vitamin A deficiency among women of reproductive age to specific causes of mortality are limited, biologically plausible mechanisms for such relationships do exist (Faisel and Pittrof 2000). A relative risk of maternal mortality was estimated for vitamin A deficiency among pregnant women aged 15–44 years, based on the best data currently available. The risk estimate for these outcomes may be modified in the future when more data that specifically address this issue are available.

To date, the only large-scale randomized controlled trial of vitamin A supplementation among women of reproductive age has been conducted in an area of southern Nepal where high rates of maternal night blindness have been reported (West et al. 1999). More than 44 000 women of reproductive age were randomized to continually receive either vitamin A (7000 μg retinol equivalents), an equivalent amount of beta-carotene, or a placebo capsule on a weekly basis over an approximate three and a half year period; that is, before and during pregnancy, throughout the postpartum period and through any subsequent pregnancy until close-out of the trial. Over 22 000 identified pregnancies were followed. Pregnancy-related mortality (defined as a death during pregnancy or prior to 12 weeks postpartum) was decreased by 40% (RR = 0.60, 95% CI 0.37–0.97) in the vitamin A group and by 49% (RR = 0.51, 95% CI 0.30–0.86) in the beta-carotene group (West et al. 1999). These findings provide support for a causal relationship between vitamin A deficiency and pregnancy-related mortality.

Data from the study in Nepal were used to estimate the relative risk of maternal mortality associated with vitamin A deficiency. The study presents several sets of mortality results for women stratified by time and cause of death during pregnancy and the postpartum period. The mortality results used for CRA analysis were those that excluded all deaths >6 weeks postpartum and all deaths attributed to reported injury which are the results that most closely conform to the ICD-10 definition of a maternal death (WHO 1992). The combined results for women in the vitamin A and beta-carotene intervention groups were used to represent non-vitamin A deficient women.

The relative risk of maternal mortality among pregnant women with vitamin A deficiency—due to a wide variety of maternal conditions (GBD

code U042)—was estimated for the CRA project from the combined protective effect of the vitamin A and beta-carotene interventions on the maternal mortality ratio (RR = 0.60, 95% CI 0.39–0.93) and a 19% estimated baseline prevalence rate of serum retinol concentrations <0.70 μmol/l observed among women in the Nepal trial (West et al. 1999). In the absence of other studies linking vitamin A deficiency to cause-specific deaths among women, the risk of maternal death (from a wide variety of maternal conditions) was extrapolated from the Nepal study. A maternal mortality ratio of 378 deaths per 100 000 live births among women in the vitamin A and beta-carotene groups combined (West et al. 1999) was used as the starting point for the adjusted relative risk calculations. The adjusted relative risk estimate derived from those data is RR = 4.51 (95% CI 2.91–6.94). The calculations are shown in Table 4.8.

5.3 Risk estimates for all other groups

Limited information is available about the global prevalence of vitamin A deficiency or its associated adverse health effects in children aged ≥5 years, in men aged 15–44 years, or in men or women aged ≥45 years. Therefore, quantitative estimates for the prevalence of vitamin A deficiency and the associated risk of adverse health outcomes were not developed for these groups.

6. Burden of disease associated with vitamin A deficiency

Summary estimates for three burden of disease measurements are shown in this chapter. The attributable fraction of cause-specific mortality associated with vitamin A deficiency among children aged 0–4 years and pregnant women aged 15–44 years are shown by subregion in Table 4.9. The estimated number of cause-specific deaths and disability-adjusted life years (DALYs) attributed to vitamin A deficiency is shown in Table 4.9 and Table 4.10, respectively.

The attributable fraction results show that worldwide, vitamin A deficiency among children is associated with an estimated 20% of measles-related mortality, 24% of diarrhoea mortality, 20% of malaria incidence and mortality, and 3% of mortality associated with other infectious causes of disease. By definition, the attributable fraction of disease associated with vitamin A deficiency itself is 100%. The attributable fractions vary widely by cause and across the different subregions. In general, the attributable fractions (for disease conditions other than vitamin A deficiency) are highest in the African and South-East Asian Regions, where vitamin A deficiency is most prevalent and child mortality rates for the causes of disease assessed in this chapter are high. Worldwide, vitamin A deficiency (serum retinol concentrations <0.70 μmol/l) among pregnant women is associated with over 20% of maternal mortality.

Table 4.9 Attributable fraction of cause-specific mortality (%) due to vitamin A deficiency for measles, diarrhoea, malaria and other infectious diseases among children, for conditions leading to maternal mortality, and for direct sequelae of vitamin A deficiency, by subregion

	Diseases among children (0–4 years)[a]				*Conditions leading to maternal mortality among women (15–44 years)*[a]	*Direct sequalae of vitamin A deficiency among all age groups and both sexes*
Subregion	*Measles*	*Diarrhoea*	*Malaria*	*Other infectious causes*	*Maternal causes*	
AFR-D	20	25	18	4	24	100
AFR-E	23	29	22	4	28	100
AMR-A	[b]	[b]	[b]	[b]	[b]	[b]
AMR-B	[b]	15	11	2	10	[b]
AMR-D	[b]	13	9	2	14	[b]
EMR-B	2	3	2	[b]	[b]	[b]
EMR-D	17	21	15	3	22	100
EUR-A	[b]	[b]	[b]	[b]	[b]	[b]
EUR-B	[b]	[b]	[b]	[b]	[b]	[b]
EUR-C	[b]	[b]	[b]	[b]	[b]	[b]
SEAR-B	29	35	27	6	24	[b]
SEAR-D	21	26	19	4	17	100
WPR-A	[b]	[b]	[b]	[b]	[b]	[b]
WPR-B	10	14	10	2	14	[b]
World	20	24	20	3	22, 21[c]	100

[a] The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

[b] A value for the attributable fraction is not included either because the prevalence of vitamin A deficiency in the subregion was zero or the cause-specific mortality was zero or nearly zero in the associated subregion-age-sex groups.

[c] The global attributable fractions are 22% (for women aged 15–29 years) and 21% (for women aged 30–44 years). They are slightly different because the total number of deaths among women in these age groups differ.

Table 4.10 Deaths (000s) from measles, malaria, diarrhoea, other infectious diseases among children, from maternal conditions attributable to vitamin A deficiency, and those directly attributed to vitamin A deficiency in vital registration systems, by subregion

	Cause-specific mortality among children (0–4 years)[a]					*Cause-specific mortality among pregnant women (15–44 years)*[a]	*All-cause mortality directly attributed to vitamin A deficiency in vital registration systems*[b]	
Subregion	*Measles*	*Diarrhoea*	*Malaria*	*Other infectious causes*	*Total*	*Maternal causes*		*Total*
AFR-D	41	46	79	3	169	24	11	202
AFR-E	34	93	90	6	223	38	13	271
AMR-A	0	0	0	0	0	0	0	0
AMR-B	0	4	0	0	4	2	0	6
AMR-D	0	2	0	0	2	2	0	4
EMR-B	0	0	0	0	0	0	0	0
EMR-D	11	52	7	3	73	14	1	87
EUR-A	0	0	0	0	0	0	0	0
EUR-B	0	0	0	0	0	0	0	0
EUR-C	0	0	0	0	0	0	0	0
SEAR-B	7	9	1	0	17	5	0	23
SEAR-D	23	107	10	6	146	21	2	169
WPR-A	0	0	0	0	0	0	0	0
WPR-B	2	9	0	1	12	3	0	16
World	118	323	187	19	647	109	28	778[c]

[a] The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

[b] Among both sexes and all age groups.

[c] Data for the measles, diarrhoea, malaria, other infectious causes, all-cause maternal mortality directly attributed to vitamin A deficiency, and the totals columns were obtained directly from annex results tables. Subregional subtotals for children aged 0–4 years were calculated by adding across disease categories and then totalling those results. Regional subtotals for maternal causes of death were calculated by adding across the 15–29 and 30–44 year-old age categories and then totalling those results. Any discrepancies in the marginal totals in this table are attributed to differences in rounding carried over from the individual columns of the background data tables.

Again, the highest attributable fractions are found in the African and South-East Asian Regions, where vitamin A deficiency and maternal mortality rates are highest.

Worldwide the majority of deaths (see Table 4.10) and DALYs (see Table 4.11) associated with vitamin A deficiency occur in Africa and South-East Asia. However, the relative distribution of deaths and DALYs varies somewhat across subregions for the different causes of disease burden. A higher proportion of the burden of disease from measles, malaria and all-cause maternal mortality occurs in Africa, while South-East Asia has a higher proportion of the disease burden from diarrhoea.

The total number of maternal and child deaths and disease-related morbidity that could potentially be averted if vitamin A deficiency were eliminated depends on several factors: (i) the attributable fraction (determined by the prevalence of vitamin A deficiency and the relative risk of an adverse health outcome); (ii) the global distribution of the adverse health outcomes; and (iii) the estimated number of affected individuals in each subregion. Subregions with a higher attributable fraction but a smaller number of individuals affected by the adverse health outcomes (due to either a small population base or a low prevalence of the condition) may contribute less in absolute terms to the overall global burden of disease when compared to subregions or specific causes of death with lower attributable fractions but a larger total number of affected individuals. Conversely, subregions with similar attributable fractions but different causes of death and/or population bases will contribute different numbers of affected individuals to a global summary.

For example, the AFR-D and SEAR-D subregions have similar attributable fractions of disease for measles (~20%), but the number of deaths attributed to vitamin A deficiency is nearly twice as high in AFR-D (41 000) when compared to SEAR-D (23 000) although the population base of children in the AFR-D subregion is only a third (13.5 million) of the population base of children (42.3 million) in the SEAR-D subregion. For diarrhoea, AFR-D and SEAR-D also have similar attributable fractions of disease (~25%), but in this case the number of deaths attributed to vitamin A deficiency is more than twice as high in SEAR-D (107 000) when compared to AFR-D (46 000). The relative contribution of these different factors (attributable fractions, global distribution of disease and population base) should be kept in mind when comparing the burden of disease attributed to vitamin A deficiency across subregions and specific causes of death.

7. Discussion

This chapter generated quantitative estimates of the global burden of disease due to vitamin A deficiency by applying the analytical framework of the CRA project to the best sources of currently available data. The results show, despite decades of achievement in paediatric detection and

Table 4.11 DALYs (000s) associated with measles, malaria, diarrhoea, and other infectious diseases among children, with maternal conditions attributable to vitamin A deficiency and with direct sequelae of vitamin A deficiency among all age groups, by subregion

	Children (0–4 years)[a]					*Pregnant women (15–44 years)*[a]	*Both sexes (all age groups)*	
Subregion	*Measles*	*Diarrhoea*	*Malaria*	*Other infectious causes*	*Total*	*Maternal causes of morbidity and mortality*	*Sequelae directly associated with vitamin A deficiency*	*Total*
AFR-D	1432	1554	2914	95	5995	662	378	7034
AFR-E	1176	3131	3345	189	7841	1095	438	9375
AMR-A	0	0	0	0	0	0	0	0
AMR-B	0	132	2	10	144	38	0	182
AMR-D	0	84	0	3	87	33	0	121
EMR-B	0	15	0	2	17	0	0	17
EMR-D	389	1746	253	88	2476	401	40	2917
EUR-A	0	0	0	0	0	0	0	0
EUR-B	0	1	0	0	1	0	1	2
EUR-C	0	0	0	0	0	0	0	0
SEAR-B	233	314	36	15	598	152	4	754
SEAR-D	790	3603	368	191	4952	637	100	5690
WPR-A	0	0	0	0	0	0	0	0
WPR-B	81	319	11	37	448	89	11	546
World	4101	10898	6931	630	22560	3106	972	26638[b]

[a] The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

[b] Data for the measles, diarrhoea, malaria, other infectious causes, maternal causes of morbidity and mortality, and sequelae directly attributed to vitamin A deficiency, and the totals columns were obtained directly from the annex results tables. Subregional subtotals for children aged 0–4 years were calculated by adding across disease categories and then totalling those results. Subregional subtotals for maternal conditions were calculated by adding across the 15–29 and 30–44 year-old age categories and then totalling those results. Any discrepancies in the marginal totals in this table are attributed to differences in rounding carried over from the individual columns of the background data tables.

control, that vitamin A deficiency remains a major public health problem among preschool-age children throughout the world. Globally, 21%, or over 127 million children aged <5 years are vitamin A deficient. Twenty per cent to 24% of early childhood deaths due to measles, diarrhoea and malaria are attributable to vitamin A deficiency, plus an additional 3% of deaths due to other infectious causes, accounting for 647 000 deaths of preschool-age children each year. Vitamin A deficiency appears to especially put children at risk of mortality due to diarrhoea, which accounts for 50% of all childhood deaths attributable to vitamin A deficiency.

New to the global view of undernutrition is a previously unrecognized, substantial burden of maternal vitamin A deficiency. Not surprisingly the burden of disease among pregnant women appears to parallel the geographic distribution seen in young children, with Asia and Africa bearing a disproportionate burden. This first attempt to define the problem suggests, conservatively, that 5.6% of all pregnant women, or approximately 7.3 million, are vitamin A deficient in a given year. Vitamin A-deficient women are at a 4.5-fold higher risk of pregnancy-related mortality than non-deficient women. The estimates generated for this project suggest that more than 20% of all maternal deaths in the world may be attributable to vitamin A deficiency. The method used to generate this particular estimate (applying the relative risk of death associated with vitamin A deficiency to all causes of maternal death) may somewhat overestimate the burden of disease related to vitamin A deficiency. It also does not address the prevalence, burden, or potential health consequences of vitamin A deficiency among non-pregnant women of reproductive age, which remain largely unknown.

In addition to estimating the number of preventable deaths, the results from this project suggest that approximately 27 million DALYs are associated with vitamin A deficiency. Given that DALYs provide a composite measure of disease burden associated with both fatal and non-fatal health conditions and that childhood mortality related to infectious diseases is the primary health outcome known to be associated with vitamin A deficiency, it is not surprising that the vast majority of the estimated DALYs (~23 million) are related to infectious disease causes of death in children.

In summary, vitamin A deficiency affects vulnerable populations throughout critical stages of life, as revealed by these estimates of disease burden in young children and pregnant women. Successful efforts to control and reduce vitamin A deficiency have the potential to improve the health and well-being of women and children around the world and to reduce the global burden of disease associated with this nutritional risk factor.

8. Expected changes in the prevalence of vitamin A deficiency

Based on the trends observed over the past 20 years, and more specifically on changes over the past 5–10 years, there is reason for optimism and the expectation that the global prevalence of vitamin A deficiency (defined as serum retinol concentrations <0.70 μmol/l) will decrease in the years leading up to 2030.

Numerous factors contribute to the current situation. In recent years a favourable global policy environment has been created and global partnerships have emerged to help guide activities aimed at the control and prevention of vitamin A deficiency. Various groups have contributed to the positive policy environment including IVACG, international organizations, bilateral agencies and individual country governments around the world.

Although these groups initially focused their attention almost exclusively on the more obvious problem of vitamin A deficiency among children, the situation is now changing. Policy-makers and programme managers are increasingly expanding their efforts in recognition of the fact that vitamin A deficiency is also prevalent among women of reproductive age and has potentially severe health consequences for them as well.

Many countries have already initiated national supplementation programmes for children (most commonly using community-based health services as a routine delivery channel or special vitamin A distribution initiatives combined with national immunization days or child health days or weeks) in an effort to prevent severe vitamin A deficiency among this age group. Although child-based supplementation programmes do not necessarily directly address the problem of vitamin A deficiency among women, other more general approaches may, if the accompanying health messages are modified to specifically encourage women as participants and programme beneficiaries. These include widespread food fortification initiatives, efforts to improve the availability of vitamin A rich foods through agricultural programmes, nutrition education programmes, etc.

Projections for the global prevalence of vitamin A deficiency for the 30-year time period from 2000 to 2030 were developed for the CRA project based on the assumption that the policy and programming environment will remain positive and that prevention and control activities will not only keep pace, but will exceed future population growth.

The global prevalence of 21.1% for serum retinol concentrations <0.70 μmol/l (in preschool-age children) in the year 2000 was used as the baseline prevalence rate. Reductions of 10%, 20% and 30% were projected over the next three decades, resulting in estimated global prevalence rates of 19.0%, 16.9% and 14.8%, in the years 2010, 2020 and 2030, respectively. Although specific programmes to address vitamin A

deficiency in women have started much more recently, the same percentage reductions (10%, 20% and 30%) in prevalence rates were assumed for the purposes of the CRA project. Starting with an assumed baseline rate of 5.6% in 2000, prevalence rates of 5.0%, 4.5% and 3.9% were projected for 2010, 2020 and 2030, respectively.

Acknowledgements

Supported by the Family Health and Child Survival (FHACS) Cooperative Agreement, between the United States Agency for International Development (USAID), Office of Health and Nutrition, and The Johns Hopkins Bloomberg School of Public Health, Department of International Health (JHU), and by the World Health Organization Global Programme on Evidence for Health Policy. The authors thank Maria Andersson and Bruno de Benoist for data used to update the vitamin A deficiency prevalence estimates, and Anuraj H. Shankar for helpful comments on malaria issues. The authors are grateful for the assistance of Steve Fishman, Jeffrey McGuckin and Jonathan Sugimoto in compiling data for the project, and for the valuable insight and advice from other colleagues in the field of international health.

Note

1 See preface for an explanation of this term.

References

Anonymous (1995) Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. The vitamin A and pneumonia working group. *Bulletin of the World Health Organization*, **73**:609–619.

Anonymous (1998a) *Nepal micronutrient status survey*. Ministry of Health, Child Health Division, HMG/N, New ERA, Micronutrient Initiative, UNICEF Nepal. World Health Organization, Kathmandu.

Anonymous (1998b) Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. WHO/CHD immunisation-linked vitamin A supplementation study group. *The Lancet*, **352**(9136):1257–1263. Erratum in: *The Lancet*, 1999; **353**:154.

Bauernfiend C (1986) *Vitamin A deficiency and its control*. Academic Press, Inc., Gainesville, FL.

Beaton GH, Martorell R, Aronson KJ et al. (1993) *Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries*. ACC/SCN State-of-the-art Series. (Nutrition Policy Discussion Paper No. 13.) United Nations Administrative Committee on Coordination/Sub-Committee on Nutrition, Geneva.

Binka FN, Ross DA, Morris SS et al. (1995) Vitamin A supplementation and childhood malaria in northern Ghana. *American Journal of Clinical Nutrition*, **61**:853–859.

Bloem MW, Wedel M, Egger RJ et al. (1990) Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhea in preschool and school children in northeastern Thailand. *American Journal of Epidemiology*, **131**:332–339.

Christian P, Thorne-Lyman AL, West KP Jr. et al. (1998a) Working after the sun goes down: exploring how night blindness impairs women's work activities in rural Nepal. *European Journal of Clinical Nutrition*, **52**:519–524.

Christian P, West KP Jr., Khatry SK et al. (1998b) Night blindness of pregnancy in rural Nepal—nutritional and health risks. *International Journal of Epidemiology*, **27**:231–237.

Christian P, West KP Jr., Khatry SK et al. (2000) Vitamin A or beta-carotene supplementation reduces symptoms of illness in pregnant and lactating Nepali women. *Journal of Nutrition*, **130**:2675–2682.

Christian P, West KP Jr., Khatry SK et al. (2001) Maternal night blindness increases risk of mortality in the first 6 months of life among infants in Nepal. *Journal of Nutrition*, **131**:1510–1512.

Coutsoudis A, Broughton M, Coovadia HM (1991) Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled, double-blind trial. *American Journal of Clinical Nutrition*, **54**: 890–895.

Daulaire NM, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR (1992) Childhood mortality after a high dose of vitamin A in a high risk population. *British Medical Journal*, **304**:207–210.

Davis TM, Skinner-Adams TS, Beilby J (1998) In vitro growth inhibition of Plasmodium falciparum by retinol at concentrations present in normal human serum. *Acta Tropica*, **69**:111–119.

Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, Smith PG (1997) Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana. *American Journal of Epidemiology*, **146**:646–654.

Ellison JB (1932) Intensive vitamin therapy in measles. *British Medical Journal*, **2**:708–711.

Faisel H, Pittrof R (2000) Vitamin A and causes of maternal mortality: association and biological plausibility. *Public Health Nutrition*, **3**:321–327.

Fawzi WW, Chalmers TC, Herrera MG, Mosteller F (1993) Vitamin A supplementation and child mortality. A meta-analysis. *Journal of the American Medical Association*, **269**:898–903.

Filteau SM, Morris SS, Abbott RA et al. (1993) Influence of morbidity on serum retinol of children in a community-based study in northern Ghana. *American Journal of Clinical Nutrition*, **58**:192–197.

Friis H, Mwaniki D, Omondi B et al. (1997) Serum retinol concentrations and *Schistosoma mansoni*, intestinal helminths, and malarial parasitemia: a cross-

sectional study in Kenyan preschool and primary school children. *American Journal of Clinical Nutrition*, **66**:665–671.

Galan P, Samba C, Luzeau R, Amedee-Manesme O (1990) Vitamin A deficiency in pre-school age Congolese children during malarial attacks. Part 2: Impact of parasitic disease on vitamin A status. *International Journal for Vitamin and Nutrition Research*, **60**:224–228.

Ghana VAST Study Team (1993) Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *The Lancet*, **342**:7–12. Erratum in: *The Lancet*, 1993;**342**:250.

Gilbert C, Foster A (2001) Childhood blindness in the context of VISION 2020—The right to sight. *Bulletin of the World Health Organization*, **79**: 227–232.

Glasziou PP, Mackerras DEM (1993) Vitamin A supplementation in infectious diseases: a meta-analysis. *British Medical Journal*, **306**:366–370.

Haskell MJ, Mazumder RN, Peerson JM et al. (1999) Use of the deuterated-retinol-dilution technique to assess total-body vitamin A stores of adult volunteers consuming different amounts of vitamin A. *American Journal of Clinical Nutrition*, **70**:874–880.

Herrera MG, Nestel P, El Amin A, Fawzi WW, Mohamed KA, Weld L (1992) Vitamin A supplementation and child survival. *The Lancet*, **340**:267–271.

Hersh BS, Tambini G, Nogueira AC, Carrasco P, de Quadros CA (2000) Review of regional measles surveillance data in the Americas, 1996–99. *The Lancet*, **355**:1943–1948.

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, **58**:295–300.

Humphrey JH, Agoestina T, Wu L et al. (1996) Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *Journal of Pediatrics*, **128**:489–496.

Hussey GD, Klein M (1990) A randomized, controlled trial of vitamin A in children with severe measles. *New England Journal of Medicine*, **323**: 160–164.

IVACG (1997) *Maternal night blindness: extent and associated risk factors*. International Life Sciences Institute, Washington, DC.

Katz J, West KP Jr., Khatry SK et al. (2000) Maternal low-dose vitamin A or beta-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition*, **71**:1570–1576.

Kjolhede CL, Stallings RY, Dibley MJ, Sadjimin T, Dawiesah S, Padmawati S (1995) Serum retinol levels among preschool children in Central Java: demographic and socioeconomic determinants. *International Journal of Epidemiology*, **24**:399–403.

Krishnan S, Krishnan AD, Mustafa AS, Talwar GP, Ramalingaswami V (1976) Effect of vitamin A and undernutrition on the susceptibility of rodents to a malarial parasite *Plasmodium berghei*. *Journal of Nutrition*, **106**: 784–791.

Mason JB, Lotfi M, Dalmiya N, Sethuraman K, Dietchler M (2001) *The micronutrient report: current progress and trends in the control of vitamin A, iodine, and iron deficiencies*. The Micronutrient Initiative, Ottawa, ON. http://www.micronutrient.org.

Micronutrient Initiative/UNICEF/Tulane University (1998) *Progress towards controlling vitamin A deficiency*. The Micronutrient Initiative, Ottawa, ON.

Milton RC, Reddy V, Naidu AN (1987) Mild vitamin A deficiency and childhood morbidity—an Indian experience. *American Journal of Clinical Nutrition*, **46**:827–829.

Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D (1988) Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *American Journal of Clinical Nutrition*, **48**:1271–1276.

Murray CJ, Lopez AD, eds. (1996a) *Global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol 1. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJ, Lopez AD, eds. (1996b) *Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions*. Global Burden of Disease and Injury, Vol 2. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJL, Lopez AD, Mathers CD, Stein C (2001) *The global burden of disease 2000 project: aims, methods and data sources*. (GPE Discussion Paper No. 36—revised). World Health Organization, Geneva.

Nalubola R, Nestel P (1999) *The effect of vitamin A nutriture on health: a review*. ILSI Press, Washington, DC.

National Research Council (1989) *Recommended Dietary Allowances*. U.S. Subcommittee on the tenth edition of the RDAs. National Academy Press, Washington, DC.

Olson JA (1996) Vitamin A. In: *Present knowledge in nutrition*. 7th edition. Ziegler EE, Filer LJJ, eds. ILSI Press, Washington, DC.

Rahmathullah L, Underwood BA, Thulasiraj RD et al. (1990) Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *New England Journal of Medicine*, **323**:929–935.

Reingold AL, Phares CR (2001) Infectious diseases. In: *International public health: diseases, programs, systems, and policies*. Merson MH, Black RE, Mills AJ, eds. Aspen Publishers, Inc., Gaithersburg, MD.

Ribaya-Mercado JD, Mazariegos M, Tang G et al. (1999) Assessment of total body stores of vitamin A in Guatemalan elderly by the deuterated-retinol-dilution method. *American Journal of Clinical Nutrition*, **69**:278–284.

Rosales FJ, Kjolhede C, Goodman S (1996) Efficacy of a single oral dose of 200,000 IU of oil-soluble vitamin A in measles-associated morbidity. *American Journal of Epidemiology*, **143**:413–422.

Rothman KH, Greenland S (1998) *Modern epidemiology*. 2nd edn. Lipponcott-Raven Publishers, Philadelphia, PA.

Samba DC, Basco LK, Bleiberg-Daniel F, Lemmonier D, Le Bras J (1992) Absence of effect of retinol on the in vitro development of *Plasmodium falciparum*. *International Journal for Vitamin and Nutrition Research*, **62**:99–100.

Semba RD, Bloem MW (2002) The anemia of vitamin A deficiency: epidemiology and pathogenesis. *European Journal of Clinical Nutrition*, **56**:271–281.

Semba RD, Miotti PG, Chiphangwi JD et al. (1998) Maternal vitamin A deficiency and infant mortality in Malawi. *Journal of Tropical Pediatrics*, **44**:232–234.

Serghides L, Kain KC (2002) Mechanism of protection induced by vitamin A in falciparum malaria. *The Lancet*, **359**:1404–1406.

Shankar AH (1995) Vitamin A and malaria. *American Journal of Clinical Nutrition*, **62**:842–843.

Shankar AH (2001) Nutritional modulation of immunity and infection. In: *Present knowledge in nutrition*. 8th edn. Bowman BA, Russell RM, eds. International Life Sciences Institute Press, Washington, DC.

Shankar AH, Genton B, Semba RD et al. (1999) Effect of vitamin A supplementation on morbidity due to *Plasmodium falciparum* in young children in Papua New Guinea: a randomised trial. *The Lancet*, **354**:203–209.

Sommer A (1982) *Nutritional blindness: xerophthalmia and keratomalacia*. Oxford University Press, New York.

Sommer A, Davidson FR (2002) Assessment and control of vitamin A deficiency: the Annecy accords. *Journal of Nutrition*, **132**:S2845–2850.

Sommer A, Tarwotjo I, Djunaedi E et al. (1986) Impact of vitamin A supplementation on childhood mortality. A randomised controlled community trial. *The Lancet*, **1**:1169–1173.

Sommer A, Tarwotjo I, Katz J (1987) Increased risk of xerophthalmia following diarrhea and respiratory disease. *American Journal of Clinical Nutrition*, **45**:77–80.

Sommer A, West KP Jr. (1996) *Vitamin A deficiency: health, survival and vision*. Oxford University Press, New York.

Sommer A, Zeger SL (1991) On estimating efficacy from clinical trials. *Statistics in Medicine*, **10**:45–52.

Stephensen CB (2001) Vitamin A, infection, and immune function. *Annual Review of Nutrition*, **21**:167–192.

Stoltzfus RJ, Jalal F, Harvey PW, Nesheim MC (1989) Interactions between vitamin A deficiency and *Plasmodium berghei* infection in the rat. *Journal of Nutrition*, **119**:2030–2037.

Sturchler D, Tanner M, Hanck A et al. (1987) A longitudinal study on relations of retinol with parasitic infections and the immune response in children of Kikwawila village, Tanzania. *Acta Tropica*, **44**:213–227.

Tabone MD, Muanza K, Lyagoubi M et al. (1992) The role of interleukin-6 in vitamin A deficiency during *Plasmodium falciparum* malaria and possible consequences for vitamin A supplementation. *Immunology*, **75**:553–554.

Thurnham DI, Singkamani R (1991) The acute phase response and vitamin A status in malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **85**:194–199.

Tielsch JM, Rahmathullah L, Katz J, Thulasiraj RD, Coles CL, Devi S (2001) *Impact of vitamin A supplementation for newborns on early infant mortality: a community-based, randomized trial in South India.* (Presented at the XX International Vitamin A Consultative Group Meeting 2001 in Hanoi, Viet Nam).

Tonascia JA (1993) *Meta-analysis of published community trials: impact of vitamin A on mortality*. (Proceedings of the Bellagio meeting on vitamin A deficiency and child mortality.) Helen Keller International, New York.

UNICEF (2001) *The state of the world's children 2001*. UNICEF, New York.

West KP Jr. (2002) Extent of vitamin A deficiency among preschool children and women of reproductive age. *Journal of Nutrition*, **132**:S2857–2866. Erratum in: *Journal of Nutrition*, 2002;**132**:3432.

West KP Jr., Katz J, Khatry SK et al. (1999) Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. *British Medical Journal*, **318**:570–575. Erratum in *British Medical Journal*, 1999;**318**:1386.

West KP Jr., Katz J, Shrestha SR et al. (1995) Mortality of infants <6 months of age supplemented with vitamin A: a randomized, double-masked trial in Nepal. *American Journal of Clinical Nutrition*, **62**:143–148.

West KP Jr., Pokhrel RP, Katz J et al. (1991) Efficacy of vitamin A in reducing preschool child mortality in Nepal. *The Lancet*, **338**:67–71.

WHO (1992) *International statistical classification of diseases and related health problems,* 10th revision. World Health Organization, Geneva.

WHO (1995) *Global prevalence of vitamin A deficiency.* (MDIS Working Paper No. 2. WHO/NUT/95.3). World Health Organization, Geneva.

WHO (1996) *Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes.* (WHO/NUT/96.10). World Health Organization, Geneva.

World Bank (1993) World development report 1993: investing in health. Oxford University Press, New York.

Chapter 5

Zinc deficiency

Laura E. Caulfield and Robert E. Black

Summary

Research conducted during the past 10–15 years suggests that zinc deficiency is widespread and affects the health and well-being of populations worldwide. The objective of this chapter is to quantify the regional and global magnitude, distribution and disease burden implications of zinc deficiency.

We conducted a systematic literature search to identify relevant studies investigating the role of zinc in human health. This search indicated that evidence on the burden of disease related to zinc deficiency would be limited to the results of randomized controlled trials (RCTs) conducted among paediatric populations in developing countries, and would provide information on whether zinc deficiency affects the incidence of diarrhoea, pneumonia and malaria illness among children aged 0–4 years. There are no global estimates of zinc deficiency in paediatric or other populations; however, the International Zinc Nutrition Consultative Group (IZiNCG) has developed a method for estimating the prevalence of inadequate zinc intakes based on the presence and bioavailability of zinc in each country's food supply.

A systematic review of relevant epidemiological research involved meta-analysis from 11 intervention trials. Results of our review indicate that zinc deficiency in children aged <5 years increases the risk of incidence for diarrhoeal disease by 1.28 (95% CI 1.10–1.50), pneumonia by 1.52 (95% CI 1.20–1.89) and malaria by 1.56 (95% CI 1.29–1.89). We extended those results as best estimates of the risk of mortality from these causes as a result of zinc deficiency. Following the IZiNCG technique, the global prevalence of zinc deficiency was estimated at 31%, ranging from 4–73% across subregions.[1] Based on these estimates, zinc deficiency was estimated to cause 176 000 diarrhoea deaths, 406 000 pneumonia deaths and 207 000 malaria deaths. The associated loss of disability-adjusted life years (DALYs) attributable to zinc deficiency amounts to more than 28 million. The burden of disease due to zinc

deficiency is borne most heavily by countries in Africa, the Eastern Mediterranean and South-East Asia. The burden was approximately equally shared between males and females.

The results of this review suggest that zinc deficiency contributes substantially to the morbidity and mortality of young children throughout the world. Available evidence from RCTs on the strength of the association between zinc deficiency and morbidity from diarrhoea, pneumonia and malaria, combined with the high estimated prevalences of inadequate zinc diets, translates into a significant burden of disease attributable to deficiency of this micronutrient. Evidence relating zinc deficiency to health outcomes in children aged >5 years and adult men and women was not available. Given the likely high prevalence of inadequate zinc intakes in these other groups, research is needed to determine the magnitude of the potential health effects.

1. Introduction

Zinc is a trace mineral essential to all forms of life because of its fundamental role in gene expression, cell development and replication (Hambridge 2000). Severe or clinical zinc deficiency was defined last century, as a condition characterized by short stature, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction and anorexia (Prasad 1991). Although severe zinc deficiency is considered rare, mild-to-moderate zinc deficiency is likely prevalent throughout the world today (Sandstead 1991). Lack of consensus on indicators of zinc deficiency has hampered efforts to document prevalences of zinc deficiency. Despite this, RCTs of zinc supplementation in areas with habitual low zinc intakes have begun to demonstrate how low dietary intakes of zinc adversely affect child health (Brown et al. 1998a; Zinc Investigators' Collaborative Group 1999, 2000). For this reason, it is important to attempt to quantify the prevalence of zinc deficiency and its contribution to the global burden of disease. The goal of this chapter is to describe the methods used to quantify the magnitude, distribution and disease burden implications of zinc deficiency.

2. Nature and definition of the risk factor

Millions of people throughout the world may have inadequate levels of zinc in the diet due to limited access to zinc-rich foods (animal products, oysters and shellfish) and the abundance of zinc inhibitors, such as phytates, common in plant-based diets (Sandstead 1991). Our understanding of the public health importance of inadequate zinc intakes has been hampered by a lack of indicators of zinc status for identifying individuals with zinc deficiency (Wood 2000).

Estimating the prevalence of zinc deficiency is difficult because plasma or serum zinc concentrations, the most widely used indicators of zinc

deficiency at the population level, have not been assessed in national or regional surveys in developing countries. Even in developed countries, such indicators are not used for methodological and cost reasons.

Zinc deficiency is largely related to inadequate intake or absorption of zinc from the diet, although excess losses of zinc during diarrhoea may also contribute (Gibson 1994; WHO 1996). The distinction between intake and absorption is important, because although some intakes of zinc may be acceptable, the levels of inhibitors (e.g. fibre and phytates) in the diet may mean that inadequate amounts of zinc are absorbed. For this reason, zinc requirements for dietary intake are adjusted upward for populations in which animal products, the best sources of zinc, are limited, and in which plant sources of zinc are similarly high in phytates. Because zinc is not well conserved in the body and because zinc deficiency is directly related to dietary zinc intake, an indirect approach to quantify the prevalence of zinc deficiency would be to examine the adequacy of zinc in the diet in various regions throughout the world.

Dietary surveys are conducted in many countries, but few such surveys exist in developing countries (Gibson 1994; Parr 1992; WHO 1996). Even when dietary intake data are available, incomplete information on the content of zinc and its bioavailability in local foods has made calculation of zinc bioavailability problematic.

2.1 Prevalence of zinc deficiency

Several alternative approaches have been taken to estimate the adequacy of the diet in various regions of the world. For example, the World Health Organization (WHO) (1996) used a factorial approach to estimate the average basal and normative zinc requirements (i.e. minimum amount of zinc to cover losses in individuals adapted or not adapted to low usual dietary intakes of zinc) for population subgroups, and then considered issues of zinc bioavailability from the typical diet in various regions of the world to derive estimates of the minimal dietary intake of zinc that would meet these requirements. They then compared the estimated dietary intakes of zinc from 210 dietary surveys conducted throughout the world as a percentage of the minimal dietary intake of zinc, and identified surveys in which the mean intake of zinc did not meet the minimal basal or normative level of intake. Overall, this method led to the conclusion that populations with inadequate intakes of zinc were likely widespread throughout the world, but concentrated in areas of the world consuming plant-based diets in which zinc was only of low to moderate bioavailability. For example, of 148 surveys conducted in populations with presumed highly bioavailable zinc (mostly western Europe and the United States of America), only one dietary survey indicated a mean intake lower than the minimal zinc intake to meet average normative requirements for zinc. In contrast, among 47 surveys conducted in populations with moderate zinc bioavailability, 40 indicated average

intakes lower than the minimal normative zinc intake, and of 15 surveys conducted in populations with low zinc bioavailability, none reported mean intakes greater than the minimal normative zinc intake. Based on this approach, it was concluded that zinc nutrition in developing countries should be a priority area for research, and emphasized the need for studies of dietary intakes and dietary constituents. Although carefully constructed, this analysis could not provide us with the required data on estimated regional prevalences of zinc deficiency.

In 2001, Brown et al. published an approach that used available data on per capita food availability from 172 countries to estimate the prevalence of inadequate zinc intakes worldwide. Subsequently IZiNCG (forthcoming) revised this approach, improving on the method for assessing the bioavailability of zinc in the food supply. We used this second approach because of the improved methodology and more conservative estimates of deficiency, and were provided with estimated prevalences of inadequate intakes of zinc in the diet in each of the 14 subregions (K. Brown, personal communication). The technique is described briefly below.

Data are available on the per capita food availability in each country based on country-level information on food production, imports and exports, as reported on food balance sheets (FBS) by the Food and Agriculture Organization of the United Nations (FAO) on an annual basis. Per capita availability of energy was estimated from this information, and population estimates for each country in 1998 (FAO 1999). Per capita zinc availability was estimated based on the zinc : energy ratio, which was derived using FAO values for energy for each food and values of the World Food Program (World Food Dietary Assessment System 1997) for the estimated zinc content of each food. To examine the bioavailability of zinc in the diet, IZiNCG gathered published information from studies of zinc absorption from test meals, and conducted a pooled analysis to derive a prediction equation for the percentage absorbable zinc based on information on the zinc, phytate, calcium and total protein content of the diet. This equation and information on the levels of zinc, phytate, calcium and total protein available per capita per meal (assuming three meals per day) calculated from the FBS database were then applied to estimate the percentage absorbable zinc for each of the 172 countries with available FBS data. The proportion of absorbable zinc ranged from 11% to 22%. Countries were then categorized as having low (<14%), moderate (15–16%) or high (>17%) mean percentage absorbable zinc in the food supply, based on their main staple food (wheat, rice, maize and other cereals, and tubers) and the contribution of animal protein to the energy available in the food supply.

The average daily zinc requirement for each country was estimated by calculating the mean of the recommended zinc intakes for low, average and high bioavailability diets for the various sexes and ages (WHO 1996), weighted by the sex and age distribution of the country's popu-

lation, as obtained from the WISTAT database (WISTAT 1994). To calculate the estimated percentage of the population with inadequate zinc intake, they assumed that the mean intake of food was equal to mean availability of food, and that the standard deviation of intake is 25% of the mean—i.e. coefficient of variation (CV) = 0.25 (WHO 1996). Under assumptions of normality, they calculated the proportion of individuals with intakes below the country-level daily zinc requirement, and thus at risk of zinc deficiency due to inadequate zinc intake (IZiNCG forthcoming). Again, this method is conservative when compared to the previously published method using bioavailability estimates, which considered only the phytate:zinc molar ratio in the food supply (Brown et al. 2001).

The method does not account for zinc intake from breast milk or from drinking water. However, breast milk is only an adequate source of zinc in the diets of infants aged less than six months, and zinc intakes from drinking water typically increase total zinc intakes by only 2% provided a usual water intake of 2 l/day.

A secondary consideration for our calculations was the selection of the appropriate counterfactual (i.e. theoretical minimum exposure) for zinc deficiency. Unlike some other exposures, zero prevalence of zinc deficiency is in theory possible, and would likely result in complete eradication of the zinc disease burden due to this risk factor. Thus, for purposes of the analysis, we designated the theoretical minimum exposure to be as "no inadequate intakes of zinc" or zero prevalence of inadequate intakes of zinc.

Using the method described above, the estimated global prevalence of zinc deficiency is 31%, and ranges from 4% to 73% (Table 5.1). The prevalences of zinc deficiency are low (4–7%) in AMR-A, EUR-A, EUR-C and WPR-A. Intermediate prevalences of 9–26% are found in AMR-B, EUR-B and WPR-B. High prevalences are found in AMR-D (68%), throughout South and Central Africa (37–62%), North Africa and the Eastern Mediterranean region (25–52%), and South and South-East Asia (34–73%).

3. Health outcomes considered

To proceed with a systematic investigation of the evidence regarding the role of zinc in human health, we disaggregated and then linked both specific health outcomes and target populations. The considered health outcomes included risk and/or severity of diarrhoea, pneumonia, malaria, measles, cognitive dysfunction, physical impairment, visual impairment or blindness and mortality. The target populations consisted of the following age–sex groups: children aged 0–4 years; children 5–14 years; women 15–44 years; men 15–44 years; all adults ≥45 years. Despite this disaggregated approach to defining risk groups, upon review of the literature described below, we concluded that there were few pub-

Table 5.1 Estimated prevalence of inadequate zinc intakes by subregion[a]

Subregion	Number of countries	Population (millions)	Energy (kcal/d)	Zinc (mg/d)	Phytate:zinc ratio	Available zinc (mg)	Mean % of adjusted requirement	% inadequate intakes (95% CI)
AFR-D	25	278.7	2453 (327)	10.0 (2.1)	25.8 (2.6)	1.14 (0.20)	57.3 (10.8)	36.5 (26.4–46.6)
AFR-E	20	322.6	2075 (370)	8.6 (1.6)	27.9 (3.7)	0.94 (0.20)	46.7 (12.4)	61.6 (49.3–73.9)
AMR-A	3	315.7	3514 (234)	12.1 (1.0)	12.6 (0.8)	2.85 (0.37)	85.3 (7.4)	6.3 (0–16.1)
AMR-B	26	418.6	2828 (244)	10.4 (1.8)	20.6 (5.7)	1.66 (1.15)	65.4 (14.8)	26.0 (17.9–34.1)
AMR-D	6	68.5	2241 (223)	7.5 (1.0)	24.7 (6.6)	0.91 (0.15)	44.5 (5.6)	68.4 (54.7–82.1)
EMR-B	10	130.4	2946 (195)	8.5 (1.1)	22.0 (2.7)	1.12 (0.40)	60.9 (6.1)	25.2 (21.1–29.3)
EMR-D	9	339.7	2544 (460)	7.8 (1.9)	25.0 (3.4)	0.91 (0.19)	52.2 (11.7)	51.8 (33.8–69.8)

EUR-A	22	409.4	3378 (154)	12.6 (1.1)	11.5 (1.8)	3.53 (0.93)	92.0 (8.4)	3.9 (2.8–5.0)
EUR-B	16	213.6	3073 (433)	10.2 (1.5)	18.4 (4.6)	1.63 (0.62)	73.2 (10.1)	12.7 (8.9–16.5)
EUR-C	6	247.0	3020 (109)	11.2 (0.7)	13.8 (1.1)	2.18 (0.37)	83.5 (4.7)	5.7 (4.4–7.0)
SEAR-B	3	285.1	2616 (203)	9.1 (1.1)	26.9 (3.4)	1.00 (0.06)	56.9 (6.0)	33.5 (14.7–52.3)
SEAR-D	6	1198.0	2356 (127)	7.9 (0.7)	27.5 (0.4)	0.85 (0.07)	43.5 (4.8)	72.5 (62.3–82.7)
WPR-A	4	148.9	2954 (122)	11.8 (0.9)	16.6 (3.4)	2.13 (1.27)	91.2 (2.9)	3.6 (3.2–4.0)
WPR-B	13	1498.3	2705 (159)	10.7 0.9)	19.0 (1.3)	1.47 (0.23)	80.5 (8.7)	8.5 (3.6–13.4)
World	172	5874.3	2706 (434)	9.9 (2.0)	21.3 (6.0)	1.51 (0.90)	66.5 (19.4)	31.3 (26.7–35.9)

[a] Presented as means (standard deviations).

Source: IZiNCG (forthcoming).

lished studies regarding the contribution of zinc deficiency to morbidity or mortality in any age group other than children aged 0–4 years. For this reason, the chapter focuses on the contribution of zinc deficiency to the global burden of disease among children aged 0–4 years.

4. Risk factor–disease relationship

4.1 Search strategy

Evidence for the relationship between zinc deficiency and various diseases was gathered through literature searches of published studies. Articles related to zinc deficiency in human populations were identified for review based upon a Medline database search of literature published 1966–2001 in English or with an English abstract. The search was conducted using combinations of the following keywords: zinc, deficiency, mortality, death, morbidity, acute respiratory infection, pneumonia, diarrhoea, measles, malaria, child, pregnancy, infant, neonatal, fetal, premature, congenital, abortion, stillbirth, miscarriage, birth weight, retardation, development, intelligence, cognitive, psychomotor and neurological. Further searches on Medline were conducted using author names and the "related articles" option.

Abstracts were reviewed to select English-language articles that examined the effect of zinc deficiency (as defined by clinical, epidemiological or biochemical assessment) or supplementation/fortification on several health outcomes of interest in human populations. These health outcomes included infant or neonatal, child or adult mortality; incidence or severity of malaria, diarrhoea, measles or acute respiratory infection; prevalence of mental retardation or cognitive dysfunction; and risk prevalence of physical impairment such as hearing or neurological dysfunction. Once copies of articles were obtained, additional publications were identified from the reference lists of those articles. The only studies excluded from review were animal studies and case reports.

4.2 Methods for combining risk estimates from individual studies

The most appropriate study design to assess prospective risk for our purposes would be a prospective cohort study. Unfortunately, no such studies were identified despite an exhaustive search. Certainly this relates in part to the fundamental problem of characterizing the zinc status of individuals discussed above. There have been, however, a significant number of RCTs of zinc supplementation examining morbidity outcomes in young children living in developing countries with presumably low intakes of zinc. The studies that were identified and included in our calculations are summarized in Table 5.2.

The studies included were RCTs of zinc supplementation for the prevention of one of three health outcomes: diarrhoea, pneumonia or

Table 5.2 Studies contributing data on the effect of zinc deficiency on morbidity among children, aged 0–4 years

Country (reference)	*Study design*	*Supplement*	*Age (months)*	*Sample size*		*Enrolment criteria*	*Outcomes measured*		
				Zinc group	*Control group*		*Diarrhoea*	*Pneumonia*	*Malaria*
Burkina Faso (Müller et al. 2001)	Continuous supplementation (6 days/ week) over a 6-month period. Malaria defined based on community-based active case detection	12.5 mg zinc as sulfate	6–31	356	353	Community-based (included for diarrhoea only)	✓	—	✓
Ethiopia (Umeta et al. 2000)	Continuous supplementation (6 days/ week) for 6 months	10 mg zinc as sulfate	6–12	92	92	Stratified based on length-for-age <–2 SD	✓	—	—
Gambia (Bates et al. 1993)	Twice weekly supplementation over a 1.25-year period. Supplement provided in a fruit-flavoured drink; malaria defined as clinic visit with confirmation by microscopic evaluation	70 mg zinc as zinc acetate	6–28	55	54	Matched on age and sex	—	—	✓
Guatemala (Ruel et al. 1997)	Daily supplementation for 28 weeks	10 mg zinc as sulfate	6–9	45	44	Community-based	✓	—	—
India (Bhandari et al. 2002)	Daily supplementation for 16 weeks	10 mg zinc to infants; 20 mg zinc to older children; as gluconate	6–35	1241	1241	Community-based	—	✓	—

continued

Table 5.2 Studies contributing data on the effect of zinc deficiency on morbidity among children, aged 0–4 years (*continued*)

Country (reference)	*Study design*	*Supplement*	*Age (months)*	*Sample size*		*Enrolment criteria*	*Outcomes measured*		
				Zinc group	*Control group*		*Diarrhoea*	*Pneumonia*	*Malaria*
India (Sazawal et al. 1997, forthcoming)	Daily supplementation for 26 weeks	10 mg zinc as gluconate, vitamin A, B, D, E	6–35	286	293	Recovered from acute diarrhoea	✓	✓	—
Jamaica (Meeks-Gardner et al. 1998)	Daily supplementation for 12 weeks	5 mg zinc as sulfate, vitamin A, B, C, D	6–24	31	30	Weight-for-height <–2 SD	✓	✓	—
Mexico (Rosado et al. 1997)	Continuous supplementation (5 days/week) for 54 weeks	20 mg zinc as methionate, half with iron	18–36	97	97	Community-based	✓	—	—
Papua New Guinea (Shankar et al. 1997, 2000)	Continuous supplementation (6 days/week) over a 46–7 week period. Malaria defined based on active case detection as well as clinic visits, confirmed by microscopic evaluation	10 mg zinc as gluconate	6–60	136	138	Community-based	✓	—	✓
Peru (Penny et al. 1999)	Daily supplementation for 26 weeks	10 mg zinc as gluconate	6–35	80	79	Recovered from persistent diarrhoea	✓	✓	—
Viet Nam (Ninh et al. 1996)	Daily supplementation for 22 weeks	10 mg zinc as sulfate	4–36	73	73	Weight-for-age and height-for-age <–2 SD	✓	✓	—

✓ Measured.
— Not measured.

malaria. In addition, there are numerous RCTs in which zinc supplements are evaluated as therapeutic agents (Zinc Investigators' Collaborative Group 2000), but these are not included. In all, nine studies contributed findings on zinc deficiency and risk of diarrhoea (Meeks-Gardner et al. 1998; Müller et al. 2001; Ninh et al. 1996; Penny et al. 1999; Rosado et al. 1997; Ruel et al. 1997; Sazawal et al. 1997; Shankar et al. 1997; Umeta et al. 2000), five contributed findings on risk of pneumonia (Bhandari et al. 2002; Meeks-Gardner et al. 1998; Ninh et al. 1996; Ruel et al. 1997; Sazawal et al. 1998), and three contributed findings on risk of malaria (Bates et al. 1993; Müller et al. 2001; Shankar et al. 2000).

The data required for this work are the risk of each health outcome associated with zinc deficiency. This was calculated as the inverse of the odds ratio or relative risk estimated from RCTs given two assumptions: subjects in the study population have some level of zinc deficiency, and supplementation with zinc eliminated zinc deficiency. Because the first of these assumptions is likely to be generally but not universally true, and the second assumption is *not* likely to be true, we view our results as conservative.

4.3 Diarrhoea

The results of the nine RCTs with findings on zinc deficiency and diarrhoea incidence are presented in Table 5.3. The results are presented for each individual study as well as a pooled estimate of all nine studies. The pooled estimate was derived using random effects models as described

Table 5.3 Zinc deficiency and risk of diarrhoea incidence

	Zinc group		*Control group*		*Relative risk*
Country (reference)	*Episode*[a]	*Follow-up*[b]	*Episode*[a]	*Follow-up*[b]	*(95% CI)*
Burkina Faso (Müller et al. 2001)	322	49126	374	47844	1.19 (1.03–1.39)
Ethiopia (Shankar et al. 1997)	27	16790	59	16790	2.22 (1.39–3.45)
Guatemala (Ruel et al. 1997)	387	8482	467	8361	1.22 (1.08–1.41)
India (Sazawal et al. 1997)	934	44866	1033	45555	1.09 (1.00–1.31)
Jamaica (Meeks-Gardner et al. 1998)	39	2604	37	2265	1.09 (0.69–1.72)
Mexico (Rosado et al. 1997)	82	42322	132	42751	1.59 (1.20–2.13)
Papua New Guinea (Umeta et al. 2000)	63	27490	77	29465	1.14 (0.82–1.59)
Peru (Penny et al. 1999)	564	13178	661	13648	1.14 (1.01–1.27)
Viet Nam (Ninh et al. 1996)	56	11242	100	11242	1.79 (1.28–2.50)
All					1.28 (1.10–1.49)

[a] Episode refers to an episode of diarrhoea as per the case definition in the individual study.

[b] Follow-up refers to the total number of child-days of follow-up or disease surveillance in each study.

in a previous pooled analysis (Zinc Investigators' Collaborative Group 1999). Although each study reported the effects of zinc supplementation on the incidence of diarrhoeal illness, we have presented estimates of the relative risk of diarrhoeal disease incidence due to zinc deficiency. As shown, the pooled estimate indicates that the relative risk of diarrhoea in young children due to zinc deficiency is 1.28 (95% CI 1.10–1.49).

In 1999, a pooled analysis was conducted of published RCTs of zinc supplementation to reduce diarrhoea and pneumonia morbidity in young children (Zinc Investigators' Collaborative Group 1999); at that time, seven of these studies had been published (Meeks-Gardner et al. 1998; Ninh et al. 1996; Penny et al. 1999; Rosado et al. 1997; Ruel et al. 1997; Sazawal et al. 1997; Umeta et al. 2000). The pooled estimate based on these studies indicated that zinc deficiency increases the risk of diarrhoea in young children by 1.33 (95% CI 1.14–1.59).

4.4 Pneumonia

The results of the five RCTs with findings on zinc deficiency and pneumonia incidence are presented in Table 5.4. The results are presented for each individual study as well as a pooled estimate across all five studies. As shown, it is estimated that zinc deficiency increased the risk of pneumonia in young children by 1.52 (95% CI 1.20–1.89).

With the exception of the study by Bhandari et al. (2002), the studies had been included in a published pooled analysis of the effects of zinc supplementation on pneumonia (Zinc Investigators' Collaborative Group 1999). The summary estimate from that analysis was of similar magnitude: the relative risk of pneumonia due to zinc deficiency in young children was 1.69 (95% CI 1.20–2.45).

Table 5.4 Zinc deficiency and risk of pneumonia incidence

	Zinc group		*Control group*		*Relative risk*
Country (reference)	*Episode*[a]	*Follow-up*[b]	*Episode*[a]	*Follow-up*[b]	*(95% CI)*
India (Bhandari et al. 2002)	88	132 000	118	134 400	1.32 (1.01–1.72)
India (Sazawal et al. 1998)	24	44 866	43	45 555	1.76 (1.08–2.94)
Jamaica (Meeks-Gardner 1998)	0	2 604	1	2 265	3.13 (0.16–100.0)
Peru (Penny et al. 1999)	9	13 178	11	13 648	1.22 (0.51–2.86)
Viet Nam (Ninh et al. 1996)	45	11 242	81	11 242	1.79 (1.25–2.56)
All					1.52 (1.20–1.89)

[a] Episode refers to an episode of pneumonia as per the case definition in the individual study.

[b] Follow-up refers to the total number of child-days of follow-up or disease surveillance in each study.

4.5 Malaria

Three RCTs of zinc supplementation to prevent malaria morbidity were identified. In Papua New Guinea, Shankar et al. (2000) found a 38% (95% CI 3–60%) reduction in malarial attacks based on clinic visits for malaria or fever with confirmed parasitaemia above a predefined threshold. Using an analogous definition, Bates et al. (1993) also found an approximately one-third reduction in malarial attacks, but it was not statistically significant ($P = 0.09$), and the authors concluded there was no effect of zinc deficiency on malarial attack rates. However, Shankar et al. (2000) obtained the original data from the study (Bates et al. 1993) and utilized random effects models to derive a pooled estimate of a 36% (95% CI 9–55%) reduction in clinic-based malarial attacks with parasitaemia with zinc supplementation. The paper by Müller et al. (2001) utilized a different methodology to detect malarial illness—community-based daily surveillance—and thus, examined a different aspect of malarial illness. They found no significant reduction in malarial incidence by treatment, with a zinc treatment odds ratio of 0.98 (95% CI 0.86–1.11). Studies with community-based malaria surveillance largely detect associations with early manifestations of a malaria episode, and on episodes tending to be less severe, whereas studies focusing on clinical malaria episodes detect effects on the progression of a malaria episode, and on cases perceived to be severe enough to warrant a visit to the health centre (Cox et al. 1994). Because of the heterogeneity of outcomes studied, and our desire to focus on malarial morbidity that contributes to the global disease burden estimates (Snow et al. 1999), we excluded the study by Müller et al. (2001) from further analysis. Instead we used Shankar's pooled analysis to derive a relative risk for malaria morbidity associated with zinc deficiency in young children of 1.56 (95% CI 1.29–1.89).

4.6 Mortality

Clearly, zinc deficiency contributes to increased risk of incidence for important childhood diseases that are predominant causes of death among children. Direct estimation of the risk of cause-specific mortality among children due to zinc deficiency is not available from the literature. Unless there were an expectation that zinc deficiency reduced case-fatality or severity of these diseases, the risk of mortality due to zinc deficiency should be at least equivalent to the risk of disease occurrence due to zinc deficiency. For this reason, we have proposed that the relative risk of mortality related to diarrhoea, pneumonia and malaria associated with zinc deficiency, are 1.28, 1.52 and 1.56, respectively (Table 5.5). These might well be conservative estimates, given the high likelihood that zinc deficiency increases the risk of severity and death during illness with diarrhoea or pneumonia (Zinc Investigators' Collaborative Group 1999, 2000). There are three pieces of direct evidence that zinc deficiency increases mortality in young children. First, Indian infants

Table 5.5 Estimated effect of zinc deficiency on morbidity and mortality due to diarrhoea, pneumonia and malaria in children aged 0–4 years

	Morbidity	*Mortality*
Illness	*Relative risk (95% CI)*	*Relative risk (95% CI)*
Diarrhoea	1.28 (1.10–1.49)	1.28 (1.10–1.49)
Pneumonia	1.52 (1.20–1.89)	1.52 (1.20–1.89)
Malaria	1.56 (1.29–1.89)	1.56 (1.29–1.89)

born small for gestation who received zinc supplements six days a week were 0.32 (95% CI 0.12–0.89) less likely to die during infancy than those receiving the control supplement (Sazawal et al. 2001). Second, Bangladeshi children who received supplements of 20 mg/d zinc as adjuvant to oral rehydration solution (ORS) during diarrhoea, were half as likely to die than those receiving ORS alone (Baqui et al. unpublished data). Third, zinc supplementation was associated with a marginally significant reduction in all-cause mortality (5 deaths vs 12 deaths, $P = 0.10$) in the study by Müller et al. (2001). With respect to malarial deaths, it should be reiterated that the reduction in malaria attacks attributable to zinc supplementation was based on clinic attack rates, that is, more severe malaria morbidity rather than less severe illness that would be detected through community-based surveillance, as conducted in the study by Müller et al. (2001). Finally, it should be noted that infections themselves cause secondary zinc deficiency because zinc is sequestered by the liver as part of the acute phase response and is thus less available for many cellular functions (Keen et al. 1993). This point provides additional rationale as to why zinc deficiency may be more strongly related to deaths than to illness incidence. This may also partially explain findings that zinc supplementation reduces the duration of diarrhoeal episodes in prospective trials, as well as in trials in which zinc supplements are provided therapeutically (Zinc Investigators' Collaborative Group 1999, 2000).

4.7 Disease causation mechanisms

The results of this body of research do not define the explicit biological mechanisms through which zinc deficiency increases disease risk in young children. There is no doubt, however, that zinc is a critical nutrient for cell replication and function and thus, critical for normal functioning of all body systems. The first system known to be compromised with even mild deficiencies of zinc is the immune system, reflecting the profound and ubiquitous role zinc plays in immune function. As recently reviewed by Shankar and Prasad (1998), zinc deficiency impairs multiple aspects of immune function, including barrier and non-specific immunity, spe-

cific immune components (lymphyocytes, monocytes and macrophages, neutrophils, natural killer cells), and mediators of immune function such as glucocorticoid and thymulin activity, and cytokine function. Given the multiple roles of zinc in the immune function, it is not surprising that zinc deficiency should confer increased risk of morbidity and mortality due to infectious diseases.

Zinc deficiency also results in reduced growth rates in animals, and there is ample evidence from RCTs that the provision of supplemental zinc to young children can reduce growth faltering in preschool-aged children. Recently, Brown et al. (1998a) published a meta-analysis of more than 52 RCTs investigating the effect of supplemental zinc on anthropometric status or growth in children. The results of their analysis indicate that improvements in zinc intakes achieved with supplemental zinc (at dosages similar to those reported here) improve the weight-for-age and height-for-age *z*-scores by 0.26 SD and 0.22 SD, respectively. It is heuristic to conclude that some of the improved growth is due to zinc-related effects which reduce morbidity incidence and duration/severity.

5. Burden of disease estimates

The estimated deaths and DALYs attributable to zinc deficiency are shown in Tables 5.6–5.7. When examined by region, the burden of zinc

Table 5.6 Deaths in children aged 0–4 years from zinc deficiency, by subregion

	Deaths (000s)		
Subregion	*Diarrhoea*	*Pneumonia*	*Malaria*
AFR-D	17	50	74
AFR-E	47	91	107
AMR-A	0	0	0
AMR-B	2	3	0
AMR-D	3	6	0
EMR-B	1	2	0
EMR-D	31	48	10
EUR-A	0	0	0
EUR-B	1	3	0
EUR-C	0	0	0
SEAR-B	2	6	0
SEAR-D	70	187	16
WPR-A	0	0	0
WPR-B	2	10	0
World	176	406	207

Table 5.7 Disease burden attributable to zinc deficiency, by subregion

	DALYs (000s)		
Subregion	*Diarrhoea*	*Pneumonia*	*Malaria*
AFR-D	604	1705	2729
AFR-E	1631	3105	3978
AMR-A	1	1	0
AMR-B	69	143	2
AMR-D	109	202	2
EMR-B	36	93	1
EMR-D	1071	1679	371
EUR-A	0	0	0
EUR-B	19	102	0
EUR-C	1	7	0
SEAR-B	84	244	21
SEAR-D	2456	6579	560
WPR-A	0	0	0
WPR-B	61	361	5
World	6142	14223	7669

deficiency and its consequences are borne most heavily by Africa, the Eastern Mediterranean and South-East Asia. This is true for both diarrhoea and pneumonia. The burden of malarial disease attributable to zinc deficiency is borne almost exclusively by those in the African Region.

6. Discussion

We estimated that zinc deficiency in children aged <5 years caused 176000 diarrhoea deaths, 406000 pneumonia deaths, and 207000 malaria deaths. The associated DALYs attributable to zinc deficiency were more than 28 million. This was because the risks of morbidity and mortality associated with zinc deficiency are relatively high, and because available data suggest that zinc deficiency—as defined by inadequate dietary zinc—is highly prevalent in many parts of the world, and particularly in parts of the world where the majority of deaths due to diarrhoea, pneumonia and malaria occur. This places zinc deficiency as a key factor conferring risk of morbidity and mortality to young children, one that is ostensibly preventable through public health action.

The evidence that zinc deficiency increases incidence risk is strong because it results from RCTs conducted in areas of the world with limited zinc available in the diet and where pneumonia, diarrhoea and malaria are public health problems. The risk estimates for diarrhoea and

pneumonia are particularly strong, based on results from nine and five RCTs, respectively. The estimated increased risk for malaria is less well studied. Our risk estimate was based on two RCTs with similar risk estimates in which clinic attack rates were the outcome of interest. We excluded the only other published RCT in which the effect of supplemental zinc on less severe malaria morbidity (detected through community surveillance) was studied and in which no increased risk of malaria was found. Clearly more research on the relation between zinc deficiency and malaria is needed to substantiate the risk estimates provided here.

The use of experimental designs has allowed for the characterization of the consequences of zinc deficiency, yet much work needs to be done in order to describe the magnitude and distribution of zinc deficiency throughout the world. This is an important task because the placement of zinc deficiency as a major contributor to the global burden of disease rests in its ubiquitous presence throughout the world. The approach used to characterize zinc deficiency was to estimate the proportion of the population living in areas with inadequate zinc in their food supply as determined from food balance sheet data compiled by FAO. This is far from the traditional approach of characterizing nutrient deficiencies using biochemical indicators. As stated earlier, however, there is no clear choice of biochemical indicator for zinc status, and the information available on zinc status based on plasma zinc concentration (the most commonly cited indicator of zinc status) would be limited to restricted samples of study participants conducted in selected regions of the world. To our knowledge, there are few if any national nutrition surveys utilizing biochemical indicators of zinc status and few laboratories capable of conducting trace mineral assays in developing countries due to the difficulties in eliminating contamination.

The advantage of the approach developed by IZiNCG is that a common methodology could be applied across similarly collected data from 172 countries, representing all 14 subregions. Further, because zinc is stored in the body in only limited amounts, and because certain key features of the diet (total energy content, animal protein availability, fibre/phytate content associated with the principal grain) largely determine the bioavailability of the zinc present in the food supply, the adequacy of dietary zinc intakes is an appropriate indicator to approximate the prevalence of zinc deficiency. There are multiple uncertainties inherent in this approach, and key assumptions include the following: (i) that per capita food availability data relates to actual dietary intake and ultimately to zinc status; (ii) that foods not included in the data (e.g. foraged foods) are not rich sources of zinc; (iii) that our knowledge of the composition of foods with respect to zinc, calcium, fibre and phytate is adequate for our purposes; (iv) that characterization of the bioavailability of zinc is correct; and (v) that we have the appropriate zinc requirement distribution and cut-point for defining adequacy of

intake. It is only through further research that we can determine the validity of the assumptions made, and judge the certainty with which we have characterized the prevalences of zinc deficiency in young children.

There are reasons to believe that the estimates presented here are conservative. First, food availability is usually greater than food intake. This effect, however, may be countered by underestimation of intake in the FAO data which do not always account for subsistence production. Second, the groups for which these numbers are likely to be most conservative are women of reproductive age and small children who may be particularly disadvantaged in terms of obtaining the best sources of zinc (animal products) in their diet. Third, dietary intake surveys, which more directly estimate the prevalence of inadequate intakes in populations, typically have estimated higher prevalences of inadequate zinc intakes than those depicted here (Parr 1992, 1996). On the other hand, because breastfeeding is an adequate source of zinc in the diets of infants aged less than six months, the same age when a large proportion of childhood mortality is concentrated, applying the risks to all children aged 0–4 years may result in substantial overestimation of disease burden in some populations.

It is also important to note that maternal or gestational zinc deficiency may affect immunological development in the newborn in ways that compromise immune function throughout the lifespan irrespective of zinc status (Caulfield et al. 1998; Shankar and Prasad 1998). Although this is well demonstrated in certain animal models, it has not been well characterized in humans, but a recent study by Osendarp et al. (2001) provides intriguing evidence of potential long-term effects on infant health in the first year of life due to maternal prenatal zinc deficiency. Fetal accumulation of zinc is a function of maternal zinc status, and therefore, newborn zinc deficiency (assessed as low serum zinc concentration) is likely among women with inadequate dietary zinc intakes during pregnancy (Caulfield et al. 1999). This deficiency is likely transitory for all but the most vulnerable (preterm or low-birth-weight infants) because the zinc content of colostrum is high and some zinc becomes available to the infant as part of the haematological changes accompanying the transition to extrauterine life (WHO 1996). Beginning at around six months of age, however, breast milk intake no longer provides sufficient zinc to meet requirements (Krebs 2000), making zinc-rich complementary foods necessary (Brown et al. 1998b). If zinc-rich sources are not available on a routine basis, zinc deficiency develops over time and persists until changes in the diet are made. Thus, it must be recognized that removal of the global burden of disease due to zinc deficiency will likely require improvements in child *and* maternal zinc intakes. In this chapter, we have considered only the burden of disease for children aged 0–4 years since no available evidence on the role of zinc in morbidity and mortality among other age groups was available. Thus, it may

be true that zinc deficiency contributes greatly to death and disability among other age groups. Defining these risk relations should be a priority area for future research.

Because low weight-for-age (usually described as underweight) also increases risk of morbidity and mortality from diarrhoea, pneumonia and malaria (see chapter 2), there is overlap between zinc deficiency and underweight as risk factors for morbidity and mortality from these causes in young children. The degree of overlap cannot be quantified empirically, but evidence from studies can provide insight in this issue. In the meta-analysis of zinc RCTs (Zinc Investigators' Collaborative Group 1999), the authors found that the effects of zinc supplementation on risk of diarrhoea and pneumonia across studies did not depend on the underlying level of malnutrition as characterized by the average *z*-score in the study subjects. However, the study by Umeta et al. (2000) did find greater reductions in morbidity in stunted as opposed to non-stunted children. Zinc supplementation has reduced morbidity with no detectable changes in growth rates (Meeks-Gardner et al. 1998). Overall, limited evidence shows that the efficacy of zinc supplementation for reducing morbidity is more substantial than for reducing growth faltering in studies in which both outcomes have been characterized. There are also studies in the literature in which improvements in immune function have been observed with zinc supplementation in well-nourished subjects (e.g. those with adequate weight); thus, although most of the research on the benefits to health from zinc supplements has been conducted in populations similarly characterized by underweight or stunting, the potential reductions in the global burden of disease due to zinc deficiency should not be limited to those who are also underweight or stunted. In the case of malaria, Shankar (2000) describes how zinc deficiency exerts fairly specific effects on malaria morbidity (increasing febrile illness accompanied by hyperparasitaemia), whereas low anthropometric status appears to exert more generalized effects. With these considerations, we conclude that although zinc deficiency and underweight co-exist in many populations, and both are risk factors for the disease outcomes described here, the majority of the disease burden attributable to zinc deficiency is not restricted to children who are generally malnourished.

In summary, the available evidence suggests that zinc deficiency contributes substantially to death and disability throughout the world, and particularly in Africa, the Eastern Mediterranean, and South-East Asia. Because epidemiological evidence is limited to studies conducted among preschool children and this analysis considers only three causes of death and disability, it is clear that further research on the role of zinc in morbidity, mortality and disability due to other causes and in other age groups is urgently needed. Further research is needed to identify indicators of exposure to zinc deficiency as well as effective strategies to reduce zinc deficiency and its consequences.

7. Projections of exposure

Currently, there are no programmes or policy initiatives in place to specifically improve the zinc intakes of human populations. This is true with respect to improving the zinc supply in foods (e.g. interventions to improve intakes of animal products which are good sources of zinc or to reduce phytates in foods which impair zinc absorption). Further, there are no examples of programmes utilizing supplemental zinc to improve zinc status, although some are beginning to use supplemental zinc as adjuvant therapy during diarrhoeal illness, based on research demonstrating the efficacy of zinc in shortening the duration of the current episode and prolonging the time until the next episode in paediatric populations with heavy disease burden. Because of the general lack of policy or programmatic initiatives to address zinc deficiency, we project that the magnitude and distribution of zinc deficiency will remain the same for the years 2010 and 2020, as presented here.

Acknowledgements

We are grateful for the support of Kenneth H. Brown in providing us with the data on the prevalence of inadequate zinc intakes in 172 countries; Sunil Sazawal for updating the pooled analyses of zinc and risk of diarrhoea and pneumonia, and Anuraj H. Shankar for conducting the pooled analysis of zinc and malaria and for his insights into the various dimensions of malarial morbidity.

This manuscript was supported in part by the Family Health and Child Survival (FHACS) Cooperative Agreement between the United States Agency for International Development, Office of Health and Nutrition, the Johns Hopkins Bloomberg School of Public Health, Department of International Health, and by the World Health Organization.

Note

1 See preface for an explanation of this term.

References

Bates CJ, Evans PH, Dardenne M et al. (1993) A trial of zinc-supplementation in young rural Gambian children. *British Journal of Nutrition*, **69**:243–255.

Bhandari N, Bahl R, Taneja S et al. (2002) Routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. *British Medical Journal*, **324**:1358.

Brown KH, Dewey KG, Allen LH (1998a) *Complementary feeding of young children in developing countries: a review of current scientific knowledge*. World Health Organization, Geneva.

Brown KH, Peerson JM, Allen LH (1998b) Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. In: Role of trace elements for health promotion and disease prevention. Sandstrom B, Walter P, eds. *Bibliotheca Nutritio et Dieta*, **54**:76–83.

Brown KH, Wuehler SE, Peerson JM (2001) The importance of zinc in human nutrition and estimation of the global prevalence of zinc deficiency. *Food and Nutrition Bulletin*, **22**:113–125.

Caulfield LE, Zavaleta N, Figueroa A (1999) Adding zinc to prenatal iron and folate supplements improves maternal and neonatal zinc status in a Peruvian population. *American Journal of Clinical Nutrition*, **69**:1257–1263.

Caulfield LE, Zavaleta N, Shankar A, Merialdi M (1998) Potential contribution of maternal zinc supplementation during pregnancy for maternal and child survival. *American Journal of Clinical Nutrition*, **68**:S499–508.

Cox MJ, Kum DE, Tavul L et al. (1994) Dynamics of malaria parasitaemia associated with febrile illness in children from a rural village of Madang, Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **88**:191–197.

FAO (1999) *FAO food balance sheets: food balance sheet country averages 1990–1997*. Food and Agriculture Organization. Available at http://apps.fao.org/lim500/nph-wrap.pl.

Gibson RS (1994) Zinc nutrition in developing countries. *Nutrition Research Reviews*, **7**:151–173.

Hambridge KM (2000) Human zinc deficiency. *Journal of Nutrition*, **130**:S1344–1349.

IZiNCG (forthcoming) *Assessment of zinc status in populations and options for the control of zinc deficiency*. (IZiNCG Technical Document No. 1). International Zinc Nutrition Consultative Group (IZiNCG). UNU/IUNS, Cornell University, Ithaca, NY.

Keen CL, Taubeneck MV, Daston GP, Rogers JM, Gershwin E (1993) Primary and secondary zinc deficiency as factor underlying abnormal CNS development. *Annals of the New York Academy of Sciences*, **678**:37–47.

Krebs N (2000) Dietary zinc and iron sources, physical growth and cognitive development of breastfed infants. *Journal of Nutrition*, **130**:S358–360.

Meeks-Gardner J, Witter M, Ramdath D (1998) Zinc supplementation effects on the growth and morbidity of undernourished Jamaican children. *European Journal of Clinical Nutrition*, **52**:34–39.

Müller O, Becher H, van Zweeden AB et al. (2001) Effect of zinc supplementation on malaria and other causes of morbidity in west African children: randomised double blind placebo controlled trial. *British Medical Journal*, **322**:1567–1573.

Ninh X, Thissen P, Collette L, Grard G, Khoi H, Keteislegers M (1996) Zinc supplementation increases growth and circulating insulin-like growth factor 1 (IGF-1) in growth retarded Vietnamese children. *American Journal of Clinical Nutrition*, **63**:514–518.

Osendarp SJ, van Raaij JM, Darmstadt GL, Baqui AH, Hautvast JG, Fuchs GJ (2001) Zinc supplementation during pregnancy and effects on growth and morbidity in low birthweight infants: a randomized placebo controlled trial. *The Lancet*, **357**:1080–1085.

Parr RM (1992) *Human dietary intakes of trace elements: a global literature survey mainly for the period 1970–1991: data listing and references*. International Atomic Energy Agency, IAEA-NAHRES, Vienna.

Parr RM (1996) Assessment of dietary intakes. In: *Trace elements in human nutrition and health*. World Health Organization, Geneva.

Penny M, Person M, Marin M et al. (1999) Randomized community-based trial of the effect of zinc supplementation, with or without other micronutrients, on the duration of persistent diarrhea in Lima, Peru. *Journal of Pediatrics*, **135**:208–217.

Prasad AS (1991) Discovery of human zinc deficiency and studies in an experimental human model. *American Journal of Clinical Nutrition*, **53**:403–412.

Rosado J, Lopez P, Monoz E, Martinez H, Allen LH (1997) Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. *American Journal of Clinical Nutrition*, **65**:13–19.

Ruel M, Rivera J, Santizo M, Lonnerdal B, Brown K (1997) The impact of zinc supplementation on morbidity from diarrhea and respiratory infections among young rural Guatemalan children. *Pediatrics*, **99**:808–813.

Sandstead HH (1991) Zinc deficiency. A public health problem? *American Journal of Diseases of Children*, **145**:853–859.

Sazawal S, Black R, Bhan M, Jalla S, Sinha A, Bhandari N (1997) Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea—a community-based, double-blind, controlled trial. *American Journal of Clinical Nutrition*, **66**:413–418.

Sazawal S, Black R, Jalla S, Mazumdar S, Sinha A, Bhan M (1998) Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children. A double-blind, controlled trial. *Pediatrics*, **102**:1–5.

Sazawal S, Black R, Monon VP et al. (2001) Zinc supplementation in infants born small for gestational age reduces mortality: a prospective randomized controlled trial. *Pediatrics*, **108**:1280–1286.

Shankar AH (2000) Nutritional modulation of malaria morbidity and mortality. *Journal of Infectious Diseases*, **182**:S37–53.

Shankar AH, Genton B, Baisor M et al. (2000) The influence of zinc supplementation on morbidity due to *Plasmodium falciparum*: a randomized trial in preschool children in Papua New Guinea. *American Journal of Tropical Medicine and Hygiene*, **62**:663–669.

Shankar AH, Genton B, Tamja S et al. (1997) Zinc supplementation can reduce malaria-related morbidity in preschool children. *American Journal of Tropical Medicine*, **57**:A434.

Shankar AH, Prasad AS (1998) Zinc and immune function: the biological basis of altered resistance to infection. *American Journal of Clinical Nutrition*, **68**:S430–434.

Snow RW, Craig M, Deichmann U, Marsh K (1999) Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bulletin of the World Health Organization*, 77:624–640.

Umeta M, West CE, Haider J, Deurenberg P, Hautvast JG (2000) Zinc supplementation and stunted infants in Ethiopia: a randomized controlled trial. *The Lancet*, **355**:2021–2026.

WHO (1996) Zinc. In: *Trace elements in human nutrition and health*. World Health Organization, Geneva.

WISTAT (1994) *Women's Indicators and Statistics Database of the United Nations*. (CD-ROM, Version 3.) United Nations. Available at http://www.un.org/Depts/unsd/gender/wistat/topiclist.htm.

Wood RJ (2000) Assessment of marginal zinc status in humans. *Journal of Nutrition*, **130**:S1350–1354.

World Food Dietary Assessment System (1997) (Computer program, Version 2.0.) University of California, Berkeley, CA.

Zinc Investigators' Collaborative Group (1999) Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *Journal of Pediatrics*, **135**:689–697.

Zinc Investigators' Collaborative Group (2000) Therapeutic effects of zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *American Journal of Clinical Nutrition*, **72**:1516–1522.

Chapter 6

High blood pressure

Carlene M.M. Lawes, Stephen Vander Hoorn, Malcolm R. Law, Paul Elliott, Stephen MacMahon and Anthony Rodgers

Summary

This chapter aims to estimate the burden of disease attributable to raised blood pressure in 2000, and the burden avoidable by distributional shifts of blood pressure. The key initial steps were to define the blood pressure variable, choose disease outcomes to be assessed, estimate current global blood pressure levels, choose a theoretical minimum and estimate risk factor–disease relationships.

Blood pressure was defined as systolic blood pressure (SBP) in mmHg. SBP was chosen principally because data are widely available for this index of blood pressure, and it appears to be at least as good a predictor of cardiovascular disease as other indices.

Based on consistent direct, continuous associations in cohort studies and evidence from randomized clinical trials, the outcomes assessed were stroke, ischaemic heart disease (IHD), hypertensive disease and other cardiac disease. Similar data suggested causal relationships with renal failure, but this could not be mapped to a Global Burden of Disease (GBD) study outcome.

Raw SBP data were obtained from studies after a systematic review of population-based surveys, and included data from about 230 surveys and over 650 000 participants. Sex-specific associations of SBP with age were estimated for each of the subregions[1] separately, based on population-weighted (by country) study estimates of mean values. There was moderate variation in the final age-specific and sex-specific estimates of mean blood pressure across the 14 subregions, with the range between the highest and lowest age-specific mean SBP levels across subregions typically being about 20 mmHg. Confidence intervals around mean SBP and standard deviations were calculated to reflect uncertainty. Trends in mean SBP over time were extrapolated from published epidemiological data.

The theoretical minimum of SBP was estimated to be mean 115 mmHg and standard deviation 6 mmHg (usual SBP), for all age, sex and subregional groups. The main basis for this estimate was the level of SBP down to which epidemiological relationships with cardiovascular disease outcomes are observed. This theoretical minimum is also consistent with the levels of SBP in populations with little or no cardiovascular disease. Furthermore, recent clinical trial data have indicated reductions in stroke after lowering blood pressure by about 10 mmHg SBP in those with mean SBP 125 mmHg.

Data on the risk factor–disease relationship were obtained from the Asia-Pacific Cohort Studies Collaboration (APCSC), an individual participant meta-analysis that combined data from 37 prospective observational cohorts involving over 425 000 individuals with 2–27 years of follow-up (mean 7 years), and in total over 3 million person-years of observation. Data from this meta-analysis were complemented by data from other overviews and large cohort studies. The main findings were direct, positive and continuous associations of usual SBP with the risks of all end-points of interest. The risks were similar by sex and subregion, except there was possibly a stronger association of blood pressure with stroke in Asian compared to non-Asian populations, due partly to the higher proportion of haemorrhagic strokes. Overall, each 10 mmHg below-usual SBP was associated with 38% (95% CI 37–39%) lower stroke risk and a 26% (95% CI 24–29%) lower risk of IHD. Each 10 mmHg below-usual SBP was associated with 46% (95% CI 40–51%) and 18% (95% CI 15–20%) lower risks of hypertensive disease and other cardiac disease. Few data were available for the GBD end-point "other cardiac disease", so, given some uncertainty about causality and the varying composition for this end-point around the world, the relative risks were halved for this outcome. There was attenuation of proportional associations with age for all these outcomes.

Data on risk reversibility came from meta-analyses of randomized controlled trials of blood pressure lowering. In total 23 trials were reviewed, which included over 71 000 participants allocated a variety of blood-pressure-lowering agents or placebo. The mean overall SBP reduction was 10 mmHg, and a total of 2632 strokes and 3693 IHD events were observed. Overall the trials confirmed the size of the reductions expected from epidemiological relationships in middle age. However, the reductions in risk in old age were larger than expected from the cohort study data.

We used the observational epidemiological data for relative risk estimates and the trial overviews for the time frame of risk reversibility. For example, in middle age the epidemiology suggests a 10 mmHg increase in SBP is associated with about 40% more stroke and 25% more IHD. The trials suggested that within 3–5 years of lowering SBP by 10 mmHg, most or all of this increased risk for stroke and hypertensive disease and

approximately two thirds for IHD and other cardiovascular disease are reversed.

The foregoing methods and assumptions allowed estimates of burden attributable to mean SBP levels of more than 115 mmHg. The analysis showed that:

- forty-nine per cent of IHD is attributable to SBP >115 mmHg worldwide (range of 40–64% by subregion), which translates into 2 991 000 deaths and 28.2 million disability-adjusted life years (DALYs) in the year 2000;
- sixty-two per cent of stroke is attributable to SBP >115 mmHg worldwide (range of 52–78% by subregion), which translates into 3 149 000 deaths and 27.8 million DALYs in the year 2000;
- seventy-six per cent of hypertensive disease is attributable to SBP >115 mmHg worldwide (range of 64–90% by subregion), which translates into 663 000 deaths and 5.4 million DALYs in the year 2000; and
- fourteen per cent of other cardiovascular disease is attributable to SBP >115 mmHg worldwide (range of 8–22% by subregion), which translates into 338 000 deaths and 2.8 million DALYs in the year 2000.

Worldwide, 7.1 million deaths (about 12.8% of the total) and 64.3 million DALYs (4.4% of the total) were estimated to be due to non-optimal blood pressure. The proportion of DALYs was lower than the proportion of deaths as most blood pressure-related cardiovascular disease events occurred in middle or old age, so the years of life lost due to premature mortality and years of life lost due to disability is a smaller percentage of the total DALYs than of the total deaths. Overall, the results suggest that a considerable proportion of cardiovascular disease is related to non-optimal blood pressure, and this translates into an important portion of deaths and years of life lost to deaths and disability worldwide. Approximately one third of the blood pressure-related attributable burden occurred in developed subregions, one third in lower mortality developing subregions (AMR-B, EMR-B, EUR-B, EUR-C, SEAR-B, WPR-B) and a further third in high mortality developing subregions (AFR-D, AFR-E, AMR-D, EMR-D, SEAR-D).

The estimates of burden attributable to non-optimal blood pressure are approximately double those from the World Health Organization (WHO) GBD study in 1990. However, the 1990 estimates did not correct for regression dilution bias, which means there was underestimation of risk of cardiovascular disease by a factor of about two. This therefore explains the almost doubling of burden attributable to blood pressure in current estimates.

1. Introduction

1.1 Defining the blood pressure variable

Blood pressure is a measure of the force that the circulating blood exerts on the walls of the main arteries. The pressure wave transmitted along the arteries with each heartbeat is easily felt as the pulse—the highest (systolic) pressure is created by the heart contracting and the lowest (diastolic) pressure is measured as the heart fills.

Blood pressure is described as a continuous variable as it is commonly reported in this manner, with mean and standard deviation values. Relative risk values for the risk factor–disease relationship are also available for this format. The standard unit for measuring blood pressure is mmHg, which may be applied to SBP, diastolic blood pressure (DBP), or alternative measurements such as mean arterial pressure and pulse pressure (PP).

Historically, many classification systems and treatment recommendations placed more emphasis on DBP, as elevated DBP was thought to confer greater risk for cardiovascular disease than elevated SBP (Kannel 1999, 2000; Lloyd-Jones et al. 1999). There is, however, now evidence for a paradigm shift to consider SBP as well as DBP (Black 1999b). Both the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) (Anonymous 1997) in 1997 and the 1999 guidelines from the WHO-International Society of Hypertension (WHO/ISH) (Anonymous 1999) now agree that both SBP and DBP should be used to classify hypertension (Black 1999a).

Prospective observational studies have provided data on whether, over the long term, there appears to be an association between blood pressure and disease end-points. Therefore, comparisons of the strength of associations for both DBP and SBP may be made. Data published from the Framingham study over the past 30 years have suggested that cardiovascular consequences do not necessarily derive principally from DBP (Kannel et al. 1969). While DBP may be a better predictor of cardiovascular disease in those aged <45 years, SBP is a better predictor of stroke and cardiovascular disease in those aged >60 years (Kannel et al. 1970, 1971). Overall, the risk of cardiovascular events was greater in the presence of isolated systolic hypertension than diastolic hypertension. For each standard deviation increase in mean SBP, the cardiovascular disease risk increased by 40–50%, whereas for DBP the increment was 30–35%. (This persisted after adjusting for age, and occurred in both men and women.) Combined systolic and diastolic hypertension carried only marginally greater risk than isolated systolic hypertension (Kannel 1996).

Other prospective studies corroborate these results with evidence that, in both sexes, the overall association between blood pressure and cardiovascular end-points is stronger for SBP than DBP (Franklin et al.

1999, 2001; Lichtenstein et al. 1985; Miall 1982; Mitchell et al. 1997; Miura et al. 2001; Sesso et al. 2000; Stamler et al. 1993). Within each level of DBP, a higher SBP was related to increased risk of IHD in a continuous and graded fashion. There was also an increase in risk with higher DBP within each SBP level, but in this latter scenario, the increases were not as steep or consistent (Stamler et al. 1993). Subjects who subsequently died from IHD were better identified by their SBP than by their DBP. Overall, SBP was a better predictor of outcome (Lichtenstein et al. 1985).

There are some data to suggest that PP (the difference between SBP and DBP) is a good predictor of cardiovascular risk (Abernethy et al. 1986; Black 1999b; Domanski et al. 1999; Frohlich 2000). However, it has not been consistently shown to be superior to SBP (Abernethy et al. 1986; Franklin 1999; Franklin et al. 1999, 2001; Sesso et al. 2000), and it was not a better predictor than SBP in the Asia-Pacific Cohort Studies Collaboration overview (APCSC 2003b); further, estimates of relative risk are available for SBP rather than PP. SBP was therefore used in preference to PP for the purposes of these analyses.

1.2 Disease outcomes

There are a number of potential disease outcomes associated with blood pressure. Blood pressure is generally accepted to have a role in accelerating atherosclerosis of the blood vessels and thereby influencing cardiovascular disease. Atherosclerosis is believed to start with "fatty streaks" on the intimal surface of blood vessels. Over time the intima is invaded by "foam cells" (lipid-laden macrophages) and plaques develop (Warlow et al. 1996). These plaques may be complicated by platelet adhesion, activation and aggregation, and formation of a thrombus. Many ischaemic cardiovascular disease events are due to "atherothromboembolism", where a fibrous plaque may obstruct blood vessel lumen resulting in infarction, or the thrombotic component of the plaque may break down and embolize (Warlow et al. 1996). It is proposed that haemorrhagic events (e.g. strokes) are due to degenerative atherosclerotic changes in blood vessels, which may cause formation of microaneurysms and fibroid necrosis, both of which may weaken the artery wall and lead to rupture (Leppala et al. 1999; MacKenzie 1996; Swales 1994; Warlow et al. 1996). Potential outcomes considered for blood pressure are as follows.

Stroke

Data from a variety of prospective cohort studies and overviews have demonstrated a strong, continuous temporal association between blood pressure and stroke (Anonymous 1998; APCSC 2003a; MacMahon and Rodgers 1993a; MacMahon et al. 1990; PSC 1995). Further, a causal association is biologically plausible and clinical trials have demonstrated reversibility (Collins et al. 1990; Neal and MacMahon 1999; Neal et al.

2000). More recent prospective studies have also assessed the association between blood pressure (BP) and stroke subtypes, such as haemorrhagic and ischaemic stroke. However, the GBD classification system for diseases and injuries has only one category for total stroke (end-point 108 G4 cerebrovascular disease, International Statistical Classification of Diseases, ninth revision [ICD-9] codes 430–438). Thus, it was not possible to analyse stroke subtypes individually in this work. Epidemiological studies show a positive association between blood pressure and fatal, non-fatal and total strokes, and total strokes were included in the analyses.

Ischaemic heart disease

As with stroke, a variety of prospective cohort studies and overviews have demonstrated a strong, continuous temporal association between blood pressure and IHD (APCSC 2003a; MacMahon and Rodgers 1993a; MacMahon et al. 1990); a causal association is biologically plausible and clinical trials have demonstrated reversibility (Collins et al. 1990; Neal and MacMahon 1999; Neal et al. 2000). The GBD classification system for diseases and injuries has a category for total IHD (end-point 107 G3 ischaemic heart disease, ICD-9 codes 410–414).

Renal disease

Cohort study data on mortality in association with hypertension do not often include renal disease as an end-point (Whelton and Klag 1989). However, the largest cohort to date, the Multiple Risk Factor Intervention Trial (MRFIT) study assessed the development of end-stage renal disease in men followed for 16 years. This study identified a strong, graded relation between both systolic and DBP and end-stage renal disease, independent of other disease associations (Klag et al. 1996). There were several limitations in this study, but many of these could potentially be addressed in analyses. Only baseline blood pressure measurements were taken, which would underestimate associations substantially, but correction factors could be applied. No women were included, but the proportional effect is the same in males and females for other disease associations, so it could be assumed to be consistent here. No information was available on anti-hypertensive agents, which could weaken the association, but would not negate it. The major limitation was that renal function was not assessed at baseline in all participants (Klag et al. 1996). This makes the issue of temporality difficult to establish, as renal disease could predispose to high blood pressure rather than the reverse.

Additional limited, but consistent, data about the relationship between blood pressure and renal failure are available from other prospective observational studies and hypertension treatment trials (MacMahon 1994; Whelton and Klag 1989). While this evidence is suggestive, it is not conclusive (Whelton and Klag 1989).

The above evidence is suggestive of an etiological role for blood pressure in the progression of renal failure. However, there is a further major consideration in choosing disease outcomes for this project. All disease outcomes must map to GBD end-points, and there is no end-point that is equivalent to renal failure. The "nephritis and nephrosis" category (end-point 121 J1, ICD-9 codes 580–589) includes a wide range of more diverse renal conditions. Therefore, apart from the more restricted "hypertensive renal disease" incorporated in the GBD end-point, hypertensive disease (below) analyses of renal failure could not be conducted.

Hypertensive disease

The GBD classification system end-point "hypertensive disease" (end-point 106 G2, ICD-9 codes 401–405) includes essential hypertension, hypertensive heart disease, hypertensive renal disease, hypertensive heart and renal disease and secondary hypertension. To some extent this is not an ideal disease outcome category. The evidence suggests continuous associations between blood pressure and disease end-points, so partitioning off those with hypertension is somewhat artificial as they are more likely to be part of a continuum rather than a distinct group. It would be preferable to have more specific disease categories that were not specifically labelled as "hypertensive". If any disease is selectively diagnosed in people with high blood pressure, the strong association with blood pressure becomes self-fulfilling. However, the choice of end-points for analyses is limited to those classified in the GBD classification system for diseases. As there are direct and positive associations with blood pressure and these outcomes, it is necessary to include this end-point, despite its shortcomings.

Other cardiovascular disease

The final end-point included in the GBD classification system associated with blood pressure is "other cardiac disease". This compromises a miscellany of cardiovascular conditions including heart failure, pulmonary heart disease, diseases of the pericardium and endocardium, conduction disorders, cardiac dysrhythmias, diseases of arteries, arterioles and capillaries, and diseases of veins and lymphatics. Numerically, one of the most important is likely to be heart failure. Data from the Framingham study suggest that for those with hypertension, the incidence of heart failure is increased sixfold relative to those who are not hypertensive (Stokes et al. 1989). The risk of congestive heart failure for highest : lowest blood pressure quintiles was two–three times (Kannel and Belanger 1991). This positive association was also apparent in analyses of data from the APCSC (APCSC secretariat, personal communication, 2001), and the risk of heart failure appears to rise continuously and steeply with increasing levels of blood pressure (Stokes et al. 1989). Clinical trials also suggest reversibility of heart failure with blood pressure lowering (Neal et al. 2000). Data from APCSC also indicate strong

positive associations with all cardiovascular deaths that are not due to stroke, IHD or hypertensive disease.

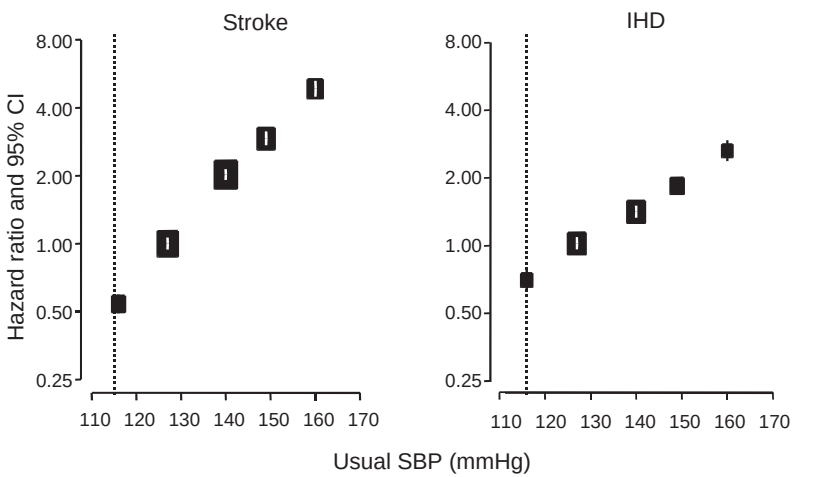
Ideally, the disease end-points would have more specific categories rather than this heterogeneous group. Unfortunately, available data do not allow for analyses by specific diagnostic category within this group. Due to the substantial number of deaths that were likely to be associated with blood pressure, it was not appropriate to drop this category altogether. Analyses, therefore, included this end-point, but as discussed later in this chapter, relative risk estimates were modified to take into account the varying composition and uncertainty of causality of all diseases within this "other cardiovascular disease" group.

1.3 Theoretical minimum

Lowest relative risk of end-points—observational studies

APCSC combined data from 37 prospective observational cohorts involving over 425 000 individuals with 2–27 years of follow-up (mean 7 years), and in total over 3 million person-years of observation (APCSC 1999). Analyses of the relationship between SBP and relative risk of cardiovascular disease in the Asia-Pacific region illustrate a continuous log linear relationship for both end-points. The lowest demonstrated relative risk for stroke and IHD occurred at approximately 115 mmHg (Figure 6.1), which suggests that this would be an appropriate level for a theoretical minimum.

Figure 6.1 Usual SBP and risk of stroke and IHD in the Asia-Pacific region



Source: APCSC data (APCSC, personal communication, 2001).

Recent data from blood-pressure-lowering trials

Recently available data from a large trial of blood pressure lowering (PROGRESS, involving 6105 participants with cerebrovascular disease) indicated benefits of blood pressure lowering even in the group with baseline SBP <140 mmHg (mean 125 mmHg) (Progress Collaborative Group 2001).

Low blood pressure populations

An alternative source of data relevant to setting a theoretical minimum comes from studies on populations with little or no cardiovascular disease, based on research since the 1930s and 1940s (Poulter and Sever 1994). These include populations that are relatively isolated and have preserved their lifestyle for many generations. In many of these populations there is no, or very low prevalence of cardiovascular disease, including studies of autopsy findings (Poulter and Sever 1994). A further feature common to these populations is low blood pressure, and no or limited increase in blood pressure with age. This pattern is consistent in isolated populations throughout the world (Table 6.1).

These studies do have limitations. In most studies, there was no discussion of how age was assessed in these remote populations; in some surveys, other criteria were used when age was unknown, such as physical appearance, number and age of children, personal knowledge of interpreters and calendars of local events such as initiation at puberty (Carvalho et al. 1989; Mann et al. 1964). Despite this, the data suggest that "low blood pressure" populations do exist (mean SBP ≤115 mmHg) where hypertension is absent or rare (Carvalho et al. 1989; He et al. 1991a, 1991b; Poulter and Sever 1994). Cardiovascular disease also tends to have a very low prevalence in these populations (Poulter and Sever 1994). Typically these populations have diets low in salt, cholesterol and fat (particularly animal fat), a lifestyle requiring heavy physical labour, and an absence of obesity (Barnes 1965; Carvalho et al. 1989; Connor et al. 1978; He et al. 1991a, 1991b; Page et al. 1974; Poulter and Sever 1994; Sever et al. 1980). Low salt intake appears to be particularly relevant to the blood pressure differences. There is also evidence from studies conducted in a variety of settings (Poulter and Sever 1994), such as Africa (Poulter et al. 1988, 1990), China (He et al. 1991a, 1991b) and the Pacific (Joseph et al. 1983; Salmond et al. 1985, 1989), that blood pressure levels rise after migration to more urbanized "acculturated" settings and the slope of the age–BP relationship increases. In addition to changes in blood pressure, body mass index and heart rate tend to increase (Poulter and Sever 1994). Pre-migration data suggest that these changes are not due to selective migration (Poulter et al. 1988). Instead, it is likely that factors such as dietary changes of increased intake of sodium, animal protein, fat and processed foods, and decreased intake of potassium and vegetable protein are important (He et al. 1991a, 1991b; Poulter and Sever 1994; Poulter et al. 1988).

Table 6.1 SBP levels in "low blood pressure" populations

Country or area (reference)	*Population*	*Mean SBP levels*	*Patterns with age*
Africa			
Tanganyika[a] (Mann et al. 1964)	Masai tribe (mostly men) with virtually no cardiovascular disease	120–125 mmHg SBP >160 mmHg rare	No age-related rise in BP
Southern Africa (Sever et al. 1980)	Tribal and urban Xhosa people	120–130 mmHg rural 130–140 mmHg urban	
Kenya (Carvalho et al. 1989)	Rural villagers in remote areas (INTERSALT study)	108–114 mmHg in males and females	
Americas			
Mexico (Connor et al. 1978)	Tarahumara Indians who lived in the mountains	105–110 mmHg	No age-related rise in BP
Brazil (Carvalho et al. 1989)	Yanamamo Indians of the Amazon rain forest and Xingu Indians (INTERSALT study)	90–105 mmHg	Virtually no increase in BP with age
Western Pacific			
China (He et al. 1991a, 1991b)	Rural Yi farmers in isolated areas	100–110 mmHg	BP does not tend to rise after puberty
Papua New Guinea (Barnes 1965)	The isolated Bomai and Yongamuggi people	105–110 mmHg for males and females	No age-related rise in BP
Papua New Guinea (Carvalho et al. 1989)	Rural villagers in remote areas (INTERSALT study)	105–110 mmHg	No age-related rise in BP
Solomon Islands (Page et al. 1974)	Six tribal societies with varying levels of acculturation	110–120 mmHg, lowest in least acculturated groups	No age-related rise in BP

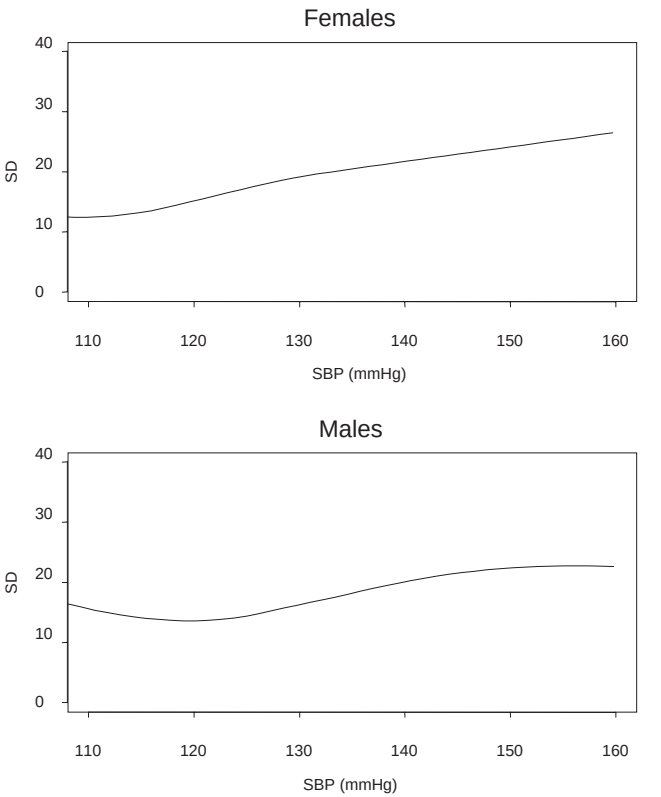
[a] Name of country correct at time of study.

Data from these studies indicate that populations do exist that have mean SBP levels of about 115 mmHg or even lower. The final decision on theoretical minimum, based on all the data, was that it would be set at 115 mmHg. This level correlated with data from cohort studies on the lowest level where accurate data are available on the association between SBP and cardiovascular disease.

Standard deviation around the theoretical minimum

The choice of standard deviation around the theoretical minimum was based on examining the relationship of the standard deviation and mean of SBP using all available data obtained from the review of blood pressure surveys discussed in the following section (Figure 6.2). From this illustration, a distribution with a mean of 115 mmHg would typically

Figure 6.2 Association between mean SBP and standard deviation



have a standard deviation of 12 mmHg (baseline) which, when correcting for regression dilution bias, would be equivalent to 6 mmHg "usual".

2. Risk factor exposure

2.1 Data on blood pressure levels

Data on global blood pressure levels were collated from three major sources. The first source was data from the MONICA (Anonymous 1989b) and INTERSALT (Anonymous 1989a) studies. These studies collected blood pressure data from a variety of world regions. The MONICA study involved surveys at 39 collaborating centres in 22 countries carried out between 1979 and 1987 (Anonymous 1989b). The INTERSALT study involved surveys at 52 collaborating centres in 32 countries carried out between 1985 and 1987 (Anonymous 1989a). These two studies provide important information about blood pressure patterns, but do not provide a truly global overview of blood pressure

distributions. The MONICA study included populations that were predominantly European in origin, neither study included populations from the Eastern Mediterranean Region, and there were limited data from South-East Asia (other than India) and Africa. It was therefore necessary to include additional blood pressure data for comparative risk assessment (CRA) analyses.

The second major source of data were obtained through a literature search using Medline and the key words "blood pressure", "hypertension", "survey", "health survey" and "cross sectional survey". Studies were reviewed and included in analyses if they fulfilled the following criteria:

- conducted from 1980 onwards;
- included randomly-selected or representative participants;
- included a sample size of over 1000 in developed countries (a smaller sample size was acceptable in other countries if other criteria were fulfilled);
- described sample size and age group of participants;
- presented mean values of blood pressure by age and sex; and
- utilized a standard protocol for blood pressure measurement.

The final sources of data were personal communications with researchers and study investigators. The authors had access to data from APCSC—a collaboration involving 37 cohorts in the Asia-Pacific region. This collaboration includes prospective cohort studies undertaken in the Asia-Pacific region with at least 5000 person-years of follow-up recorded or planned, and data on date of birth or age, sex and blood pressure have been collated (APCSC 1999). Blood pressure data from eligible studies that had been collected from 1980 onwards were included in the SBP database. Data were also available from a previous global review of blood pressure levels for the last round of GBD, and these data were also included where the above criteria were fulfilled (P. Elliott, personal communication, 2001). Finally, authors of surveys/studies were contacted and age-specific and sex-specific data requested, where they had not been published in this format.

Many studies have not published data in the format required for this project (e.g. age-specific and sex-specific mean SBP level), and unfortunately time and resource constraints limited attempts to obtain all of these data from researchers. It was also very difficult to obtain results of surveys that have, for example, been published only in local/national reports but not in peer-reviewed journals. Access to these data would have been greatly improved if these reports were more widely available in electronic format, such as on the Internet. Details of studies currently included are presented in Table 6.2.

Table 6.2 Studies currently included in blood pressure data review

Subregion	*Country or area*	*Study (reference)*	*Year published*	*Sample size*	*Age range (years)*
AFR-D	Gambia	van der Sande et al. (1997)	1997	6041	16–≥76
	Ghana	Nyarko et al. (1994)	1994	79	20–50
	Liberia	Giles et al. (1994)	1994	3588	20–≥55
	Mauritius	Nan et al. (1991)	1991	4905	25–74
	Nigeria	Akinkug (P. Elliot, personal communication, 2001)	1980–1994	1411	30–≥60
	Nigeria	Bunker et al. (1992)	1992	559	25–54
	Nigeria	Idahosa (1985)	1985	1450	15–≥70
	Nigeria	Idahosa (1987)	1983	1225	20–64
	Nigeria	Idahosa and Ilawole (1984)	1984	585	18–54
	Nigeria	Ogunlesi et al. (1991)	1991	404	18–54
	Nigeria	Okesina et al. (1999)	1999	500	11–≥50
	Nigeria	Oviasu and Okupa (1980a, 1980b)	1980	1263	30–≥60
	Senegal	Astagneau et al. (1992)	1992	2300	15–86
	Senegal	Lang et al. (1988)	1988	1862	15–≥54
	Seychelles	Bovet et al. (1991)	1991	1081	25–64
	Sierra Leone	Lisk et al. (1999)	1999	1204	15–≥75
				28457	
AFR-E	Democratic Republic of the Congo	M'Buyamba-Kabangu et al. (1986, 1987)	1987	987	10–60
	Ethiopia	Pauletto et al. (1994)	1994	4869	15–≥65
	Kenya	INTERSALT study (Anonymous 1989a)	1988	176	20–59
	Kenya	Poulter et al. (1984)	1984	1737	17–≥65
	Malawi	Simmons et al. (1986)	1983	988	15–65
	South Africa	CORIS study (P. Elliot, personal communication, 2001)	1980–1994	5260	30–≥60
	South Africa	Mollen (P. Elliot, personal communication, 2001)	1980–1984	1429	30–≥60
	South Africa	Morbid (P. Elliot, personal communication, 2001)	1980–1994	779	30–≥60
	South Africa	Seedat (P. Elliot, personal communication, 2001)	1980–1994	2800	30–≥60

continued

Table 6.2 Studies currently included in blood pressure data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Year published*	*Sample size*	*Age range (years)*
	South Africa	Seedat et al. (1982)	1982	1 982	<20–70
	South Africa	Steyn et al. (1985)	1985	976	15–64
	South Africa	Steyn et al. (1996)	1996	986	15–64
	United Republic of Tanzania	Edwards et al. (2000)	2000	1 695	15–≥55
	United Republic of Tanzania	Kitange et al. (1993)	1993	1 670	15–19
	United Republic of Tanzania	Swai et al. (1993)	1993	7 272	15–≥65
	Zimbabwe	Allain and Matenga (T. Allain, personal communication, 2001)	1997	270	60–≥80
	Zimbabwe	Hunter et al. (2000)	2000	515	15–≥45
	Zimbabwe	INTERSALT study (Anonymous 1989a)	1988	195	20–59
	Zimbabwe	Mufunda et al. (2000)	2000	775	25–≥55
				35 361	
AMR-A	Canada	Joffres et al. (1992)	1992	20 582	18–74
	Halifax	MONICA study (Anonymous 1989b)	1989	857	25–64
	Labrador	INTERSALT study (Anonymous 1989a)	1988	161	20–59
	St Johns	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	USA	Sprafka et al. (1990)	1990	4 641	25–74
	USA	Hutchinson et al. (1997)	1997	15 743	45–64
	USA NHANES	Burt et al. (1995); NHANES web site (NCHS 2002)	1995	13 037	18–74
	Chicago	INTERSALT study (Anonymous 1989a)	1988	196	20–59
	Goodman	INTERSALT study (Anonymous 1989a)	1988	186	20–59
	Goodman	INTERSALT study (Anonymous 1989a)	1988	198	20–59
	Hawaii	INTERSALT study (Anonymous 1989a)	1988	187	20–59
	Jackson	INTERSALT study (Anonymous 1989a)	1988	184	20–59
	Jackson	INTERSALT study (Anonymous 1989a)	1988	199	20–59
	Stanford	MONICA study (Anonymous 1989b)	1989	1 504	25–64
				57 875	

AMR-B	Argentina	Delena (P. Elliot, personal communication, 2001)	1980–1994	891	30–≥60
	Argentina	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Bahamas	Nassau (P. Elliot, personal communication, 2001)	1980–1994	1673	30–≥60
	Barbados	Foster et al. (1993)	1980–1993	464	30–≥60
	Barbados	Ischib (P. Elliot, personal communication, 2001)	1980–1994	694	30–≥60
	Belize	Simmons et al. (1983)	1983	1268	20–69
	Brazil	Costa et al. (1990); P. Elliot, personal communication, 2001	1990	2897	30–≥60
	Brazil	P. Elliot, personal communication, 2001; Ribeiro and Ribeiro (1986); Ribeiro et al. (1981)	1981–1986	3114	30–≥60
	Brazil	Fuchs et al. (2001); F. D. Fuchs, personal communication, 2001	2001	1174	18–≥60
	Xingu	INTERSALT study (Anonymous 1989a)	1988	198	20–59
	Yanomamo	INTERSALT study (Anonymous 1989a)	1988	195	20–59
	Chile	Barrios (P. Elliot, personal communication, 2001)	1980–1994	888	30–≥60
	Chile	L. Jadue, personal communication, 2001; Jadue et al. (1999)	1999	3113	25–64
	Colombia	INTERSALT study (Anonymous 1989a)	1988	191	20–59
	Jamaica	Miall (P. Elliot, personal communication, 2001)	1980–1994	1974	30–≥60
	Jamaica	R. Wilks et al. personal communication, 2001	1980 onwards	2085	25–74
	Mexico	Gonzalez-Villalpando et al. (1999); C. Gonzalez, personal communication, 2001	1999	2281	35–64
	Mexico	INTERSALT study (Anonymous 1989a)	1988	172	20–59
	Mexico	Rosenthal et al. (1989)	1989	645	19–25
	Mexico	L. Yamamoto, personal communication, 2001	1996	825	20–90
	Paraguay	Ramirez et al. (1995)	1995	9585	18–74
	Saint Lucia	Khaw and Rose (1982)	1982	359	15–≥65
	Trinidad and Tobago	INTERSALT study (Anonymous 1989a)	1988	176	20–59
	Trinidad and Tobago	Tobago (P. Elliot, personal communication, 2001)	1980–1994	1284	30–≥60
	Uruguay	Latir (P. Elliot, personal communication, 2001)	1980–1994	512	30–≥60
				36858	

continued

Table 6.2 Studies currently included in blood pressure data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Year published*	*Sample size*	*Age range (years)*
AMR-D	Ecuador	Cornejo et al. (2000)	2000	10605	19–≥98
				10605	
EMR-B	Iran (Islamic Republic of)	SarrafZadegan and AminiNik (1997)	1997	6532	19–70
	Jordan	H. Jaddou, personal communication, 2001	2000	2276	25–≥70
	Saudi Arabia	Khalid et al. (1994)	1994	1093	10–76
	Saudi Arabia	Soyannwo et al. (1998)	1998	5305	0–≥70
	Tunisia	Ghannem and Hadj-Fredj (1997); H. Ghannem, personal communication, 2001	1997	957	20–≥70
	Tunisia	Ghannem et al. (2001); H. Ghannem, personal communication, 2001	2001	1569	13–19
				17732	
EMR-D	Egypt	Ashour et al. (1995); Ibrahim et al. (1995)	1995	6600	25–≥70
				6600	
EUR-A	Belgium				
	Charleroi	INTERSALT study (Anonymous 1989a)	1988	157	20–59
	Charleroi	MONICA study (Anonymous 1989b)	1989	678	25–64
	Ghent	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Ghent	MONICA study (Anonymous 1989b)	1989	1021	25–64
	Belgium; Luxembourg	MONICA study (Anonymous 1989b)	1989	1934	25–64
	Former Czechoslovakia	Czech (P. Elliot, personal communication, 2001)	1980–1994	2345	30–≥60
	Denmark	Andersen et al. (1994)	1994	6009	17
	Denmark	INTERSALT study (Anonymous 1989a)	1988	199	20–59
	Glostrup	MONICA study (Anonymous 1989b)	1989	3785	25–64

Finland	FINNIII (P. Elliot, personal communication, 2001)	1980–1994	17196	30–≥60
Finland	Puska et al. (1993)	1993	1398	25–64
Finland	Vartiainen et al. (2000)	2000	7619	30–59
Joensuu	INTERSALT study (Anonymous 1989a)	1988	200	20–59
Kuopio	MONICA study (Anonymous 1989b)	1989	2789	25–64
Turku	INTERSALT study (Anonymous 1989a)	1988	200	20–59
Turku; Loimaa	MONICA study (Anonymous 1989b)	1989	3276	25–64
N. Karelia	MONICA study (Anonymous 1989b)	1989	3133	25–64
France				
Bas-Rhin	MONICA study (Anonymous 1989b)	1989	1523	25–64
Lille	MONICA study (Anonymous 1989b)	1989	1685	25–64
Former German	INTERSALT study (Anonymous 1989a)	1988	198	20–59
Democratic Republic				
Berlin-Lichtenberg	MONICA study (Anonymous 1989b)	1989	1235	25–64
Cottbus county	MONICA study (Anonymous 1989b)	1989	1396	25–64
Halle county	MONICA study (Anonymous 1989b)	1989	2551	25–64
Karl-Marx-Stadt	MONICA study (Anonymous 1989b)	1989	2652	25–64
Germany	Heinemann et al. (1995)	1995	1947	25–64
Germany	Hoffmeister et al. (1994)	1994	14847	25–69
Germany	MONICA study (Anonymous 1989b)	1989	889	25–64
Augsburg (Rural)	MONICA study (Anonymous 1989b)	1989	2215	25–64
Augsburg (Urban)	MONICA study (Anonymous 1989b)	1989	1803	25–64
Bernried	INTERSALT study (Anonymous 1989a)	1988	197	20–59
Bremen	MONICA study (Anonymous 1989b)	1989	1666	25–64
Heidelberg	INTERSALT study (Anonymous 1989a)	1988	196	20–59
Rhein-Neckar	MONICA study (Anonymous 1989b)	1989	3010	25–64
Iceland	INTERSALT study (Anonymous 1989a)	1988	200	20–59
Iceland	MONICA study (Anonymous 1989b)	1989	1745	25–64
Italy	Fogari et al. (1997)	1997	8760	20–59
Italy	Nine populations (Anonymous 1981)	1981	6699	20–59
Italy	Vaccarino et al. (1995)	1981	3401	<30–≥50

continued

Table 6.2 Studies currently included in blood pressure data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Year published*	*Sample size*	*Age range (years)*
	Bassiano	INTERSALT study (Anonymous 1989a)	1988	199	20–59
	Brianza	MONICA study (Anonymous 1989b)	1989	1641	25–64
	Friuli	MONICA study (Anonymous 1989b)	1989	1852	25–64
	Gubbio	INTERSALT study (Anonymous 1989a)	1988	199	20–59
	Latina	MONICA study (Anonymous 1989b)	1989	1785	25–64
	Mirano	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Naples	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Israel	Gofin et al. (1995)	1995	1858	50–84
	Israel	Kark (P. Elliot, personal communication, 2001)	1980–1994	832	30–≥60
	Malta	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Malta	MONICA study (Anonymous 1989b)	1989	1901	25–64
	Netherlands	Bosma et al. (1994)	1994	3015	45–70
	Netherlands	INTERSALT study (Anonymous 1989a)	1988	199	20–59
	Norway	Trumso (P. Elliot, personal communication, 2001)	1980–1994	9022	30–≥60
	Portugal	INTERSALT study (Anonymous 1989a)	1988	198	20–59
	Slovenia	Gradsk (P. Elliot, personal communication, 2001)	1980–1994	653	30–≥60
	Spain	Masia et al. (1998)	1998	1748	24–74
	Manresa	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Torrejon	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Catalonia	MONICA study (Anonymous 1989b)	1989	2569	25–64
	Sweden	Asplund-Carlson and Carlson (1994)	1994	1564	40–50
	N. Sweden	MONICA study (Anonymous 1989b)	1989	1623	25–64
	Switzerland,				
	Ticino	MONICA study (Anonymous 1989b)	1989	1551	25–64
	Vaud; Fribourg	MONICA study (Anonymous 1989b)	1989	1618	25–64
	United Kingdom	British Regional Heart Study (P. Elliot, personal communication, 2001)	1980–1994	1792	30–≥60

	United Kingdom	Mann et al. (1988)	1988	12092	25–59
	England,	Bajekal et al. (1999)	1999	12555	16–≥75
	Birmingham	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Northern Ireland,				
	Belfast	INTERSALT study (Anonymous 1989a)	1988	199	20–59
	Belfast	MONICA study (Anonymous 1989b)	1989	2358	25–64
	Scotland	Hawth (P. Elliot, personal communication, 2001)	1980–1994	2286	30–≥60
	Scotland,	Smith et al. (1989)	1989	10359	40–59
	Glasgow	MONICA study (Anonymous 1989b)	1989	1247	25–64
	Wales,				
	South Wales	INTERSALT study (Anonymous 1989a)	1988	199	20–59
	Ireland	MacAuley et al. (1996)	1996	603	16–74
	Ireland	Shelley et al. (1991, 1995)	1991–1995	1433	30–≥60
				191304	
EUR-B	Poland	Davis et al. (1994)	1994	729	46–52
	Krakow	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Warsaw	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Warsaw	MONICA study (Anonymous 1989b)	1989	2646	25–64
	Uzbekistan	King et al. (1998)	1998	1956	35–≥65
	Former Yugoslavia	MONICA study (Anonymous 1989b)	1989	1575	25–64
				7306	
EUR-C	Hungary	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	Budapest	MONICA study (Anonymous 1989b)	1989	1512	25–64
	Lithuania	Bosma et al. (1994)	1994	2149	45–70
	Russian Federation	Puska et al. (1993)	1993	837	25–64
	The former Soviet Union[a]	INTERSALT study (Anonymous 1989a)	1988	194	20–59
	Kaunas	MONICA study (Anonymous 1989b)	1988	1462	25–64
	Moscow	MONICA study (Anonymous 1989b)	1989	1425	25–64
	Moscow	MONICA study (Anonymous 1989b)	1989	2404	25–64
	Novosibirsk	MONICA study (Anonymous 1989b)	1989	2820	25–64
	Novosibirsk	MONICA study (Anonymous 1989b)	1989	1623	25–64
				14626	

continued

Table 6.2 Studies currently included in blood pressure data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Year published*	*Sample size*	*Age range (years)*
SEAR-B	Sri Lanka	Mendis et al. (1988)	1988	9 405	20–84
	Sri Lanka	Mohidn (P. Elliot, personal communication, 2001)	1980–1994	704	30–≥60
				10 109	
SEAR-D	India	B.V. Babu, personal communication, 2001; Y.S. Kusuma, personal communication, 2001	1993 onwards	295	15–≥55
	India	B.V. Babu, personal communication, 2001; Y.S. Kusuma, personal communication, 2001	2001	1 094	20–≥60
	India	Gilberts et al. (1994)	1994	10 260	20–≥70
	India	Gupta et al. (1995)	1995	2 212	20–≥70
	India	India (P. Elliot, personal communication, 2001)	1980–1994	2 078	30–≥60
	India	Misra et al. (2001); A. Misra, personal communication, 2001	2001	679	14–25
	India	Singh et al. (1997a)	1997	1 806	25–64
	India	Singh et al. (1997b)	1997	1 935	25–≥64
	India	Singh et al. (1998)	1997	2 310	25–64
	India	Reddy (P. Elliot, personal communication, 2001)	1980–1994	5 574	30–≥60
	Ladakh	INTERSALT study (Anonymous 1989a)	1988	200	20–59
	New Delhi	INTERSALT study (Anonymous 1989a)	1988	199	20–59
				19 408	
WPR-A	Australia	APCSC-Busselton (APCSC secretariat, personal communication, 2001)	1990 onwards	976	15–≥70
	Australia	APCSC-Perth (APCSC secretariat, personal communication, 2001)	1990 onwards	6 456	15–≥70
	Australia	Gliksman et al. (1990)	1990	2 284	9–15
	Australia	Jamrozik and Hockey (1989); P. Elliot, personal communication, 2001	1989	9 222	30–≥60

Newcastle	MONICA study (Anonymous 1989b)	1989	2464	25–64
Perth	MONICA study (Anonymous 1989b)	1989	1782	25–64
Japan	1990 National Survey (Sakata and Labarthe 1996)	1980–1994	8470	30–≥70
Japan	APCSC-Aito Town (APCSC secretariat, personal communication, 2001)	1980 onwards	1720	15–≥70
Japan	APCSC-Akabane (APCSC secretariat, personal communication, 2001)	1980 onwards	1834	15–≥70
Japan	APCSC-Ohasama (APCSC secretariat, personal communication, 2001)	1980 onwards	2240	30–≥60
Japan	Baba et al. (1991)	1991	10346	30–74
Japan	Okayama et al. (1993)	1993	5921	30–69
Japan	Shimamoto et al. (1989)	1989	1894	40–69
Osaka	INTERSALT study (Anonymous 1989a)	1988	197	20–59
Tochigi	INTERSALT study (Anonymous 1989a)	1988	194	20–59
Toyama	INTERSALT study (Anonymous 1989a)	1988	200	20–59
New Zealand	APCSC-Fletcher challenge (APCSC secretariat, personal communication, 2001)	1980 onwards	10462	15–≥70
New Zealand	Bullen et al. (1998)	1998	986	65–84
New Zealand	Flight et al. (1984)	1984	327	14–15
New Zealand	National Survey (Ministry of Health 1999)	1999	4379	15–≥80
Auckland	MONICA study (Anonymous 1989b)	1989	1583	25–64
Singapore	APCSC-Kinmen (APCSC secretariat, personal communication, 2001)	1980 onwards	2793	45–≥70
Singapore	APCSC-Singapore Heart Survey (APCSC secretariat, personal communication, 2001)	1980 onwards	2450	15–≥70
Singapore	Hughes et al. (1990)	1990	2141	18–69
Singapore	Singapore National Health Survey (P. Elliot, personal communication, 2001)	1980–1994	2486	30–≥60
			83 807	

continued

Table 6.2 Studies currently included in blood pressure data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Year published*	*Sample size*	*Age range (years)*
WPR-B	China	APCSC–Anzhen (APCSC secretariat, personal communication, 2001)	1980 onwards	8 378	30–≥70
	China	APCSC-Anzhen02 (APCSC secretariat, personal communication, 2001)	1980 onwards	4 152	30–69
	China	APCSC-East Beijing (APCSC secretariat, personal communication, 2001)	1980 onwards	1 198	5–≥70
	China	APCSC-Hong Kong SAR (APCSC secretariat, personal communication, 2001)	1980 onwards	998	60–≥70
	China	APCSC-Hong Kong SAR (APCSC secretariat, personal communication, 2001)	1980 onwards	2 019	≥70
	China	APCSC-Seven Cities cohort (APCSC secretariat, personal communication, 2001)	1980 onwards	37 635	15–≥70
	China	APCSC-Six Cohorts (APCSC secretariat, personal communication, 2001)	1980 onwards	19 387	30–59
	China	APCSC-Tianjin (APCSC secretariat, personal communication, 2001)	1980 onwards	9 335	15–≥70
	China	He et al. (1991a); Klag et al. (1993)	1991–1993	14 055	15–≥65
	China	PRC-USA study (Huang et al. 1994; People's Republic of China-United States Cardiovascular and Cardiopulmonary Epidemiology Research Group 1992)	1992–1994	8 885	35–54

Beijing	INTERSALT study (Anonymous 1989a)	1988	200	20–59
Beijing	MONICA study (Anonymous 1989b)	1989	1 672	25–64
Nanning	INTERSALT study (Anonymous 1989a)	1988	200	20–59
Tianjin	INTERSALT study (Anonymous 1989a)	1989	200	20–59
Taiwan, China	APCSC–CVDFACTS/Two Townships (APCSC secretariat, personal communication, 2001)	1980 onwards	7 004	0–≥70
Taiwan, China	INTERSALT study (Anonymous 1989a)	1988	181	20–59
Republic of Korea	INTERSALT study (Anonymous 1989a)	1988	198	20–59
Republic of Korea	Kim et al. (1994)	1994	21 240	30–≥70
Papua New Guinea	INTERSALT study (Anonymous 1989a)	1988	162	20–59
Papua New Guinea	King et al. (1985)	1985	1 455	20–≥55
Papua New Guinea	Lindeberg et al. (1994)	1994	203	20–86
Pacific	PACIFIC (P. Elliot, personal communication, 2001)	1980–1994	7 454	30–≥60
Pacific	Patrick et al. (1983)	1983	1 039	20–60
Pacific	PUKAPK (P. Elliot, personal communication, 2001)	1980–1994	253	30–≥60
Pacific	RARTNG (P. Elliot, personal communication, 2001)	1980–1994	249	30–≥60
			147 752	

[a] Russia in the original publication.

Figure 6.3 SBP data coverage expressed as total study sample size, by geographical region

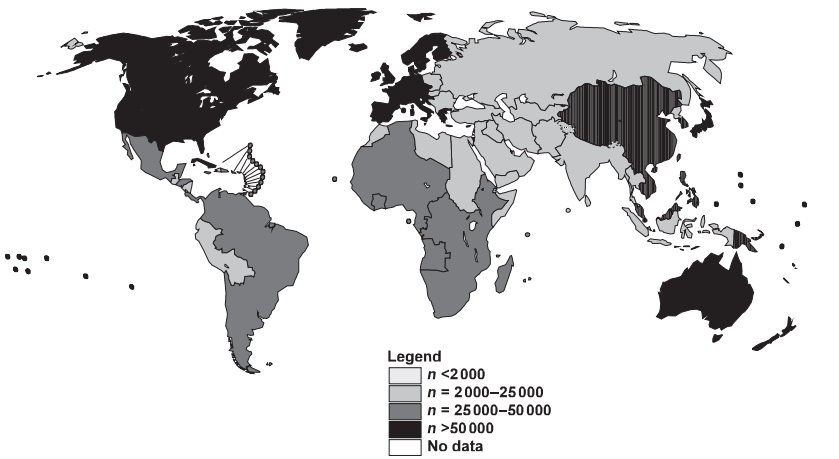


Figure 6.3 illustrates data coverage by geographical region. Data from about 230 studies (total sample size of over 660 000 participants) have been included.

The subregions with the most data—studies including a total of more than 50 000 participants—were AMR-A, EUR-A, WPR-A and WPR-B. All other subregions had data on a total of >2000 participants.

Approximately half of the studies from which data were obtained utilized random sampling of individuals or households (54%)—including stratified random sampling (see Appendix A). Forty-six per cent of studies obtained samples by other methods such as house-to-house or workplace surveys. Response rates were documented in half of the studies. Of those studies that did provide these data, the response rate was >80% in 42% of studies, between 50–80% in 54% of studies, and documented to be <50% in only five studies. For completeness, full documentation of sampling method, response rate and blood pressure measuring techniques is presented in Appendix A. A summary is given in Table 6.3.

2.2 Methodology to estimate mean and standard deviation of blood pressure

Study summary data were taken from all data sources (i.e. summary statistics and not individual participant data were available for analysis). Mean SBP, standard deviation, sample size and age ranges from all data sources were extracted and entered into an Excel database. Scatter plots of these SBP data for each subregion, utilizing the midpoints in study age categories, are presented in Figures 6.4–6.7.

Table 6.3 Blood pressure measuring techniques of studies included in review

	Yes (%)	*No (%)*	*Not stated (%)*
Trained and certified staff	95	NA	5
Sphygmomanometer			3
Standard/mercury	92	NA	NA
Electronic	5	NA	NA
Multiple cuff sizes used	49	28	23
2–3 BP measures taken after ≥5 mins rest	92	2	6

NA Not applicable.

The SBP data obtained from the literature came from studies that included different age ranges and were presented broken down by different age categories from that required for the CRA project. For this reason a method was needed that made complete use of all the available data. First, exploratory data analysis techniques were utilized to assess the general shape of association as well as to check for data errors. Secondly, models were fit to the data and country-level blood pressure estimates were made. Finally, subregional estimates were obtained by pooling across the country-level estimates. This approach is explained in greater detail below.

SBP–age relationships

The data from the surveys were used to assess the shape of the association of SBP with age for all data combined and for each subregion and sex separately using Splus software. At this stage no assumptions were made about the shape of association, and therefore non-parametric methods were applied (i.e. the generalized additive model). When the shape of the association was examined using all of the blood pressure data, there appeared to be an approximately linear association from the age of about 30–70 years in males and females (Figure 6.8). When the analyses were repeated by subregion, the association increased approximately linearly from age 30 years for females (20 years for males) until approximately 70 years in all subregions, despite variation in the slope and overall starting SBP level.

In many subregions, SBP levels appeared to flatten for those aged >70 years, although there was some variation between the subregions in the point at which the association levelled off. In a few subregions, particularly the "A" subregions, there was no obvious levelling out of SBP in the 70–79 year age group; however, data for those aged ≥80 years were particularly scarce, so a flattening out of SBP is still possible in these subregions. The shape of the association in those aged >70 years within each subregion was influenced by the fact that there were considerably less

Figure 6.4 Mean SBP–age relationship for input data by subregion, for females

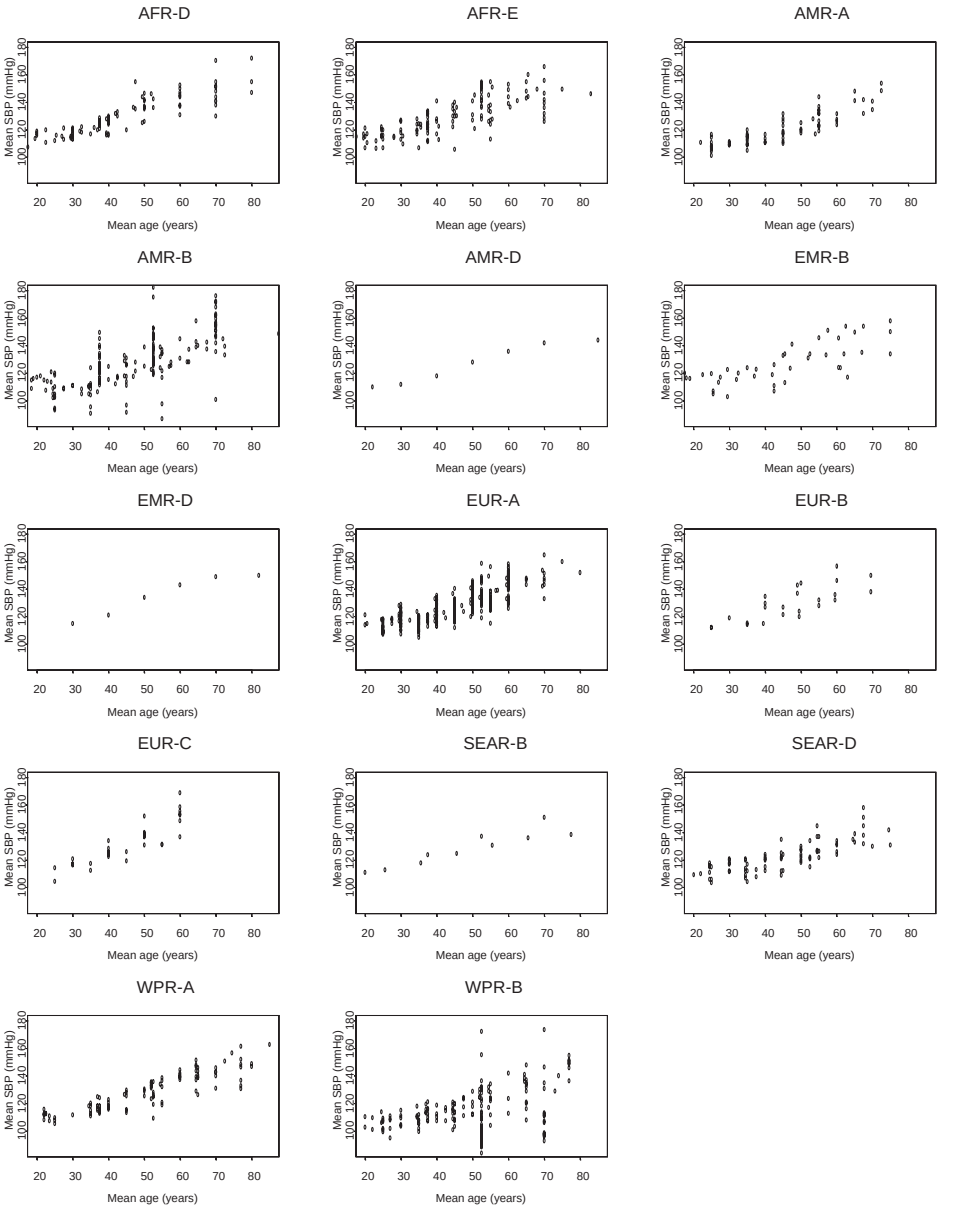


Figure 6.5 Mean SBP–age relationship for input data by subregion, for males

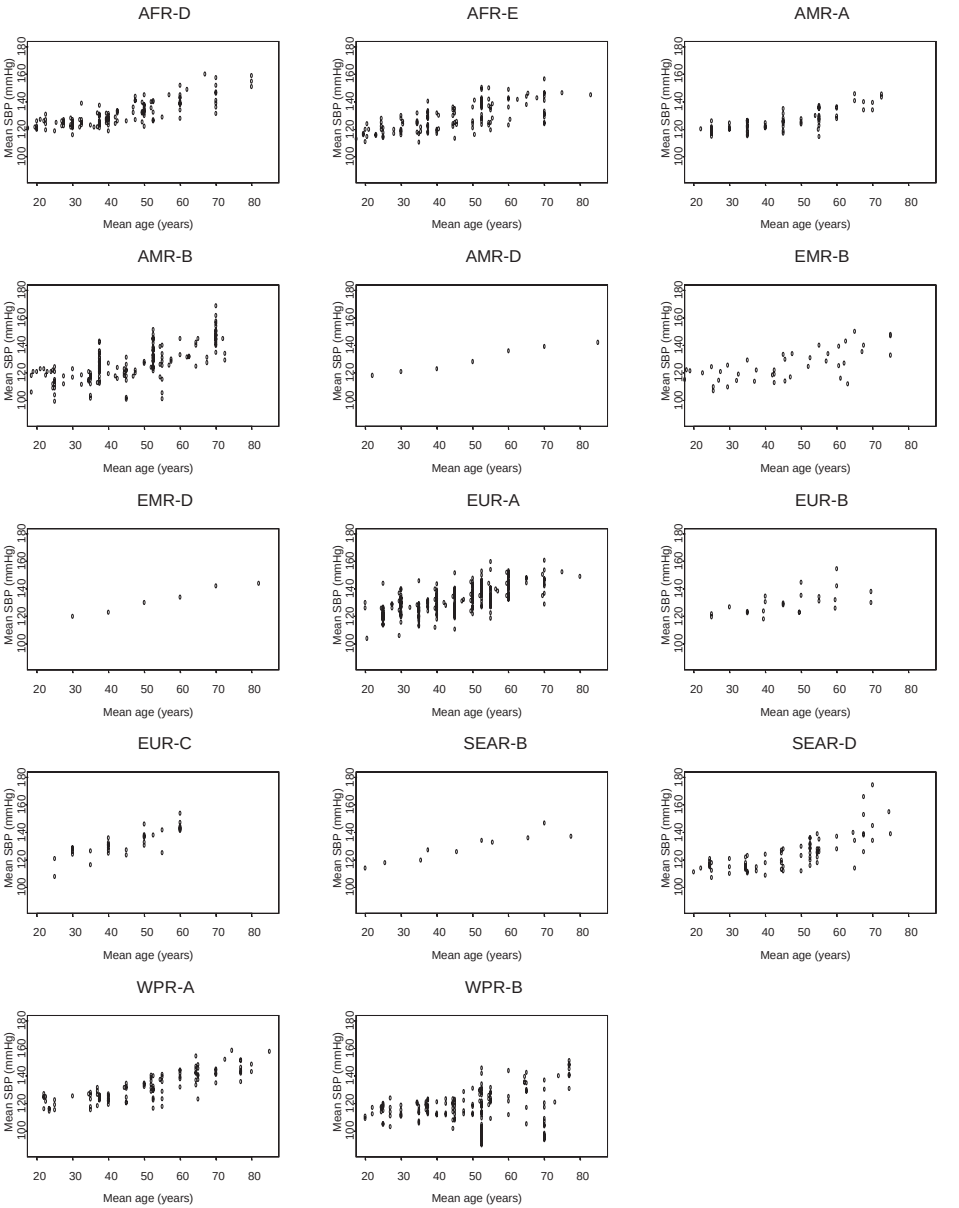


Figure 6.6 The relationship of standard deviation of mean SBP with age by subregion, for females

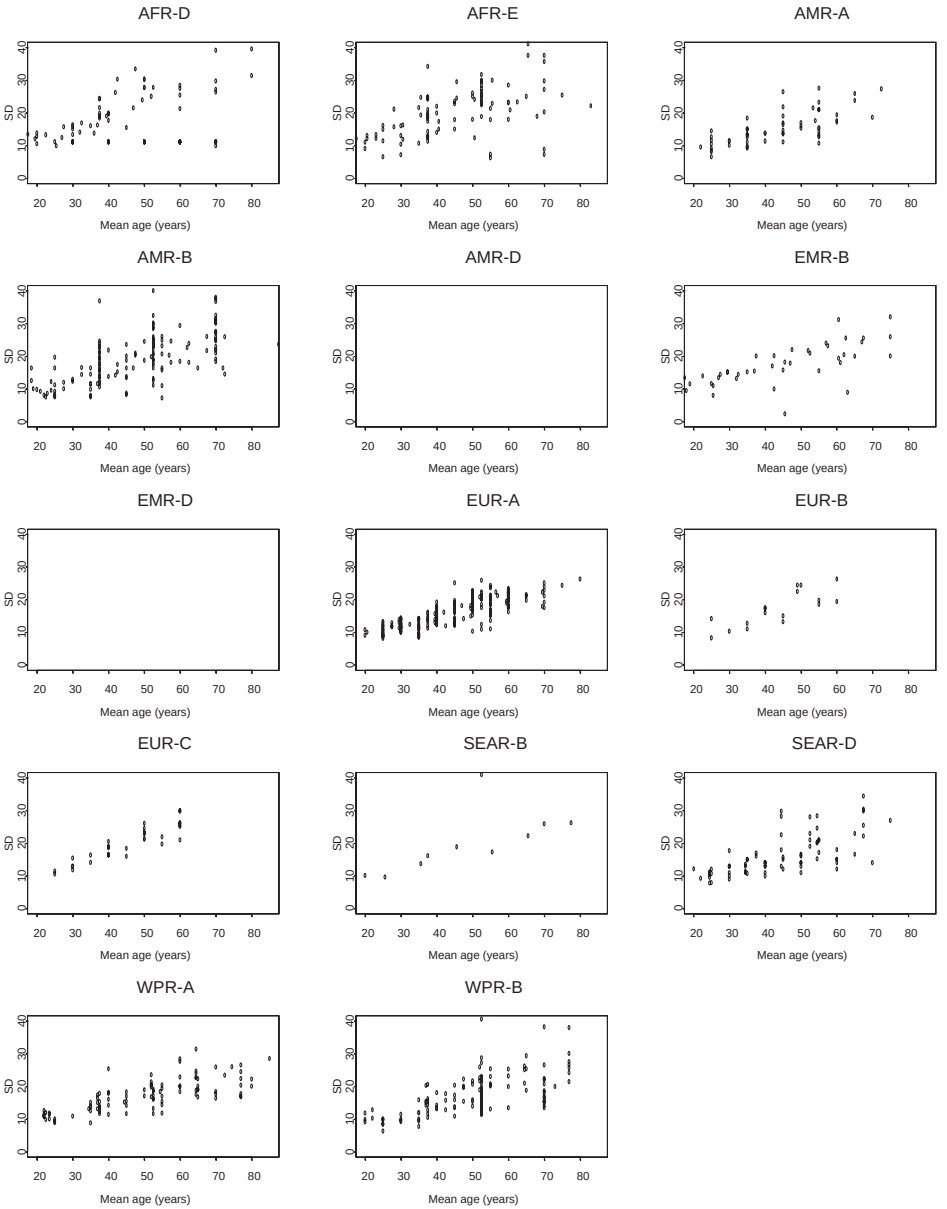


Figure 6.7 The relationship of standard deviation of mean SBP with age by subregion, for males

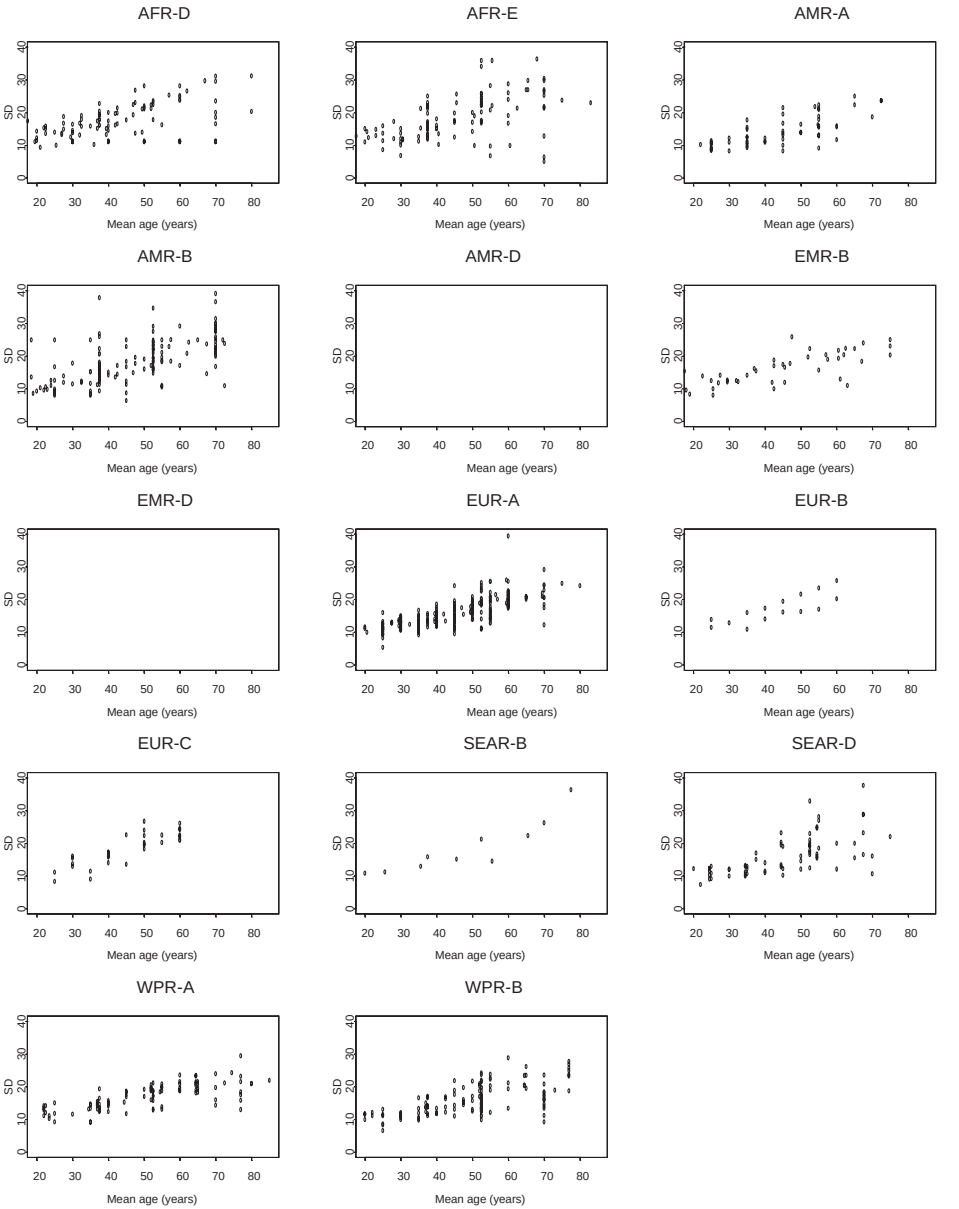
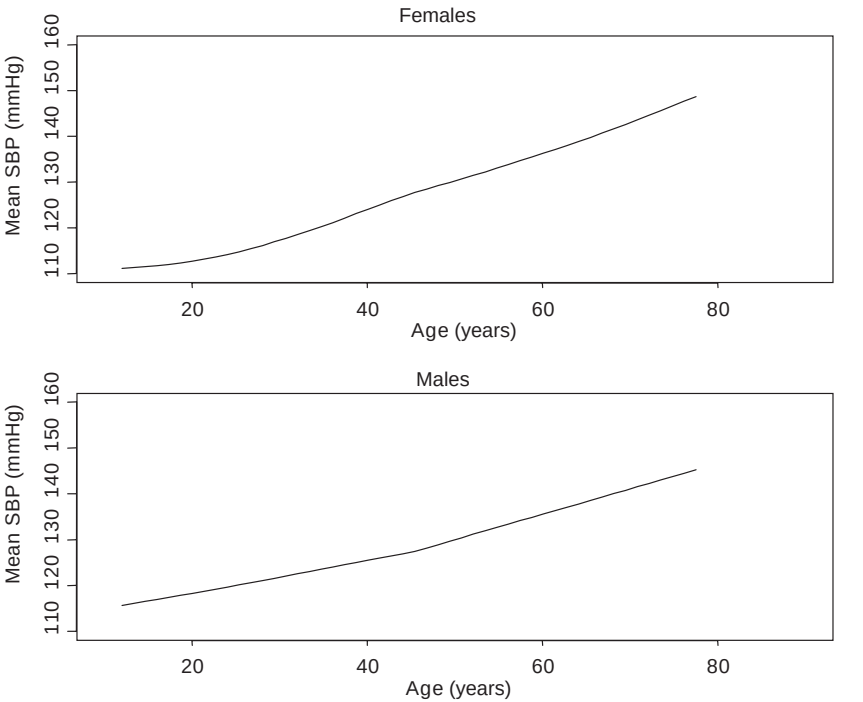


Figure 6.8 The SBP–age association for all studies combined



survey data available for females and males aged >70 years. The literature clearly indicates that SBP tends to rise linearly until the eighth or ninth decade (Franklin et al. 1997; Kannel 1996, 1999; Whelton 1994; Whelton et al. 1994), after which it levels out (Franklin et al. 1997; Kannel 1996, 1999; Whelton 1994; Whelton et al. 1994). Therefore, it was assumed that in all subregions SBP levels increased linearly to 70 years of age in both males and females, after which (i.e. the ≥70 year groups) levels flattened out. This approach was appropriate given the limitations of the data for those aged >70 years, and the information from the literature indicating that this pattern is widespread. It was also more conservative than assuming that the levels of SBP continue to increase with age.

The trend with age in industrialized subregions such as AMR-A, EUR-A, WPR-A corresponds with evidence in the literature, which shows a consistency of relationship between age and blood pressure in surveys in industrialized countries (Kannel 1999; Whelton et al. 1994). The literature suggests that between the third, fourth and seventh decades the rate of rise in SBP is approximately 0.6–0.8 mmHg/year for women and approximately 0.3–0.5 mmHg/year for men in industrialized populations

(Whelton et al. 1994). By the seventh decade women tend to have levels of SBP equal or exceeding those in men (Whelton et al. 1994). These findings concur with those for industrialized subregions in the current analyses. There were similar patterns in most developing countries, that is, an age-related rise in blood pressure which is consistently higher for systolic than DBP. SBP tends to rise linearly, and the age-related rise in blood pressure during adulthood is steeper for women than men (Kannel 1999; Whelton et al. 1994). However, the size of the age-related increase in blood pressure varies by subregion.

Country-level estimates

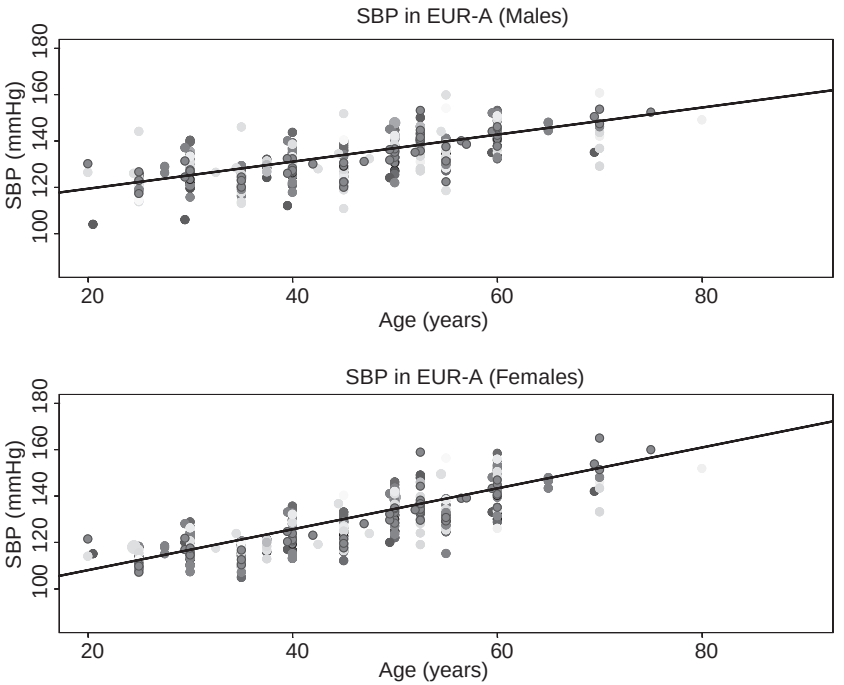
After gathering all country-level studies, we obtained country-level estimates for countries where data were available. There were studies available that were nationally representative and these were used solely to derive the respective country-level estimates. In these cases any additional studies from those countries were not utilized as they only contributed additional heterogeneity to the best estimates obtained from the nationally representative data. There were eight countries where this was possible: Australia, Canada, Egypt, Germany, Japan, Paraguay, the United Kingdom of Great Britain and Northern Ireland and the United States of America. There were sufficient data to assess SBP in 61 additional countries and for these a regression approach was required so that all remaining study-level data could be described as well as extrapolated within countries where data did not cover all age groups. The following model was applied to both males and females:

$$Y_{ij} = \beta_{1i}\ \text{subregion} + \beta_{2i}\ \text{age} + \beta_{3i}\ \text{subregion} \times \text{age} + \beta_{4j}\ \text{country}$$

This equation expresses how the study summary data were modelled to estimate blood pressure levels for each country separately. SBP was regressed against several explanatory covariates: age was included as a continuous variable, linear between 30 and 70 as described in the previous section. Subregion was categorical and the "subregion x age" interaction term included allowing for differing slopes of SBP with age between subregions. Country was included as a dummy variable and in this way the resulting beta coefficients can be used to assess the inter-country variation after controlling for age and subregional differences. The *i* and *j* subscripts denote the *i*th subregion and *j*th country within each subregion. Finally, the model was weighted by the sample size collected within each age group in each study to make the mean blood pressure estimates.

The modelling process is illustrated in Figure 6.9 where study level data within EUR-A were available for 18 of the 26 countries. The figure also shows, for the purpose of illustration only, the overall relationship of blood pressure with age in this subregion. It is clear from this figure that there is significant variation around the overall relationship with age

Figure 6.9 SBP data from studies in EUR-A



and also that a great deal of this variation is due to the differing patterns of blood pressure between countries. This occurred in most of the other subregions, especially where there were a large number of countries. In this example, each of the 18 countries within EUR-A was estimated to have the same overall slope within this subregion but at differing absolute levels.

Mean SBP was estimated for each country for each of the five relevant GBD age groups (>30 years) by using the fitted regression model to predict the best estimates within each country at the midpoints of each age group. A similar approach was used to estimate the standard deviations for each age, sex and country combination.

Subregional level estimates

Estimates for each of the 14 subregions were made by weighting across the country-level estimates by their respective population sizes. For example, the following estimates for females were made for countries within WPR-A (Table 6.4). The weight given to each country within this subregion is equal to the percentage of total subregional population for each of the three respective countries.

Table 6.4 Estimates of age-specific mean SBP levels (mmHg) for females in WPR-A by country and pooled for the whole subregion

	Age group (years)			
Country	*30–44*	*45–59*	*60–69*	*70–79*
Australia/New Zealand	116.7	127.3	136	139.5
Percentage of subregion	14%	11%	8%	9%
Japan	121.0	133.7	144.3	148.6
Percentage of subregion	79%	85%	88%	88%
Singapore	113.9	126.1	136.3	140.3
Percentage of subregion	4%	2%	1%	1%
WPR-A total	120	133	144	148

Table 6.5 Estimates of mean SBP levels (mmHg) by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	123	136	146	150	150	127	135	141	144	144
AFR-E	121	131	140	143	143	124	130	135	137	137
AMR-A	114	127	138	143	149	122	129	137	141	144
AMR-B	115	130	142	147	147	122	131	138	141	141
AMR-D	117	129	139	143	143	123	131	136	139	139
EMR-B	126	137	147	150	150	125	132	139	143	143
EMR-D	121	135	146	150	150	123	131	138	141	141
EUR-A	122	136	147	151	151	130	138	144	147	147
EUR-B	122	141	154	161	161	128	140	149	153	153
EUR-C	125	143	158	164	164	129	138	146	149	149
SEAR-B	120	130	139	142	142	122	131	138	141	141
SEAR-D	117	126	132	135	135	118	127	134	137	137
WPR-A	120	133	144	148	148	127	137	145	148	148
WPR-B	115	127	137	141	141	117	126	133	136	136

Country-level estimates were possible in 69 countries (with 61 of these derived from the model described above) for both sexes representing all 14 subregions. For most of the subregions there was reasonable data coverage based on the literature review. However, there were some subregions for which very few data were found and estimation at the country level proved difficult. Therefore, high level of coverage, as in the example above, was not possible for all of the subregions. The two South-East Asian subregions are an example of this: data on only one country in each of these two subregions were obtained (N.B. India was the country

Table 6.6 Estimates of SBP standard deviations by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	20	25	29	31	31	17	21	25	27	27
AFR-E	13	18	22	23	23	13	16	19	20	20
AMR-A	14	19	22	24	24	14	17	20	21	21
AMR-B	15	21	26	28	28	16	20	23	24	24
AMR-D	15	19	23	24	24	15	18	21	22	22
EMR-B	15	17	19	20	20	15	19	22	24	24
EMR-D	15	19	23	24	24	15	18	21	22	22
EUR-A	15	19	22	23	23	14	18	21	23	23
EUR-B	16	23	28	31	31	16	21	26	28	28
EUR-C	17	23	29	31	31	16	21	25	27	27
SEAR-B	15	20	23	25	25	13	18	22	24	24
SEAR-D	14	18	20	21	21	14	19	23	24	24
WPR-A	15	18	21	22	22	15	18	21	22	22
WPR-B	16	22	27	29	29	14	19	24	25	25

Note: Reported standard deviations are derived from baseline SBP (i.e. one-off measures), which when corrected for regression dilution bias were used in all calculations on the "usual" scale.

for which estimation was possible in SEAR-D). It was assumed that in these data-sparse subregions, any country-level estimates belonging to those subregions were representative of the respective overall subregional blood pressure levels. Estimates of SBP distribution are presented in Tables 6.5 and 6.6.

2.3 Methodology to estimate uncertainty around mean and standard deviation SBP

The level of uncertainty around the means and standard deviations also had to be estimated. The approach described in the previous section to estimate the means and standard deviations makes as complete use as possible of all available data. However, there will always be increased uncertainty associated when generalizing from the data collected. Assessing the uncertainty in SBP estimation involved considering three main sources:

1. countries with nationally representative survey data;
2. countries that had multiple studies that were heterogeneous; and
3. countries with little or no data.

First, for the eight countries where very reliable large-scale nationally representative data were available, the standard errors were taken

directly from those study data. This uncertainty reflects, almost entirely, sampling variation in those studies and was generally small.

Second, for each of the 61 countries for which data were modelled, standard errors were obtained from the model predictions made for each country, age and sex combination. These standard errors reflected the variability of the data at the study level within each country. Significant inter-study variation within a particular country resulted in a larger standard error for that country. Conversely, in cases where studies consistently provided similar blood pressure levels, standard errors were very small.

Finally, an additional type of uncertainty was incorporated to reflect that when pooling country-level estimates to the subregional level there were varying degrees of missing information between the subregions. The "A" subregions all had excellent coverage with greater than 95% of the populations in these subregions represented in the available study data. On the other hand, only data on Sri Lanka were available in SEAR-B with no study data available on all remaining countries in that subregion, providing only 6% coverage. To allow for this varying coverage, an additional factor was introduced that depended on the proportion of total subregional population covered. The regression modelling approach described earlier provided a way of summarizing how much variability between countries was unaccounted for by age, sex and subregional differences. For example, the country coefficients ranged approximately 20–25 mmHg for females across all the countries included in the model. The degree of inter-country variation provided an indication of uncertainty in countries without data and therefore provided a basis from which to determine a suitable level of uncertainty within each subregion. One way to achieve this was to assume that the proportion of the subregion without any data had uncertainty equal to the inter-country variation. In effect, missing countries are assigned an uncertainty equivalent to choosing a country at random from the distribution of country effects (i.e. similar to a random effects approach).

The uncertainty for countries with complete, partial and no data, each obtained as described above, were then used in the relationship for pooled standard error of the mean weighted by population size. The following example illustrates how this was achieved for females aged 30–44 years in AMR-A.

$$\text{Var(Pooled mean SBP in AMR-A)} = w_1^2\ \text{var(mean SBP – USA)} + w_2^2\ \text{var(mean SBP – Canada)} + w_3^2\ \text{var(mean SBP – Cuba)}$$

where w_1, w_2 and w_3 are the weights equal to proportion of total subregional population in each of the three countries in AMR-A. In this example, variance estimates (i.e. square of the standard error) were derived directly from existing estimates for the United States and Canada, as there were data available for these two countries. There were no data available for Cuba and therefore the final term depended on all the other

Table 6.7 Values of 95% CI around mean SBP (mmHg) by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–40*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	(119–128)	(131–141)	(141–152)	(144–157)	(144–157)	(123–132)	(130–140)	(136–146)	(138–150)	(138–150)
AFR-E	(116–125)	(127–136)	(135–144)	(137–148)	(137–148)	(121–128)	(126–134)	(130–140)	(132–142)	(132–142)
AMR-A	(113–115)	(126–128)	(137–139)	(141–144)	(148–150)	(122–123)	(128–130)	(136–138)	(140–142)	(142–145)
AMR-B	(112–118)	(127–132)	(139–145)	(144–150)	(144–150)	(120–124)	(129–133)	(136–140)	(139–144)	(139–144)
AMR-D	(110–125)	(121–137)	(130–148)	(133–152)	(133–152)	(116–130)	(123–138)	(128–145)	(129–148)	(129–148)
EMR-B	(122–129)	(134–140)	(143–150)	(146–154)	(146–154)	(122–128)	(129–135)	(136–143)	(139–146)	(139–146)
EMR-D	(114–128)	(127–142)	(138–154)	(142–159)	(142–159)	(116–130)	(124–139)	(130–147)	(132–150)	(132–150)
EUR-A	(121–124)	(134–137)	(145–148)	(150–153)	(150–153)	(129–131)	(137–139)	(143–146)	(145–148)	(145–148)
EUR-B	(116–128)	(135–147)	(148–161)	(153–168)	(153–168)	(122–134)	(134–147)	(142–156)	(145–160)	(145–160)
EUR-C	(121–128)	(139–146)	(154–162)	(159–169)	(159–169)	(126–132)	(135–142)	(142–151)	(145–154)	(145–154)
SEAR-B	(112–128)	(121–139)	(129–149)	(131–153)	(131–153)	(113–130)	(121–140)	(128–148)	(130–151)	(130–151)
SEAR-D	(115–119)	(123–128)	(129–135)	(131–139)	(131–139)	(116–121)	(125–129)	(131–138)	(134–141)	(134–141)
WPR-A	(119–121)	(132–134)	(142–145)	(146–150)	(146–150)	(126–128)	(136–137)	(144–145)	(147–149)	(147–149)
WPR-B	(113–116)	(126–128)	(135–139)	(139–143)	(139–143)	(116–118)	(125–127)	(131–135)	(134–138)	(134–138)

Table 6.8 Values of 95% CI around the standard deviation of mean SBP by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–40*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	(18–22)	(22–29)	(23–37)	(24–40)	(24–40)	(15–18)	(20–24)	(23–30)	(24–32)	(24–32)
AFR-E	(11–18)	(14–22)	(17–29)	(17–32)	(17–32)	(10–16)	(13–20)	(13–25)	(14–27)	(14–27)
AMR-A	(12–17)	(17–21)	(20–26)	(21–28)	(21–28)	(12–15)	(16–19)	(18–23)	(18–25)	(18–25)
AMR-B	(12–17)	(18–21)	(22–27)	(23–30)	(23–30)	(14–18)	(17–20)	(19–24)	(20–26)	(20–26)
AMR-D	(12–19)	(15–23)	(18–30)	(18–33)	(18–33)	(12–18)	(15–22)	(15–27)	(16–29)	(16–29)
EMR-B	(12–17)	(12–22)	(11–26)	(10–28)	(10–28)	(14–16)	(17–21)	(20–25)	(21–27)	(21–27)
EMR-D	(12–19)	(15–23)	(18–30)	(18–33)	(18–33)	(12–18)	(15–22)	(15–27)	(16–29)	(16–29)
EUR-A	(14–15)	(18–20)	(21–23)	(22–25)	(22–25)	(14–15)	(18–19)	(20–23)	(22–24)	(22–24)
EUR-B	(13–19)	(20–25)	(23–34)	(24–38)	(24–38)	(13–18)	(18–24)	(20–30)	(21–34)	(21–34)
EUR-C	(15–18)	(22–25)	(27–32)	(29–34)	(29–34)	(15–17)	(20–23)	(23–27)	(25–29)	(25–29)
SEAR-B	(12–18)	(17–23)	(20–28)	(21–30)	(21–30)	(11–16)	(15–21)	(17–26)	(18–29)	(18–29)
SEAR-D	(13–16)	(16–19)	(18–23)	(19–25)	(19–25)	(13–16)	(17–21)	(19–26)	(20–28)	(20–28)
WPR-A	(14–16)	(17–19)	(19–23)	(20–24)	(20–24)	(14–16)	(17–19)	(19–22)	(20–23)	(20–23)
WPR-B	(14–17)	(20–23)	(24–29)	(25–32)	(25–32)	(13–15)	(18–20)	(22–26)	(23–28)	(23–28)

countries in the regression model and the variance in this case was equal to 20 mmHg. For subregions with low population coverage, this approach would result in much larger uncertainty. Having calculated the overall variance of the mean for a subregion, it was then converted into a 95% CI. A similar approach was taken to estimate the uncertainty for blood pressure standard deviations. Results are shown in Tables 6.7 and 6.8.

3. Blood pressure–disease relationships

Data on the relationship between blood pressure and disease outcomes come from two main types of study (MacMahon 1994). Prospective observational studies provide data from which the effects of prolonged blood pressure differences can be estimated (MacMahon et al. 1990). Trials provide data about the effects of short-term blood pressure reduction (Collins et al. 1990) or risk reversal. Results from prospective observational studies are discussed in this section.

3.1 Risk accumulation

A large number of observational studies have been conducted in a variety of settings that examine the association between blood pressure and disease. However, the results of many of these individual studies are limited. Many observational studies had small sample sizes, or an insufficient number of end-points and therefore lacked the power required to provide reliable estimates of associations for different population subgroups (e.g. sex and age groups) and/or specific diagnostic categories (MacMahon et al. 1990). Individual studies have not always provided information on the direction of the association at lower blood pressure levels, making it difficult to assess whether the observed association is continuous or has a threshold level. In addition, these studies frequently do not standardize the size of the association for bias and confounding—in particular regression dilution bias (MacMahon et al. 1990). This bias occurs when associations are calculated from "one-off" measures of blood pressure (i.e. measures taken once on one occasion) rather than "usual" blood pressure. (There is further discussion of this bias in the next section.) Overviews of observational studies, or meta-analyses of trials, overcome many of the size limitations of individual studies. At the time of writing, four major overviews have been conducted, and their main design features are summarized in Table 6.9. In contrast to the first three overviews, which utilized tabular data, the APCSC (1999) involved analyses of individual participant data. Therefore, it could more reliably adjust for confounding and provide more reliable risk estimates.

Of the four overviews, all included the stroke end-point, but only two included analyses for the IHD end-point (MacMahon et al. 1990; APCSC 2003a). Only APCSC included analyses for hypertensive disease and other cardiovascular disease (APCSC 2003a). Further advantages with this study are that all analyses were based on individual participant

Table 6.9 Characteristics of major cohort study overviews

Study characteristics	*MacMahon et al. (1990)*	*Prospective Studies Collaboration (PSC 1995)*	*Eastern Collaborative Research Group (Anonymous 1998)*	*Asia-Pacific Cohort Studies Collaboration (APCSC 2003a)*
Aims	To determine the strength of the association between BP and stroke and IHD throughout BP range	To assess the relationship between BP and total blood cholesterol and stroke, and determine how the strength of the relationship between BP and stroke varied with age	To assess the relationship between BP and total blood cholesterol and stroke in Asian populations, and determine whether the strength of the relationship varied with type of stroke	To produce subregion, age- and sex-specific blood pressure associations for stroke (including subtypes), IHD and total cardiovascular disease
Number of cohort studies included	9	45	18	37
Population included	Mostly from USA, but also from Europe, Puerto Rico and Hawaii (largely Caucasian)	Asia, Australia, Europe, Hawaii, the Middle East, USA	China (13 cohorts), Japan (5)	Australia (4), mainland China (14), Hong Kong SAR (1), Japan (12), New Zealand (1), Republic of Korea (1), Singapore (2), Taiwan, China (2)
Number of participants	420000	450000	124774	425251
% male	96%	61%	61%	57%
Age range (years)	25–84	15–99	18–98	20–107
Mean age at baseline	—	—	48 years	47 years
Follow-up	Range 6–25 years Mean 10 years	Range 5–30 years Mean 15 years	Range 2–17 years Mean 9 years	Range 2–27 years Mean 7 years

— No data.

data and provided age-specific analyses of all end-points. APCSC was therefore used as the primary data source for relative risk estimates of all end-points.

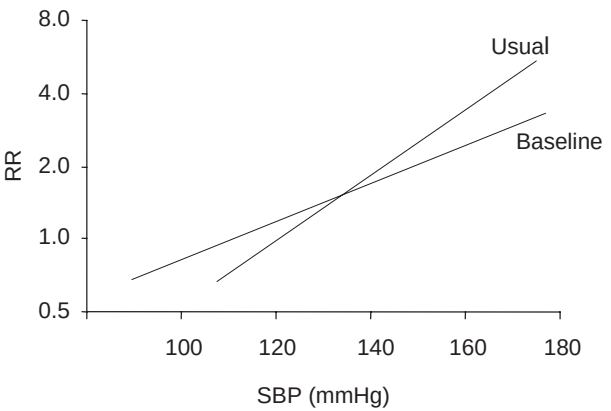
Analytical issues

Regression dilution bias has particular relevance in observational studies of blood pressure, and must be accounted for in analyses. This bias occurs as baseline or one-off measures of blood pressure are subject to random fluctuations, due partly to the measurement process and partly to any real but temporary deviations at the baseline visit from the usual blood pressure level (MacMahon et al. 1990). Therefore, baseline blood pressure values have a wider distribution than the "usual" blood pressure values. With repeated measures there is a "regression to the mean" of values (MacMahon 1994) whereby an initially extreme observation tends to become less extreme with replication (Strachan and Rose 1991). This imprecision in measurement not only influences distribution, but will also affect the association with disease outcomes (MacMahon et al. 1990) (Figure 6.10).

The baseline distribution has a shallower slope on the curve relation of blood pressure to relative risk of stroke and IHD, which means there is an underestimation of the strength of the association between blood pressure and disease incidence ("regression dilution bias") (MacMahon 1994). If not corrected for, this bias systematically dilutes the apparent importance of blood pressure and can result in systematic and substantial underestimation of risk of disease with usual blood pressure (MacMahon et al. 1990).

The size of the dilution is directly related to the extent to which blood pressure measurements are subject to regression to the mean. Several

Figure 6.10 Effects of regression dilution bias on the association between SBP and relative risk of cardiovascular disease



major meta-analyses conducted in recent years aimed to address these limitations with correction for regression dilution bias (Anonymous 1998; APCSC 2003a; MacMahon et al. 1990; PSC 1995). It is possible to use repeated measures of blood pressure to obtain an estimate of the attenuation factor in order to correct for this bias in the analysis. Data from cohort studies suggest that for DBP, the relationship with stroke/IHD is about 60% steeper if 4-year mean blood pressure values are used rather than mean values at baseline (Garcia-Palmieri and Costas 1986; Paul et al. 1963). As a result, a correction factor of 1.6 was used in early meta-analyses (MacMahon et al. 1990). However, other studies suggest that the association with usual blood pressure is twice as strong as that with baseline DBP (Aromaa 1981; Hughes and Pocock 1992) and a correction factor of 2.1 overall has been applied in the subsequent prospective studies collaboration (PSC) and Eastern meta-analyses (Anonymous 1998; PSC 1995). The APCSC meta-analyses primarily used SBP rather than DBP. The overall attenuation factor was 1.84 (APCSC 2003a). This concurs with other un-published data (PSC secretariat, personal communication) and these later meta-analyses are the most reliable source of estimates for risk accumulation.

A summary of the main results of the four prospective study overviews is presented in Table 6.10. While SBP is primarily being used to classify blood pressure in these analyses, some analyses have only published risk estimates in terms of DBP; therefore data for both indices have been presented for completeness. The risk estimates do appear slightly different across overviews, partly explained by different age distributions within the overviews.

Stroke

There is evidence of a positive association between blood pressure and all types of stroke (Anonymous 1998; APCSC 2003a; MacMahon et al. 1990; PSC 1995). All of the overviews have demonstrated heterogeneity among studies in the strength of the association between blood pressure and stroke risk, and a major factor contributing to this variability is attenuation with age (APCSC 2003a; PSC 1995).

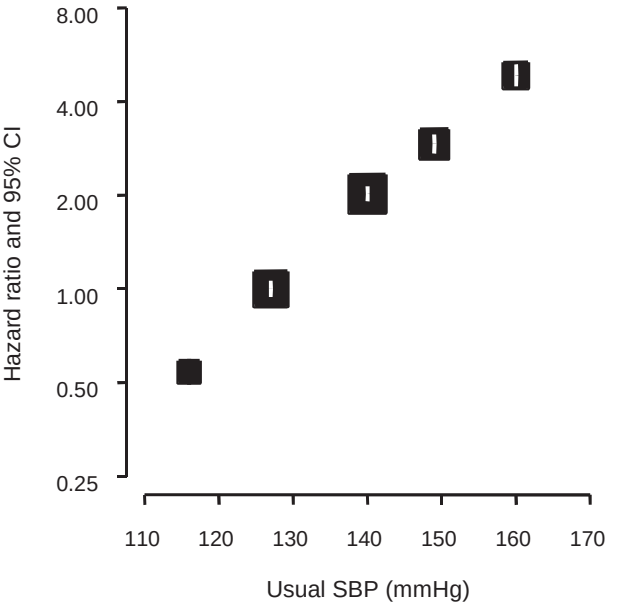
The slope of the association between relative risk of stroke (plotted on a log scale) and mean usual blood pressure is roughly constant, implying a log-linear relationship (Figure 6.11). This means that the relative difference in risk associated with an absolute difference in usual blood pressure is similar at all levels of blood pressure, at least within the range studied. There is no good evidence of a threshold level below which lower levels of blood pressure were no longer associated with lower relative risks of stroke (down to SBP 115 mmHg). Likewise, there was no evidence of a threshold level above which the relative risk of stroke increases much more rapidly (Anonymous 1998; APCSC 2003a; MacMahon et al. 1990; PSC 1995). The strength of the overall relation was not altered by restricting analyses to those with and without a

Table 6.10 Summary results of major cohort study overviews

Study end-points	*MacMahon et al. (1990)*	*Prospective Studies Collaboration (PSC 1995)*	*Eastern Collaborative Research Group (Anonymous 1998)*	*Asia-Pacific Cohort Studies Collabration (APCSC 2003a)*
Stroke end-points	843 strokes 599 (71%) fatal	13 397 participants were recorded as having had a stroke	1 798 strokes 995 (55%) fatal 39% had data on subtype of which 42% haemorrhagic	4 355 strokes 60% fatal 1 335 were haemorrhagic 1 347 were ischaemic
BP–stroke association	Log linear continuous relationship with no threshold BP level			
	5 mmHg ↓ DBP RR = 0.66 (34% reduction in stroke risk) Association does not differ by sex, or fatal/non-fatal	5 mmHg ↓ DBP RR = 0.73 (95% CI 0.68–0.75) (27% reduction in stroke risk) Association differs by age but not by sex	5 mmHg ↓ DBP RR = 0.56 (95% CI 0.53–0.59) (44% reduction in stroke risk) Association differs by stroke subtype	5 mmHg ↓ DBP or 10 mmHg ↓ SBP RR = 0.62 (0.61–0.63) (38% reduction in stroke risk) Association did not differ by sex, or fatal/non-fatal events, attenuated by age
IHD end-points	4 856 IHD events 4 260 (88%) fatal	—	—	3 560 IHD events 56% fatal
BP–IHD association	Log linear continuous relationship	—	—	Log linear continuous relationship
	5 mmHg ↓ DBP RR = 0.79 (21% reduction in IHD risk) Association does not differ by sex	—	—	5 mmHg ↓ DBP or 10 mmHg ↓ SBP RR = 0.74 (0.71–0.76) (25% reduction in IHD risk) Association did not differ by sex, or fatal/non-fatal events, attenuated by age

— No data.
↓ Decreased.

Figure 6.11 Usual SBP and risk of stroke in the Asia-Pacific region



Source: APCSC, personal communication, 2001.

history of cardiovascular disease at baseline (APCSC 2003a; PSC 1995).

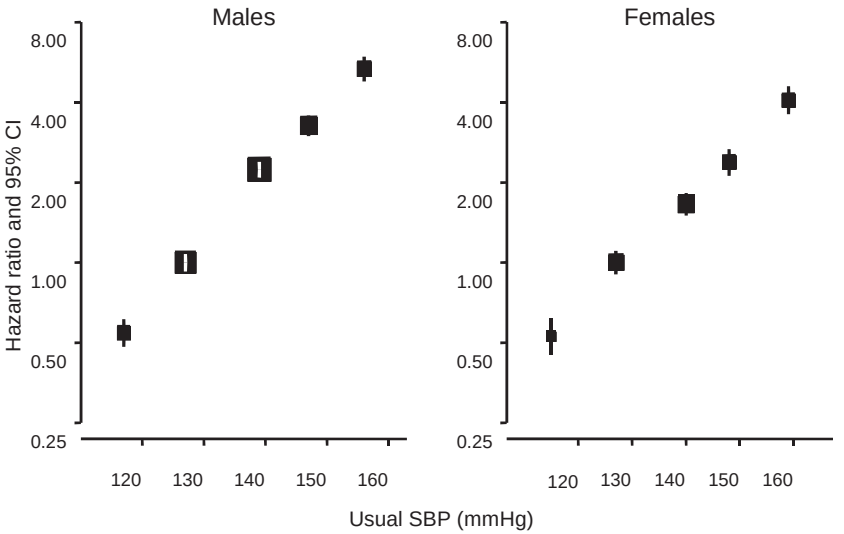
There has been no evidence in any of the overviews that the strength of association between blood pressure and stroke varies by sex (Figure 6.12). This is consistent for all age subgroups, so it is not necessary to have sex-specific estimates for CRA.

Age has an important influence on the size of the SBP-stroke relationship, as the associations are steeper for those in younger age groups (Figure 6.13). While the proportional change in stroke risk per unit change in blood pressure is less extreme in old age than in middle age, the relationship remains positive for all age groups (APCSC 2003a; PSC 1995).

The different age distributions within the four overviews therefore explain the slightly different relative risk estimates. This limits the ability to directly compare the overall relative risk estimates across the overviews, as it is only appropriate to compare age-specific results. It is therefore necessary to use age-specific risk estimates for blood pressure, provided by the APCSC data. There were no statistically significant differences in the age-specific relative risk for blood pressure and stroke between subgroups, or for stroke subtypes in APCSC analyses (2003a).

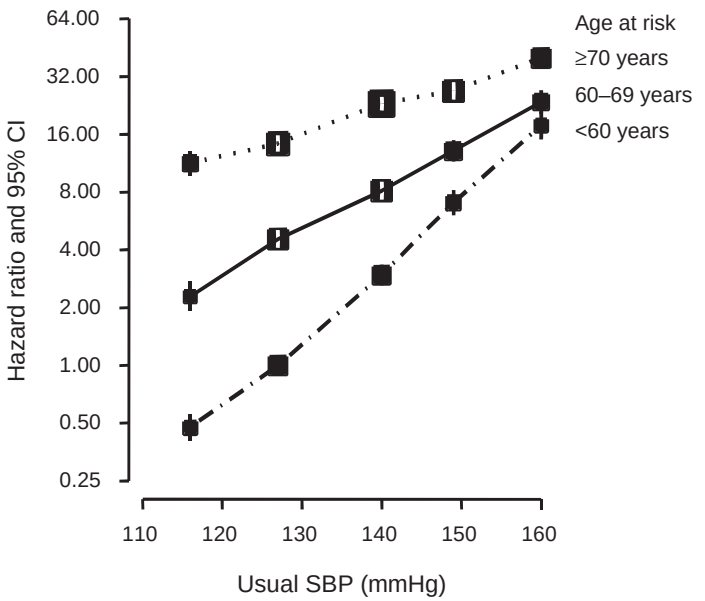
Risk estimates for the association between blood pressure and total stroke are shown in Table 6.11. These estimates of relative risk were vir-

Figure 6.12 Usual SBP and risk of stroke event in males and females



Source: APCSC, personal communication, 2001.

Figure 6.13 Usual SBP and risk of stroke by age



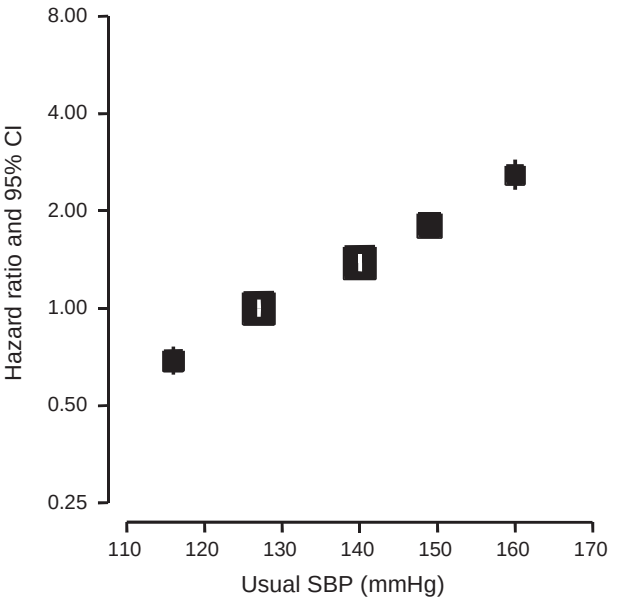
Source: Reprinted, by permission of the publisher, from APCSC (2003a) Blood pressure and cardiovascular disease in the Asia-Pacific region. *Journal of Hypertension*, **21**:707–716.

Table 6.11 Relative risk of total stroke event with a 10 mmHg decrease in usual SBP

Age group (years)	*Relative risk (95% CI)*	*Events*
30–44	0.42 (0.38–0.47)	249
45–59	0.50 (0.49–0.52)	1 602
60–69	0.64 (0.62–0.66)	1 349
70–79	0.73 (0.70–0.76)	1 250
≥80	0.83 (0.78–0.88)	738

Source: APCSC, personal communication, 2001.

Figure 6.14 Usual SBP and risk of IHD in the Asia-Pacific region



Source: APCSC, personal communication, 2001.

tually unchanged when analyses adjusted for cholesterol, smoking, alcohol or past history of cardiovascular disease in the APCSC cohorts that provided these additional data.

Ischaemic heart disease

Two overviews have published data on the association between blood pressure and risk of IHD. As with stroke, the relationship between blood pressure and IHD was log-linear with no apparent threshold levels of blood pressure (Figure 6.14).

The slope of the association of blood pressure with IHD is less than that for stroke, each 10 mmHg decrease in usual SBP was associated with about a 25% lower risk of IHD. However, in most studies the absolute effects of IHD tended to be greater because IHD was so much more common than stroke (MacMahon et al. 1990).

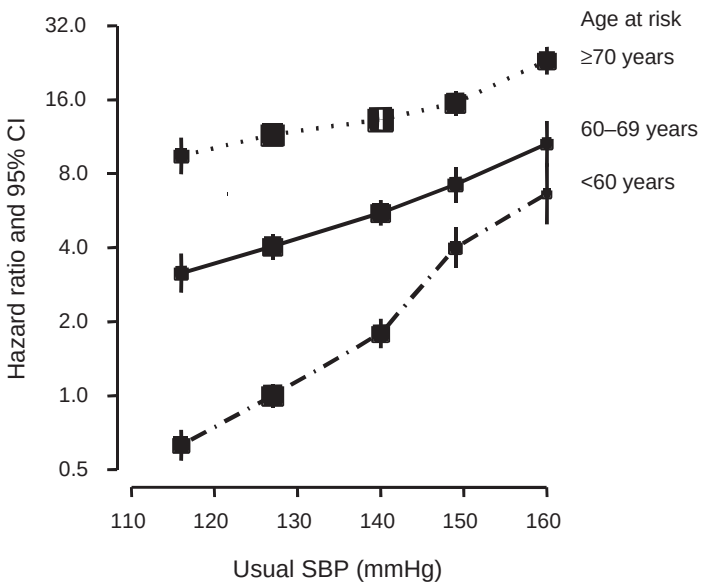
The blood pressure IHD association was attenuated with age (Figure 6.15), and did not differ significantly between males and females (APCSC 2003a; PSC secretariat, personal communication). A comparison of the strength of the SBP association with IHD between Asia and Australasia demonstrated that there were no differences between the age-specific relative risks in the two subgroups.

Age-specific relative risk estimates for IHD from the APCSC cohort are presented in Table 6.12. These estimates are consistent with unpublished data from PSC. They were virtually unchanged when analyses adjusted for potential confounders such as cholesterol, smoking, alcohol or past history of cardiovascular disease in the APCSC cohorts that provided these additional data.

Hypertensive disease

The APCSC project provides the only age-specific estimates for this endpoint, and each 10 mmHg decrease in usual SBP was associated with

Figure 6.15 Usual SBP and risk of IHD by age



Source: Reprinted, by permission of the publisher, from APCSC (2003a) Blood pressure and cardiovascular disease in the Asia-Pacific region. *Journal of Hypertension*, **21**:707–716.

Table 6.12 Relative risk of IHD event with a 10 mmHg decrease in usual SBP

Age group (years)	*Relative risk (95% CI)*	*Events*
30–44	0.52 (0.42–0.65)	95
45–59	0.60 (0.57–0.64)	727
60–69	0.75 (0.72–0.79)	779
70–79	0.80 (0.76–0.84)	844
≥80	0.94 (0.88–1.01)	601

Source: APCSC, personal communication, 2001.

Table 6.13 Relative risk of death from hypertensive disease with a 10 mmHg decrease in usual SBP

Age group (years)	*Relative risk (95% CI)*	*Events*
30–44	0.16 (0.07–0.37)	2
45–59	0.40 (0.24–0.67)	7
60–69	0.57 (0.46–0.71)	28
70–79	0.65 (0.53–0.81)	48
≥80	0.63 (0.50–0.81)	47

Source: APSCS, personal communication, 2001.

46% (95% CI 40–51%) lower risk of hypertensive disease. There were no statistically significant differences between males and females or Asia and Australasia for this end-point. As with other cardiovascular end-points, there was attenuation with age. Age-specific relative risk estimates are shown in Table 6.13.

Other cardiovascular end-points

The category "other cardiac disease" includes end-points such as heart failure. Overall, each 10 mmHg decrease in usual SBP was associated with 18% (95% CI 15–20%) lower risk of other cardiac disease. The age-specific APCSC associations for this composite end-point are shown in Table 6.14.

There were no statistically significant differences in associations by sex or subregion, although there were relatively few data to assess this reliably. This end-point was defined as all cardiovascular deaths other than those due to stroke, IHD or hypertensive disease. Numerically most of these were ascribed to heart failure. Given some uncertainty about causality and the varying composition for this end-point around the world, the relative risk reductions were halved for this outcome to avoid any potential overestimation of effects.

Table 6.14 Relative risk of death from "other cardiac disease" with a 10 mmHg decrease in usual SBP

Age group (years)	*Relative risk (95% CI)*	*Events*
30–44	0.66 (0.45–0.96)	32
45–59	0.76 (0.69–0.84)	258
60–69	0.83 (0.78–0.89)	500
70–79	0.90 (0.84–0.96)	551
≥80	0.92 (0.85–1.00)	507

Source: APCSC, personal communication, 2001.

3.2 Risk reversibility

As already alluded to, prospective observational studies provide data on the association between blood pressure and stroke and IHD, but they do not provide data on the impact of blood pressure lowering on these outcomes (MacMahon et al. 1990). From prospective studies alone it is not possible to tell whether outcomes are reversible, or whether the association reflects, to some extent, irreversible cumulative effects of blood pressure differences that have persisted for years (Collins and Peto 1994).

The results from randomized clinical trials do provide data on reversibility. They are relevant to assessing how rapidly, and to what extent, the epidemiologically expected reductions in stroke and IHD are produced by lowering blood pressure (Collins and Peto 1994; Collins et al. 1990). They therefore provide estimates of the proportion of the potential long-term benefit from a particular blood pressure difference that may be expected within a few years of blood pressure lowering. This section will discuss how results from trials can be utilized in CRA analyses.

Data sources on risk reversal

A variety of trials have studied the impact of blood pressure lowering. However, as with prospective studies, individual studies usually lack sufficient power to reliably detect moderate changes in events (Collins and Peto 1994; Collins et al. 1990; He and Whelton 2000). To accurately detect small but potentially important differences in risk reduction of cardiovascular disease (e.g. 10–15%), it is necessary for trials to record many hundreds of end-points. At least 1000 events would be necessary to reliably detect a 15% difference in risk of myocardial infarction (MacMahon and Neal 2000). Since most have not achieved this, overviews are necessary to provide more accurate estimates of the impact of blood pressure lowering on stroke and IHD. Results from these overviews will contribute to estimates of "risk reversibility".

A variety of overviews of trials have been published. These include:

- an overview of 14 randomized trials including nearly 37 000 individuals and almost 190 000 patient years of follow-up (Collins and Peto 1994; Collins et al. 1990). This overview was subsequently updated including three additional trials (MacMahon and Rodgers 1993a, 1993b). The updated review included 17 trials (four large, 13 small) of pharmacological treatment including over 47 000 individuals with over 12 000 aged over 60 years, mean follow-up 4.9 years (MacMahon and Rodgers 1993a, 1993b).
- a review by He and Whelton (1999) included 10 trials, a total of 18 542 participants, and an average follow-up of four years (He and Whelton 1999).
- Psaty et al. (1997) included 18 long-term randomized trials in their review, which included over 48 000 patients followed up for an average of five years in the United States, Europe, Scandinavia, Australia and Japan (Psaty et al. 1997).
- the analyses from the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLT) included data from 15 trials, 74 696 individuals, mean age 62 years and 53% male (Neal et al. 2000).
- a review by Pahor et al. (2000) included nine trials and 27 743 individuals (Pahor et al. 2000).
- an updated meta-analysis conducted on all trials included in previous overviews.

Estimates of risk reversibility

Stroke

Overviews of randomized controlled trials have all confirmed the reversibility of stroke with blood pressure lowering (Collins and Peto 1994; Collins et al. 1990; He and Whelton 1999; MacMahon and Rodgers 1993a, 1993b; Neal et al. 2000; Pahor et al. 2000; Psaty et al. 1997). The cohort study overviews already discussed suggested that a 10 mmHg lower SBP (or a 5 mmHg lower DBP) was associated with about a 30–40% lower risk of stroke. A major overview of clinical trials has demonstrated a quantitatively similar result with this level of blood pressure reduction (Collins and Peto 1994; Collins et al. 1990; MacMahon and Rodgers 1993a, 1993b). Analyses of additional trials in subsequent published overviews have had similar results (He and Whelton 1999; Neal et al. 2000; Psaty et al. 1997). The updated meta-analysis categorized trials of drugs vs placebo by drug classes, and found consistent results for each class of drug vs placebo and all trials combined (Table 6.15).

These results suggest that potentially all of the excess risk of stroke due to blood pressure can be reversed. The trial overviews also concur with cohort studies in that the reductions were similar for fatal and

Table 6.15 Clinical trials comparing a blood pressure-lowering drug with placebo or no treatment

Trial	Participants		Stroke		IHD		Mean age (years)	% male	Net reduction[a]		RR (95% CI)	
	A	C	A	C	A	C			SBP	DBP	Stroke	IHD
Beta blocker and/or diuretic vs placebo or no treatment												
ANBPS (Anonymous 1980)	1721	1706	13	22	33	33	50	63	—	6	0.59 (0.30–1.16)	0.99 (0.61–1.60)
Barraclough (Anonymous 1973)[b]	58	58	0	0	1	2	56	43	15	10	—	0.50 (0.05–5.36)
Carter (1970)	49	48	10	21	2	2	NA	57	—	—	0.47 (0.25–0.88)	0.98 (0.14–6.68)
Coope and Warrender (1986)	419	465	20	39	35	38	69	31	18	11	0.57 (0.34–0.96)	1.02 (0.66–1.59)
EWPHE (Amery et al. 1985)	416	424	32	48	48	59	72	30	21	8	0.68 (0.44–1.04)	0.83 (0.58–1.18)
HDFP (Anonymous 1979a, 1979b, 1982a, 1982b, 1984)	5485	5455	102	158	275	343	51	55	—	6	0.64 (0.50–0.82)	0.80 (0.68–0.93)
HSCSG I II III (Anonymous 1974)[b]	233	219	43	52	7	12	59	41	25	12	0.78 (0.54–1.11)	0.55 (0.22–1.37)
MRC older (Anonymous 1992)	2183	2213	101	134	128	159	70	42	14	7	0.76 (0.59–0.98)	0.82 (0.65–1.02)
MRC young (Anonymous 1985)	8700	8654	60	109	222	234	52	52	11.5	6	0.55 (0.40–0.75)	0.94 (0.79–1.13)
Oslo (Helgeland 1980; Leren and Helgeland 1986)	406	379	0	5	14	10	45	100	17	10	0.08 (0.00–1.53)	1.31 (0.59–2.91)
SHEP (Anonymous 1991)[b]	2365	2371	105	162	104	142	72	43	12	4	0.65 (0.51–0.83)	0.73 (0.57–0.94)
STOP H (Dahlof et al. 1991)	812	815	30	55	31	32	76	37	20	8	0.55 (0.35–0.85)	0.97 (0.60–1.58)
USPHS (Smith 1977)[b]	193	196	1	6	15	18	44	80	15	10	0.17 (0.02–1.39)	0.85 (0.44–1.63)
VA (Anonymous 1967, 1970)[b]	254	257	6	23	11	15	51	100	17	10	0.26 (0.11–0.64)	0.74 (0.35–1.58)
VA-NHL BI (Anonymous 1978; Perry 1977)	508	504	0	0	8	5	38	81	—	7	—	1.59 (0.52–4.82)
Wolff and Lindeman (1966)	45	42	2	1	0	0	49	32	—	20	1.87 (0.18–19.84)	—
Summary[c]	23847	23806	525	835	934	1104	59	49	13	6	0.63 (0.57–0.70)	0.85 (0.78–0.92)

ACE inhibitors vs placebo												
HOPE (Yusuf et al. 2000)	4654	4652	156	226	459	570	66	73	3	1	0.69 (0.57–0.84)	0.81 (0.72–0.91)
PART 2 (MacMahon et al. 2000)	308	309	7	4	24	35	61	82	6	4	1.76 (0.52–5.94)	0.69 (0.42–1.13)
PROGESS (Progress Collaborative Group 2001)	3051	3054	307	420	115	154	64	70	9	4	0.73 (0.64–0.84)	0.75 (0.59–0.95)
QUIET (Cashin-Hemphill et al. 1999)	878	872	1	1	48	54	58	82	—	—	0.99 (0.06–15.85)	0.88 (0.61–1.29)
SCAT (Teo et al. 2000)	229	231	2	9	8	13	61	89	4	3	0.22 (0.05–1.03)	0.62 (0.26–1.47)
Summary[c]	9111	9118	473	660	654	826	65	73	5	2	0.72 (0.64–0.80)	0.79 (0.72–0.87)
Calcium antagonists vs placebo												
PREVENT (Pitt et al. 2000)	417	408	5	5	19	20	57	80	5	4	0.98 (0.29–3.35)	0.93 (0.50–1.72)
Syst-Eur (Staessen et al. 1997)	2398	2297	49	80	60	76	70	33	11	5	0.59 (0.41–0.83)	0.76 (0.54–1.06)
Summary[c]	2815	2705	54	85	79	96	68	40	10	5	0.61 (0.44–0.85)	0.79 (0.59–1.06)

Key: A, active treatment group; C, control group.

— No data.

NA Not applicable.

[a] Net BP reduction = blood pressure difference between the randomized groups (i.e. BP change in treatment group minus BP change in placebo group).

[b] These trials also included older classes of drugs such as methyldopa and alkaloids.

[c] Summary mean age, % male and net SBP and DBP change are weighted by study size for those studies that provided data on net changes in both SBP and DBP. Weighting by number of IHD events made little material difference.

non-fatal strokes, and for males and females (He and Whelton 1999). The recently completed PROGRESS trial also demonstrated similar relative risk reductions for those classified as hypertensive and non-hypertensive at the start of the trial (Progress Collaborative Group 2001). In contrast to the treatment effect demonstrated in drug vs placebo trials, the treatment effect of one drug class vs another was relatively minor. Another important piece of information from the trial overviews is the time frame of this risk reversal: the data suggest that these reductions in risk of stroke occurred after only 2–3 years of blood pressure treatment (He and Whelton 1999; MacMahon and Rodgers 1993a).

Ischaemic heart disease

Overviews of randomized controlled trials have also confirmed the reversibility of IHD with blood pressure lowering (Collins and Peto 1994; Collins et al. 1990; He and Whelton 1999; MacMahon and Rodgers 1993a, 1993b; Neal et al. 2000; Pahor et al. 2000; Psaty et al. 1997). The cohort studies suggested that a 10 mmHg lower SBP (or a 5 mmHg lower DBP) was associated with about a 20–25% lower risk of IHD. Overviews of clinical trials have demonstrated that this magnitude of blood pressure reduction is associated with about a 15–20% reduction in IHD (Collins et al. 1990; He and Whelton 1999; MacMahon and Rodgers 1993a), which was confirmed by the updated meta-analysis (Table 6.15).

There were similar reductions for fatal and non-fatal strokes, for males and females (He and Whelton 1999), and for those with and without hypertension (Progress Collaborative Group 2001). As with stroke, these reductions in risk occurred after 2–3 years of blood pressure treatment (He and Whelton 1999; MacMahon and Rodgers 1993a). These data suggest that approximately two thirds of blood pressure related risk of IHD (not all) was reversed in this time frame.

The data indicate that within 3–5 years, 10 mmHg lower SBP resulted in reversal of most or all of the epidemiologically expected risk for stroke events and approximately two thirds of IHD. Likewise, it will be assumed that most or all of the expected risk for hypertensive disease and approximately two thirds of other cardiovascular disease will be reversed in this time frame. The time frames for reversibility from trials are important for estimating avoidable burden, but the trial relative risk estimates will not be used. There are a variety of problems with the generalizability of trial relative risk data, which make it less appropriate than prospective study data. These limitations include the fact that many trials only used mortality as an end-point (Linjer and Hansson 1997) and they were not powered for adequate subgroup analyses (e.g. age and sex subgroups). Overall, using relative risks from cohort studies will lead to conservative estimates of relative risk and avoidable burden because the clinical trial data have not to date demonstrated the age attenuation in relative risks that is observed in the epidemiological data.

In summary, data from the APCSC will be used for risk accumulation complemented by data from other overviews such as PSC. The main findings were direct, positive and continuous associations of usual SBP with the risks of all end-points of interest. The risks were similar by sex and subregion, except for a stronger association of blood pressure with stroke in Asian compared to non-Asian populations, due partly to the higher proportion of haemorrhagic strokes. Few data were available for the GBD end-point "other cardiac disease" and so given some uncertainty about causality and the varying composition for this end-point around the world, the relative risks will be halved for this outcome. There was attenuation of proportional associations with age for all these outcomes.

Data on risk reversibility come from overviews of all unconfounded randomized trials of blood pressure lowering. For the CRA analyses, it is proposed to use the observational epidemiological data for risk accumulation and use the trial overviews for the time frame of risk reversibility. For example, in middle age the epidemiology suggests that a 10 mmHg increase in SBP is associated with about 40% more stroke and 25% more IHD. The trials suggest that within 3–5 years of lowering SBP by 10 mmHg, most or all of this increased risk for stroke and hypertensive disease is reversed and approximately two thirds for IHD and cardiovascular disease.

4. Results

4.1 Attributable fraction

The "attributable fraction" refers to the proportion of disease burden that would theoretically not have occurred if the population distribution of blood pressure had been equal to that of the theoretical minimum (mean SBP of 115 mmHg). The attributable fractions for each of the end-points increased initially with age in males and females, but then declined for the oldest age groups, reflecting the balance between increasing mean SBP, and decreasing relative risks with age.

Stroke

Globally, 62% of stroke is attributable to SBP >115 mmHg (range of 52–78% by subregion). Subregions with the lowest attributable fractions included AFR-E, AMR-D, SEAR-D and EMR-D. In contrast, EUR-B and EUR-C had the highest values. In most subregions the attributable fraction for males and females were similar (within 5%).

Ischaemic heart disease

Globally, 49% of IHD is attributable to SBP >115 mmHg (range of 40–64% by subregion). Subregions with the lowest attributable fractions included AMR-A, AMR-D, SEAR-D and WPR-B. In contrast, EUR-B and EUR-C had the highest values.

Hypertensive disease

Globally, 76% of hypertensive disease is attributable to SBP >115 mmHg (range of 64–90% by subregion). Subregions with the lowest attributable fractions included AFR-E, EMR-D, AMR-D and SEAR-D. In contrast, EUR-B and EUR-C had the highest values.

Other cardiovascular disease

Globally, 14% of other cardiovascular disease is attributable to SBP >115 mmHg (range of 8–22% by subregion). Subregions with the lowest attributable fractions included AMR-D, EMR-D, SEAR-D and WPR-B. In contrast, EUR-B and EUR-C had the highest values.

4.2 Attributable burden

For the year 2000, WHO estimated that there were 55.9 million deaths and 1455 million DALYs worldwide; about 22% of these deaths and 7% of these DALYs were due to ischaemic heart disease and stroke. The burden of disease was distributed across the developed and developing world (e.g. about one quarter of all stroke deaths and one third of IHD deaths occurred in the least developed subregions), and predominantly affected those aged >60 years.

The "attributable burden" refers to the number of deaths or DALYs that would theoretically not have occurred if the population distribution of blood pressure had been equal to that of the theoretical minimum (mean SBP of 115 mmHg). In total, the attributable burden equated to 3.1 million stroke deaths, just under 3.0 million IHD deaths, about 0.7 million hypertensive disease deaths and 0.3 million other cardiovascular disease deaths. For DALYs these figures were 27.8 million stroke DALYs, 28.2 million IHD DALYs, 5.4 million hypertensive disease DALYs and 2.8 million other cardiovascular disease DALYs (Table 6.16).

Worldwide this means that 7.1 million deaths (about 12.8% of the total) and 64.3 million DALYs (4.4% of the total) were estimated to be due to non-optimal blood pressure. The proportion of DALYs was lower than the proportion of deaths, as most blood pressure-related cardiovascular disease events occurred in middle or old age, so the years of life lost due to premature mortality and years of life lost due to disability is a smaller percentage of the total DALYs than of the total deaths.

The age group with the greatest attributable deaths for both males and females was 70–79 years. The number of attributable deaths then declined, reflecting the smaller denominator population, and the smaller total number of events in the oldest age group. For DALYs, this decline occurred sooner, as there are less years of life lost and years of life lived with disability with advancing age. For example, 48% of excess IHD deaths were in those aged ≥70 years, compared to 24% of excess DALYs.

For each end-point, the attributable deaths were higher for males than females for the age categories 30–44, 45–59 and 60–69 years. In

Table 6.16 Attributable deaths and DALYs for systolic blood pressure >115mmHg, by cardiocvascular end-point and subregion

	Deaths (000s)				*DALYs (000s)*			
Subregion	*Stroke*	*Ischaemic heart disease*	*Hypertensive disease*	*Other cardio-vascular disease*	*Stroke*	*Ischaemic heart disease*	*Hypertensive disease*	*Other cardio-vascular disease*
AFR-D	93	82	20	19	982	893	197	204
AFR-E	91	67	21	15	1014	760	214	173
AMR-A	104	203	37	26	824	1548	247	164
AMR-B	133	129	53	18	1376	1303	425	141
AMR-D	14	13	10	3	145	132	87	23
EMR-B	28	71	27	6	300	811	230	68
EMR-D	101	176	43	15	987	1922	387	183
EUR-A	263	290	56	70	1729	2079	263	381
EUR-B	210	263	58	40	1839	2320	447	272
EUR-C	513	603	35	35	4134	5239	312	333
SEAR-B	115	100	48	9	1185	1050	458	103
SEAR-D	451	650	49	36	4262	7080	539	446
WPR-A	91	51	7	11	736	400	33	63
WPR-B	944	291	198	35	8315	2664	1601	247
World	3149	2991	663	338	27829	28201	5440	2801

contrast, attributable deaths were higher for females in the oldest age groups: 70–79 and ≥80 years. There was a similar trend for attributable DALYs. This was due to older females having higher mean SBP (and therefore greater attributable fraction) than males, and there are also a larger number of cardiovascular deaths occurring in older females compared to older males.

Stroke

The subregion with the highest attributable stroke burden was WPR-B (944 000 deaths, 8.3 million DALYs), followed by EUR-C (513 000 deaths, 4.1 million DALYs) and SEAR-D (451 000 deaths, 4.3 million DALYs).

Ischaemic heart disease

SEAR-D had the highest attributable IHD burden (650 000 deaths, 7.1 million DALYs), followed by EUR-C (603 000 deaths, 5.2 million DALYs), EUR-A (290 000 deaths, 2.1 million DALYs) and WPR-B (291 000 deaths, 2.6 million DALYs).

Hypertensive disease

The attributable burden for hypertensive disease, was highest in WPR-B (198 000 deaths, 1.6 million DALYs), followed by EUR-B and A for deaths (58 000 and 56 000, respectively) and SEAR-D and B for DALYs (539 000 and 458 000, respectively).

Other cardiovascular disease

The highest attributable burden for other cardiovascular disease was in EUR-A (70 000 deaths, 381 000 DALYs), SEAR-D (36 000 deaths, 446 000 DALYs) and EUR-B (40 000 deaths, 272 000 DALYs).

Overall, approximately one third of attributable DALYs occurred in the most developed subregions (23.3 million), a further third (20.3 million) in low mortality developing subregions and a final third (20.7 million) in high mortality developing subregions. A higher proportion of these deaths and DALYs were from IHD than stroke in developed and high mortality developing subregions, but more were stroke than IHD in low mortality developing subregions.

These results indicate where most of the worldwide attributable cardiovascular disease burden occurred, and provide any given subregion with an indication of absolute size of the attributable burden. However, the age structure, population size and the number of estimated events occurring in a subregion, influences the ranking of subregions by absolute number of attributable deaths and DALYs. The relative impact of the attributable DALYs indicates that between 3–33% of all deaths and 1–17% of all DALYs across the subregions were attributable to non-optimal blood pressure. Approximately 22% of all deaths and 11% of

all DALYs were attributable to non-optimal blood pressure in developed subregions, 14% and 5.0%, respectively, in low mortality developing subregions, and 7.5% and 2.5%, respectively, in high mortality developing subregions.

5. Discussion

5.1 Attributable deaths and DALYs

The analyses in this chapter suggest that globally, a substantial proportion of cardiovascular disease is attributable to non-optimal blood pressure, defined as mean SBP >115 mmHg. Overall, about two thirds of stroke, one half of IHD, and about three quarters of hypertensive disease were attributable to non-optimal blood pressure. The attributable fractions were higher in the more developed parts of the world than the least developed regions, as would be expected given the higher blood pressure levels.

Worldwide, 7.1 million deaths (about 12.8% of the total) and 64.3 million DALYs (4.4% of the total) were estimated to be due to non-optimal blood pressure. Overall, the results suggest that a considerable proportion of cardiovascular disease is related to non-optimal blood pressure and this translates into an important portion of deaths and years of life lost to deaths and disability worldwide.

5.2 Attributable deaths and DALYs by subregion

In absolute terms, most of the excess burden of cardiovascular disease occurred in the populous subregions of WPR-B, SEAR-D and EUR-C; each subregion accounted for approximately 15–20% of worldwide attributable deaths and DALYs. The relative impact that attributable deaths and DALYs have in different subregions may also be calulcated as the proportion of all deaths and DALYs attributable to non-optimal SBP (i.e. mean >115 mmHg) within each specific subregion. Overall, between 3–33% of all deaths and 1–17% of all DALYs across the subregions were attributable to non-optimal blood pressure. Excess cardiovascular disease burden was highest in European subregions where mean blood pressure levels were highest.

5.3 Comparison with the first WHO GBD study

The WHO GBD study in 1990 estimated that 8.7% of all deaths were due to stroke and 12.4% were due to IHD worldwide, compared to 9.5% and 12.5% in the current 2000 WHO estimates. Worldwide, 2.8% of all DALYs were from stroke in 1990 and 2.9% in 2000, and for IHD these percentages were 3.4% in 1990 and 3.8% in 2000. These percentages relate to worldwide estimates, and will vary across subregions. The 2000 WHO estimates indicated that about 5.8% of DALYs were due to stroke in developed subregions, which compares to 5.0%, and

the percentage of DALYs attributed to IHD across these studies was 9.2% (2000), compared to 9.0% in 1990. (Murray and Lopez 1996).

In terms of attributable burden, both GBD studies have estimated the total number of deaths and DALYs attributable to non-optimal blood pressure. A key difference is that the current estimates of burden attributable to blood pressure are approximately double those of the 1990 estimates. Worldwide 5.8% of deaths and 1.4% of DALYs were attributable to blood pressure in 1990, compared to 12.8% of deaths and 4.4% of DALYs in these analyses.

Potential reasons for the increases in the estimates include differences in the estimates of blood pressure prevalence; the theoretical minimum or comparison blood pressure group; the relative risk estimates; and in the way that DALYs were estimated. There were some differences in the studies used to estimate blood pressure prevalence and the comparison blood pressure level (110 vs 115 mmHg), but these would not have been sufficient to account for an approximate doubling of the burden attributable to blood pressure. A particularly important difference however, relates to the relative risk estimates used. The 1990 estimates did not correct for regression dilution bias. As discussed earlier, this bias occurs when relative risk estimates are based on one-off measures of blood pressure, which are subject to random fluctuations. Correcting for this bias with re-measurement data results in "regression to the mean" of blood pressure values, and a steeper association between blood pressure and disease outcomes. Without correction for this bias there will be systematic underestimation of risk of cardiovascular disease by a factor of about two. This therefore explains the almost doubling of burden attributable to blood pressure in the current estimates, and also indicates that the current estimates are the most comprehensive, accurate and robust.

6. Estimating future exposure

We used the following basic steps for estimating future exposure, with each step to some extent dictating the following step.

1. The literature was reviewed to assess what is already known about trends in blood pressure in different populations.
2. Regions were categorized into broad groupings based on likely direction of changes in blood pressure levels over time.
3. The future trends in blood pressure distribution were estimated.

6.1 Literature review of blood pressure trends over time

There is considerable evidence in the literature that changes in risk factors such as blood pressure occur over time. For example, a variety of studies from different world regions and populations have demonstrated increases and decreases in blood pressure levels.

Established market economies (AMR-A, EUR-A, WPR-A)

A large number of studies have documented reductions in mean blood pressure levels in populations in "A" subregions over the past 30 years. These studies have included populations in countries such as the United Kingdom (Capewell et al. 1999; McCarron et al. 2001), New Zealand and Australia (Bonita 1993; Bonita and Beaglehole 1986, 1987; Capewell et al. 2000; Dobson et al. 1999), the United States (Burt et al. 1995; Garraway and Whisnant 1987; McGovern et al. 1996), Finland (Tuomilehto et al. 1991; Vartiainen et al. 1994), Iceland (Sigfusson et al. 1991), Switzerland (Wietlisbach et al. 1997) and Japan (Okayama et al. 1993; Sakata and Labarthe 1996; Shimamoto et al. 1989; Ueshima et al. 2000).

The populations surveyed, the methodologies used, and the time periods and durations covered varied greatly between studies, however, mean SBP levels have decreased by up to 5–10 mmHg for a 10-year period (Bonita 1993; Bonita and Beaglehole 1986, 1987; Capewell et al. 1999, 2000; McCarron et al. 2001; Shimamoto et al. 1989; Sigfusson et al. 1991; Vartiainen et al. 1994; Ueshima et al. 2000). However, in more recent studies (from the mid-1980s onwards) these decreases have been less than 5 mmHg per 10 years (Dobson et al. 1999; McGovern et al. 1996; Okayama et al. 1993; Sakata and Labarthe 1996; Wietlisbach et al. 1997). Data also indicate that the reduction in mean SBP levels has been greatest in the oldest age groups (e.g. mean SBP levels from national Japanese survey data declined by about 2 mmHg in those aged 30–39 and 40–49 years between 1980 and 1990, but by 3–5 mmHg in those aged >70 years) (Sakata and Labarthe 1996).

Low mortality subregions (AMR-B, EMR-B, EUR-B, EUR-C, SEAR-B, WPR-B)

These subregions are quite varied and there are little reliable time trend data. Survey data from the Czech Republic demonstrated only small changes in blood pressure between 1985 and 1992 (Bobak et al. 1997). In China, there is some evidence of increasing blood pressure levels in the past 10 years (Chow and Muyinda 1999; Wu et al. 1996), and in the Republic of Korea, between 1984 and 1999 there were only small changes in the prevalence of hypertension (Suh 2001).

High mortality subregions (AFR-D, AFR-E, AMR-D, EMR-D, SEAR-D)

Very little reliable longitudinal survey data are available in these subregions. However, data from a variety of more "traditional" populations with lower blood pressure have demonstrated that as those populations become more industrialized, risk factor profiles such as blood pressure change. This is particularly evident in migration studies where there is evidence from studies conducted in a variety of settings (Poulter and Sever 1994), such as Africa (Poulter et al. 1988, 1990), China (He et al.

1991a, 1991b) and the Pacific (Joseph et al. 1983; Salmond et al. 1985, 1989), that blood pressure levels rise after migration to more urbanized settings. Pre-migration data suggest that these changes are not due to selective migration (Poulter et al. 1988). Instead, it is likely that factors such as dietary changes of increased intake of sodium, animal protein, fat, and processed foods, and decreased intake of potassium, and vegetable protein are important (He et al. 1991a, 1991b; Poulter and Sever 1994; Poulter et al. 1988). Obviously, the lifestyle and blood pressure changes in an entire population will be slower than those that occur in migrant groups.

Potential categories of blood pressure change

Data presented above indicate that subregions may be classified into three broad groups, and changes in blood pressure over the next 10, 20 and 30 years may be based on trends already documented. Assuming that the absolute increases and decreases in SBP are similar for males and females but greater in the older age groups, the following general scenario was considered.

These changes suggest that:

- the A subregions will experience small decreases in mean SBP levels over the next 30 years, which is consistent with recent literature (Dobson et al. 1999; McGovern et al. 1996; Okayama et al. 1993; Sakata and Labarthe 1996; Wietlisbach et al. 1997). However, with time these reductions attenuate.
- in the case of B and C subregions, there is no change initially in mean SBP levels, but in the following 10-year and 20-year periods there are small decreases in SBP as improvements in lifestyle occur.
- in the case of D and E subregions, small increases in mean SBP levels occur over the entire 30-year period; however these are greater at the beginning (2000–2010) and then start to lessen and level out (See Table 6.17).

Due to the limited data available, these estimates are susceptible to a high degree of uncertainty. There is a wide range of factors that could influence future risk factor levels, and it is difficult to capture these factors even with sophisticated modelling. A decision was therefore made to use a relatively simple, but transparent method for the purposes of these analyses.

Estimates of mean blood pressure levels over time

Tables 6.18–6.20 summarize mean SBP levels by subregion, sex and age in 2010, 2020 and 2030.

Table 6.17 Scenario for changes in mean SBP levels (mmHg) by age and subregion over the next 10, 20 and 30 years

	30–44 years	*45–59 years*	*60–69 years*	*70–79 years*	*≥80 years*
A subregions					
2000 to 2010	–1.5	–2.5	–3.5	–4.5	–4.5
2010 to 2020	–1.0	–2.0	–3.0	–3.5	–3.5
2020 to 2030	–0.5	–1.5	–2.5	–3.0	–3.0
B and C subregions					
2000 to 2010	0	0	0	0	0
2010 to 2020	–1.0	–2.0	–3.0	–4.0	–4.0
2020 to 2030	–1.5	–2.5	–3.5	–4.5	–4.5
D and E subregions					
2000 to 2010	1.0	2.0	3.0	4.0	4.0
2010 to 2020	0.5	1.5	2.5	3.5	3.5
2020 to 2030	0.5	1.5	2.5	3.5	3.5

Table 6.18 Estimates of mean SBP (mmHg) by subregion, sex and age in 2010

	Sex and age group (years)							
	Females				*Males*			
Subregion	*30–44*	*45–59*	*60–69*	*70–79*[a]	*30–44*	*45–59*	*60–69*	*70–79*[a]
AFR-D	124	138	149	154	128	137	144	148
AFR-E	122	133	143	147	125	132	138	141
AMR-A	112.5	124.5	134.5	138.5	120.5	126.5	133.5	136.5
AMR-B	115	130	142	147	122	131	138	141
AMR-D	118	131	142	147	124	133	139	143
EMR-B	126	137	147	150	125	132	139	143
EMR-D	122	137	149	154	124	133	141	145
EUR-A	120.5	133.5	143.5	146.5	128.5	135.5	140.5	142.5
EUR-B	122	141	154	161	128	140	149	153
EUR-C	125	143	158	164	129	138	146	149
SEAR-B	120	130	139	142	122	131	138	141
SEAR-D	118	128	135	139	119	129	137	141
WPR-A	118.5	130.5	140.5	143.5	125.5	134.5	141.5	143.5
WPR-B	115	127	137	141	117	126	133	136

[a] The same SBP levels apply to those aged ≥80 years.

Table 6.19 Estimates of mean SBP (mmHg) by subregion, sex and age in 2020

	Sex and age group (years)							
	Females				*Males*			
Subregion	*30–44*	*45–59*	*60–69*	*70–79*[a]	*30–44*	*45–59*	*60–69*	*70–79*[a]
AFR-D	124.5	139.5	151.5	157.5	128.5	138.5	146.5	151.5
AFR-E	122.5	134.5	145.5	150.5	125.5	133.5	140.5	144.5
AMR-A	111.5	122.5	131.5	135	119.5	124.5	130.5	133
AMR-B	114	128	139	143	121	129	135	137
AMR-D	118.5	132.5	144.5	150.5	124.5	134.5	141.5	146.5
EMR-B	125	135	144	146	124	130	136	139
EMR-D	122.5	138.5	151.5	157.5	124.5	134.5	143.5	148.5
EUR-A	119.5	131.5	140.5	143	127.5	133.5	137.5	139
EUR-B	121	139	151	157	127	138	146	149
EUR-C	124	141	155	160	128	136	143	145
SEAR-B	119	128	136	138	121	129	135	137
SEAR-D	118.5	129.5	137.5	142.5	119.5	130.5	139.5	144.5
WPR-A	117.5	128.5	137.5	140	124.5	132.5	138.5	140
WPR-B	114	125	134	137	116	124	130	132

[a] The same SBP levels apply to those aged ≥80 years.

Table 6.20 Estimates of mean SBP (mmHg) by subregion, sex and age in 2030

	Sex and age group (years)							
	Females				*Males*			
Subregion	*30–44*	*45–59*	*60–69*	*70–79*[a]	*30–44*	*45–59*	*60–69*	*70–79*[a]
AFR-D	125	141	154	161	129	140	149	155
AFR-E	123	136	148	154	126	135	143	148
AMR-A	111	121	129	132	119	123	128	130
AMR-B	112.5	125.5	135.5	138.5	119.5	126.5	131.5	132.5
AMR-D	119	134	147	154	125	136	144	150
EMR-B	123.5	132.5	140.5	141.5	122.5	127.5	132.5	134.5
EMR-D	123	140	154	161	125	136	146	152
EUR-A	119	130	138	140	127	132	135	136
EUR-B	119.5	136.5	147.5	152.5	125.5	135.5	142.5	144.5
EUR-C	122.5	138.5	151.5	155.5	126.5	133.5	139.5	140.5
SEAR-B	117.5	125.5	132.5	133.5	119.5	126.5	131.5	132.5
SEAR-D	119	131	140	146	120	132	142	148
WPR-A	117	127	135	137	124	131	136	137
WPR-B	112.5	122.5	130.5	132.5	114.5	121.5	126.5	127.5

[a] The same SBP levels apply to those aged ≥80 years.

Acknowledgements

Particular thanks are due to the Asia-Pacific Cohort Studies Collaboration secretariat, and all study collaborators for allowing us to access and analyse their data for estimates of relative risk. The Prospective Studies Collaboration assisted with analyses and provided unpublished data on relative risk estimates that could be compared with those presented here.

The authors are grateful to Varsha Parag and Derrick Bennett for biostatistical support, including analyses of data from the Asia-Pacific Cohort Studies Collaboration. Angela Hurley provided valuable research assistance and Clarissa Gould-Thorpe lent much appreciated secretarial support.

Note

1 See the preface for an explanation of this term.

References

Abernethy J, Borhani NO, Hawkins CM et al. (1986) Systolic blood pressure as an independent predictor of mortality in the hypertension detection and follow-up program. *American Journal of Preventive Medicine*, **2**:123–132.

Amery A, Birkenhager W, Brixko P et al. (1985) Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *The Lancet*, **1**:1349–1354.

Andersen LB (1994) Blood pressure, physical fitness and physical activity in 17-year-old Danish adolescents. *Journal of Internal Medicine*, **236**:323–329.

Anonymous (1967) Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *Journal of the American Medical Association*, **202**:1028–1034.

Anonymous (1970) Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. *Journal of the American Medical Association*, **213**:1143–1152.

Anonymous (1973) Control of moderately raised blood pressure. Report of a co-operative randomized controlled trial. *British Medical Journal*, **3**:434–436.

Anonymous (1974) Effect of antihypertensive treatment on stroke recurrence. Hypertension-Stroke Cooperative Study Group. *Journal of the American Medical Association*, **229**:409–418.

Anonymous (1978) Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Plan and preliminary results of a two-year feasibility trial for a multicenter intervention study to evaluate the benefits versus the disadvantages of treating mild hypertension. Prepared for the Veterans Administration-National Heart, Lung, and Blood Institute Study Group for evaluating treatment in mild hypertension. *Annals of the New York Academy of Sciences*, **304**:267–292.

Anonymous (1979a) Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. *Journal of the American Medical Association*, **242**: 2562–2571.

Anonymous (1979b) Five-year findings of the hypertension detection and follow-up program. II. Mortality by race-sex and age. Hypertension Detection and Follow-up Program Cooperative Group. *Journal of the American Medical Association*, **242**:2572–2577.

Anonymous (1980) The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *The Lancet*, **1**:1261–1267.

Anonymous (1981) Distribution of some risk factors for atherosclerosis in nine Italian population samples. The research group ATS-RF2 of the Italian National Research Council. *American Journal of Epidemiology*, **113**: 338–346.

Anonymous (1982a) The effect of treatment on mortality in "mild" hypertension: results of the hypertension detection and follow-up program. *New England Journal of Medicine*, **307**:976–980.

Anonymous (1982b) Five-year findings of the hypertension detection and follow-up program. III. Reduction in stroke incidence among persons with high blood pressure. Hypertension Detection and Follow-up Program Cooperative Group. *Journal of the American Medical Association*, **247**:633– 638.

Anonymous (1984) Effect of stepped care treatment on the incidence of myocardial infarction and angina pectoris. 5-year findings of the hypertension detection and follow-up program. *Hypertension*, **6**:I198–206.

Anonymous (1985) MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *British Medical Journal*, **291**:97–104.

Anonymous (1989a) The INTERSALT co-operative research group. Appendix tables. Centre-specific results by age and sex. *Journal of Human Hypertension*, **3**:331–407.

Anonymous (1989b) The WHO MONICA project. A worldwide monitoring system for cardiovascular diseases: cardiovascular mortality and risk factors in selected communities. *World Health Statistics*, *A*:27–149.

Anonymous (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the systolic hypertension in the elderly program (SHEP). SHEP Cooperative Research Group. *Journal of the American Medical Association*, **265**: 3255–3264.

Anonymous (1992) Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *British Medical Journal*, **304**:405–412.

Anonymous (1997) The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Archives of Internal Medicine*, **157**:2413–2446.

Anonymous (1998) Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. *The Lancet*, **352**:1801–1807.

Anonymous (1999) 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. Guidelines Subcommittee. *Journal of Hypertension*, **17**:151–183.

Aromaa A (1981) Blood pressure level, hypertension and five-year mortality in Finland. *Acta Medica Scandinavica—Supplementum*, **646**:43–50.

Ashour Z, Ibrahim MM, Appel LJ, Ibrahim AS, Whelton PK (1995) The Egyptian National Hypertension Project (NHP). Design and rationale. The NHP Investigative Team. *Hypertension*, **26**:880–885.

APCSC (1999) Determinants of cardiovascular disease in the Asia-Pacific region: protocol for a collaborative overview of cohort studies. *Cardiovascular Disease Prevention*, **2**:281–289.

APCSC (2003a) Blood pressure and cardiovascular disease in the Asia-Pacific region. *Journal of Hypertension*, **21**:707–716.

APCSC (2003b) Blood pressure indices as risk factors for cardiovascular disease in the Asia Pacific region: a pooled analysis. *Hypertension*, **42**:69–75.

Asplund-Carlson A, Carlson LA (1994) Studies in hypertriglyceridaemia. 1. Serum triglyceride distribution and its correlates in randomly selected Swedish middle-aged men. *Journal of Internal Medicine*, **236**:57–64.

Astagneau P, Lang T, Delarocque E, Jeannee E, Salem G (1992) Arterial hypertension in urban Africa: an epidemiological study on a representative sample of Dakar inhabitants in Senegal. *Journal of Hypertension*, **10**:1095–1101.

Baba S, Pan WH, Ueshima H et al. (1991) Blood pressure levels, related factors, and hypertension control status of Japanese and Americans. *Journal of Human Hypertension*, **5**:317–332.

Bajekal M, Boreham R, Erens B et al. (1999) *Health survey for England '98*. The Department of Health, London.

Barnes R (1965) Comparisons of blood pressure and blood cholesterol levels in New Guineans and Australians. *Medical Journal of Australia*, **1**:611–617.

Black HR (1999a) Isolated systolic hypertension in the elderly: lessons from clinical trials and future directions. *Journal of Hypertension*, **17**:S49–54.

Black HR (1999b) The paradigm has shifted, to systolic blood pressure. *Hypertension*, **34**:386–387.

Bobak M, Skodova Z, Pisa Z, Poledne R, Marmot M (1997) Political changes and trends in cardiovascular risk factors in the Czech Republic, 1985–92. *Journal of Epidemiology and Community Health*, **51**:272–277.

Bonita R (1993) Stroke trends in Australia and New Zealand: mortality, morbidity, and risk factors. *Annals of Epidemiology* **3**:529–533.

Bonita R, Beaglehole R (1986) Does treatment of hypertension explain the decline in mortality from stroke? *British Medical Journal*, **292**:191–192.

Bonita R, Beaglehole R (1987) The decline in stroke mortality: the limited role of antihypertensive therapy. *New Zealand Medical Journal*, **100**:454–456.

Bosma H, Appels A, Sturmans F, Grabauskas G, Gostautas A (1994) Differences in mortality and coronary heart disease between Lithuania and the Netherlands: results from the WHO Kaunas-Rotterdam Intervention Study (KRIS). *International Journal of Epidemiology*, **23**:12–19.

Bovet P, Shamlaye C, Kitua A, Riesen WF, Paccaud F, Darioli R (1991) High prevalence of cardiovascular risk factors in the Seychelles (Indian Ocean). *Arteriosclerosis and Thrombosis*, **11**:1730–1736.

Bullen C, Simmons G, Trye P, Lay-Yee R, Bonita R, Jackson R (1998) Cardiovascular disease risk factors in 65–84 year old men and women: results from the Auckland University heart and health study 1993–4. *New Zealand Medical Journal*, **111**:4–7.

Bunker CH, Ukoli FA, Nwankwo MU et al. (1992) Factors associated with hypertension in Nigerian civil servants. *Preventive Medicine*, **21**:710–722.

Burt VL, Culter JA, Higgins M et al. (1995) Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension*, **26**:60–69.

Capewell S, Beaglehole R, Seddon M, McMurray J (2000) Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. *Circulation*, **102**:1511–1516.

Capewell S, Morrison CE, McMurray JJ (1999) Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. *Heart* **81**:380–386.

Carter AB (1970) Hypotensive therapy in stroke survivors. *The Lancet*, **1**: 485–489.

Carvalho JJ, Baruzzi RG, Howard PF et al. (1989) Blood pressure in four remote populations in the INTERSALT study. *Hypertension*, **14**:238–246.

Cashin-Hemphill L, Holmvang G, Chan RC, Pitt B, Dinsmore RE, Lees RS (1999) Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet. Quiet investigators. Quinapril ischemic event trial. *American Journal of Cardiology*, **83**:43–74.

Chow CM, Muyinda MB (1999) Cardiovascular diseases in the People's Republic of China: the patterns and challenges. *ProCor.* Available at http://www.procor.org/procor-hma/msg00406.html.

Collins R, Peto R (1994) Antihypertensive drug therapy: Effects on stroke and coronary heart disease. In: *Textbook of hypertension*. Swales J, ed. Blackwell Scientific Publications, Oxford.

Collins R, Peto R, MacMahon S et al. (1990) Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *The Lancet*, **335**:827–838.

Connor WE, Cerqueira MT, Connor RW, Wallace RB, Malinow MR, Casdorph HR (1978) The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. *American Journal of Clinical Nutrition*, **31**:1131–1142.

Coope J, Warrender TS (1986) Randomised trial of treatment of hypertension in elderly patients in primary care. *British Medical Journal*, **293**:1145–1151.

Cornejo C, Vinueza R, Moscoso F et al. (2000) Prevalence of arterial hypertension in the urban adult population of Ecuador: Quito, Guayaquil, and Cuenca—the PREHTAE study. *Cardiovascular Prevention*, **3**:47–58.

Costa E, Rose GA, Klein CH et al. (1990) Salt and blood pressure in Rio Grande do Sul, Brazil. *Bulletin of the Pan American Health Organization*, **24**:159–176.

Cox DR (1972) Regression models and life tables (with discussion). *Journal of the Royal Statistical Society*, **34**:187.

Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO (1991) Morbidity and mortality in the Swedish trial in old patients with hypertension (STOP-hypertension). *The Lancet*, **338**:1281–1285.

Davis CE, Pajak A, Rywik S et al. (1994) Natural menopause and cardiovascular disease risk factors. The Poland and US collaborative study on cardiovascular disease epidemiology. *Annals of Epidemiology*, **4**:445–448.

Dobson AJ, McElduff P, Heller R, Alexander H, Colley P, D'Este K (1999) Changing patterns of coronary heart disease in the hunter region of New South Wales, Australia. *Journal of Clinical Epidemiology*, **52**:761–771.

Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF (1999) Isolated systolic hypertension: prognostic information provided by pulse pressure. *Hypertension*, **34**:375–380.

Edwards R, Unwin N, Mugusi F et al. (2000) Hypertension prevalence and care in an urban and rural area of Tanzania. *Journal of Hypertension*, **18**:145–152.

Flight RJ, McKenzie-Pollock M, Hamilton MA, Salmond CE, Stokes YM (1984) The health status of fourth form students in Northland. *New Zealand Medical Journal*, **97**:1–6.

Fogari R, Zoppi A, Marasi G et al. (1997) The epidemiology of resting heart rate in a male working population: association with blood pressure, age, smoking habits and other cardiovascular risk factors. *Journal of Cardiovascular Risk*, **4**:209–213.

Foster C, Rotimi C, Fraser H et al. (1993) Hypertension, diabetes, and obesity in Barbados: findings from a recent population-based survey. *Ethnicity and Disease*, **3**:404–412.

Franklin SS (1999) Ageing and hypertension: the assessment of blood pressure indices in predicting coronary heart disease. *Journal of Hypertension*, **17**:S29–36.

Franklin SS, Gustin Wt, Wong ND et al. (1997) Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. *Circulation*, **96**:308–315.

Franklin SS, Khan SA, Wong ND, Larson MG, Levy D (1999) Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation*, **100**:354–360.

Franklin SS, Larson MG, Khan SA et al. (2001) Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham heart study. *Circulation*, **103**:1245–1249.

Frohlich ED (2000) Recognition of systolic hypertension for hypertension. *Hypertension*, **35**:1019–1020.

Fuchs SC, Petter JG, Accordi MC et al. (2001) Establishing the prevalence of hypertension. Influence of sampling criteria. *Arquivos Brasileiros de Cardiologia*, **76**:445–452.

Garcia-Palmieri MR, Costas R Jr. (1986) Risk factors of coronary heart disease: a prospective epidemiologic study in Puerto Rico. In: *Progress in cardiology*. Vol 14. Goodwin JF, Yu PH, eds. Lea and Febiger, Philadelphia, PA.

Garraway WM, Whisnant JP (1987) The changing pattern of hypertension and the declining incidence of stroke. *Journal of the American Medical Association*, **258**:214–217.

Ghannem H, Darioli R, Limam K et al. (2001) Epidemiology of cardiovascular risk factors among schoolchildren in Sousse, Tunisia. *Journal of Cardiovascular Risk*, **8**:87–91.

Ghannem H, Hadj-Fredj A (1997) Prevalence of cardiovascular risk factors in the urban population of Sousse in Tunisia. *Journal of Public Health Medicine*, **19**:392–396.

Gilberts EC, Arnold MJ, Grobbee DE (1994) Hypertension and determinants of blood pressure with special reference to socioeconomic status in a rural South Indian community. *Journal of Epidemiology and Community Health*, **48**: 258–261.

Giles WH, Pacque M, Greene BM et al. (1994) Prevalence of hypertension in rural West Africa. *American Journal of the Medical Sciences*, **308**:271–275.

Gliksman MD, Dwyer T, Wlodarczyk J (1990) Differences in modifiable cardiovascular disease risk factors in Australian schoolchildren: the results of a nationwide survey. *Preventive Medicine*, **19**:291–304.

Gofin J, Kark JD, Abramson JH, Epstein L (1995) Trends in blood pressure levels over time in middle-aged and elderly Jerusalem residents. *European Heart Journal*, **16**:1988–1994.

Gonzalez-Villalpando C, Stern MP, Haffner SM, Gonzalez Villapando ME, Gaskill S, Rivera Martinez D (1999) Prevalence of hypertension in a Mexican population according to the sixth report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. *Journal of Cardiovascular Risk*, **6**:177–181.

Gupta R, Guptha S, Gupta VP, Prakash H (1995) Prevalence and determinants of hypertension in the urban population of Jaipur in western India. *Journal of Hypertension*, **13**:1193–1200.

Haheim LL, Holme I, Hjermann I, Leren P (1993) The predictability of risk factors with respect to incidence and mortality of myocardial infarction and total mortality. A 12-year follow-up of the Oslo study, Norway. *Journal of Internal Medicine*, **234**:17–24.

He J, Klag MJ, Whelton PK et al. (1991a) Migration, blood pressure pattern, and hypertension: the Yi migrant study. *American Journal of Epidemiology*, **134**:1085–1101.

He J, Tell GS, Tang YC, Mo PS, He GQ (1991b) Effect of migration on blood pressure: the Yi people study. *Epidemiology*, **2**:88–97.

He J, Whelton PK (1999) Elevated systolic blood pressure as a risk factor for cardiovascular and renal disease. *Journal of Hypertension—Supplement*, **17**:S7–13.

He J, Whelton PK (2000) Selection of initial antihypertensive drug therapy. *The Lancet*, **356**:1942–1943.

Heinemann L, Barth W, Hoffmeister H (1995) Trend of cardiovascular risk factors in the East German population 1968–1992. *Journal of Clinical Epidemiology*, **48**:787–795.

Helgeland A (1980) Treatment of mild hypertension: a five year controlled drug trial. The Oslo study. *American Journal of Medicine*, **69**:725–732.

Hoffmeister H, Mensink GB, Stolzenberg H (1994) National trends in risk factors for cardiovascular disease in Germany. *Preventive Medicine*, **23**:197–205.

Hughes K, Yeo PP, Lun KC et al. (1990) Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. Differences in risk factor levels. *Journal of Epidemiology and Community Health*, **44**:29–35.

Huang Z, Wu X, Stamler J et al. (1994) A north-south comparison of blood pressure and factors related to blood pressure in the People's Republic of China: a report from the PRC-USA collaborative study of cardiovascular epidemiology. *Journal of Hypertension*, **12**:1103–1112.

Hughes MD, Pocock SJ (1992) Within-subject diastolic blood pressure variability: implications for risk assessment and screening. *Journal of Clinical Epidemiology*, **45**:985–998.

Hunter JM, Sparks BT, Mufunda J, Musabayane CT, Sparks HV, Mahomed K (2000) Economic development and women's blood pressure: field evidence from rural Mashonaland, Zimbabwe. *Social Science and Medicine*, **50**: 773–795.

Hutchinson RG, Watson RL, Davis CE et al. (1997) Racial differences in risk factors for atherosclerosis. The ARIC study. Atherosclerosis risk in communities. *Angiology*, **48**:279–290.

Ibrahim MM, Rizk H, Appel LJ et al. (1995) Hypertension prevalence, awareness, treatment, and control in Egypt. Results from the Egyptian national hypertension project (NHP). NHP investigative team. *Hypertension*, **26**: 886–890.

Idahosa PE (1985) Blood pressure pattern in urban Edos. *Journal of Hypertension—Supplement*, **3**:S379–381.

Idahosa PE (1987) Hypertension: an ongoing health hazard in Nigerian workers. *American Journal of Epidemiology*, **125**:85–91.

Idahosa PE, Ilawole M (1984) Towards Nigeria's first national blood pressure survey: a pilot study of arterial blood pressure in members of the national youth service corps. *Journal of Hypertension, Supplement*, **2**:S209–211.

Jadue L, Vega J, Escobar MC et al. (1999) Risk factors for non communicable diseases: methods and global results of the CARMEN program basal survey. *Revista Medica de Chile*, **127**:1004–1013.

Jamrozik K, Hockey R (1989) Trends in risk factors for vascular disease in Australia. *Medical Journal of Australia*, **150**:14–18.

Jeng JS, Lee TK, Chang YC et al. (1998) Subtypes and case-fatality rates of stroke: a hospital-based stroke registry in Taiwan (SCAN-IV). *Journal of the Neurological Sciences*, **156**:220–226.

Joffres MR, Hamet P, Rabkin SW, Gelskey D, Hogan K, Fodor G (1992) Prevalence, control and awareness of high blood pressure among Canadian adults. Canadian heart health surveys research group. *Canadian Medical Association Journal*, **146**:1997–2005.

Joseph JG, Prior IA, Salmond CE, Stanley D (1983) Elevation of systolic and diastolic blood pressure associated with migration: the Tokelau island migrant study. *Journal of Chronic Diseases*, **36**:507–516.

Kannel WB (1996) Blood pressure as a cardiovascular risk factor: prevention and treatment. *Journal of the American Medical Association*, **275**:1571–1576.

Kannel WB (1999) Historic perspectives on the relative contributions of diastolic and systolic blood pressure elevation to cardiovascular risk profile. *American Heart Journal*, **138**:205–210.

Kannel WB (2000) Elevated systolic blood pressure as a cardiovascular risk factor. *American Journal of Cardiology*, **85**:251–255.

Kannel WB, Belanger AJ (1991) Epidemiology of heart failure. *American Heart Journal*, **121**:951–957.

Kannel WB, Gordon T, Schwartz MJ (1971) Systolic versus diastolic blood pressure and risk of coronary heart disease. The Framingham study. *American Journal of Cardiology*, **27**:335–346.

Kannel WB, Schwartz MJ, McNamara PM (1969) Blood pressure and risk of coronary heart disease: the Framingham study. *Diseases of the Chest*, **56**: 43–52.

Kannel WB, Wolf PA, Verter J, McNamara PM (1970) Epidemiologic assessment of the role of blood pressure in stroke. The Framingham study. *Journal of the American Medical Association*, **214**:301–310.

Khalid ME, Ali ME, Ahmed EK, Elkarib AO (1994) Pattern of blood pressures among high and low altitude residents of southern Saudi Arabia. *Journal of Human Hypertension*, **8**:765–769.

Khaw KT, Rose G (1982) Population study of blood pressure and associated factors in St Lucia, West Indies. *International Journal of Epidemiology*, **11**:372–377.

Kim JS, Jones DW, Kim SJ, Hong YP (1994) Hypertension in Korea: a national survey. *American Journal of Preventive Medicine*, **10**:200–204.

King H, Abdullaev B, Djumaeva S, Nikitin V, Ashworth L, Dobo MG (1998) Glucose intolerance and associated factors in the Fergana valley, Uzbekistan. *Diabetic Medicine*, **15**:1052–1062.

King H, Collins A, King LF et al. (1985) Blood pressure in Papua New Guinea: a survey of two highland villages in the Asaro valley. *Journal of Epidemiology and Community Health*, **39**:215–219.

Kitange HM, Swai AB, Masuki G, Kilima PM, Alberti KG, McLarty DG (1993) Coronary heart disease risk factors in sub-Saharan Africa: studies in Tanzanian adolescents. *Journal of Epidemiology and Community Health*, **47**:303–307.

Klag MJ, He J, Whelton PK, Chen JY, Qian MC, He GQ (1993) Alcohol use and blood pressure in an unacculturated society. *Hypertension*, **22**:365–370.

Klag MJ, Whelton PK, Randall BL et al. (1996) Blood pressure and end-stage renal disease in men. *New England Journal of Medicine*, **334**:13–18.

Lang T, Pariente P, Salem G, Tap D (1988) Social, professional conditions and arterial hypertension: an epidemiological study in Dakar, Senegal. *Journal of Hypertension*, **6**:271–276.

Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP (1999) Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. *Stroke*, **30**:2535–2540.

Leren P, Helgeland A (1986) Oslo hypertension study. *Drugs*, **31**:S41–45.

Lichtenstein MJ, Shipley MJ, Rose G (1985) Systolic and diastolic blood pressures as predictors of coronary heart disease mortality in the Whitehall study. *British Medical Journal*, **291**:243–245.

Lindeberg S, Nilsson-Ehle P, Terent A, Vessby B, Schersten B (1994) Cardiovascular risk factors in a Melanesian population apparently free from stroke and ischaemic heart disease: the Kitava study. *Journal of Internal Medicine*, **236**:331–340.

Linjer E, Hansson L (1997) Underestimation of the true benefits of antihypertensive treatment: an assessment of some important sources of error. *Journal of Hypertension*, **15**:221–225.

Lisk DR, Williams DE, Slattery J (1999) Blood pressure and hypertension in rural and urban Sierra Leoneans. *Ethnicity and Disease*, **9**:254–263.

Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Levy D (1999) Differential impact of systolic and diastolic blood pressure level on JNC-VI staging. Joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*, **34**:381–385.

MacAuley D, McCrum EE, Stott G et al. (1996) Physical activity, physical fitness, blood pressure, and fibrinogen in the Northern Ireland health and activity survey. *Journal of Epidemiology and Community Health*, **50**:258–263.

MacKenzie JM (1996) Intracerebral haemorrhage. *Journal of Clinical Pathology*, **49**:360–364.

MacMahon S (1994) Blood pressure and risks of cardiovascular disease. In: *Textbook of hypertension*. Swales J, ed. Blackwell Scientific Publications, Oxford.

MacMahon S, Neal B (2000) Differences between blood-pressure-lowering drugs. *The Lancet*, **356**:352–353.

MacMahon S, Peto R, Cutler J et al. (1990) Blood pressure, stroke, and coronary heart disease. Part I, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *The Lancet*, **335**:765–774.

MacMahon S, Rodgers A (1993a) The effects of anti-hypertensive treatment on vascular disease: reappraisal of the evidence in 1994. *Journal of Vascular Medicine and Biology*, **4**:265–271.

MacMahon S, Rodgers A (1993b) The effects of blood pressure reduction in older patients: an overview of five randomized controlled trials in elderly hypertensives. *Clinical and Experimental Hypertension (New York)*, **15**: 967–978.

MacMahon S, Sharpe N, Gamble G et al. (2000) Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. PART-2 collaborative research group. Prevention of atherosclerosis with ramipril. *Journal of the American College of Cardiology*, **36**:438–443.

Mann GV, Shaffer RD, Anderson RS, Sandstead HH (1964) Cardiovascular disease in the Masai. *Journal of Atherosclerosis*, **4**:289–312.

Mann JI, Lewis B, Shepherd J et al. (1988) Blood lipid concentrations and other cardiovascular risk factors: distribution, prevalence, and detection in Britain. *British Medical Journal Clinical Research Ed.*, **296**:1702–1706.

Masia R, Pena A, Marrugat J et al. (1998) High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. REGICOR investigators. *Journal of Epidemiology and Community Health*, **52**:707–715.

M'Buyamba-Kabangu JR, Fagard R, Lijnen P et al. (1986) Epidemiological study of blood pressure and hypertension in a sample of urban Bantu of Zaire. *Journal of Hypertension*, **4**:485-491.

M'Buyamba-Kabangu JR, Fagard R, Staessen J, Lijnen P, Amery A (1987) Correlates of blood pressure in rural and urban Zaire. *Journal of Hypertension*, **5**:371–375.

McCarron P, Okasha M, McEwen J, Smith GD (2001) Changes in blood pressure among students attending Glasgow University between 1948 and 1968: analyses of cross sectional surveys. *British Medical Journal*, **322**:885–889.

McGovern PG, Pankow JS, Shahar E et al. (1996) Recent trends in acute coronary heart disease—mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. *New England Journal of Medicine*, **334**:884–890.

Mendis S, Ranasinghe P, Dharmasena BD (1988) Prevalence of hypertension in Sri Lanka. A large population study in the central province. *Public Health*, **102**:455–462.

Miall WE (1982) Systolic or diastolic hypertension—which matters most? *Clinical and Experimental Hypertension—Part A, Theory and Practice*, **4**:1121–1131.

Ministry of Health (1999) *NZ food: NZ people. Key results of the 1997 national nutrition survey*. Ministry of Health, Wellington.

Misra A, Sharma R, Pandey RM, Khanna N (2001) Adverse profile of dietary nutrients, anthropometry and lipids in urban slum dwellers of northern India. *European Journal of Clinical Nutrition*, **55**:727–734.

Mitchell GF, Moye LA, Braunwald E et al. (1997) Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. *Circulation*, **96**:4254–4260.

Miura K, Dyer AR, Greenland P et al. (2001) Pulse pressure compared with other blood pressure indexes in the prediction of 25-year cardiovascular and all-cause mortality rates: The Chicago Heart Association Detection Project in Industry Study. *Hypertension*, **38**:232–237.

Mufunda J, Scott LJ, Chifamba J et al. (2000) Correlates of blood pressure in an urban Zimbabwean population and comparison to other populations of African origin. *Journal of Human Hypertension*, **14**:65–73.

Murray CJL, Lopez AD, eds. (1996) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol. 1. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Nan L, Tuomilehto J, Dowse G et al. (1991) Prevalence and medical care of hypertension in four ethnic groups in the newly-industrialized nation of Mauritius. *Journal of Hypertension*, **9**:859–866.

NCHS (2002) *The National Health and Nutrition Examination Survey (NHANES) III*. National Center for Health Statistics. Available at http://www.cdc.gov/nchs/nhanes.htm.

Neal B, MacMahon S (1999) An overview of 37 randomised trials of blood pressure lowering agents among 270 000 individuals. World Health Organization-International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. *Clinical and Experimental Hypertension (New York)*, **21**:517–529.

Neal B, MacMahon S, Chapman N (2000) Effects of ace inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *The Lancet*, **356**:1955–1964.

Nyarko NK, Adubofour KO, Ofei F, Pobee JO, Owusu SK (1994) Serum lipids and lipoprotein in adult Ghanaians. *Journal of Internal Medicine*, **236**: 251–253.

Ogunlesi A, Osotimehin B, Abbiyessuku F et al. (1991) Blood pressure and educational level among factory workers in Ibadan, Nigeria. *Journal of Human Hypertension*, **5**:375–380.

Okayama A, Ueshima H, Marmot MG, Nakamura M, Kita Y, Yamakawa M (1993) Changes in total serum cholesterol and other risk factors for cardio-

vascular disease in Japan 1980–1989. *International Journal of Epidemiology*, **22**:1038–1047.

Okesina AB, Oparinde DP, Akindoyin KA, Erasmus RT (1999) Prevalence of some risk factors of coronary heart disease in a rural Nigerian population. *East African Medical Journal*, **76**:212–216.

Oviasu VO, Okupa FE (1980a) Arterial blood pressure and hypertension in Benin in the equatorial forest zone of Nigeria. *Tropical and Geographical Medicine*, **32**:241–244.

Oviasu VO, Okupa FE (1980b) Relation between hypertension and occupational factors in rural and urban Africans. *Bulletin of the World Health Organization*, **58**:485–489.

Page LB, Damon A, Moellering RC, Jr. (1974) Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation*, **49**:1132–1146.

Pahor M, Psaty BM, Alderman MH et al. (2000) Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *The Lancet*, **356**: 1949–1954.

Patrick RC, Prior IA, Smith JC, Smith AH (1983) Relationship between blood pressure and modernity among Ponapeans. *International Journal of Epidemiology*, **12**:36–44.

Paul O, Lepper M, Phelan W, Dupertuis G, MacMillan A, McKean H (1963) A longitudinal study of coronary heart disease. *Circulation*, **28**:20–31.

Pauletto P, Caroli M, Pessina AC, Dal Palu C (1994) Hypertension prevalence and age-related changes of blood-pressure in semi-nomadic and urban Oromos of Ethiopia. *European Journal of Epidemiology*, **10**:159–164.

People's Republic of China—United States Cardiovascular and Cardiopulmonary Epidemiology Research Group (1992) An epidemiological study of cardiovascular and cardiopulmonary disease risk factors in four populations in the People's Republic of China. Baseline report from the PRC-USA collaborative study. *Circulation*, **85**:1083–1096.

Perry HM, Jr. (1977) Treatment of mild hypertension. Preliminary results of a two-year feasibility trial. *Circulation Research*, **40**:I180–187.

Pitt B, Byington RP, Furberg CD et al. (2000) Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*, **102**:1503–1510.

Poulter N, Khaw KT, Hopwood BE et al. (1984) Blood pressure and associated factors in a rural Kenyan community. *Hypertension*, **6**:810–813.

Poulter N, Sever P (1994) Blood pressure in other populations. A. Low blood pressure populations and the impact of rural-urban migration. In: *Textbook of hypertension*. Swales J, ed. Blackwell Scientific Publications, Oxford.

Poulter NR, Khaw KT, Hopwood BE et al. (1990) The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *British Medical Journal*, **300**:967–972.

Poulter NR, Khaw KT, Sever PS (1988) Higher blood pressures of urban migrants from an African low-blood pressure population are not due to selective migration. *American Journal of Hypertension*, **1**:S143–145.

Progress Collaborative Group (2001) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *The Lancet*, **358**:1033–1041.

Prospective Studies Collaboration (PSC) (1995) Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 45 000 people in 45 prospective cohorts. *The Lancet*, **346**:1647–1653.

Psaty BM, Smith NL, Siscovick DS et al. (1997) Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *Journal of the American Medical Association*, **277**:739–745.

Puska P, Matilainen T, Jousilahti P et al. (1993) Cardiovascular risk factors in the Republic of Karelia, Russia, and in North Karelia, Finland. *International Journal of Epidemiology*, **22**:1048–1055.

Ramirez MO, Pino CT, Furiasse LV, Lee AJ, Fowkes FG (1995) Paraguayan national blood pressure study: prevalence of hypertension in the general population. *Journal of Human Hypertension*, **9**:891–897.

Ribeiro AB, Ribeiro MB (1986) Epidemiological and demographic considerations. Hypertension in underdeveloped countries. *Drugs*, **31**:S23–28.

Ribeiro MB, Ribeiro AB, Neto CS et al. (1981) Hypertension and economic activities in São Paulo, Brazil. *Hypertension*, **3**:II-233–237.

Rosenthal J (1989) The epidemiology of blood pressure in young Mexican adults. *Journal of Hypertension*, **7**:355–360.

Sakata K, Labarthe DR (1996) Changes in cardiovascular disease risk factors in three Japanese national surveys 1971–1990. *Journal of Epidemiology*, **6**:93–107.

Salmond CE, Joseph JG, Prior IA, Stanley DG, Wessen AF (1985) Longitudinal analysis of the relationship between blood pressure and migration: the Tokelau Island migrant study. *American Journal of Epidemiology*, **122**: 291–301.

Salmond CE, Prior IA, Wessen AF (1989) Blood pressure patterns and migration: a 14-year cohort study of adult Tokelauans. *American Journal of Epidemiology*, **130**:37–52.

SarrafZadegan N, AminiNik S (1997) Blood pressure pattern in urban and rural areas in Isfahan, Iran. *Journal of Human Hypertension*, **11**:425–428.

Seedat YK, Seedat MA, Hackland DB (1982) Prevalence of hypertension in the urban and rural Zulu. *Journal of Epidemiology and Community Health*, **36**:256–261.

Sesso HD, Stampfer MJ, Rosner B et al. (2000) Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men. *Hypertension*, **36**:801–807.

Sever PS, Gordon D, Peart WS, Beighton P (1980) Blood-pressure and its correlates in urban and tribal Africa. *The Lancet*, **2**:60–64.

Shelley E, Daly L, Collins C et al. (1995) Cardiovascular risk factor changes in the Kilkenny health project. A community health promotion programme. *European Heart Journal*, **16**:752–760.

Shelley E, Daly L, Kilcoyne D, Graham I, Mulcahy R (1991) Risk factors for coronary heart disease: a population survey in county Kilkenny, Ireland, in 1985. *Irish Journal of Medical Science*, **160**:S22–28.

Shimamoto T, Komachi Y, Inada H et al. (1989) Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation*, **79**:503–515.

Sigfusson N, Sigvaldason H, Steingrimsdottir L et al. (1991) Decline in ischaemic heart disease in Iceland and change in risk factor levels. *British Medical Journal*, **302**:1371–1375.

Simmons D (1983) Blood pressure, ethnic group, and salt intake in Belize. *Journal of Epidemiology and Community Health*, **37**:38–42.

Simmons D, Barbour G, Congleton J et al. (1986) Blood pressure and salt intake in Malawi: an urban rural study. *Journal of Epidemiology and Community Health*, **40**:188–192.

Singh RB, Beegom R, Ghosh S et al. (1997a) Epidemiological study of hypertension and its determinants in an urban population of North India. *Journal of Human Hypertension*, **11**:679–685.

Singh RB, Beegom R, Mehta AS et al. (1998) Prevalence and risk factors of hypertension and age-specific blood pressures in five cities: a study of Indian women. NKP Salve Institute of Medical Sciences, Nagpur, India. Five city study group. *International Journal of Cardiology*, **63**:165–173.

Singh RB, Sharma JP, Rastogi V, Niaz MA, Singh NK (1997b) Prevalence and determinants of hypertension in the Indian social class and heart survey. *Journal of Human Hypertension*, **11**(1):51–56.

Smith WM (1977) Treatment of mild hypertension: results of a ten-year intervention trial. *Circulation Research*, **40**:I98–105.

Smith WC, Tunstall-Pedoe H, Crombie IK, Tavendale R (1989) Concomitants of excess coronary deaths--major risk factor and lifestyle findings from 10 359 men and women in the Scottish Heart Health Study. *Scottish Medical Journal*, **34**:550–555.

Soyannwo MA, Kurashi NY, Gadallah M et al. (1998) Blood pressure pattern in Saudi population of Gassim. *African Journal of Medicine and Medical Sciences*, **27**:107–116.

Sprafka JM, Burke GL, Folsom AR, Luepker RV, Blackburn H (1990) Continued decline in cardiovascular disease risk factors: results of the Minnesota Heart Survey, 1980–1982 and 1985–1987. *American Journal of Epidemiology*, **132**:489–500.

Staessen J, Fagard R, Thijs L, Celis H et al. (1997) Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *The Lancet*, **350**:757–764.

Stamler J, Stamler R, Neaton JD (1993) Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Archives of Internal Medicine*, **153**:598–615.

Steyn K, Fourie J, Lombard C, Katzenellenbogen J, Bourne L, Jooste PL (1996) Hypertension in the black community of the Cape Peninsula, South Africa. *East African Medical Journal*, **73**:758–763.

Steyn K, Jooste PL, Langenhoven ML et al. (1985) Coronary risk factors in the coloured population of the Cape Peninsula. *South African Medical Journal*, **67**:619–625.

Stokes J 3rd., Kannel WB, Wolf PA, D'Agostino RB, Cupples LA (1989) Blood pressure as a risk factor for cardiovascular disease. The Framingham study—30 years of follow-up. *Hypertension*, **13**:I13–18.

Strachan D, Rose G (1991) Strategies of prevention revisited: Effects of imprecise measurement of risk factors on the evaluation of "high-risk" and "population-based" approaches to prevention of cardiovascular disease. *Journal of Clinical Epidemiology*, **44**:1187–1196.

Suh I (2001) Cardiovascular mortality in Korea: a country experiencing epidemiologic transition. *Acta Cardiologica*, **56**:75–81.

Swai AB, McLarty DG, Kitange HM et al. (1993) Low prevalence of risk factors for coronary heart disease in rural Tanzania. *International Journal of Epidemiology*, **22**:651–659.

Swales J (1994) *Textbook of hypertension*. Blackwell Scientific Publications, Oxford.

Teo KK, Burton JR, Buller CE et al. (2000) Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: the Simvastatin/Enalapril coronary atherosclerosis trial (SCAT). *Circulation*, **102**:1748–1754.

Tuomilehto J, Bonita R, Stewart A, Nissinen A, Salonen JT (1991) Hypertension, cigarette smoking, and the decline in stroke incidence in eastern Finland. *Stroke*, **22**:7–11.

Ueshima H, Zhang XH, Choudhury SR (2000) Epidemiology of hypertension in China and Japan. *Journal of Human Hypertension*, **14**:765–769.

Vaccarino V, Borgatta A, Gallus G, Sirtori CR (1995) Prevalence of coronary heart disease risk factors in northern-Italian male and female employees. *European Heart Journal*, **16**:761–769.

van der Sande MA, Bailey R, Faal H et al. (1997) Nationwide prevalence study of hypertension and related non-communicable diseases in the Gambia. *Tropical Medicine and International Health*, **2**:1039–1048.

Vartiainen E, Jousilahti P, Alfthan G, Sundvall J, Pietinen P, Puska P (2000) Cardiovascular risk factor changes in Finland, 1972–1997. *International Journal of Epidemiology*, **29**:49–56.

Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P (1994) Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *British Medical Journal*, **309**:23–27.

Warlow C, Dennis M, VanGijn J et al. (1996) *Stroke. A practical guide to management*. Blackwell Science Ltd, Oxford.

Whelton P, He J, Klag M (1994) Blood pressure in westernised populations. In: *Textbook of hypertension*. Swales J, ed. Blackwell Scientific Publications, Oxford.

Whelton PK (1994) Epidemiology of hypertension. *The Lancet*, **344**:101–106.

Whelton PK, Klag MJ (1989) Hypertension as a risk factor for renal disease. Review of clinical and epidemiological evidence. *Hypertension*, **13**:I19–27.

Wietlisbach V, Paccaud F, Rickenbach M, Gutzwiller F (1997) Trends in cardiovascular risk factors (1984–1993) in a Swiss region: results of three population surveys. *Preventive Medicine*, **26**:523–533.

Wolff FW, Lindeman RD (1966) Effects of treatment in hypertension. Results of a controlled study. *Journal of Chronic Diseases*, **19**:227–240.

Wu X, Huang Z, Stamler J et al. (1996) Changes in average blood pressure and incidence of high blood pressure 1983–1984 to 1987–1988 in four population cohorts in the People's Republic of China. The PRC–USA Cardiovascular and Cardiopulmonary Epidemiology Research Group. *Journal of Hypertension*, **14**:1267–1274.

Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *New England Journal of Medicine*, **342**:145–153.

Appendix A: Sampling methods, response rate and measuring techniques in blood pressure studies included in the review

Africa

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
AFR-D	Gambia	van der Sande et al. (1997)	Multi-stage stratified cluster sampling based on the 1993 census	94.9%	?Trained & certified staff Automated electronic sphg ?cuff 2 measures taken ?position after ?mins rest, ?arm
	Ghana	Nyarko et al. (1994)	Employees from the University of Ghana were randomly selected	Not stated	Trained & certified staff ?sphg ?cuff ?measure taken ?position after ?mins rest, ?arm
	Liberia	Giles et al. (1994)	House-to-house survey of adults in rural area	84%	?Trained & certified staff Automated digital sphg ?cuff 2 measures taken sitting after 5 mins rest, L arm
	Mauritius	Nan et al. (1991)	Population clusters were selected randomly by 2-stage process based on census	83.4–88.9% (M and F)	?Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Nigeria	Akinkug (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Nigeria	Bunker et al. (1992)	Sample of urban civil servants from six ministries of Bendel State	Not stated	Trained & certified staff Standard sphg various cuffs 3 measures taken sitting after 5 mins rest, ?arm
	Nigeria	Idahosa (1985)	Sample of males from the Edos tribal group in Benin	Not stated	Trained & certified staff Automated sphg various cuffs 3 measures taken sitting after 5 mins rest, ?arm

continued

Africa (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Nigeria	Idahosa (1987)	Cross sectional survey in Bendel, Nigeria	Not stated	Trained & certified staff Automated digital sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Nigeria	Idahosa and Llwawole (1984)	Survey of Corps members stationed in Bendel State	Not stated	Trained & certified staff Standard sphg one cuff 3 measures taken sitting after 5 mins rest, R arm
	Nigeria	Ogunlesi et al. (1991)	Sample taken from male employees at a factory in Ibadan, Nigeria	Not stated	Trained & certified staff Automated sphg various cuffs ?measure taken sitting after 5 mins rest, R arm
	Nigeria	Okesina et al. (1999)	Houses in villages selected randomly, then individuals randomly selected	Not stated	?Trained & certified staff Standard sphg ?cuff ?measures taken sitting after ?mins rest, ?arm
	Nigeria	Oviasu and Okupa (1980a, 1980b)	Cross sectional survey of workers in state capital secretariat	95%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, L arm
	Senegal	Astagneau et al. (1992)	Random inclusion of households using a town map	96% households then 86% individuals	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ?arm
	Senegal	Lang et al. (1988)	Sample taken from cross-sectional survey of employees of six companies in Dakar, Senegal	97%	Trained & certified staff Standard mercury sphg ?cuff ?measure taken sitting after 5 mins rest, ?arm
	Seychelles	Bovet et al. (1991)	Age and sex strata random sampling from national census	84–89%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

	Sierra Leone	Lisk et al. (1999)	Multistage random sampling from census	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, L arm
AFR-E	Democratic Republic of the Congo	M'Buyamba-Kabangu et al. (1986, 1987)	Rural population sampled from one village and compared to random sample of urban population	Not stated	Trained & certified staff Standard aneroid sphg one cuff 5 measures taken sitting after 5 mins rest, R arm
	Ethiopia	Pauletto et al. (1994)	From the outpatient department of a rural hospital	Not stated	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Kenya	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Kenya	Poulter et al. (1984)	Random from census	Not stated	Trained & certified staff Standard sphg ?cuff 2 measures taken ?position after 5 mins rest, ?arm
	Malawi	Simmons et al. (1986)	Two cross sectional surveys of an urban estate and "typical" rural villages	96.9%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	South Africa	CORIS study (P. Elliot, personal communication, 2001)	A stratified sample by age and sex from census data	Not stated	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	South Africa	Mollen (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm

continued

Africa (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	South Africa	Morbid (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	South Africa	Seedat (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	South Africa	Seedat et al. (1982)	House-to-house study of urban and rural population	Not stated	Trained & certified staff Standard aneroid sphg various cuffs 3 measures taken sitting after 5 mins rest, ?arm
	South Africa	Steyn et al. (1985)	A stratified sample by age and sex from census data	Not stated	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	South Africa	Steyn et al. (1996)	A stratified proportional sample from target population using census data	Not stated	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	United Republic of Tanzania	Edwards et al. (2000)	Randomized cluster sampling based on households from census—all adults in house	80–85% (Shari) 64–79% (Ilala)	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

United Republic of Tanzania	Kitange et al. (1993)	Whole population in four villages, random sample in four	60–94%	?Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
United Republic of Tanzania	Swai et al. (1993)	Community based survey of eight villages in three areas in rural United Republic of Tanzania	90.9–96%	Trained & certified staff Standard mercury sphg ?cuff 2 measures taken sitting after ?mins rest, R arm
Zimbabwe	Allain and Matenga (T. Allain, personal communication, 2001)	Stratified sampling	Not stated	Trained & certified staff Standard sphg ? various cuffs 2 measures taken sitting after 5 mins rest, R arm
Zimbabwe	Hunter et al. (2000)	From health facilities	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Zimbabwe	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Zimbabwe	Mufunda et al. (2000)	Random sampling of household clusters, then sampled adults according to "probability proportionate to size"—over sampling of older age groups	56% of potentially eligible, 79% of those contacted	Trained & certified staff Automated and standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

? Specific details not given.

Americas

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
AMR-A	Canada	Joffres et al. (1992)	A probability sample was selected from the health insurance registries in each province	64–69%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Halifax	MONICA study (Anonymous 1989b)	Sample from public health service register	41–63%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Labrador	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	St Johns	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	USA	Sprafka et al. (1990)	Clusters of 1 000 households in the metropolitan area were randomly selected	68.1%	Trained & certified staff RZ sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	USA	Hutchinson et al. (1997)	Random sample from study centres	Not stated	Trained & certified staff Standard sphg various cuffs 3 measures taken sitting after 5 mins rest, R arm
	USA (NHANES III)	Burt et al. (1995); NHANES web site (NCHS 2002)	Stratified multistage probability sample designs	77%	Trained & certified staff Standard sphg various cuffs 3 measures taken sitting after 5 mins rest, R arm
	Chicago	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Goodman	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

	Goodman	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Hawaii	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Jackson	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Jackson	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Stanford	MONICA study (Anonymous 1989b)	Sample from commercial household directory	66%	Trained & certified staff Semi-automated sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
AMR-B	Argentina	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Argentina	Delena (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Bahamas	Nassau (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Barbados	Foster et al. (1993)	A stratified random sample was drawn from enumeration registers in the Bridgetown area of Barbados	46%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

continued

Americas (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Barbados	Ischib (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Belize	Simmons et al. (1983)	Sample of seven largest villages in Belize road, Cayo district, using electoral roll	92%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 10 mins rest, L arm
	Brazil	Costa et al. (1990)	Random survey of residents in Rio Grande do Sul	94.4%	?Trained & certified staff Standard sphg ?cuff ?2 measures taken sitting after 5 mins rest, ?arm
	Brazil	Fuchs et al. (2001); F.D. Fuchs, personal communication, 2001	Representative survey of urban population in Porto Alegre	93%	Trained & certified staff Aneroid sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Brazil	Ribeiro and Ribeiro (1986); Ribeiro et al. (1981)	Random selection of individuals from city of São Paulo	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Xingu	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Yanomamo	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Chile	Barrios (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm

Chile	L. Jadue, personal communication, 2001; Jadue et al. (1999)	Stratified sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
Colombia	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Jamaica	Miall (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
Jamaica	R. Wilks et al. personal communication, 2001	Stratified sampling from Sparush Town, Jamaica	64%	Trained & certified staff Standard sphg various cuff sizes 2 measures taken sitting after 5 mins rest, R arm
Mexico	Gonzalez-Villalpando et al. (1999); C. Gonzalez, personal communication, 2001	Random sample of population from a selected area—a complete household survey was performed	80.2%	Trained & certified staff RZ sphg various cuffs 3 measures taken sitting after 5 mins rest, R arm
Mexico	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Mexico	Rosenthal (1989)	Random sample of students enrolled in Mexico City college system	97%	Trained & certified staff Standard sphg one cuff 3 measures taken sitting after 5 mins rest, R arm
Mexico	L. Yamamoto, personal communication, 2001	Random stratified sample in Mexico city	87%	Trained & certified staff Standard sphg various cuff sizes 2 measures taken sitting after 5 mins rest, ? arm

continued

Americas (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Paraguay	Ramirez et al. (1995)	Multistage sampling process, within country	Not stated	?Trained & certified staff Aneroid sphg ?cuff 2 measures taken sitting after 10 mins rest, either arm
	Saint Lucia	Khaw and Rose (1982)	A random sample, stratified by age and sex from 2 of the 7 valleys, based on census data	97%	?Trained & certified staff RZ sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	Trinidad and Tobago	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Trinidad and Tobago	Tobago (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Uruguay	Latir (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
AMR-D	Ecuador	Cornejo et al. (2000)	Multistage stratified sample in three cities in Ecuador	99%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 10 mins rest, R arm

? Specific details not given.

Eastern Mediterranean

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
EMR-B	Iran (Islamic Republic of)	SarrafZadegan and AminiNik (1997)	Random cluster sampling	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 10 mins rest, R arm
	Jordan	Jaddou HY (H. Jaddou, personal communication, 2001)	Stratified sample from the population	62%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Saudi Arabia	Khalid et al. (1994)	Recruited from two areas with the assistance of the head of tribes	Not stated	Trained & certified staff Standard sphg ?cuff 3 measures taken sitting after 10 mins rest, R arm
	Saudi Arabia	Soyannwo et al. (1998)	Cross-sectional house-to-house population survey	73.6%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Tunisia	Ghannem and Hadj-Fredj (1997); H. Ghannem, personal communication, 2001	Random stratified sample of adult urban population using household survey	71.1%	Trained & certified staff Electronic sphg various cuffs 3 measures taken sitting after 15 mins rest, ?arm
	Tunisia	Ghannem et al. (2001); H. Ghannem, personal communication, 2001	Random stratified sample of schoolchildren from the urban region of Sousse	95.4%	Trained & certified staff Electronic sphg various cuffs 2 measures taken sitting after 10 mins rest, ?arm
EMR-D	Egypt	Ashour et al. (1995); Ibrahim et al. (1995)	Multistage probability sample of clusters of households	85%	Trained & certified staff standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

? Specific details not given.

Europe

Subregion	Country or area	Study (reference)	Sampling methods	Response rate	BP measurement
EUR-A	Belgium, Charleroi	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Charleroi	MONICA study (Anonymous 1989b)	Sample from population register	59%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Ghent	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Ghent	MONICA study (Anonymous 1989b)	Sample from public health service register	54–57%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Belgium; Luxembourg	MONICA study (Anonymous 1989b)	Sample from electoral register	54–54%	Trained & certified staff RZ sphg one cuff 2 measures taken lying after 5 mins rest, either arm
	Former Czechoslovakia	Czech (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Denmark	Andersen (1994)	Sample from schools	Not stated	?Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	Denmark	INTERSALT study (Anonymous 1989a)	Community sample	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

Glostrup	MONICA study (Anonymous 1989b)	Sample from population register	79–80%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Finland	Puska et al. (1993)	Stratified random sample from population registers	68–81%	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 15 mins rest, R arm
Finland	Vartiainen et al. (2000)	Sample from population register	70–85%	Trained & certified staff ?sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
Joensuu	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Kuopio	MONICA study (Anonymous 1989b)	Sample from population register	85%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
Turku	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Turku/Loimaa	MONICA study (Anonymous 1989b)	Sample from population register	86%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
N. Karelia	MONICA study (Anonymous 1989b)	Sample from population register	80%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
France, Bas-Rhin	MONICA study (Anonymous 1989b)	Sample from population register	86%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm

continued

Europe (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Lille	MONICA study (Anonymous 1989b)	Sample from communities & electoral roll	65–80%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Former German Democratic Republic	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Berlin-Lichtenberg	MONICA study (Anonymous 1989b)	Sample from national X-ray screening register	70–80%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Cottbus county	MONICA study (Anonymous 1989b)	Sample from national X-ray screening register	77%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Halle county	MONICA study (Anonymous 1989b)	Sample from national X-ray screening register	88%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Karl-Marx-Stadt	MONICA study (Anonymous 1989b)	Sample from national X-ray screening register	90%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Germany	Heinemann et al. (1995)	Random sample from urban and rural population	Not stated	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	Germany	MONICA study (Anonymous 1989b)	Sample from national X-ray screening register	72%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Augsburg (Rural)	MONICA study (Anonymous 1989b)	Sample from population register	82–84%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

Augsburg (Urban)	MONICA study (Anonymous 1989b)	Sample from population register	76–80%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Bernried	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Bremen	MONICA study (Anonymous 1989b)	Sample from resident register	71%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Heidelberg	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Rhein-Neckar	MONICA study (Anonymous 1989b)	Sample from population register	74%	Trained & certified staff Automatic/standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
Iceland	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Iceland	MONICA study (Anonymous 1989b)	Sample from national roster	76%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, either arm
Italy	Fogari et al. (1997)	All men belonging to the same working community	Not stated	Trained & certified staff Standard sphg various cuffs 3 measures taken sitting after 5 mins rest, R arm
Italy	Nine populations (Anonymous 1981)	Random sample of nine populations from eight areas	62%	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 4 mins rest, R arm
Italy	Vaccarino et al. (1995)	All employees of IBM asked to participate	45%	Trained & certified staff ?sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm

continued

Europe (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Bassiano	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Brianza	MONICA study (Anonymous 1989b)	Sample from population register	70–71%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Friuli	MONICA study (Anonymous 1989b)	Sample from regional health roll	80–82%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Gubbio	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Latina	MONICA study (Anonymous 1989b)	Sample from electoral rolls	76%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Mirano	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Naples	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Israel	Gofin et al. (1995)	All residents in a geographically defined area asked to participate	85%	Trained & certified staff Standard sphg ?cuff 3 measures taken sitting after 5 mins rest, R arm
	Israel	Kark (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm

Malta	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Malta	MONICA study (Anonymous 1989b)	Sample from electoral rolls	62%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
Netherlands	Bosma et al. (1994)	Sample taken from a 10-year follow-up to the Kaunus-Rotterdam Intervention Study (KRIS)	Not stated	Trained & certified staff ?sphg ?cuff ?measures taken sitting after ?mins rest, ?arm
Netherlands	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Norway	Trumso (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
Portugal	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Slovenia	Gradsk (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
Spain	Masia et al. (1998)	Two-stage population random sample stratified by age from census data	72.7%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, ?arm
Catalonia	MONICA study (Anonymous 1989b)	Sample from population register	76–79%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

continued

Europe (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Manresa	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, ?arm
	Torrejon	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Sweden	Asplund-Carlson and Carlson (1994)	Selected at random	63%	Trained & certified staff standard sphg ?cuff ?measure taken sitting after no rest, ? arm
	N. Sweden	MONICA study (Anonymous 1989b)	Sample from population register	84–86%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Switzerland, Vaud; Fribourg	MONICA study (Anonymous 1989b)	Sample from population register	61–69%	Trained & certified staff RZ sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	United Kingdom	British Regional Heart Study (P. Elliot, personal communication, 2001)	Random sample from general practice registers	77%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	United Kingdom	Mann et al. (1988)	Opportunistic case finding from GP lists and random sampling from age–sex registers	73%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, ?arm
	England	Bajekal et al. (1999)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm

	Birmingham	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Northern Ireland, Belfast	MONICA study (Anonymous 1989b)	Sample from GP lists	57–70%	Trained & certified staff RZ sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Scotland	Hawth (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
	Scotland	Smith et al. (1989)	Sample taken from selected districts then random sampling from GP lists	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Scotland, Glasgow	MONICA study (Anonymous 1989b)	Sample from GP lists	50–64%	Trained & certified staff RZ sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Wales, South Wales	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Ireland	MacAuley et al. (1996)	Random sample	70%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, L arm
	Ireland	Shelley et al. (1995, 1991)	Random sample from electoral roll in two communities	70–75%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
EUR-B	Poland	Davis et al. (1994)	A stratified random sample of the population	Not stated	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	Krakow	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

continued

Europe (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Warsaw	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Warsaw	MONICA study (Anonymous 1989b)	Sample from electoral register	74%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Uzbekistan	King et al. (1998)	Sample of semi-rural and urban population taken from house-to-house census	Not stated	Trained & certified staff Standard mercury sphg ?cuff ?measure taken sitting after 10 mins rest, R arm
	Former Yugoslavia	MONICA study (Anonymous 1989b)	Sample from population register	82%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
EUR-C	Hungary	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Budapest	MONICA study (Anonymous 1989b)	Sample from population register	75–80%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, either arm
	Lithuania	Bosma et al. (1994)	Sample taken from a 10 year follow-up to the Kaunus-Rotterdam Intervention Study (KRIS)	Not stated	Trained & certified staff ?sphg ?cuff ?measure taken sitting after ?mins rest, ?arm

Russian Federation	Puska et al. (1993)	Stratified random sample from population registers	77–92%	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 15 mins rest, R arm
The former Soviet Union[a]	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Kaunas	MONICA study (Anonymous 1989b)	Sample from GP lists	70%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Moscow	MONICA study (Anonymous 1989b)	Sample from GP lists	78%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Moscow	MONICA study (Anonymous 1989b)	Sample from GP lists	67%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Novosibirsk	MONICA study (Anonymous 1989b)	Sample from electoral list	69%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
Novosibirsk	MONICA study (Anonymous 1989b)	Sample from electoral list	73%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm

? Specific details not given.

[a] Russia in the original publication.

South-East Asia

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
SEAR-B	Sri Lanka	Mendis et al. (1988)	Everybody visiting patients at a teaching hospital in Sri Lanka	Not stated	Trained & certified staff Standard sphg ?cuff 1 measure taken sitting after 5 mins rest, ?arm
	Sri Lanka	Mohidn (P. Elliot, personal communication, 2001)	Not stated	Not stated	Trained & certified staff ?standard sphg ?cuff 2 measures taken sitting after 5 mins rest, ?arm
SEAR-D	India	B.V. Babu, personal communication, 2001; Y.S. Kusuma, personal communication, 2001	Random sampling in the state of Andhra Pradesh	98%	Trained & certified staff standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	India	B.V. Babu, personal communication, 2001; Y.S. Kusuma, personal communication, 2001	Multistage sampling from rural and urban areas	99%	Trained & certified staff standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	India	Gilberts et al. (1994)	Cross-sectional survey conducted door-to-door in a rural south Indian community	Not stated	Trained & certified staff standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	India	Gupta et al. (1995)	Randomly chosen wards from different areas of the city	57.3–87.9% (F–M)	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, ?arm

India	India (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
India	Misra et al. (2001); A. Misra, personal communication, 2001 Delhi	Multistage cluster sampling from twenty schools and colleges located in south Delhi	100%	Trained & ?certified staff Standard mercury sphg one cuff 2–3 measures taken sitting after 5 mins rest, ?arm
India	Reddy (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
India	Singh et al. (1997a)	Using census data, selected wards in district at random, then street blocks, then households	81.3%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
India	Singh et al. (1997b)	Using census data, selected two villages in the district at random, then street blocks, then households	86.6%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
India	Singh et al. (1998)	Using census data randomly selected streets, then household clusters	83–90%	Trained & certified staff Standard sphg ?cuff 1 measure taken sitting after 5 mins rest, ?arm
Ladakh	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
New Delhi	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

? Specific details not given.

Western Pacific

Subregion	Country or area	Study (reference)	Sampling methods	Response rate	BP measurement
WPR-A	Australia	APCSC-Busselton (APCSC secretariat, personal communication, 2001)	A stratified random sample representative of population	Not stated	Trained & certified staff standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Australia	APCSC-Perth (APCSC secretariat, personal communication, 2001)	Stratified random sampling of Perth metropolitan area	>70%	Trained & certified staff standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Australia	Gliksman et al. (1990)	Two-stage probability sampling of all school children in Australia	Not stated	Trained & certified staff standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Australia	Jamrozik and Hockey (1989); P. Elliot, personal communication, 2001	Random sample from electoral register	75%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Newcastle	MONICA study (Anonymous 1989b)	Sample from electoral register	68–82%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Perth	MONICA study (Anonymous 1989b)	Sample from electoral register	81–84%	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Japan	1990 National Survey (Sakata and Labarthe 1996)	Randomly selected from National Health Survey districts	81.5%	Trained & certified staff standard sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

Japan	APCSC-Aito Town (APCSC secretariat, personal communication, 2001)	Random sample of Aito town residents	75%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
Japan	APCSC-Akabane (APCSC secretariat, personal communication, 2001)	All residents living in Akabane town	77.6%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, ?arm
Japan	APCSC-Ohasama (APCSC secretariat, personal communication, 2001)	Non-hospitalized adults in Ohasama invited to participate	50%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
Japan	Baba et al. (1991)	Multistage stratified probability sampling of loose clusters of geographical areas based on census data	79.1%	?Trained & certified staff standard sphg one cuff 1 measure taken sitting after 5 mins rest, ?arm
Japan	Okayama et al. (1993)	Randomly selected from national census	81–89%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
Japan	Shimamoto et al. (1989)	Selected samples of men and women in the Akita district	74.5–82.8%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
Osaka	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

continued

Western Pacific (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Tochigi	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Toyama	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	New Zealand	APCSC-Fletcher challenge (APCSC secretariat, personal communication, 2001)	Employees of one centre, and random sample from electoral roll	74%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	New Zealand	Bullen et al. (1998)	Age stratified random sampling from electoral rolls	66–68%	Trained & certified staff RZ sphg ?cuff 2 measures taken sitting after 5 mins rest, ?arm
	New Zealand	Flight et al. (1984)	Randomly chosen schools and students	81%	Trained & certified staff standard sphg one cuffs 1 measure taken sitting after 5 mins rest, ?arm
	New Zealand	National Survey (Ministry of Health 1999)	Random sample of individuals from random households constructed from census data	Not stated	Trained & certified staff Hawksley Random sphg various cuffs 3 measures taken sitting after 1 min rest, L arm
	Auckland	MONICA study (Anonymous 1989b)	Sample from electoral register	81%	Trained & certified staff Electronic RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

	Singapore	APCSC-Kinmen (APCSC secretariat, personal communication, 2001)	All registered residents aged ≥50 years in two townships invited to participate	77.4%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	Singapore	Hughes et al. (1990)	Random samples of census districts, units, houses, then individuals (weighted)	52–66%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	Singapore	Singapore National Health survey (P. Elliot, personal communication, 2001)	Random selection of households from national database, then random selection of individuals	45–65%	Trained & certified staff Standard sphg one cuff 3 measures taken sitting after 5 mins rest, R arm
	Singapore	APCSC-Singapore Heart Survey (APCSC secretariat, personal communication, 2001)	Random sampling of population of Singapore	Not stated	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
WPR-B	China	APCSC-Anzhen (APCSC secretariat, personal communication, 2001)	Stratified random sampling and cluster sampling in Beijing area	85%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	China	APCSC-Anzhen02 (APCSC secretariat, personal communication, 2001)	Cluster sampling	Not stated	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm

continued

Western Pacific (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	China	APCSC-East Beijing (APCSC secretariat, personal communication, 2001)	Cluster sampling in individuals in East district of Beijing	Not stated	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	China	APCSC-Hong Kong SAR (APCSC secretariat, personal communication, 2001)	Stratified random sampling in Hong Kong SAR	85%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	China	APCSC-Hong Kong SAR (APCSC secretariat, personal communication, 2001)	Stratified random sampling in Hong Kong SAR	85%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	China	APCSC-Seven Cities cohort (APCSC secretariat, personal communication, 2001)	Study samples selected from Chinese populations of farmers, workers and fishermen	Not stated	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	China	APCSC-Six Cohorts (APCSC secretariat, personal communication, 2001)	Cluster sampling of six cohorts in villages, including farmers of Shanxi, Shaanxi, Guangxi, Jiangsu province, minors of Hebei province and fishermen of Zhejiang	≥85%	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm

China	APCSC-Tianjin (APCSC secretariat, personal communication, 2001)	A stratified random sample drawn from urban areas of the city	Not stated	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
China	He et al. (1991a); Klag et al. (1993)	Random cluster samples of townships in three areas	85.2%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
China	PRC-USA study (Huang et al. 1994; People's Republic of China–United States Cardiovascular and Cardiopulmonary Epidemiology Research Group 1992)	Study samples selected randomly from four Chinese populations (two urban and two rural)	80–95%	Trained & certified staff Standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
Beijing	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Beijing	MONICA study (Anonymous 1989b)	Sample from register of households	89–90%	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
Nanning	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
Tianjin	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm

continued

Western Pacific (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sampling methods*	*Response rate*	*BP measurement*
	Taiwan, China	APCSC-CVDFACTS/ Two Townships (APCSC secretariat, personal communication, 2001)	Two townships in Taiwan, China	Not stated	Trained & certified staff standard sphg ?cuff 2 measures taken sitting after 5 mins rest, R arm
	Taiwan, China	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Republic of Korea	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Republic of Korea	Kim et al. (1994)	Randomly selected districts then households and individuals	81.8%	Trained & certified staff Standard sphg various cuffs 2 measures taken sitting after 5 mins rest, L arm
	Papua New Guinea	INTERSALT study (Anonymous 1989a)	A stratified random sample representative of population	Not stated	Trained & certified staff RZ sphg various cuffs 2 measures taken sitting after 5 mins rest, R arm
	Papua New Guinea	King et al. (1985)	Purposive cluster samples from six chosen communities	60–85%	Trained & certified staff RZ sphg ?cuff 2 measures taken sitting after 10 mins rest, R arm

Papua New Guinea	Lindeberg et al. (1994)	Randomly selected within specific age range during a period of seven weeks—some non-randomized subjects included due to low participation	45–63% overall 40–59% for BP	Trained & certified staff Standard sphg various cuffs 3 measures taken sitting after ?min rest, ?arm
Pacific	PACIFIC (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
Pacific	Patrick et al. (1983)	A census of all households was conducted in three communities selected for sampling	90.2%	Trained & certified staff Zero-muddler sphg various cuffs 2 measures taken sitting after ?min rest, ?arm
Pacific	PUKAPK (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm
Pacific	RARTNG (P. Elliot, personal communication, 2001)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, ? arm

? Specific details not given.
Key: Sphg, sphygmomanometer; RZ, random zero.

Chapter 7

High cholesterol

Carlene M.M. Lawes, Stephen Vander Hoorn, Malcolm R. Law and Anthony Rodgers

Summary

Cholesterol is a fat-like substance, found in the blood stream and also in bodily organs and nerve fibres. While there are different etiological roles for various types of cholesterol, such as high and low density lipoprotein, the large majority of descriptive and epidemiological data are available only for total cholesterol levels. Therefore, in this analysis, cholesterol was defined as total serum cholesterol expressed in millimoles per litre of blood (mmol/l) a continuous variable with mean and standard deviation.

The primary outcomes assessed were ischaemic heart disease (Global Burden of Disease [GBD] study end-point 107) and non-fatal stroke (end-point 108). Ischaemic heart disease (IHD) was chosen on the basis of clear and consistent positive associations observed in cohort studies and evidence of reversibility in clinical trials of cholesterol lowering treatments. Cholesterol is positively associated with ischaemic stroke, but has a qualitatively different association with haemorrhagic stroke. As endpoints must all be mapped to the GBD classification system for disease, total stroke was used in the analyses. However, application of relative risk estimates to the 14 subregions[1] were adjusted to reflect differences in stroke subtypes. Cholesterol has been observed to be inversely associated with a number of other outcomes such as cancer and chronic respiratory disease. However, evidence suggests that these associations are due to the effects of disease on cholesterol, rather than vice versa. Consequently these outcomes were not included.

Raw cholesterol data were obtained from studies after a systematic review of population-based surveys, which included about 160 surveys and almost 640 000 participants. Sex-specific associations of cholesterol with age were estimated for each of the subregions separately, based on country-weighted study estimates of mean values. There was moderate variation in the final age- and sex-specific estimates of mean cholesterol

across the 14 subregions, with the range between the highest and lowest age-specific mean cholesterol levels typically being about 2 mmol/l.

A theoretical-minimum-risk distribution of cholesterol (i.e. one that would yield the lowest population risk of adverse health outcomes) was taken as 3.8 standard deviation 0.6 mmol/l (usual) for all age, sex and subregional groups. The main basis for this estimate was the level of cholesterol down to which epidemiological relationships with cardiovascular disease outcomes are observed, and clinical trial data showing benefits from cholesterol lowering among those with below-average cholesterol levels. This theoretical minimum was also consistent with the levels of cholesterol in populations with little cardiovascular disease.

For the comparative risk assessment (CRA) analyses, observational epidemiological data were used to estimate the hazard ratios for the risk factor–disease relationship and trial meta-analyses for the time frame of risk reversibility. Data on hazard ratios for IHD were included from an overview of the ten largest observational studies conducted in populations from industrialized countries. This overview included data from 494 804 participants followed for 7–23 years, among whom 18 811 IHD events were observed. There was evidence of differences in the strength of the association by age but no difference between males and females. These data were closely similar in size and shape to the associations seen in an overview of 29 cohorts involving 353 065 participants from the Asia-Pacific region. In this individual participant meta-analysis, 2937 strokes were observed as well as 2838 IHD events. Overall, each 0.6 mmol/l lowering of usual cholesterol was associated a 27% reduction in IHD. A 1 mmol/l lowering of cholesterol was associated with a 13% (range 6–19%) reduction in total stroke, predominantly due to the effect on ischaemic stroke.

An overview of 49 trials of cholesterol lowering indicated that risk reductions in IHD of 11%, 24%, 33% and 36% are associated with a 1 mmol/l reduction in cholesterol after 1, 2, 3–5 and >5 years, respectively. Taking into account the size of the reduction in cholesterol, there was no clear difference in effects according to how the cholesterol reduction was achieved, either by diet or any one of several classes of drugs. These data indicated that in middle age, the risks associated with high cholesterol are reversed within a few years of cholesterol lowering. A meta-analysis of cholesterol lowering trials also confirmed a reduction in risk of stroke with cholesterol lowering.

The foregoing methods and assumptions allowed estimates of burden attributable to cholesterol levels of more than 3.8 mmol/l. Overall, 56% of IHD mortality and disease burden was attributable to cholesterol >3.8 mmol/l worldwide (range of 44–68% by subregion). This translated into 3 609 000 deaths in the year 2000. Also 32% of ischaemic stroke was attributable to cholesterol >3.8 mmol/l worldwide (range of 25–45% by subregion), which translated into 805 000 deaths in the year 2000.

Worldwide, 4.4 million deaths (about 7.9% of the total) and 40.4 million disability-adjusted life years (DALYs) (2.8% of the total) were estimated to be due to non-optimal cholesterol. The proportion of DALYs was lower than the proportion of deaths as most cholesterol-related cardiovascular disease events occurred in middle or old age, so the years of life lost due to premature mortality and years of life lost due to disability is a smaller percentage of the total DALYs than of the total deaths. Overall, the results suggest that a considerable proportion of cardiovascular disease is attributable to non-optimal cholesterol, defined as mean cholesterol >3.8 mmol/l, and this translates into an important portion of deaths and years of life lost to deaths and disability worldwide. Approximately 40% of the cholesterol-related attributable burden occurred in developed subregions, 20% in low mortality developing subregions (AMR-B, EMR-B, EUR-B, EUR-C, SEAR-B, WPR-B), and a further 40% in high mortality developing subregions (AFR-D, AFR-E, AMR-D, EMR-D, SEAR-D).

In absolute terms, most of the excess burden of cardiovascular disease occurred in the populous regions, as would be expected. The relative impact of attributable deaths and DALYs—calculated as the proportion of all deaths and DALYs attributable to non-optimal cholesterol (i.e. mean >3.8 mmol/l)—was highest in the European subregions, where mean cholesterol levels were highest.

1. Introduction

Cholesterol is a fat-like substance, found in the blood stream and also in bodily organs and nerve fibres. Most cholesterol in the body is made by the liver from a wide variety of foods, but especially from saturated fats, such as those found in animal products. A diet high in saturated fat content, heredity, and various metabolic conditions such as type II diabetes, influence an individual's level of cholesterol.

1.1 Choice of exposure variable

Cholesterol was described as a continuous variable, as it is commonly reported in this manner with mean and standard deviation values. The System Internationale (SI) unit for measuring cholesterol is millimoles per litre of blood (mmol/l), but in some studies, particularly those from the United States of America and Japan, it is reported in milligrams per decilitre of blood (conversion factor 1 mg/dl = 0.02586 mmol/l). Total cholesterol was chosen in preference to other potential measures of risk associated with blood lipids (e.g. high density lipoprotein [HDL cholesterol] and low density lipoprotein [LDL cholesterol]) as more data and information were available on both risk factor levels and the risk-factor–disease relationship (relative risk values) for total cholesterol.

1.2 Disease outcomes

A number of diseases are associated with non-optimal cholesterol levels. Cholesterol is thought to amplify and accelerate atherosclerosis, and influence IHD and ischaemic stroke events, but the exact mechanisms are unclear. It has been proposed that cholesterol, particularly LDL cholesterol which accounts for about 60% of total cholesterol in the circulation, is taken up by macrophages. When cholesterol levels are high, macrophages take up more cholesterol than they can metabolize and become "foam cells". These cells are important in the early stages of atheromatous plaque formation (Bronner et al. 1995; Gorelick et al. 1997; Warlow et al. 1996).

By contrast, there is no positive association between cholesterol and haemorrhagic stroke, and some research indicates that those people with lower levels of cholesterol are at greater risk of haemorrhagic stroke (Leppala et al. 1999; Neaton et al. 1992; Yano et al. 1994). The mechanisms are unclear, but low levels of cholesterol may weaken the endothelium of small intracranial vessels which, in combination with high blood pressure, may rupture, and/or result in "osmotic fragility" of red blood cells, thereby increasing the risk of haemorrhage (Bronner et al. 1995; Iso et al. 1989; Tanaka et al. 1982; Warlow et al. 1996). Potential outcomes considered as affected by cholesterol are described below.

Ischaemic heart disease

Data from prospective cohort studies have demonstrated a strong, continuous temporal association between cholesterol and IHD (APCSC 2003; Law et al. 1994b, 1994c; Lewington and MacMahon 1999; Neaton and Wentworth 1992; Neaton et al. 1992). Further, a causal association is biologically plausible and clinical trials have demonstrated reversibility (Bucher et al. 1998; LaRosa et al. 1999; Law et al. 1994b; Pignone et al. 2000; Ross et al. 1999). The GBD classification system for diseases and injuries has a category for total IHD (end-point 107 G3 ischaemic heart disease, the International Statistical Classification of Diseases, ninth revision [ICD-9] codes 410–414) (Bucher et al. 1998; LaRosa et al. 1999; Pignone et al. 2000; Ross et al. 1999).

Stroke

Data on the association between cholesterol and stroke are more complex. Most major cohort studies and overviews have shown that cholesterol is positively associated with ischaemic stroke (Anonymous 1998a; Neaton et al. 1992; PSC 1995). However, there appears to be a qualitatively different association with haemorrhagic stroke, with some studies observing a negative association (APCSC 2003; Neaton et al. 1992) and others a null association with this outcome (Suh et al. 2001). There are no specific GBD end-points for stroke subtypes, only for total

stroke (end-point 108 G4 cerebrovascular disease, ICD-9 codes 430–438). However, application of RR estimates to the subregions will reflect differences in stroke subtypes, as discussed later in this chapter.

Other disease and injury outcomes

Cholesterol has been observed to be inversely associated with a number of other outcomes such as cancer and chronic respiratory disease (Law et al. 1994a). However, evidence suggests that these associations are due to the effects of disease on cholesterol, rather than vice versa (Law et al. 1994a). Consequently these outcomes were not included.

2. Risk factor exposure

2.1 Data on cholesterol levels

Data on global cholesterol levels were collated from three major sources. The first source was the MONICA study (Anonymous 1989), which collected cholesterol data from 39 collaborating centres in 22 countries and was carried out between 1979 and 1987. This study provides important information about cholesterol patterns, but does not provide a truly global overview of cholesterol distributions. It included populations that were predominantly European in origin, and did not include populations from the Eastern Mediterranean, South-East Asian or African Regions. Further, MONICA data were collected in the early 1980s, and more recent data are also available now. We therefore found it necessary to include additional cholesterol data for this analysis.

The second major source of data was a literature search using Medline and the key words "cholesterol", "survey" "health survey" and "cross-sectional survey". Studies were reviewed, and included in analyses if they fulfilled the following criteria:

- conducted from 1980 onwards;
- included randomly selected or representative participants;
- had a sample size of over 1000—however, a smaller sample size was acceptable in specific regions, or age groups where data were limited, if the study fulfilled the other criteria;
- described sample size and age group of participants;
- presented mean values of cholesterol by age and sex; and
- utilized a standard protocol for cholesterol measurement.

The final source of data was personal communications with researchers and study investigators. The authors had access to data from the Asia-Pacific Cohort Studies Collaboration (APCSC), a collaboration involving 37 cohorts in the Asia-Pacific region, which includes at least 5000 person-years of follow-up recorded or planned. Data on date of

birth or age, sex, and cholesterol have been recorded and collated (APCSC 1999). Cholesterol data from eligible studies that had been collected from 1980 onwards were included in the cholesterol database. In addition, authors of surveys/studies were contacted and age and sex-specific data requested, where these had not been available in the published format.

Many studies did not publish data in the format required for this project (e.g. omitting age- and sex-specific mean cholesterol levels), and unfortunately time and resource constraints limited attempts to obtain all of these data from researchers. It was also very difficult to obtain results of surveys that have only been published in local/national reports but not in peer-reviewed journals. Access to these data would have been greatly improved had these reports been more widely available in electronic formats such as on the Internet. Details of studies currently included are presented in Table 7.1.

In total, approximately 1900 abstracts were reviewed. Data from about 160 surveys (total sample size of almost 640 000 participants) have been included. Figure 7.1 illustrates data coverage by geographical region.

No data were available for AMR-D comprising Bolivia, Ecuador, Guatemala, Haiti, Nicaragua and Peru, and very limited data (studies totalling <2000 participants) for SEAR-B and EMR-D. Data on more than 50 000 participants were obtained for AMR-A, EUR-A, WPR-A and WPR-B, owing to many studies being available and large sample sizes.

Figure 7.1 Cholesterol data coverage expressed as total study sample size, by geographical region

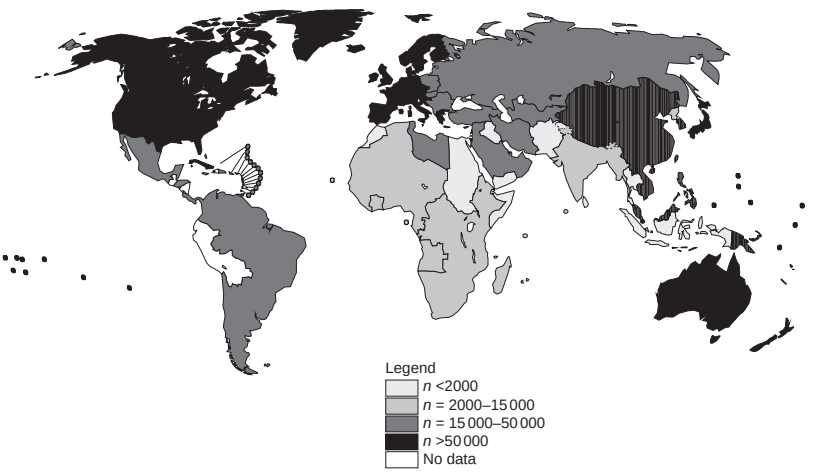


Table 7.1 Studies currently included in the cholesterol data review

Subregion	*Country or area*	*Study (reference)*	*Sample size*	*Age range (years)*
AFR-D	Ghana	Nyarko et al. (1994)	79	20–50
	Nigeria	Erasmus et al. (1994)	417	11–≥60
	Nigeria	Okesina et al. (1999)	500	11–≥50
	Seychelles	Bovet et al. (1991)	1055	25–64
			2051	
AFR-E	South Africa	Oelofse et al. (1996)	986	15–64
	South Africa	Steyn et al. (1987, 1985)	976	15–64
	United Republic of Tanzania	Kitange et al. (1993)	1409	15–19
	United Republic of Tanzania	Swai et al. (1993)	7272	15–≥65
	Zimbabwe	Allain et Matenga (T. Allain et al. personal communication, 2001)	261	60–≥80
			10904	
AMR-A	Canada	Connelly et al. (1992)	1169	42–59
	Canada	Lupien et al. (1985)	1169	42–59
	Halifax	MONICA study (Anonymous 1989)	837	25–64
	USA	Abbott et al. (1997)	971	71–93
	USA	Brown et al. (1993)	14521	45–64
	USA	Burke et al. (1991)	4545	25–74
	USA	Donker et al. (1997)	1411	7–11
	USA	Eisenberg et al. (1986)	2477	35–64
	USA	Ettinger et al. (1992)	4814	65–≥85
	USA	Ferrara et al. (1997)	2339	50–≥80
	USA	Hutchinson et al. (1997)	15743	45–64
	USA	Johnston et al. (1993)	7836	20–≥75
	USA	Sprafka et al. (1990)	4641	25–74
	USA	Srinivasan et al. (1991)	4020	5–26
	USA	Wallace and Colsher (1992)	1959	71–≥95
	USA	Yano et al. (1986)	1363	60–≥75
	Stanford	MONICA study (Anonymous 1989)	1430	25–64
			86995	
AMR-B	Brazil	INCLEN (Anonymous 1992b)	406	35–65
	Chile	INCLEN (Anonymous 1992b)	399	35–65
	Chile	Jadue et al. (1999); L. Jadue, personal communication, 2001	1591	25–64
	Colombia	INCLEN (Anonymous 1992b)	200	35–65

continued

Table 7.1 Studies currently included in the cholesterol data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sample size*	*Age range (years)*
	Dominican Republic	Aono et al. (1997)	2000	20–76
	Jamaica	Wilks et al. (2001)	1134	25–74
	Mexico	Gonzalez et al. (1999, 2001)	2251	35–64
	Mexico	Posadas-Romero et al. (1995)	33660	20–70
	Mexico	Yamamoto et al. (2001)	825	20–90
			42466	
EMR-B	Bahrain	al-Mahroos et al. (2000)	2090	40–59
	Jordan	H. Jaddou, personal communication, 2001	2273	25–≥70
	Kuwait	Olusi et al. (1997)	751	1–≥70
	Saudi Arabia	al-Nuaim et al. (1996, 1997)	4539	15–≥60
	Saudi Arabia	al-Nuaim (1997)	2960	25–64
	Saudi Arabia	al Shammari et al. (1994)	1005	<35–≥65
	Saudi Arabia	Mitwalli et al. (1994)	966	<25–≥55
	Tunisia	Ghannem et al. (2001); H. Ghannem, personal communication, 2001	1497	13–19
			16081	
EMR-D	Pakistan	Molla et al. (1990)	634	4–59
			634	
EUR-A	Belgium	Kesteloot et al. (1987)	18090	<20–≥55
	Charleroi	MONICA study (Anonymous 1989)	646	25–64
	Ghent	MONICA study (Anonymous 1989)	1260	25–64
	Denmark, Glostrup	MONICA study (Anonymous 1989)	3780	25–64
	Finland	Lakka and Salonen (1992)	2492	42–60
	Finland	Myllkangas et al. (1995)	2210	45–64
	Finland	Nikkila and Heikkinen (1990)	535	85
	Finland	Nissinen et al. (1987)	6523	25–64
	Finland	Puska et al. (1993)	1398	25–64
	Finland	Vartiainen et al. (2000)	10025	30–59
	Finland	Vikari et al. (1985)	3654	3–18
	Kuopio	MONICA study (Anonymous 1989)	2789	25–64
	Turku; Loimaa	MONICA study (Anonymous 1989)	3283	25–64
	N. Karelia	MONICA study (Anonymous 1989)	3138	25–64

Table 7.1 Studies currently included in the cholesterol data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sample size*	*Age range (years)*
	France,			
	Haute-Garonne	MONICA study (Anonymous 1989)	1 265	25–64
	Lille	MONICA study (Anonymous 1989)	1 436	25–64
	Former German Democratic Republic,			
	Berlin-Lichtenberg	MONICA study (Anonymous 1989)	1 197	25–64
	Cottbus county	MONICA study (Anonymous 1989)	1 377	25–64
	Germany	Heinemann et al. (1995)	1 939	25–64
	Germany	Hoffmeister et al. (1994)	15 436	25–69
	Germany	Herman et al. (1988)	1 696	25–69
	Germany	MONICA study (Anonymous 1989)	1 015	25–64
	Augsburg (Rural)	MONICA study (Anonymous 1989)	2 109	25–64
	Augsburg (Urban)	MONICA study (Anonymous 1989)	1 667	25–64
	Bremen	MONICA study (Anonymous 1989)	1 625	25–64
	Rhein-Neckar	MONICA study (Anonymous 1989)	3 066	25–64
	Iceland	MONICA study (Anonymous 1989)	1 743	25–64
	Israel	Eisenberg et al. (1986)	1 588	35–64
	Israel	Greenland et al. (1993)	1 200	9–18
	Italy	Cesana et al. (1989)	1 387	25–≥55
	Italy	Nine populations (Anonymous 1981)	6 699	20–59
	Italy	Salvaggio et al. (Law and Wald 1994; Salvaggio et al. 1991)	8 953	18–65
	Italy	Vaccarino et al. (1995)	3 401	<30–≥50
	Brianza	MONICA study (Anonymous 1989)	1 647	25–64
	Friuli	MONICA study (Anonymous 1989)	1 849	25–64
	Latina	MONICA study (Anonymous 1989)	1 773	25–64
	Netherlands	Bosma et al. (1994)	3 015	45–70
	Netherlands	Vershuren et al. (1994)	41 622	20–59
	Norway	Graff-Iverson et al. (1998)	7 523	40–54
	Norway	Thune et al. (1998)	6 307	20–49
	Spain	Masia et al. (1998)	1 670	24–74
	Catalonia	MONICA study (Anonymous 1989)	2 544	25–64

continued

Table 7.1 Studies currently included in the cholesterol data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sample size*	*Age range (years)*
	Sweden	Asplund-Carlson and Carlson (1994)	1 564	40–50
	Sweden	Rosengren et al. (2000)	798	50
	Gothenburg	MONICA study (Anonymous 1989)	1 354	25–64
	Switzerland, Ticino	MONICA study (Anonymous 1989)	1 483	25–64
	Vaud; Fribourg	MONICA study (Anonymous 1989)	1 582	25–64
	United Kingdom	Brown et al. (1994)	3 939	70–≥80
	England	Bajekal et al. (1999)	11 162	16–≥75
	England	Razay et al. (1992)	1 218	40–69
	Northern Ireland, Belfast	MONICA study (Anonymous 1989)	2 327	25–64
	Scotland	Smith et al. (1989)	10 359	40–59
	Scotland, Glasgow	MONICA study (Anonymous 1989)	1 143	25–64
	Multiple sites in EUR-A	Kafatos et al. (1991)	2 114	70–79
			237 704	
EUR-B	Poland, Tarnobrzeg Voivodship	MONICA study (Anonymous 1989)	2 700	25–64
	Warsaw	MONICA study (Anonymous 1989)	2 591	25–64
	Turkey	Mahley et al. (1995); R. Mahley, personal communication, 2001	8 882	20–≥70
	Turkey	Onat et al. (1992)	3 687	30–≥70
			17 860	
EUR-C	Former Czechoslovakia	MONICA study (Anonymous 1989)	2 552	25–64
	Estonia	Olferev et al. (1990, 1991)	2 936	20–54
	Hungary	Biro et al. (1996)	2 559	18–≥60
	Hungary	Kafatos et al. (1991)	42	70–79
	Budapest	MONICA study (Anonymous 1989)	1 486	25–64
	Pecs	MONICA study (Anonymous 1989)	1 584	25–64
	Lithuania	Bosma et al. (1994)	2 149	45–70
	Russian Federation	Puska et al. (1993)	837	25–64
	The former Soviet Union[a], Kaunas	MONICA study (Anonymous 1989)	1 462	25–64
	Novosibirsk C	MONICA study (Anonymous 1989)	2 538	25–64

Table 7.1 Studies currently included in the cholesterol data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sample size*	*Age range (years)*
	Novosibirsk I	MONICA study (Anonymous 1989)	1436	25–64
			19581	
SEAR-B	Indonesia	INCLEN (Anonymous 1992b)	210	35–65
	Thailand	Bhuripanyo et al. (1993)	911	30–≥60
	Thailand	INCLEN (Anonymous 1992b)	416	35–65
			1537	
SEAR-D	India	Chadha et al. (1997)	2124	25–64
	India	Misra et al. (2001)	508	20–70
	India	Misra et al. (2001)	652	14–25
	India	Reddy et al. (1994)	380	40–≥70
			3664	
WPR-A	Australia	APCSC-Busselton (APCSC secretariat, personal communication, 2001)	976	15–≥70
	Australia	APCSC-Perth (APCSC secretariat, personal communication, 2001)	6456	15–≥70
	Australia	Bennett and Magnus (1994)	6096	25–64
	Australia	Boulton et al. (1995)	856	8–9
	Australia	Glikman et al. (1990)	1743	9–15
	Australia	Simons et al. (1991)	3182	60–≥80
	Australia	van Beurden et al. (1991)	9238	18–98
	Newcastle	MONICA study (Anonymous 1989)	2396	25–64
	Perth	MONICA study (Anonymous 1989)	1758	25–64
	Japan	1990 National Survey (Sakata and Labarthe 1996)	7836	30–≥70
	Japan	APCSC-Aito Town (APCSC secretariat, personal communication, 2001)	1720	15–≥70
	Japan	APCSC-Akabane (APCSC secretariat, personal communication, 2001)	1834	15–≥70
	Japan	APCSC-Ohasama (APCSC secretariat, personal communication, 2001)	2240	30–≥60
	Japan	Choudhury et al. (1994)	832	35–59
	Japan	Okayama et al. (1993)	5921	30–69
	Japan	Serum Lipid Survey (Anonymous 1996)	33234	4–99
	New Zealand	APCSC-Fletcher challenge (APCSC secretariat, personal communication, 2001)	10462	15–≥70

continued

Table 7.1 Studies currently included in the cholesterol data review (*continued*)

Subregion	*Country or area*	*Study (reference)*	*Sample size*	*Age range (years)*
	New Zealand	Bullen et al. (1998)	986	65–84
	New Zealand	Flight et al. (1984)	323	14–15
	New Zealand	Mann et al. (1991)	2363	18–64
	New Zealand	National Survey (Ministry of Health 1999)	3223	15–≥80
	Singapore	APCSC-Singapore Heart Survey (APCSC secretariat, personal communication, 2001)	2450	15–≥70
	Singapore	Hughes et al. (1990)	2058	18–69
			109 750	
WPR	China	APCSC-Anzhen02 (APCSC secretariat, personal communication, 2001)	4152	30–69
	China	APCSC-Hong Kong SAR (APCSC secretariat, personal communication, 2001)	2019	≥70
	China	APCSC-Seven Cities cohort (APCSC secretariat, personal communication, 2001)	37635	15–≥70
	China	APCSC-Six Cohorts (APCSC secretariat, personal communication, 2001)	19387	30–59
	China	INCLEN (Anonymous 1992b)	1188	35–65
	China	Tao et al. (1992)	4280	35–54
	China	Tian et al. (1995)	631	15–64
	China	Yang et al. (1986)	1054	15–≥55
	China	Zhuang et al. (1986)	4072	0–102
	Beijing	MONICA study (Anonymous 1989)	1673	25–64
	Hong Kong SAR	Fong et al. (1994)	696	20–≥60
	Hong Kong SAR	Woo et al. (1997)	1010	25–74
	Taiwan, China	APCSC-CVDFACTS/Two Townships (APCSC secretariat, personal communication, 2001)	7004	0–≥70
	Papua New Guinea	Lindeberg et al. (1994)	166	20–86
	Papua New Guinea	Scrimgeour et al. (1989)	121	17–59
	Philippines	INCLEN (Anonymous 1992b)	274	35–65
			90 057	

[a] Russia in original publication.

Table 7.2 Cholesterol measuring techniques of studies included in this review

	Yes (%)	*Not stated (%)*
Trained staff	94	6
Approved laboratory[a]	94	6
Fasting sample		28
All	47	NA
Some	4	NA
None	21	NA
Storage of sample		43
Refrigeration	16	NA
Deep freeze	30	NA
Storage not necessary	11	NA
Analysis method		34
Enzymatic	56	NA
Extraction	6	NA
Other	4	NA

NA Not applicable.

[a] Laboratory associated with a hospital, university or research institution.

Approximately half of the studies utilized random sampling of individuals or households, including stratified random sampling; the other half used methods such as house-to-house or workplace surveys. Response rates were documented in 72% of the studies, of which response rate was >80% in 32% of them, between 50% and 80% (including those where response was >80% in some subcategories) in 63% of them, and documented to be lower than 50% in only six studies. For completeness, full documentation of sampling method, response rate and cholesterol measuring techniques are presented in Appendix A, which is intended only for those who require more data on individual studies. A summary is given in Table 7.2.

In most studies, a laboratory was associated with a hospital, university or research institution, and the staff appeared to have received appropriate training. Whether the blood sample was taken after the individual had fasted has an impact on lipid subfractions such as triglycerides rather than on total cholesterol, but this information also provides an indication of the consistency with which samples were taken, and the degree of detail given in publications. The majority of analyses were performed using newer enzymatic techniques, rather than the older extraction analyses.

2.2 Methodology to estimate mean and standard deviation of cholesterol data

Mean cholesterol, standard deviation, sample size and age ranges from all reviewed data sources were extracted and entered into an Excel database. Scatter plots of these cholesterol data for each subregion, utilizing the midpoints in study age categories, are presented below in Figures 7.2–7.5.

The cholesterol data obtained from published studies including various age ranges were presented by age categories that were different from those required for the CRA project. For this reason, a method was needed which would make complete use of the available data and then combine them to produce estimates for subregions and age groups. The first step was to assess the general shape of association using all the available data. Second, associations were estimated for each subregion separately where sufficient data were available. For subregions with limited data, the association was estimated using complete data available from other subregions. Finally, these subregional age–cholesterol associations for males and females were used to predict subregional cholesterol levels.

It should be noted that no step specifically estimates mean cholesterol at the country level; this approach is explained in greater detail below.

Age–cholesterol relationships

The data from the literature were first used to assess the shape of the association of cholesterol with age using SPLUS software. At this stage no assumptions were made about the shape of association and therefore non-parametric methods were applied.

Figures 7.2 and 7.3 demonstrate that there were variable amounts of data available among the different subregions, so initially analyses were limited to those subregions with the most data spread across all age groups. The six subregions thus examined were AMR-A, AMR-B, EMR-B, EUR-A, WPR-A and WPR-B. Previous analyses had demonstrated that the shape of the age–cholesterol relationship may vary depending on absolute level of cholesterol (APCSC secretariat, personal communication, 2001). Therefore, analyses of pooled data from the six subregions were stratified by overall cholesterol levels into plausible low (<4.7 mmol/l), medium (4.7–5.5 mmol/l) and high (>5.5 mmol/l) groups (Figure 7.6), as we describe below using the example of WPR-A.

The purpose of determining the overall shape of the association between cholesterol and age was to enable extrapolation to other subregions where only limited data were available. The method utilized for subregions with sparse data is detailed below. The associations between age and cholesterol for both females and males were non-linear. The association for females increased between the ages of 30 and 65 years, and then fell slightly afterwards. For males, the association increased

Figure 7.2 Scatter plots of mean cholesterol (mmol/l) against age by subregion, for females

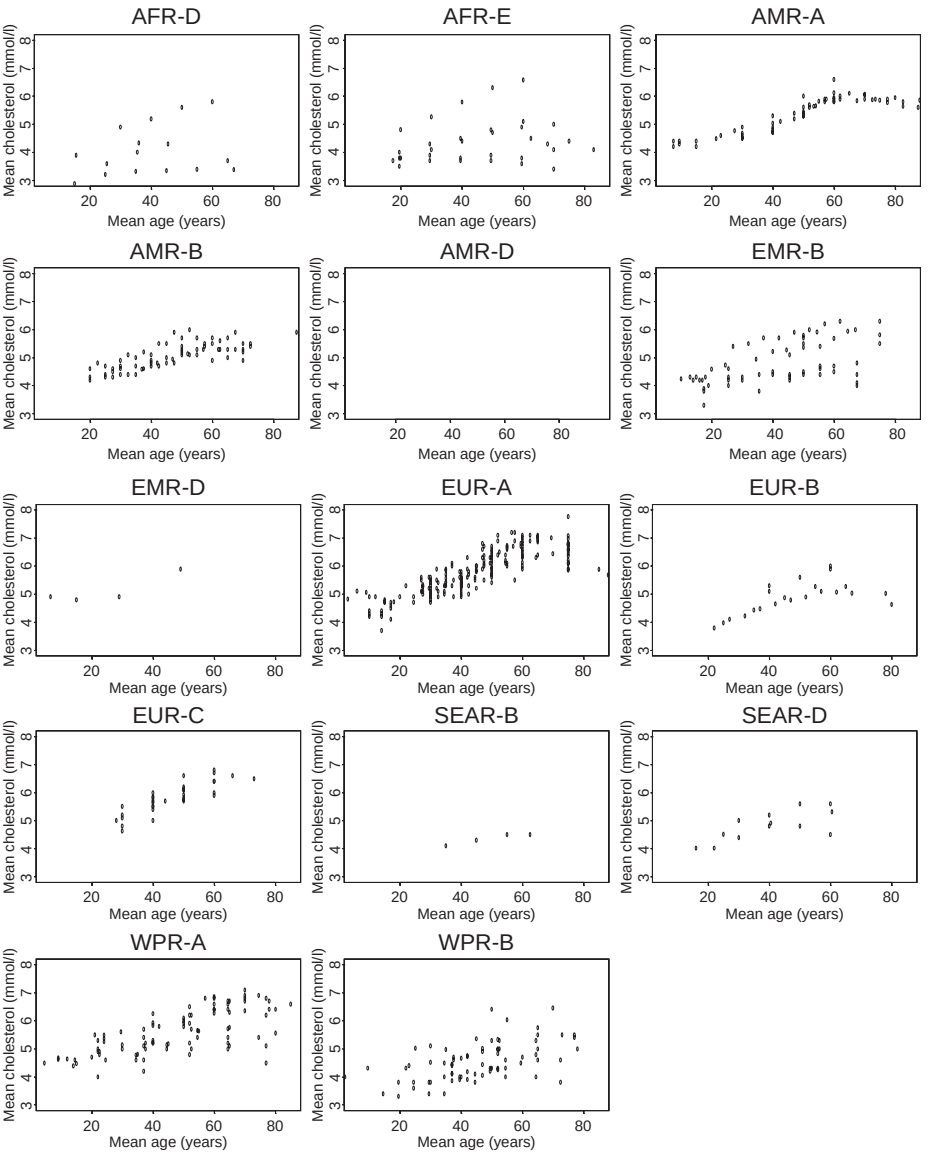


Figure 7.3 Scatter plots of mean cholesterol (mmol/l) against age by subregion, for males

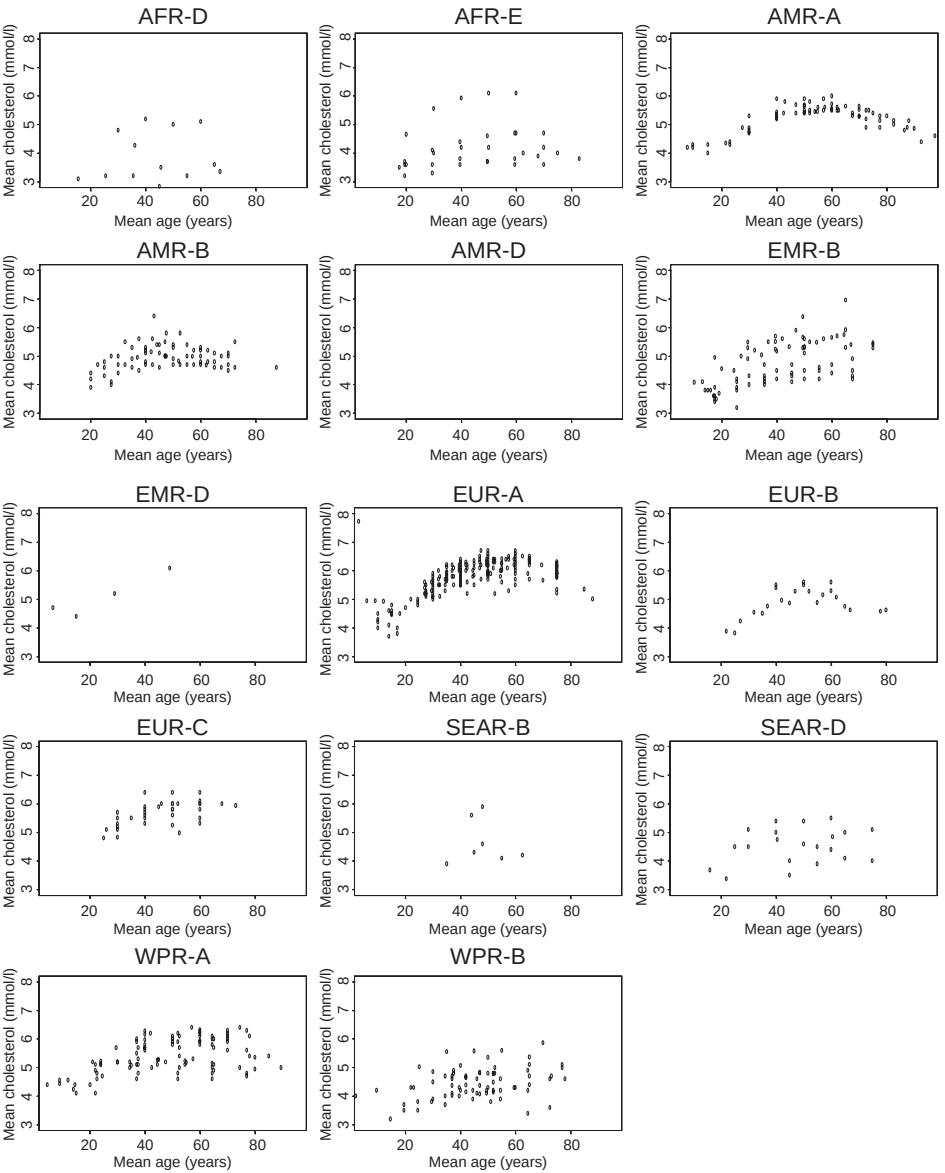


Figure 7.4 Scatter plots of mean cholesterol standard deviation (mmol/l) against age by subregion, for females

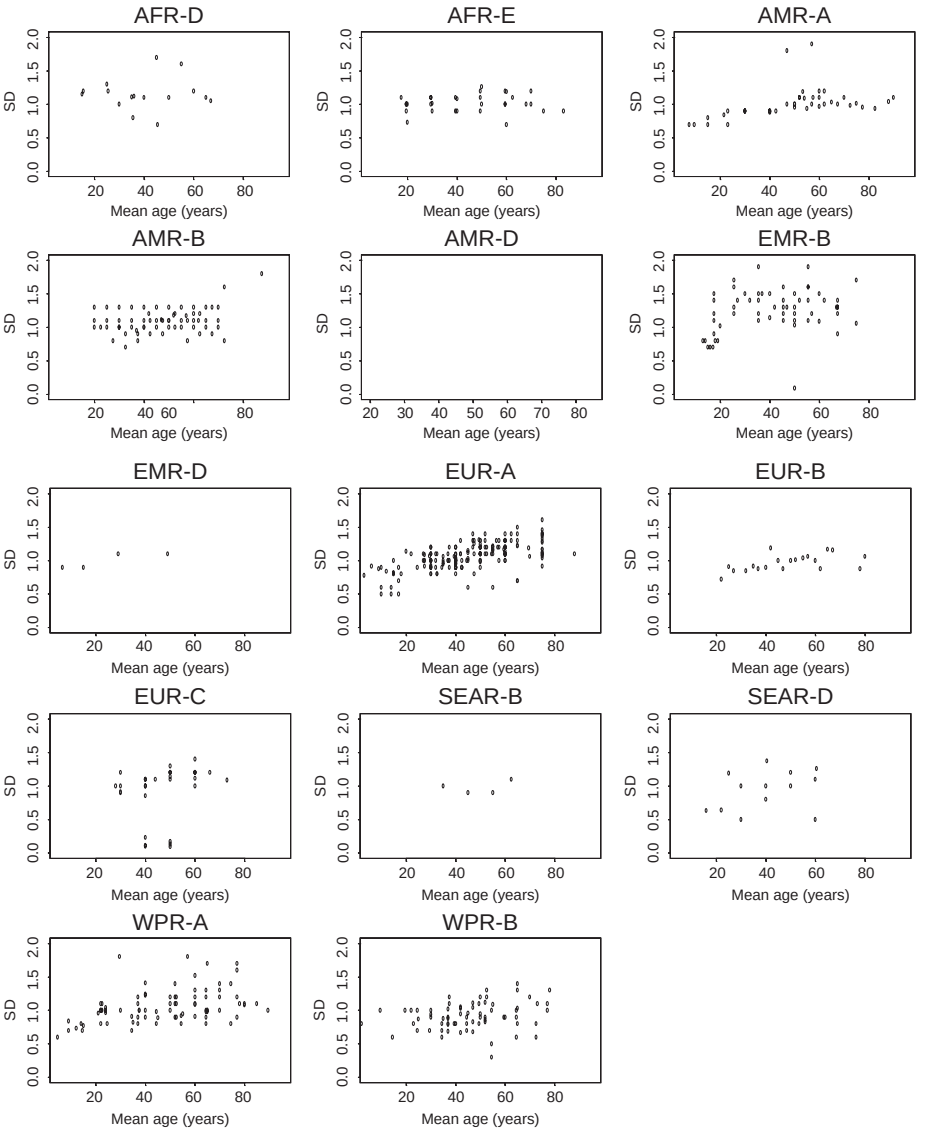


Figure 7.5 Scatter plots of mean cholesterol standard deviation (mmol/l) against age by subregion, for males

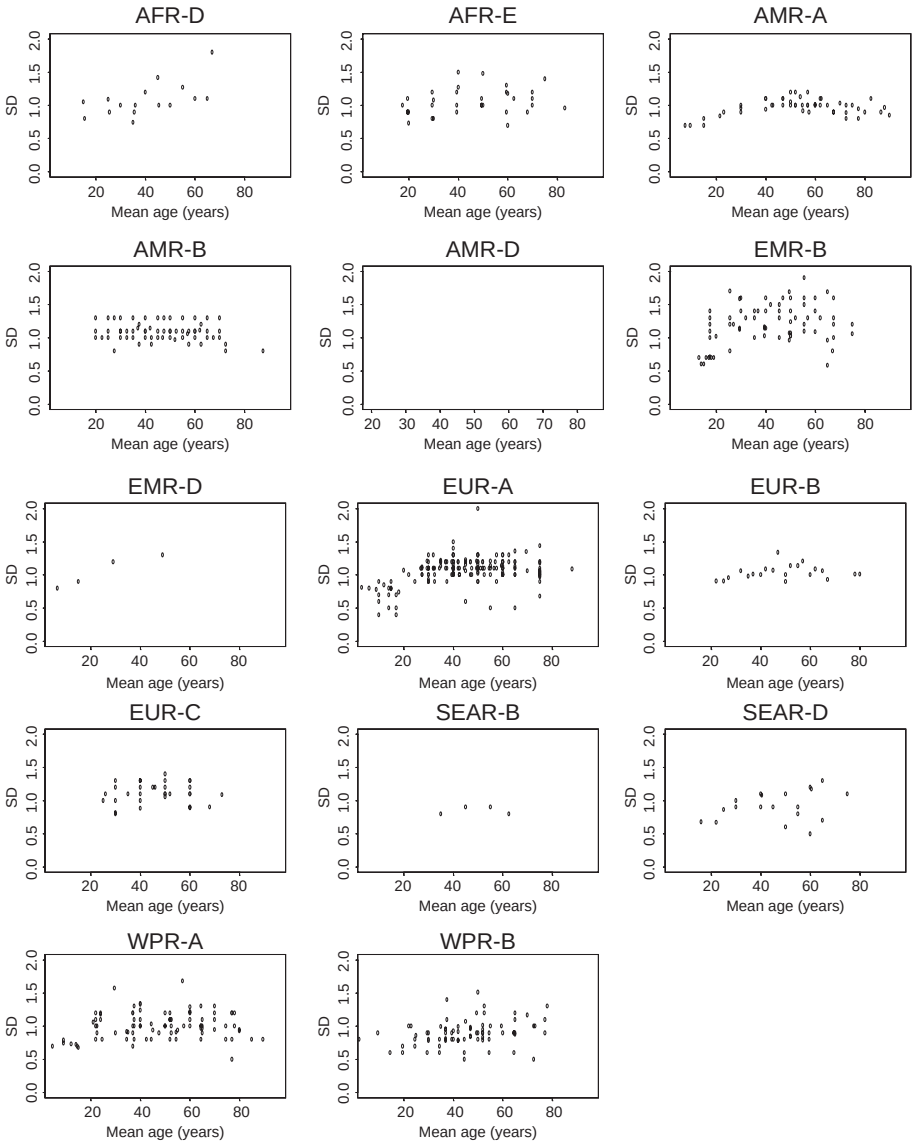
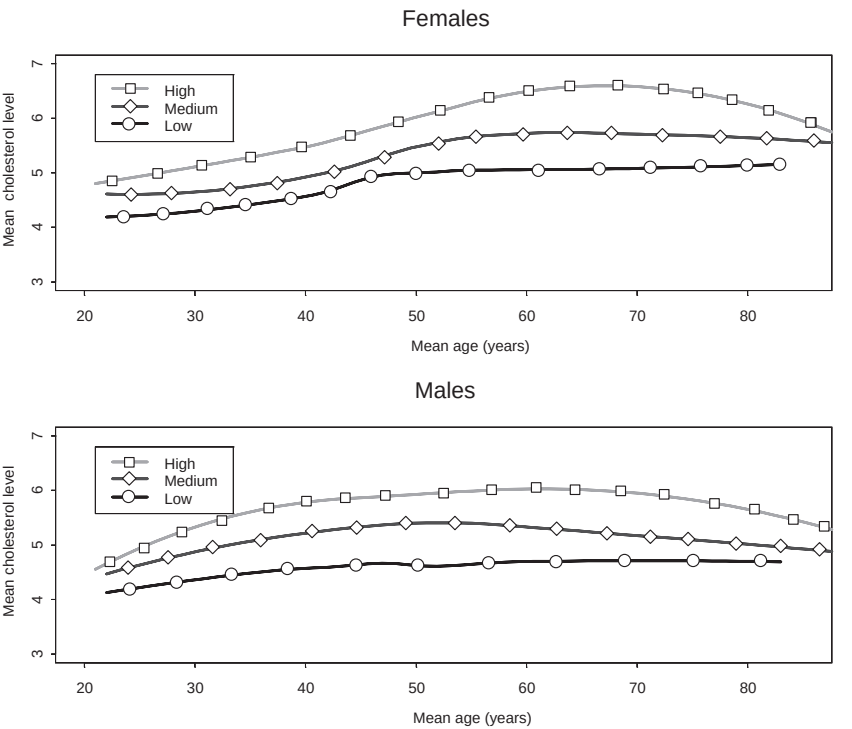


Figure 7.6 The cholesterol–age association from pooled data of six subregions[a] for populations with high, medium and low cholesterol levels



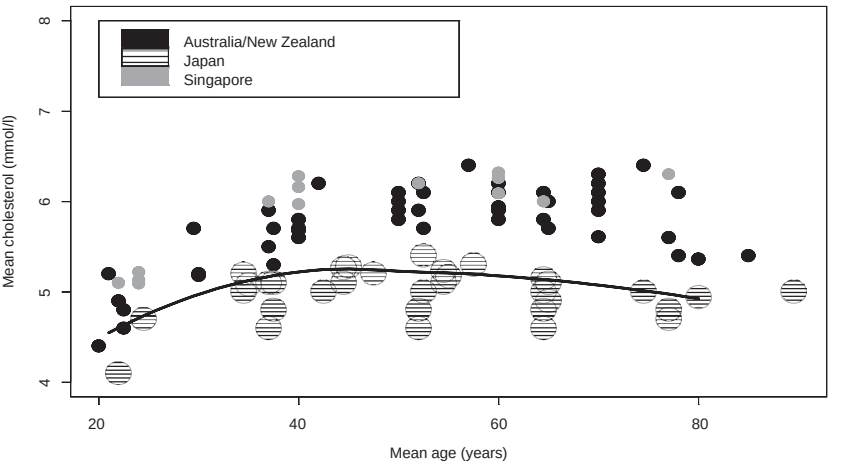
[a] AMR-A, AMR-B, EMR-B, EUR-A, WPR-A and WPR-B.

Note: Overall cholesterol levels–Low = <4.7 mmol/l; Medium = 4.7–5.5 mmol/l; High = >5.5 mmol/l.

between the ages of 30 and 50 years, and then flattened before declining slightly in older age. Very little data were available in the populations aged >80 years, and therefore it is unclear whether cholesterol continues to decrease beyond the age of 70–79 years. These patterns were consistent among high, medium and low cholesterol subgroups; however, the gradient of the increase was greatest in the high cholesterol groups, and least in the low cholesterol groups.

Having established the non-linear association between age and mean cholesterol, the second step involved estimating the shape and level of this association for males and females in each subregion separately. The methodology differed by subregion depending on the available data. There were sufficient data to estimate the associations for males and females in six of the 14 subregions (AMR-A, AMR-B, EUR-A, EMR-B,

Figure 7.7 Combining cholesterol data (mmol/l) from country studies in WPR-A



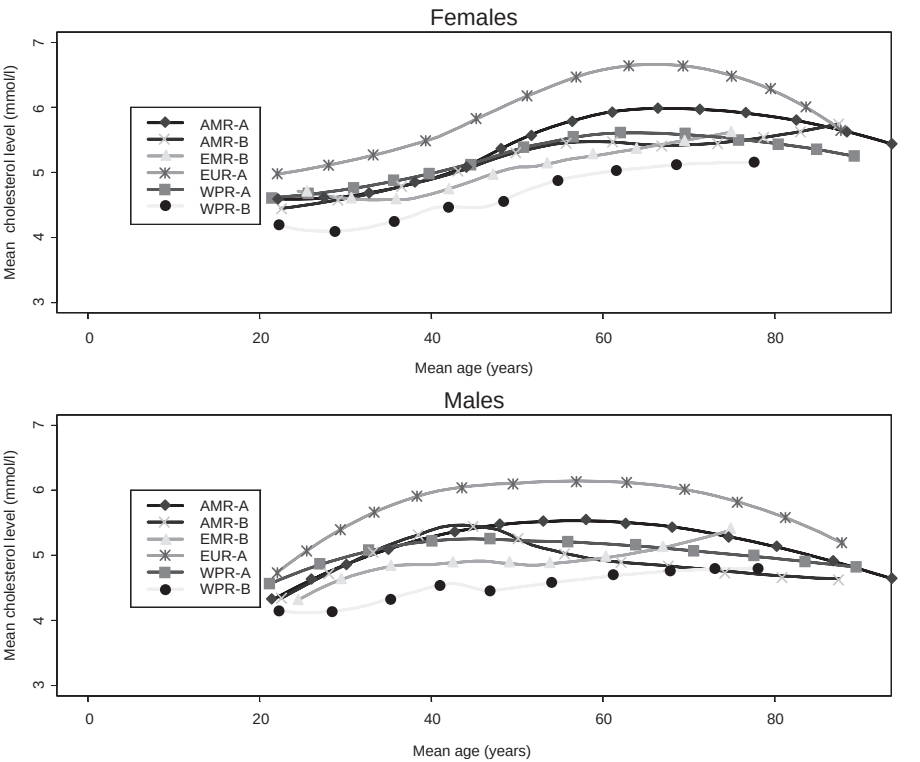
WPR-A and WPR-B). For example, for males in WPR-A, data were available from four countries (Australia, Japan, New Zealand and Singapore). The scatter plot in Figure 7.7 presents these cholesterol data at the country level.

Cholesterol data differed among and between these countries, with the size of the plot circles proportional to the population size and study size where more than one study was available within a country (Figure 7.7). Cholesterol levels were consistently lower for Japan across all age groups. The curve of best fit through these data weighted by study size within each country and by country population size within each subregion was estimated (i.e. a weighted regression line). Clearly, the fitted curve is weighted mostly to the Japanese studies due to Japan having the largest population size.

Although there was significant variation in the overall cholesterol levels between the different subregions, the shape of association across age groups was consistent for the six subregions where sufficient data were available (Figure 7.8).

For six of the remaining subregions (AFR-D, AFR-E, EUR-B, EUR-C, SEAR-B and SEAR-D), insufficient data were available to draw the age–cholesterol association accurately. Within these subregions, the available cholesterol data were pooled together to give age standardized mean levels weighted by country. That is, a single mean cholesterol level was estimated for each subregion with sparse data for males and females separately. Based on this level, one of three "age–cholesterol curves" was

Figure 7.8 The association of cholesterol with age for males and females in six subregions



chosen (Figure 7.6), and this curve was then shifted (up or down) to correspond with the calculated age adjusted mean cholesterol level for that subregion. Using this methodology, the "low cholesterol" curve (overall cholesterol <4.7 mmol/l) was used for AFR-D and AFR-E, the "middle cholesterol" curve (overall cholesterol 4.7–5.5 mmol/l) was used for EUR-B, SEAR-B and SEAR-D, and the "high cholesterol" curve (overall cholesterol >5.5 mmol/l) was used for EUR-C.

Of the two remaining subregions, no data were collected in this review for AMR-D, so data from AMR-B were used to estimate the mean cholesterol levels. In the one study for EMR-D, which included only 634 individuals, the overall mean cholesterol level was skewed by particularly high cholesterol levels in the oldest age group, compared to age patterns observed in other subregions. This was thought not to be representative of that subregion, therefore data from EMR-B were used to estimate cholesterol levels for EMR-D.

Estimates of mean cholesterol and standard deviation

Estimates of mean cholesterol for each of the age groups were made using the age–cholesterol associations outlined above for each subregion and sex separately. Utilizing these associations, age-specific estimates for each subregion were obtained by using midpoints of each GBD age group and predicting the subregional average cholesterol levels. Cholesterol values for those aged >80 years were assumed to be the same as the 70–79 age group due to the extremely limited availability of cholesterol levels in the populations studied with a mean age >80 years. (Figures 7.2 and 7.3 demonstrate that very few subregions had any data for those with a mean age of >80 years.) A similar approach was used to estimate the standard deviations for each age, sex and subregion category. Current mean cholesterol results are presented in Table 7.3, and standard deviations are in Table 7.4.

2.3 Uncertainty of mean and standard deviation of cholesterol levels

The uncertainty of the means and standard deviations of population distributions of cholesterol also had to be estimated. The approach described in the previous section to estimate the means and standard deviations makes as complete use as possible of all available data.

Table 7.3 Estimates of mean cholesterol levels (mmol/l) by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	4.6	5.1	5.2	5.2	5.2	4.5	4.7	4.7	4.7	4.7
AFR-E	4.6	5.1	5.2	5.2	5.2	4.5	4.7	4.7	4.7	4.7
AMR-A	4.8	5.6	6.0	5.9	5.9	5.2	5.5	5.5	5.2	5.2
AMR-B	4.8	5.4	5.4	5.2	5.2	5.3	5.0	4.9	4.8	4.8
AMR-D	4.8	5.4	5.4	5.2	5.2	5.3	5.0	4.9	4.8	4.8
EMR-B	4.6	5.1	5.4	5.6	5.6	4.8	4.9	5.1	5.4	5.4
EMR-D	4.6	5.1	5.4	5.6	5.6	4.8	4.9	5.1	5.4	5.4
EUR-A	5.4	6.3	6.7	6.5	6.5	5.9	6.1	6.1	5.9	5.9
EUR-B	4.6	5.3	5.5	5.4	5.4	5.0	5.1	5.2	5.2	5.2
EUR-C	5.4	6.2	6.6	6.5	6.5	5.5	5.8	5.8	5.7	5.7
SEAR-B	4.0	4.5	4.6	4.6	4.6	5.0	5.1	5.2	5.2	5.2
SEAR-D	4.9	5.7	5.8	5.7	5.7	4.8	5.0	5.0	5.0	5.0
WPR-A	4.9	5.5	5.6	5.4	5.4	5.2	5.2	5.1	5.0	5.0
WPR-B	4.3	4.8	5.1	5.1	5.1	4.5	4.6	4.7	4.8	4.8

Table 7.4 Estimates of cholesterol standard deviations (mmol/l) by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	1.0	1.0	1.0	1.1	1.1	0.9	1.0	1.0	1.0	1.0
AFR-E	1.0	1.0	1.0	1.1	1.1	0.9	1.0	1.0	1.0	1.0
AMR-A	0.9	1.1	1.1	1.0	1.0	1.0	1.0	1.0	0.9	0.9
AMR-B	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1
AMR-D	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1
EMR-B	1.4	1.4	1.4	1.2	1.2	1.4	1.4	1.3	1.1	1.1
EMR-D	1.4	1.4	1.4	1.2	1.2	1.4	1.4	1.3	1.1	1.1
EUR-A	1.0	1.2	1.2	1.1	1.1	1.2	1.2	1.1	1.1	1.1
EUR-B	1.0	1.1	1.1	1.1	1.1	1.0	1.0	1.0	1.0	1.0
EUR-C	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1
SEAR-B	0.8	0.9	0.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0
SEAR-D	1.0	1.1	1.1	1.1	1.1	1.0	1.0	1.0	1.0	1.0
WPR-A	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.8	0.8
WPR-B	1.0	1.1	1.3	1.2	1.2	1.1	1.1	1.2	1.1	1.1

Note: Reported standard deviations are derived from baseline cholesterol (i.e. one-off measures), which when corrected for regression dilution bias were used in all calculations on the "usual" scale.

However, there will always be errors associated with generalizing from the data collected to the subregional level. From the perspective of uncertainty, subregions can be divided into three main categories:

1. subregions where most of the countries have nationally representative surveys;
2. subregions with a lower coverage of countries and/or countries for which well designed surveys exist but on sub-national populations; and
3. subregions with countries where few studies and little or no data existed.

A subregion in which a national study is available for most of the countries would be expected to have low uncertainty (e.g. AMR-A and WPR-A). The remaining 12 subregions can be placed into either category 2 or 3, depending on the number of high-quality studies available. For these, subregional means and standard deviations were estimated from available data. Examining the heterogeneity observed between

different countries in these subregions provided a basis to quantify the uncertainty associated with data quality as well as extrapolation (see Figures 7.2 and 7.3). There may be a variety of causes underlying the heterogeneity, including sampling error and real sub-population differences. However, a subregion whose estimate is based on data from sub-national studies that suggest a wider range of mean cholesterol levels would have greater uncertainty. An example of this occurred in WPR-B, where, in the absence of a single national study for China, an estimate had to be based on all eligible studies even though there were significant differences between studies. Conversely, in WPR-A, heterogeneity is due in greater part to real population differences (i.e. Japan and Australia/New Zealand have substantially different cholesterol levels).

A simulation approach was taken to incorporate the uncertainty introduced in estimating mean cholesterol levels to reflect both sampling error as well as the variation of studies within countries. For each subregion separately, the simulation proceeded by reiterating the same weighted regression approach described earlier (i.e. weighted regression of mean cholesterol on mean age). Each iteration involved re-sampling of data points 10 000 times by treating each study as a random effect (i.e. two components of variation: study sampling error plus variation of study within country). The regression analysis was then re-iterated to obtain uncertainty distributions.

For subregions where insufficient data were available to assess the second component of variation accurately between countries, data were utilized from the data-rich subregions. Specifically, the average inter-country variation observed in AMR-A, AMR-B, EUR-A, EMR-B, WPR-A and WPR-B was applied to the remaining eight subregions.

Similar simulations were utilized to estimate the uncertainty intervals around the estimated standard deviations, the only difference being that the sampling distribution for the standard deviations was based on a chi-square in place of a normal distribution. Results from these simulations are provided in Tables 7.5 and 7.6.

2.4 Theoretical-minimum-risk exposure distribution

To make a judgment on the theoretical minimum cholesterol level, the evidence of the association between cholesterol and relative risk of cardiovascular end-points and data from "low cholesterol" populations were examined.

Lowest relative risk of end-points

A variety of prospective studies have examined the association between cholesterol and cardiovascular end-points. There is strong evidence that increased cholesterol is associated with increased risk of IHD, and the relationship is approximately linear on a logarithmic scale (Law 1999; Law et al. 1994b).

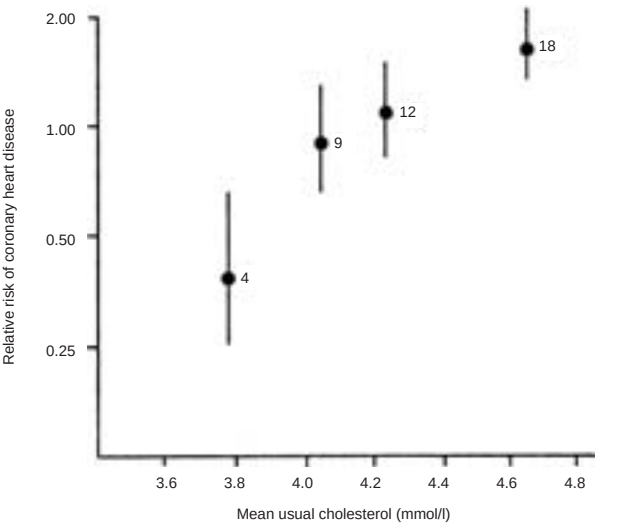
Table 7.5 Values of 95% CI for mean cholesterol (mmol/l) by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	(4.0–5.2)	(4.5–5.7)	(4.5–5.9)	(4.4–6.0)	(4.4–6.0)	(3.9–5.1)	(4.1–5.3)	(4.0–5.4)	(3.9–5.5)	(3.9–5.5)
AFR-E	(4.0–5.2)	(4.5–5.7)	(4.5–5.9)	(4.4–6.0)	(4.4–6.0)	(3.9–5.1)	(4.1–5.3)	(4.0–5.4)	(3.9–5.5)	(3.9–5.5)
AMR-A	(4.5–5.1)	(5.5–5.7)	(5.9–6.1)	(5.7–6.1)	(5.7–6.1)	(4.9–5.5)	(5.4–5.6)	(5.4–5.6)	(5.0–5.4)	(5.0–5.4)
AMR-B	(4.1–5.5)	(5.1–5.7)	(5.2–5.6)	(5.0–5.4)	(5.0–5.4)	(4.6–6.0)	(4.7–5.3)	(4.7–5.1)	(4.6–5.0)	(4.6–5.0)
AMR-D	(4.1–5.5)	(5.1–5.7)	(5.2–5.6)	(5.0–5.4)	(5.0–5.4)	(4.6–6.0)	(4.7–5.3)	(4.7–5.1)	(4.6–5.0)	(4.6–5.0)
EMR-B	(4.0–5.2)	(4.5–5.7)	(4.8–6.0)	(5.0–6.2)	(5.0–6.2)	(4.2–5.4)	(4.3–5.5)	(4.5–5.7)	(4.8–6.0)	(4.8–6.0)
EMR-D	(4.0–5.2)	(4.5–5.7)	(4.8–6.0)	(5.0–6.2)	(5.0–6.2)	(4.2–5.4)	(4.3–5.5)	(4.5–5.7)	(4.8–6.0)	(4.8–6.0)
EUR-A	(5.1–5.7)	(6.0–6.6)	(6.4–7.0)	(6.2–6.8)	(6.2–6.8)	(5.6–6.2)	(5.8–6.4)	(5.8–6.4)	(5.6–6.2)	(5.6–6.2)
EUR-B	(4.2–5.0)	(5.0–5.6)	(5.2–5.8)	(5.1–5.7)	(5.1–5.7)	(4.6–5.4)	(4.8–5.4)	(4.9–5.5)	(4.9–5.5)	(4.9–5.5)
EUR-C	(4.8–6.0)	(5.6–6.8)	(5.9–7.3)	(5.7–7.3)	(5.7–7.3)	(5.1–5.9)	(5.5–6.1)	(5.5–6.1)	(5.4–6.0)	(5.4–6.0)
SEAR-B	(3.4–4.6)	(3.9–5.1)	(3.9–5.3)	(3.8–5.4)	(3.8–5.4)	(4.4–5.6)	(4.5–5.7)	(4.5–5.9)	(4.4–6.0)	(4.4–6.0)
SEAR-D	(4.5–5.3)	(5.4–6.0)	(5.5–6.1)	(5.4–6.0)	(5.4–6.0)	(4.2–5.4)	(4.4–5.6)	(4.3–5.7)	(4.2–5.8)	(4.2–5.8)
WPR-A	(4.6–5.2)	(5.2–5.8)	(5.3–5.9)	(5.0–5.8)	(5.0–5.8)	(4.9–5.5)	(4.9–5.5)	(4.8–5.4)	(4.6–5.4)	(4.6–5.4)
WPR-B	(3.9–4.7)	(4.5–5.1)	(4.8–5.4)	(4.8–5.4)	(4.8–5.4)	(4.1–4.9)	(4.3–4.9)	(4.4–5.0)	(4.5–5.1)	(4.5–5.1)

Table 7.6 Values of 95% CI for standard deviation of cholesterol (mmol/l) by subregion, sex and age

	Sex and age group (years)									
	Females					*Males*				
Subregion	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.9–1.3)	(0.9–1.3)	(0.7–1.1)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)
AFR-E	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.9–1.3)	(0.9–1.3)	(0.7–1.1)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)
AMR-A	(0.8–1.0)	(1.0–1.2)	(1.0–1.2)	(0.9–1.1)	(0.9–1.1)	(0.9–1.1)	(0.9–1.1)	(0.9–1.1)	(0.8–1.0)	(0.8–1.0)
AMR-B	(1.0–1.2)	(1.0–1.2)	(1.1–1.3)	(1.0–1.4)	(1.0–1.4)	(1.0–1.2)	(1.0–1.2)	(1.0–1.2)	(0.9–1.3)	(0.9–1.3)
AMR-D	(1.0–1.2)	(1.0–1.2)	(1.1–1.3)	(1.0–1.4)	(1.0–1.4)	(1.0–1.2)	(1.0–1.2)	(1.0–1.2)	(0.9–1.3)	(0.9–1.3)
EMR-B	(1.2–1.6)	(1.1–1.7)	(1.2–1.6)	(1.0–1.4)	(1.0–1.4)	(1.2–1.6)	(1.1–1.7)	(1.1–1.5)	(0.9–1.3)	(0.9–1.3)
EMR-D	(1.2–1.6)	(1.1–1.7)	(1.2–1.6)	(1.0–1.4)	(1.0–1.4)	(1.2–1.6)	(1.1–1.7)	(1.1–1.5)	(0.9–1.3)	(0.9–1.3)
EUR-A	(0.9–1.1)	(0.9–1.5)	(1.0–1.4)	(1.0–1.2)	(1.0–1.2)	(1.1–1.3)	(0.9–1.5)	(0.9–1.3)	(1.0–1.2)	(1.0–1.2)
EUR-B	(0.8–1.2)	(0.9–1.3)	(0.9–1.3)	(0.9–1.3)	(0.9–1.3)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)
EUR-C	(0.9–1.3)	(0.9–1.3)	(1.0–1.4)	(1.0–1.4)	(1.0–1.4)	(0.9–1.3)	(0.9–1.3)	(0.9–1.3)	(0.9–1.3)	(0.9–1.3)
SEAR-B	(0.6–1.0)	(0.7–1.1)	(0.7–1.1)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)
SEAR-D	(0.8–1.2)	(0.9–1.3)	(0.9–1.3)	(0.9–1.3)	(0.9–1.3)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)	(0.8–1.2)
WPR-A	(0.7–1.1)	(0.8–1.0)	(0.8–1.0)	(0.8–1.0)	(0.8–1.0)	(0.7–1.1)	(0.8–1.0)	(0.8–1.0)	(0.7–0.9)	(0.7–0.9)
WPR-B	(0.7–1.3)	(0.9–1.3)	(1.2–1.4)	(1.0–1.4)	(1.0–1.4)	(0.8–1.4)	(0.9–1.3)	(1.1–1.3)	(0.9–1.3)	(0.9–1.3)

Figure 7.9 The association between cholesterol and IHD in the Shanghai Factory Workers Study



Source: Reprinted, by permission of the publisher, from Chen et al. (1991). Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *British Medical Journal*, **303**:276–282.

In populations from industrialized countries (e.g. Europe and North America), this relationship has seldom been demonstrated below a cholesterol level of 4.5–5.0 mmol/l (Chen et al. 1991). However, in other populations such as China, data suggest that this relationship may continue, without a threshold, below cholesterol levels of about 4.0 mmol/l (Chen et al. 1991; Law and Wald 1994; Law et al. 1994b) (Figure 7.9). Based on this evidence it would be feasible to set a theoretical minimum of usual cholesterol of at least 3.8 mmol/l.

Another source of data is clinical trials of cholesterol lowering from recent meta-analyses. Trials included in these overviews achieved substantial reduction in cholesterol with no adverse effects. The reductions are summarized in Table 7.7. These reductions of cholesterol also occurred in the lowest cholesterol group, i.e. those with baseline mean cholesterol of about 5.0 mmol/l. The aggregated data from trials therefore indicate that a substantial reduction in cholesterol is possible, across different baseline cholesterol levels, without risk of substantial adverse effects.

Further, the recently completed large-scale Heart Protection study (Heart Protection Study Collaborative Group 2002a, 2002b) demonstrated that cholesterol lowering in those with average or below average

Table 7.7 Reduction in cholesterol achieved by trials of statins

Trial	*Baseline mean cholesterol (mmol/l)*	*Mean cholesterol reduction (%)*	*Final mean cholesterol (mmol/l)*
LRC	7.5	9	6.9
HHS	7.4	10	6.7
WOSCOPS	7.0	20	5.6
4S	6.8	26	5.0
AFCAPS/TexCAPS	5.7	19	4.6
LIPID	5.6	18	4.6
CARE	5.4	20	4.3

Source: LaRosa et al. (1999) and Pignone et al. (2000).

total cholesterol levels was still associated with reduced risk of cardiovascular disease. This trial included over 20 000 participants and found no evidence of a threshold level below which lowering cholesterol did not produce a lower risk.

Low cholesterol populations

An alternative source of data relevant to setting a theoretical minimum comes from examining mean cholesterol levels in studies of so-called "unacculturated" populations with little cardiovascular disease and low cholesterol levels (Poulter and Sever 1994). Unacculturated generally refers to those populations that are relatively isolated and have preserved their lifestyle over many generations.

An overview of typical cholesterol values in men aged 45–64 years in different populations noted that while mean cholesterol ranged from 5.5 to 7.0 mmol/l in many industrialized populations, it was much lower in hunter-gatherer societies where mean values were as low as 3.0–3.5 mmol/l (Law 1999; Law and Wald 1994). Data from individual studies around the world that have focused on these "low cholesterol" populations are summarized in Table 7.8. In the Shanghai study, there was a strongly positive and apparently independent relation between cholesterol concentration and death from IHD, even at these lower levels (Chen et al. 1991) (Figure 7.10).

Typically, the data show that there is a very low prevalence of cardiovascular disease in these populations, which exhibit an absence of obesity due to diets low in salt, cholesterol and fat (particularly animal fat), and a lifestyle requiring heavy physical labour (Barnes 1965; Carvalho et al. 1989; Connor et al. 1978; He et al. 1991a, 1991b; Page et al. 1974; Poulter and Sever 1994; Sever et al. 1980). There is also evidence of low blood pressure levels, and no age-related rise in either cholesterol or blood pressure levels. Data from these studies indicate that many of these populations have mean cholesterol levels of about

Table 7.8 Cholesterol levels in low cholesterol populations

Country (reference)	*Population*	*Mean cholesterol levels*	*Patterns with age*
Africa			
Tanganyika[a] (Mann et al. 1964)	Masai tribe (mostly males) with virtually no cardiovascular disease.	3.0–3.7 mmol/l; >5.2 mmol/l rare	No evidence of increasing cholesterol with advancing age
Americas			
Mexico (Casdorph 1972; Connor et al. 1978)	Tarahumara Indians who lived in the mountains	3.0–3.5 mmol/l	No age-related rise in cholesterol
Western Pacific			
China (Fan et al. 1990)	An ecological study of 6500 individuals rural China	3.3 mmol/l	—
China (Chen et al. 1991)	9021 males and females aged 35–64 years at baseline in urban Shanghai	3.1–5.4 mmol/l (baseline) 3.8–4.6 mmol/l (3 years)	— —
Papua New Guinea (Barnes 1965)	The isolated Bomai and Yongamuggi people	3.4–3.6 mmol/l for males and females	—
Solomon Islands (Page et al. 1974)	Six tribal societies with varying levels of acculturation	3.0–3.7 mmol/l in least acculturated groups	No age-related rise in cholesterol

— No data.

[a] Country name correct as at time of study.

3.8 mmol/l or lower. Therefore, setting a theoretical minimum at 3.8 mmol/l is justified based on all of the data.

Safety of low cholesterol levels

Concerns have been expressed over whether lowering cholesterol may be harmful, and therefore setting a theoretical minimum too low may have adverse consequences. Some data have suggested a negative association between cholesterol and haemorrhagic stroke (Iso et al. 1989); however, a recent analysis has suggested that this is in fact more likely to be a null association (Suh et al. 2001). It should also be noted that even if there were a small increase in risk of haemorrhagic stroke for people with very low cholesterol levels, this would be outweighed overall by the benefits resulting from lower risk of IHD (Bucher et al. 1998; Law et al. 1994a).

There is no strong consistent evidence that low or reduced cholesterol concentrations increase mortality from non-cardiovascular diseases such as cancer or infection (Law et al. 1994a). Overviews of trials have not

detected increases in causes of non-cardiovascular disease mortality (Hebert et al. 1997; LaRosa et al. 1999) despite achieving relatively large decreases in cholesterol. In many cases, the apparent association is actually due to disease causing low cholesterol rather than vice versa (Law et al. 1994a). A recent meta-analysis of trials found no convincing evidence that the risk of "non-illness"-related mortality (deaths from suicide, accident or trauma) was strongly associated with cholesterol lowering (Muldoon et al. 2001).

Finally, data relating to low cholesterol levels come from research on those with heterozygous familial hypobetalipoproteinaemia. These individuals have cholesterol levels as low as 2.0–3.0 mmol/l and a prolonged life expectancy, as coronary artery disease is avoided—but no recognized adverse effects from the low cholesterol (Law 1999).

Standard deviation of the theoretical-minimum-risk exposure distribution

The choice of standard deviation around the theoretical minimum was based on examining the relationship of the standard deviation and mean of cholesterol using all available data from our review of the literature (Figure 7.10). From this illustration, a distribution with a mean of 3.8 mmol/l would typically have a standard deviation of 0.9 mmol/l (baseline), which equates to 0.6 mmol/l (usual).

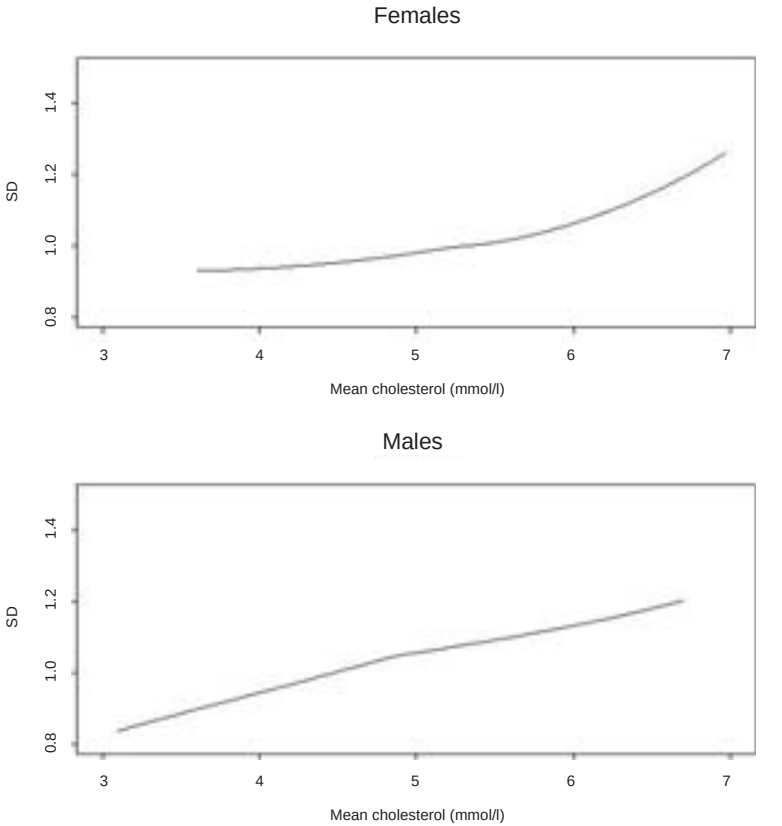
3. Cholesterol–disease relationships

Data on the relationship between cholesterol and disease outcomes come from two main types of studies (MacMahon 1994). Prospective observational studies provide data from which the effects of prolonged cholesterol differences can be estimated (MacMahon et al. 1990), that is, hazard ratios. Trials provide data about the effects of short-term cholesterol reduction (Collins et al. 1990), or risk reversal. Results from prospective observational studies will be considered first.

3.1 Data sources for hazard ratios

Observational studies have been conducted in a variety of settings that examine the association between cholesterol and disease. However, the results of many of these individual studies are limited. Many observational studies have small sample sizes or an insufficient number of end-points, and therefore lack the power required to provide reliable estimates of associations for different population subgroups (e.g. sex and age groups) and/or specific diagnostic categories (MacMahon et al. 1990). Individual studies do not always provide information on the direction of the association at lower cholesterol levels, making it difficult to assess whether the observed association is continuous or has a threshold level. In addition, these studies frequently do not standardize the size of the association for bias and confounding—in particular,

Figure 7.10 Association between mean cholesterol and standard deviation for review data



regression dilution bias (MacMahon et al. 1990). This bias occurs when associations are calculated from "one-off" measures of cholesterol rather than "usual" cholesterol. (There is further discussion of this bias in the next section.)

Overviews or meta-analysis of observational studies, or meta-analyses, overcome many of the size limitations of individual studies. At the time of writing four major overviews have been conducted that included data on cholesterol, and their main design features are summarized in Table 7.9.

In contrast to the first three meta-analyses, which utilized tabular data, the APCSC (1999) involved analyses of individual participant data. Therefore, it can more reliably adjust for confounding and provide more reliable estimates of hazard ratios.

Table 7.9 Characteristics of major cholesterol cohort study overviews

Study characteristics	*Law et al. (1994b)*	*Prospective Studies Collaboration (PSC 1995)*	*Eastern Collaborative Research Group (Anonymous 1998a)*	*Asia-Pacific Cohort Studies Collaboration (APCSC secretariat, personal communication, 2001)*
Aims	To estimate by how much and how quickly a given reduction in cholesterol concentration will reduce the risk of IHD	To assess the relationship between BP and total blood cholesterol and stroke, and determine how the strength of the relationship between BP and stroke varied with age	To assess the relationship between BP and total blood cholesterol and stroke in Asian populations, and determine whether the strength of the relationship varied with type of stroke	To produce region, age- and sex-specific blood pressure and cholesterol associations for stroke (including subtypes), IHD, and total cardiovascular disease
Number of studies included	10	45	18	29
Regions included	England, Scotland, Europe, Hawaii and Israel	Asia, Australia, Europe, Hawaii, the Middle East and USA	China (13 cohorts), Japan (5)	Australia (3), mainland China (9), Hong Kong SAR (1), Japan (12), New Zealand (1), Republic of Korea (1), Singapore (1), Taiwan, China (1)
Number of participants	494804	450000	124774	353065
% male	100%	61%	61%	57%
Age range (years)	35–84	15–99	18–98	20–107
Mean age at baseline	Not available	Not available	48 years	47 years
Follow-up	Range of 7–23 years	Range of 5–30 years, mean 15 years	Range unknown, mean 9 years	Range of <1–29 years, mean 7 years

BP Blood pressure.

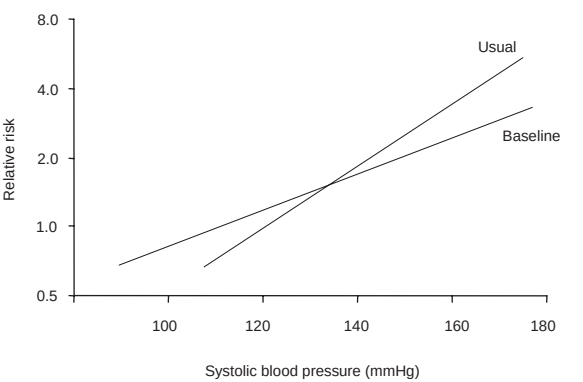
Of the four overviews, only two included analyses for the IHD end-point; Law et al. (1994b) and APCSC (APCSC secretariat, personal communication, 2001). The former will be used as the primary data source for relative risk estimates of IHD due to the greater sample size. Three overviews included data on cholesterol and stroke (Anonymous 1998a; APCSC secretariat, personal communication, 2001; PSC 1995). However, only APCSC analyses were based on individual participant data and provided age-specific analyses of total stroke and stroke subtypes. It will therefore be the primary data source for relative risk estimates of stroke.

3.2 Analysis issues

An important factor that must be accounted for with estimates of the association between cholesterol and cardiovascular end-points from observational data is regression dilution bias. This bias occurs because baseline or one-off measures of cholesterol are subject to random fluctuations, due partly to the measurement process, and partly to any real but temporary deviations at the baseline from the usual cholesterol level (MacMahon et al. 1990). Therefore, baseline cholesterol values have a wider distribution than the "usual" cholesterol values. With repeated measures there is a "regression to the mean" of values (MacMahon 1994), whereby an initially extreme observation tends to become less abnormal with replication (Strachan and Rose 1991).

This imprecision in measurement not only influences distribution, but also affects the association with disease outcomes (MacMahon et al. 1990). Figure 7.11 illustrates the effect of regression dilution

Figure 7.11 Effects of regression dilution bias on the association between blood pressure and relative risk of cardiovascular disease



bias for blood pressure, but the same would be true for cholesterol. The baseline distribution has a shallower slope than usual cholesterol on the curve-relation of cholesterol to relative risk of disease. Analyses have suggested that correcting for regression dilution bias increases the slope of the association by as much as 61% (Law et al. 1994c). If this bias is not corrected, the strength of the association between cholesterol and disease incidence is underestimated ("regression dilution bias") (MacMahon 1994). This systematically dilutes the apparent importance of cholesterol and can result in systematic and substantial underestimation of risk of disease with usual cholesterol (MacMahon et al. 1990).

The size of the dilution is directly related to the extent to which cholesterol measurements are subject to regression to the mean. Several major meta-analyses conducted in recent years aimed to address these limitations with correction for regression dilution bias (Anonymous 1998a; APCSC 1999; PSC 1995). It is possible to use repeated measures on cholesterol to obtain an estimate of the attenuation factor in order to correct for this bias in the analysis. An attenuation factor of 1.82 was calculated from remeasurement data in the Prospective Studies Collaboration (PSC) (1995), and 1.90 in the Eastern study (Anonymous 1998a). In the APCSC, analyses of remeasurement data from cohorts estimated that the correction factor was 1.8. (APCSC secretariat, personal communication, 2001). Here, use of the term "usual cholesterol" indicates that the association between cholesterol and the disease end-point has been corrected for regression dilution bias.

The surrogate dilution effect is another factor that should be considered specifically in cholesterol studies. This effect arises because observational studies underestimate the effect of lower cholesterol relative to the trials (Law et al. 1994c). In a cohort study, a 1 mmol/l lower cholesterol concentration is associated with about 0.67 mmol/l of LDL, but in cholesterol lowering trials, a 1 mmol/l lower total cholesterol is usually comparable to 1 mmol/l lower LDL. Law et al. (1994c) adjusted for both regression dilution bias and the surrogate dilution effect in their analyses, and the final correction factor was 1.61.

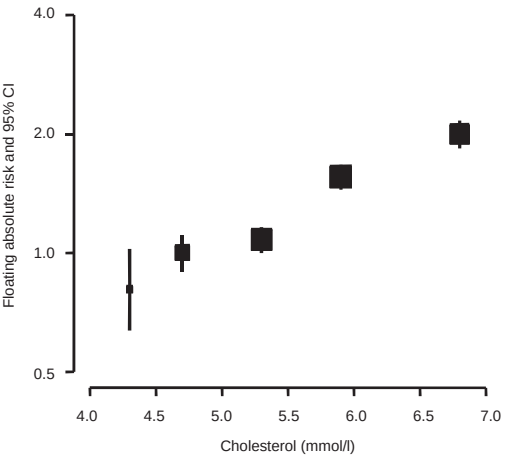
3.3 Estimates of cholesterol–disease relationships

A summary of the results of the four prospective study overviews is presented in Table 7.10, and each of these end-points will now be considered in detail.

Cholesterol and IHD

Analyses from the APCSC overview (APCSC secretariat, personal communication, 2001) and that by Law et al. (1994b) demonstrated that the relative risk of IHD increased with increasing cholesterol level, and that the association was roughly linear when plotted on a log scale (Figure 7.12 and 7.13).

Figure 7.12 Usual cholesterol level and risk of IHD in the Asia-Pacific region



Source: APCSC data (APCSC secretariat, personal communication, 2001).

This means that the proportional difference in risk associated with a given absolute difference in usual cholesterol is similar at all levels of cholesterol, at least within the range studied. This continuous association showed no evidence of a threshold level of cholesterol, below which lower levels of cholesterol are no longer associated with lower relative risks of IHD (down to almost 4.0 mmol/l). Further, there was no evidence of an upper threshold level above which the relative risk of IHD increased much more rapidly (Anonymous 1998a; APCSC secretariat, personal communication, 2001; Law et al. 1994c; PSC 1995).

Overall, the analyses in both the APCSC (APCSC secretariat, personal communication, 2001) and by Law et al. (1994b) suggested that a 0.6 mmol/l lower cholesterol was associated with 24–27% lower risk of IHD. There was no evidence of a difference in the size of the association between males and females or fatal and non-fatal IHD end-points.

Age has an important influence on the size of the cholesterol–end-point relationship, as the associations are steeper for those in younger age groups. (This also largely accounts for the apparent heterogeneity between the cholesterol–IHD associations in the cohorts in Figure 7.13.) This limits the ability to compare directly the overall relative risk estimates across the overviews, as it is only appropriate to compare age-specific results. The gradient of the cholesterol–IHD association varies with age at baseline, the gradient being much steeper for younger

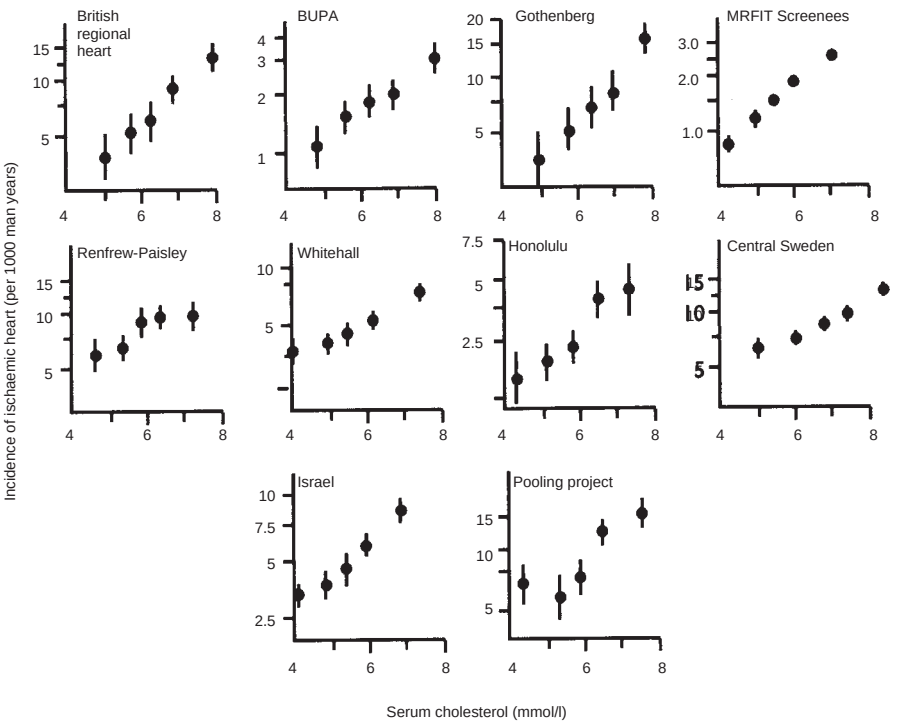
Table 7.10 Summary results of major cohort study overviews

Study end-points	*Law et al. (1994b)*	*Prospective Studies Collaboration (PSC 1995)*	*Eastern Collaborative Research Group (Anonymous 1998a)*	*Asia-Pacific Cohort Studies Collaboration (APCSC secretariat, personal communication, 2001)*
IHD end-points	18811 IHD events recorded	—	—	2838 IHD events, 1607 (57%) fatal
	0.6 mmol/l ↓ cholesterol associated with overall reduction of IHD of 27% from 10 studies combined	—	—	0.6 mmol/l ↓ cholesterol RR = 0.76 (95% CI 0.73–0.79) (24% reduction in IHD)
Stroke end-points	—	13397 participants were recorded as having had a stroke	1798 strokes, 995 (55%) fatal, 39% had data on subtype of which 42% haemorrhagic	2937 strokes, 56% fatal
	—	1 mmol/l ↑ cholesterol RR = 0.98 (95% CI 0.94–1.01)	0.6 mmol/l ↓ cholesterol RR = 0.92 (95% CI 0.72–1.17) (8% reduction in stroke)	1 mmol/l ↓ cholesterol RR = 0.87 (95% CI 0.81–0.94) (13% reduction in stroke)

Key: ↑, raised; ↓, decreased.

— No data.

Figure 7.13 Incidence of ischaemic heart disease and usual cholesterol level in 10 cohort studies



Source: Reprinted, by permission of the publisher, from Law et al. (1994b) By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *British Medical Journal*, **308**:367–372.

age groups. While the proportional change in IHD risk per unit change in cholesterol is less extreme in old age than in middle age, the relationship remains positive for all age groups (APCSC secretariat, personal communication, 2001; Law et al. 1994b). It is therefore necessary to use age-specific estimates for hazard ratios in all cholesterol analyses for CRA.

The results of both overviews are relatively consistent, but due to the larger number of participants and end-points in the review by Law et al. (1994b), these relative risk estimates, transformed for application to GBD age groups, were used in the analyses of this chapter. Table 7.11 presents relative risks from the overview by Law et al. (1994b) transformed into GBD age groups for a 1 mmol/l difference in usual cholesterol.

Table 7.11 Relative risk of IHD associated with a 1 mmol/l difference in usual cholesterol

Age group (years)	*Relative risk (95% CI)*
30–44	0.51 (0.36–0.73)
45–59	0.50 (0.45–0.56)
60–69	0.70 (0.62–0.79)
70–79	0.77 (0.69–0.86)
≥80	0.75 (0.67–0.84)

Source: Modified from overview by Law et al. (1994b).

Cholesterol and stroke

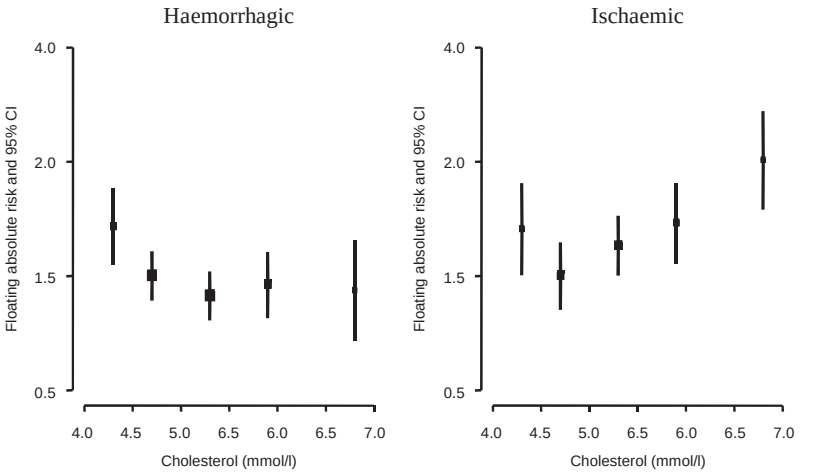
Few data are available on the association between cholesterol and stroke, and the relationship is more complex. Many individual cohorts and the PSC have found no association between cholesterol and risk of stroke death (PSC 1995). However, recent meta-analyses and other studies have reported that this apparent null association may be principally due to a quantitatively different association between cholesterol and the two major types of stroke—haemorrhagic and ischaemic. A variety of studies have attempted to clarify these associations. Table 7.12 summarizes some of the largest cohort studies undertaken, with several hundred recorded stroke events by subtype.

Several of these studies showed evidence of a positive association between cholesterol and risk of ischaemic stroke (Anonymous 1998a; Benfante et al. 1994; Iso et al. 1989; Jorgensen et al. 1995; Leppala et al. 1999; Neaton et al. 1992, 1993; Yano et al. 1994). Other individual studies failed to find an association between cholesterol and ischaemic stroke (Nakayama et al. 1997; Szatrowski et al. 1984; Tanaka et al. 1982), but the extent of misclassification of stroke subtype was uncertain in these studies. The association of cholesterol with haemorrhagic stroke is less clear, with some analyses suggesting either a negative (Anonymous 1998a; Iso et al. 1989; Leppala et al. 1999; Neaton et al. 1992, 1993; Yano et al. 1989, 1994) or null association (Iribarren et al. 1996; Suh et al. 2001).

Analyses from the APCSC show the different association of cholesterol with stroke subtypes (Figure 7.14); a positive association for ischaemic stroke and a negative/null association for haemorrhagic stroke. In the CRA analyses, data from the APCSC overview were used, given the size and availability on individual data.

The age-specific relative risks of haemorrhagic and ischaemic stroke with a 1 mmol/l difference in usual cholesterol are presented in Table 7.13.

Figure 7.14 Usual cholesterol level and risk of haemorrhagic and ischaemic stroke



Source: APCSC data (APCSC secretariat, personal communication, 2001).

Overall, APCSC data indicated that the association of cholesterol with stroke varies with age at baseline, the gradient being much steeper for younger age groups. As discussed in relation to IHD, this means that the proportional change in stroke risk per unit change in cholesterol is less extreme in old age than in middle age (APCSC secretariat, personal communication, 2001). It is therefore necessary to use age-specific estimates for hazard ratios in all cholesterol analyses for CRA. There was no evidence of differences in the association between males and females, so sex-specific estimates are not necessary.

Despite having data from the APCSC, it is difficult to incorporate the different cholesterol-stroke subtype associations into CRA analyses as the only GBD end-point for stroke relates to total stroke. It is not possible to conduct analyses for ischaemic and haemorrhage stroke independently, and it is not appropriate simply to apply the relative risk for total stroke events to all 14 subregions, since there is evidence that the relative proportions of haemorrhagic and ischaemic stroke vary among them (Anderson et al. 1993; Bamford et al. 1990; Chen et al. 1992; Giroud et al. 1991; Hung 1993; Jeng et al. 1998; Nakayama et al. 1997; Suzuki et al. 1987; Thrift et al. 2001; Wu et al. 1992). Analyses of total stroke must therefore be modified to reflect these differing proportions, and the different types of association between cholesterol and stroke

Table 7.12 Data from major cohort studies on the association between cholesterol and risk of stroke subtype

Study	*Participants*	*Ischaemic stroke*	*Haemorrhagic stroke*
The American MRFIT study (Iso et al. 1989; Neaton et al. 1992, 1993)	350 000 males At 6 years, 230 fatal strokes had occurred At 12 years, 765 stroke deaths had occurred	Risk of death was significantly increased with increasing cholesterol at both points of follow-up	Risk of haemorrhagic stroke death highest in those with lowest cholesterol (if DBP ≥90 mmHg) at 6 and 12 years
American Kaiser Permanente Study (Iribarren et al. 1996)	61 756 individuals At 16 years 386 haemorrhagic strokes recorded	—	No relationship among those aged 40–64 years Negative association between low cholesterol and risk of haemorrhagic stroke in elderly males
British Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Leppala et al. 1999)	28 519 males aged 50–69 years At 8 years 1 057 males had a stroke	Cholesterol was associated with increased risk of cerebral infarction at levels ≥7 mmol/l	Cholesterol was inversely associated with the risk of intracerebral haemorrhage (Leppala et al. 1999)
Copenhagen Stroke Study (Jorgensen et al. 1995)	Included over 1 000 males who had suffered a stroke	Cholesterol was positively associated with risk of ischaemic stroke	—
A cohort study in Sweden (Gatchev et al. 1993)	54 000 participants At 20 years, 347 haemorrhagic strokes had been reported	—	Relative risk for cerebral haemorrhage increased with decreasing cholesterol level in females, but the risk function was U-shaped in males
Honolulu Heart Program (Benfante et al. 1994; Yano et al. 1989, 1994)	Over 6 000 Japanese males in Hawaii followed for 15 years (252 ischaemic strokes) Over 7 000 of these males followed for 18 years (116 haemorrhagic strokes)	A continuous increase in isch. stroke rates with increasing levels of cholesterol	An inverse association between cholesterol and the risk of haemorrhagic stroke, at least in males with cholesterol in the lowest quintile
Korea Medical Insurance Corporation study (Suh et al. 2001)	114 793 males in the Republic of Korea, aged 35–59 years followed for 6 years	—	No overall association between the relative risk of intracerebral haemorrhage and total cholesterol
Eastern Stroke and CHD Collaborative project (Anonymous 1998a)	Overview of 18 cohort studies in China and Japan, 11 studies, >60 000 participants included data on stroke subtype (494 non-haemorrhagic and 404 haemorrhagic strokes)	A positive association between cholesterol and non-haemorrhagic stroke	An inverse association between cholesterol and haemorrhagic stroke (Anonymous 1998a)

— No data.

Table 7.13 Relative risk of stroke with a 1 mmol/l difference in usual cholesterol

	Risk of stroke event	
Age group (years)	*Haemorrhagic stroke relative risk (95% CI)*	*Ischaemic stroke relative risk (95% CI)*
30–44	1.03 (0.64–1.64)	0.66 (0.34–1.26)
45–59	1.09 (0.92–1.28)	0.66 (0.56–0.77)
60–69	1.13 (0.90–1.41)	0.77 (0.65–0.92)
70–79	1.08 (0.84–1.40)	0.92 (0.76–1.10)
≥80	1.43 (0.99–2.07)	0.84 (0.70–1.00)

Source: APCSC data (APCSC secretariat, personal communication, 2001).

subtype. It was therefore necessary to estimate subregion- and age-specific proportions of ischaemic and haemorrhagic fatal and non-fatal strokes so that weighted RR values could be applied. (An assumption was made that these are the same for males and females.)

Several steps were undertaken to estimate stroke subtype proportions, and these are outlined in Appendix B. They included using data from "gold-standard" studies of stroke incidence, and other observational data on stroke subtypes by subregion. Having estimated the relative percentage of stroke subtypes by age, sex and subregion, the APCSC values of RR for ischaemic stroke were smoothed and then weighted as per these percentages. (Smoothed RRs for the five age groups were 0.61, 0.69, 0.76, 0.82 and 0.90.) No association was found between cholesterol and haemorrhagic stroke.

3.4 Risk reversal

As already alluded to, prospective observational studies provide data on the association between cholesterol and stroke and IHD, but they do not provide data on the impact of cholesterol lowering on these outcomes over time (MacMahon et al. 1990). From prospective studies alone, it is not possible to tell whether outcomes are reversible, or whether the association reflects, to some extent, irreversible cumulative effects of cholesterol differences that have persisted for years (Collins and Peto 1994).

The results from randomized clinical trials do provide data on reversibility. They are relevant to assessing how rapidly, and to what extent, the epidemiologically expected reductions in stroke and IHD are produced by lowering cholesterol levels (Collins and Peto 1994; Collins et al. 1990). They therefore provide estimates of the proportion of the potential long-term benefit from a particular cholesterol difference that may be expected within a few years of cholesterol lowering.

Data sources on risk reversal

A variety of trials have studied the impact of cholesterol lowering. However, as with blood pressure lowering trials, individual studies usually lacked sufficient power to reliably detect moderate changes in events (Collins and Peto 1994; Collins et al. 1990; He and Whelton 2000). To accurately detect small but potentially important differences in risk reduction of cardiovascular disease (e.g. 10–15%), it is necessary for trials to record many hundreds of end-points. Since most have not achieved this, overviews are necessary to provide more accurate estimates of the impact of cholesterol lowering on stroke and IHD. Results from these overviews will contribute to estimates of "risk reversibility".

A number of cholesterol lowering trials as well as major meta-analyses of such trials have been undertaken (Atkins et al. 1993; Blauw et al. 1997; Bucher et al. 1998; Byington et al. 2001; Crouse et al. 1997, 1998; Hebert et al. 1995, 1997; Holme 1990; LaRosa et al. 1999; Law et al. 1994b; Pignone et al. 2000; Ross et al. 1999; M. Law, personal communication, 2001). Most of these trials assessed the impact of lowering cholesterol on IHD, but data are also available on stroke. Results of an updated meta-analysis of all trials included in these previous overviews are given in Tables 7.14–7.16.

Estimates of risk reversal

Cholesterol and risk of IHD

Trials of cholesterol lowering may be broadly grouped into "dietary interventions", "non-statin drugs" (e.g. fibrates), and "statin drugs". Many individual trials and a number of meta-analyses (including the updated meta-analysis) have analysed the association between cholesterol lowering and IHD. Overall, the trials have demonstrated a significant reduction in risk of IHD for those treated.

The current and previous meta-analyses of the early trials demonstrated a risk reduction in those treated of about 10–15%, with dietary interventions or non-statin drugs such as fibrates or resins (Atkins et al. 1993; Bucher et al. 1998; Holme 1990). Later trials with statins, that achieved larger reductions in cholesterol, produced risk reductions of up to 25–30% (Table 7.14) (Bucher et al. 1998; LaRosa et al. 1999; Pignone et al. 2000; Ross et al. 1999). One recently published overview included diet, fibrates, resins and statins (Bucher et al. 1998), but most recent meta-analyses have limited their analyses to statins. The review suggested that the effects of statins on risk reduction could be greater than other agents, but cautioned that analyses were based on between-study treatment comparisons rather than within study comparisons. Therefore, any apparent differences in drug efficacy may have been due to other factors such as differences in study design or populations. For example, participants in statin trials tended to be older, with higher event rates than on other trials, which may partly be responsible for differences in trial

Table 7.14 Clinical trials of cholesterol lowering by dietary interventions

Trial	Participants		Stroke		IHD		Mean age (years)	% female	Cholesterol reduction	Follow-up	RR (95% CI)	
	A	C	A	C	A	C					Stroke	IHD
DART (Burr et al. 1989; Law et al. 1994b)	1018	1015	—	—	132	144	56.6	0.0	0.3	2.0	—	0.91 (0.73–1.14)
Hjermann et al. (1981)	604	628	3	3	19	36	45.0	0.0	>1.0	6.5	1.04 (0.21–5.13)	0.55 (0.32–0.95)
Los Angeles (Dayton et al. 1968)	424	422	13	22	45	67	65.5	0.0	0.9	8.0	0.59 (0.30–1.15)	0.67 (0.47–0.95)
MRC (Anonymous 1968)	199	194	2	0	45	51	—	0.0	1.00	3.7	4.87 (0.24–100.90)	0.86 (0.61–1.22)
MRC (Research Committee to the Medical Council 1965)	123	129	—	—	43	44	—	0.0	0.5	6.0	—	1.02 (0.73–1.44)
Minnesota (Frantz et al. 1975, 1989; Law et al. 1994b)	4922	4853	—	—	131	121	50.0	51.5	0.7	5.0	—	1.07 (0.84–1.36)
Oslo (Leren 1970)	206	206	7[a]	5[a]	79	94	45.0	0.0	1.1	11.0	1.40 (0.45–4.34)	0.84 (0.67–1.06)
STARS (Law et al. 1994b; Watts et al. 1992)	60	30	0	1	3	5	51.0	0.0	1.1	3.0	0.17 (0.01–4.04)	0.30 (0.08–1.17)
St Mary's (Law et al. 1994b; Rose et al. 1965)	28	52	0	0	8	11	56.8	—	0.6	2.0	—	1.45 (0.67–3.17)
Sydney (Law et al. 1994b; Woodhill et al. 1978)	221	237	—	—	37	24	49.0	0	0.3	5.0	—	1.65 (1.02–2.67)
	7805	7766	25	34	542	597	50.9[b]	32.5	0.7[b]	5.6[b]	0.80 (0.48–1.32)	0.92 (0.82–1.02)

Key: A, active treatment group; C, control group.

— No data.

[a] Only fatal events reported.

[b] "Weighted mean" totals (weighted by person-years of follow-up).

Table 7.15 Clinical trials of cholesterol lowering by other non-statin interventions

Trial	Participants		Stroke		IHD		Mean age (years)	% female	Cholesterol reduction	Follow-up	RR (95% CI)	
	A	C	A	C	A	C					Stroke	IHD
Acheson and Hutchison[a] (1972)	47	48	25	27	—	—	—	31.6	0.6	3.5	0.95 (0.66–1.36)	—
CLAS (Blankenhorn et al. 1987)	94	94	0	0	1	5	54.2	0.0	1.3	2.0	—	0.20 (0.02–1.68)
Coronary Drug Project (Anonymous 1975)	2222	2789	231	311	596	839	54.0	0.0	0.6	6.0	1.01 (0.73–1.41)	0.89 (0.82–0.97)
Dorr et al. (1978)	1149	1129	0[c]	1[c]	19	31	53.9	52.0	0.5	2.1	0.33 (0.01–8.03)	0.60 (0.34–1.06)
FATS (Brown et al. 1990; Law et al. 1994b)	94	52	0	0	2	0	46.7	0.0	1.5	2.5	—	2.79 (0.14–57.03)
Gross and Figueredo (1973)	23	29	0[c]	1[c]	1	0	57.1	71.2	0.6	3.0	0.42 (0.02–9.78)	3.75 (0.16–87.98)
Helsinki (Frick et al. 1987)	2051	2030	6[c]	4[c]	56	84	47.3	0.0	0.7	5.0	1.48 (0.42–5.25)	0.66 (0.47–0.92)
Lipid Research Clinic (Anonymous 1984)	1906	1900	17	14	155	187	47.0	0.0	0.7	7.4	1.21 (0.60–2.45)	0.83 (0.67–1.01)
McCaughan[b] (Law et al. 1994b; McCaughan 1981)	88	30	0	0	2	3	49.8	0.0	0.7	1.0	—	0.23 (0.04–1.30)
Miettinen (Miettinen et al. 1985)	612	610	0	8	19	9	48.0	0.0	0.5	5.0	0.06 (0.00–1.01)	2.10 (0.96–4.61)

Newcastle (Anonymous 1971b)	244	253	—	—	57	94	52.0	19.5	0.6	5.0	—	0.63 (0.48–0.83)
NHLBI (Brensike et al. 1984; Law et al. 1994b)	59	57	—	—	8	11	46.1	19.0	0.9	5.0	—	0.70 (0.30–1.62)
POSCH (Buchwald and Campos 1995; Buchwald et al. 1990)	421	417	14	15	82	125	51.0	9.3	1.5	9.7	0.92 (0.45–1.89)	0.65 (0.51–0.83)
Scottish (Anonymous 1971a)	350	367	—	—	59	79	53.0	20.7	0.6	6.0	—	0.78 (0.58–1.06)
Stockholm (Carlson and Rosenhamer 1988)	279	276	6	5	82	123	59.0	20.4	0.8	5.0	1.19 (0.37–3.84)	0.66 (0.53–0.83)
Veterans (Detre and Shaw 1974; Law et al. 1994b)	145	284	—	—	42	69	51.0	0.0	0.6	5.0	—	1.19 (0.86–1.65)
WHO (Anonymous 1978, 1980)	5331	5296	25	17	167	208	45.0	0.0	0.6	5.3	1.14 (0.79–2.70)	0.80 (0.65–0.97)
	15115	15661	155	169	1348	1867	48.6[d]	5.6%	0.7[d]	5.8[d]	1.01 (0.82–1.24)	0.82 (0.77–0.87)

Key: A, active treatment group; C, control group.

— No data.

[a] This was not strictly a randomized trial but is included in many meta-analyses. Exclusion of this trial does not significantly alter the overall RR and 95% CI.

[b] This was a multi-factorial trial but is included in many meta-analyses. Exclusion of this trial does not significantly alter the overall RR and 95% CI.

[c] Only fatal events reported.

[d] "Weighted mean" totals (weighted by person-years of follow-up).

Table 7.16 Clinical trials of cholesterol lowering by statin interventions

Trial	Participants		Stroke		IHD		Mean age (years)	% female	Cholesterol reduction	Follow-up	RR (95% CI)	
	A	C	A	C	A	C					Stroke	IHD
4S (Anonymous 1994b, 1995)	2221	2223	70	98	464	691	59.0	18.6	1.8	5.4	0.71 (0.53–0.97)	0.67 (0.61–0.74)
ACAPS (Furberg et al. 1994a)	460	459	0	5	5	9	61.7	48.5	0.9	2.8	0.09 (0.01–1.64)	0.55 (0.19–1.64)
AFCAPS/TEXCAPS (Downs et al. 1998)	3304	3301	—	—	57	95	58.3	15.0	1.1	5.2	—	0.60 (0.43–0.83)
CARE (Sacks et al. 1996)	2081	2078	54	78	212	274	59.0	13.8	1.1	5.0	—	0.77 (0.65–0.91)
CCAIT (Crouse et al. 1998; Waters et al. 1993; Waters et al. 1994)	165	164	2	0	7	7	53.0	19.0	1.0	2.0	4.97 (0.24–102.74)	0.99 (0.36–2.77)
EXCEL (Bradford et al. 1990, 1991; Crouse et al. 1998; Shear et al. 1992)	6582	1663	10	1	47	18	56.0	41.0	1.6	0.9	2.53 (0.32–19.72)	0.66 (0.38–1.13)
HPS (Heart Protection Study Collaborative Group 2002a, 2002b)	10269	10267	444	585	898	1212	—	24.7	1.3	5.0	0.76 (0.67–0.86)	0.74 (0.68–0.80)
KAPS (Salonen et al. 1995)	224	223	2	4	3	8	57.5	0.0	1.2	3.0	0.50 (0.09–2.69)	0.37 (0.10–1.39)
KLIS (Anonymous 2000)	2219	1634	47	41	65	47	58.0	0.0	0.5	5.0	0.84 (0.56–1.28)	1.02 (0.70–1.47)

LIPID (Anonymous 1998b; White et al. 2000)	4512	4502	169	204	557	715	62.0	16.8	1.0	6.1	0.83 (0.68–1.01)	0.78 (0.70–0.86)
LRT (Weintraub et al. 1994)	203	201	0	1	14	5	62.0	28.0	2.0	4.0	0.33 (0.01–8.05)	2.77 (1.02–7.55)
MAAS (Anonymous 1994a; Crouse et al. 1998; Dumont 1993)	193	188	1	2	11	7	55.3	11.8	1.5	4.0	0.49 (0.04–5.33)	1.53 (0.61–3.86)
MARS (Blankenhorn et al. 1993)	134	136	0	0	22	31	58.0	9.0	1.8	2.2	—	0.72 (0.44–1.18)
PLAC1 (Byington et al. 1995; Pitt et al. 1995)	206	202	0	2	8	17	57.0	22.5	1.3	3.0	0.20 (0.01–4.06)	0.46 (0.20–1.05)
PLAC2 (Crouse et al. 1992, 1995, 1998; Furberg et al. 1994b)	75	76	1	3	4	10	61.7	14.6	1.3	3.0	0.34 (0.04–3.17)	0.41 (0.13–1.24)
PMSG (Anonymous 1993)	530	532	0	3	0	7	55.0	23.3	1.2	0.5	0.11 (0.01–2.07)	0.07 (0.00–1.17)
REGRESS (Jukema et al. 1995)	450	435	3	5	8	13	55.7	0.0	1.3	2.0	0.58 (0.14–2.41)	0.59 (0.25–1.42)
Sahni (Law et al. 1994b; Sahni et al. 1991)	79	78	0	0	3	4	60.2	30.5	0.7	1.0	—	0.74 (0.17–3.20)
WOSCOPS (Anonymous 1992a; Shepherd et al. 1995)	3302	3293	46	51	174	248	55.2	0.0	1.1	4.9	0.90 (0.61–1.34)	0.70 (0.58–0.84)
	37209	31655	849	1083	2599	3418	58.8[a]	14.6%	1.2[a]	5.1[a]	0.77 (0.70–0.84)	0.73 (0.70–0.77)

Key: A, active treatment group; C, control group.

— No data.

[a] "Weighted mean" totals (weighted by person-years of follow-up).

results (Bucher et al. 1998). Another review is more relevant in addressing this issue. It examined the proportional reduction in risk from each trial titrated to a cholesterol reduction of 0.6 mmol/l as a yardstick. There was a dose–response relationship with bigger reductions in risk in trials attaining bigger cholesterol reductions, and statins tended to achieve greater reduction in total cholesterol. It was clear however, that for each method of lowering cholesterol (different drugs, diet and surgery), the proportional reduction in risk was close to that expected from the cholesterol reduction, suggesting little difference in relative effect of agents (Law et al. 2003).

Evidence from meta-analyses suggested that there were similar benefits from cholesterol lowering for males and females, and fatal and non-fatal events, but there was no evidence of age attenuation (LaRosa et al. 1999; Law et al. 1994b). However, trials are often not powered for such age subgroup analysis and often include only a narrow age band. On the whole, no substantial evidence has been presented for a significant difference in risk reduction of IHD between trials among those individuals with or without a prior history of cardiovascular disease (Atkins et al. 1993; Crouse et al. 1997, 1998; Hebert et al. 1997; Holme 1990; LaRosa et al. 1999; Law et al. 1994b).

Further important results from meta-analyses of cholesterol reduction trials relate to the time frame of the achieved benefits. A major overview published by Law et al. (1994b) included 28 trials of diet and non-statin drugs, 45 254 individuals and 4421 deaths from IHD. It demonstrated that most of the benefits were evident after 5 years of sustained cholesterol lowering. In the first two years, a 0.6 mmol/l reduction in cholesterol was associated with a 7% (95% CI 0–14%) lower risk of IHD, but after 5 years, it was 25% (15–35%) (Law et al. 1994b). An updated overview which included more cholesterol lowering trials including statins has confirmed these patterns with a 1.0 mmol/l reduction in LDL cholesterol associated with a 11% (95% CI 4–18%) lower risk of IHD at year 1. At 2 years this increased to 24% (17–30%), at 3–5 years it was 33% (28–37%), and after 5 years it was 36% (26–45%). (Law et al. 2003).

Most other reviews have not reported events according to duration of treatment, and instead only give an "average" risk reduction for the entire period of follow-up. A risk reduction of 20% after 5 years of follow-up, for example, for a given age group is a combined risk reduction for 1, 2, 3, 4 and 5 years, rather than a true representation of the risk reduction for a cohort of people after 5 years of treatment, which would be greater than 20%. These data are a vital component to interpreting the time frames and extent of reversibility. The majority of the benefit of cholesterol lowering was achieved after 5 years (Law et al. 1994b). At this time, virtually all of the risk predicted by the observational studies had been reversed. There is no evidence that the effects of

cholesterol lowering on risk of IHD differ between males and females (Byington et al. 2001; LaRosa et al. 1999; Law et al. 1994b).

Cholesterol and risk of stroke

Early observational studies, trials and overviews did not find an association between cholesterol and stroke. Part of the reason for this was that the analyses involved total stroke, and "concealed" differences in the type of association between cholesterol and each stroke subtype (Crouse et al. 1998). Early trials also only achieved small reductions in cholesterol and included few, mostly fatal, stroke events, which made the influence of cholesterol lowering difficult to detect (Crouse et al. 1998; Law 1999). Trials also tended to be of short duration, so that the long-term reduction in stroke was "diluted" by the absence of an early effect (Law 1999).

Data from individual trials are presented in Tables 7.14–7.16. As with IHD end-points, there were similar risk reduction in males and females and no evidence of age attenuation (Byington et al. 2001). However, trials were often not powered for this subgroup analysis and included only a narrow age-band.

The larger, more recent trial overviews have found a positive association between cholesterol and total stroke, and the size of the risk reduction in more recent overviews was about 20–25% (Blauw et al. 1997; Bucher et al. 1998; Crouse et al. 1997, 1998; Hebert et al. 1997; Ross et al. 1999). Overviews have also noted a stronger association with non-fatal strokes (which comprise a higher proportion of ischaemic strokes) than fatal strokes (which comprise a greater proportion of haemorrhagic strokes) (Atkins et al. 1993; Blauw et al. 1997; Byington et al. 2001; Ross et al. 1999). One of the most recent overviews performed subgroup analysis and suggested different associations between cholesterol and haemorrhagic and ischaemic strokes (Byington et al. 2001), as predicted by the observational data.

In summary, the data from clinical trials of cholesterol lowering indicated that after 5 years, a reduction of approximately 0.6 mmol/l of cholesterol resulted in reversal of most or all of the epidemiologically expected risk for IHD (about 27%). Interpretation is more difficult for stroke as many studies have combined ischaemic and haemorrhagic strokes into one category, when the association of cholesterol with ischaemic stroke differs from that of haemorrhagic stroke. Even when stroke subtype is specified, there will likely be differing rates of misclassification of stroke subtype between studies. However, more recent trial overviews appear to concur with the epidemiological data and suggest that total stroke risk can be reversed, but associations differ by stroke subtype. Unfortunately, analyses have not specifically analysed results by duration, so similar time frames for the cholesterol-IHD association will have to be used. These time frames for reversibility from trials will be

used in CRA analyses, but the relative risk estimates from cohort studies will be used in preference to those from trials for both stroke and IHD. Cohort studies are much larger than the trials, their statistical power is greater, and they are also better able to examine associations across a wide range of cholesterol values (Law 1999). Furthermore, age-specific estimates are more readily available.

4. Results

4.1 Attributable fraction

The "attributable fraction" refers to the proportion of disease burden that would theoretically not have occurred if the population distribution of cholesterol had been equal to that of the theoretical minimum (mean cholesterol = 3.8mmol/l).

Stroke

Globally, 32% of ischaemic stroke was attributable to a total cholesterol level >3.8 mmol/l (range of 25–45% by subregion). Subregions with the lowest attributable fractions included AFR-D, AFR-E and WPR-B. In contrast, EUR-C and EUR-A had the highest values. In most subregions, the attributable fractions were slightly lower for males than females.

Ischaemic heart disease

Globally, 56% of IHD was attributable to a total cholesterol level >3.8 mmol/l (range of 44–68% by subregion). Subregions with the lowest attributable fractions included AFR-D, SEAR-B and WPR-B. In contrast, EUR-C and EUR-A had the highest values.

4.2 Attributable disease burden

For the year 2000, the World Health Organization (WHO) estimated that there were 55.9 million deaths and 1455 million DALYs worldwide; approximately 22% of these deaths and 7% of these DALYs were due to ischaemic heart disease and stroke. The burden of disease was distributed across the developed and developing world (e.g. about one quarter of all stroke deaths and one third of IHD deaths occurred in the least developed regions), and predominantly affected those aged >60 years.

The "attributable burden" refers to the number of deaths or DALYs that would theoretically not have occurred if the population distribution of cholesterol had been equal to that of the theoretical minimum (mean cholesterol = 3.8mmol/l). In total, the attributable burden equated to 805 000 stroke deaths, and about 3.6 million IHD deaths. For DALYs, these figures were 8.3 million stroke DALYs, and 32.1 million IHD DALYs (Table 7.17).

Table 7.17 Attributable deaths and DALYs for cholesterol >3.8 mmol/l by subregion and cardiovascular end-point

	Stroke	*IHD*	*Stroke*	*IHD*
Subregion	*Deaths (000s)*		*DALYs (000s)*	
AFR-D	18	68	219	738
AFR-E	21	68	267	767
AMR-A	33	317	377	2086
AMR-B	31	136	448	1425
AMR-D	3	15	47	150
EMR-B	7	75	89	836
EMR-D	26	188	287	2037
EUR-A	96	451	779	2600
EUR-B	45	235	474	1984
EUR-C	176	729	1637	5683
SEAR-B	18	94	224	1016
SEAR-D	145	851	1542	9548
WPR-A	20	58	219	389
WPR-B	165	322	1724	2847
World	805	3609	8332	32105

Worldwide this means that 4.4 million deaths (about 7.9% of the total) and 40.4 million DALYs (2.8% of the total) were estimated to be due to non-optimal cholesterol. The proportion of DALYs was lower than the proportion of deaths, as most cholesterol-related cardiovascular disease events occurred in middle or old age, so the years of life lost due to premature mortality and years of life lost due to disability is a smaller percentage of the total DALYs than of the total deaths.

The age group with the greatest attributable deaths for both males and females was 70–79 years. The number of attributable deaths then declined, reflecting the smaller denominator population, and the smaller total number of events in the oldest age group. For DALYs, this decline occurred sooner, as there are less years of life lost and years of life lived with disability with advancing age.

For each end-point, the attributable deaths were higher for males than females for the age groups 30–44 and 45–59 years. In contrast, attributable deaths were higher for females in the oldest age groups, 70–79 and ≥80 years. There was a similar trend for attributable DALYs. This was due to older females having higher mean cholesterol (and therefore greater attributable fraction) than males, and there are also a larger

number of cardiovascular deaths occurring in older females compared to older males.

Stroke

The subregions with the highest attributable ischaemic stroke burden were EUR-C (176 000 deaths, 1.6 million DALYs), WPR-B (165 000 deaths, 1.7 million DALYs) and SEAR-D (145 000 deaths, 1.5 million DALYs).

Ischaemic heart disease

The subregions with the highest attributable IHD burden were SEAR-D (851 000 deaths, 9.6 million DALYs) and EUR-C (729 000 deaths, 5.7 million DALYs).

Overall, approximately 40% of attributable DALYs occurred in the most developed subregions (16.2 million), 40% (15.6 million) in high mortality developing subregions, and 20% (8.6 million) in low mortality developing subregions. A higher proportion of these deaths and DALYs were from IHD than stroke in all subregions.

These results indicate where most of the worldwide attributable cardiovascular disease burden occurred, and provide any given subregion with an indication of absolute size of the attributable burden. However, the age structure, population size, and the number of estimated events occurring in a subregion, influences the ranking of subregions by absolute number of attributable deaths and DALYs. The relative impact of the attributable DALYs indicates that between about 2–25% of all deaths and 0.5–12% of all DALYs across the subregions were attributable to non-optimal cholesterol. Approximately 16% of all deaths and 8% of all DALYs were attributable to excess cardiovascular disease in developed subregions, and about 5% and 2% in high and low mortality developing subregions, respectively.

5. Discussion

5.1 Attributable deaths and disease burden

The analyses in this chapter suggest that globally, a substantial proportion of cardiovascular disease is attributable to non-optimal cholesterol, defined as mean cholesterol >3.8 mmol/l. Overall, about one third of ischaemic stroke and over half of IHD was attributable to non-optimal cholesterol. The attributable fractions were higher in the more developed parts of the world than the least developed regions, as would be expected given the higher cholesterol levels.

Worldwide, 4.4 million deaths (about 7.9% of the total) and 40.4 million DALYs (2.8% of the total) were estimated to be due to non-optimal cholesterol. Overall, the results suggest that a considerable proportion of cardiovascular disease is related to non-optimal cholesterol

and this translates into an important portion of deaths and years of life lost to deaths and disability worldwide.

5.2 Attributable deaths and disease burden by subregion

In absolute terms, most of the excess burden of cardiovascular disease occurred in subregions WPR-B, SEAR-D and EUR-C; approximately 10–20% of worldwide attributable deaths and DALYs occurred in these subregions. The relative impact that attributable deaths and DALYs have in different subregions may also be calculated as the proportion of all deaths and DALYs attributable to non-optimal cholesterol (i.e. mean >3.8mmol/l) within each specific subregion. Overall, between 2% and 25% of all deaths and 0.5 and 12% of all DALYs across subregions were attributable to non-optimal cholesterol. This excess burden was highest in European subregions where mean cholesterol levels were highest.

6. Trends in mean cholesterol levels over time by age, sex and subregion

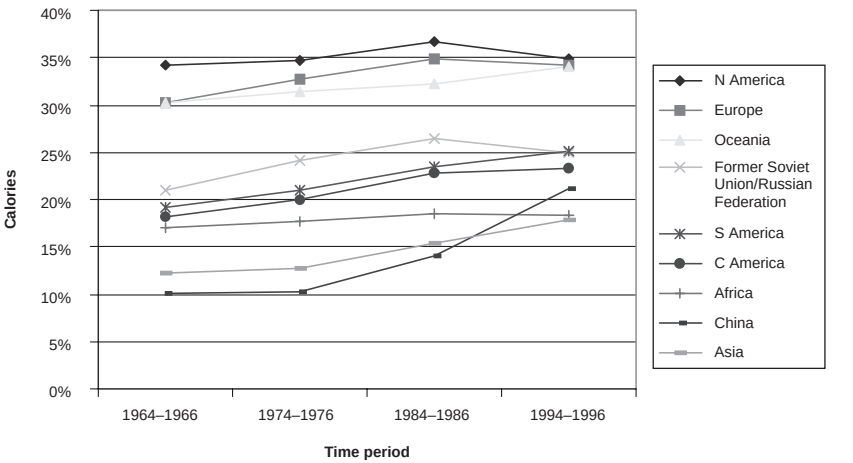
The CRA project includes estimates of avoidable burden, that is, the reduction in future burden that would be observed if current levels of exposure to a risk factor were reduced to those specified by a counterfactual distribution of exposure. To perform these calculations an estimate must be made of cholesterol distributions in the future under a "business-as-usual" scenario. This requires estimates of changes in current cholesterol levels 10, 20 and 30 years into the future by age, sex and subregion.

Several basic steps were necessary to produce these estimates and each one to some extent dictated the next. First, the literature was reviewed to assess what we already know about trends in cholesterol in different populations. Second, subregions were categorized into broad groupings based on likely direction of changes in cholesterol levels over time. Third, the future trends in cholesterol distribution were estimated.

6.1 Literature review of cholesterol trends over time

There is evidence in the literature that risk factors such as cholesterol change over time, and a variety of studies from different world regions and populations have demonstrated increases and decreases in cholesterol levels (Capewell et al. 2000; Dobson et al. 1999; Evans et al. 2001; Law and Wald 1994; McGovern et al. 1996; Sakata and Labarthe 1996; Sigfusson et al. 1991; Suh 2001; Tuomilehto et al. 1991; Vartiainen et al. 1994, 2000). These data were reviewed by subregion. In addition, data on fat intake from the Food and Agriculture Organization of the United Nations (FAO) were reviewed as fat intake correlates with mean cholesterol levels. Changes in mean cholesterol levels in recent literature relate predominantly to AMR-A, EUR-A and WPR-A.

Figure 7.15 Percentage of total calories from fat per capita per day



The best available FAO data (www.fao.org) cover the whole world, but the country groupings differ from those of WHO. FAO data may be presented as the total number of calories supplied as fat per day, or percentage of daily calories supplied as fat (Figure 7.15). (These data only relate to total fat, and have not been subdivided further, e.g. into saturated or animal fat vs unsaturated fat.)

AMR-A AND EUR-A

Studies in the United Kingdom of Great Britain and Northern Ireland (Capewell et al. 1999; Law and Wald 1994), the United States (Law and Wald 1994; McGovern et al. 1996), Finland (Tuomilehto et al. 1991; Vartiainen et al. 1994, 2000), Iceland (Sigfusson et al. 1991) and other parts of Europe (Law and Wald 1994) have documented reductions in mean cholesterol levels. In the more recent studies from the 1980s onwards, these decreases have been approximately 0.02–0.03 mmol/l of cholesterol per year in males and females (Capewell et al. 2000; Dobson et al. 1999; Evans et al. 2001; McGovern et al. 1996; Vartiainen et al. 2000). FAO data also show a levelling or decline of mean cholesterol levels recently in North America (AMR-A) and Europe (EUR-A). The direction of these trends correlates with those demonstrated for blood pressure in the same studies.

WPR-A

Reduction in mean cholesterol levels has been documented in New Zealand and Australia (Capewell et al. 2000; Dobson et al. 1999; Law

and Wald 1994). In contrast, there appears to have been an increase in mean cholesterol levels in Japan since the 1980s (Law and Wald 1994; Okayama et al. 1993; Sakata and Labarthe 1996) in the order of about 0.03–0.04 mmol/l per year (Sakata and Labarthe 1996). This would result in an overall increase in cholesterol levels in WPR-A, owing to the larger population size of Japan. WPR-A covers countries that would be included by FAO in Asia (Japan) and Oceania (Australia, New Zealand and the Pacific), where trends in fat consumption indicate that cholesterol levels are increasing.

EUR-B and EUR-C

Some decreases in cholesterol have been recorded recently in parts of eastern Europe (Bobak et al. 1997), but the data are limited. The FAO region that covers the former Soviet Union and the Russian Federation most closely maps to EUR-B and C, and also suggests a levelling off and possible decline in fat consumption.

WPR-B

Mean cholesterol levels appear to be increasing in China and in the Republic of Korea (Evans et al. 2001; Suh 2001), which correlates with increases in fat consumption in China.

Other subregions

Very few data were available on several developing subregions (AFR-D, E, AMR-B, D, EMR-B, D, SEAR-B and D); however, certain data demonstrated that as regions become more industrialized or "acculturated", risk factor profiles such as blood pressure and cholesterol change. This is particularly evident in migration studies conducted in a variety of settings (Poulter and Sever 1994), such as Africa (Poulter et al. 1988, 1990), China (He et al. 1991a, 1991b), and the Pacific (Joseph et al. 1983; Salmond et al. 1985, 1989), which suggest that blood pressure and cholesterol levels rise after people migrate to more urbanized "acculturated" settings. The trends are as follows.

AMR-B and D: FAO data from Central and South America suggest that overall, fat consumption is increasing.

EMR-B and D; SEAR-B and D: These subregions are all included in the FAO grouping of Asia where levels of fat consumption are increasing.

AFR-D and E: FAO data suggest small increases in fat consumption.

6.2 Potential categories of cholesterol change

Data presented above indicate that mean cholesterol levels appear to be decreasing in many of the most developed subregions, while they are increasing or plateauing in less developed subregions. However, estimating how long the current trends will continue and quantifying the changes is difficult.

A published meta-analysis assessed the quantitative importance of dietary fat to blood concentrations of total cholesterol (Clarke et al. 1997). However, these results are difficult to extrapolate to FAO data as they relate to isocaloric replacement of fats by carbohydrates. The FAO data demonstrated not only increasing caloric fat intake, but also increasing caloric intake from other sources and overall. Therefore, the same associations do not apply. The following potential scenario was therefore based on current evidence of time trends, and previously documented changes in mean cholesterol levels.

Owing to the limited data available, these estimates are susceptible to a high degree of uncertainty. A wide range of factors could influence future risk factor levels, and it is difficult to capture these factors even with sophisticated modelling. A decision was thus made to use a relatively simple, but transparent method for the purposes of these analyses.

Estimates of mean cholesterol levels over time

Table 7.18 presents an overview of the cholesterol trends over time, by subregion. The following estimates summarize mean cholesterol levels by subregion, sex and age, currently and in 2010, 2020 and 2030 (Tables 7.19–7.22).

Table 7.18 Scenario for changes in mean cholesterol levels (mmol/l) by subregion over the next 10, 20 and 30 years[a]

Subregion	*2000 to 2010*	*2010 to 2020*	*2020 to 2030*	*Comment*
AMR-A	↓ 0.3 mmol/l	↓ 0.3 mmol/l	↓ 0.2 mol/l	↓ attenuating over time
EUR-A	↓ 0.3 mmol/l	↓ 0.3 mmol/l	↓ 0.2 mol/l	↓ attenuating over time
WPR-A	↑ 0.2 mmol/l	→ plateau	↓ 0.1 mol/l	↑ due to influence of Japan over next 10 years, then plateau and start to decrease
AMR-B, D	↑ 0.2mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau
EUR-B, C	→ plateau	↓ 0.1 mol/l	↓ 0.1 mol/l	→ plateau initially then start to decrease as some evidence on this already happening in some regions
WPR-B	↑ 0.3 mmol/l	↑ 0.2 mmol/l	↑ 0.1 mmol/l	↑ attenuating over time
SEAR	↑ 0.2 mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau
EMR	↑ 0.2 mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau
AFR	↑ 0.2 mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau

Key: ↑, increase; ↓, decrease; →, plateau.

[a] Assumes the same absolute change in cholesterol for all age and sex subgroups.

Table 7.19 Current CRA estimates of mean cholesterol (mmol/l) by subregion, sex and age

	Sex and age group (years)							
	Females				*Males*			
Subregion	*30–44*	*45–59*	*60–69*	*70–79*[a]	*30–44*	*45–59*	*60–69*	*70–79*[a]
AFR-D	4.6	5.1	5.2	5.2	4.5	4.7	4.7	4.7
AFR-E	4.6	5.1	5.2	5.2	4.5	4.7	4.7	4.7
AMR-A	4.8	5.6	6.0	5.9	5.2	5.5	5.5	5.2
AMR-B	4.8	5.4	5.4	5.2	5.3	5.0	4.9	4.8
AMR-D	4.8	5.4	5.4	5.2	5.3	5.0	4.9	4.8
EMR-B	4.6	5.1	5.4	5.6	4.8	4.9	5.1	5.4
EMR-D	4.6	5.1	5.4	5.6	4.8	4.9	5.1	5.4
EUR-A	5.4	6.3	6.7	6.5	5.9	6.1	6.1	5.9
EUR-B	4.6	5.3	5.5	5.4	5.0	5.1	5.2	5.2
EUR-C	5.4	6.2	6.6	6.5	5.5	5.8	5.8	5.7
SEAR-B	4.0	4.5	4.6	4.6	5.0	5.1	5.2	5.2
SEAR-D	4.9	5.7	5.8	5.7	4.8	5.0	5.0	5.0
WPR-A	4.9	5.5	5.6	5.4	5.2	5.2	5.1	5.0
WPR-B	4.3	4.8	5.1	5.1	4.5	4.6	4.7	4.8

[a] The same cholesterol levels apply to those aged ≥80 years.

Table 7.20 Estimates of mean cholesterol (mmol/l) by subregion, sex and age in 2010

	Sex and age group (years)							
	Females				*Males*			
Subregion	*30–44*	*45–59*	*60–69*	*70–79*[a]	*30–44*	*45–59*	*60–69*	*70–79*[a]
AFR-D	4.8	5.3	5.4	5.4	4.7	4.9	4.9	4.9
AFR-E	4.8	5.3	5.4	5.4	4.7	4.9	4.9	4.9
AMR-A	4.5	5.3	5.7	5.6	4.9	5.2	5.2	4.9
AMR-B	5.0	5.6	5.6	5.4	5.5	5.2	5.1	5.0
AMR-D	5.0	5.6	5.6	5.4	5.5	5.2	5.1	5.0
EMR-B	4.8	5.3	5.6	5.8	5.0	5.1	5.3	5.6
EMR-D	4.8	5.3	5.6	5.8	5.0	5.1	5.3	5.6
EUR-A	5.1	6.0	6.4	6.2	5.6	5.8	5.8	5.6
EUR-B	4.6	5.3	5.5	5.4	5.0	5.1	5.2	5.2
EUR-C	5.4	6.2	6.6	6.5	5.5	5.8	5.8	5.7
SEAR-B	4.2	4.7	4.8	4.8	5.2	5.3	5.4	5.4
SEAR-D	5.1	5.9	6.0	5.9	5.0	5.2	5.2	5.2
WPR-A	5.1	5.7	5.8	5.6	5.4	5.4	5.3	5.2
WPR-B	4.6	5.1	5.4	5.4	4.8	4.9	5.0	5.1

[a] The same cholesterol levels apply to those aged ≥80 years.

Table 7.21 Estimates of mean cholesterol (mmol/l) by subregion, sex and age in 2020

	Sex and age group (years)							
	Females				Males			
Subregion	30–44	45–59	60–69	70–79[a]	30–44	45–59	60–69	70–79[a]
AFR-D	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AFR-E	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AMR-A	4.2	5.0	5.4	5.3	4.6	4.9	4.9	4.6
AMR-B	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
AMR-D	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
EMR-B	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EMR-D	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EUR-A	4.8	5.7	6.1	5.9	5.3	5.5	5.5	5.3
EUR-B	4.5	5.2	5.4	5.3	4.9	5.0	5.1	5.1
EUR-C	5.3	6.1	6.5	6.4	5.4	5.7	5.7	5.6
SEAR-B	4.3	4.8	4.9	4.9	5.3	5.4	5.5	5.5
SEAR-D	5.2	6.0	6.1	6.0	5.1	5.3	5.3	5.3
WPR-A	5.1	5.7	5.8	5.6	5.4	5.4	5.3	5.2
WPR-B	4.8	5.3	5.6	5.6	5.0	5.1	5.2	5.3

[a] The same cholesterol levels apply to those aged ≥80 years.

Table 7.22 Estimates of mean cholesterol (mmol/l) by subregion, sex and age in 2030

	Sex and age group (years)							
	Females				Males			
Subregion	30–44	45–59	60–69	70–79[a]	30–44	45–59	60–69	70–79[a]
AFR-D	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AFR-E	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AMR-A	4.0	4.8	5.2	5.1	4.4	4.7	4.7	4.4
AMR-B	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
AMR-D	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
EMR-B	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EMR-D	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EUR-A	4.6	5.5	5.9	5.7	5.1	5.3	5.3	5.1
EUR-B	4.4	5.1	5.3	5.2	4.8	4.9	5.0	5.0
EUR-C	5.2	6.0	6.4	6.3	5.3	5.6	5.6	5.5
SEAR-B	4.3	4.8	4.9	4.9	5.3	5.4	5.5	5.5
SEAR-D	5.2	6.0	6.1	6.0	5.1	5.3	5.3	5.3
WPR-A	4.9	5.5	5.6	5.4	5.2	5.2	5.1	5.0
WPR-B	4.9	5.4	5.7	5.7	5.1	5.2	5.3	5.4

[a] The same cholesterol levels apply to those aged ≥80 years.

Acknowledgements

Particular thanks are due to the Asia-Pacific Cohort Studies Collaboration secretariat, and all study collaborators for allowing us to access and analyse their data for estimates of relative risk. The Prospective Studies Collaboration assisted with analyses and provided unpublished data on relative risk estimates that could be compared with those presented here.

The authors are grateful to Varsha Parag and Derrick Bennett for biostatistical support. Angela Hurley provided valuable research assistance and Clarissa Gould-Thorpe provided secretarial support.

Note

1 See preface for an explanation of this term.

References

Abbott RD, Sharp DS, Burchfiel CM et al. (1997) Cross-sectional and longitudinal changes in total and high-density-lipoprotein cholesterol levels over a 20-year period in elderly men: the Honolulu Heart Program. *Annals of Epidemiology*, **7**:417–424.

Acheson J, Hutchinson EC (1972) Controlled trial of clofibrate in cerebral vascular disease. *Atherosclerosis*, **15**:177–183.

al-Mahroos F, al-Roomi K, McKeigue PM (2000) Relation of high blood pressure to glucose intolerance, plasma lipids and educational status in an Arabian Gulf population. *International Journal of Epidemiology*, **29**:71–76.

al-Nuaim AR (1997) Serum total and fractionated cholesterol distribution and prevalence of hypercholesterolemia in urban and rural communities in Saudi Arabia. *International Journal of Cardiology*, **58**:141–149.

al-Nuaim AR, al-Rubeaan K, al-Mazrou Y, al-Attas O, al-Daghari N (1996) Prevalence of hypercholesterolemia in Saudi Arabia, epidemiological study. *International Journal of Cardiology*, **54**:41–49.

al-Nuaim AR, al-Rubeaan K, al-Mazrou Y, al-Attas O, al-Daghari N (1997) Serum total, fractionated cholesterol concentration distribution and prevalence of hypercholesterolemia in Saudi Arabia, regional variation. *Annals of Saudi Medicine*, **17**:179–184.

al-Shammari SA, Ali M, al-Shammari A, al-Maatouq M, Tennier A, Armstrong K (1994) Blood lipid concentrations and other cardiovascular risk factors among Saudis. *Family Practice*, **11**:153–158.

Anderson CS, Jamrozik KD, Burvill PW, Chakera TM, Johnson GA, Stewart-Wynne EG (1993) Determining the incidence of different subtypes of stroke: results from the Perth Community Stroke Study, 1989–1990. *Medical Journal of Australia*, **158**:85–89.

Anonymous (1968) Controlled trial of soya-bean oil in myocardial infarction. *The Lancet*, **2**:693–699.

Anonymous (1971a) Ischaemic heart disease: a secondary prevention trial using clofibrate. Report by a research committee of the Scottish Society of Physicians. *British Medical Journal*, **4**:775–784.

Anonymous (1971b) Trial of clofibrate in the treatment of ischaemic heart disease. Five-year study by a group of physicians of the Newcastle upon Tyne region. *British Medical Journal*, **4**:767–775.

Anonymous (1975) Clofibrate and niacin in coronary heart disease. *Journal of the American Medical Association*, **231**:360–381.

Anonymous (1978) A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. *British Heart Journal*, **40**:1069–1118.

Anonymous (1980) WHO cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Report of the Committee of Principal Investigators. *The Lancet*, **2**:379–385.

Anonymous (1981) Distribution of some risk factors for atherosclerosis in nine Italian population samples. The research group ATS-RF2 of the Italian National Research Council. *American Journal of Epidemiology,* **113**: 338–346.

Anonymous (1984) The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *Journal of the American Medical Association*, **251**:351-364.

Anonymous (1989) The WHO MONICA Project. A worldwide monitoring system for cardiovascular diseases: cardiovascular mortality and risk factors in selected communities. *World Health Statistics*, *A*:27–149.

Anonymous (1992a) A coronary primary prevention study of Scottish men aged 45–64 years: trial design. The West of Scotland Coronary Prevention Study Group. *Journal of Clinical Epidemiology*, **45**:849–860.

Anonymous (1992b) Risk factors for cardiovascular disease in the developing world. A multicentre collaborative study in the International Clinical Epidemiology Network (INCLEN). INCLEN Multicentre Collaborative Group. *Journal of Clinical Epidemiology*, **45**:841–847.

Anonymous (1993) Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. The Pravastatin Multinational Study Group for Cardiac Risk Patients. *American Journal of Cardiology*, **72**:1031–1037.

Anonymous (1994a) Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *The Lancet*, **344**:633–638.

Anonymous (1994b) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *The Lancet*, **344**:1383–1389.

Anonymous (1995) Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *The Lancet*, **345**:1274–1275.

Anonymous (1996) Current state of and recent trends in serum lipid levels in the general Japanese population. Research Committee on Serum Lipid Level

Survey 1990 in Japan. *Journal of Atherosclerosis and Thrombosis*, **2**: 122–132.

Anonymous (1998a) Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. *The Lancet*, **352**:1801–1807.

Anonymous (1998b) Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *New England Journal of Medicine*, **339**: 1349–1357.

Anonymous (2000) Pravastatin use and risk of coronary events and cerebral infarction in Japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. *Journal of Atherosclerosis and Thrombosis*, **7**: 110–121.

Aono H, Ozawa H, Bello MC, Ito M, Saito I (1997) Prevalence of risk factors for coronary heart disease among Dominicans in the Dominican republic: comparison with Japanese and Americans using existing data. *Journal of Epidemiology*, **7**:238–243.

APCSC (1999) Determinants of cardiovascular disease in the Asia Pacific region: protocol for a collaborative overview of cohort studies. *Cardiovascular Disease Prevention*, **2**:281–289.

Asplund-Carlson A, Carlson LA (1994) Studies in hypertriglyceridaemia. 1. Serum triglyceride distribution and its correlates in randomly selected Swedish middle-aged men. *Journal of Internal Medicine*, **236**:57–64.

Atkins D, Psaty BM, Koepsell TD, Longstreth WT Jr., Larson EB (1993) Cholesterol reduction and the risk for stroke in men. A meta-analysis of randomized, controlled trials. *Annals of Internal Medicine*, **119**:136–145.

Bajekal M, Boreham R, Erens B et al. (1999) *Health Survey for England '98*. The Department of Health, London.

Bamford J, Sandercock P, Dennis M, Burn J, Warlow C (1990) A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project—1981–86.2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. *Journal of Neurology, Neurosurgery and Psychiatry*, **53**:16–22.

Barnes R (1965) Comparisons of blood pressure and blood cholesterol levels in New Guineans and Australians. *Medical Journal of Australia*, **1**:611–617.

Benfante R, Yano K, Hwang LJ, Curb JD, Kagan A, Ross W (1994) Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men. Implications of shared risk. *Stroke*, **25**:814–820.

Bennett SA, Magnus P (1994) Trends in cardiovascular risk factors in Australia. Results from the National Heart Foundation's Risk Factor Prevalence Study, 1980–1989. *Medical Journal of Australia*, **161**:519–527.

Bhuripanyo K, Tatsanavivat P, Matrakool B, Muktabhant B, Bhuripanyo P, Harnthaveesompol S (1993) A prevalence survey of lipids abnormalities of rural area in Amphoe Phon, Khon Kaen. *Journal of the Medical Association of Thailand*, **76**:101–108.

Biro G, Antal M, Zajkas G (1996) Nutrition survey of the Hungarian population in a randomized trial between 1992–1994. *European Journal of Clinical Nutrition,* **50**:201–208.

Blankenhorn DH, Azen SP, Kramsch DM et al. (1993) Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). The MARS Research Group. *Annals of Internal Medicine*, **119**:969–976.

Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L (1987) Beneficial effects of combined colestipol–niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *Journal of the American Medical Association*, **257**:3233–3240.

Blauw GJ, Lagaay AM, Smelt AH, Westendorp RG (1997) Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. *Stroke*, **28**:946–950.

Bobak M, Skodova Z, Pisa Z, Poledne R, Marmot M (1997) Political changes and trends in cardiovascular risk factors in the Czech Republic, 1985–92. *Journal of Epidemiology and Community Health*, **51**:272–277.

Bosma H, Appels A, Sturmans F, Grabauskas V, Gostautas A (1994) Differences in mortality and coronary heart disease between Lithuania and the Netherlands: results from the WHO Kaunas-Rotterdam Intervention Study (KRIS). *International Journal of Epidemiology*, **23**:12–19.

Boulton TJ, Cockington RA, Hamilton-Craig I, Magarey AM, Mazumdar J (1995) A profile of heart disease risk factors and their relation to parents' education, fathers' occupation and family history of heart disease in 843 South Australian families: the Adelaide Children's WHO Collaborative Study. *Journal of Paediatrics and Child Health*, **31**:200–206.

Bovet P, Shamlaye C, Kitua A, Riesen WF, Paccaud F, Darioli R (1991) High prevalence of cardiovascular risk factors in the Seychelles (Indian Ocean). *Arteriosclerosis and Thrombosis*, **11**:1730–1736.

Bradford RH, Shear CL, Chremos AN et al. (1991) Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Archives of Internal Medicine*, **151**:43–49.

Bradford RH, Shear CL, Chremos AN et al. (1990) Expanded clinical evaluation of lovastatin (EXCEL) study: design and patient characteristics of a double-blind, placebo-controlled study in patients with moderate hypercholesterolemia. *American Journal of Cardiology*, **66**:B44–55.

Brensike JF, Levy RI, Kelsey SF et al. (1984) Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. *Circulation*, **69**:313–324.

Bronner LL, Kanter DS, Manson JE (1995) Primary prevention of stroke. *New England Journal of Medicine*, **333**:1392–1400.

Brown G, Albers JJ, Fisher LD, Schaefer SM et al. (1990) Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *New England Journal of Medicine*, **323**: 1289–1298.

Brown SA, Hutchinson R, Morrisett J et al. (1993) Plasma lipid, lipoprotein cholesterol, and apoprotein distributions in selected US communities. The Atherosclerosis Risk in Communities (ARIC) Study. *Arteriosclerosis and Thrombosis*, **13**:1139–1158.

Brown SL, Salive ME, Harris TB, Simonsick EM, Guralnik JM, Kohout FJ (1994) Low cholesterol concentrations and severe depressive symptoms in elderly people. *British Medical Journal*, **308**:1328–1332.

Bucher HC, Griffith LE, Guyatt GH (1998) Effect of HMGcoA reductase inhibitors on stroke. A meta-analysis of randomized, controlled trials. *Annals of Internal Medicine*, **128**:89–95.

Buchwald H, Campos CT (1995) Program on the surgical control of the hyperlipidemias: 1994 report. *Journal of Cardiovascular Pharmacology*, **25**:S3–10.

Buchwald H, Varco RL, Matts JP et al. (1990) Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *New England Journal of Medicine*, **323**: 946–955.

Bullen C, Simmons G, Trye P, Lay-Yee R, Bonita R, Jackson R (1998) Cardiovascular disease risk factors in 65–84 year old men and women: results from the Auckland University Heart and Health Study 1993–4. *New Zealand Medical Journal*, **111**:4–7.

Burke GL, Sprafka JM, Folsom AR, Hahn LP, Luepker RV, Blackburn H (1991) Trends in serum cholesterol levels from 1980 to 1987. The Minnesota Heart Survey. *New England Journal of Medicine,* **324**:941–946.

Burr ML, Fehily AM, Gilbert JF et al. (1989) Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *The Lancet*, **2**:757–761.

Byington RP, Davis BR, Plehn JF et al. (2001) Reduction of stroke events with Pravastatin: the Prospective Pravastatin Pooling (PPP) Project. *Circulation*, **103**:387–392.

Byington RP, Jukema JW, Salonen JT et al. (1995) Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. *Circulation*, **92**:2419–2425.

Capewell S, Beaglehole R, Seddon M, McMurray J (2000) Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. *Circulation*, **102**:1511–1516.

Capewell S, Morrison CE, McMurray JJ (1999) Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. *Heart*, **81**: 380–386.

Carlson LA, Rosenhamer G (1988) Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. *Acta Medica Scandinavica*, **223**:405–418.

Carvalho JJ, Baruzzi RG, Howard PF et al. (1989) Blood pressure in four remote populations in the INTERSALT Study. *Hypertension*, **14**:238–246.

Casdorph HR (1972) Normal limits for serum-cholesterol. *The Lancet*, **1**:1076.

Cesana G, Ferrario M, Sega R, Duzioni F, Zanettini R, Grieco A (1989) [New problems in occupational medicine: findings on the risk of coronary heart disease in the services industry]. *Medicina del Lavoro*, **80**:192–200.

Chadha S, Gopinath N, Shekhawat S (1997) Urban–rural differences in the prevalence of coronary heart disease and its risk factors in Delhi. *Bulletin of the World Health Organization*, **75**:31–38.

Chen D, Roman G, Wu G et al. (1992) Stroke in China (Sino-MONICA-Beijing study) 1984–1986. *Neuroepidemiology*, **11**:15–23.

Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W (1991) Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *British Medical Journal*, **303**:276–282.

Choudhury SR, Ueshima H, Kita Y et al. (1994) Alcohol intake and serum lipids in a Japanese population. *International Journal of Epidemiology*, **23**: 940–947.

Clarke R, Frost C, Collins R, Appleby P, Peto R (1997) Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *British Medical Journal*, **314**:112-117.

Collins R, Peto R (1994) Antihypertensive drug therapy: effects on stroke and coronary heart disease. In: *Textbook of hypertension*. Swales J, ed. Blackwell Scientific Publications, Oxford.

Collins R, Peto R, MacMahon S et al. (1990) Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *The Lancet*, **335**:827–838.

Connelly PW, MacLean DR, Horlick L, O'Connor B, Petrasovits A, Little JA (1992) Plasma lipids and lipoproteins and the prevalence of risk for coronary heart disease in Canadian adults. Canadian Heart Health Surveys Research Group. *Canadian Medical Association Journal*, **146**:1977–1987.

Connor WE, Cerqueira MT, Connor RW, Wallace RB, Malinow MR, Casdorph HR (1978) The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. *American Journal of Clinical Nutrition,* **31**:1131–1142.

Crouse JR 3rd, Byington RP, Bond MG et al. (1992) Pravastatin, lipids, and atherosclerosis in the carotid arteries: design features of a clinical trial with carotid atherosclerosis outcome. *Controlled Clinical Trials*, **13**:495–506.

Crouse JR 3rd, Byington RP, Bond MG et al. (1995) Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology*, **75**:455–459.

Crouse JR 3rd, Byington RP, Furberg CD (1998) HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis*, **138**:11–24.

Crouse JR 3rd, Byington RP, Hoen HM, Furberg CD (1997) Reductase inhibitor monotherapy and stroke prevention. *Archives of Internal Medicine*, **157**:1305–1310.

Dayton S, Pearce ML, Goldman H et al. (1968) Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. *The Lancet*, **2**:1060–1062.

Detre KM, Shaw L (1974) Long-term changes of serum cholesterol with cholesterol-altering drugs in patients with coronary heart disease. Veterans Administration Drug–Lipid Cooperative Study. *Circulation*, **50**:998–1005.

Dobson AJ, McElduff P, Heller R, Alexander H, Colley P, D'Este K (1999) Changing patterns of coronary heart disease in the hunter region of New South Wales, Australia. *Journal of Clinical Epidemiology*, **52**:761–771.

Donker GA, Labarthe DR, Harrist RB et al. (1997) Low birth weight and serum lipid concentrations at age 7–11 years in a biracial sample. *American Journal of Epidemiology*, **145**:398–407.

Dorr AE, Gundersen K, Schneider JC Jr, Spencer TW, Martin WB (1978) Colestipol hydrochloride in hypercholesterolemic patients—effect on serum cholesterol and mortality. *Journal of Chronic Diseases*, **31**:5–14.

Downs JR, Clearfield M, Weis S et al. (1998) Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *Journal of the American Medical Association*, **279**:1615–1622.

Dumont JM (1993) Effect of cholesterol reduction by simvastatin on progression of coronary atherosclerosis: design, baseline characteristics, and progress of the Multicenter Anti-Atheroma Study (MAAS). *Controlled Clinical Trials*, **14**:209–228.

Eisenberg S, Heiss G, Friedlander Y et al. (1986) Comparison of plasma lipids, lipoproteins and dyslipoproteinemia in Israel and the United States. The Lipid Research Clinics Program Prevalence Study. *Atherosclerosis*, **59**:63–74.

Erasmus RT, Uyot C, Pakeye T (1994) Plasma cholesterol distribution in a rural Nigerian population—relationship to age, sex and body mass. *Central African Journal of Medicine*, **40**:299–302.

Ettinger WH, Wahl PW, Kuller LH et al. (1992) Lipoprotein lipids in older people. Results from the Cardiovascular Health Study. The CHS Collaborative Research Group. *Circulation*, **86**:858–869.

Evans A, Tolonen H, Hense HW et al. (2001) Trends in coronary risk factors in the WHO MONICA project. *International Journal of Epidemiology*, **30**:S35–40.

Fan WX, Parker R, Parpia B et al. (1990) Erythrocyte fatty acids, plasma lipids, and cardiovascular disease in rural China. *American Journal of Clinical Nutrition*, **52**:1027–1036.

Ferrara A, Barrett-Connor E, Shan J (1997) Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984–1994. *Circulation*, **96**:37–43.

Flight RJ, McKenzie-Pollock M, Hamilton MA, Salmond CE, Stokes YM (1984) The health status of fourth form students in Northland. *New Zealand Medical Journal*, **97**:1–6.

Fong PC, Tam SC, Tai YT, Lau CP, Lee J, Sha YY (1994) Serum lipid and apolipoprotein distributions in Hong Kong Chinese. *Journal of Epidemiology and Community Health*, **48**:355–359.

Frantz ID Jr, Dawson EA, Ashman PL et al. (1989) Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. *Arteriosclerosis*, **9**:129–135.

Frantz ID Jr, Dawson EA, Kuba K, Brewer ER, Gatewood LC, Bartch GE (1975) The Minnesota Coronary Survey: effct of diet on cardiovascular events and deaths. *Circulation*, **51–2**:I–4.

Frick MH, Elo O, Haapa K, Heinonen OP et al. (1987) Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *New England Journal of Medicine*, **317**:1237–1245.

Furberg CD, Adams HP Jr, Applegate WB et al. (1994a) Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation*, **90**:1679–1687.

Furberg CD, Byington RP, Crouse JR, Espeland MA (1994b) Pravastatin, lipids, and major coronary events. *American Journal of Cardiology*, **73**:1133–1134.

Gatchev O, Rastam L, Lindberg G, Gullberg B, Eklund GA, Isacsson SO (1993) Subarachnoid hemorrhage, cerebral hemorrhage, and serum cholesterol concentration in men and women. *Annals of Epidemiology*, **3**:403–409.

Ghannem H, Darioli R, Limam K et al. (2001) Epidemiology of cardiovascular risk factors among schoolchildren in Sousse, Tunisia. *Journal of Cardiovascular Risk*, **8**:87–91.

Giroud M, Milan C, Beuriat P et al. (1991) Incidence and survival rates during a two-year period of intracerebral and subarachnoid haemorrhages, cortical infarcts, lacunes and transient ischaemic attacks. The Stroke Registry of Dijon: 1985–1989. *International Journal of Epidemiology*, **20**:892–899.

Gliksman MD, Dwyer T, Wlodarczyk J (1990) Differences in modifiable cardiovascular disease risk factors in Australian schoolchildren: the results of a nationwide survey. *Preventive Medicine,* **19**:291–304.

Gonzalez-Villalpando C, Stern MP, Haffner SM, Gonzalez Villapando ME, Gaskill S, Rivera Martinez D (1999) Prevalence of hypertension in a Mexican population according to the sixth report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. *Journal of Cardiovascular Risk*, **6**:177–181.

Gorelick PB, Schneck M, Berglund LF, Feinberg W, Goldstone J (1997) Status of lipids as a risk factor for stroke. *Neuroepidemiology*, **16**:107–115.

Graff-Iversen S, Stensvold I, Lund-Larsen PG, Nodarse LO, Tverdal A, Urdal P (1998) Serum lipids in postmenopausal or perimenopausal women using estrogen alone, estrogen with levonorgestrel, or estrogen with norethisterone, compared with nonusers: results from a cross-sectional study in two Norwegian counties 1985–1988. *Journal of Clinical Epidemiology*, **51**: 1311–1316.

Greenland P, Goldbourt U, Yaari S et al. (1993) Divergent age-associated patterns of high density lipoprotein cholesterol and its percentage in Jewish and Moslem Arab Israeli children and adolescents: the Petach Tikva Project. *American Journal of Epidemiology*, **137**:549–558.

Gross L, Figueredo R (1973) Long-term cholesterol-lowering effect of colestipol resin in humans. *Journal of the American Geriatrics Society*, **21**:552–556.

He J, Klag MJ, Whelton PK et al. (1991a) Migration, blood pressure pattern, and hypertension: the Yi Migrant Study. *American Journal of Epidemiology*, **134**:1085–1101.

He J, Tell GS, Tang YC, Mo PS, He GQ (1991b) Effect of migration on blood pressure: the Yi People Study. *Epidemiology*, **2**:88–97.

He J, Whelton PK (2000) Selection of initial antihypertensive drug therapy. *The Lancet*, **356**:1942–1943.

Heart Protection Study Collaborative Group (2002a) MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. *The Lancet*, **360**:23–33.

Heart Protection Study Collaborative Group (2002b) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *The Lancet*, **360**:7–22.

Hebert PR, Gaziano JM, Chan KS, Hennekens CH (1997) Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *Journal of the American Medical Association*, **278**:313–321.

Hebert PR, Gaziano JM, Chan KS, Hennekens CH (1997) Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *Journal of the American Medical Association*, **278**: 313–321.

Hebert PR, Gaziano JM, Hennekens CH (1995) An overview of trials of cholesterol lowering and risk of stroke. *Archives of Internal Medicine*, **155**:50–55.

Heinemann L, Barth W, Hoffmeister H (1995) Trend of cardiovascular risk factors in the East German population 1968–1992. *Journal of Clinical Epidemiology*, **48**:787–795.

Herman B, Helmert U, Greiser E (1988) Factors related to blood lipid levels—the Bremen baseline health survey of the German Cardiovascular Prevention Study. *Public Health*, **102**:565–575.

Hjermann I, Velve Byre K, Holme I, Leren P (1981) Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. *The Lancet*, **2**:1303–1310.

Hoffmeister H, Mensink GB, Stolzenberg H (1994) National trends in risk factors for cardiovascular disease in Germany. *Preventive Medicine*, **23**: 197–205.

Holme I (1990) An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. *Circulation*, **82**:1916–1924.

Hughes K, Yeo PP, Lun KC et al. (1990) Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. Differences in risk factor levels. *Journal of Epidemiology and Community Health*, **44**:29–35.

Hung TP (1993) Changes in mortality from cerebrovascular disease and clinical pattern of stroke in Taiwan. *Journal of the Formosan Medical Association*, **92**:687–696.

Hutchinson RG, Watson RL, Davis CE et al. (1997) Racial differences in risk factors for atherosclerosis. The ARIC study. Atherosclerosis risk in communities. *Angiology*, **48**:279–290.

Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S (1996) Low total serum cholesterol and intracerebral hemorrhagic stroke: is the association confined to elderly men? The Kaiser Permanente Medical Care Program. *Stroke*, **27**:1993–1998.

Iso H, Jacobs DR, Jr, Wentworth D, Neaton JD, Cohen JD (1989) Serum cholesterol levels and six-year mortality from stroke in 350 977 men screened for the multiple risk factor intervention trial. *New England Journal of Medicine*, **320**:904–910.

Jadue L, Vega J, Escobar MC et al. (1999) Risk factors for non communicable diseases: methods and global results of the CARMEN program basal survey. *Revista Medica de Chile,* **127**:1004–1013.

Jeng JS, Lee TK, Chang YC et al. (1998) Subtypes and case-fatality rates of stroke: a hospital-based stroke registry in Taiwan (SCAN-IV). *Journal of the Neurological Sciences*, **156**:220–226.

Johnson CL, Rifkind BM, Sempos CT et al. (1993) Declining serum total cholesterol levels among US adults. The National Health and Nutrition Examination Surveys. *Journal of the American Medical Association*, **269**: 3002–3008.

Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS (1995) Intracerebral hemorrhage versus infarction: stroke severity, risk factors, and prognosis. *Annals of Neurology*, **38**:45–50.

Joseph JG, Prior IA, Salmond CE, Stanley D (1983) Elevation of systolic and diastolic blood pressure associated with migration: the Tokelau Island Migrant Study. *Journal of Chronic Diseases*, **36**:507–516.

Jukema JW, Bruschke AV, van Boven AJ et al. (1995) Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation*, **91**:2528–2540.

Kafatos A, Schlienger JL, Deslypere JP, Ferro-Luzzi A, Cruz JA (1991) Nutritional status: serum lipids. Euronut SENECA investigators. *European Journal of Clinical Nutrition*, **45**:S53–61.

Kesteloot H, Geboers J, Pietinen P (1987) On the within-population relationship between dietary habits and serum lipid levels in Belgium. *European Heart Journal*, **8**:821–831.

Kitange HM, Swai AB, Masuki G, Kilima PM, Alberti KG, McLarty DG (1993) Coronary heart disease risk factors in sub-Saharan Africa: studies in Tanzanian adolescents. *Journal of Epidemiology and Community Health*, **47**:303–307.

Lakka TA, Salonen JT (1992) Physical activity and serum lipids: a cross-sectional population study in eastern Finnish men. *American Journal of Epidemiology*, **136**:806–818.

LaRosa JC, He J, Vupputuri S (1999) Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *Journal of the American Medical Association*, **282**:2340–2346.

Law MR (1999) Lowering heart disease risk with cholesterol reduction: evidence from observational studies and clinical trials. *European Heart Journal Supplement*, **1**:S3–S8.

Law MR, Thompson SG, Wald NJ (1994a) Assessing possible hazards of reducing serum cholesterol. *British Medical Journal*, **308**:373–379.

Law MR, Wald NJ (1994) An ecological study of serum cholesterol and ischaemic heart disease between 1950 and 1990. *European Journal of Clinical Nutrition*, **48**:305–325.

Law MR, Wald NJ, Rudnicka AR (2003) Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *British Medical Journal*, **326**:1423.

Law MR, Wald NJ, Thompson SG (1994b) By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *British Medical Journal*, **308**:367–372.

Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A (1994c) Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *British Medical Journal*, **308**:363–366.

Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP (1999) Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. *Stroke*, **30**:2535–2540.

Leren P (1970) The Oslo diet–heart study. Eleven-year report. *Circulation*, **42**:935–942.

Lewington S, MacMahon S (1999) Blood pressure, cholesterol, and common causes of death: a review. Prospective studies collaboration. *American Journal of Hypertension*, **12**:S96–98.

Li SC, Schoenberg BS, Wang CC, Cheng XM, Bolis CL, Wang KJ (1985) Cerebrovascular disease in the People's Republic of China: epidemiologic and clinical features. *Neurology*, **35**:1708–1713.

Lindeberg S, Nilsson-Ehle P, Terent A, Vessby B, Schersten B (1994) Cardiovascular risk factors in a Melanesian population apparently free from stroke and ischaemic heart disease: the Kitava study. *Journal of Internal Medicine*, **236**:331–340.

Lupien PJ, Moorjani S, Rochon J et al. (1985) Lipid profile of a French-Canadian population: 1. Association of plasma lipid and lipoprotein levels with age, relative body weight and education. *Canadian Medical Association Journal*, **133**:1127–1133.

MacMahon S (1994) Blood pressure and risks of cardiovascular disease. In: *Textbook of hypertension*. Swales J, ed. Blackwell Scientific Publications, Oxford.

MacMahon S, Peto R, Cutler J et al. (1990) Blood pressure, stroke, and coronary heart disease. Part I, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *The Lancet*, **335**:765–774.

Mahley RW, Palaoglu KE, Atak Z et al. (1995) Turkish Heart Study: lipids, lipoproteins, and apolipoproteins. *Journal of Lipid Research*, **36**: 839–859.

Mann GV, Shaffer RD, Anderson RS, Sandstead HH (1964) Cardiovascular disease in the Masai. *Journal of Atherosclerosis*, **4**:289–312.

Mann JI, Duncan A, Ball MJ et al. (1991) Blood lipid levels in New Zealand. *New Zealand Medical Journal,* **104**:371–374.

Mann JI, Lewis B, Shepherd J et al. (1988) Blood lipid concentrations and other cardiovascular risk factors: distribution, prevalence, and detection in Britain. *British Medical Journal*, **296**:1702–1706.

Masia R, Pena A, Marrugat J et al. (1998) High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. REGICOR investigators. *Journal of Epidemiology and Community Health*, **52**:707–715.

McCaughan D (1981) The long-term effects of probucol on serum lipid levels. *Archives of Internal Medicine*, **141**:1428–1432.

McGovern PG, Pankow JS, Shahar E et al. (1996) Recent trends in acute coronary heart disease—mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. *New England Journal of Medicine*, **334**:884–890.

Miettinen TA, Huttunen JK, Naukkarinen V et al. (1985) Multifactorial primary prevention of *cardiovascular* diseases in middle-aged men. Risk factor changes, incidence, and mortality. *Journal of the American Medical Association*, **254**:2097–2102.

Ministry of Health (1999) *NZ food: NZ people. Key results of the 1997 National Nutrition Survey*. Ministry of Health, Wellington.

Misra A, Sharma R, Pandey RM, Khanna N (2001) Adverse profile of dietary nutrients, anthropometry and lipids in urban slum dwellers of northern India. *European Journal of Clinical Nutrition*, **55**:727–734.

Mitwalli AH, al-Maatouq A, al-Wakeel J, Alam AA (1994) Hypercholesterolemia in healthy adult males—a public survey in central Saudi Arabia. *Annals of Saudi Medicine*, **14**:499–502.

Molla A, Manser WW, Lalani R, Badruddin SH, Mohammad Z, Khurshid M (1990) Blood lipids in a healthy Karachi population. *Journal of Tropical Medicine and Hygiene*, **93**:295–299.

Muldoon MF, Manuck SB, Mendelsohn AB, Kaplan JR, Belle SH (2001) Cholesterol reduction and non-illness mortality: meta-analysis of randomised clinical trials. *British Medical Journal*, **322**:11–15.

Myllykangas M, Pekkanen J, Rasi V, Haukkala A, Vahtera E, Salomaa V (1995) Haemostatic and other cardiovascular risk factors, and socioeconomic status among middle-aged Finnish men and women. *International Journal of Epidemiology*, **24**:1110–1116.

Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H (1997) A 15.5-year follow-up study of stroke in a Japanese provincial city. The Shibata Study. *Stroke*, **28**:45–52.

Neaton JD, Blackburn H, Jacobs D et al. (1992) Serum cholesterol level and mortality findings for men screened in the multiple risk factor intervention trial. Multiple Risk Factor Intervention Trial Research Group. *Archives of Internal Medicine*, **152**:1490–1500.

Neaton JD, Wentworth D (1992) Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316 099 white men. Multiple Risk Factor Intervention Trial Research Group. *Archives of Internal Medicine*, **152**: 56–64.

Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller L (1993) Risk factors for death from different types of stroke. Multiple risk factor intervention trial research group. *Annals of Epidemiology*, **3**:493–499.

Nikkila M, Heikkinen J (1990) Serum cholesterol, high-density lipoprotein cholesterol and five-year survival in elderly people. *Age and Ageing*, **19**:403–408.

Nissinen A, Piha T, Tuomilehto J, Romo M, Puska P (1987) Comparison of the levels of cardiovascular risk factors between eastern and south-western Finland in 1982. *Acta Medica Scandinavica*, **222**(5):389–400.

Nyarko NK, Adubofour KO, Ofei F, Pobee JO, Owusu SK (1994) Serum lipids and lipoprotein in adult Ghanaians. *Journal of Internal Medicine*, **236**: 251–253.

Oelofse A, Jooste PL, Steyn K et al. (1996) The lipid and lipoprotein profile of the urban black South African population of the Cape Peninsula—the BRISK study. *South African Medical Journal*, **86**:162–166.

Okayama A, Ueshima H, Marmot MG, Nakamura M, Kita Y, Yamakawa M (1993) Changes in total serum cholesterol and other risk factors for cardiovascular disease in Japan 1980–1989. *International Journal of Epidemiology*, **22**:1038–1047.

Okesina AB, Oparinde DP, Akindoyin KA, Erasmus RT (1999) Prevalence of some risk factors of coronary heart disease in a rural Nigerian population. *East African Medical Journal*, **76**:212–216.

Olferev AM, Volozh OI, Polesskii VA et al. (1990) Characteristics of the plasma lipid profile in the male population of Tallinn aged 20–54 years. *Cor et Vasa*, **32**:441–447.

Olferev AM, Volozh OI, Sokolova MA et al. (1991) Characteristics of the blood serum lipoprotein pattern in female Tallinn residents aged 35–54 years. *Cor et Vasa*, **33**:472–479.

Olusi SO, Prabha K, Sulaiman A (1997) Prevalence of hypercholesterolemia in a Kuwati hospital outpatient population. *Annals of Saudi Medicine*, **17**:108–111.

Onat A, Surdum-Avci G, Senocak M, Ornek E, Gozukara Y (1992) Plasma lipids and their interrelationship in Turkish adults. *Journal of Epidemiology and Community Health*, **46**:470–476.

Page LB, Damon A, Moellering RC, Jr. (1974) Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation*, **49**:1132–1146.

Pignone M, Phillips C, Mulrow C (2000) Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials. *British Medical Journal*, **321**:983–986.

Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME (1995) Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. *Journal of the American College of Cardiology*, **26**:1133-1139.

Posadas-Romero C, Tapia-Conyer R, Lerman-Garber I et al. (1995) Cholesterol levels and prevalence of hypercholesterolemia in a Mexican adult population. *Atherosclerosis*, **118**:275–284.

Poulter N, Sever P (1994) Blood pressure in other populations. A. Low blood pressure populations and the impact of rural–urban migration. In: *Textbook of hypertension*. Swales J, ed. Blackwell Scientific Publications, Oxford.

Poulter NR, Khaw KT, Hopwood BE et al. (1990) The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *British Medical Journal*, **300**:967–972.

Poulter NR, Khaw KT, Sever PS (1988) Higher blood pressures of urban migrants from an African low-blood pressure population are not due to selective migration. *American Journal of Hypertension*, **1**:S143–145.

PSC (1995) Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 45 000 people in 45 prospective cohorts. *The Lancet,* **346**:1647–1653.

Puska P, Matilainen T, Jousilahti P et al. (1993) Cardiovascular risk factors in the Republic of Karelia, Russia, and in North Karelia, Finland. *International Journal of Epidemiology*, **22**:1048–1055.

Razay G, Heaton KW, Bolton CH (1992) Coronary heart disease risk factors in relation to the menopause. *Quarterly Journal of Medicine*, **85**: 889–896.

Reddy KK, Ramachandraiah T, Reddanna P, Thyagaraju K (1994) Serum lipid peroxides and lipids in urban and rural Indian men. *Archives of Environmental Health*, **49**:123–127.

Research Committee to the Medical Council (1965) Low-fat diet in myocardial infarction: a controlled trial. *The Lancet*, **2**:501–504.

Robinson D, Bevan EA, Hinohara S, Takahashi T (1992) Seasonal variation in serum cholesterol levels—evidence from the UK and Japan. *Atherosclerosis*, **95**:15–24.

Rose GA, Thomson WB, Williams RT (1965) Corn oil in treatment of ischaemic heart disease. *British Medical Journal*, **1**:1531–1533.

Rosengren A, Eriksson H, Larsson B et al. (2000) Secular changes in cardiovascular risk factors over 30 years in Swedish men aged 50: the study of men born in 1913, 1923, 1933 and 1943. *Journal of Internal Medicine*, **247**: 111–118.

Ross SD, Allen IE, Connelly JE et al. (1999) Clinical outcomes in statin treatment trials: a meta-analysis. *Archives of Internal Medicine*, **159**: 1793–1802.

Sacks FM, Pfeffer MA, Moye LA et al. (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *New England Journal of Medicine*, **335**:1001–1009.

Sahni R, Maniet AR, Voci G, Banka VS (1991) Prevention of restenosis by lovastatin after successful coronary angioplasty. *American Heart Journal*, **121**:1600–1608.

Sakata K, Labarthe DR (1996) Changes in cardiovascular disease risk factors in three Japanese national surveys 1971–1990. *Journal of Epidemiology*, **6**:93–107.

Salmond CE, Joseph JG, Prior IA, Stanley DG, Wessen AF (1985) Longitudinal analysis of the relationship between blood pressure and migration: the Tokelau Island Migrant Study. *American Journal of Epidemiology*, **122**:291–301.

Salmond CE, Prior IA, Wessen AF (1989) Blood pressure patterns and migration: a 14-year cohort study of adult Tokelauans. *American Journal of Epidemiology*, **130**:37–52.

Salonen R, Nyyssonen K, Porkkala E et al. (1995) Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on *atherosclerotic* progression in carotid and femoral arteries. *Circulation*, **92**:1758–1764.

Salvaggio A, Periti M, Miano L, Quaglia G, Marzorati D (1991) Coffee and cholesterol, an Italian study. *American Journal of Epidemiology*, **134**: 149–156.

Scrimgeour EM, McCall MG, Smith DE, Masarei JR (1989) Levels of serum cholesterol, triglyceride, HDL-cholesterol, apoproteins A-I and B, and plasma glucose, and prevalence of diastolic hypertension and cigarette smoking in Papua New Guinea highlanders. *Pathology*, **21**:46–50.

Sever PS, Gordon D, Peart WS, Beighton P (1980) Blood-pressure and its correlates in urban and tribal Africa. *The Lancet*, **2**:60–64.

Shear CL, Franklin FA, Stinnett S et al. (1992) Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. Effect of patient characteristics on lovastatin-induced changes in plasma concentrations of lipids and lipoproteins. *Circulation*, **85**:1293–1303.

Shepherd J, Cobbe SM, Ford I et al. (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *New England Journal of Medicine*, **333**:1301–1307.

Sigfusson N, Sigvaldason H, Steingrimsdottir L et al. (1991) Decline in ischaemic heart disease in Iceland and change in risk factor levels. *British Medical Journal*, **302**:1371–1375.

Simons LA, Friedlander Y, McCallum J et al. (1991) The Dubbo study of the health of elderly: correlates of coronary heart disease at study entry. *Journal of the American Geriatrics Society*, **39**:584–590.

Smith WC, Tunstall-Pedoe H, Crombie IK, Tavendale R (1989) Concomitants of excess coronary deaths—major risk factor and lifestyle findings from 10 359 men and women in the Scottish Heart Health Study. *Scottish Medical Journal*, **34**:550–555.

Sprafka JM, Burke GL, Folsom AR, Luepker RV, Blackburn H (1990) Continued decline in cardiovascular disease risk factors: results of the Minnesota Heart Survey, 1980–1982 and 1985–1987. *American Journal of Epidemiology*, **132**:489–500.

Srinivasan SR, Wattigney W, Webber LS, Berenson GS (1991) Race and gender differences in serum lipoproteins of children, adolescents, and young adults—emergence of an adverse lipoprotein pattern in white males: the Bogalusa Heart Study. *Preventive Medicine,* **20**:671–84.

Steyn K, Benade AJ, Langenhoven ML, Joubert G, Rossouw JE (1987) Hypercholesterolaemia in the coloured population of the Cape Peninsula (CRISIC study). *South African Medical Journal*, **71**:483–486.

Steyn K, Jooste PL, Langenhoven ML et al. (1985) Coronary risk factors in the coloured population of the Cape Peninsula. *South African Medical Journal*, **67**:619–625.

Strachan D, Rose G (1991) Strategies of prevention revisited: effects of imprecise measurement of risk factors on the evaluation of "high-risk" and "population-based" approaches to prevention of cardiovascular disease. *Journal of Clinical Epidemiology*, **44**:1187–1196.

Sudlow CL, Warlow CP (1997) Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International stroke incidence collaboration. *Stroke*, **28**:491–499.

Suh I (2001) Cardiovascular mortality in Korea: a country experiencing epidemiologic transition. *Acta Cardiologica*, **56**:75–81.

Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ (2001) Low serum cholesterol and haemorrhagic stroke in men: Korea medical insurance corporation study. *The Lancet*, **357**:922–925.

Suzuki K, Kutsuzawa T, Takita K et al. (1987) Clinico-epidemiologic study of stroke in Akita, Japan. *Stroke*, **18**:402–406.

Swai AB, McLarty DG, Kitange HM et al. (1993) Low prevalence of risk factors for coronary heart disease in rural Tanzania. *International Journal of Epidemiology*, **22**:651–659.

Szatrowski TP, Peterson AV, Jr., Shimizu Y et al. (1984) Serum cholesterol, other risk factors, and cardiovascular disease in a Japanese cohort. *Journal of Chronic Diseases*, **37**:569–584.

Tanaka H, Ueda Y, Hayashi M et al. (1982) Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. *Stroke*, **13**:62–73.

Tao S, Li Y, Xiao Z et al. (1992) Serum lipids and their correlates in Chinese urban and rural populations of Beijing and Guangzhou. PRC-USA Cardiovascular and Cardiopulmonary Epidemiology Research Group. *International Journal of Epidemiology*, **21**:893–903.

Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA (2001) Incidence of the major stroke subtypes: initial findings from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke*, **32**:1732–1738.

Thune I, Njolstad I, Lochen ML, Forde OH (1998) Physical activity improves the metabolic risk profiles in men and women: the Tromso Study. *Archives of Internal Medicine*, **158**:1633–1640.

Tian HG, Nan Y, Liang XQ et al. (1995) Relationship between serum lipids and dietary and non-dietary factors in a Chinese population. *European Journal of Clinical Nutrition*, **49**:871–882.

Tuomilehto J, Bonita R, Stewart A, Nissinen A, Salonen JT (1991) Hypertension, cigarette smoking, and the decline in stroke incidence in eastern Finland. *Stroke*, **22**:7–11.

Vaccarino V, Borgatta A, Gallus G, Sirtori CR (1995) Prevalence of coronary heart disease risk factors in northern-Italian male and female employees. *European Heart Journal*, **16**:761–769.

van Beurden EK, James R, Henrikson D, Tyler C, Christian J (1991) The North Coast Cholesterol Check Campaign. Results of the first three years of a large-scale public screening programme. *Medical Journal of Australia*, **154**:385–391.

Vartiainen E, Jousilahti P, Alfthan G, Sundvall J, Pietinen P, Puska P (2000) Cardiovascular risk factor changes in Finland, 1972–1997. *International Journal of Epidemiology*, **29**:49–56.

Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P (1994) Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *British Medical Journal*, **309**:23–27.

Verschuren WM, Boerma GJ, Kromhout D (1994) Total and HDL-cholesterol in the Netherlands: 1987–1992. Levels and changes over time in relation to age, gender and educational level. *International Journal of Epidemiology*, **23**:948–956.

Viikari J, Akerblom HK, Nikkari T et al. (1985) Atherosclerosis precursors in Finnish children and adolescents. IV. Serum lipids in newborns, children and adolescents. *Acta Paediatrica Scandinavica, Supplement*, **318**:103–109.

Wallace RB, Colsher PL (1992) Blood lipid distributions in older persons. Prevalence and correlates of hyperlipidemia. *Annals of Epidemiology*, **2**:15–21.

Warlow C, Dennis M, VanGijn J et al. (1996) *Stroke. A practical guide to management*. Blackwell Science Ltd, Oxford.

Waters D, Higginson L, Gladstone P et al. (1994) Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation*, **89**:959–968.

Waters D, Higginson L, Gladstone P, Kimball B, LeMay M, Lesperance J (1993) Design features of a controlled clinical trial to assess the effect of an HMG CoA reductase inhibitor on the progression of coronary artery disease. Canadian Coronary Atherosclerosis Intervention Trial Investigators Montreal, Ottawa, and Toronto, Canada. *Controlled Clinical Trials*, **14**:45–74.

Watts GF, Lewis B, Brunt JN et al. (1992) Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). *The Lancet*, **339**:563–569.

Weintraub WS, Boccuzzi SJ, Klein JL et al. (1994) Lack of effect of lovastatin on restenosis after coronary angioplasty. Lovastatin Restenosis Trial Study Group. *New England Journal of Medicine*, **331**:1331–1337.

White HD, Simes RJ, Anderson NE et al. (2000) Pravastatin therapy and the risk of stroke. *New England Journal of Medicine*, **343**:317–326.

Woo J, Leung SS, Ho SC, Sham A, Lam TH, Janus ED (1997) Dietary practices and lipid intake in relation to plasma lipid profile in Hong Kong Chinese. *European Journal of Clinical Nutrition,* **51**:467–471.

Woodhill JM, Palmer AJ, Leelarthaepin B, McGilchrist C, Blacket RB (1978) Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Advances in Experimental Medicine and Biology*, **109**:317–330.

Wu Y, Yao C, Wu Z et al. (1992) Interim report of Sino-MONICA-Beijing for the years 1985–1989. *Chinese Medical Sciences Journal*, **7**:125–129.

Yang XS, Kesteloot H, Huang DX (1986) Serum cholesterol in China and the West. *Chinese Medical Journal*, **99**:183–186.

Yano K, Popper JS, Kagan A, Chyou PH, Grove JS (1994) Epidemiology of stroke among Japanese men in Hawaii during 24 years of follow-up: the Honolulu Heart Program. *Health Reports*, **6**:28–38.

Yano K, Reed DM, Curb JD, Hankin JH, Albers JJ (1986) Biological and dietary correlates of plasma lipids and lipoproteins among elderly Japanese men in Hawaii. *Arteriosclerosis*, **6**:422–433.

Yano K, Reed DM, MacLean CJ (1989) Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke*, **20**:1460–1465.

Zhuang HZ, Hana QQ, Chen HZ (1986) Study of serum lipids and lipoproteins of healthy subjects in Shanghai. *Chinese Medical Journal*, **99**:657–659.

Appendix A: Sampling methods, response rate and cholesterol measuring techniques of studies included in cholesterol data review

Africa

Subregion	*Country or area*	*Study reference*	*Sampling methods*	*Response rate*	*Cholesterol measurement*
AFR-D	Ghana	Nyarko et al. (1994)	Employees from the University of Ghana were randomly selected	*	Trained staff & certified lab All fasting samples Storage of sample unnecessary, enzymatic analysis
	Nigeria	Erasmus et al. (1994)	Recruitment from a rural village	82%	Trained staff & certified lab Non-fasting samples Storage of sample unnecessary, extraction analysis
	Nigeria	Okesina et al. (1999)	Houses in villages selected randomly, then individuals randomly selected	*	All fasting samples ?where sample stored, enzymatic-colorimetric analysis
	Seychelles	Bovet et al. (1991)	Age and sex stratified random sample from national census	84–89%	Certified lab All fasting samples Sample stored in freezer, enzymatic analysis

AFR-E	South Africa	Oelofse et al. (1996)	A stratified proportional sample from target population using census data	*	Trained staff Non-fasting samples Sample stored in fridge, enzymatic analysis
	South Africa	Steyn et al. (1985, 1987)	A stratified sample by age and sex from census data	*	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	United Republic of Tanzania	Kitange et al. (1993)	Whole population in four villages, and a random sample in another four villages	60–94%	Certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	United Republic of Tanzania	Swai et al. (1993)	Community-based survey of eight villages in three regions in rural United Republic of Tanzania	90.9–96%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Zimbabwe	Allain and Matenga (T. Allain et al., personal communication, 2001)	Stratified sampling	*	Trained staff & certified lab Some fasting samples Sample analysed immediately ? method

* Data unavailable.

? Specific details not given.

Americas

Subregion	*Country or area*	*Study reference*	*Sampling methods*	*Response rate*	*Cholesterol measurement*
AMR-A	Canada	Connelly et al. (1992)	Probability sample from health insurance register	60–70%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	Canada	Lupien et al. (1985)	Random sample from provincial electoral register	60%	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II)
	Halifax	MONICA study (Anonymous 1989)	Sample from public health service register	41–63%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	USA	Abbott et al. (1997)	Sample from long-term study	*	Trained staff & certified lab All fasting samples Sample stored in fridge, ?method of analysis (LRC program)
	USA	Brown et al. (1993)	Sample from four communities	42–68%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	USA	Burke et al. (1991)	Clusters of 40 households in the metropolitan area were randomly selected	*	Trained staff & certified lab Non-fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II: LRC program)
	USA	Donker et al. (1997)	Sample by age and race from survey of school-age children	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (Technicon Autoanalyzer: LRC program)

USA	Eisenberg et al. (1986)	Random sample from population register	74–85%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (LRC program)
USA	Ettinger et al. (1992)	Random sample from health care register	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
USA	Ferrara et al. (1997)	Stratified sample by age and sex using community study	80%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
USA	Hutchinson et al. (1997)	Random sample from study centres	*	Trained & certified staff All fasting samples Sample stored in freezer, enzymatic analysis
USA	Johnson et al. (1993)	Stratified sample from four separate national surveys	67–84%	Trained staff & certified lab Some fasting samples Sample stored in freezer, enzymatic analysis
USA	Sprafka et al. (1990)	Clusters of 1 000 households in the metropolitan area were randomly selected	68%	Trained staff & certified lab Non-fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II: LRC program)
USA	Srinivasan et al. (1991)	Sample from specific bi-racial community	65–85%	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II: LRC program)
USA	Wallace and Colsher (1992)	Sample from cohort studies using target population from two counties	50–80%	Trained staff & certified lab Some fasting samples ?where sample stored, ?method of analysis (derived and not directly measured)

continued

Americas (*continued*)

Subregion	*Country or area*	*Study reference*	*Sampling methods*	*Response rate*	*Cholesterol measurement*
	USA	Yano et al. (1986)	Random sample from cohort studies	86%	Trained staff & certified lab All fasting samples Sample stored in freezer, ?method of analysis (LRC program)
	Stanford	MONICA study (Anonymous 1989)	Sample from commercial household directory	66%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, extraction analysis
AMR-B	Brazil	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	82–92%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Chile	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	67–76%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Chile	Jadue et al. (1999), L. Jadue, personal communication, 2001	Stratified sample	*	Trained staff All fasting samples Immediate analysis enzymatic analysis
	Colombia	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	83%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

Dominican Republic	Aono et al. (1997)	Clusters of 2 000 individuals from public health regions were randomly selected	72–77%	Trained staff & certified lab ?fasting sample Sample stored in freezer, ?method of analysis
Jamaica	R. Wilks et al., personal communication, 2001	Stratified sampling from Sparush Town	64%	Trained staff All fasting samples ?where sample stored, ?method of analysis
Mexico	Gonzalez et al. (1999), C. Gonzalez, personal communication, 2001	Random sample of population from a selected area—a complete household survey was performed	80.2%	Trained staff & certified lab All fasting samples Sample stored in freezer, extraction analysis
Mexico	Posadas-Romero et al. (1995)	Random sample from population register	58%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
Mexico	L. Yamamoto et al., personal communication, 2001	Random stratified sample in Mexico City	87%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis

AMR-D

* Data unavailable.

? Specific details not given.

Eastern Mediterranean

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
EMR-B	Bahrain	al-Mahroos et al. (2000)	Stratified sample by age from national population register	62%	Trained staff & ?certified lab Some fasting samples ?where sample stored, enzymatic analysis
	Jordan	H. Jaddou, personal communication, 2001	Stratified sample from the population	62%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Kuwait	Olusi et al. (1997)	Sample taken from outpatient requests	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
	Saudi Arabia	al-Nuaim et al. (1996, 1997)	Stratified cluster random sample from target population using census data	92%	Trained staff & certified lab ?fasting sample Sample stored in freezer, enzymatic calorimetric analysis
	Saudi Arabia	al-Nuaim (1997)	Stratified random sample from target population using census data	92%	Trained staff & certified lab ?fasting sample Sample stored in freezer, enzymatic calorimetric analysis

	Saudi Arabia	al-Shammari et al. (1994)	Random sample from family practice health clinics	*	Trained staff & ?certified lab Some fasting samples ?where sample stored, enzymatic analysis
	Saudi Arabia	Mitwalli et al. (1994)	Random sample as males were invited to participate in cholesterol screening campaign at several public gatherings in Riyadh City	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
	Tunisia	Ghannem et al. (2001), H. Ghannem, personal communication, 2001	Random stratified sample of schoolchildren from the urban region of Sousse	95.4%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
EMR-D	Pakistan	Molla et al. (1990)	Sample of employees and students at Aga Khan University hospital, and students from a local school	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis

* Data unavailable.

? Specific details not given.

Europe

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
EUR-A	Belgium	Kesteloot et al. (1987)	Sample from a survey performed in the Belgian army	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
	Charleroi	MONICA study (Anonymous 1989)	Sample from population register	59%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Ghent	MONICA study (Anonymous 1989)	Sample from public health service register	54–57%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Denmark, Glostrup	MONICA study (Anonymous 1989)	Sample from population register	79–80%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	Finland	Lakka and Salonen (1992)	Random sample from selected region	83%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	Finland	Myllkangas et al. (1995)	Stratified random sample from population register	79%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Finland	Nikkila and Heikkinen (1990)	Sample from health survey	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
	Finland	Nissinen et al. (1987)	Random sample from population of two areas using the national population register	76–80%	Trained staff & certified lab ?fasting sample Storage not necessary, enzymatic analysis

Finland	Puska et al. (1993)	Stratified random sample from population register	68–81%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
Finland	Vartiainen et al. (2000)	Stratified random sample from population register	70–85%	Trained staff & certified lab ?fasting sample Storage not necessary, enzymatic analysis
Finland	Vikari et al. (1985)	Multicentre study using random selected children and adolescents	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Kuopio	MONICA study (Anonymous 1989)	Sample from population register	85%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
Turku; Loimaa	MONICA study (Anonymous 1989)	Sample from population register	86%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
N. Karelia	MONICA study (Anonymous 1989)	Sample from population register	80%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
France				
Haute-Garonne	MONICA study (Anonymous 1989)	Sample from population register	86%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Lille	MONICA study (Anonymous 1989)	Sample from communities & electoral roll	65–80%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Germany	Heinemann et al. (1995)	Random sample from urban and rural population	*	Trained staff & certified lab ?fasting samples ?where sample stored, enzymatic analysis

continued

Europe (*continued*)

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
	Germany	Herman et al. (1988)	Random sample from health survey	71%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (Boehringer Mannheim CHOD-PAP)
	Germany	Hoffmeister et al. (1994)	Randomly selected districts on resident registries	69%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
	Germany	MONICA study (Anonymous 1989)	Sample from national X-ray screening register	72%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
	Augsburg (Rural)	MONICA study (Anonymous 1989)	Sample from population register	82–84%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Augsburg (Urban)	MONICA study (Anonymous 1989)	Sample from population register	76–80%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Bremen	MONICA study (Anonymous 1989)	Sample from resident register	71%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Rhein-Neckar	MONICA study (Anonymous 1989)	Sample from population register	74%	?Trained staff & ?certified lab ?fasting sample ?where sample stored, enzymatic analysis

Former German Democratic Republic,				
Berlin-Lichtenberg	MONICA study (Anonymous 1989)	Sample from national X-ray screening register	70–80%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
Cottbus county	MONICA study (Anonymous 1989)	Sample from national X-ray screening register	77%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
Iceland	MONICA study (Anonymous 1989)	Sample from national roster	76%	Trained staff & certified lab All fasting samples Storage not necessary, extraction analysis
Israel	Eisenberg et al. (1986)	Random sample from population register	72–81%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (LRC program)
Israel	Greenland et al. (1993)	Random sample of school-age children from population register	*	Trained staff & certified lab All fasting samples Storage not necessary, ?method of analysis (Gilford automated instrument)
Italy	Cesana et al. (1989)	Sample from routine screening of bank employees	*	?Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Italy	Nine populations (Anonymous 1981)	Random sample of nine populations from eight regions	62%	Trained staff & certified lab All fasting sample ?where sample stored, ?method of analysis

continued

Europe (*continued*)

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
	Italy	Salvaggio et al. (Law and Wald 1994; Salvaggio et al. 1991)	Sample from a study on preventative medicine	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Italy	Vaccarino et al. (1995)	All employees of IBM asked to participate	45%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
	Brianza	MONICA study (Anonymous 1989)	Sample from population register	70–71%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	Friuli	MONICA study (Anonymous 1989)	Sample from regional health roll	80–82%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Latina	MONICA study (Anonymous 1989)	Sample from electoral rolls	76%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	Netherlands	Vershuren et al. (1994)	Random sample of population selected from the municipal registry of each town	50–57%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
	Netherlands	Bosma et al. (1994)	Sample taken from a 10-year follow-up to the Kaunus-Rotterdam Intervention Study (KRIS)	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Norway	Graff-Iverson et al. (1998)	Sample from health survey	89%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis

Norway	Thune et al. (1998)	Population-based cohort study	81%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
Spain	Masia et al. (1998)	Two-stage population random sample stratified by age from census data	73%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Catalonia	MONICA study (Anonymous 1989)	Sample from population register	76–79%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
Sweden	Asplund-Carlson and Carlson (1994)	Selected at random from population register	63%	Trained staff & certified lab All fasting samples Sample stored in freezer, ?method of analysis (Boehringer Mannheim)
Sweden	Rosengren et al. (2000)	Selected at random	55–76%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
Gothenburg	MONICA study (Anonymous 1989)	Sample from population register	84–86%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Switzerland, Ticino	MONICA study (Anonymous 1989)	Sample from population register	79–83%	?Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
Vaud; Fribourg	MONICA study (Anonymous 1989)	Sample from population register	61–69%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
United Kingdom	Brown et al. (1994)	Sample from health survey	55%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis

continued

Europe (*continued*)

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
	United Kingdom	Mann et al. (1988)	Opportunistic case finding from GP lists and random sampling from age-sex registers	73%	Trained staff & certified lab Some fasting samples ?where sample stored, enzymatic analysis
	England	Bajekal et al. (1999)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	England	Razay et al. (1992)	Stratified random sample from regional health survey	73%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Northern Ireland, Belfast	MONICA study (Anonymous 1989)	Sample from GP lists	57–70%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Scotland	Smith et al. (1989)	Sample taken from selected districts, then random sampling from GP lists	*	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
	Scotland, Glasgow	MONICA study (Anonymous 1989)	Sample from GP lists	50–64%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Multiple sites in EUR-A	Kafatos et al. (1991)	Stratified random sample by age and sex of target population from 11 countries	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic-colorimetric analysis

EUR-B	Poland, Tarnobrzeg Voivodship	MONICA study (Anonymous 1989)	Sample from electoral register	70–80%	Trained staff & certified lab All fasting samples Sample stored in freezer, direct analysis
	Warsaw	MONICA study (Anonymous 1989)	Sample from electoral register	74%	Trained staff & certified lab All fasting samples Sample stored in fridge, direct analysis
	Turkey	Mahley et al. (1995), R. Mahley, personal communication, 2001	Random sample of six regions in Turkey	*	Trained staff & certified lab All fasting sample Sample stored in freezer, enzymatic analysis
	Turkey	Onat et al. (1992)	Random sample from population register	85%	Trained staff & certified lab Some fasting samples ?where sample stored, enzymatic analysis
EUR-C	Former Czechoslovakia	MONICA study (Anonymous 1989)	Random sample from population register	*	Trained staff & certified lab All fasting samples Sample stored in fridge, direct analysis
	Estonia	Olferev et al. (1990, 1991)	Random sample from population register	70–72%	?Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
	Hungary	Biro et al. (1996)	Random sample from Budapest and seven counties in Hungary	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Hungary	Kafatos et al. (1991)	Stratified random sample by age and sex of target population from 11 countries	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic-colorimetric analysis

continued

Europe (*continued*)

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
	Budapest	MONICA study	Sample from population register (Anonymous 1989)	75–80%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
	Pecs	MONICA study	Sample from population register (Anonymous 1989) (Anonymous 1989)	70–80%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Lithuania	Bosma et al. (1994)	Sample taken from a 10-year follow-up to the Kaunus-Rotterdam Intervention Study (KRIS)	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Russian Federation	Puska et al. (1993)	Stratified random sample from population registers	77–92%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	The former Soviet Union[a], Kaunas	MONICA study (Anonymous 1989)	Sample from GP lists	70%	Trained staff & certified lab All fasting samples Sample stored in freezer, extraction analysis
	Novosibirsk	MONICA study (Anonymous 1989)	Sample from electoral list	69%	Trained staff & certified lab All fasting samples Sample stored in freezer, extraction analysis

* Data unavailable.

? Specific details not given.

[a] Russia in original publication.

South-East Asia

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
SEAR-B	Indonesia	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	70%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Thailand	Bhuripanyo et al. (1993)	Stratified random sample from community survey	79%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Thailand	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	70–73%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
SEAR-D	India	Reddy et al. (1994)	Sampled from electoral register	48–76%	Trained staff & certified lab All fasting samples Storage not necessary, ?method of analysis
	India	Chadha et al. (1997)	Cluster random sample from target population	*	?Trained staff & ?certified lab ?fasting sample ?where sample stored, ?method of analysis
	India	Misra et al. (2001), A. Misra, personal communication, 2001	Stratified systematic random sampling using electoral list	40%	Trained staff & ?certified lab All fasting samples Storage not necessary, enzymatic analysis
	India	A. Misra, personal communication, 2001	Multistage cluster sampling from 20 schools and colleges located in south Delhi	100%	Trained staff & ?certified lab All fasting samples Storage not necessary, enzymatic analysis

* Data unavailable.

? Specific details not given.

Western Pacific

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
WPR-A	Australia	APCSC-Busselton (APCSC secretariat, personal communication, 2001)	A stratified random sample representative of population	*	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
	Australia	APCSC-Perth (APCSC secretariat, personal communication, 2001)	Stratified random sampling of Perth metropolitan area	>70%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Australia	Bennett and Magnus (1994)	Systematic probability sample from electoral roles	75%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
	Australia	Boulton et al. (1995)	Cross-sectional sample of schoolchildren from South Australia	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Australia	Gliksman et al. (1990)	Two-stage probability sampling of all school children in Australia	*	Trained staff & certified lab All fasting samples Sample stored in fridge, ?method of analysis (LRC program)
	Australia	Simons et al. (1991)	Sample from regional population	73%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
	Australia	van Beurden et al. (1991)	Sample from community screening sessions	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

Newcastle	MONICA study (Anonymous 1989)	Sample from electoral register	68-82%	Trained staff & certified lab All fasting samples Sample stored in fridge, extraction & enzymatic analysis
Perth	MONICA study (Anonymous 1989)	Sample from electoral register	81–84%	Trained staff & certified lab All fasting samples Sample stored in fridge, extraction & enzymatic analysis
Japan	APCSC-Aito Town (APCSC secretariat, personal communication, 2001)	Random sample of Aito town residents	75%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Japan	APCSC-Akabane (APCSC secretariat, personal communication, 2001)	All residents living in Akabane town	77.6%	Trained staff & certified lab All fasting samples ?sample stored in freezer, ?method of analysis
Japan	APCSC-Ohasama (APCSC secretariat, personal communication, 2001)	Non-hospitalized adults in Ohasama invited to participate	50%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Japan	Choudhury et al. (1994)	Sample from population register	88%	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
Japan	Okayama et al. (1993)	Randomly selected from national census	81–89%	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis

continued

Western Pacific (*continued*)

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
	Japan	Robinson et al. (Law and Wald 1994; Robinson et al. 1992)	Sample from medical centre	*	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
	Japan	Serum lipid Survey (Anonymous 1996)	Sample from 39 institutes from various districts	*	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	Japan	1990 National Survey (Sakata and Labarthe 1996)	Randomly selected from National Health Survey districts	81.5%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	New Zealand	APCSC-Fletcher challenge (APCSC secretariat, personal communication, 2001)	Employees of one centre, and random sample from electoral roll	74%	Trained staff & certified lab Non-fasting samples Storage not necessary, enzymatic analysis
	New Zealand	Bullen et al. (1998)	Age stratified random sampling from electoral rolls	66–68%	Trained staff & certified lab Non-fasting samples Sample not necessary, enzymatic analysis
	New Zealand	Flight et al. (1984)	Randomly chose schools then students	81%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	New Zealand	Mann et al. (1991)	Random sample from electoral roll	94%	Trained staff & certified lab Fasting samples Sample stored in freezer, enzymatic analysis

	New Zealand	National Survey (Ministry of Health 1999)	Random sample of individuals from random households constructed from census data	*	Trained staff & certified lab Non-fasting samples Sample stored in freezer, ?method of analysis
	Auckland	MONICA study (Anonymous 1989)	Sample from electoral register	81%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, extraction analysis
	Singapore	APCSC-Singapore Heart Survey (APCSC secretariat, personal communication, 2001)	Random sampling of population of Singapore	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Singapore	Hughes et al. (1990)	Random sample of census districts, units, houses, then individuals (weighted)	52–66%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
WPR-B	China	APCSC-Anzhen 02 (APCSC secretariat, personal communication, 2001)	Cluster sampling	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	APCSC-Hong Kong SAR (APCSC secretariat personal communication, 2001)	Stratified random sampling in Hong Kong SAR	85%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	APCSC-Seven Cities cohort (APCSC secretariat, personal communication, 2001)	Study samples selected from Chinese populations of farmers, workers and fishermen	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

continued

Western Pacific (*continued*)

Subregion	*Country or area*	*Study reference*	*Sampling*	*Response rate*	*Cholesterol measurement*
	China	APCSC-Six Cohorts (APCSC secretariat, personal communication, 2001)	Cluster sampling of six cohorts in villages, including farmers of Shanxi, Shaanxi, Guangxi, Jiangsu province, minors of Hebei province and fishermen of Zhejiang	≥85%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	76–99%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	Tao et al. (1992)	Cluster sampling from four regions in China	87–88%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	China	Tian et al. (1995)	Random survey of population in Tianjin	96%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	China	Yang et al. (1986)	Sample from Beijing region	*	Trained staff & certified lab Non-fasting samples Sample stored in freezer, ?method of analysis
	China	Zhuang et al. (1986)	Sample from specific region using urban and rural population	*	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
	Beijing	MONICA study (Anonymous 1989)	Sample from register of households	89–90%	Trained staff & certified lab ?fasting sample

				?where sample stored, ?method of analysis
Hong Kong SAR	Fong et al. (1994)	Sample from population register	*	Trained staff & certified lab All fasting samples Sample stored in freezer, ?method of analysis
Hong Kong SAR	Woo et al. (1997)	Random selection, asked to participate by telephone call	40%	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
Taiwan, China	APCSC-CVDFACTS/Two Townships (APCSC secretariat, personal communication, 2001)	Two townships in Taiwan, China	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Papua New Guinea	Lindeberg et al. (1994)	Randomly selected within specific age range during a period of seven weeks—some non-randomized subjects included due to low participation	45–63%	Trained & certified lab All fasting samples Sample stored in freezer, ?method of analysis
Papua New Guinea	Scrimgeour et al. (1989)	Randomly selected from three rural communities and one urban community	58–64% (F) 52–60% (M)	Trained & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Philippines	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	91%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

* Data unavailable.

? Specific details not given.

Appendix B: Methodology for estimating stroke subtypes by age, sex, subregion and fatal and non-fatal events

Subregional- and age-specific proportions of ischaemic and haemorrhagic fatal and non-fatal strokes were estimated so that weighted RRs could be applied. Based on published data, an assumption was made that these are the same for males and females. Several steps were undertaken to estimate stroke subtype proportions, and these are outlined below.

Step 1. Assess age patterns of haemorrhagic and ischaemic stroke

The most reliable data on age patterns of stroke subtypes are available from a small selection of "gold standard" incidence studies, most of which were included in a review (Sudlow and Warlow 1997). These studies include the Melbourne stroke study (Thrift et al. 2001), Oxfordshire stroke project (Bamford et al. 1990), Perth community stroke study (Anderson et al. 1993) and the Dijon study (Giroud et al. 1991). Broadly, similar age patterns have also been seen in other studies.

Utilizing the combined age-specific data from these four studies, the percentage of ischaemic strokes in 10-year age categories is presented in Figure B.1. (The number of strokes in the youngest age group is small compared to the other age groups and is therefore less reliable.)

Figure B.1 Percentage of ischaemic strokes by age using data from four "gold standard" studies with linear regression line

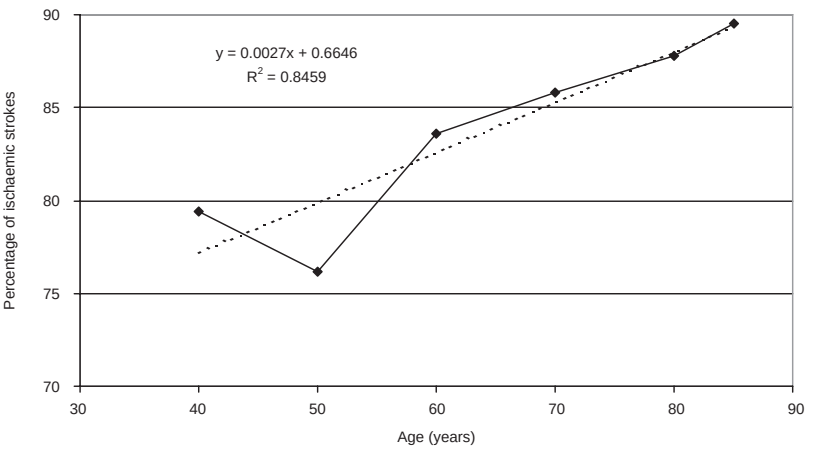


Table B.1 Estimates of the proportion of stroke subtypes by age

	Age group (years)				
Stroke subtypes	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
% ischaemic	77	81	84	87	89
% haemorrhagic	23	19	16	13	11

The linear regression was then used to estimate the proportions of ischaemic stroke by GBD age groups using the midpoint in each GBD age category. The remaining strokes were classified as haemorrhagic (Table B.1).

Step 2. Estimate the age-specific subtype proportions for fatal and non-fatal events

Table B.1 relates to total strokes, but these proportions will differ for fatal and non-fatal strokes as the case fatality rates for the ischaemic and haemorrhagic strokes are different. The "gold standard" incidence studies (Sudlow and Warlow 1997) suggest that the one-month case fatality rates range from 10% to 23% (crude average = 14%) for ischaemic stroke, and 35% to 54% (crude average = 45%) for haemorrhagic stroke. If it is assumed that these case fatality rates apply for all age groups, these crude percentages can be applied to each age group to provide estimates of the overall proportion of stroke subtypes for fatal and non-fatal events (Table B.2).

These percentages may then be converted in proportions of ischaemic and haemorrhagic stroke within the fatal and non-fatal categories for each age group (Table B.3).

Table B.2 Estimates of subtype proportions for fatal and non-fatal events by age

Age group (years)	*Total stroke (%)*		*Fatal stroke (%)*		*Non-fatal stroke (%)*	
	Ischaemic	*Haemorrhagic*	*Ischaemic*	*Haemorrhagic*	*Ischaemic*	*Haemorrhagic*
30–44	77	23	11	10	66	13
45–59	81	19	11	9	70	10
60–69	84	16	12	7	72	9
70–79	87	13	12	6	75	7
≥80	89	11	12	5	77	6

Table B.3 Percentage of stroke subtypes within fatal and non-fatal categories

	Fatal stroke (%)		*Non-fatal stroke (%)*	
Age group (years)	*Ischaemic*	*Haemorrhagic*	*Ischaemic*	*Haemorrhagic*
30–44	51	49	84	16
45–59	57	43	87	13
60–69	62	38	89	11
70–79	68	32	91	9
≥80	72	28	93	7

Step 3. Estimate how these age-specific subtype proportions can be applied to different regions

The age-specific subtype proportions in Table B.3 would only apply to subregions such as AMR-A and EUR-A, from where the data on which the estimates were based came. Estimates were also required for other subregions. The literature suggests that haemorrhagic stroke is relatively more common (about 30–40% of all strokes) in Japan (Nakayama et al. 1997; Suzuki et al. 1987), China (Chen et al. 1992; Wu et al. 1992) and Taiwan, China (Hung 1993; Jeng et al. 1998) and lower in countries in North America and Europe (about 10–15% of all strokes) (Sudlow and Warlow 1997). Unfortunately, reliable data on the remainder of the world are extremely limited or non-existent, and there are no internally consistent WHO estimates available.

The level of cholesterol is important in determining the overall ratio of ischaemic to haemorrhagic strokes in any world region (APCSC 1999). Subregions may therefore be crudely ranked based on their mean cholesterol levels, grouped into three basic subregional categories, and average percentages of haemorrhagic stroke applied. An example is given in Table B.4.

Table B.4 Subregional grouping by mean cholesterol and percentage haemorrhagic stroke[a]

Subregional grouping	*Cholesterol level*	*Overall % haemorrhagic stroke*
AMR-A, EUR-A, EUR-C	≥5.8 mmol/l	15
AFR-D, AFR-E, AMR-B, AMR-D, EMR-B, EMR-D, EUR-B, SEAR-D, WPR-A	5.1–5.7 mmol/l	20
SEAR-B, WPR-B	≤5.0 mmol/l	30

[a] Based on mean cholesterol levels for individuals aged 60–69 years.

The case fatality rates used previously (14% ischaemic, 45% haemorrhagic) are applicable to WPR-A, AMR-A and EUR-A, but case fatality would be higher in other subregions. Limited data are available, but when case fatality rates of 20% for ischaemic stroke and 60% for haemorrhagic stroke (Chen et al. 1992; Li et al. 1985) are applied to other subregions, five potential scenarios result (Table B.5).

These proportions may then be translated into age-specific proportions for fatal and non-fatal ischaemic and haemorrhagic strokes (Table B.6).

Table B.5 Subregional grouping by mean cholesterol and percentage haemorrhagic stroke

Subregional grouping	*% haemorrhagic stroke*	*Ischaemic stroke case fatality (%)*	*Haemorrhagic case fatality (%)*
EUR-A, AMR-A	15	14	45
EUR-C	15	20	60
WPR-A	20	14	45
EMR-B, EMR-D, EUR-B, AFR-D, AFR-E, AMR-B, AMR-D, SEAR-D	20	20	60
SEAR-B, WPR-B	30	20	60

Table B.6 Proportion of fatal and non-fatal stroke subtypes by age and subregion

	Fatal stroke (%)		*Non-fatal stroke (%)*	
Age group (years)	*Ischaemic*	*Haemorrhagic*	*Ischaemic*	*Haemorrhagic*
EUR-A, AMR-A				
30–44	51	49	84	16
45–59	57	43	87	13
60–69	62	38	89	11
70–79	68	32	91	9
≥80	72	28	93	7
EUR-C				
30–44	53	47	87	13
45–59	59	41	90	10
60–69	64	36	91	9
70–79	69	31	93	7
≥80	73	27	94	6

continued

Table B.6 Proportion of fatal and non-fatal stroke subtypes by age and subregion (*continued*)

	Fatal stroke (%)		*Non-fatal stroke (%)*	
Age group (years)	*Ischaemic*	*Haemorrhagic*	*Ischaemic*	*Haemorrhagic*
WPR-A				
30–44	41	59	78	22
45–59	48	52	82	18
60–69	53	47	85	15
70–79	60	40	88	12
≥80	64	36	90	10
EMR-B, EMR-D, EUR-B, AFR-D, AFR-E, AMR-B, AMR-D, SEAR-D				
30–44	43	57	82	18
45–59	50	50	85	15
60–69	55	45	88	12
70–79	61	39	91	9
≥80	66	34	92	8
SEAR-B, WPR-B				
30–44	28	72	70	30
45–59	35	65	77	23
60–69	41	59	81	19
70–79	49	51	85	15
≥80	54	46	88	12

Chapter 8

Overweight and obesity (high body mass index)

W. Philip T. James, Rachel Jackson-Leach, Cliona Ni Mhurchu, Eleni Kalamara, Maryam Shayeghi, Neville J. Rigby, Chizuru Nishida and Anthony Rodgers

Summary

It is widely acknowledged that being overweight is associated with an amplified risk of disease, particularly if body fat is deposited within the abdomen, as suggested by a high waist-circumference measurement. This chapter aims to estimate the burden of disease attributable to overweight and obesity as indicated by a high body mass index (BMI), by age, sex and subregion.[1]

BMI, which is calculated as weight (kg) divided by height squared (m^2), was chosen as a simple measurement of body weight in relation to height. While increases in both body fat and lean tissue cause increments in BMI, relationships between body weight and health are conventionally expressed in terms of BMI rather than body fat. Data on population weight and height, often collected as part of general medical or economic surveys, were obtained, typically from specially-commissioned analyses from ministries of health. Where these data sets or published representative information were lacking, earlier data published for each country were used. All information based on studies of select groups within a population were excluded. In addition, only data obtained by actual measurement of heights and weights by trained observers were included. As data were not available for some countries, it was necessary to extrapolate from data for other countries or subregions when deriving estimates of BMIs for the different age groups in each subregion.

Analyses of the relationship between BMI and both mortality and morbidity suggested that the theoretical optimum mean population BMI was approximately 21 kg/m^2. This value is far removed from those now found in many parts of the world. The analyses based on this continuous relationship therefore replaced the usual categorical analyses based on rates of overweight and obesity in the different subregions.

The disease outcomes assessed in relation to excess weight were type II diabetes (diabetes mellitus), ischaemic heart disease, stroke, hypertensive heart disease, osteoarthritis, and cancers of the postmenopausal breast, colon, endometrium and kidney. As it was evident that adult BMIs of >21 kg/m^2 were associated with the development of disease, the burden of disease attributable to high BMI was calculated from this baseline. New analyses based on 33 cohort studies carried out within the Asia-Pacific region were used to estimate the incremental risk of cardiovascular disease associated with each unit increase in BMI above 21 kg/m^2. The relationship between BMI and the risk of type II diabetes was derived from both unpublished and published data comprising measured anthropometry and fasting blood sugar measurements, extracted from nationally representative studies. Equivalent increments in the risks of co-morbidities associated with body-weight gain were assumed for all parts of the world.

High mean BMIs and elevated rates of overweight and obesity were found in the Americas, Europe, the Middle East and in the Western Pacific. It is estimated that rates of obesity vary geographically from 2–3% in some Asian countries to 75% in several Pacific Island nations. Currently, there are more than 300 million obese and more than 750 million overweight individuals in the world.

The proportions of the global burden of disease attributable to increases in BMI were 58% for type II diabetes, 21% for ischaemic heart disease, 39% for hypertensive disease, 23% for ischaemic stroke, 12% for colon cancer, 8% for postmenopausal breast cancer and 32% for endometrial cancer in women, and 13% for osteoarthritis. This means that the global burden of disease attributable to excess BMI in adults amounted to more than 30 million disability-adjusted life years (DALYs) in 2000, mostly incurred from ischaemic heart disease and type II diabetes. There were two and a half million deaths associated with this exposure. These are average global figures and there are remarkable variations by subregion and by disease. Thus EUR-C has the greatest burden of DALYs, this being dominated by the impact of high BMI on ischaemic heart disease, whereas the two African subregions have the lowest burden of DALYs. The burden of diabetes attributable to high BMI is greatest in WPR-B and AMR-B, with AMR-A also having a substantial burden. DALYs attributable to stroke were also dominated by the impact of high BMIs in both EUR-C and WPR-B, while the burden of DALYs caused by cancer was substantial in the European subregions, AMR-A, AMR-B and WPR-B.

Current trends were used to predict the increases in BMI and disease burden that are likely to occur by 2030, assuming that no new measures are taken to counteract the rapid recent increases in body weight in all parts of the world. On this basis, it is predicted that the burden of disease will increase substantially in most parts of the world, but there will probably be remarkable variations by subregion.

1. Introduction

Although the measurement and analysis of body weights and heights have been recognized as general indices of health for many years, it is only comparatively recently that the World Health Organization (WHO) has set out criteria for assessing underweight and overweight in both children and adults (WHO 1995). These new analyses of the impact of excess body weight came from insurance data generated in the first half of the 20th century which were used to identify optimum weights-for-height above which life expectancy was reduced, for both men and women. In the second half of the 20th century, it became clear that abnormalities in blood lipids relating to the risks of ischaemic heart disease were amplified by excessive body-weight gain, as was the risk of high blood pressure, type II diabetes, gallbladder disease and some cancers. It also became clear that the mechanical impact of excess body weight induced breathlessness and promoted arthritis in the weight-bearing joints. In developed countries, overweight women were stigmatized, with marked consequences on their sense of well-being, social interactions and even their employment and marriage prospects.

The traditional concerns of governments and policy-makers have focused on undernutrition, with greater emphasis being placed on the continuing problem of childhood protein–energy malnutrition, which is found especially in children aged 0–4 years. This condition is still prevalent in many countries despite economic progress (James et al. 2000), as described in chapter 2. Many nations now have reasonable systems for monitoring children's growth and can provide estimates of the prevalence of stunting, wasting and overweight in children aged <5 years (de Onis and Blössner 2000). Unfortunately, the value of monitoring the weights and heights of older children and adults has not been appreciated until fairly recently. Since the 1997 WHO Expert Consultation on Obesity (WHO 2000), there has been a substantial increase in the number of publications presenting newly-analysed data from past studies in different parts of the world. Thus, the regular national NHANES surveys in the United States of America (Stevens et al. 1999) allowed the magnitude of the problem of overweight to be recognized, and many cardiovascular surveys, for example the WHO MONICA surveys (Dobson et al. 1998), also documented high prevalences of overweight and obesity in Europe and Australasia. Other surveys such as the INTERSALT study (Dyer and Elliott 1999) revealed high prevalences of excess weight in some developing countries, including Brazil (James and Francois 1988). The data presented by many of these studies are not representative and do not include validation of the measurements of height and body weight. Nevertheless, it is apparent that many new national surveys are now being undertaken and a much more extensive database is expected to become available within the next few years.

This chapter was based on an extensive search of the literature to identify appropriate data sets and also specifically-commissioned analyses provided by a number of individuals, organizations and governments.

2. Choice of exposure variable

2.1 Definitions of body weight and of risk factors

The use of the BMI

The present analysis is based exclusively on the use of the BMI, which is calculated as weight (kg) divided by height squared (m^2). The height and weight of both children and adults are crude indices of the impact of many environmental factors, (including diet and infections) on the genetic growth potential of the individual over short and long periods of time, and affect many health outcomes.

BMI is the most appropriate simple indicator by which weight-for-height can be related to health outcome. WHO (1995) therefore proposed the use of BMI to monitor both undernutrition and overweight. The power of height is taken as 2.0 although it has been shown in many analyses that 1.5 might be more appropriate for women on the basis that this index in population studies proves to be approximately height-independent (Micozzi et al. 1986). Nevertheless, international convention, as represented by two major WHO Technical Consultations (WHO 1995, 2000), endorsed the use of a common BMI scheme for adults irrespective of sex or age.

Preliminary analyses of the global burden of disease associated with higher BMI, based on the current data sets, suggested that the population distribution of BMI values for men and women in each age group provided more valuable information than simply the proportions of the population who are classified as overweight and obese. These categories of overweight and obesity are used extensively by clinicians for patient management decisions, by the public and by policy-makers. Therefore, the proportions of overweight and obese people in the population are included in this chapter despite the fact that this information was not used in the calculation of the contribution of different values of BMI to the disease burden.

In these subsidiary analyses, the standard WHO BMI categories were used, except that the term "overweight" was taken as referring to BMI values of 25.0–29.9 kg/m^2 only and did not include the "obese" category, i.e. BMI of $\geq$30 kg/m^2, since these two groups, overweight and obesity, are often referred to independently. More extreme categories of obesity have been specified (WHO 2000), but were not included in the current global analyses.

Recently, it has been proposed that a lower BMI range of "healthy", "normal" or "acceptable" weights should be applied to groups of Asian

people (see below), but in the current analysis an assessment was made of the impact of increments in BMI on disease risk in different parts of the world, which was therefore not dependent on different schemes for categorizing overweight and obesity.

Body weight in children

It has become increasingly common for epidemiologists to express heights and weights of children in terms of the same BMI as used in adults, despite detailed analyses showing that BMI varies by age and sex during growth. Criteria have therefore now been developed for specifying the normal weight-for-height of children in terms of BMI for each age group, by sex, until adult height is achieved at approximately 18 years of age. There are three approaches to the categorical analysis of BMI in children: the traditional approach whereby an "abnormal" group is taken to be more than two standard deviations from the mean, the new International Obesity Task Force (IOTF) approach that relates BMI categories in childhood to the accepted classification in adults (Cole et al. 2000), and a new Centers for Disease Control and Prevention (CDC) set of standards whereby obesity is specified as >95th BMI percentile of carefully selected representative data from the United States (Ogden et al. 2002).

It is recognized that children of similar body proportions but of different heights at the same age will have different BMI values and that to obtain height-independent indices would require a sequential adjustment in the power value of height from about age 5 years upwards (Franklin 1999). Nevertheless, given that population comparisons are being made here, rather than the monitoring of the growth of individuals, weights and heights for children have been expressed in terms of BMI and these calculations have been applied only to children aged 5–18 years. The large body of nationally representative data for children aged <5 years collated by WHO and presented in chapter 2 provides the relevant information for this age group. However, the burden of disease estimates presented here are only for adults aged ≥30 years. This age limit was chosen because there are as yet insufficient prospective studies of an appropriate magnitude in children and young adults to allow quantitative analyses of the impact of excess weight gain on the incidence of noncommunicable diseases in individuals aged <30 years.

2.2 Other exposure determinants

Body fat

It is often assumed that health-related data would ideally be related to good measures of body fatness, and that the combination of weight and height in the form of BMI provides a crude index of body fatness. In practice, however, too few studies have measured body fatness and health outcomes at different ages and in different societies to allow an analysis

of whether a more specific measure of body fat than BMI would give greater predictive power for health outcomes. Given the many prospective studies that use BMI, the current convention has been maintained while recognizing that recent data show that different ethnic groups have substantially different proportions of body fat at the same value of BMI. For example, the ratio of fat : lean tissue is highest in Indian people, while values for Chinese people are intermediate between those for Indians and Caucasian peoples (Deurenberg et al. 2002), and Polynesians are increasingly recognized as having a relatively high proportion of lean tissue (Swinburn et al. 1999). On this basis, Deurenberg and colleagues have suggested that different BMI values should be chosen if the intention is to standardize international comparisons on the basis of body fat (Deurenberg et al. 1998, 2002). There are, however, no international studies as yet which would allow all population groups to be set a particular BMI value based on their fat : lean tissue ratios and the relationship of these indices to health outcomes.

Therefore, this chapter maintains the current convention of using BMI as an indicator of body fatness in adults. It is recognized that not only do women have substantially more fat tissue than men at equivalent BMIs (Shetty and James 1994), but also that both men and women lose lean tissue during the course of their adult lives such that, at an equivalent BMI, a 75-year-old man or woman has substantially greater proportion of fat than a 25 year old (James et al. 1988). This is not a cohort effect since the same changes have been shown, at least in men, in the Baltimore study of ageing, which evaluated the changing body composition of the same men over a 50-year period (James et al. 1989).

Corrections for unusual body proportions

The proportions of the major body parts which contribute to height may be different in different ethnic groups. For example, some African tribes are considered to have exceptionally long legs, whereas the indigenous populations of Central America are often cited as being small with very short legs (Norgan 1994a). It can readily be shown that even if the proportions of both the trunk and legs are equal in very short and tall peoples, the actual BMIs of these peoples will be very different. This has led Norgan (1994b) to develop a simple correction for BMI measurement based on the ratio of sitting height to total height. Although this is well-recognized (WHO 1995) and is valuable when looking at particular groups, the limited availability of good data on sitting height meant that it was not possible to incorporate this correction for BMI into the current analyses.

Waist circumference

Originally it was hoped that sufficient data would become available on waist circumference to allow an assessment of the usefulness of this measure in predicting the health of different communities. There are

many analyses that demonstrate that waist circumference provides a reasonable indicator of the quantity of abdominal fat, which correlates with the amount of intra-abdominal or visceral fat (Despres et al. 2001). This fat is considered to be metabolically rather different from subcutaneous fat in its responsiveness to dietary change and in its array of metabolite and hormonal outputs. An excess of abdominal fat has been associated with a range of metabolic abnormalities and diseases (Despres et al. 2001). The measurement of waist circumference is often found to be more valuable than BMI itself, for example, in predicting the likelihood of ischaemic heart disease (Lapidus et al. 1984; Larsson et al. 1984) or diabetes (Chan et al. 1994). The National Institutes of Health (NIH) report from the United States (NIH 1998) used waist circumference measurements as a suitable indicator of additional risk within a given range of BMI. In some studies, there seems to be additional predictive power when the waist:hip ratio rather than just waist circumference is used. The hip measurement indicates the degree of fat accumulation around the hips and this deposition may help in some way to limit the health impact of abdominal fat accumulation (Seidell et al. 2001b). Nevertheless, there seems to be increasing acceptance that, for general use, a single measure of waist circumference provides a simple index of fat distribution and additional risk (Seidell et al. 2001a).

Proposals have been also made for lower cut-off points for measurements of waist circumference for use in Asian communities (WHO/IASO/IOTF 2000) and new Chinese analyses have also proposed different values (Zhou 2002). There is also now increasing evidence that many communities, e.g. African and Hispanic Americans in the United States, Indians in India and elsewhere, the Chinese and Latin Americans have a greater propensity as adults to accumulate excess adipose tissue in the abdominal area than Caucasians in Europe or the United States (Ford et al. 2002; Sánchez-Castillo et al. 2003; Sargeant et al. 2002; Singh et al. 1995; Zhou et al. 2002). Although the selective accumulation of abdominal fat is indicative of a much greater risk of diabetes, hypertension, ischaemic heart disease, strokes and gall bladder disease, cross-sectional studies of the African diaspora in West Africa, the Caribbean and the United States show that the relationship of waist circumference to disease seemed to vary by region, perhaps because of concomitant regional dietary differences (Okosun et al. 1998, 2000). Nationally representative data and long-term cohort studies of the health impact of different indices of abdominal obesity in different communities are also currently insufficient to allow the use of some measures of waist circumference to estimate the BMI–disease relationship in different parts of the world.

The propensity to abdominal obesity within a community seems to be markedly influenced by stunting or a small size in childhood (Schroeder et al. 1999) and also by size at birth (Barker 1998). Changes in the hypothalamic–pituitary–adrenal axis controlling pituitary hormone and

corticosteroid metabolism in response to fetal nutritional deprivation and early postnatal events are also evident experimentally (Seckl et al. 2001) and abdominal obesity is associated with abnormal control of corticosteroid metabolism (Björntorp and Rosmond 1999). Evidence from India shows that children aged 4 and 8 years who were born small and later showed accelerated growth had a propensity to abdominal obesity with greater insulin resistance and higher blood pressure (Yajnik 2000). The current data available on a global basis do not, however, allow a systematic adjustment of health risk based on birth weights in different parts of the world, or the prediction of childhood BMIs from infant birth weights. A substantial proportion of the world's population that has been existing on marginal diets for centuries may have been sensitized to excess body-weight gain, this being reflected in the greater propensity to accumulate abdominal fat and in the higher prevalence of the metabolic syndrome of multiple risk factors for chronic diseases of adults such as diabetes, hypertension and ischaemic heart disease in Hispanic and non-Caucasian ethnic groups (Ford et al. 2002).

3. Methods of identifying sources and studies

3.1 Studies of interest

Studies of interest were identified using the following methods:

- Searches of the Medline and Embase databases were conducted systematically for all 191 countries of the world. Medline searches were performed with the keywords "BMI" and "obesity", each paired with "cardiovascular disease", "hyperlipidaemia", "cholesterol", "stroke", "ischaemic heart disease", "osteoarthritis", "diabetes mellitus type II", "cerebrovascular disease", and in combination with each country name, i.e. 2 x 8 x 191 searches. *Example*: BMI AND cardiovascular disease AND country X. Both United Kingdom and American English spellings were used in the searches. Embase searches were performed with the keywords "BMI", "obesity", "body mass", "body height", "weight", "children", and "adults". Countries were not specified in these searches.
- IOTF contacted each WHO Regional Nutrition Officer to request help with the analyses. The precise format for these was specified and each region was asked to help identify appropriate contacts from whom reliable national data on both BMI and diet could be obtained.
- Numerous direct contacts were made with governments and individuals to determine whether unpublished data were available. It is significant that with obesity now becoming a high profile issue throughout the world, many investigators, on learning of this

project, stated that they now wished to publish in their own right information on prevalence rates that had remained unpublished for several years.

- Relevant data sets were retrieved from online databases, or purchased and re-analysed. These included a United States Agency for International Development (USAID)-sponsored series of Demographic and Health Surveys (DHS) conducted by Macro International, the United States National Health and Nutrition Examination Survey (NHANES) III, and the 1998 Health Survey for England.
- Analyses of 33 cardiovascular cohort studies being conducted in the Asia-Pacific region and participating in the Asia-Pacific Cohort Studies Collaboration (APCSC) were also used to derive the relative risks of cardiovascular disease associated with increases in BMI.

For data from the identified studies, the following inclusion criteria were used.

- Nationally representative data were preferred.
- Clinical data were excluded whenever possible because they reflect a subgroup of the population with particular medical problems and could not be considered nationally representative.
- Only measured anthropometric data were used to assess the national information on BMI. A good correlation between measured and reported weights and heights can be found (Flegal and Troiano 2000), but many international analyses of reported vs measured heights and weights, including those from the United States, reveal discrepancies which underestimate weight and overestimate height, these discrepancies being particularly apparent in the groups of overweight people (see Niedhammer et al. 2000). Australian analyses have also shown that there can be very substantial differences in the prevalences of overweight and obesity as judged by the two approaches (Anonymous 1999). Nevertheless, for prospective analyses, the overall associations between reported weights and heights and health outcomes are unlikely to be seriously affected, even if the magnitude of the association becomes more uncertain. Therefore, some results of major studies employing self-reported weights and heights were used to illustrate disease relationships (although the quantitative associations used in estimates of impact on the health of the population are all derived from studies employing actual measurement of BMI). Given the levels of inaccuracy and bias associated with self-reported BMI, the use of such data was considered inappropriate for the purpose of estimating exposure. A small bias could have a substantial impact on the estimated prevalences of overweight and obesity in the tail of the BMI distribution. This criterion excludes many high profile publications that rely on self-reported weights and heights, particularly from

European Union surveys, and a large number of studies from the United States.

- A sufficiently large sample size was required, with preference being given to studies investigating ≥1000 individuals. For countries with no data, studies with smaller samples were not excluded.
- The earliest cut-off date for data collection was 1990, whenever possible. Where no suitable studies were available, studies dating from 1980 onwards were considered.
- For diabetes, only representative population measures of fasting plasma glucose were used. Ideally, representative data from children and adults tested with a standard glucose load are desirable for a full assessment of the prevalence of diabetes in relation to BMI, but there are very few studies with nationally representative data available from developing countries. No studies which involved the self-reporting of the presence of diabetes were considered appropriate for estimating national prevalences of diabetes, since surveys have repeatedly shown that representative assessments of population groups find a substantial proportion of unrecognized cases of diabetes within the community. In general, as age and BMI increase, the number of individuals with unrecognized diabetes also increases and there can therefore be substantial systematic biases. On this basis, only nationally representative data on fasting blood glucose levels, in combination with measured weights and heights, were used to assess the risk of diabetes associated with body-weight gain. The reason for relying on prevalence rather than incidence data for diabetes to estimate risk in relation to excess body weight is set out in a later section.

3.2 Measurements in children

The quantitative assessments of the disease burden caused by high BMI reported here only apply to adults aged ≥30 years. However estimates were also made of BMI values among children, by age, sex and subregion. This was for two reasons. First, these estimates are relevant to estimates of avoidable burden, since BMI levels track over time and so they will guide projections of the distribution of adult BMI in the next few decades. Second, high BMI is responsible for a disease burden in children and there is increasing evidence that high BMI in childhood markedly enhance the risks of disease once these children become adults; these relationships need to be included in hazard size estimates in the future. Therefore, these analyses attempted to estimate the distribution of BMIs for each 1-year age group for ages 5–18 years (i.e. until the typical end of child and adolescent normal growth [see the WHO Expert Technical Consultation on Anthropometry, WHO 1995]) and for ages 18–29 years combined.

In analysing the basis of overweight in children (Dietz and Bellizzi 1999), a concept was developed by IOTF which allowed a coherent set of nationally representative data on BMI percentiles at age 18 years to be obtained from both developed countries (prior to the recent emergence of many children with clear clinical obesity) and developing countries. The percentile values corresponding to BMIs of 25 and 30 kg/m^2 at age 18 years were used to derive sex- and age-specific cut-off points for the categorical analysis of overweight (see Cole et al. 2000). In the United States, CDC have also produced reference curves, but these are based arbitrarily on the 85th and 95th percentiles of carefully selected nationally representative data (Ogden et al. 2002). The data for this chapter are presented according to the IOTF system, Roberts and Dallal (2001) having concluded that the IOTF reference levels were more suitable for international comparisons.

4. Estimating mean BMI and prevalences of overweight and obesity

Given that representative data were not available for all 191 countries, it proved necessary to undertake a number of extrapolations. Some of the principal approaches are set out below.

4.1 Description of subregional availability of data

AFR-D

Childhood mean BMI data were from Mali and Senegal. In adults, subregional estimates were based on data from Cameroon, the Gambia, Ghana, Nigeria, Mali and Senegal. Data were also obtained for the Seychelles but were not included in the estimate. Mean BMI data are outlined in Table 8.1.

AFR-E

In children, subregional mean BMI data were from Ethiopia, South Africa and Zimbabwe. In adults, estimates were based on data from Ethiopia, Kenya, Malawi, South Africa, the United Republic of Tanzania and Zimbabwe. Data available from Kenya and the United Republic of Tanzania were limited to females only. Mean BMI data are outlined in Table 8.2.

AMR-A

For children, subregional mean BMI data were derived from both Canada and the United States. Although the Canadian data were not nationally representative, it was felt that these data should be used until nationally representative data become available in the required format. In adults, data were available from all countries in the subregion. Data from Cuba were provided in different age categories and were adjusted

Table 8.1 Mean BMI in AFR-D

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Cameroon[a] (Rotimi et al. 1995)	Male	—	23.7	24.4	24.0	—	—	—
	Female	—	24.6	24.8	25.0	—	—	—
Gambia (Van der Sande et al. 1997)	Male	—	19.6	20.5	20.9	21.0	20.0	—
	Female	—	21.0	21.9	21.8	21.3	20.9	—
Ghana (DHS data provided by Macro International 1998)	Male	—	—	—	—	—	—	—
	Female	—	21.8	22.4	21.4	—	—	—
Mali (Re-analysed by Ferro-Luzzi, personal communication)	Male	14.8	18.9	20.5	20.8	20.3	19.6	20.2
	Female	14.9	19.9	21.1	20.6	20	19.5	20.8
Nigeria (Okesina et al. 1999)	Male	—	19.8	20.9	21.5	—	—	—
	Female	—	21.0	21.8	20.3	—	—	—
Senegal (Re-analysed by Ferro-Luzzi, personal communication)	Male	14.2	18.2	19.9	21.0	20.7	19.8	19.2
	Female	14.3	19.6	21.4	22.1	22.2	21.3	20.7
Seychelles (Bovet et al. 1991)	Male	—	22.9	23.5	23.1	23.2	—	—
	Female	—	23.2	25.7	27.2	27.5	—	—

— No data.

[a] Data provided for Cameroon were estimated from graphs as actual figures were not available.

according to the methodology outlined in section 4.4. Mean BMI data are outlined in Table 8.3.

AMR-B

Data on mean BMI in childhood were derived using findings from Argentina, Brazil and Mexico. The standard deviation for mean BMI in children was not available. To estimate standard deviation, the methodology outlined in section 4.6 was applied to data from EMR-B. For adults, subregional data were taken from Argentina, Barbados, Brazil, Mexico and Paraguay. Data were also obtained for Saint Lucia but were not included in the subregional analysis. Mean BMI data are outlined in Table 8.4.

AMR-D

Limited data were available for this subregion and neither population sample presented for children was considered to be nationally representative. However, it was considered inappropriate to exclude these data and to extrapolate from other subregions. For Guatemala, only data from children living in high altitude areas were considered in the calculations. Data for adults were only available for females. Subregional estimates for females were used to derive estimates for males, using

Table 8.2 Mean BMI in AFR-E

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Ethiopia (Re-analysed by Ferro-Luzzi, personal communication)	Male	14.2	17.5	18.3	18.0	18.0	17.9	19.8
	Female	14.5	18.9	18.6	17.3	16.7	17.6	18.6
Kenya (DHS data provided by Macro International, 1998)	Male	—	—	—	—	—	—	—
	Female	—	21.7	22.3	22.0	—	—	—
Malawi (Chilima and Ismail 1998)	Male	—	—	—	19.8	19.8	19.7	—
	Female	—	—	—	20.5	20.5	19.6	—
South Africa (T. Puoane et al. 1998, unpublished document)[a]	Male	13.8	21.5	24.2	25.3	24.8	24.4	—
	Female	14.0	24.4	28.5	29.9	28.8	27.7	—
United Republic of Tanzania (DHS data provided by Macro International, 1996)	Male	—	—	—	—	—	—	—
	Female	—	21.8	22.3	21.6	—	—	—
Zimbabwe (Re-analysed by Ferro-Luzzi, personal communication)	Male	15.3	19.5	20.8	21.0	21.0	20.1	20.0
	Female	15.4	21.3	23.0	23.5	21.8	20.5	20.3

— No data.

[a] Anthropometric patterns in South Africa: results from the National Demographic and Adult Health Survey 1998.

Table 8.3 Mean BMI in AMR-A

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Canada (Hanley et al. 2000;[a] Macdonald et al. 1997[b])	Male	19.1	23.7	25.6	26.8	26.6	26.3	—
	Female	20.2	23.2	24.1	26.3	26.7	26.4	—
Cuba (Provided by C. Nishida, personal communication, 1992)[b]	Male	—	22.2	23.5	23.5	—	—	—
	Female	—	22.4	24.3	25.4	—	—	—
USA (NHANES)[b]	Male	18.5	24.2	26.6	27.8	27.5	26.8	25.1
	Female	18.6	24.0	26.4	28.0	27.6	27.0	25.0

— No data.

[a] Childhood data.

[b] Adult data.

Table 8.4 Mean BMI in AMR-B

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Argentina (Hernandez et al. 1987)	Male	17.1	23.6	25.4	27.4	27.8	26.6	—
	Female	18.0	22.3	24.0	26.3	26.7	26.5	—
Barbados[a] (Rotimi et al. 1995)	Male	—	25.5	25.5	26.4	—	—	—
	Female	—	28.0	28.3	29.2	—	—	—
Brazil (Monteiro and Conde 1999)	Male	16.9	22.1	23.8	24.2	24.1	—	—
	Female	17.4	23.0	25.4	26.3	26.3	—	—
Mexico (Arroyo et al. 2000; C.P. Sánchez Castillo, personal communication, 2002[b])	Male	19.2	24.6	27.2	27.6	27.0	25.7	24.7
	Female	19.8	25.3	28.3	29.6	28.8	27.3	25.5
Paraguay[a] (Jimenez et al. 1998)	Male	—	22.3	25.2	25.1	23.1	—	—
	Female	—	21.9	27.0	29.4	27.6	—	—
Saint Kitts and Nevis, and Saint Lucia[a,b] (Rotimi et al. 1995)	Male	—	23.5	23.8	24.2	—	—	—
	Female	—	26.0	26.6	27.2	—	—	—

— No data.

[a] Data for Barbados, Paraguay, Saint Kitts and Nevis, and Saint Lucia were estimated from graphs as actual figures were not available.

[b] Childhood data.

Table 8.5 Mean BMI in AMR-D

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Guatemala (DHS 1998;[a] Martorell et al. 1995[b])	Male	14.6	—	—	—	—	—	—
	Female	14.9	24.4	25.8	26.8	—	—	—
Peru (DHS data provided by Macro International, 1996;[a] Gonzales et al. 1994[b])	Male	15.2	—	—	—	—	—	—
	Female	15.3	24.4	25.8	26.5	—	—	—

— No data.

[a] Adult data.

[b] Childhood data.

methodology outlined in section 4.4. The methodology outlined in section 4.4 was also used to obtain estimates for upper age categories. The original mean BMI data for females are outlined in Table 8.5.

EMR-B

In children, subregional data were from Bahrain, Lebanon and Saudi Arabia. In adults, regional estimates were derived from Bahrain, Cyprus,

Table 8.6 Mean BMI in EMR-B

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Bahrain (al-Mannai et al. 1996;[a,b] Musaiger and al-Mannai 2001;[a,c] Musaiger and Gregory 2000[d])	Male	16.0	22.9	27.2	26.7	25.1	—	—
	Female	16.9	24.6	30.4	30.0	29.9	—	—
Iran (Islamic Republic of) (Pishad 1996)[a]	Male	—	21.0	23.8	24.3	23.1	22.7	—
	Female	—	21.8	24.7	25.0	24.1	22.5	—
Jordan (Ajlouni et al. 1998)[a]	Male	—	24.9	27.0	28.5	28.0	26.2	—
	Female	—	26.3	30.8	32.5	31.9	30.1	—
Kuwait (al-Isa 1995)[a]	Male	—	26.7	28.3	28.6	25.0	—	—
	Female	—	26.7	30.3	31.5	29.8	—	—
Lebanon (Data re-analysed by N. Hwalla and N. Adra, 1996)[a,b]	Male	17.8	23.5	25.8	26.7	26.1	25.5	23.5
	Female	17.8	22.3	25.4	28.1	29.2	27.2	26.0
Saudi Arabia (al-Nuaim et al. 1996)[a]	Male	—	23.5	26.1	27.0	26.0	—	—
	Female	21.0	24.5	27.6	28.7	27.0	—	—
United Arab Emirates (el Mugamer et al. 1995)[a]	Male	—	24.7	25.6	26.5	24.6	—	—
	Female	—	26.8	27.8	28.8	25.4	—	—

— No data.

[a] Adult data.

[b] 18–29 years.

[c] >30 years.

[d] Childhood data.

the Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Saudi Arabia and the United Arab Emirates. Only data for Lebanon were provided in the appropriate age categories; all other data were subject to the methodology outlined in section 4.4. Mean BMI data are outlined in Table 8.6.

EMR-D

Childhood data were not available in this subregion in the required format. Using the methodology outlined in section 4.5, it was concluded that it would be most appropriate to use data from the AFR-E subregion in order to determine the estimates for children. Mean BMI data for adults were limited to Pakistan and Egypt (females only). No data were available for the ≥80 years age category, therefore the methodology outlined in section 4.4 was applied. Mean BMI data are outlined in Table 8.7.

EUR-A

Availability of mean BMI data is described in Table 8.8.

Table 8.7 Mean BMI for adults in EMR-D

		Mean BMI (kg/m^2) Age group (years)					
Country (reference)	*Sex*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Egypt (DHS, data provided by Macro International, 1992–1995)	Male	—	—	—	—	—	—
	Female	25.3	27.2	27.1	—	—	—
Pakistan (Data provided by Dr Habibullah, 1998)	Male	20.7	21.8	21.9	21.6	21.0	—
	Female	21.1	22.5	22.7	22.3	21.3	—

— No data.

EUR-B

In children, data on mean BMI were available from Bulgaria, Poland, Slovakia and Turkey. In adults, data on mean BMI were available from Romania, Slovakia, Tajikistan, Turkey and Uzbekistan, and are outlined in Table 8.9.

EUR-C

Limited data were available for children in EUR-C, from the Russian Federation only. In adults, data were available for Hungary, Latvia, Lithuania and the Russian Federation and are outlined in Table 8.10.

SEAR-B

There were no data available for children in this subregion, thus data from AFR-E were used, as specified in section 4.5. As no data for adults were available for Indonesia or Sri Lanka, subregional figures were based on data from Thailand, as outlined in Table 8.11. Normally these data would have been excluded as they came from attendees at a dental clinic. However, as no other data were available in the required format at the time, it was decided that they should be included in the absence of any more appropriate data.

SEAR-D

Data for children were available from Nepal. Data for adults were available for Bangladesh, India (females only) and Nepal. Mean BMI values available are shown in Table 8.12.

WPR-A

Data were available for both children and adults for Australia and Japan, as outlined in Table 8.13.

WPR-B

As no data were available for children in WPR-B, data from AFR-E were used as specified in section 4.5. Data for adults were available for China,

Table 8.8 Mean BMI in EUR-A

		Mean BMI (kg/m²) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Belgium (Stam Moraga 1999)[a]	Male	—	24.8	25.3	26.5	26.3	26.1	—
	Female	—	23.1	24.1	27.2	27.8	27.9	—
Croatia (Data re-analysed by A. Kaic-Rak, 1992)[b]	Male	18.2	—	—	—	—	—	—
	Female	18.1	—	—	—	—	—	—
Czech Republic (V. Hainer, personal communication, 1997–1998)[b]	Male	—	25.5	26.9	28.2	28.6	—	—
	Female	—	23.6	25.7	28.3	29.8	—	—
Denmark (A. Robertson, personal communication 1995);[a] (Data re-analysed by A. Nielsen 1986–1997)[b]	Male	17.3	22.3	24.8	25.8	26	—	—
	Female	17.5	21.0	23.0	24.0	24.4	—	—
Finland (Lahti-Koski et al. 2000)[a]	Male	—	25.3	26.1	27.9	28.4	—	—
	Female	—	24.0	24.8	27.7	28.4	—	—
Germany (Bergmann and Mensink 1999, provided by G. Mensink;[a] Kromeyer-Hauschild et al. 1999[b])	Male	17.1	24.7	26.7	27.9	28.1	27.8	—
	Female	17.3	23.6	25.0	27.4	28.9	28.1	—
Greece (N. Katsilambros, unpublished data, 2000;[a,c] Trichopoulou et al. 2000[a,d])	Male	—	27.5	27.7	28.5	28.3	28.1	—
	Female	—	25.4	26.7	30.1	30.5	30.4	—
Iceland (V. Gudnason, unpublished data, 1991–1996)[a]	Male	—	25.1	26.2	27.1	27.7	26.3	25.5
	Female	—	28.5	24.9	26.4	27.8	26.4	26.2
Malta (A. Robertson, personal communication, 1994)[a]	Male	—	26.0	26.7	27.4	27.6	—	—
	Female	—	25.2	26.2	30.4	30.7	—	—
Netherlands (Data from the National Institute of Public Health and the Environment, and data from the MORGEN study, provided by T.L.S. Visscher, 1993–1997)[a]	Male	—	23.6	25.2	26.4	26.5	—	—
	Female	—	23.1	24.3	25.8	27.1	—	—
Portugal (Do Carmo et al. unpublished data presented at ECO 2000)[a]	Male	—	—	24.7	27.2	27.4	—	—
	Female	—	22.4	25.9	27.0	28.2	—	—
Spain (M. Fox, personal communication, 1990–1994;[a] (Moreno et al. 2000[b])	Male	18.9	24.2	25.8	26.8	—	—	—
	Female	19.0	22.6	24.7	27.4	—	—	—
Switzerland (M. Fox, personal communication, 1992/1993;[a] Zimmerman et al. 2000[b])	Male	17.2	23.0	24.4	25.7	25.8	25.5	—
	Female	17.3	21.2	22.1	23.5	24.3	24.3	—
United Kingdom (Health Survey for England, data re-analysed by IOTF 1998)[a,b]	Male	18.1	24.8	26.5	27.5	27.6	27.2	25.8
	Female	18.5	24.7	26.2	27.1	28.1	27.2	25.6

— No data.

[a] Adult data

[b] Childhood data.

[c] 18–29 years.

[d] >30 years.

Table 8.9 Mean BMI in EUR-B

Country (reference)	Sex	Mean BMI (kg/m^2) Age group (years) 5–14	15–29	30–44	45–59	60–69	70–79	≥80
Bulgaria (Data re-analysed by S. Petrova, 1998)[b]	Male	18.0	—	—	—	—	—	—
	Female	17.9	—	—	—	—	—	—
Poland (Data re-analysed by I. Palczewska, 1999)[b]	Male	17.6	—	—	—	—	—	—
	Female	17.3	—	—	—	—	—	—
Romania (N. Hâncu, personal communication, 1999)[a]	Male	—	23.9	26.4	27.1	—	—	—
	Female	—	22.5	26.9	28.0	—	—	—
Slovakia (K. Babinska, personal communication, 1995–1999);[a] (Data collated by A. Bederova and re-analysed by K. Babinska, 1995–1999)[b]	Male	18.0	21.7	26.7	27.7	28.4	26.8	—
	Female	18.2	20.8	24.5	27.0	28.9	28.2	—
Tajikistan (A. Robertson, personal communication, 1998)[a]	Male	—	17.8	20.8	25.4	26.8	—	—
	Female	—	18.0	20.4	25.5	27.3	—	—
Turkey (Data re-analysed by G. Pekcan and N. Rak, 1993–1999)	Male	16.7	21.9	25.6	26.3	26.3	25.6	24.8
	Female	16.8	24.0	27.7	29.6	29.4	29.2	27.5
Uzbekistan (A. Robertson, personal communication, 1999)[a]	Male	—	20.7	21.2	22.5	—	—	—
	Female	—	20.2	20.1	22.0	—	—	—

— No data.

[a] Adult data.

[b] Childhood data.

Table 8.10 Mean BMI in EUR-C

Country (reference)	Sex	Mean BMI (kg/m^2) Age group (years) 5–14	15–29	30–44	45–59	60–69	70–79	≥80
Hungary (Zajkas and Biro 1998)	Male	—	24.0	26.8	28.1	28.4	25.4	25.0
	Female	—	22.4	25.4	28.2	29.8	27.0	27.7
Latvia (A. Robertson, personal communication, 1997)	Male	—	25.6	27.0	29.0	29.2	—	—
	Female	—	22.1	24.2	27.6	28.8	—	—
Lithuania (A. Robertson, personal communication, 1999)	Male	—	24.8	25.7	26.5	26.8	—	—
	Female	—	23.2	24.9	27.6	28.7	—	—
Russian Federation (Data re-analysed by AD Deev, Russian Longitudinal Monitoring Survey—RLMS 1992)	Male	18.1	22.8	25.1	25.9	25.6	25.2	24.8
	Female	17.7	22.8	26.6	28.5	28.6	27.2	25.2

— No data.

Table 8.11 Mean BMI for adults in SEAR-B

		Mean BMI (kg/m^2) Age group (years)					
Country (reference)	*Sex*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Thailand (Chaichareon et al. 1992)	Male	20.8	22.6	23.4	23.0	22.6	22.6
	Female	20.8	22.7	23.9	24.3	22.5	22.5

Table 8.12 Mean BMI in SEAR-D

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Bangladesh (M. Q-K and K. Talukder, personal communication, 2000)	Male	—	19.0	19.5	18.9	19.1	18.0	—
	Female	—	19.7	19.9	19.2	18.7	19.7	—
India (DHS data provided by Macro International, 1998)	Male	—	—	—	—	—	—	—
	Female	—	19.5	20.9	21.6	—	—	—
Nepal (Data re-analysed by A. Ferro-Luzzi personal communication, 1997)[a,b]	Male	14.4	19.0	20.1	19.8	19.6	18.2	19.4
	Female	18.5	20.4	20.7	20.2	19.6	19.1	16.0

— No data.

[a] Adult data.

[b] Childhood data.

Table 8.13 Mean BMI in WPR-A

		Mean BMI (kg/m^2) Age group (years)						
Country (reference)	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Australia (National Nutrition Survey 1995, data re-analysed by T. Gill, 2000)	Male	18.1	24.6	26.8	26.8	27.6	27.1	24.7
	Female	18.6	22.5	24.6	27.1	27.2	26.4	25.4
Japan (Yoshiike et al. 1998)	Male	17.6	21.8	23.0	23.4	22.7	22.3	21.5
	Female	16.9	20.5	22.1	23.3	23.5	23.0	22.3

Table 8.14 Mean BMI in WPR-B

Country (reference)	Sex	Mean BMI (kg/m^2) Age group (years) 15–29	30–44	45–59	60–69	70–79	≥80
China	Male	21.6	22.9	23.2	23.0	22.3	—
	Female	22.7	23.0	23.7	23.9	22.6	—
Malaysia (Khor et al. 1999)	Male	21.6	23.6	23.0	21.4	—	—
	Female	22.3	24.8	24.5	22.6	—	—
Republic of Korea (Jones et al. 1994)	Male	22.5	22.8	23.2	21.8	21.6	20.8
	Female	21.1	21.8	23.0	22.4	22.2	21.1
Samoa (McGarvey 1991)	Male	24.9	25.8	28.0	27.7	26.5	—
	Female	26.0	27.9	30.3	29.8	28.6	—
Solomon Islands (Eason et al. 1987)	Male	22.9	23.5	23.6	—	—	—
	Female	24.4	24.9	24.2	—	—	—
Viet Nam (Giay and Khoi 1994)	Male	19.3	19.5	19.0	18.2	—	—
	Female	19.8	19.4	18.6	17.8	—	—

— No data.

Malaysia, the Republic of Korea, Samoa, the Solomon Islands and Viet Nam, as outlined in Table 8.14.

4.2 Obtaining subregional estimates from country-specific estimates

In order to obtain subregional estimates of mean BMI, prevalences of overweight and obesity and their associated standard errors for sex- and age-specific categories, a meta-analysis was initially considered. In this approach, estimates from different studies would be combined into a single weighted estimate, using the variance of the estimate as the weight. The combined estimate of the variances would then be the inverse of the sum of the study-specific variances. There were two major drawbacks which made this approach unsuitable.

- Countries with unknown variances would be excluded from the subregional analysis for the estimate of mean BMI or prevalences of overweight and obesity.
- The method of weighting by the variance of the study (which is highly dependent on the sample size and the design of the study, with "better", larger studies having the smallest variances) assumes an equal population for each sample. The approach does not take into account differences in population sizes.

A second approach was to obtain a single estimate of mean BMI and the prevalences of overweight and obesity by using a population-weighted average. Standard deviations were estimated using standard statistical relationships.[2]

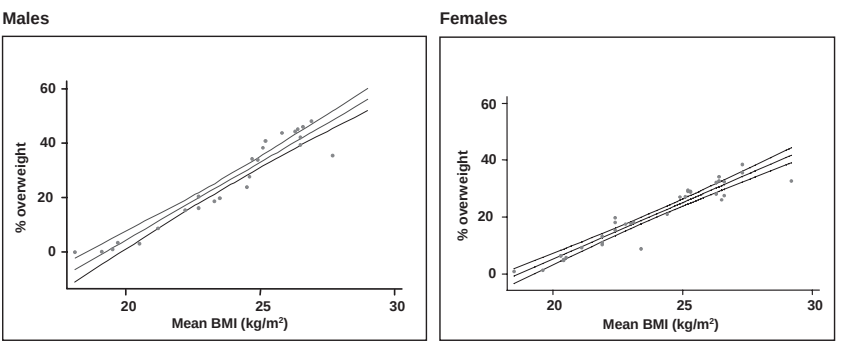
For simplicity, a simple average of the standard errors of the prevalences of overweight or obesity was used to obtain subregional estimates. In cases where no country data were available and the prevalences of overweight or obesity were based on predictions, the subregional standard error was that of the prediction.

4.3 Converting mean BMI to proportions of overweight and obesity and vice versa

BMI distributions are skewed in almost all age and sex categories throughout the world. Thus mean BMI with standard deviation does not accurately describe the whole BMI distribution and usually no further details of the distribution are available. However, Rose and Shipley (1990) showed that the prevalence of obesity (BMI ≥30 kg/m^2) was highly correlated with mean BMI in the selected group of adults, the prevalence of obesity increasing by 4.22% per unit (1 kg/m^2) increase in mean BMI. This approach was repeated in the present analysis, which was based on adult data (all ages ≥18 years combined) from 36 countries with continuous and categorical data for females and 26 countries with continuous and categorical data for males (Table 8.15). The mean BMI values for countries used in this estimation varied widely from 18.1 kg/m^2 to 29.2 kg/m^2. Mali was excluded from the current analyses in males because it was an outlier. Mean sex-specific BMI vs percentages of overweight and obesity are shown in Figures 8.1 and 8.2.

There is a clear positive linear association for both sexes. The regression equations that describe the graphs are:

Figure 8.1 Mean BMI and percentage of the adult population that is overweight



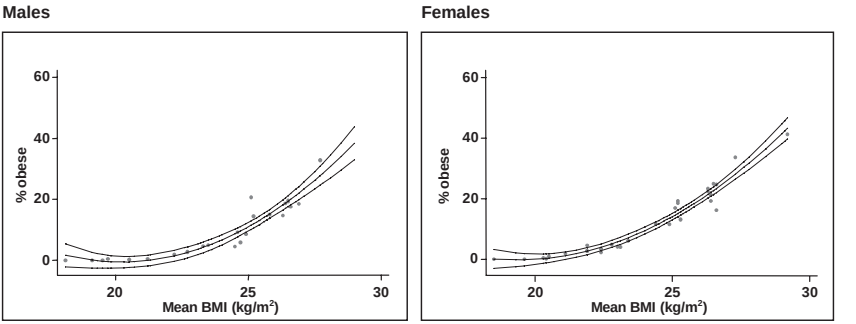
Note: These data points relate to population surveys from the countries listed in Table 8.15. The linear regression is shown together with the 95% confidence intervals of the prediction.

Table 8.15 Countries from which mean BMI data were used to derive equations for calculating the percentages of overweight and obese adults in the population

For female overweight and obesity	*For male overweight and obesity*
Australia	Australia
Bangladesh	Bangladesh
Brazil	Brazil
China	China
Denmark	Denmark
Egypt	Ethiopia
Ethiopia	Germany
Germany	Hungary
Ghana	Iceland
Guatemala	Japan
Hungary	Kuwait
Iceland	Lebanon
Japan	Nepal
Kenya	Norway
Kuwait	Republic of Korea
Lebanon	Russian Federation
Malawi[a]	Senegal
Mali	Slovakia
Nepal	Switzerland
Norway	Thailand
Peru	Turkey
Republic of Korea	United Kingdom
Russian Federation	USA
Senegal	Uzbekistan
Slovakia	Zimbabwe
South Africa[a]	
Switzerland	
Thailand	
Turkey	
United Kingdom	
United Republic of Tanzania	
USA	
Uzbekistan	
Zimbabwe	

[a] Overweight only.

Figure 8.2 Mean BMI and percentage of the adult population that is obese



Note: The predicted relationship is shown, together with the 95% confidence intervals of the prediction. The quadratic equations are given below.

$$\text{Males } (\%\ overweight) = -110.4 + 5.7 \times (mean\ BMI) \quad (1)$$

$$\text{Females } (\%\ overweight) = -74.2 + 3.97 \times (mean\ BMI) \quad (2)$$

In both cases, the β coefficient was highly statistically significant and the models accounted for >90% of the total variation. There was also a strong correlation between mean BMI and percentages of obese adults in the population, as seen in Figure 8.2.

$$\text{Males } (\%\ obese) = 205.1 - 20.4 \times (mean\ BMI) + 0.5 \times (mean\ BMI)^2 \quad (3)$$

$$\text{Females } (\%\ obese) = 168.5 - 17.4 \times (mean\ BMI) + 0.4 \times (mean\ BMI)^2 \quad (4)$$

The following conditions applied:

- the predictions had to be positive (since they are percentages);
- the predictions must be <100; and
- the sum of the predicted percentages of people in the overweight and obese categories must be ≤100 (the sum is equal to 100 in the extreme case whereby no individuals belong to the underweight or normal BMI categories).

These conditions hold simultaneously for mean BMIs of 21.3–29.7 kg/m^2 for males and 20.1–33.9 kg/m^2 for females. Predictions which fell outside these ranges were therefore not considered. These four models (Equations 1–4) for predicting the prevalences of overweight and obesity from mean BMIs were then applied to other populations when necessary.

Finally, the assumption was made that the equations held true for each age group and every country, so that the estimates could be

derived uniformly. This assumption seemed justified because wherever data were available the patterns of mean BMI and percentages of overweight and obesity were similar across age groups in most of the countries assessed.

4.4 Age and sex extrapolation

Obtaining estimates for the required age groups

Apart from data personally donated to or re-analysed by IOTF, all other data were reported in different age categories from those required for this work. To obtain data in these age categories, it was assumed that:

- the numbers of persons in each year within an age group were the same and equal to the total number of people in the age group divided by the number of years in the age group.
- the mean BMI and the standard deviation for each year within an age group were the same and equal to the mean BMI and standard deviation in the age group as a whole.

Single years or convenient groups of years were treated as different strata which were then combined to obtain the desired estimates in any age categorization.

Extrapolation to adult age groups for which no data were available

It was not always possible to obtain data for all age groups, particularly for the oldest (70–79 and ≥80 years) at a subregional level. WPR-B, where this problem was initially encountered for both sexes in people aged >70 years, is used as an example, although data subsequently became available for this subregion.

In the majority of the available data worldwide, the mean BMI increased with age and then started falling with rising age. Figure 8.3 shows the relationship between mean BMI and age in WPR-B. It was assumed that the mean BMI remained constant within each age group and changed only when moving from one age group to another.

The following regression equations describe the graphs:

$$\text{Females } (\textit{Mean BMI}) = 16.71 + 0.27 \times (\textit{age}) - 0.0024 \times (\textit{age}^2)$$

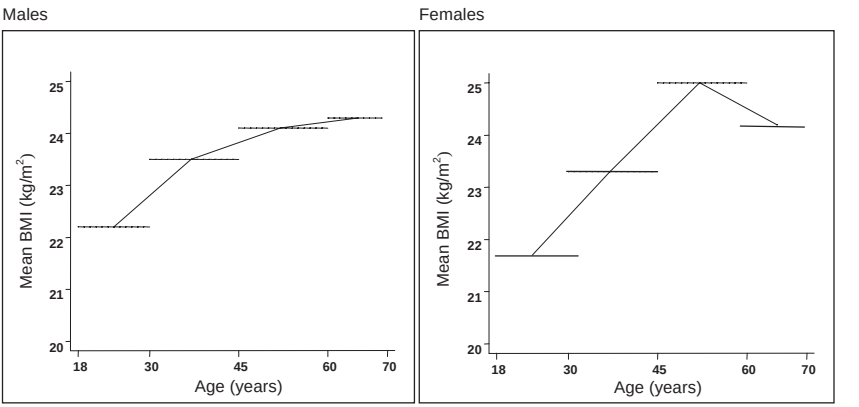
$$\text{Males } (\textit{Mean BMI}) = 16.62 + 0.14 \times (\textit{age}) - 0.0011 \times (\textit{age}^2)$$

Using these equations, the sex-specific mean BMI for each single year from age 70 years and above could be predicted. The overall mean BMI in the age group 70–79 years was set equal to the average of the mean BMIs for the individual years. The same procedure was used to estimate the mean BMI in the age group ≥80 years. The results are shown in Table 8.16. The illustrated approach was used for EMR-B.

Table 8.16 Predicted mean BMI values in the oldest age groups in WPR-B

	Mean BMI (kg/m²)	
Age group (years)	*Females*	*Males*
70–79	23.9	24.2
≥80	22.8	23.8

Figure 8.3 The relationship between mean BMI and age in WPR-B



Extrapolating data from one sex to the other

Many countries reported results either for both sexes combined or for one sex only. For example, on a subregional basis, no suitable data were available for males in AMR-D. The crude mean BMI for females in all subregions (calculated as the mean of the subregion-specific estimates for all ages combined) was 23.7 kg/m² and was 0.4 units greater than the crude mean BMI for men in all subregions ($P=0.7$). To determine whether this was the case in each age group, the age-specific differences in mean BMI between females and males were estimated for all subregions. For all age groups apart from the oldest (i.e. ≥80 years), the mean BMI for females was greater than that for males, as shown in Table 8.17.

These values served as correction factors when using data from males to estimate mean BMI for females and vice versa (without considering whether the differences between mean BMI for males and for females were significant). Thus, for each age group the respective correction factor was subtracted from mean BMI values for females to obtain the values for males. In most studies, it is found that women tend to have

Table 8.17 Age-dependent differences between mean BMI for females and for males

	Age group (years)					
	18–29	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Differences in mean BMI (females – males)	0.3	0.5	0.7	0.8	0.3	–0.1

higher BMIs than men and this seems to be related to the deposition of fat rather than metabolically active lean tissue with body-weight gain. Women lay down a lower proportion of lean tissue and thus have to put on more weight before the slower increase in the mass of lean tissue raises the basal metabolic rate sufficiently to add to the exercise costs of their greater weight and achieve an energy output which finally matches their energy intake (James and Reeds 1997).

4.5 Estimating childhood data

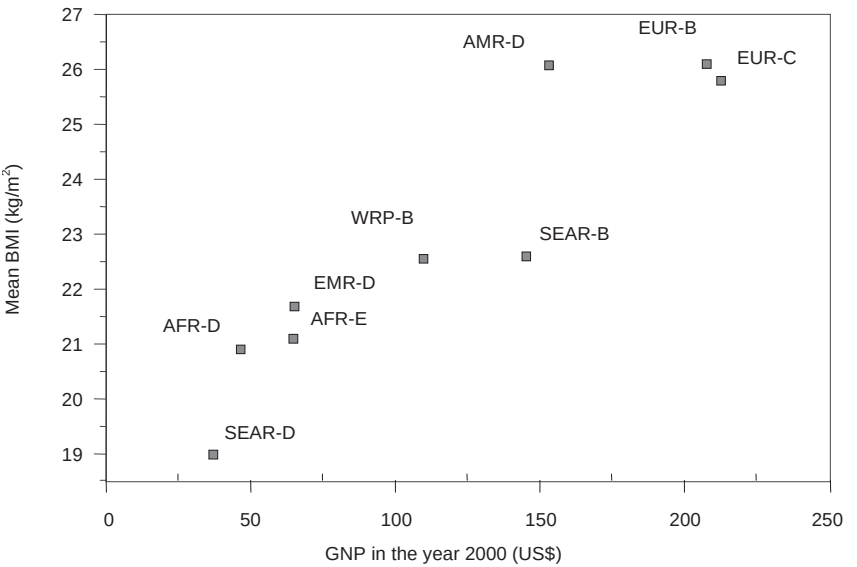
When no data were available for children for any of the countries within a subregion, an estimate was made of the distribution of BMI in children for that subregion by extrapolating from subregions with data and having equivalent economies, as judged by their gross national products (GNP). In the absence of any other data, WPR-A was extrapolated for AMR-A.

In general, plotting the mean age-standardized BMI for adults for each subregion (calculated as a simple average of population-weighted means for both sexes and for all ages ≥18 years) vs GNP (on a subregional basis) shows a broad relationship between increasing GNP and mean BMI in subregions with GNPs of <US$ 10 000 per year (Figure 8.4). For countries with the lowest GNPs, the assumption was made that BMIs for children would be similar in subregions with low GNP and low mean BMI for adults. This is subject to large uncertainty, given the complex underlying factors that determine body weight and height.

At the time of writing, no data were available for children in EMR-D and WPR-B. The GNPs of countries in EMR-D were similar to those in AFR-E; the average GNP in EMR-D was US$ 652 (with a range of US$ 110–1290), whereas the average GNP in AFR-E was US$ 647, (with a range of US$ 80–3520). Mean BMI values were also similar in both populations, with values being slightly higher in EMR-D. The distribution of BMIs in children in AFR-E was therefore applied to EMR-D. The distributions of GNP and BMI for adults in SEAR-B and WPR-B were also similar, but there were no data for children, so the AFR-E values were used for these subregions, AFR-E being the closest to these subregions economically and also in terms of BMI.

Further problems arose when the mean BMIs for children were available, but not the standard deviations, as in AMR-B. The standard

Figure 8.4 The relationship between mean BMI for adults and GNP in nine subregions



deviations of BMIs for children in AMR-B were therefore also assumed to have the same variability as in EMR-B.

Very little in the way of categorical data was available for children and it was therefore necessary to extrapolate extensively, pending appropriate data becoming available.

4.6 The estimated mean BMI and standard deviation for each subregion, by age and sex

These data are presented in the standard format proposed for the CRA project. The mean BMIs for each year for ages 5–17 years inclusive for males and females separately were obtained and are given in Tables 8.18 and 8.19.

The initial BMI analyses were made as previously, considering children in 1-year age groups, firstly for the countries with data. From these values, the mean BMIs of the 1-year age groups within the subregion were estimated. Assuming equivalent numbers of people in each year of each specified age group, it was possible to provide mean BMIs, standard deviations and confidence intervals for the age groups 5–14 years and 15–29 years used in the CRA analyses. It was recognized that these values could not be used in the usual way to predict different categories of excess weight because of the normal changes in body weight

Table 8.18 The mean BMIs for children and adults in all subregions, by sex and age[a]

		Mean BMI (kg/m²) Age group (years)																		
Subregion	*Sex*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	14.2	14.0	14.1	14.1	14.5	14.6	14.7	14.9	15.1	15.7	16.1	16.3	16.9	20.1	21.2	21.7	20.5	20.5	20.0
	Female	13.9	13.6	13.8	14.0	14.0	14.5	15.1	15.1	15.9	17.0	17.2	19.0	18.9	21.3	22.1	21.0	21.0	20.2	20.8
AFR-E	Male	14.1	13.8	13.8	13.9	13.9	14.1	14.5	16.2	16.1	16.7	17.5	17.8	18.1	19.6	21.0	21.2	20.8	22.0	19.8
	Female	13.9	13.6	13.6	13.8	14.1	14.1	14.6	16.9	17.0	17.8	18.7	19.4	20.2	21.7	22.9	22.8	22.3	20.4	18.9
AMR-A	Male	15.9	16.4	16.9	17.2	18.2	18.5	19.4	20.0	20.5	22.5	22.2	22.5	23.4	24.5	26.4	27.6	27.4	26.7	25.1
	Female	16.0	16.0	17.3	17.2	18.3	18.6	19.8	20.1	22.1	22.3	22.2	22.9	23.0	24.1	26.1	27.7	27.5	26.9	25.0
AMR-B	Male	15.4	15.6	15.7	16.0	16.3	16.7	17.0	17.5	18.2	18.8	19.4	20.1	20.4	23.7	25.0	25.6	25.5	26.1	24.7
	Female	15.2	15.6	16.0	16.2	16.6	17.0	17.5	18.6	19.8	20.4	20.8	21.5	21.7	24.1	26.2	27.3	27.1	26.9	25.5
AMR-D	Male	15.8	15.5	14.9	15.3	15.2	15.1	15.9	16.0	17.1	17.6	18.8	19.4	20.1	24.1	25.3	25.9	26.0	26.3	26.3
	Female	15.6	15.3	15.2	15.1	14.9	14.7	16.0	16.7	18.9	19.2	20.5	21.7	22.1	24.4	25.8	26.6	26.8	26.6	26.2
EMR-B	Male	15.4	15.7	16.9	16.7	17.9	17.4	17.6	19.7	19.5	21.3	20.8	22.3	23.8	21.9	24.6	25.3	24.3	23.1	23.5
	Female	15.2	15.4	16.4	17.2	16.3	18.0	18.9	19.1	20.5	21.7	22.0	21.6	21.4	22.8	25.8	26.5	25.5	23.3	26.0
EMR-D	Male	14.1	13.8	13.8	13.9	13.9	14.1	14.5	16.2	16.1	16.7	17.5	17.8	18.1	20.7	21.8	21.9	21.6	21.0	20.1
	Female	13.9	13.6	13.6	13.8	14.1	14.1	14.6	16.9	17.0	17.8	18.7	19.4	20.2	22.3	23.8	22.8	22.3	21.3	18.9

EUR-A	Male	16.2	16.6	16.5	16.7	16.9	17.3	18.1	18.6	19.6	19.8	21.0	22.2	22.5	24.7	26.3	27.2	27.8	27.5	26.1
	Female	16.3	16.2	16.5	16.4	17.2	17.6	18.7	18.9	20.1	20.5	22.1	22.3	22.9	23.5	25.1	27.5	28.4	27.8	25.8
EUR-B	Male	15.1	15.5	15.5	16.0	16.7	17.2	18.6	18.4	18.6	19.3	19.7	20.4	20.6	22.1	25.0	26.5	27.3	25.8	24.8
	Female	15.0	15.2	15.5	15.8	16.4	16.9	17.6	18.2	18.9	19.9	20.0	20.5	21.4	23.2	25.6	27.9	28.8	29.0	27.5
EUR-C	Male	16.4	15.7	17.0	17.4	17.1	17.8	18.0	18.8	19.6	20.5	20.6	21.4	21.6	23.3	25.2	26.1	25.9	25.2	24.8
	Female	15.7	15.6	16.4	16.9	17.1	17.1	17.9	18.2	19.4	20.2	21.3	21.3	21.3	23.1	26.5	28.4	28.7	27.2	25.4
SEAR-B	Male	14.1	13.8	13.8	13.9	13.9	14.1	14.5	16.2	16.1	16.7	17.5	17.8	18.1	20.8	22.6	23.4	23.0	22.6	22.6
	Female	13.9	13.6	13.6	13.8	14.1	14.1	14.6	16.9	17.0	17.8	18.7	19.4	20.2	20.8	22.7	23.9	24.3	22.5	22.5
SEAR-D	Male	13.8	14.3	13.9	13.6	14.1	14.2	14.4	15.2	14.8	15.8	16.3	17.2	17.7	19.0	19.6	19.0	19.2	18.0	19.4
	Female	14.1	14.2	13.8	14.2	14.5	14.2	14.8	15.2	17.1	18.0	18.5	19.1	20.3	19.5	20.8	21.4	18.9	19.6	16.0
WPR-A	Male	16.3	15.6	15.9	16.5	16.8	17.6	18.1	19.2	19.9	20.4	20.9	21.4	21.8	22.4	23.7	23.9	23.3	22.8	21.9
	Female	16.2	15.3	15.6	16.0	16.4	17.0	17.5	18.4	19.5	19.8	20.1	20.5	20.5	20.9	22.5	23.8	23.9	23.3	22.6
WPR-B	Male	14.1	13.8	13.8	13.9	13.9	14.1	14.5	16.2	16.1	16.7	17.5	17.8	18.1	21.5	22.8	23.1	22.8	22.3	20.8
	Female	13.9	13.6	13.6	13.8	14.1	14.1	14.6	16.9	17.0	17.8	18.7	19.4	20.2	22.5	22.8	23.5	23.6	22.6	21.1

[a] Data analysed by 1-year age groups in childhood.

Note: Figures in shaded cells were estimated as outlined in the methodology section.

Table 8.19 The standard deviations of the BMIs for children and adults in all subregions, by sex and age[a]

		Age group (years)																		
Subregion	*Sex*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	1.5	1.3	1.9	1.5	1.1	1.2	1.7	1.3	1.5	1.6	1.7	2.0	2.0	2.0	3.4	5.4	2.9	2.9	2.7
	Female	1.3	1.3	1.3	1.2	1.3	1.6	1.6	1.9	2.1	3.0	2.4	2.6	2.7	3.8	3.9	4.6	3.8	3.6	2.3
AFR-E	Male	1.4	1.2	1.2	1.2	1.1	1.4	1.0	3.0	2.1	2.3	2.4	2.4	2.4	3.1	5.2	4.6	4.2	3.6	1.8
	Female	1.3	1.3	1.3	1.3	1.2	1.8	1.4	2.6	2.5	3.0	2.9	2.9	2.9	4.2	4.8	5.2	5.1	5.1	2.4
AMR-A	Male	1.7	2.5	2.9	4.2	4.3	4.3	4.4	4.5	4.5	4.7	4.7	4.7	4.8	4.8	5.0	5.0	4.4	4.3	4.1
	Female	4.0	4.0	4.1	4.1	4.3	4.3	4.4	4.5	4.7	4.7	4.7	4.8	4.8	5.9	7.1	6.5	6.1	5.8	4.9
AMR-B	Male	1.5	1.4	2.3	1.9	2.8	4.1	3.8	3.7	3.7	3.9	3.6	3.5	3.2	4.1	4.1	4.3	4.0	3.9	3.8
	Female	1.4	2.1	2.8	3.8	3.3	3.6	3.9	4.1	4.1	4.7	4.0	4.2	5.1	4.8	5.1	5.3	5.2	5.2	4.3
AMR-D	Male	1.1	1.0	1.0	1.3	1.3	1.3	1.4	1.3	1.2	1.4	1.5	1.5	1.6	2.8	3.8	4.0	3.5	3.5	3.5
	Female	1.2	1.0	1.0	1.8	1.8	1.8	1.8	1.8	2.3	2.5	1.7	2.4	2.6	3.4	4.4	4.6	4.1	4.1	4.1
EMR-B	Male	1.5	2.0	2.9	2.1	3.0	2.4	2.9	4.5	4.0	3.4	3.8	3.2	3.7	3.8	4.1	3.9	4.0	3.7	3.6
	Female	1.4	1.9	2.2	5.2	2.6	2.9	3.4	4.1	4.3	4.8	5.3	5.7	4.9	4.1	5.1	5.3	4.8	3.7	5.8
EMR-D	Male	1.4	1.2	1.2	1.2	1.1	1.4	1.0	3.0	2.1	2.3	2.4	2.4	2.4	5.6	6.9	4.8	5.8	5.8	5.8
	Female	1.3	1.3	1.3	1.3	1.2	1.8	1.4	2.6	2.5	3.0	2.9	2.9	2.9	7.3	8.5	6.5	7.4	7.4	7.4

EUR-A	Male	1.2	3.9	2.1	2.3	2.4	2.4	2.9	2.9	3.2	3.0	2.9	3.6	3.6	3.8	3.7	3.9	3.8	3.8	3.7
	Female	1.7	2.2	2.0	2.1	2.6	2.6	3.2	3.1	3.1	3.2	4.2	3.9	3.4	4.1	4.7	4.7	5.2	4.9	4.3
EUR-B	Male	1.6	2.1	2.2	2.8	2.7	2.6	3.0	2.9	2.9	3.1	2.7	2.6	2.4	3.2	3.9	3.8	3.7	3.6	4.8
	Female	2.0	1.8	2.2	2.3	2.4	2.7	2.9	3.0	2.7	2.9	2.6	2.6	3.1	4.2	5.2	6	5.1	4.7	4.8
EUR-C	Male	2.5	2.6	2.9	3.2	2.6	3.0	2.6	3.1	3.1	3.3	2.3	2.3	2.6	2.9	3.5	3.9	3.8	3.9	3.9
	Female	2.5	2.6	2.8	3.1	3.3	2.9	2.9	2.8	2.5	3.1	3.1	3.0	2.4	4.2	5.0	5.1	5.2	5.1	5.0
SEAR-B	Male	1.4	1.2	1.2	1.2	1.1	1.4	1.0	3.0	2.1	2.3	2.4	2.4	2.4	2.2	2.8	2.3	3.9	2.5	2.5
	Female	1.3	1.3	1.3	1.3	1.2	1.8	1.4	2.6	2.5	3.0	2.9	2.9	2.9	3.6	2.3	2.1	4.1	4.5	4.5
SEAR-D	Male	1.4	0.8	0.9	1.2	1.1	0.9	1.0	1.4	1.4	1.3	1.6	1.7	1.7	2.1	3.2	2.8	2.9	2.7	3.1
	Female	0.9	1.2	1.3	1.9	1.5	1.2	1.4	1.6	2.7	2.1	2.2	2.6	2.2	3.2	4.0	4.6	3.7	5.9	2.0
WPR-A	Male	2.4	1.3	1.6	1.8	2.0	2.3	2.5	2.6	2.9	2.9	3.0	2.9	3.0	3.5	3.4	3.2	3.2	3.2	3.6
	Female	1.8	1.1	1.2	1.3	1.5	1.6	1.8	2.0	2.1	2.1	2.2	2.2	2.2	3.8	4.1	3.7	3.7	3.8	3.7
WPR-B	Male	1.4	1.2	1.2	1.2	1.1	1.4	1.0	3.0	2.1	2.3	2.4	2.4	2.4	2.7	3.3	3.1	3.3	3.6	1.8
	Female	1.3	1.3	1.3	1.3	1.2	1.8	1.4	2.6	2.5	3.0	2.9	2.9	2.9	5.2	4.1	3.6	5.0	3.7	1.9

[a] Data analysed by 1-year age groups in childhood.

Note: Figures in shaded cells were estimated as outlined in the methodology section.

Table 8.20 Mean BMIs by subregion, sex and age

		Mean BMI (kg/m^2) Age group (years)						
Subregion	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	14.6	19.2	21.2	21.7	20.5	20.5	20.0
	Female	14.6	20.6	22.1	21.0	21.0	20.2	20.8
AFR-E	Male	14.7	19.2	21.0	21.2	20.8	22.0	19.8
	Female	14.9	21.2	22.9	22.8	22.3	20.4	18.9
AMR-A	Male	18.5	24.1	26.4	27.6	27.4	26.7	25.1
	Female	18.8	23.8	26.1	27.7	27.5	26.9	25.0
AMR-B	Male	16.7	22.9	25.0	25.6	25.5	26.1	24.7
	Female	17.3	23.5	26.2	27.3	27.1	26.9	25.5
AMR-D	Male	15.8	23.0	25.3	25.9	26.0	26.3	26.3
	Female	16.1	23.7	25.8	26.6	26.8	26.6	26.2
EMR-B	Male	17.8	22.0	24.6	25.3	24.3	23.1	23.5
	Female	17.9	22.5	25.8	26.5	25.5	23.3	26.0
EMR-D	Male	14.7	20.0	21.8	21.9	21.6	21.0	20.1
	Female	14.9	21.6	23.8	22.8	22.3	21.3	18.9
EUR-A	Male	17.6	24.2	26.3	27.2	27.8	27.5	26.1
	Female	17.9	23.3	25.1	27.5	28.4	27.8	25.8
EUR-B	Male	17.1	21.7	25.0	26.5	27.3	25.8	24.8
	Female	17.0	22.7	25.6	27.9	28.8	29.0	27.5
EUR-C	Male	18.0	22.9	25.2	26.1	25.9	25.2	24.8
	Female	17.6	22.7	26.5	28.4	28.7	27.2	25.4
SEAR-B	Male	14.7	20.2	22.6	23.4	23.0	22.6	22.6
	Female	15.0	20.5	22.7	23.9	24.3	22.5	22.5
SEAR-D	Male	14.4	18.6	19.6	19.0	19.2	18.0	19.4
	Female	15.0	19.5	20.8	21.4	18.9	19.6	16.0
WPR-A	Male	17.7	22.2	23.7	23.9	23.3	22.8	21.9
	Female	17.2	20.8	22.5	23.8	23.9	23.3	22.6
WPR-B	Male	14.7	20.8	22.8	23.1	22.8	22.3	20.8
	Female	15.0	21.9	22.8	23.5	23.6	22.6	21.1

Note: Figures in shaded cells were estimated as outlined in the methodology section.

and BMI during childhood development. The data on mean BMIs are presented in Table 8.20. Table 8.21 contains the standard deviations for these estimates, while Table 8.22 lists the number of subjects measured and used in this analysis, in order to provide a preliminary perspective on the validity of these estimates.

4.7 Final estimates of the prevalence of overweight and obesity, by age, sex and subregion

Table 8.23 shows the subregional prevalences of overweight, as defined by a BMI of between 25.0 and 29.9 kg/m^2. For the age groups 5–14 years

Table 8.21 The standard deviations of the mean BMI estimates by subregion, sex and age

		Age group (years)						
Subregion	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	1.5	2.0	3.4	5.4	2.9	2.9	2.7
	Female	1.6	3.5	3.9	4.6	3.8	3.6	2.3
AFR-E	Male	1.6	2.9	5.2	4.6	4.2	3.6	1.8
	Female	1.7	3.9	4.8	5.2	5.1	5.1	2.4
AMR-A	Male	3.8	4.8	5.0	5.0	4.4	4.3	4.1
	Female	4.3	5.7	7.1	6.5	6.1	5.8	4.9
AMR-B	Male	2.9	4.0	4.1	4.3	4.0	3.9	3.8
	Female	3.4	4.7	5.1	5.3	5.2	5.2	4.3
AMR-D	Male	1.2	2.5	3.8	4.0	3.5	3.5	3.5
	Female	1.7	3.1	4.4	4.6	4.1	4.1	4.1
EMR-B	Male	2.9	3.7	4.1	3.9	4.0	3.7	3.6
	Female	3.3	4.4	5.1	5.3	4.8	3.7	5.8
EMR-D	Male	1.6	4.9	6.9	4.8	5.8	5.8	5.8
	Female	1.8	6.3	8.5	6.5	7.4	7.4	7.4
EUR-A	Male	2.6	3.7	3.7	3.9	3.8	3.8	3.7
	Female	2.6	4.1	4.7	4.7	5.2	4.9	4.3
EUR-B	Male	2.6	3.1	3.9	3.8	3.7	3.6	4.8
	Female	2.5	3.9	5.2	6.0	5.1	4.7	4.8
EUR-C	Male	2.9	2.8	3.5	3.9	3.8	3.9	3.9
	Female	2.8	3.9	5.0	5.1	5.2	5.1	5.0
SEAR-B	Male	1.6	2.2	2.8	2.3	3.9	2.5	2.5
	Female	1.8	3.5	2.3	2.1	4.1	4.5	4.5
SEAR-D	Male	1.1	2.0	3.2	2.8	2.9	2.7	3.1
	Female	1.6	3.0	4.0	4.6	3.7	5.9	2.0
WPR-A	Male	2.2	3.4	3.4	3.2	3.2	3.2	3.6
	Female	1.7	3.5	4.1	3.7	3.7	3.8	3.7
WPR-B	Male	1.6	2.6	3.3	3.1	3.3	3.6	1.8
	Female	1.8	4.2	4.1	3.6	5.0	3.7	1.9

Note: Figures in shaded cells were estimated as outlined in the methodology section.

and 15–29 years, these prevalence figures can be used in their condensed form because allowances have already been made for the age- and sex-specific cut-off points in the BMI percentiles corresponding to a BMI of 25.0 kg/m^2 at age 18 years. The rather crude nature of the calculation of BMI does not take into account the different ages at which pubertal changes occur in different subregions of the world; but the figures for prevalence are more robust and usable than the data on mean BMI described earlier, given the implications of definitions and cut-offs for overweight and obesity among adolescents.

Table 8.22 The number of subjects used when estimating the mean and standard deviation in each age category for Tables 8.20 and 8.21

		Age group (years)						
Subregion	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	1254	2394	2008	1625	474	236	32
	Female	1180	4333	3695	1893	450	196	24
AFR-E	Male	3120	3899	1969	1295	879	333	18
	Female	3340	9099	5687	2265	1514	519	4
AMR-A	Male	2822	8585	11133	5286	2530	1773	695
	Female	2944	13641	14664	6405	2455	1825	781
AMR-B	Male	59127	39400	5590	3829	798	13	—
	Female	57726	38066	7290	5603	865	17	—
AMR-D	Male	1378	204	—	—	—	—	—
	Female	1325	7120	5652	337	—	—	—
EMR-B	Male	1000	4761	3717	2060	1170	227	102
	Female	1271	5541	3617	2193	1099	267	70
EMR-D	Male	—	8535	7626	4641	2482	1870	—
	Female	—	12129	11256	5103	2354	1418	—
EUR-A	Male	8549	8935	13341	14339	4471	2581	359
	Female	9215	10132	14966	16798	5615	3413	566
EUR-B	Male	4063	3472	1402	2381	499	298	52
	Female	4240	6138	3184	3411	1012	353	63
EUR-C	Male	1202	1966	2776	1949	860	210	79
	Female	1150	2171	3349	2415	1442	561	233
SEAR-B	Male	—	503	395	215	93	27	13
	Female	—	1273	988	423	105	20	12
SEAR-D	Male	392	919	765	412	159	36	5
	Female	392	2430	2224	790	134	38	3
WPR-A	Male	949	5074	7784	7676	4303	2191	482
	Female	895	5557	9390	9418	5179	3023	767
WPR-B	Male	—	3014	2636	2406	1397	—	—
	Female	—	4307	4026	3499	1882	—	—

— No data.

The prevalences of obesity corresponding to the subregional groupings by sex and age are listed in Table 8.24. Again, the accepted WHO criterion is taken, i.e. BMI ≥30 kg/m^2, and children have been assessed in relation to the cut-off percentile for BMI proposed by IOTF. This percentile varies by age and sex during childhood as growth and pubertal changes occur, but these collated values provide an overall estimate of the prevalences of substantial excess weight in both children and adults.

The estimated standard errors for the prevalences of overweight and obesity are given in Tables 8.25 and 8.26.

Table 8.23 The prevalence of overweight in children and adults, by subregion, sex and age

		Prevalence of overweight (%) Age group (years)						
Subregion	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	0.0	1.3	3.7	11.0	4.9	6.7	0.7
	Female	0.2	5.0	11.7	8.6	13.7	7.4	0.8
AFR-E	Male	0.4	0.1	0.5	1.3	1.9	0.7	0.0
	Female	0.7	5.9	8.4	7.1	1.2	1.8	0.0
AMR-A	Male	17.0	26.9	41.8	43.9	45.9	43.6	42.7
	Female	19.0	19.3	22.6	28.5	34.6	33.4	35.0
AMR-B	Male	19.5	30.1	45.3	47.2	43.9	42.3	42.8
	Female	19.8	28.0	39.0	39.5	40.2	31.1	29.9
AMR-D	Male	16.8	24.0	33.8	37.2	38.8	40.6	40.6
	Female	15.0	26.3	38.0	41.2	32.3	31.5	30.0
EMR-B	Male	15.1	18.1	33.1	37.2	23.8	25.5	36.4
	Female	17.7	17.9	39.5	37.8	25.1	24.0	25.0
EMR-D	Male	0.3	4.8	11.4	11.9	10.4	7.9	5.0
	Female	0.7	12.2	22.6	23.9	13.9	9.1	0.0
EUR-A	Male	15.3	29.7	47.4	53.2	52.8	57.2	46.9
	Female	18.0	17.3	28.1	39.4	41.9	50.0	37.7
EUR-B	Male	16.9	14.3	37.8	42.7	40.8	43.9	28.8
	Female	15.0	17.6	30.8	32.1	32.8	42.9	36.5
EUR-C	Male	20.0	20.5	37.1	41.6	39.3	42.2	35.8
	Female	16.9	17.1	33.6	37.8	38.1	36.3	31.0
SEAR-B	Male	0.3	2.7	19.0	27.0	24.7	17.5	17.5
	Female	0.7	5.5	20.3	34.6	37.1	21.9	21.9
SEAR-D	Male	0.0	0.0	6.6	9.4	5.4	4.9	0.0
	Female	0.0	3.9	12.9	18.8	8.7	6.8	0.0
WPR-A	Male	17.2	17.2	27.3	28.8	24.0	20.9	14.4
	Female	19.3	9.4	15.8	25.0	28.5	26.3	22.3
WPR-B	Male	1.5	13.8	24.3	27.0	28.3	13.6	9.0
	Female	1.4	10.5	18.7	21.8	21.6	14.0	9.6

Note: Figures in shaded cells were estimated as outlined in the methodology section.

5. Risk factor–disease relationships

This section reviews evidence for causality relating BMI to different disease and injury outcomes; provides a rationale for choosing 21.0±1.0 kg/m^2 (mean±SD) as the BMI value of theoretical population minimum-risk of adverse health effects; and summarizes the sources of data for the hazard estimates required for estimates of the attributable fraction for the population. To date, there have been no systematic reviews of cohort studies that present age- and sex-specific associations of adverse health outcomes with BMI as a continuous variable (rather than for

Table 8.24 The estimated prevalences of obesity, by subregion, sex and age

		Prevalence of obesity (%) Age group (years)						
Subregion	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	0.2	0.0	0.0	0.3	1.2	0.3	0.0
	Female	0.1	0.9	2.7	0.9	2.8	0.4	0.0
AFR-E	Male	0.2	0.0	0.1	0.0	0.0	0.4	0.0
	Female	0.1	0.5	2.5	2.1	0.9	0.4	0.0
AMR-A	Male	8.4	11.5	19.0	24.2	23.9	19.5	8.0
	Female	9.4	12.7	23.7	32.2	28.9	24.3	15.0
AMR-B	Male	7.1	9.2	18.5	22.2	19.7	20.0	20.7
	Female	5.7	11.8	28.5	38.5	32.8	22.6	20.8
AMR-D	Male	3.2	3.3	9.0	12.1	16.3	18.1	18.1
	Female	2.6	5.6	14.6	19.4	24.6	23.3	20.8
EMR-B	Male	6.1	3.7	6.8	8.9	6.2	3.0	9.1
	Female	3.3	6.4	14.5	17.1	18.0	15.8	25.0
EMR-D	Male	0.2	0.9	1.7	1.7	2.0	2.5	0.0
	Female	0.1	4.4	12.4	13.9	7.3	4.6	0.0
EUR-A	Male	9.4	6.9	14.4	18.7	22.7	19.2	11.6
	Female	13.2	9.5	13.5	22.5	31.6	34.3	15.7
EUR-B	Male	3.2	2.4	11.0	15.1	15.0	12.6	13.5
	Female	2.6	7.2	22.8	31.6	32.3	39.5	33.3
EUR-C	Male	5.7	1.9	9.2	14.7	14.7	8.9	9.0
	Female	3.7	5.7	22.2	35.4	36.4	26.8	18.2
SEAR-B	Male	0.2	0.5	2.3	2.3	2.2	7.5	7.5
	Female	0.1	0.6	3.1	5.5	5.7	9.4	9.4
SEAR-D	Male	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Female	0.0	0.8	2.9	4.9	0.8	0.2	0.0
WPR-A	Male	8.4	7.2	4.7	4.5	3.7	3.3	1.9
	Female	9.4	3.5	4.5	5.7	6.5	5.3	3.5
WPR-B	Male	0.4	1.2	4.8	6.5	7.6	0.4	0.0
	Female	0.3	1.7	6.7	9.7	10.0	3.4	1.1

Note: Figures in shaded cells were estimated as outlined in the methodology section. The obesity rates in children were particularly variable in some subregions, e.g. EUR-B, because they were based on relatively small samples and the obesity cut-off point reflects an extreme percentile distribution of BMIs.

cut-off points, so that the full impact can be captured), and all affected outcomes and for different subregions. Therefore some trade-offs had to be made to obtain the best estimates of hazard size for this project. The following analysis is based on a series of systematic reviews, the two principal ones being of BMI and vascular disease, and BMI and cancer.

Table 8.25 The estimated standard errors of the measured or predicted prevalence of overweight, by subregion, sex and age

		Standard errors of the prevalence of overweight *Age group (years)*						
Subregion	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	0.05	1.74	2.24	2.47	2.37	3.65	2.05
	Female	0.21	0.84	0.99	1.62	2.43	3.26	2.70
AFR-E	Male	0.27	0.75	1.11	2.22	2.54	2.27	—
	Female	0.16	0.71	1.19	2.21	1.28	1.52	—
AMR-A	Male	2.29	2.32	2.00	2.31	2.59	2.57	2.40
	Female	2.39	1.34	0.80	1.06	1.33	1.11	1.50
AMR-B	Male	5.30	3.42	2.26	2.60	2.80	2.89	—
	Female	5.50	1.54	0.82	0.98	0.84	0.84	—
AMR-D	Male	3.15	0.61	—	—	—	—	—
	Female	2.87	1.50	1.60	6.45	—	—	—
EMR-B	Male	5.31	3.92	8.02	3.50	3.72	4.14	14.50
	Female	5.51	2.52	2.42	2.86	2.98	3.36	21.60
EMR-D	Male	0.26	0.00	—	—	—	—	—
	Female	0.16	1.46	1.10	5.00	—	—	—
EUR-A	Male	2.85	2.32	1.66	1.64	2.59	2.04	2.90
	Female	2.75	1.92	1.01	1.23	2.23	1.65	2.60
EUR-B	Male	3.15	2.15	3.03	3.79	5.05	7.50	6.30
	Female	2.84	1.09	1.24	2.27	4.30	5.75	6.10
EUR-C	Male	3.74	2.28	1.70	1.95	4.50	12.65	11.65
	Female	3.49	2.05	1.35	1.75	4.30	6.55	7.85
SEAR-B	Male	0.25	0.64	2.00	3.00	4.50	7.30	10.50
	Female	0.15	0.56	1.30	2.30	4.70	9.20	11.90
SEAR-D	Male	0.00	3.32	2.52	3.20	4.21	—	—
	Female	0.00	0.85	1.58	1.80	2.00	4.90	—
WPR-A	Male	2.32	2.23	1.72	1.78	2.11	2.43	3.59
	Female	2.42	1.36	0.85	0.95	1.19	1.36	2.19
WPR-B	Male	0.24	2.25	2.60	2.90	2.71	2.80	3.18
	Female	0.14	0.65	0.82	0.84	0.89	0.96	0.87

— No data.

Note: Figures in shaded cells were estimated as outlined in the methodology section.

5.1 Evidence for causality

Traditionally, excess body weight and obesity have been considered as risk factors in epidemiological terms, despite the fact that the International Statistical Classification of Diseases (ICD) has specified obesity as a disease in its own right since 1948. The effects of excess weight as a risk factor are at least partly mediated through changes in other risk

Table 8.26 The estimated standard errors of the measured or predicted prevalences of obesity, by subregion, sex and age

		Standard errors of the prevalence of obesity *Age group (years)*						
Subregion	*Sex*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	0.11	0.53	0.67	0.89	0.85	1.10	—
	Female	0.11	0.43	0.73	1.21	1.00	1.03	—
AFR-E	Male	0.27	0.35	0.66	0.35	0.38	1.51	—
	Female	0.16	0.34	0.90	1.89	2.06	1.48	—
AMR-A	Male	1.80	1.19	0.90	1.14	1.57	1.62	1.20
	Female	1.90	1.09	0.99	0.92	1.08	1.05	1.40
AMR-B	Male	3.40	1.52	1.09	1.61	1.32	0.95	—
	Female	2.10	0.92	0.74	0.94	0.79	0.63	—
AMR-D	Male	1.01	0.11	—	—	—	—	—
	Female	1.31	0.73	1.45	5.50	—	—	—
EMR-B	Male	3.40	1.99	2.35	2.40	2.35	2.68	8.70
	Female	2.10	1.58	2.31	3.14	3.42	3.46	25.0
EMR-D	Male	0.26	0.00	—	—	—	—	—
	Female	0.16	0.77	1.20	4.10	—	—	—
EUR-A	Male	1.71	1.86	1.46	2.29	2.36	1.42	2.25
	Female	1.98	1.84	0.99	1.21	2.21	1.39	2.25
EUR-B	Male	1.00	0.78	2.76	2.40	4.40	4.30	4.70
	Female	1.29	0.49	1.04	2.37	4.15	5.55	5.90
EUR-C	Male	1.94	0.86	1.25	1.65	4.10	2.10	7.50
	Female	1.37	0.97	1.15	1.75	4.25	6.05	9.00
SEAR-B	Male	0.25	0.24	0.70	1.00	1.50	5.10	7.30
	Female	0.15	0.16	0.60	1.10	2.30	6.50	8.40
SEAR-D	Male	0.00	0.00	—	—	—	—	—
	Female	0.00	0.23	0.50	0.80	—	—	—
WPR-A	Male	1.80	1.15	0.91	1.04	1.26	1.46	2.05
	Female	1.90	1.02	0.74	0.89	1.09	1.24	1.74
WPR-B	Male	0.24	0.70	0.85	1.17	1.11	0.90	—
	Female	0.14	0.46	0.70	1.08	1.14	1.00	0.63

— No data.

Note: Figures in shaded cells were estimated as outlined in the methodology section.

factors, such as blood pressure and abnormal blood lipids. More recently, it has become clear that excess weight is not only of value in predicting the risk of suffering from particular diseases, but that intentional weight loss reduces these intermediate risk factors (such as high blood pressure); and experimental evidence is also emerging for reduced disease outcomes (Sjöström et al. 1999). This experimental evidence provides the strongest evidence of causality and is summarized in the following sections. The observational evidence from cohort studies linking

Table 8.27 Health outcomes considered in relation to excess body-weight gain

	ICD revision				
Disease	*ICD-6/7*[a]	*ICD-8*[b]	*ICD-9 BTL*	*ICD-9*	*ICD-10*
Ischaemic heart disease	A081	A083	B27	410–414, Proportion of: 427.1, 427.4, 427.5, 428, 429.0–429.2, 429.9, 440.9	I20–I25
Cerebrovascular disease	A070	A085	B29	430–438	I60–I69
Hypertensive disease	A083, A084	A082	B26	401–405	I10–I13
Type II diabetes	…	…	…	…	E11
Osteoarthritis	…	…	…	715	M15–M19
Colon and rectum cancers	A047, A048	A048, A049	B093, B094	153, 154	C18–C21
Breast cancer (females only)	A051	A054	B113	174	C50
Endometrial cancer	A053	A056	B122	179, 182	C54–C55

BTL Basic tabulation list.

… Not available.

[a] Intermediate list of 150 causes.

[b] List A: list of 150 causes.

BMI to adverse health outcomes is also described in more detail in the subsequent sections, as these studies provided estimates of exposure–disease hazard size. Together, these sources of data show that the associations found between BMI and many disease outcomes satisfy the widely-accepted criteria for causal relationships: they are strong, consistent, have a dose–response relationship and are biologically plausible (Hill 1965).

5.2 Health outcomes caused by excess body weight

The health outcomes that were considered are presented in Table 8.27; the causal relationship between excess body weight and these conditions is dealt with later.

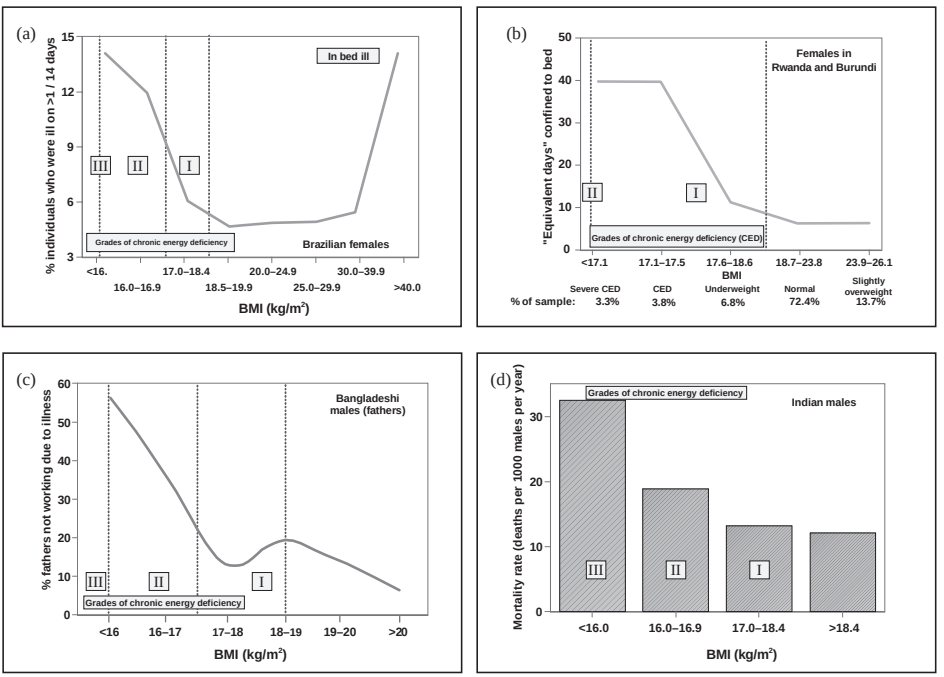
5.3 The optimum population BMI (theoretical-minimum-risk)

The theoretical-minimum-risk distribution of BMI in the population is that which is associated with the lowest health risks related to BMI. This choice of the theoretical minimum needs to take into account the fact that there are hazards associated with low as well as high BMIs (Shetty

and James 1994). The optimum trade-off is based on a balance between the level down to which the risk of developing diseases associated with high BMI persists (described in subsequent sections, but generally 20 kg/m^2, once the confounding effects of smoking and co-morbid prevalent diseases are accounted for) and the health hazards and reduced physical capacity found at lower BMIs. The handicaps related to underweight stem from a chronic dietary energy deficit and other phenomena related to undernutrition. These are summarized in Figures 8.5 and 8.6.

Analyses have been made (James and Francois 1994) of the relationship between the proportion of adults in the population who are underweight (i.e. BMI of <18.5 kg/m^2) and the median BMI of the population. This definition of underweight was accepted by WHO in both the 1995

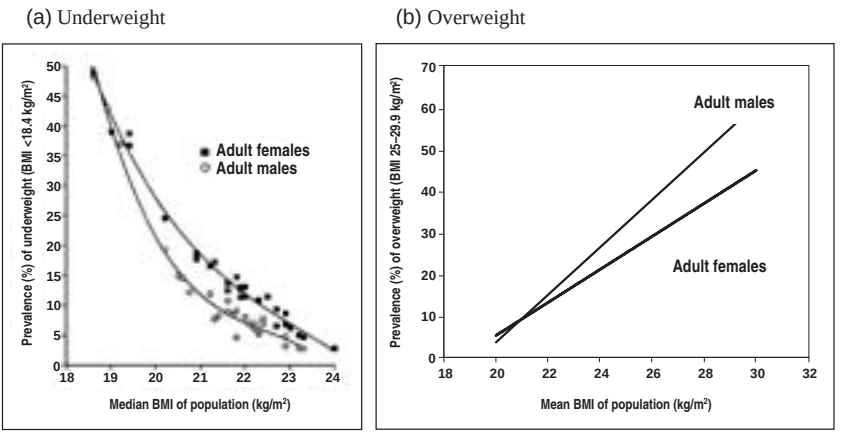
Figure 8.5 Morbidity and mortality at lower BMIs



Note: Data for Figure 8.5 were collated by Shetty and James (1994).

Source: (a) de Vasconcellos, based on data presented at a meeting "Functional Significance of Low Body Mass Index (BMI)", Rome 4–6 November, 1992. Fig. 6.3: BMI and the probability of illness among Brazilian women (PNSN Survey 1989, de Vasconcellos, personal communication); (b) P. Francois, unpublished data, 1990. BMI and "equivalent days" of illness from collated times of impaired activity among women in Rwanda and Burundi, 1982; (c) Adapted from J. Pryer, 1990. BMI and loss of labour days due to illness in Bangladesh; (d) Satyanarayana et al. 1991. Mortality rates for men according to BMI categories (Hyderabad).

Figure 8.6 Median or mean BMI and the prevalence of (a) underweight and (b) overweight in different populations



Source: (a) James and Francois (1994); (b) Regression lines taken from Figure 8.1.

report on the uses of anthropometry (WHO 1995) and in the more recent report on obesity (WHO 2000). Figure 8.6(a) presents unpublished representative data obtained from 27 large national surveys of developing countries. By specifying underweight adults as those with a BMI of <18.5 kg/m^2 it becomes clear that an optimum median BMI needs to be about 22.0 or more to ensure that fewer than about 10% of women are underweight (see below).

In order to compare the proportions of people with low and high BMIs in the population at different mean BMIs, data relating underweight (i.e. BMIs of <18.5 kg/m^2), to overweight, (i.e. BMIs of ≥25.0 kg/m^2), are required. To simplify this comparison, the two figures are presented side by side in Figure 8.6, but it should be noted that they are drawn from different data sets and that the data relating to underweight are presented in relation to the median rather than the mean BMI. However, at lower BMIs the mean and median values are very similar. It can be seen that when Figures 8.6(a) and (b) are compared, a BMI of 21.0–22.0 kg/m^2 emerges as an optimum BMI at which the chances of there being substantial proportions of either underweight or overweight people in the population are minimized. At a BMI of about 21 kg/m^2, the minimum proportion of underweight and overweight people in the population is about 10% for males, according to Figure 8.6(a), and for both sexes, according to Figure 8.6(b). To achieve a proportion of only 10% of women being underweight requires that the mean BMI of the population be about 22.5 kg/m^2. However, at this mean BMI already

about 15% of the female population is overweight, according to Figure 8.6(a). Given the clear evidence for health hazards in women, even at BMIs of 23 kg/m^2 and above (Willett et al. 1995), and the modest handicaps currently evident for women within the first grade of underweight, i.e. BMIs of 17.0–18.4 kg/m^2 (James et al. 1988), we concluded that at present a universal mean BMI of 21.0 kg/m^2 should be chosen as the optimum for both sexes in populations throughout the world.

Overall, the theoretical-minimum-risk was estimated to occur at a BMI of 21.0 ± 1.0 kg/m^2 (mean ± SD). It should be noted that this is below the level which some cohort studies have estimated to be the nadir of associations with mortality. This is because of the corrections for effects of disease on BMI that have been employed here and the focus on non-fatal as well as fatal events. This optimum BMI is similar to the lower limit of the range proposed by the WHO Technical Consultation on Obesity (WHO 2000), i.e. 21.0–23.0 kg/m^2. The inclusion of the upper limit of 23.0 kg/m^2 in the original WHO Technical Consultation stemmed from a concern that in some developing countries there might be a need for higher reserves of body energy to cope with potential natural disasters and crop failures leading to food deprivation. In practice, as will become evident, the increase in the rates of diseases associated with increases in BMI is evident from BMIs of about 20 kg/m^2.

5.4 Body weight and cardiovascular disease

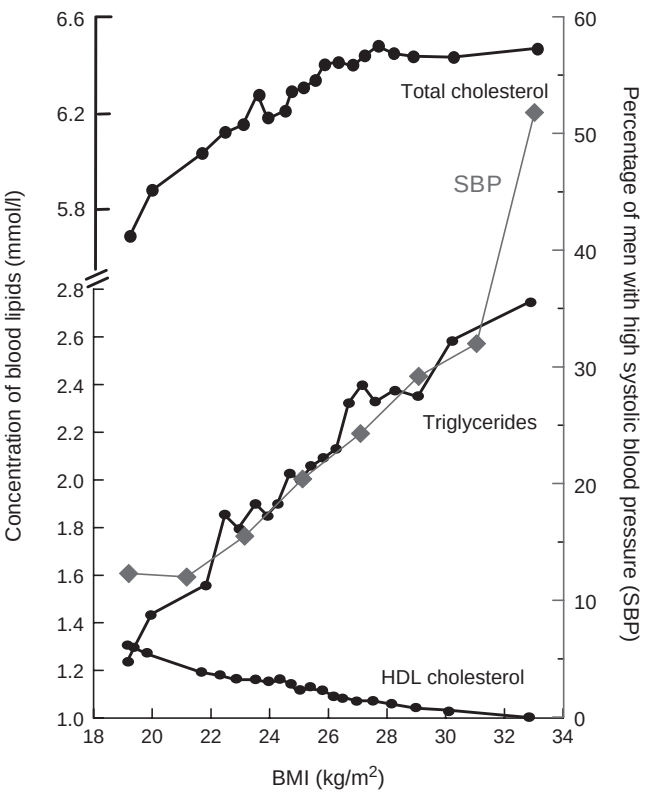
Causal relationships between excess weight and cardiovascular disease

Non-optimum levels of blood pressure, cholesterol and glucose are leading causes of cardiovascular disease. There is strong evidence that excess body weight is associated with adverse levels of these risk factors. A recent Cochrane systematic review focusing on randomized controlled trials (Mulrow et al. 2001) identified 18 trials totalling 2611 hypertensive participants with an average body weight of 84 kg. The data suggested that weight loss in the range of 4–8% of body weight produced an average reduction in systolic blood pressure of 3.0 mmHg, consistent with earlier reviews (Goldstein 1992; MacMahon et al. 1987). It has also been clearly shown in meta-analyses of intervention trials that losing excess weight improves blood lipid profiles (Dattilo and Kris-Etherton 1992), with a fall in total serum cholesterol and triglyceride levels, and an increase in high density lipoprotein (HDL) concentrations. It is reasonable to expect that such reductions in major intermediate risk factors would translate into reduced incidence of cardiovascular disease. Direct evidence from randomized trials on clinical outcomes is limited, owing to the challenges in the modern environment to achieve and maintain weight loss. Nonetheless, evidence is emerging for substantial reductions in diabetes incidence in trials which have weight loss as a major feature of the intervention in individuals at high risk. A detailed discussion can

be found in, for example, Williamson and Pamuk (1993) and in the latest publications from Sweden, where very large numbers of individuals are currently in the middle of long-term trials of the health impact of weight loss induced by surgical reconstruction of the intestine (Sjöström et al. 1999, 2000).

There is also evidence from prospective observational cohort studies for positive associations between BMI and a range of cardiovascular disease outcomes. These data provide the main source of estimates of hazard size in this analysis and are summarized in the relevant following sections. Some further insight into causality from selected cross-sectional and prospective studies is summarized in Figure 8.7, which

Figure 8.7 The relationship between BMI, high blood pressure (systolic pressure ≥160 mmHg) and concentrations of blood lipid in men aged 40–59 years in the United Kingdom



Source: Adapted from Shaper et al. (1997).

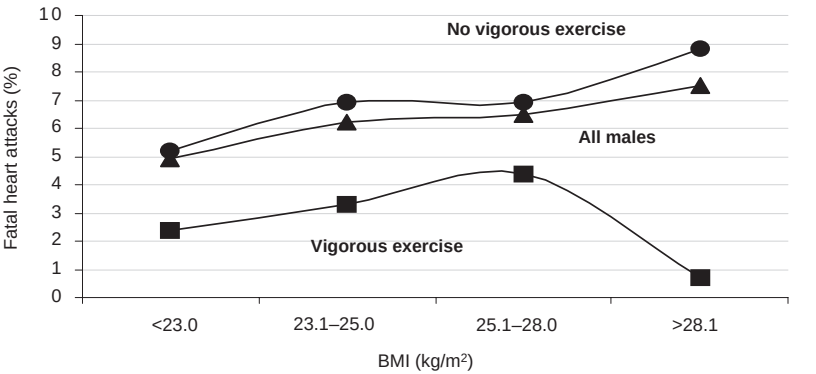
shows a progressive rise in total cholesterol with increasing BMI, from a BMI of 20 kg/m^2, and a sustained fall in HDL from BMI 20–30 kg/m^2. In addition, there is a clear association between high BMI and increases in serum triacylglyceride (triglyceride) concentration. Many studies have shown that there is a potential independent additional risk of ischaemic heart disease with increases in triglyceride concentrations.

The mechanisms by which increased body weight leads to the induction of cardiovascular diseases and excess mortality are not always clear. The effect is partly related to the frequent concomitant lack of physical fitness and physical activity in the overweight, but it is generally accepted that body-weight gain *per se* enhances insulin resistance, and thus physical inactivity is not the sole explanation. The development of insulin resistance is a powerful predictor of excess levels of triglycerides in the blood and of the propensity to develop type II diabetes.

In the INTERSALT study (Dyer et al. 1989), a significant association was found between BMI and systolic and diastolic blood pressures, which was independent of age, alcohol intake, smoking habits and urinary sodium and potassium excretion (this excretion rate being taken as an index of intake). Other cross-sectional analyses with measurements of BMI, blood pressure and lipids in West Africa, the Caribbean and the United States have also clearly shown increases in BMI associated with rising blood pressure (Wilks et al. 1996). Several mechanisms may explain why changes in body weight lead to alterations in blood pressure. Physical activity is one contributor, with inactivity tending to promote both weight gain and blood pressure increases. Weight change induced by diet without altering physical activity, however, also leads to changes in blood pressure. The mechanisms by which weight gain promotes a rise in blood pressure may involve the accentuation of insulin resistance, increases in the tone of the sympathetic nervous system control of the arterioles and the production by the adipose tissue itself of a variety of vasoactive cytokines and hormones, such as angiotensinogen, which increase blood pressure (Gorzelniak et al. 2002). These vasoactive compounds act in part by reducing sodium excretion by the kidney, thereby increasing the blood volume and therefore blood pressure.

It is well recognized that physical inactivity is an important contributor to body-weight gain and also increases the risk of diabetes, cardiovascular disease and some cancers. Data on the risks of excess BMI stratified by levels of physical inactivity (e.g. Figure 8.8 and also Paffenbarger et al. 1970) show that the hazards of high BMI are present at all levels of physical activity. This indicates that physical inactivity does not account for the full relationship between BMI and disease.

Figure 8.8 BMI, vigorous exercise and incidence of fatal heart attacks among male British civil servants



Note: This study was based on observations of 17 944 male British civil servants aged 40–65 years who self-reported at survey between 1968 and 1970. BMI values were taken at age 40–59 years. Average follow-up was 8.5 years. Death certificates were supplied by the National Health Service Central Register. Rates were standardized for age. Note that the group with the highest BMI and reporting vigorous exercise was "fewer than five people".

Source: Adapted from Morris et al. (1980) (Table III p. 1209). Morris defined vigorous exercise as >6 METS (metabolic equivalents, ml oxygen/kg min^{-1}) or 7.5 kcal min^{-1}, e.g. swimming, hill climbing, gardening, brisk walking, for longer than 30 minutes per day.

Systematic review of BMI and cardiovascular disease outcomes: the Asia-Pacific Cohort Studies Collaboration (APCSC)

To date, the only available systematic review providing age-, sex- and outcome-specific hazard size as a continuous variable is the APCSC, which included data from 33 cohorts (12 studies from Japan, 11 from mainland China, two from Singapore, two from Taiwan [China], one from Hong Kong Special Administrative Region of China [Hong Kong SAR], one from the Republic of Korea, one from New Zealand and three from Australia) (Table 8.28). The heights and body weights of individual participants were measured in all studies and BMI was calculated. Data from participants recorded as having a BMI of <12 kg/m^2 or >60 kg/m^2 were excluded from the analysis.

There was evidence of confounding due to disease at baseline and therefore health events that occurred within the first 3 years of follow-up were excluded from all analyses. Smokers were not excluded, but smoking was included as a covariate in all analyses. Participants were categorized as "smokers" if they classed themselves as current smokers, former smokers or ever-smokers (people who have smoked at any time), and as "non-smokers" if they indicated that they had never smoked.

Some cohorts included a smoking category entitled "not current"; participants in this category were excluded from the analyses since it was not possible to determine if they were former smokers or never-smokers.

In total, 310 283 participants contributed 2 148 354 person-years of follow-up with a mean duration of 6.9 years. Data on baseline BMI, smoking habits and >3 years of follow-up were available for these participants. The mean age of the participants at baseline was 47 years and 41% were female. Ten per cent of participants were from Japan, 15% were from mainland China, 55% were from other parts of Asia (Singapore, Taiwan [China], Hong Kong SAR and the Republic of Korea), and 20% were from Australia and New Zealand (ANZ). The contributing data sets are set out in Table 8.28.

The overall mean baseline BMI was 23.6 kg/m^2. The mean BMI for the Asian populations was 22.9 kg/m^2 while that for the ANZ populations was 26.4 kg/m^2. Table 8.29 presents the calculated increments in risk of cardiovascular disease associated with a one unit (1 kg/m^2) decrease in BMI and Figure 8.9 summarizes the relationship of BMI with all ischaemic heart disease events (adjusted for age, sex, cohort and smoking).

Figure 8.9 The relationship between BMI and all ischaemic heart disease events in the Asia-Pacific Cohort Studies Collaboration

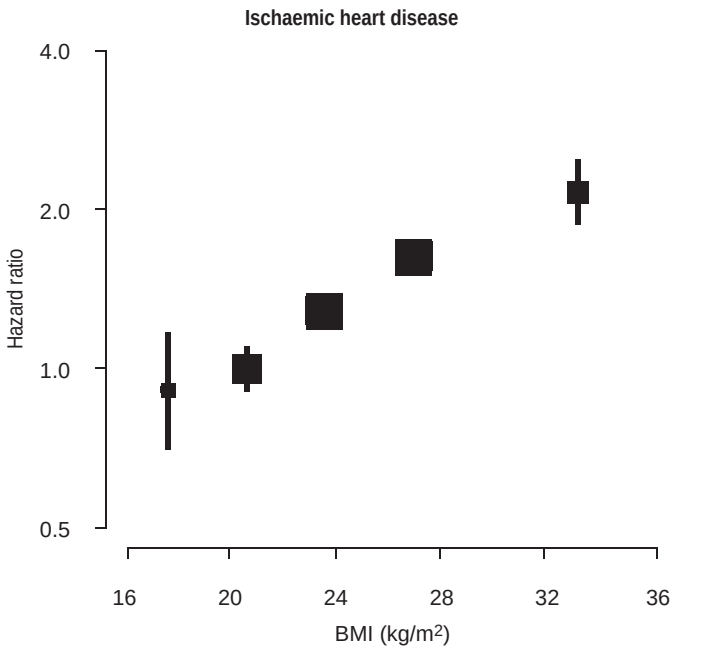


Table 8.28 Asia Pacific Cohort Studies Collaboration: cohorts contributing to the analyses of BMI

Country or area	Study name	n	Start year	Mean follow-up (years)	% female	Mean age (years)	BMI (kg/m^2)		No. of stroke events	No. of haemorrhagic stroke events	No. of ischaemic stroke events	No. of IHD events
							Mean	SD				
Australia	Busselton	7166	1966–1981	21.2	52	44	24.7	3.8	619	57	118	915
	Melbourne	41051	1990–1994	5.7	59	55	26.9	4.4	21	8	5	84
	Perth	10118	1979–1994	12.7	48	45	25.2	3.9	55	9	4	164
Mainland China	Anzhen	8165	1991	4.3	55	53	23.9	3.7	130	32	91	24
	Anzhen 02	735	1992	3.0	1	46	24.1	3.1	3	0	3	0
	Capital Iron & Steel Company	3664	1974	13.3	0	45	23.0	2.7	116	37	75	52
	CISCH	2132	1992	3.3	51	44	24.7	3.5	9	0	0	13
	East Beijing	321	1979	14.8	20	41	23.5	3.5	8	3	4	3
	Fangshan	1407	1991	3.7	67	47	24.0	3.4	15	2	9	3
	Huashan	44	1992	3.1	27	55	22.9	2.9	1	1	0	0
	Seven Cities Cohorts	10282	1987	9.8	53	52	22.1	3.2	164	112	52	37
	Six Cohorts	8824	1982	8.3	12	45	21.1	2.4	109	33	71	43
	Tianjin	4487	1984	6.0	39	53	22.9	3.8	116	43	10	36
	Yunnan	6238	1992	4.5	3	55	21.6	2.9	59	46	12	3
Hong Kong SAR	Hong Kong	842	1985	3.4	67	77	22.0	3.9	12	1	0	23
Taiwan, China	CVDFACTS	5387	1989	6.6	56	47	23.5	3.4	22	6	4	7
	Kinmen	178	1993	3.5	51	67	23.1	3.8	4	0	0	3

continued

Table 8.28 Asia Pacific Cohort Studies Collaboration: cohorts contributing to the analyses of BMI (*continued*)

Country or area	Study name	n	Start year	Mean follow-up (years)	% female	Mean age (years)	BMI (kg/m^2)		No. of stroke events	No. of haemorrhagic stroke events	No. of ischaemic stroke events	No. of IHD events
							Mean	SD				
Japan	Aito Town	1124	1980	15.4	59	51	22.9	3.1	20	4	0	8
	Akabane	1804	1985	11.3	56	54	22.5	3.0	35	5	14	27
	Civil Service Workers	9020	1991	6.6	33	47	22.5	2.7	1	0	0	1
	Hisayama	1427	1961	19.9	56	55	21.6	2.7	285	55	209	78
	Konan	1033	1987	7.0	56	51	21.9	3.0	10	2	6	3
	Miyama	986	1988	6.5	56	60	22.2	3.0	4	0	2	1
	Ohasama	2155	1992	4.2	64	59	23.3	3.1	47	9	33	2
	Saitama	3534	1986	9.7	62	54	22.4	2.9	47	11	24	20
	Shibata	2207	1977	16.8	58	56	22.5	3.0	173	30	67	62
	Shigaraki Town	2457	1991	4.8	59	57	22.5	3.0	3	1	2	1
	Shirakawa	4590	1974	16.8	54	48	21.5	2.8	74	24	36	60
	Tanno/Soubetsu	737	1977	15.3	14	51	22.9	2.9	42	12	15	31
New Zealand	Fletcher Challenge	2383	1992	4.8	22	40	26.5	4.3	21	2	5	29
Republic of Korea	KMIC	160159	1990	5.5	33	44	23.0	2.5	999	295	429	256
Singapore	Singapore Heart	2326	1982	12.5	49	40	23.4	4.3	69	8	21	63
	Singapore NHS92	3300	1992	6.2	52	39	23.2	4.2	39	3	13	21
Total or average[a]		310283		6.9	41	47	23.0	3.1	3332	851	1334	2073

IHD Ischaemic heart disease.

[a] Weighted by person years of follow-up. Total person-years of follow-up is 2 148 354.

Table 8.29 Asia Pacific Cohort Studies Collaboration: summary of associations of cardiovascular disease with a one-unit (1 kg/m^2) decrease in BMI, by age

	No. of studies	*No. of participants*	*No. of events*	*Hazard ratio*[a]	*95% CI*
All ischaemic heart disease events					
30–44 years	31	137 916	73	0.89	(0.84–0.95)
45–59 years	32	205 109	504	0.91	(0.88–0.93)
60–69 years	33	76 301	511	0.95	(0.93–0.97)
70–79 years	28	28 366	576	0.96	(0.94–0.98)
≥80 years	26	5 869	414	0.97	(0.95–1.00)
Deaths from hypertensive disease					
30–44 years	31	136 265	0	1.00	(1.00–1.00)
45–59 years	32	205 007	5	0.92	(0.74–1.13)
60–69 years	33	76 272	16	0.86	(0.76–0.96)
70–79 years	28	28 446	29	0.89	(0.82–0.98)
≥80 years	26	5 979	39	0.94	(0.86–1.03)
All ischaemic stroke events					
30–44 years	31	137 917	41	0.85	(0.77–0.94)
45–59 years	32	205 109	411	0.92	(0.88–0.95)
60–69 years	33	76 345	345	0.94	(0.91–0.97)
70–79 years	28	28 449	316	0.94	(0.91–0.98)
≥80 years	26	5 967	222	0.98	(0.94–1.02)

Note: The first 3 years of follow-up were excluded and results were adjusted for age, sex, cohort and smoking habits.

[a] The age pattern of the hazard ratios presented was smoothed and the resulting age-specific estimates were used to derive the estimates of global burden of disease attributable to BMI:

Ischaemic heart disease: 0.88, 0.92, 0.93, 0.95, 0.98.

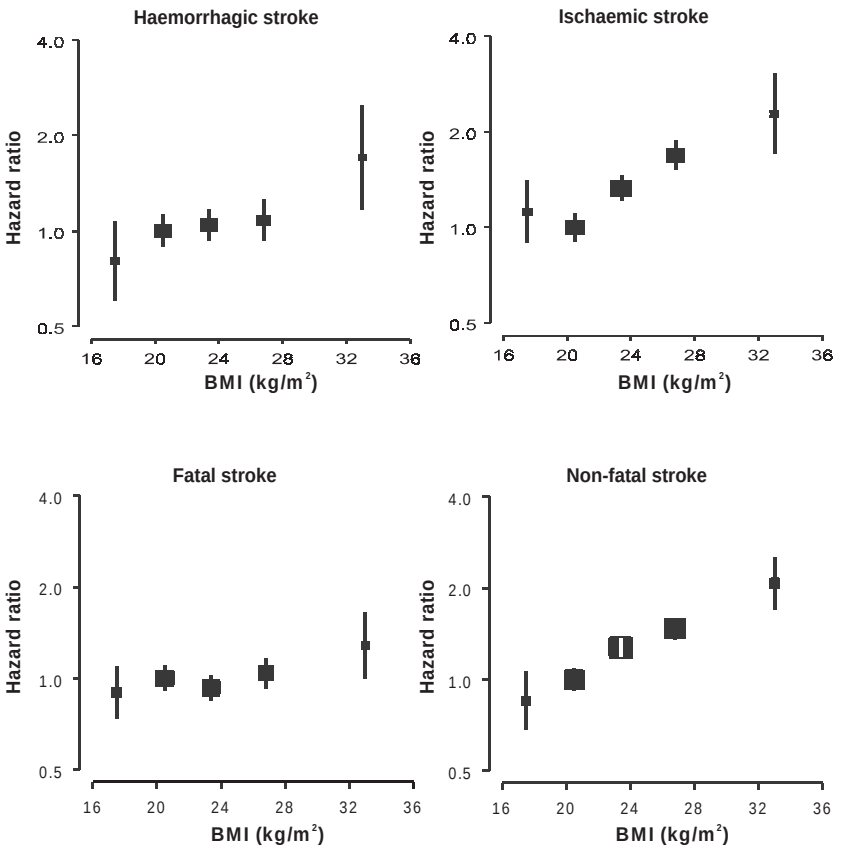
Hypertensive disease: 0.88, 0.91, 0.93, 0.95, 0.97.

Ischaemic stroke: 0.82, 0.85, 0.88, 0.90, 0.93.

The overall reduction in risk of ischaemic heart disease associated with a reduction in BMI of one unit in the age group 45–59 years in the APCSC data amounted to 9%, a very similar figure to that provided by the large North American and European prospective studies (reviewed in the next section).

The findings for stroke from the APCSC meta-analysis are displayed in Figure 8.10. A continuous relationship between increasing BMI and risk of non-fatal stroke is evident, but little association was seen between BMI and the risk of fatal stroke. In examining stroke subtypes, a continuous relationship between increasing BMI and risk of ischaemic stroke was apparent, but a weaker association was seen between BMI and the

Figure 8.10 The relationship between stroke events and BMI in adults in the cohort studies of the Asia-Pacific Cohort Study Collaboration



risk of haemorrhagic stroke. This suggests that the lack of association seen between BMI and fatal stroke may reflect in part the higher proportion of fatal strokes that are of the haemorrhagic subtype. Therefore estimates of global burden of disease attributable to stroke in this work were based solely on ischaemic stroke for which a continuous association with BMI is evident.

Other systematic reviews of BMI and cardiovascular outcomes

A systematic review of large cohort studies investigating ischaemic heart disease has recently been completed (Whitlock et al. 2002). These studies were almost all from North America and Europe and are described in Table 8.30. Most of the studies included measured BMI and dealt with

Table 8.30 The relationship between risk of ischaemic heart disease and BMI: large North American and European prospective cohort studies[a]

Study (reference)	*Maximum no. of cases analysed*	*Type of IHD outcome*	*BMI*	*Age at recruitment (years)*	*Shape of association*	*Risk reduction per kg/m² BMI reduction (%)*[b]
Nurses' Health study (Willett et al. 1995)	1292	Fatal and non-fatal	Self-reported	30–55	Positive	11
Adventist Mortality study (Lindsted et al. 1991)	1004	Fatal	Self-reported	30–89	Positive	8
British civil servants' study (Morris et al. 1980)	977	Fatal and non-fatal	Not reported	40–59	Positive? (no significance tests)	4
British Regional Heart study (Shaper et al. 1997)	974	Fatal and non-fatal	Measured	40–59	Positive	7
Manitoba Follow-Up study (Tate et al. 1998)	915	Fatal and non-fatal	Measured	18–62	Positive or J-shaped	4
Social Insurance Institution study (Rissanen et al. 1990)	868	Non-fatal	Measured	25–64	Positive	4
Whitehall study (Jarrett et al. 1982)	727	Fatal	Measured	40–64	Positive	6
NHANES I Epidemiologic Follow-up study (Cooper and Ford 1992)	(Male) 563 (Female) 696	Fatal and non-fatal	Measured	25–75 25–75	Not significant Positive or J-shaped	(Male) 6 (Female) 2
Gothenburg men's study (Rosengren 1999)	686	Fatal	Measured	47–55	J-shaped	8
Framingham study (Higgins et al. 1988)	(Male) 659 (Female) 540	Fatal and non-fatal	Measured	35–69 35–69	Positive or J-shaped Positive or J-shaped	(Male) 5 (Female) 4
Seven Countries study (Keys et al. 1972)	632	Fatal and non-fatal	Measured	40–59	Positive or J-shaped	7
Physicians' Health study (Rexrode 2001)	548	Fatal and non-fatal	Self-reported	40–84	Positive	7
Eastern and Southwestern Finland study (Jousilahti et al. 1999)	520	Fatal and non-fatal	Measured	25–64	Positive or J-shaped	4
Honolulu Heart Program (Rhoads and Kargan 1983)	511	Non-fatal	Measured	45–68	Positive	10

IHD Ischaemic heart disease.

[a] Studies recording 500 or more cases of IHD.

[b] Adapted from Whitlock et al. (2002). The large American Cancer Society (1960–1972) cohort (Calle et al. 1999; Stevens et al. 1998) recorded self-reported height and weight. However, cause-specific associations have not been published. A positive association between risk of all cardiovascular death, steeper in younger age groups, has been shown.

non-fatal as well as fatal outcomes. All but one showed a positive or J-shaped relationship between BMI and the risk of either fatal or non-fatal ischaemic heart disease. When the potential reduction in risk was calculated for each unit decrease in BMI, results were found to be reasonably similar, with most studies indicating a 5–10% reduction in rates of ischaemic heart disease. The overall unweighted average reduction in risk per unit BMI difference was 6%, with studies using self-reported BMI giving a weighted average of 9%, whereas the weighted average for the studies using measured BMI amounted to a 5% reduction. The mean age at death for these cohorts was estimated to be age 50–60 years, indicating that these data are highly consistent with those of the APCSC outlined earlier.

The conclusions of other systematic reviews are also consistent with the APCSC results, although comparisons are limited by the use of BMI categories; the main results are summarized in Table 8.31.

5.5 Type II diabetes

Causal relationships between excess weight and type II diabetes

The relationship between excess body-weight gain and type II diabetes is now considered so strong that there is increasing use of the term "diabesity" as a unifying concept. Not only is there a close association between higher BMIs and the risk of developing type II diabetes, but weight gain itself has also been identified as a particularly important risk factor. The impact of weight gain is markedly enhanced if it occurs in young adults who were already overweight or obese when they entered adult life (Colditz et al. 1995). More direct evidence for the importance of increases in weight in the development of diabetes comes from intervention studies. Over 80% of very obese diabetic adults treated by gastric bypass surgery to induce marked weight loss, for example 30 kg, become non-diabetic and over an 8-year post-surgery follow-up period, the incidence of new cases of diabetes in these patients is minimal (Sjöström et al. 2000). Four prospective studies, three of which were randomly controlled intervention studies, have also shown that changes in diet and exercise that induce a modest loss of weight in overweight or obese subjects with glucose intolerance can markedly reduce the subsequent development of type II diabetes over periods of 3–6 years (Diabetes Prevention Program Research Group 2002; Eriksson and Lindgarde 1991; Tuomilehto et al. 2001; Xiao-Ren Pan 1997). Weight-loss trials among obese patients with type II diabetes have also shown marked improvements in diabetic states or even a return to normal glucose tolerance. Lean et al. (1990) have also shown that the degree of weight loss achieved in newly-diagnosed patients with type II diabetes predicts their future life span. Williamson and Pamuk (1993) also observed that in the United States overweight and obese women with co-morbidities have not only a reduced overall mortality but also a selective reduction in death from

Table 8.31 The relationship between BMI and the development of cardiovascular disease: analyses from two systematic reviews

Table 8.31(a) Australia

	Relative risks associated with overweight and obesity							
	Overweight (BMI 25–29.9 kg/m²)				*Obese (BMI ≥30 kg/m²)*			
	Males		*Females*		*Males*		*Females*	
	<65	*≥65*	*<65*	*≥65*	*<65*	*≥65*	*<65*	*≥65*
Ischaemic heart disease based on Harris et al. (1993, 1997); Manson et al. (1990); Rimm et al. (1995)	1.35	1.00	1.40	1.00	1.80	1.20	2.00	1.25
Ischaemic stroke based on Rexrode et al. (1997)	1.35	1.00	1.25	1.00	1.50	1.15	1.60	1.20
Hypertension based on Ascherio et al. (1992); Sjöström et al. (1992); Witteman et al. (1989)	1.40	1.40	1.40	1.40	2.35	2.35	2.35	2.35

Source: Mathers et al. (1999).

Table 8.31(b) United Kingdom

	Relative risks associated with obesity (BMI ≥30 kg/m²)	
	Males	*Females*
Myocardial infarction	3.2	1.5
Stroke	1.3	1.3
Hypertension	2.6	4.2
Angina	1.8	1.8

Note: Relative risks specified only in relation to obesity (BMI ≥30 kg/m²). Derived from 48 unspecified studies after a systematic review of 3537 studies.

Source: National Audit Office (2001).

diabetes-related conditions if they intentionally lose modest amounts of weight of up to 9 kg (Williamson and Pamuk 1993).

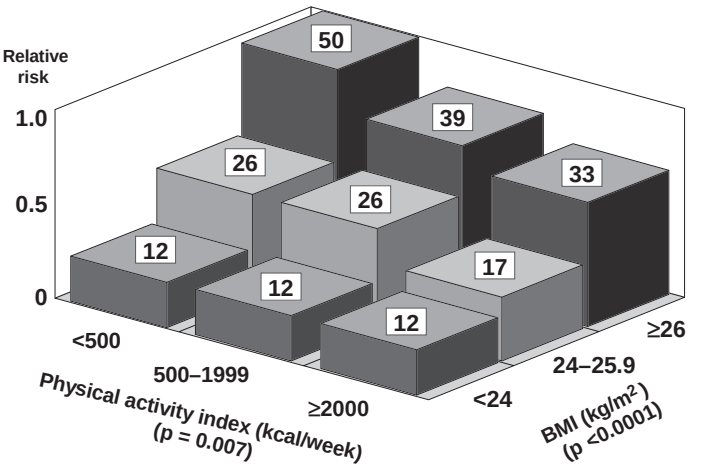
The mechanisms whereby weight gain leads to the development of type II diabetes are the subject of intense investigation, with the development of insulin resistance seen as dominant. Type II diabetes develops when the pancreatic capacity to generate insulin cannot maintain the markedly increased demand induced by insulin resistance. Insulin resis-

tance itself is affected not only by increases in weight, particularly if the extra energy is stored in abdominal, i.e. visceral, fat, but also by dietary composition. Dietary fat induces insulin resistance (Marshall et al. 1994; Sarkkinen et al. 1996; Vessby et al. 2001) and there is increasing interest in the possibility that rapidly absorbed carbohydrates, which cause sudden increases in concentrations of blood glucose, place extra demands on the pancreas (Willett et al. 2002). Adipose tissue itself, particularly visceral adipose tissue, secretes cytokines such as interleukin-6 (IL-6) and tumour necrosis factor (TNFα) which are recognized to be important inducers of insulin resistance. Circulating adiponectin, an adipocyte-derived hormone which markedly improves insulin sensitivity is reduced as the fat cells expand with body-weight gain, and is also modulated by sex hormones (Nishizawa et al. 2002). Physical inactivity also contributes to insulin resistance, with vigorous exercise leading to a rapid restoration of insulin sensitivity.

The quantitative contributions of each of these components are still uncertain, but the carefully controlled Chinese Prevention study on preventing type II diabetes (Xiao-Ren Pan et al. 1997) provides some information. In this study, three groups of overweight adults with glucose intolerance were assigned to either a low fat, low saturated fat and high vegetable and fruit diet, or to a modest increase in physical activity equivalent to 30 minutes of brisk walking daily, or were advised on both dietary and physical activity interventions. There was a marked and equivalent reduction in the incidence of type II diabetes in all three groups over the 6 years of follow-up. This implies that there is little interaction between diet and physical activity but that both can contribute to the development of insulin sensitivity.

Physical activity is potentially a major confounding effect. Physical activity is recognized as beneficial in enhancing the sensitivity of tissues to insulin, thereby enhancing the body's capacity to handle glucose. As noted above, increasing physical activity alone without dietary change reduced the incidence of diabetes in modestly overweight Chinese adults with glucose intolerance (Xiao-Ren Pan et al. 1997). This finding was consistent with those from a further two major controlled trials from Finland and the United States, which suggested that the combination of changes in diet and activity together with only modest weight losses reduced the incidence of type II diabetes in susceptible adults by 56%, this benefit increasing to 76% in those aged >60 years (Diabetes Prevention Program 2002; Tuomilehto et al. 2001). In these trials, the modest weight loss, for example 5%, was induced by a low-fat diet combined with physical activity. Given the important effect of physical activity, the quantification of any interaction between BMI and physical activity when determining the risk of onset of type II diabetes is necessary. As with coronary disease, the increase in risk of diabetes with increasing BMI is seen at all levels of physical activity (Figure 8.11).

Figure 8.11 The interaction of higher BMIs with physical activity in determining the age-adjusted incidence of type II diabetes per 10 000 person-years of follow-up, in males



Note: "Incidence" relates to the age-adjusted incidence of type II diabetes per 10 000 person-years of follow-up in male graduates of the University of Pennsylvania.

Source: Adapted from Helmrich et al. (1991).

Sources of hazard size estimates for BMI and type II diabetes

Incidence studies

The conclusions of systematic reviews from Australia (Anonymous 1999; Mathers et al. 1999) and the United Kingdom of Great Britain and Northern Ireland (National Audit Office 2001) are given in Table 8.32. In one of the Australian reports (Mathers et al. 1999), the risks of developing diabetes were arbitrarily halved in an attempt to take into account the impact of physical activity on diseases relating to obesity (see below). The first three of the four studies (Carey et al. 1997; Colditz et al. 1990, 1995; Njolstad et al. 1998) noted by this report involved very large groups of professionals in the United States (e.g. >100 000 subjects with individual prospective follow-ups of 12–18 years). Unfortunately, these data are based on self-reported heights, weights and disease. Although weights and heights reported in these study populations are found to have a good correlation with observed measurements, they are still likely to systematically underestimate the actual prevalences of overweight and obesity. The Victoria report (Anonymous 1999) looked at this issue and

Table 8.32 The relative risks of developing type II diabetes associated with overweight and obesity, as assessed by two governmental reviews

		Overweight (BMI 25.0–29.9 kg/m²)		*Obese (BMI ≥30 kg/m²)*	
Study	*Age (years)*	*Males*	*Females*	*Males*	*Females*
Australia[a] (Mathers et al. 1999)	<65	1.8	1.8	3.2	3.2
	≥65	1.8	1.8	3.2	3.2
United Kingdom (National Audit Office 2001)	All ages	—	—	5.2	12.7

— No data.

[a] Relative risk values arbitrarily halved to help account for any independent impact of physical activity or residual confounding.

found from its own analysis that "people who are obese selectively underestimated their weight and/or overestimated their height more than others. As a result, the proportion of people who are obese by measurement is 60% higher than estimates based on self-reported height and weight. The greatest discrepancies are found in adolescent men and older people". How this systematic underestimation of obesity impacts on the estimates of relative risk per BMI unit is unclear, but it may well result in overestimation, i.e. a bias away from the null. This is because the distribution of self-reported BMI is narrower than the distribution of actual BMI, and so the slope of associations between BMI and risk of disease is artificially steep. The use of self-reported disease status is another source of uncertainty in hazard estimates because in many such studies diabetes has been found to be underreported or under-diagnosed (Harris et al. 1998). If undrrecording of diabetes is associated with BMI level, this would also result in bias in hazard estimates (away from the null, if relatively more cases of diabetes failed to be identified among people with low BMI).

The prospective studies on male and female health professionals in the United States (Chan et al. 1994; Colditz et al. 1995) suggest age-adjusted relative risks of self-reported diabetes of between 4 and 14 in men aged 40–75 years and reporting a BMI of about 30 vs <23 kg/m²; whereas the relative risk for self-reported diabetes in the nurses of similar age and with reported BMIs of about 30 was about 28 compared with the rates for nurses with reported BMIs of <22 kg/m². A more robust estimate of the relative risk of developing type II diabetes comes from a detailed Norwegian study based on a sampling system which is representative of their most northern county and in which objective measurements of weight and height as well as measurements of fasting glucose concentrations were made (Table 8.33).

Table 8.33 Relative risk of developing type II diabetes in Norwegian men and women aged 35–52 years, by sex-specific quartiles of baseline BMIs

Quartiles of baseline BMI (kg/m²)		*Relative risk of type II diabetes over 12 years*	
Males	*Females*	*Males*	*Females*
<23.2	<22.0	1.0	1.0
23.2–25.0	22.0–24.1	1.8	1.8
25.1–27.0	24.2–27.1	2.5	2.1
≥27.1	≥27.2	13.0	30.0

Note: The above relative risk of developing diabetes for both males and females are interpolated from a graph in Njolstad et al. (1998).

By chance, the quartiles of BMI for men again allow an approximate distinction between those with BMIs of <23.0 kg/m² and <25.0 kg/m², i.e. their second quartile, the upper limit of which coincides with the WHO distinction between normal and overweight. The values for women need to be adjusted. These data relate to men and women aged 35–64 years, but were age-standardized. Nevertheless, it is clear that the relative risks of diabetes as derived from these data in general agree with data from the United States prospective studies, and that the values given for the upper quartile will be low estimates of the true risk of diabetes in those Norwegian men and women who have a BMI of ≥30.0 kg/m².

Prevalence studies

The ideal source of estimates of the hazard size would be large long-term trials or, in their absence, large, long-term cohort studies with direct measurements of BMI and blood glucose. The principal cause of type II diabetes appears to be excess weight gain in childhood and in adult life, and so relatively short-term prospective studies of the incidence of diabetes may not capture the full impact of persistent excess BMI. Large, nationally representative cross-sectional studies are available that use objective measurements of BMI and diabetes (in contrast to the few large, long-term prospective studies outlined earlier). Although the diagnosis of diabetes may itself lead to a loss in weight, this is likely to result in only a moderate bias to the null, since current BMI correlates so closely with BMI levels over many previous decades. The estimates of hazard size for this analysis of the burden of diabetes attributable to BMI were therefore derived from the age- and sex-specific associations of type II diabetes (based on fasting glucose values) with BMI from the Japanese National survey (Yoshike, personal communication; see Figure 8.12). The incremental risks for the required age categories were estimated on a linear basis (Table 8.34).

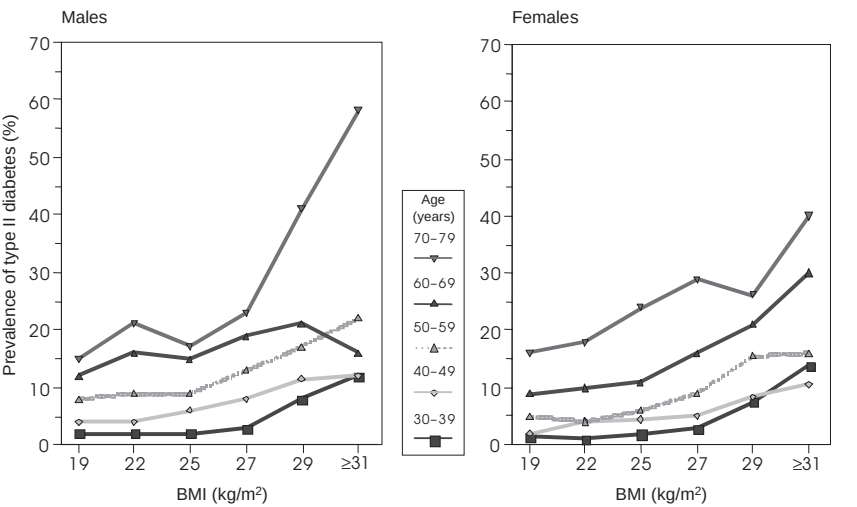
Table 8.34 The relative risk of developing type II diabetes, per unit (1 kg/m^2) increase in BMI

			Age group (years)						
Disease	*Sex*	*Country source*	*15–17*	*18–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Type II diabetes	Males	Japan	—	—	1.36	1.24	1.18	1.27	1.27
	Females	Japan	—	—	1.47	1.34	1.21	1.20	1.20

— No data.

Source: These estimates were taken from a diagram of results (from the Japanese National survey) and are likely to be subject to some inaccuracy.

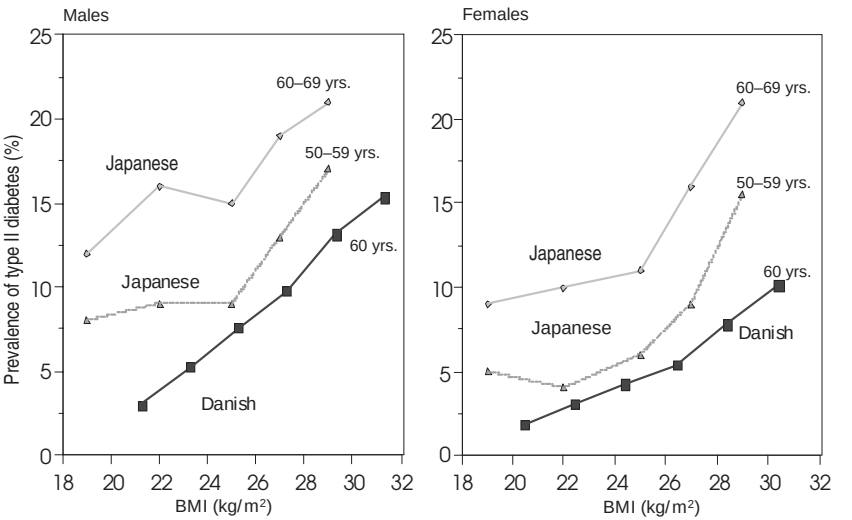
Figure 8.12 The prevalence of type II diabetes (based on fasting blood glucose concentrations) by age, sex, BMI and decade of adult life, in a representative sample of the Japanese population



Note: Based on rates of type II diabetes determined from measurements of fasting blood glucose ≥126 mg/dl or where treatment is already being given for type II diabetes (Yoshike, personal communication).

The proportional increases in the prevalence of diabetes associated with a given increase in BMI were consistent in the Japanese national survey with associations observed in a Danish representative survey (Drivsholm et al. 2001; see Figure 8.13). They are also broadly consistent with the results of prospective studies that measured weight and height, that is, the Norwegian study that assessed the risk of diabetes,

Figure 8.13 A comparison of the prevalence of type II diabetes (based on fasting blood glucose concentrations and measured BMI) in Danish and Japanese adults of comparable age



with measurements of blood glucose (Table 8.33) and the United States NHANES III analyses of prevalence rates of diagnosed diabetes (Table 8.35).

A perspective on the overall burden of ill-health associated with higher BMI can be gauged from nationally representative studies of measured BMI and the prevalence of type II diabetes. Thus Must et al. (1999) used the NHANES III study and highlighted the marked 20-fold increase in prevalence rates of reported type II diabetes in men and women aged >55 years compared with those aged <55 years, even in people with a measured "normal weight", that is, with BMIs of <25.0 kg/m^2. Superimposed on this age-related increase was the impact of high BMIs: the prevalence ratios for people aged <55 years with high BMI compared with those with a normal weight varied from 3.3 in men and 3.8 in women with BMIs of 25–29.9 kg/m^2, up to 8–11 in men and women with BMIs of 35–39.9 kg/m^2 (but with very broad confidence limits). Prevalence ratios were lower in the older age groups (1.8 in the overweight men and women, and 4.2 in men and 3.2 in women with BMIs of 35–39.9 kg/m^2).

Recently, there has been an interest in the issue of ethnic differences in the incidence of co-morbidities that result from increases in weight, with reports of an increased propensity to diabetes in Pima Indians, in those of Hispanic origin and in Asians, compared to the American Cau-

Table 8.35 Estimated prevalence ratios of type II diabetes by weight status category in adults in the United States-representative NHANES III study

	Prevalence ratio of type II diabetes				
	Weight status category				
Age group (years)	*Adjusted prevalence in individuals of normal weight*[a]	*Overweight (BMI 25.0–29.9 kg/m²)*	*Obesity class 1 (BMI 30.0–34.9 kg/m²)*	*Obesity class 2 (BMI 35.0–39.9 kg/m²)*	*Obesity class 3 (BMI ≥40.0 kg/m²)*
Males					
<55	0.2	3.27 (1.17–9.05)	10.14 (4.03–25.08)	7.95 (2.44–25.23)	18.08 (6.71–46.84)
≥55	5.3	1.77 (1.26–2.47)	2.56 (1.71–3.74)	4.23 (2.09–7.59)	3.44 (1.11–8.32)
Females					
<55	0.4	3.82 (1.75–8.21)	2.49 (1.01–6.12)	10.67 (4.02–27.11)	12.87 (5.69–28.05)
≥55	7.9	1.81 (1.41–2.31)	2.19 (1.56–3.01)	3.24 (2.13–4.67)	5.76 (4.17–7.42)

[a] For people with BMI of 18.5–24.9 kg/m, prevalence data were specified only for white adults, with current smokers included if aged <55 years, but also former smokers in the age group ≥55 years. Data for both age groups are adjusted for age, and prevalence ratios are adjusted for race and ethnicity, as well as smoking status. The ratios are set out in relation to the group of individuals of normal weight. The 95% confidence limits are shown in parentheses.

Note: The prevalence of type II diabetes depended on self-reporting because fasting glucose levels were available for only 44% of the sample.

Source: Must et al. (1999).

casian population (Edelstein et al. 1997; Seidell et al. 2001a). Figure 8.13 shows that the prevalence of diabetes in the Japanese population markedly exceeds that in the Danish population, for both sexes and for each BMI category, but the gradient of risk appears to be roughly the same in the two communities. Similar enhanced risks of diabetes are evident in Mexicans assessed in the latest national survey of the prevalence of diabetes and other diseases in relation to excess weight in Mexico (Sánchez-Castillo et al. 2003). These data were compared with the recalculated data relating only to those with fasting blood glucose measurements, from the NHANES III study in the United States. Prevalence rates for type II diabetes are 2–3-fold greater in Mexicans than in non-Hispanic Caucasians in the United States, on an age-standardized basis and, more importantly, prevalences in Mexicans exceed those in people of the United States, when BMI is taken into account. The differences were somewhat smaller, but still statistically significant when the age-dependent prevalences of diabetes were related to the waist circumferences of the two national groups. In the year 2000, the prevalence of abdominal obesity was greater in Mexicans than in non-Hispanic Caucasians in the United States, as measured in the NHANES III study (Sánchez-Castillo et al. 2003). Similar data are now emerging from mainland China Hong Kong SAR and India. In the near future, these comparisons may be extended so that the increment in risk for each pop-

ulation at each BMI level, taking age into account, can be obtained with some assurance on the basis of measured body weights, heights and fasting glucose levels. It will also be necessary to take into account the relationship between BMI and diabetes in Pacific Islanders, which may well prove to be different from that in other peoples, given their greater lean tissue : fat ratios (Bell et al. 2001). Nevertheless, it seems reasonable on present evidence to conclude that although in Asians and some other populations the absolute risk of type II diabetes is amplified, the incremental gradient of risk of diabetes in relation to increasing BMI is approximately the same as that found in Caucasians. On this basis, similar values for relative risk can be applied to all subregional groups.

5.6 Osteoarthritis

There is a well-documented association between high BMI and the development of osteoarthritis in both men and women (Cicuttini and Spector 1998). Osteoarthritis is an abnormality which involves damage to and eventually the destruction of the articular cartilage of the joint. New bone is formed at the joint surfaces, probably in response to the cartilaginous damage. The relationship between excess weight and the development of osteoarthritis has been studied in a number of population-based prospective, cross-sectional and retrospective trials, showing excess weight as the most important preventable risk factor for osteoarthritis. Cross-sectional studies have consistently reported increased risks of osteoarthritis in association with body-weight gain, with early studies suggesting a 2–7-fold greater risk in those individuals in the top compared with the bottom tertile of BMI (Table 8.36) and, in some studies, a greater risk in women than men (Cicuttini and Spector 1998). As the data were adjusted for race, ethnicity and smoking as well as age, no age-related data were available, but these are the best nation-

Table 8.36 Prevalence of osteoarthritis by weight status category, in adults

	Prevalence of osteoarthritis (%)					
	Weight status category					
Sex	*Underweight BMI <18.5*	*Normal weight BMI 18.5–24.9*	*Overweight BMI 25.0–29.9*	*Obesity class 1 BMI 30.0–34.9*	*Obesity class 2 BMI 35.0–39.9*	*Obesity class 3 BMI ≥40.0*
Males ($n = 6\,987$)	0.39	2.59	4.55	4.66	5.46	10.04
Females ($n = 7\,689$)	7.79	5.22	8.51	9.94	10.39	17.19

Source: Table 3 in Must et al. (1999).

ally representative data available for assessing the quantitative impact of BMI increases on the prevalence of osteoarthritis.

A number of mechanisms have been proposed to explain the association of adult body-weight gain with osteoarthritis. The physical burden associated with an increased load on the joints seems straightforward, but changes in movement and gravitational stresses as weight gain occurs are also a factor. Other mechanisms have, however, been invoked, including systemic changes in metabolism associated with hypertension, raised blood glucose and cholesterol concentrations, insulin resistance and elevated concentrations of blood uric acid, as well as hormonal changes induced by the metabolic effects of additional adipose tissue (Cicuttini and Spector 1998). Several of these factors could be acting on the metabolic integrity of the articular cartilage, as could other dietary factors, such as high fat intake, which have also been linked to this disease. The associations with hypertension tend to disappear once concomitant increased body weight is taken into account, and the link with hypercholesterolaemia is not sufficiently robust to warrant special consideration. Abnormal glucose metabolism is a more plausible mechanism, with the possible involvement of growth hormone (Cicuttini and Spector 1998), but epidemiological studies have not shown a consistent link between type II diabetes and osteoarthritis. Raised uric acid concentrations have been associated with osteoarthritis, but again data supporting the relationships are inconsistent.

It is clear that excess weight gain precedes the development of osteoarthritis rather than the reverse. This was initially reported in retrospective recall studies of reported former weights (Anderson and Felson 1998; Hart and Spector 1993), but three studies (Anderson and Felson 1998; Cicuttini et al. 1996; Hart and Spector 1993) have shown a strong association of excess weight gain with asymptomatic radiological evidence of osteoarthritis, such radiological evidence having been clearly shown to be a predictor of future disability (Acheson et al. 1974; Hochberg et al. 1989). Twin studies have shown that the heavier twin has a greater risk of developing osteoarthritis (Cicuttini et al. 1996), and the incidence of osteoarthritis is markedly enhanced in overweight women (Schouten et al. 1992). In population studies, the incidence of disability once osteoarthritis has developed is also particularly marked if the subjects are obese (Verbrugge et al. 1991). In addition to predicting the greater risk of developing osteoarthritis, weight gain has also been shown to enhance the progression of the disease. Among middle-aged women with early stage unilateral knee damage, those who were overweight had a 34% chance of developing osteoarthritis in the contralateral knee within 2 years and 22% also showed radiological progression of the disease in the initially affected joint (Cicuttini and Spector 1998).

Detailed population studies regarding the incremental risk of developing osteoarthritis of any joint over a wide range of BMIs are rare,

however, with Must et al. (1999) being the principal source of data. Must et al. used the NHANES III study with measurements of BMI and with reported rates of disability from osteoarthritis to derive risk values. Given the need to consider the linear relationship between BMI and disabilities rather than the type of categorical analyses shown in Table 8.36, the Must et al. (1999) study was used here. This study, as well as several others, shows that the absolute risk of osteoarthritis is greater in women than in men, but that the incremental risk of osteoarthritis per unit increase in BMI is approximately the same in both sexes. On the basis of this survey in the United States, the relative risks of osteoarthritis were derived without regard to adult ages or sex, as shown in Table 8.37. These analyses were not adjusted either for age or smoking status, but Must et al. (1999) found that there were no interactions between weight class and race or ethnicity for either sex.

Gout

Gout is a metabolic disease of uric acid metabolism, which has a genetic component and which involves acute episodes of arthritis leading to chronic arthritis and disability. Although much less common than osteoarthritis, gout has also been linked with excess weight gain in both cross-sectional and longitudinal studies (Cicuttini and Spector 1998). The abdominal distribution of body fat seems to be a particularly important risk factor, in keeping with mechanistic studies which suggest that hormonal or other agents which alter uric acid metabolism, such as diet and alcohol, are involved in precipitating an attack of gout. Although multivariate analyses have shown the importance of BMI from as early as age 35 years and excess weight gain as distinct risk factors (Roubenoff et al. 1991), with other large studies suggesting that excess weight as early as in adolescence is predictive of gout, there is no clear picture of the prevalence of or associated disability linked to gout on an international basis. Thus, although weight reduction is clearly recognized as potentially important in avoiding and limiting the risk of gout and its associated handicaps, it was decided not to include estimates of the

Table 8.37 The relative risk of developing osteoarthritis per unit (1 kg/m^2) increase in BMI

			Age group (years)						
Disease	*Sex*	*Country source*	*15–17*	*18–29*	*30–44*	*45–69*	*60–69*	*70–79*	*≥80*
Osteoarthritis	Males	USA	—	—	1.04	1.04	1.04	1.04	1.04
	Females	USA	—	—	1.04	1.04	1.04	1.04	1.04

— No data.

effects of excess BMI on gout and only to use data on weight gain in association with osteoarthritis.

5.7 Cancer

There have recently been two major re-analyses, incorporating systematic reviews, of the associations between excess weight gain and the development of different forms of cancer (Bergström et al. 2001; IARC 2002), which supersede those of Australia (Mathers et al. 1999) and the United Kingdom (National Audit office 2001). The latest review by the International Agency for Research on Cancer (IARC) lists the risk of different cancers in relation to both body weight and physical activity (IARC 2002). These analyses concluded that cancers of the colon, breast (postmenopausal), endometrium and kidney were statistically related to weight gain, each analysis being usually based on a systematic review of a large number of both case–control and prospective studies. The present analysis also drew heavily on the recent series of meta-analyses conducted by IARC staff and colleagues, which provided estimates of the coefficient of risk per unit BMI increase (Bergström et al. 2001). Since this chapter used continuous rather than categorical data, the conclusions of the main IARC report on statistically significant findings are used to select the cancers to be considered, but the coefficients of risk are taken from Bergström et al. (2001). Table 8.38 sets out these estimates. In view of the much lower incidence of and the uncertainty of the global statistics for kidney cancer, the estimates of the burden of cancer were confined to cancers of the breast in postmenopausal women, colon and endometrium.

Breast cancer

A distinction needs to be made between the risks of developing breast cancer before and after the menopause. Premenopausal breast cancer is less likely to develop in women with high BMIs, but this effect is only seen at BMIs of about >28 kg/m^2 and rates of mortality are not lower among women with higher BMIs. For the present analyses, the role of excess weight gain in the development and the burden of disease from breast cancer was confined to cases arising in postmenopausal women. Over 100 studies conducted in many populations have found that women with higher BMIs are at greater risk of postmenopausal breast cancer (IARC 2002). Bergström et al. (2001) used 27 of these studies to quantitatively evaluate the impact of excess weight. Age, age at menarche, parity, alcohol intake and diet are recognized confounders, but when all of these were taken into account the coefficient of risk per unit BMI was still statistically significant (Table 8.38). Furthermore, there are studies which overall suggest that those women who have limited their weight gain or have lost weight in early adult life tend to have a reduced risk of postmenopausal breast cancer (IARC 2002). Over 50 studies (e.g. Huang et al. 1997; Tretli 1989; Törnberg and Carstensen 1994) also

Table 8.38 The relative risks of developing cancer associated with increases in BMI, as calculated for European populations

Cancer	*Coefficient (±95% CI)*[a] *(Increase in incidence rates per unit [1 kg/m²] increase in BMI)*	*Relative risk of developing cancer*		*No. of studies*
		Overweight[b]	*Obesity*[c]	
Postmenopausal breast	1.03 (1.02–1.04)	1.12	1.25	13
Colon	1.03 (1.01–1.05)	1.15	1.33	6
Endometrial	1.10 (1.07–1.14)	1.59	2.52	4
Kidney	1.06 (1.03–1.08)	1.36	1.84	2

[a] Coefficient describes the increase in incidence rates per unit increase in BMI irrespective of age (and includes the 95% confidence intervals) based on covariance analysis.

[b] Defined as BMI 25.0–29.0 kg/m²; the relative risk is calculated from each study's provision of the distribution of BMIs within the studied population.

[c] Defined as BMI ≥30.0 kg/m²; the relative risk is calculated from each study's provision of the distribution of BMIs within the studied population.

Notes: 27 eligible studies but analysis restricted to cohort studies with incident cases only; adjustment for age, reproductive factors, alcohol and diet did not materially affect the relationship.

No effect was seen when restricting the data to incident cases; all studies accounted for age, diet (where data were available), alcohol and/or physical activity.

Data provided for men but the data were almost identical for women (1.07, CI 1.05–1.09). Studies were restricted to incident cases, with age adjustment and allowance for smoking but these restrictions did little to influence the results from the seven studies considered.

Source: Bergström et al. (2001).

suggest that women with a higher BMI at the time of diagnosis have poorer survival and an increased likelihood of recurrent breast cancer, irrespective of their menopausal status and after adjusting for the stage of cancer development and the type of treatment used.

Mechanistically, it seems clear that the risk of developing postmenopausal breast cancer is increased in women with raised plasma and tissue concentrations of estrogens. The activity of these hormones is greater when there are lower circulating concentrations of the sex hormone-binding globulin (SHBG). Obesity, with its associated insulin resistance, lowers SHBG levels; overweight women are also found to have higher circulating concentrations of total and bioavailable androgens and estrogens. Confirmation of the importance of these hormonal changes comes from the observation that women exposed to combined estrogens and progesterones as part of postmenopausal hormone replacement therapy subsequently have increased rates of breast cancer, the risk being greater in those on combined compared with estrogen-alone treatment (Weiderpass et al. 1999). The reduced risk associated with a late menarche and in women with anovulatory cycles is considered to relate to the lower exposure of the breast to bioactive estrogens (IARC 2002).

Colon cancer

Bergström et al. (2001) considered 19 studies, 12 of which were prospective, which generally tended to show a stronger relationship between excess weight and incidence of cancer in men than in women. The studies also allowed an assessment to be made of the confounding effects of physical activity, age, family history of colon cancer, ethnicity, social class and diet. For the full quantitative analyses, only six studies could be included (Gerhardsson et al. 1990; Giovannucci et al. 1995; Kune et al. 1990; Lee and Paffenbarger 1992; Martinez et al. 1997; Thun et al. 1992); and in these studies no sex-specific differences could be found, nor did restricting the analysis to incident cases alter the estimate. The same general relationships of weight to the development of large colonic adenomas were found in the IARC analyses (IARC 2002), the development of adenoma being seen as part of the progression of cellular changes leading to the development of colon cancer. Although fewer studies have considered rectal cancers separately, no relationship was found between BMI and rectal cancer.

The mechanisms by which weight gain might accentuate the risk of developing large adenomas and colon cancer are unclear, but the stronger association of high BMIs with large rather than small adenomas suggests that excess weight operates at a relatively late stage in the promotion of tumour formation. Excess weight is associated with a wide range of hormonal and metabolic effects that may be involved in the promotion of cancer. Dietary factors could, in theory, be confounders with high meat intake, especially processed meat, and a low intake of fibre-rich vegetables and fruit being particularly linked to colon cancer and also being part of a weight-gain-inducing, energy-dense diet. However, several of the studies also assessed diet and the impact of higher BMIs seemed to be independent of the direct dietary effects.

Endometrial cancer

Both case–control and cohort studies have shown a relationship between higher BMI and increased risk of developing endometrial cancer, even after adjusting for other risk factors relating to the reproductive system, such as age at birth of first child and parity (Le Marchand et al. 1991). There was a remarkably consistent relationship between high BMI and risk of endometrial cancer in 22 of the 25 studies assessed by IARC (2002), studies which considered only cancer incidence and adjusted for all suggested confounders showing similar relationships. Bergström et al. (2001) used four of the seven cohort and 17 case–control studies reviewed by IARC (2002) to calculate by meta-analysis the incremental risk shown in Table 8.38. The overall risks of endometrial cancer appeared to be equivalent at different ages, but adult weight gain seems to be particularly important whatever the early adult weight status. Upper body fatness may be particularly conducive to the process of car-

cinogenesis, but the standard measures of abdominal fatness have given inconsistent results.

The dominant mechanistic theory relates to the unopposed estrogen hypothesis, according to which estrogenic contraceptives or hormone replacement therapy enhance the risk of endometrial cancer, whereas progesterone-containing preparations confer protection. Estrogens are known to induce endometrial proliferation via local production of insulin growth factor (IGF-1), whereas progesterone induces the production of an endometrial IGF-1-binding protein. Women with low levels of plasma SHBG, high levels of androgens and, after the menopause, elevated levels of total and bioavailable estrogens have an increased risk of endometrial cancer, as have younger women with the polycystic ovarian disease, which is associated with chronic anovulation and therefore low rates of production of progesterone. All these findings, therefore, fit the concept of excess available bioactive estrogen, which induces endometrial cell proliferation. Insulin resistance and higher concentrations of circulating IGF-1 induced by the lower concentrations of IGF-binding proteins in women who gain weight may also be involved. The IARC report notes that, given the substantial changes in insulin resistance, IGF-1 and estrogen status which accompany weight loss, it is possible that weight reduction quite late in life could reduce the risk of the estrogen-promoted cancers of the postmenopausal breast and endometrium.

5.8 Body weight and total mortality

Clearly, the net associations of BMI with total mortality will depend crucially on the component causes of death, which vary substantially by age, sex and population. Effects on total mortality were not estimated directly in these analyses for this reason, only cause-specific estimates being made. However, for completeness, data relating BMI to total mortality (usually derived from middle-aged North American populations) are reviewed here.

An extensive review of the relationship between BMI and total all-cause mortality, based on a detailed systematic review, was published by Troiano et al. (1996). About 1000 citations dating from 1861 to 1991 were identified; of these, 22 suitable studies were selected, with 56 substudy groups (e.g. in relation to age, ethnicity, sex and smoking status) and 354 BMI groups. Most of the studies dealt with Caucasian men, but 14 substudies assessed Caucasian women. Only two substudies in Asian men (not women) were available and one substudy in Samoan men and women combined was assessed. The authors distinguished data derived from insurance companies from data derived from other populations because they demonstrated that insurance data, particularly those from the United States, were associated with lower mortality in relation to BMI than that found in the general population. It was inferred that these data, which formed the basis of many earlier official reviews on the

impact of obesity for governments, for example, in the United States and the United Kingdom, related to groups in society who were relatively affluent and therefore, for a variety of reasons, able to sustain better health.

Troiano et al. (1996) demonstrated evidence of a U-shaped curve of mortality in relation to BMI, but this curve varied depending on whether the data were derived from the United States or elsewhere (predominantly northern Europe and Scandinavia). When all data were included, as shown in Table 8.39, there was clear evidence of a minimum mortality at BMIs of 24–27 kg/m^2, the lower value being that obtained with longer, i.e. 30-year follow-ups of adults. Most of these data relate to individuals who were aged about 50 years and were followed for 30 years. The table dealing with all the studies shows a statistically significant increase of *z*-scores when the *z*-scores exceed 1.65. Clearly, even BMIs of ≤23 and ≥28 kg/m^2 are associated with higher mortality in these overall groups. It is noteworthy, however, that these analyses included

Table 8.39 The probability of death associated with BMI level, for either 10 or 30 years of follow-up (smokers and non-smokers included)

	Odds ratio		*z-score differences*	
BMI (kg/m^2)	*10 years*	*30 years*	*10 years*	*30 years*
19	2.08	2.89	1.16	2.29
20	1.86	1.97	1.64	2.43
21	1.65	1.48	2.00	2.50
22	1.46	1.21	1.74	2.32
23	1.30	1.06	1.25	1.68
24	1.16	—	0.84	—
25	1.07	1.00	0.50	0.11
26	1.01	1.07	0.18	0.82
27	—	1.20	—	1.45
28	1.04	1.39	0.63	2.10
29	1.15	1.68	1.27	2.87
30	1.36	2.12	2.18	3.84
31	1.73	2.69	3.04	4.84
32	2.23	3.49	3.13	5.03

— No data.

Notes: The odds ratios relate to the probability of death, with the lowest mortality for any BMI group taken as 1.0, the odds of the other groups then being calculated as the log of the increased mortality ratio. A z-score of ≥1.65 is evidence for a statistically significant increase ($P < 0.05$, one-tailed). Note that the minimum mortality occurred at a BMI of 27 kg/m^2 when there was a 10-year follow-up, but at 24 kg/m^2 with a 30-year follow-up. Men and women, smokers and non-smokers, USA and non-USA studies included.

Source: Data are from Table 4 of Troiano et al. (1996).

both smokers and non-smokers. Non-smokers, considered over the 30-year period, had systematically lower risks at any BMI than smokers and Troiano et al. (1996) used these data for their baseline mortality curves.

There has been extensive discussion over the last 30 years regarding the repeated finding of higher mortality rates associated with lower BMIs. It was recognized that the original inclusion of data from smokers in such calculations had a marked effect because smokers are at greater risk of mortality, but tend to be thinner because of their reduction in appetite and their increased metabolic rate, that is, increased total energy expenditure, which leads to lower body weights when these effects are in energy balance. Thus the excess of smokers in the group of "thin" adults imposes higher mortality rates on the group overall, despite the lower BMIs.

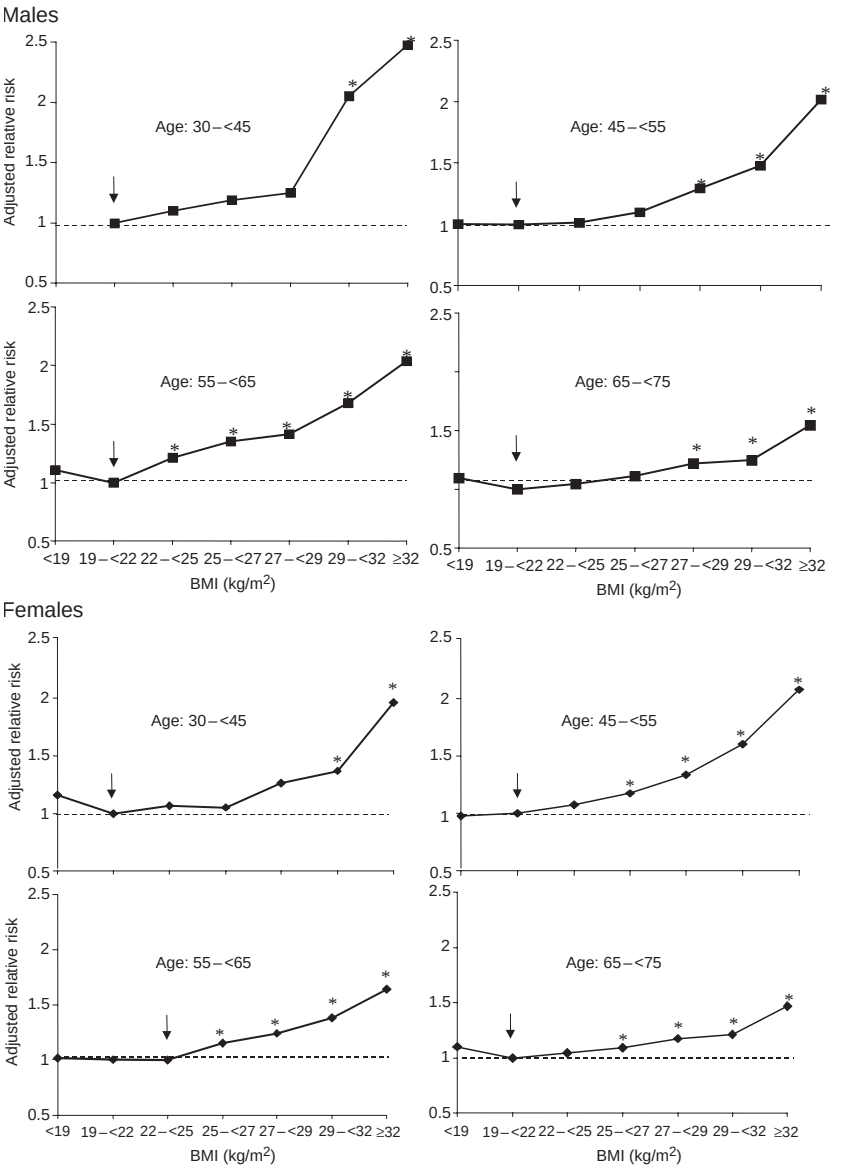
Further, the mortality rates of the groups with low BMIs may be enhanced by the presence of individuals with as yet undiagnosed diseases, for example, cancer, who may have lost weight before symptoms emerged or a diagnosis was made. A convention has therefore developed whereby the early deaths are excluded and only those deaths that occur 2–5 years after the initiation of any study are considered. By doing this, it is frequently found that the U-shaped curve converts to a J-shaped curve or log-linear relationship.

The data previously considered were standardized to men and women aged about 50 years. Stevens et al. (1998) have recently presented a detailed analysis based on about 325 000 men and women taking part in the American Cancer Society's Cancer Prevention Study. As already noted, this analysis in the United States relates to a relatively affluent fraction of the population and unfortunately used reported, not measured, weights and heights. Nevertheless, the sample is valuable in indicating the likely effect of age when assessing total mortality rates over a 12-year follow-up period. For this purpose, data were expressly chosen which related only to life-long non-smokers. Figure 8.14 shows the age-related risk of death from all causes. Note that men and women with a BMI of 19.0–21.9 kg/m^2 had the lowest total mortality. Small increases in risk were apparent at BMIs of 22.0–27.0 kg/m^2, but the increase in relative risk was more obvious in men than in women and in those aged <75 years. The risk of death from cardiovascular disease related to BMI was more clear-cut than the relative risk for all causes of death, as found in many studies (see below).

Figure 8.15 shows the decline in relative risk per unit increase in BMI with age. A very clear trend is seen, with the incremental risks being statistically significantly above those for the reference group up to the age of 75 years.

From Figure 8.14, it seems reasonable to conclude that the ideal BMI should be between 19.0 and 21.9 kg/m^2. These values relate to the individual risk of death in groups within a single population (in this

Figure 8.14 The relative risk of death from all causes, according to age and BMI: American Cancer Society's studies using self-reported weights and heights for BMI calculations

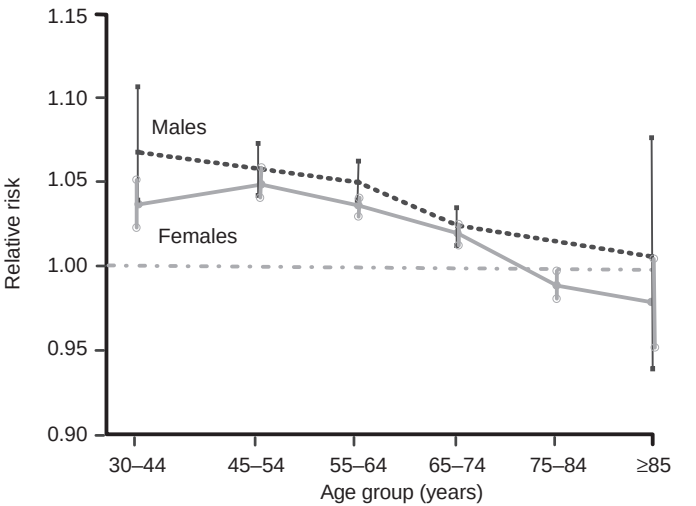


Key: Arrow denotes the BMI for minimum risk.

* Signifies a statistically different risk from that at BMIs of 19–22 kg/m^2.

Source: Data reformatted by Stevens from Stevens et al. (1998).

Figure 8.15 The change with age in the relative risk of death from all causes associated with a one-unit (1 kg/m^2) increase in BMI, in never-smokers



Note: The bars represent 95% confidence intervals and the trends are significant in all cases.

Source: Taken from Stevens et al. (1998) with the reference group having a BMI of 19.0–21.9 kg/m^2 in each age group.

case, the United States) and seem to apply to all age groups considered in the CRA analysis, from age 30–79 years. These findings are in keeping with the earlier analyses of the relationship between mean BMI and the minimizing of the prevalence of overweight, but would allow a higher proportion of underweight, which in a developing country would be a disadvantage. Given that the circumstances encountered by thin adults in the United States are probably different to those in developing countries, it seems reasonable to conclude that the data reinforce the choice of a low value for the minimum population mean BMI of 21.0–22.0 kg/m^2.

5.9 Excluded health outcomes

A number of other conditions have been widely quoted as concomitants of body-weight gain in affluent societies, including breathlessness, sleep apnoea, back pain, dermatitis, reactive depression and social isolation, menstrual disorders, infertility and gall bladder disease. The reasons for excluding these conditions are as follows.

Breathlessness: this is hard to quantify on an international basis and comparable data to those obtained in affluent societies in relation to excess weight are difficult to find in many parts of the world. It is also not clear to what extent different degrees of physical fitness in different parts of the world might affect an assessment of perceived breathlessness in those with excess weight.

Sleep apnoea is a well-described clinical complication of excess weight, which affects very obese children and adults. There are few data on its prevalence however, and it is generally considered to occur in those with more extreme forms of obesity.

Back pain: there are many causes of back pain, which is a very prevalent condition with substantial economic implications. Few studies however provide reliable estimates of hazard due to any specific risk.

Dermatitis: skin problems occur commonly in people who are obese, but few data are available other than from the developed world. Again, the description of skin problems associated with obesity is largely clinical and therefore this condition is not included.

Reactive depression and social isolation: it is well recognized that the societal response to obese individuals varies widely across the world. In some developing countries, the overweight and obese have traditionally been seen as successful individuals who are sufficiently wealthy or resourceful to have acquired enough food. In these circumstances, there is little indication of any social isolation or ensuing depression resulting from the overweight and obese being excluded from social interactions. This is quite different from accounts widely reported in North America and Europe where being obese, particularly for children and young women, is a social stigma which has clearly been related to poorer access to employment opportunities, lower earning power, a tendency to marry less affluent partners and a tendency to become personally distressed and socially isolated. Given the diversity in cultural perceptions of the benefits or handicaps of being overweight or obese, no attempt has been made at this stage to use representative data on body weight in adults in relation to mental health outcome.

Menstrual disorders and infertility: although severe underweight and anorexia nervosa have classically been associated with amenorrhoea and infertility, obesity is now increasingly recognized as a major feature of, for example, polycystic ovarian disease, which is associated with menstrual abnormalities, hirsutism and infertility. Weight loss markedly improves the condition of patients with this disorder and restores fertility. Little is known about the prevalence of this disease in different societies. The issue of infertility does not seem as yet to be of great societal concern if considered simply in terms of the probability of maintaining the population size. There is also no suggestion that the marked decline

in fertility seen, for example, in Europe (France, Italy and Spain), relates to the increasing prevalence of adiposity. Societal and social issues appear to be of far greater importance, so this outcome is also excluded from the current analysis.

Gallbladder disease: it has been recognized for several decades that excess weight gain is associated with a greater propensity to the development of gallstones and gall bladder disease. This relationship is clear-cut in developed societies, but as data on gall bladder disease are not collected systematically in many countries it is not possible to undertake an appropriate international analysis of the risk associated with weight gain.

5.10 Risk reversibility

The evidence on the reversibility of health hazards after reducing excessive BMIs has been given in each section setting out the relationship between increases in BMI and the development of individual diseases such as type II diabetes, ischaemic heart disease, hypertension and stroke, as well as cancers. The speed of reversibility depends on the condition. Thus an elevated blood pressure associated with weight gain can start to reverse within days of the beginning of weight loss; in association with other dietary measures and increased physical activity, lower body weights can also then limit the incidence of hypertension for 10 years (Stamler et al. 1980). Changes in blood lipids also begin within days of weight loss, although the restitution of low concentrations of HDL cholesterol to normal requires a period of several weeks at a stable lower body weight (Dattilo and Kris-Etherton 1992). The impact of weight loss on the development of ischaemic heart disease is more difficult to distinguish from other dietary changes accompanying the intended weight loss. Thus when individuals at a high risk of suffering a myocardial infarction are trained to markedly reduce their intake of fat, together with their intake of salt and sugars, as well as undertaking exercise training, they lose substantial amounts of weight and show a marked decrease not only in the principal risk factors for ischaemic heart disease (i.e. hypertension, dyslipidaemias and glucose intolerance) but also show a reduction within weeks in the incidence of angina and then in rates of myocardial infarction (Ornish et al. 1990); this is clearly evident within a 5-year period. The time needed to alter insulin resistance is also short (i.e. within a few days to weeks) and the resulting reduced incidence of type II diabetes becomes evident within 1 or 2 years, although to obtain statistically robust data in most studies about 3 years is needed (Tuomilehto et al. 2001).

6. Results

Tables 8.40–8.42 show the proportion of the included diseases, the number of deaths and disease burden attributable to increases in BMI

above 21.0 kg/m^2 in the different subregions of the world in 2000. Figure 8.16 summarizes the contributions of the diseases considered in this analysis to the total global burden of ill-health attributable to the effect of high BMI in 2000.

No lives are lost because of arthritis, but the global total mortality for cancers is appreciable, amounting to 74 000 for colon cancer, 47 000 for breast cancer and 32 000 for endometrial cancer, i.e. a total of 153 000 cancer deaths in 2000. However, these figures are dwarfed by the 491 000 deaths from diabetes, 489 000 from ischaemic stroke, 1 168 000 from ischaemic heart disease and 290 000 from hypertensive disease. Thus by considering only the major diseases affected by high BMI, a total of 2 592 000 deaths in 2000 were attributable to this risk factor. There are marked regional differences in this mortality burden, some of which reflect major differences in population sizes.

It is evident from the impact of weight gain on risk of arthritis that those subregions with a large proportion of adults with high BMIs, for example, AMR-A, AMR-B, EUR-A and EUR-B, are likely to have more of a burden linked directly to the physical demands of weight bearing, but much depends on the quality of the documentation of degrees of handicap associated with arthritis globally. The proportions of diabetes attributable to BMI increases range from 38–88% according to subregion. For diabetes and cardiovascular diseases, while the gradient of

Figure 8.16 The contribution of high BMI to the global burden of ill-health in the year 2000

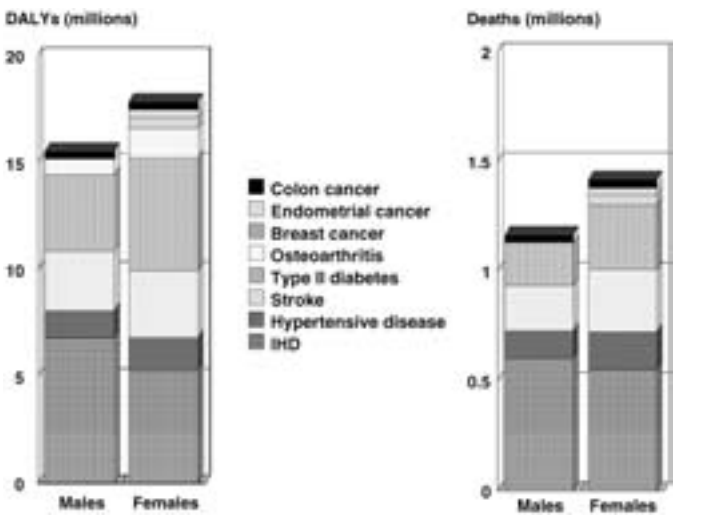


Table 8.40 Percentage of different diseases which is attributable to high BMI in adults aged ≥30 years, by subregion

	Osteoarthritis		*Colon cancer*		*Postmenopausal breast cancer*		*Endometrial cancer*		*Type II diabetes*		*Stroke*[a]		*Ischaemic heart disease*		*Hypertensive disease*	
Subregion	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
AFR-D	6	6	4	5	NA	3	NA	15	38	46	14	13	13	12	24	22
AFR-E	7	9	5	7	NA	4	NA	25	44	58	17	20	15	19	29	32
AMR-A	22	24	17	18	NA	12	NA	52	83	88	40	37	37	32	63	58
AMR-B	17	23	13	16	NA	10	NA	46	71	83	34	40	32	37	52	60
AMR-D	18	21	13	14	NA	8	NA	41	69	77	31	34	31	32	52	54
EMR-B	15	15	10	13	NA	7	NA	43	62	72	26	32	30	32	45	51
EMR-D	10	15	7	11	NA	5	NA	34	55	72	18	25	21	26	36	44
EUR-A	22	24	18	18	NA	13	NA	50	78	84	35	31	35	29	56	50
EUR-B	15	22	15	19	NA	12	NA	48	71	84	35	41	34	38	56	65
EUR-C	17	25	14	19	NA	13	NA	52	68	83	33	37	33	33	56	64
SEAR-B	9	10	7	8	NA	4	NA	24	44	56	18	21	17	19	32	36
SEAR-D	2	5	1	4	NA	2	NA	14	13	43	3	10	4	10	7	21
WPR-A	11	12	8	9	NA	5	NA	28	55	65	20	18	19	15	31	27
WPR-B	9	10	7	8	NA	5	NA	26	47	62	18	19	17	18	30	34
World	11	14	11	13	NA	8	NA	42	50	66	21	25	21	22	36	41

NA Not applicable.

[a] Percentage of stroke attributable to high BMI was based upon estimates for ischaemic stroke. The fractions for total stroke are given in the annex tables for the chapter (see the CD-ROM accompanying this book).

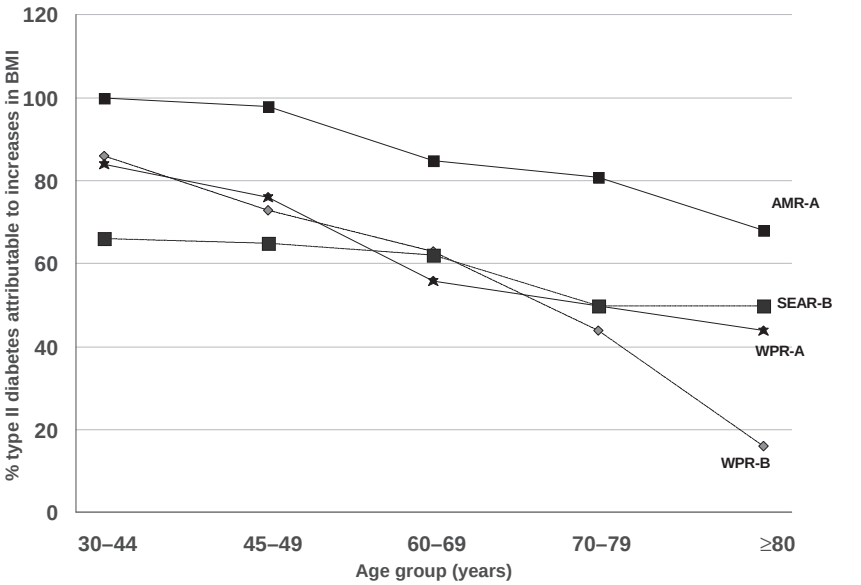
Table 8.41 Mortality (000s) from diseases caused by high BMI in adults aged ≥30 years, by subregion

Subregion	*Osteoarthritis*	*Colon cancer*	*Postmenopausal breast cancer*	*Endometrial cancer*	*Type II diabetes*	*Stroke*	*Ischaemic heart disease*	*Hypertensive disease*	*Total*
AFR-D	0	0	0	0	7	7	14	4	32
AFR-E	0	1	1	0	16	11	20	7	56
AMR-A	0	12	8	4	62	28	135	22	271
AMR-B	0	4	4	5	103	35	78	33	262
AMR-D	0	1	0	2	11	4	9	6	33
EMR-B	0	1	0	0	10	5	33	14	63
EMR-D	0	1	2	0	22	16	65	19	125
EUR-A	0	25	14	8	70	66	167	29	379
EUR-B	0	5	3	3	23	51	137	36	258
EUR-C	0	10	6	6	16	124	284	21	467
SEAR-B	0	2	1	1	32	13	34	19	102
SEAR-D	0	1	2	0	35	24	82	9	153
WPR-A	0	3	1	1	9	10	15	2	41
WPR-B	0	9	4	2	74	95	95	68	347
World	0	74	47	32	491	489	1168	290	2592

Table 8.42 Burden of disease in DALYs (000s) from diseases caused by high BMI in adults aged ≥30 years, by subregion

Subregion	*Osteoarthritis*	*Colon cancer*	*Postmenopausal breast cancer*	*Endometrial cancer*	*Type II diabetes*	*Stroke*	*Ischaemic heart disease*	*Hypertensive disease*	*Total*
AFR-D	37	6	5	2	148	110	199	57	564
AFR-E	55	9	14	5	240	188	282	94	887
AMR-A	243	104	77	46	1 171	400	1 243	195	3 479
AMR-B	193	41	40	77	1 367	504	892	309	3 423
AMR-D	22	5	5	22	164	51	91	62	422
EMR-B	33	7	6	4	273	84	447	136	990
EMR-D	70	12	17	6	515	217	865	208	1 910
EUR-A	348	185	127	66	876	619	1 271	166	3 658
EUR-B	176	46	35	37	401	559	1 304	306	2 864
EUR-C	266	95	66	69	526	1 291	2 741	208	5 262
SEAR-B	85	21	18	7	555	175	406	201	1 468
SEAR-D	95	8	20	5	916	309	1 156	117	2 626
WPR-A	74	31	11	9	224	135	134	11	629
WPR-B	421	104	45	33	1 503	1 280	1 139	709	5 234
World	2 118	676	486	386	8 877	5 921	12 170	2780	33 414

Figure 8.17 Selected subregional differences in the age-related proportion of type II diabetes attributable to increases in BMI in women



relative risk was considered the same in the different subregions, the absolute risk varied substantially because of other determinants of these diseases such as dietary variation, which causes additional changes in both serum cholesterol levels and blood pressure.

Figure 8.17 presents subregional differences in the age-related proportion of type II diabetes attributable to high BMI in women. The picture of differences is magnified and the clear downward gradient in the attributable fraction with increasing age is evident. Similar relationships are observed for all three cardiovascular end-points, but not for the cancers or osteoarthritis, where relative risks were independent of age.

7. Discussion

These analyses highlight the very substantial burden of ill-health incurred by increases in adult BMIs with the greatest impact in disease specific terms being the burden associated with the development of type II diabetes. The attributable fraction for high BMIs does vary markedly by subregion, which implies that other factors contribute to or interact with increases in BMI. The overall burden by subregion, however, depends on

the prevalences of both high BMIs and of the particular disease (e.g. ischaemic heart disease) as well as the overall size of the population. The current analyses do not take account of the interactions with other risk factors, for example, physical inactivity, which could confound the estimated burden attributable to high BMIs *per se*. However, increases in body weight also amplify other major risk factors such as blood pressure and blood cholesterol levels, and so discriminating a selective effect of high BMIs from dietary factors and physical activity is not straightforward. Nevertheless, on the basis of the current data, the impact of increases in BMI on the development of type II diabetes and on cardiovascular diseases and cancers in most parts of the world is substantial.

This is the first global analysis of the risks attributable to high BMIs and the results reinforce the recent recognition by WHO (2000) that this is one of the largest unrecognized public health problems that now need to be addressed. With the seemingly inexorable rise in mean BMIs in various populations, the projected impact on the global health burden will be very substantial by 2030 unless effective public health measures can be introduced soon.

8. Future exposure

8.1 Regional time trends in adult BMIs

There are as yet only a modest number of studies dealing with BMI changes in different populations, the most comprehensive being that conducted by Pelletier and Rahn (1998). In this study, a series of small data sets were found for several countries within different regions of the world. The data sets differed by sex, age and setting, i.e. whether they were studied in a clinical context, were related to urban or rural groups or differed in terms of their economic status. By specifying these variables, Pelletier and Rahn (1998) were able to identify the magnitude and significance of these variables and still develop generic equations for the overall BMI changes with time in different regions. These estimates of time trends per decade are presented in Table 8.43.

Given the fact that these data relate to the 1980s and that the equations are often based on data from clinics or other small groups, more recent evidence from larger and more representative samples was sought, again with the specification that the BMIs should be measured and that mean BMI values were available.

Popkin et al. (2002) have recently presented valuable new data on annual increments in the prevalence of overweight and obesity. Unfortunately this approach does not use the continuous approach to BMI–risk relationships and extrapolating from the equations for the curvilinear relationship between the mean BMI and the prevalence of

Table 8.43 Predicted regional rates of change in BMI per decade for adults

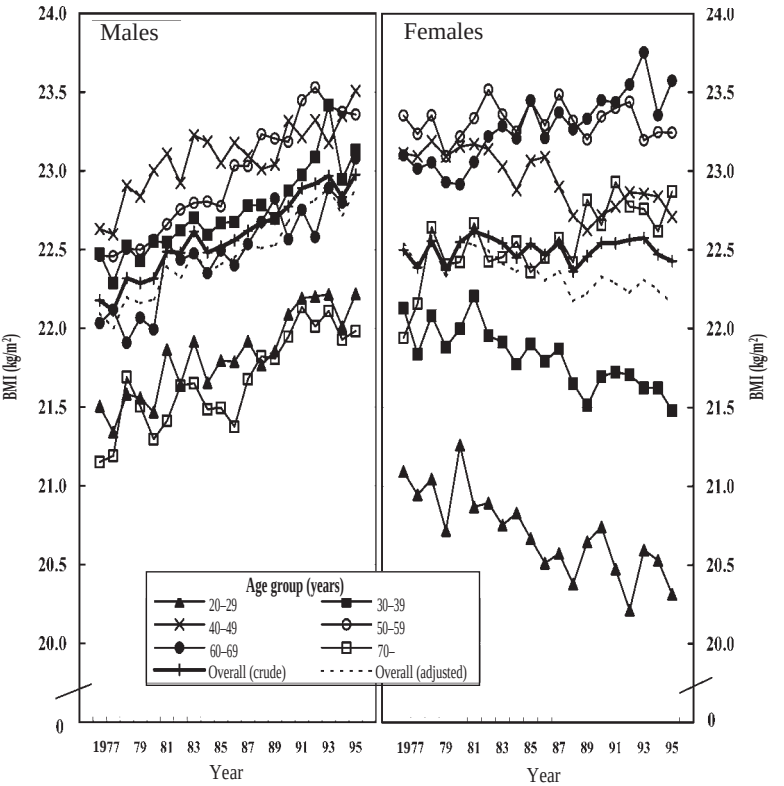
Country or area	*Mean BMI change per decade*
Sub-Saharan Africa	0.207
South and South-East Asia	0.169
India	0.048
Australasia	–0.295
Polynesia and Micronesia	0.957
Latin America and the Caribbean	0.112
China	0.106

obesity at BMIs of ≥30 kg/m^2 (see Figure 8.2) proved too inaccurate, given the data provided on annual increment in obesity and the need to extrapolate to 2030.

There is, however, a series of recent analyses that attempt to look at changes in body weight over the last 10–40 years. Some of these analyses, for example from Brazil (Monteiro et al. 1995), several European countries (Molarius et al. 2000), India (Shetty 2002), Japan (Yoshiike 2002), and the United States (Flegal and Troiano 2000), are based on repeated national representative data and allow some preliminary subregional estimates to be developed. To these data it was possible to add background data sets while recognizing that many were not representative of a country, let alone a subregion and that sex-specific rates may well be very different in different societal settings.

The uncertainty associated with assuming that both sexes and all age groups are likely to respond in the same way over the next 30 years is illustrated by Figure 8.18, which sets out the detailed age- and sex-based time trends in mean BMI for the Japanese population (Yoshiike 2002). It is evident that whereas the mean BMI for men has increased in a linear fashion between 1977 and 1995 in all age groups, the mean BMI for women aged <50 years has shown a progressive reduction amounting to about 0.3 BMI units per decade. Given that the mean BMI is now 20.4 kg/m^2 for young women aged 20–29 years and 22.2 kg/m^2 for women aged 30–49 years, it is clear that predicting a continuation of this trend for the subsequent 35 years, that is, to 2030, would mean that the average BMI of the younger women would fall to 19.1 kg/m^2; this in turn would imply an appreciable increase in the proportion of underweight women with potentially increased morbidity (Shetty and James 1994). Yet we know that Japanese children, both girls and boys, are becoming heavier. Therefore modelling the changes in BMI by age and sex for the next 30 years presents difficulties. What is clear, however, is that the age-related changes in BMI were

Figure 8.18 Annual changes in mean BMI, by age and sex



Note: Adjusted for age distribution by use of the new world population (WHO 1993).
Source: The National Nutrition Survey, Japan, 1976–1995.

maintained from 1976 to 1995 so these are unlikely to change, unless the weights of Japanese children have shown a particularly acute recent increase.

Bearing in mind the uncertainty of these predictions, the assumption was made that the current trends in any subregion would persist in unremitting manner for the next 30 years. It was assumed that data obtained from a country within a subregion would apply to the whole adult population within that subregion. Where more than one data set was available, the values were adjusted not only for the intervals of study and the date on which measurements were made, but also for the differential population numbers in the countries being measured, with appropriate adjustments to the overall population numbers in the subregion. Only adult data were considered; no allowances were made for

children's BMIs since this would have additionally required the prediction of the probability that the current BMIs of children, expressed in percentiles of BMI for age and sex, would be maintained on the same percentiles into adult life on the basis of the BMI percentile charts produced by the IOTF (Cole et al. 2000). Where the data only covered adults aged ≤60 years, it was assumed that the same delta changes were also occurring in the older age groups, thus maintaining the current age-related differences in mean BMI within the subregion.

Different subregional approaches

Given the paucity of data, the following extrapolations proved necessary for certain subregions.

AFR-D: The data relied predominantly on the observed changes in BMI in Ghanaian women, with additional data being available from Mauritius and the Seychelles. The latter two island data sets for both sexes were then used in conjunction with data from South Africa to assess the differential sex-specific trends. These differentials were then used in conjunction with the Ghanaian female data to derive male values for the subregion.

AFR-E: Here it proved necessary to use data on the secular increases found in rural South African men and women (Temple et al. 2001). It was expected that urban trends might have been greater, but given categorical analyses suggesting more modest increases in the prevalence of overweight in the United Republic of Tanzania and Zambia, the rural South African data were applied to the whole subregion.

AMR-A: This was relatively straightforward given the availability of data sets from both Canada (Tremblay et al. 2002) and the United States (Flegal and Troiano 2000). The changing prevalence of overweight and obesity in Cuba was noted (Rodriguez-Ojea et al. 2002), but it was not possible to obtain suitable data on mean BMI changes. Therefore the North American data sets were applied to the whole subregion.

AMR-B: There are ample Brazilian data on secular trends and a series of unpublished analyses from other countries, but the only published and available Brazilian data were those giving overall adult values (Monteiro et al. 1995). However, new analyses from a national survey carried out in Mexico in 2000 were made available (Sánchez-Castillo et al. 2003), together with earlier representative Mexican data provided by Arroyo and colleagues (Arroyo et al. 2000).

AMR-D: In the absence of satisfactory data, the equations of Pelletier and Rahn (1998) were applied.

EMR-B: Kuwaiti data (al-Isa 1997) were applied to the whole subregion, it being recognized that there were numerous published data sets from small clinical and other studies available, as well as several recent unpub-

lished national data sets which highlight the marked secular trends in the subregion.

EMR-D: Moroccan categorical analyses (Benjelloun 2002) having suggested marked BMI increases, the Kuwaiti data were also applied to this subregion.

EUR-A: There were ample data sets from Belgium, Denmark, Finland, Germany, the Netherlands and the United Kingdom that could be used to derive an overall set of population-adjusted, sex-specific and age-related predictions.

EUR-B: Reliance was placed on data on secular trends in Poland.

EUR-C: Although some categorical Hungarian trends data were available, it was concluded from subregional cross-sectional data that the Polish trends data should be applied to this subregion.

SEAR-B: In the absence of data on mean BMI trends, Pelletier and Rahn's equation (1998) for south and east Asia was used.

SEAR-D: Indian data from the repeated nationally-representative surveys were used for this subregion.

WPR-A: Both Australian and the extensive Japanese representative data could be used for this subregion.

WPR-B: Although new data sets are becoming available for the numerically dominant country (China), comparable data sets with mean BMIs from a variety of adult men and women were only available from Zhou (2002). To these data sets were added information from Malaysia, the Republic of Korea and Samoa.

The predicted mean BMIs for the different subregions in 2030 are set out in Table 8.44. As already indicated, these predicted values encompass considerable uncertainties but do suggest that if current trends continue then in some subregions (e.g. AMR-A, AMR-B, EUR-A and EUR-B) half of the adults in each of several age groups will have estimated BMIs of >30 kg/m^2, that is, the WHO classification of obesity. Given that there is now intense concern about escalating rates of obesity, it is very likely that new public health measures will be adopted to limit this rise, but so far the efforts of millions of people in affluent societies to either slim or limit weight gain seems to have been of only modest success. The challenge is to arrest the current trends towards increases in BMI and, if possible, to reverse the public health burden associated with weight gain. Although traditionally the prevalence rates of overweight and obesity are used as an index of the health burden, the current analyses show that the full range of BMIs should be considered. This in turn emphasizes the need to take population-based approaches to preventive strategies for minimizing the hazards of excess weight gain.

Table 8.44 Predicted mean BMIs in each subregion in 2030, by sex and age

		BMI (kg/m^2) Age (years)				
Subregion	*Sex*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	21.9 (3)[a]	22.4 (3)	21.2 (3)	21.2 (3)	20.7 (4)
	Female	23.3 (5)	22.2 (6)	22.2 (6)	21.4 (6)	22.0 (6)
AFR-E	Male	23.1 (10)	23.3 (10)	22.9 (10)	24.1 (10)	21.9 (11)
	Female	28.0 (22)	27.9 (22)	27.4 (23)	25.5 (25)	24.0 (27)
AMR-A	Male	28.8 (9)	31.1 (13)	31.4 (15)	28.0 (5)	28.4 (13)
	Female	29.5 (13)	32.0 (16)	30.3 (10)	29.2 (9)	27.3 (9)
AMR-B	Male	28.0 (12)	28.0 (9)	27.9 (9)	28.5 (9)	27.1 (10)
	Female	29.2 (12)	30.0 (10)	28.9 (7)	28.7 (7)	27.5 (8)
AMR-D	Male	25.7 (2)	26.3 (2)	26.4 (2)	26.7 (2)	26.7 (2)
	Female	26.2 (2)	27.0 (2)	27.2 (2)	27.0 (2)	26.6 (2)
EMR-B	Male	27.8 (13)	27.8 (10)	24.9 (3)	23.7 (3)	24.1 (3)
	Female	29.0 (12)	28.9 (9)	26.1 (2)	23.9 (3)	26.6 (2)
EMR-D	Male	23.3 (7)	23.4 (7)	23.1 (7)	22.6 (8)	21.6 (8)
	Female	25.8 (8)	24.6 (8)	24.1 (8)	23.1 (9)	20.7 (10)
EUR-A	Male	28.2 (7)	29.9 (10)	30.5 (10)	30.2 (10)	28.5 (9)
	Female	25.7 (2)	30.2 (10)	31.1 (10)	30.5 (10)	28.5 (11)
EUR-B	Male	28.0 (12)	29.5 (11)	30.3 (11)	28.8 (12)	27.8 (12)
	Female	27.2 (6)	29.6 (6)	30.6 (6)	30.4 (5)	28.7 (4)
EUR-C	Male	28.2 (12)	28.1 (8)	28.9 (12	28.2 (12)	26.8 (8)
	Female	27.3 (3)	28.2 (–1)	27.7 (–4)	27.0 (–1)	26.6 (5)
SEAR-B	Male	23.2 (3)	24.0 (3)	23.6 (3)	23.2 (3)	23.2 (3)
	Female	23.3 (3)	24.5 (3)	24.9 (3)	23.1 (3)	23.1 (3)
SEAR-D	Male	21.6 (10)	20.8 (10)	21.0 (9)	19.8 (10)	21.2 (9)
	Female	21.7 (4)	22.0 (3)	19.5 (3)	20.2 (3)	16.6 (4)
WPR-A	Male	25.1 (6)	25.8 (8)	25.2 (8)	24.4 (7)	23.5 (7)
	Female	21.5 (–4)	23.5 (–1)	25.1 (5)	24.5 (5)	23.8 (5)
WPR-B	Male	26.1 (15)	26.4 (14)	26.1 (15)	25.6 (15)	23.6 (14)
	Female	26.1 (15)	26.8 (14)	26.9 (14)	25.9 (15)	24.4 (16)

[a] Figures in parentheses refer to the percentage increase over the 2000 estimate.

8.2 The implications of excessive weight gain among children

The foregoing analyses of the disease burden associated with increases in BMI relate only to adults aged ≥30 years. However, there is now rapidly mounting concern regarding the increasing prevalence of overweight and obesity in children (Ebbeling et al. 2002). The impact of psychosocial, physical and metabolic problems has not been incorporated in the current analyses, but may well have to be considered within the next 5–10 years. Overweight children in many countries are handicapped by the social stigma of being considered overtly fat by their peers. In

addition, these children have a propensity to bone and joint deformation during their growing phase, as well as breathlessness and, in more extreme cases, sleep apnoea arising from the mechanical handicap of being heavy. It is now clear that overweight children also have higher blood pressure, serum lipid abnormalities and increasing insulin resistance, all of which are hallmarks of early metabolic disease and susceptibility to atherosclerosis and other cardiovascular problems (DiPietro et al. 1994; Must et al. 1992; Unger et al. 1990). Within the last 5 years, paediatricians have observed that clinics for children with type I diabetes now include a remarkably increasing number of very overweight children with type II diabetes. In many parts of the world, type II diabetes occurring in adolescence is now a more prevalent condition than type I diabetes (Rosenbloom et al. 1999). As with adult type II diabetes, these children show a remarkable improvement in their glucose-handling capacity and in other risk factors if they lose weight, but many soon develop a need for insulin therapy and their condition becomes difficult to control. Children with poorly controlled diabetes are known to have accelerated atherosclerosis with microvascular disease leading to blindness and renal failure in their early 30s. Concern regarding obesity and type II diabetes in children is now being accentuated by the recognition that mothers who develop gestational diabetes produce larger babies who are then very susceptible to pre-adolescent obesity and to the development of type II diabetes in adolescence (Silverman et al. 1998).

People who are overweight in childhood are more prone to be obese when they enter adult life and these individuals are also likely to continue to gain weight in adulthood. Such individuals then have up to a 100-fold increased risk of developing type II diabetes compared with normal weight children who do not gain excessive weight once they are adults (Colditz et al. 1995). Early data from insurance companies also showed that heavy young adults had a much greater likelihood of suffering premature deaths (Blair and Haines 1966) and this is now recognized to be related to their greater propensity to hypertension, dyslipidaemia, glucose intolerance with insulin resistance and accelerated cardiovascular disease. These observations are relevant to any assessment of the future burden of disease arising from high BMIs in adults because the rapidly rising prevalence of overweight and obesity in children is likely to amplify the currently predicted risks of excess weight in young adults.

Acknowledgements

We are most grateful for the support of numerous individuals and institutions in gathering data for this analysis. In addition we wish to acknowledge the assistance of Mrs Jean James in preparing the manuscript for this chapter.

The following contributed invaluably by providing re-analysed data to assist in the IOTF's analyses: N. Adra, P. Arroyo, K. Babinska, G. Biro, A. Deev, T.P. Gill, N. Hwalla, M. Lahti-Koski, B. Lajos, A. Ferro-Luzzi, A. Kaic-Rak, G. Mensink, J.C. Montero, A. Nielsen, I. Palczewska, G. Pekcan, N. Rak, C.P. Sánchez-Castillo, G. Whitlock and the Asia-Pacific Cohort Studies Collaboration.

In addition, the following assisted by allowing access to data or suggesting sources:
T. Athanassouli, W. Becker, Z. Brazdova, W. Chen, W. Freire, V. Gudnason, K. Habibullah, U. Hagman, B. Heitman, N. Katsilambros, J. Luthy, V. Lambert, A.O. Musaiger, A. Neilson, L. Ovesen, R. Prattala, W. Rand, K.S. Reddy, A. Robertson, J. Seidell, L. Steingrimsdottir, M.Q.-K. and K. Talukder, R. Uauy, and M. Vasconcellos.

Notes

1 See preface for an explanation of this term.

2 The standard deviation (SD) was sometimes missing for different sexes and age groups. This problem was dealt with as follows:

SD missing for one sex; for example, there were some subregions where SDs were available only for females

For all subregions with SDs available for both men and women, SDs were in general higher in females than males. The mean difference between the SDs of females and males varied from 0.24–2.25 units, with the largest differences observed between higher SD values. For example, subregions with SDs of >5–6 units in women tended to have SDs in these women which were >1 unit higher than those in men, whereas with female SD values of 3–4.5, the sex differences in SDs were <1.

The mean of the differences when the SD values were <1 unit was 0.6 units, and for those >1 unit was 1.63. As a result, to estimate male SD from female SD in subregions where SD values were <5 in most age groups, a simple subtraction of 0.6 from the SD for females was used to estimate the male SD. In other subregions where SDs were higher in females, a value of 1 was subtracted from the female SD to estimate the corresponding male SD. The same approach was applied to all age groups. These differences in SDs by sex are then reflected in the differences in prevalences of overweight and obesity in men and women with the same mean BMI.

For example, in AMR-D an SD was available for females only and the values varied from 3.8–4.6 units. Subtracting 0.6 from these gave the corresponding values for men of 3.2, 3.8 and 4.0. In EMR-D, again only SDs for women were obtained with values varying from 6.4 to 8.5. In this case, the correction factor of 1.6 was applied to obtain the estimates for men.

SD missing for some age groups

There was no clear pattern of SD by age group. For the age groups where no SDs were available, it was assumed that the SD was equal to an average

of the observed SD for the subregion. For example, in AMR-D, the mean SD for females aged 18–59 years was (3.4+4.4+4.6)/3=4.13.

This figure was then applied to the remaining age groups where no SDs for females were available.

References

Acheson RM, Kelsy JL, Ginsburg GN (1974) The New Haven survey of joint diseases. XVI. Impairment, disability and arthritis. *British Journal of Preventive Medicine*, **27**:168–176.

Ajlouni K, Jaddou H, Batieha A (1998) Obesity in Jordan. *International Journal of Obesity and Related Metabolic Disorders*, **22**:624–628.

al-Isa AN (1995) Prevalence of obesity among adult Kuwaitis. *International Journal of Obesity*, **19**:431–433.

al-Isa AN (1997) Temporal changes in body mass index and prevalence of obesity among Kuwaiti men. *Annals of Nutrition and Metabolism*, **41**:307–314.

Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB (1999) Annual deaths attributable to obesity in the United States. *Journal of the American Medical Association*, **282**:1530–1538.

al-Mannai A, Dickerson JW, Morgan JB, Khalfan H (1996) Obesity in Bahraini adults. *Journal of the Royal Society of Health*, **116**:30–32, 37–40.

al-Nuaim AR, al-Rubeaan K, al-Mazrou Y, al-Attas O, al-Daghari N, Khoja T (1996) High prevalence of overweight and obesity in Saudi Arabia. *International Journal of Obesity*, **20**:547–552.

Anderson JJ, Felson DT (1998) Factors associated with osteoarthritis of the knee in the first national health and nutritional examination survey (NHANES I). *American Journal of Epidemiology*, **128**:179–189.

Anonymous (1999) *Victorian burden of disease study: morbidity*. Public Health Division, Department of Human Services, Melbourne.

Arroyo P, Loria A, Fernández V et al. (2000) Prevalence of pre-obesity and obesity in urban adult Mexicans in comparison with other large surveys. *Obesity Research*, **8**:179–185.

Ascherio A, Rimm EB, Giovannucci EL et al. (1992) A prospective study of nutritional factors and hypertension among US men. *Circulation*, **86**:1475–1484.

Barker DJP (1998) *Mothers, babies and health in later life*. Churchill Livingstone, London.

Bell AC, Swinburn BA, Simmons D, Wang W, Amosa H, Gatland B (2001) Heart disease and diabetes risk factors in Pacific Islands communities and associations with measures of body fat. *New Zealand Medical Journal*, **114**:364–365.

Benjelloun S (2002) Nutrition transition in Morocco. *Public Health Nutrition*, **5**:135–140.

Bergmann KE, Mensink GBM (1999) Korpermasse und Ubergewicht. *Gesundheitswesen*, **62**:S115–120.

Bergström A, Pisani P, Tenet V, Wolk A, Adami HO (2001) Overweight as an avoidable cause of cancer in Europe. *International Journal of Cancer*, **91**:421–430.

Berkham LF, Breslow L (1983) *Health and ways of living: the Alameda county studies*. Oxford University Press. New York.

Björntorp P, Rosmond R (1999) The hypothalamic origin of the metabolic Syndrome X. *Annals of the New York Academy of Sciences*, **892**:297–307.

Blair BF, Haines LW (1966) Mortality experience according to build at the higher durations. *Transactions of the Actuarial Society,* **18**:35–41.

Bovet P, Shamlaye C, Kitua A et al. (1991) High prevalence of cardiovascular risk factors in the Seychelles (Indian Ocean). *Arteriosclerosis Thrombosis*, **11**:1730–1736.

Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr (1999) Body-mass index and mortality in a prospective cohort of US adults. *New England Journal of Medicine*, **341**:1097–1105.

Carey VJ, Walters EE, Colditz GA et al. (1997) Body fat distribution and risk on non-insulin dependent diabetes mellitus in women. The nurses' health study. *American Journal of Epidemiology*, **145**:614–619.

Chaichareon P, Leeiahagul P, Tanphaichitr V (1992) Body mass index in adults with dental diseases. *Internal Medicine*, **8**:113–117.

Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1994) Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*, **17**:961–969.

Chilima DM, Ismail SJ (1998) Anthropometric characteristics of older people in rural Malawi. *European Journal of Clinical Nutrition*, **52**:643–649.

Cicuttini FM, Baker JR, Spector TD (1996) The association of obesity with osteoarthritis of the hand and knee in women: a twin study. *Journal of Rheumatology*, **23**:1221–1226.

Cicuttini FM, Spector TD (1998) Obesity, arthritis and gout. In: *Handbook of obesity.* Bray GA, Bouchard C, James WPT, eds. Marcel Dekker Inc, New York.

Colditz GA, Willett WC, Rotnitzky A, Manson JE (1995) Weight gain as a risk factor for clinical diabetes mellitus in women. *Annals of Internal Medicine*, **122**:481–486.

Colditz GA, Willett WC, Stampfer MJ et al. (1990) Weight gain as a risk factor for clinical diabetes mellitus in women. *American Journal of Epidemiology*, **132**:501–513.

Cole TJ, Bellizzi MC, Flegal KM, Dietz WH (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. *British Medical Journal*, **320**:1240–1243.

Cooper RS, Ford E (1992) Comparability of risk factors for coronary heart disease among blacks and whites in the NHANES-I Epidemiologic Follow-up Study. *Annals of Epidemiology*, **2**:637–645.

Dattilo AM, Kris-Etherton PM (1992) Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *American Journal of Clinical Nutrition*, **56**:320–328.

Dawber TR, Meadors GF, Moore FE (1951) Epidemiological approaches to heart disease: the Framingham study. *American Journal of Public Health*, **41**:279–286.

de Onis M, Blössner M (2000) Prevalence and trends of overweight among preschool children in developing countries. *American Journal of Clinical Nutrition*, **72**:1032–1039.

Despres JP, Lemieux I, Prud'homme D (2001) Treatment of obesity: need to focus on high risk abdominally obese patients. *British Medical Journal*, **322**:716–720.

Deurenberg P, Deurenberg-Yap M, Guricci S (2002) Asians are different from Caucasians and from each other in their body mass index/body fat percent relationship. *Obesity Reviews*, **3**:141–146.

Deurenberg P, Yap M, van Staveren WA (1998) Body mass index and percent body fat: a meta-analysis among different ethnic groups. *International Journal of Obesity*, **22**:1164–1171.

Diabetes Prevention Program Research Group (2002) Reduction in the incidence of Type 2 diabetes with lifestyle intervention or Metformin. *New England Journal of Medicine*, **346**:393–403.

Dietz WH, Bellizzi MC (1999) Assessment of childhood and adolescent obesity. *American Journal of Clinical Nutrition*, **70**:S117–175.

DiPietro L, Mossberg HO, Stunkard AJ (1994) A 40-year history of overweight children in Stockholm: life time overweight, morbidity and mortality. *International Journal of Obesity and Related Metabolic Disorders*, **18**:585–590.

Dobson AJ, Evans A, Ferrario M et al. (1998) Changes in estimated coronary risk in the 1980s: data from 38 populations in the WHO MONICA project. World Health Organization. Monitoring trends and determinants in cardiovascular diseases. *Annals of Medicine*, **30**:199–205.

Drivsholm T, Ibsen H, Schroll M, Davidsen M, Borch-Johnsen K (2001) Increasing prevalence of diabetes mellitus and impaired glucose tolerance among 60-year-old Danes. *Diabetic Medicine*, **18**:126–132.

Dyer, AR, Elliot P (1989) The INTERSALT study: relations of body mass index to blood pressure. INTERSALT Co-operative Research Group. *Journal of Human Hypertension*, **3**:299–308.

Eason RJ, Pada J, Wallace R, Henry A, Thornton R (1987) Changing patterns of hypertension, diabetes, obesity and diet among Melanesians and Micronesians in the Solomon Islands. *Medical Journal of Australia*, **146**:465–469, 473.

Ebbeling CB, Pawlak DB, Ludwig DS (2002) Childhood obesity: public-health crisis, common sense cure. *The Lancet*, **360**:473–482.

Edelstein SL, Knowler WC, Bain RP et al. (1997) Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes*, **46**:701–710.

Eichholzer M, Luthy J, Gutzwiller F (1999) Epidemiology of overweight in Switzerland: results of the Swiss National Health Survey 1992–3. *Schweizerische Medizinische Wochenschrift*, **129**:353–361.

el Mugamer IT, Ali Zayat AS, Hossain MM, Pugh RN (1995) Diabetes, obesity and hypertension in urban and rural people of Bedouin origin in the United Arab Emirates. *Journal of Tropical Medical Hygiene*, **98**:407–415.

Epstein FH, Napier JA, Block WD et al. (1970) The Tecumseh study: design, progress, and perspectives. *Archives of Environmental Health*, **21**:402–407.

Eriksson KF, Lindgarde F (1991) Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia*, **34**:891–898.

Flegal KM, Troiano RP (2000) Changes in the distribution of body mass index of adults and children in the US population. *International Journal of Obesity*, **24**:807–818.

Ford ES, Giles WH, Dietz WH (2002) Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *Journal of the American Medical Association*, **287**: 356–359.

Franklin MF (1999) Comparison of weight and height relations in boys from 4 countries. *American Journal of Clinical Nutrition*, **70**:S157–162.

Gerhardsson de Verdier M, Hagman U, Steineck G, Rieger A, Norell SE (1990) Diet, body mass and colorectal cancer: a case-referent study in Stockholm. *International Journal of Cancer*, **46**: 832–838.

Giay T, Khoi HH (1994) Use of body mass index in the assessment of adult nutritional status in Vietnam. *European Journal of Clinical Nutrition*, **48**:S124–130.

Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1995) Physical activity, obesity, and risk for colon cancer and adenoma in men. *Annals of Internal Medicine*, **122**:327–334.

Goldstein DJ (1992) Beneficial health effects of modest weight loss. *International Journal of Obesity*, **16**:397–415.

Gonzales GF, Villena A, Gonez C, Zevallos M (1994) Relationship between body mass index, age, and serum adrenal androgen levels in Peruvian children living at high altitude and at sea level. *Human Biology*, **66**:145–153.

Gorzelniak K, Engeli S, Janke J, Luft FC, Sharma AM (2002) Hormonal regulation of the human adipose-tissue renin-angiotensin system: relationship to obesity and hypertension. *Journal of Hypertension*, **20**:965–973.

Hanley AJ, Harris SB, Gittelsohn J, Wolever TM, Saksvig B, Zinman B (2000) Overweight among children and adolescents in a Native Canadian community: prevalence and associated factors. *American Journal of Clinical Nutrition*, **71**:693–700.

Harris ML, Goldstein DA, Flegal KM et al. (1998) Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. *Diabetes Care*, **21**:518–524.

Harris TB, Ballard-Barbasch R, Madans J, Makuc DM, Feldman JJ (1993) Overweight, weight loss, and risk of coronary heart disease in older women. The NHANES I Epidemiologic Follow-up Study. *American Journal of Epidemiology*, **137**:1318–1327.

Harris TB, Launer LJ, Madans J, Feldman JJ (1997) Cohort study of effect of being overweight and change in weight on risk of coronary heart disease in old age. *British Medical Journal*, **314**:1791–1794.

Hart DJ, Spector TD (1993) The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford study. *Journal of Rheumatology*, **20**:331–335.

Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr (1991) Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *New England Journal of Medicine*, **325**:147–152.

Hernandez RE, Cardonnet LJ, Libman C, Gagliardino JJ (1987) Prevalence of diabetes and obesity in an urban population of Argentina. *Diabetes Research and Clinical Practice*, **3**:277–283.

Higgins M, Kannel W, Garrison R et al. (1988) Hazards of obesity—the Framingham experience. *Acta Medica Scandinavica, Supplementum*, **723**:23–36.

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, **58**:295–300.

Hochberg MC, Lawrence RC, Everett DF, Coroni-Huntley J (1989) Epidemiological associations of pain in osteoarthritis of the knee: data from the National Health and Nutrition Examination Survey and Nutrition Examination-I Epidemiological Follow-up Survey. *Seminars in Arthritis and Rheumatism*, **18**:4–9.

Huang Z, Hankinson SE, Colditz GA et al. (1997) Dual effects of weight and weight gain on breast cancer risk. *Journal of the American Medical Association*, **278**:1407–1411.

IARC (2002) *IARC Handbook of cancer prevention, Vol. 6. Weight control and physical activity*. Vainio H, Bianchini F, eds. International Agency for Research on Cancer, Lyon.

James WPT, Ferro Luzzi A, Waterlow JC (1988) Definition of chronic energy deficiency in adults. Report of a Working Party of the International Dietary Energy Consultative Group. *European Journal of Clinical Nutrition*, **42**:969–981.

James WPT, Ralph A, Ferro-Luzzi A (1989) Energy needs of the elderly: a new approach. In: *Human nutrition. Ageing and the elderly.* Munro HN, Danford DE, eds. Plenum Press, New York.

James WPT, Francois P (1994) The choice of cut-off point for distinguishing normal body weight from underweight or 'chronic energy deficiency' in adults. *European Journal of Clinical Nutrition*, **48**:S179–184.

James WPT, Norum K, Smitasiri S et al. (2000) *Ending malnutrition by 2020: an agenda for change in the millennium*. (Final report to the ACC/SCN by the Commission on the nutrition challenges of the 21st century. Supplement to the Food and Nutrition Bulletin, September/October 2000.) UNU International Nutrition Foundation, USA.

James WPT, Reeds PJ (1997) Nutrient partitioning. In: *Handbook on obesity.* Bray GA, Bouchard C and James WPT, eds. Marcel Dekker Inc, New York.

Jarrett RJ, Shipley MJ, Rose G (1982) Weight and mortality in the Whitehall study. *British Medical Journal*, **285**:535–537.

Jimenez JT, Palacios M, Canete F et al. (1998) Prevalence of diabetes mellitus and associated cardiovascular risk factors in an adult urban population in Paraguay. *Diabetic Medicine*, **15**:334–338.

Jones DW, Kim JS, Andrew ME, Kim SJ, Hong YP (1994) Body mass index and blood pressure in Korean men and women: the Korean National Blood Pressure Survey. *Journal of Hypertension*, **12**:1433–1437.

Jousilahti P, Vartiainen E, Tuomilehto J et al. (1999) Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation*, **99**:1165–1172.

Kain J, Uauy R, Vio F, Albala C (2002) Trends in overweight and obesity prevalence in Chilean children: comparison of three definitions. *European Journal of Clinical Nutrition*, **56**:200–204.

Keys A, Aravanis C, Blackburn H et al. (1972) Coronary heart disease: overweight and obesity as risk factors. *Annals of Internal Medicine*, **77**:15–27.

Khor GL, Yusof AM, Siong Tee E, Kandiah M, Lee Huang MS (1999) Prevalence of overweight among Malaysian adults from rural communities. *Asia Pacific Journal of Clinical Nutrition*, **8**:272–279.

Kromeyer-Hauschild K, Zellner K, Jaeger U, Hoyer H (1999) Prevalence of overweight and obesity among school children in Jena (Germany). *International Journal of Obesity*, **23**:1143–1150.

Kune GA, Kune S, Watson LF (1990) Body weight and physical activity as predictors of colorectal cancer risk. *Nutrition and Cancer*, **13**:9–17.

Lahti-Koski M, Vartiainen E, Mannisto S, Pietinen P (2000) Age, education and occupation as determinants of trends in body mass index in Finland from 1982 to 1997. *International Journal of Obesity*, **24**:1669–1676.

Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjöström L (1984) Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *British Medical Journal*, **289**:1257–1261.

Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G (1984) Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *British Medical Journal*, **288**:1401–1404.

Lean ME, Powrie JK, Anderson AS, Garthwaite PH (1990) Obesity, weight loss and prognosis in type 2 diabetes. *Diabetic Medicine*, **7**:228–233.

Lee I-M and Paffenbarger RS Jr (1992) Quetelet's index and risk of colon cancer in college alumni. *Journal of the National Cancer Institute*, **84**:1326–1331.

Le Marchand L, Wilkens LR, Mi MP (1991) Early-age body size, adult weight gain and endometrial cancer risk. *International Journal of Cancer*, **48**: 807–811.

Lew EA, Garfinkel L (1979) Variations in mortality by weight among 750 000 men and women. *Journal of Chronic Diseases*, **32**:563–576.

Lindsted K, Tonstad S, Kuzma JW (1991) Body mass index and patterns of mortality among Seventh-day Adventist men. *International Journal of Obesity*, **15**:397–406.

Macdonald SM, Reeder BA, Chen Y, Despres JP (1997) Obesity in Canada: a descriptive analysis. Canadian Heart Health Surveys Research Group. *Canadian Medical Association Journal*, **157**:S3–9.

MacMahon S, Cutler J, Brittain E, Higgins M (1987) Obesity and hypertension: epidemiological and clinical issues. *European Heart Journal*, **8**:S57–70.

Manson JE, Colditz GA, Stampfer MJ et al. (1990) A prospective study of obesity and risk of coronary heart disease in women. *New England Journal of Medicine*, **322**:882–889.

Marshall JA, Shetterly S, Hoag S et al. (1994) Dietary fat predicts conversion from impaired glucose tolerance to NIDDM. The San Luis Valley Diabetes study. *Diabetes Care*, **17**:50–56.

Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA (1997) Leisure-time physical activity, body size and colon cancer in women. Nurses' Health Study Research Group. *Journal of the National Cancer Institute*, **89**:948–955.

Martorell R, Schroeder DG, Rivera JA, Kaplowitz HJ (1995) Patterns of linear growth in rural Guatemalan adolescents and children. *Journal of Nutrition*, **125**:S1060–1067.

Mathers C, Vos T, Stevenson C (1999) The Burden of disease and injury in Australia, 1999. (AIHW Catalogue No. PHE 17.) AIHW, Canberra.

McCarthy SN, Harrington KE, Kiely M et al. (2001) Analyses of the anthropometric data from the North/South Ireland Food Consumption Survey. *Public Health Nutrition*, **4**:1099–1106.

McGarvey ST (1991) Obesity in Samoans and a perspective on its etiology in Polynesians. *American Journal of Clinical Nutrition*, **53**:S1586–1594.

Micozzi MS, Albanes D, Jones DY, Chumlea WC (1986) Correlations of body mass indices with weight, stature, and body composition in men and women in NHANES I and II. *American Journal of Clinical Nutrition*, **44**:725–731.

Molarius A, Seidell JC, Sans S, Tuomilehto J, Kuulasmaa K (2000) Educational level, relative body weight, and changes in their association over 10 years: an international perspective from the WHO MONICA project. *American Journal of Public Health*, **90**:1260–1268.

Monteiro CA, Conde WL (1999) Time trends in overweight prevalence in children, adolescents and adults from less and more developed regions of

Brazil. In: *Progress in obesity research*. Guy Grand B, Ailhaud G, eds. John Libbey & Company, London.

Monteiro CA, Mondini L, de Souza AL, Popkin BM (1995) The nutrition transition in Brazil. *European Journal of Clinical Nutrition*, **49**:105–113.

Moreno LA, Sarria A, Fleta J, Rodriguez G, Bueno M (2000) Trends in body mass index and overweight prevalence among children and adolescents in the region of Aragon (Spain) from 1985 to 1995. *International Journal of Obesity*, **24**:925–931.

Morris JN, Everitt MG, Pollard R et al. (1980) Vigorous exercise in leisure-time: protection against coronary heart disease. *The Lancet*, **2**:1207–1210.

Mulrow DC, Chiquette E, Angel L et al. (2000) Dieting to reduce body weight for controlling hypertension in adults. *Cochrane Database System Review*, **2**:CD000484 [online database].

Musaiger AO, al-Mannai MA (2001) Weight, height, body mass index and prevalence of obesity among adult population in Bahrain. *Annals Human Biology*, **10**:346–350.

Musaiger AO, Gregory WB (2000) Profile of body composition of school children in Bahrain. *International Journal of Obesity*, **24**:1093–1096.

Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH (1992) Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *New England Journal of Medicine*, **327**:1350–1355.

Must A, Spadano J, Coakley EH (1999) The disease burden associated with overweight and obesity. *Journal of the American Medical Association*, **282**:1523–1529.

National Audit Office (2001) *Tackling obesity in England. A report by the Comptroller and Auditor General*. National Audit Office, London.

Niedhammer I, Bugel I, Bonenfant S, Goldberg M, Leclerc A (2000) Validity of self-reported weight and height in the French GAZEL cohort. *International Journal of Obesity Related Metabolic Disorders*, **24**:1111–1118.

NIH (1998) *Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: the evidence report*. US Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute, USA.

Nishizawa H, Shimomura I, Kishida K et al. (2002) Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes*, **51**:2734–2741.

Njolstad I, Arnesen E, Lund-Larsen PG (1998) Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12-year follow-up of the Finnmark study. *American Journal of Epidemiology*, **147**:49–58.

Norgan NG (1994a) Population differences in body composition in relation to the body mass index. *European Journal of Clinical Nutrition*, **48**:S10–27.

Norgan NG (1994b) Relative sitting height and the body mass index. *Annals of Human Biology*, **21**:78–82.

Ogden CL, Kuczmarski RJ, Flegal KM et al. (2002) Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics*, **109**:45–60.

Okesina AB, Oparinde DP, Akindoyin KA, Erasmus RT (1999) Prevalence of some risk factors of ischaemic heart disease in a rural Nigerian population. *East African Medical Journal*, **76**:212–217.

Okosun IS, Cooper RS, Rotimi CN, Osotimehin B, Forrester T (1998) Association of waist circumference with risk of hypertension and type 2 diabetes in Nigerians, Jamaicans, and African-Americans. *Diabetes Care*, **21**:1836–1842.

Okosun IS, Rotimi CN, Forrester TE et al. (2000) Predictive value of abdominal obesity cut-off points for hypertension in Blacks from West African and Caribbean islands nations. *International Journal of Obesity*, **24**:180–186.

Ornish D, Brown SE, Scherwitz LW et al. (1990) Can lifestyle changes reverse coronary heart disease? *The Lancet*, **336**:129–133.

Paffenbarger RS Jr, Laughlin MD, Gima AS, Black RA (1970) Work activity of longshoremen as related to death from coronary heart disease and stroke. *New England Journal of Medicine*, **282**:1109–1114.

Parsons TJ, Power C, Logan S, Summerbell CD (1999) Childhood predictors of adult obesity: a systematic review. *International Journal of Obesity*, **23**: S1–107.

Pelletier DL and Rahn M (1998) Trends in body mass index in developing countries. *Food and Nutrition Bulletin*, **19**:223–239.

Pishdad GR (1996) Overweight and obesity in adults aged 20–74 in southern Iran. *International Journal of Obesity*, **20**:963–965.

Popkin BM (2002) An overview on the nutrition transition and its health implications: the Bellagio meeting. *Public Health Nutrition*, **5**:93–103.

Reilly JJ, Dorosty AR, Emmett PM, ALSPAC Study Team (2000) Identification of the obese child: adequacy of the body mass index for clinical practice and epidemiology. *International Journal of Obesity*, **24**:1623–1627.

Rexrode KM, Buring JE, Manson JE (2001) Abdominal and total adiposity and risk of coronary heart disease in men. *International Journal of Obesity*, **25**:1047–1056.

Rexrode KM, Hennekens CH, Willett WC et al. (1997) A prospective study of body mass index, weight change, and risk of stroke in women. *Journal of the American Medical Association*, **277**:1539–1545.

Rhoads GG, Kagan A (1983) The relation of coronary disease, stroke, and mortality to weight in youth and in middle age. *The Lancet*, **1**:492–495.

Rimm EB, Stampfer MJ, Giovannucci E et al. (1995) Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *American Journal of Epidemiology*, **141**:1117–1127.

Rissanen A, Heliövaara M, Knekt P et al. (1990) Risk of disability and mortality due to overweight in a Finnish population. *British Medical Association*, **301**:835-837.

Roberts SB, Dallal GE (2001) The new childhood growth charts. *Nutrition Reviews*, **59:**31–36.

Rodriguez-Ojea A, Jimenez S, Berdasco A, Esquivel M (2002) The nutrition transition in Cuba in the nineties: an overview. *Public Health Nutrition*, **5**:129–133.

Rose G, Shipley M (1990) The population mean predicts the number of deviant individuals. *British Medical Journal*, **301**:1031–1034.

Rosenbloom AL, Joe JR, Young RS, Winter WE (1999) Emerging epidemic of type 2 diabetes in youth. *Diabetes Care*, **22**:345–354.

Rosengren A, Wedel H, Wilhelmsen L (1999) Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. *European Heart Journal*, **20**:269–277.

Rotimi CN, Cooper RS, Ataman SL et al. (1995) Distribution of anthropometric variables and the prevalence of obesity in populations of West African origin. *Obesity Research*, **3**:S95–105.

Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC (1991) Incidence and risk factors for gout in white men. *Journal of the American Medical Association*, **266**:3004–3007.

Sargeant LA, Bennett FI, Forrester TE, Cooper RS, Wilks RJ (2002) Predicting incident diabetes in Jamaica: the role of anthropometry. *Obesity Research*, **10**:792–798.

Sarkkinen E, Schwab U, Niskanen L et al. (1996) The effects of monounsaturated-fat enriched diet and polyunsaturated-fat enriched diet on lipid and glucose metabolism in subjects with impaired glucose tolerance. *European Journal of Clinical Nutrition*, **50**:592–598.

Sanchez-Castillo CP, Velázquez-Monroy O, Berber A et al. (2003) Anthropometric cut-off points for predicting chronic diseases in the Mexican National Health Survey 2000. *Obesity Research*, **11**:442–451.

Schouten JSAG, van den Ouweland FA, Valkenburg HA (1992) A twelve year follow-up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. *Annals of the Rheumatic Diseases*, **51**:932–937.

Schroeder DG, Martorell R, Flores R (1999) Infant and child growth and fatness and fat distribution in Guatemalan adults. *American Journal of Epidemiology*, **149**:177–185.

Seckl JR, Walker BR (2001) Minireview: 11 β-hydroxysteroid dehydrogenase Type 1: a tissue-specific amplifier of glucocorticoid action. *Endocrinology*, **142**:1371–1376.

Seidell JC, Kahn HS, Williamson DF, Lissner L, Valdez R (2001a) Report from a Centers for Disease Control and Prevention Workshop on use of adult anthropometry for public health and primary health care. *American Journal of Clinical Nutrition*, **73**:123–126.

Seidell JC, Perusse L, Despres JP, Bouchard C (2001b) Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk

factors: the Quebec Family study. *American Journal of Clinical Nutrition*, **74**:315–321.

Shaper AG, Wannamethee SG, Walker M (1997) Body weight: implications for the prevention of coronary heart disease, stroke and diabetes mellitus in a cohort study of middle aged men. *British Medical Journal*, **314**:1311–1317.

Shetty PS (2002) Nutrition transition in India. *Public Health Nutrition*, **5**: 175–182.

Shetty PS, James WPT (1994) *Body Mass Index. A measure of chronic energy deficiency in adults*. (FAO Food and Nutrition Paper No. 56.) Food and Agriculture Organization of the United Nations, Rome.

Silverman BL, Rizzo TA, Cho NH, Metzger BE (1998) Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. *Diabetes Care*, **21**:B142–149.

Singh RB, Niaz MA, Agarwal P, Beegum R, Rastogi SS, Singh NK (1995) Epidemiologic study of central obesity, insulin resistance and associated disturbances in the urban population of North India. *Acta Cardiologica*, **3**:215–225.

Sjöström CD, Lissner L, Wedel H, Sjöström L (1999) Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study. *Obesity Research*, **7**:477–484.

Sjöström CD, Peltonen M, Wedel H, Sjöström L (2000) Differentiated long-term effects of intentional weight loss on diabetes and hypertension. *Hypertension*, **36**:20–25.

Sjöström L, Larsson B, Backman L et al. (1992) Swedish obese subjects (SOS). Recruitment for an intervention study and a selected description of the obese state. *International Journal of Obesity Related Metabolic Disorders*, **16**:465–479.

Stamler J, Farinaro E, Mojonnier L, Hall Y, Moss D, Stamler R (1980) Prevention and control of hypertension by nutritional-hygienic means. Long-term experience of the Chicago Coronary Prevention Evaluation Program. *Journal of the American Medical Association*, **243**:1819–1823.

Stam-Moraga MC (1999) Sociodemographic and nutritional determinants of obesity in Belgium. *International Journal of Obesity*, **23**:S1–9.

Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH (1985) A prospective study of post-menopausal estrogen therapy and coronary heart disease. *New England Journal of Medicine*, **313**:1044–1049.

Stevens J, Cai J, Juhaeri, Thun MJ, Williamson DF, Wood JL (1999) Consequences of the use of different measures of effect to determine the impact of age on the association between obesity and mortality. *American Journal of Epidemiology*, **150**:399–407.

Stevens J, Cai J, Panuk ER, Williamson DF, Thun MJ, Wood JL (1998) The effect of age on the association between body-mass index and mortality. *New England Journal of Medicine*, **338**:1–7.

Swinburn BA, Ley SJ, Carmichael HE, Plank LD (1999) Body size and composition in Polynesians. *International Journal of Obesity*, **23**:1178–1183.

Tate RB, Manfreda J, Cuddy TE (1998) The effect of age on risk factors for ischemic heart disease: the Manitoba Follow-up study, 1948–1993. *Annals of Epidemiology*, **8**:415–421.

Temple NJ, Steyn K, Hoffman M, Levitt NS, Lombard CJ (2001) The epidemic of obesity in South Africa: a study in a disadvantaged community. *Ethnic Disorders*, **11**:431–437.

Thun MJ, Calle EE, Namboodiri MM et al. (1992) Risk factors for fatal colon cancer in a large prospective study. *Journal of the National Cancer Institute*, **84**:1491–1500.

Tremblay MS, Katzmarzyk PT, Willms JD (2002) Temporal trends in overweight and obesity in Canada, 1981–1996. *International Journal of Obesity*, **26**:518–543.

Tretli S (1989) Height and weight in relation to breast cancer morbidity and mortality. A prospective study of 570 000 women in Norway. *International Journal of Cancer,* **44**:23–30.

Trichopoulou A, Gnardellis C, Lagiou A, Benetou V, Trichopoulos D (2000) Body Mass Index in relation to energy expenditure among adults in Greece. *Epidemiology*, **11**:333–336.

Troiano RP, Frongillo EA, Sobal J, Levitsky DA (1996) The relationship between body weight and mortality: a quantitative analysis of combined information from existing studies. *International Journal of Obesity*, **20**:63–75.

Tuomilehto J, Lindstöm J, Eriksson JG et al. (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*, **344**:1343–1350.

Törnberg SA, Carstensen JM (1994) Relationship between Quetelet's index and cancer of breast and female genital tract in 47 000 women followed for 25 years. *British Journal of Cancer*, **69**:358–361.

Unger R, Kreeger L, Christoffel KK (1990) Childhood obesity. Medical and familial correlates and age of onset. *Clinical Pediatrics*, **29**:368–373.

van der Sande MA, Bailey R, Faal H et al. (1997) Nationwide prevalence study of hypertension and related non communicable diseases in the Gambia. *Tropical Medicine and International Health*, **12**:1039–1048.

Verbrugge LM, Gates, DM, Ike RW (1991) Risk factors for disability among US adults with arthritis. *Journal of Clinical Epidemiology*, **44**:167–182.

Vessby B, Uusitupa M, Hermansen K et al. (2001) Substituting dietary monounsaturated for saturated fat improves insulin sensitivity in healthy men and women—the KANWU study. *Diabetologia*, **44**:312–319.

Visscher TL, Kromhout D, Seidell JC (2002) Long-term and recent time trends in the prevalence of obesity among Dutch men and women. *International Journal of Obesity Related Metabolic Disord*ers, **26**:1218–1224.

Weiderpass E, Adami HO, Baron JA et al. (1999) Risk of endometrial cancer following estrogen replacement with and without progestins. *Journal of the National Cancer Institute*, **91**:1131–1137.

Whitlock G, Lewington S, Ni Mhurchu C (2002) Coronary heart disease and body mass index: a systematic review of the evidence from large prospective cohort studies. *Seminars and Vascular Medicine*, **2**:369–381.

WHO (1985) *Energy and protein requirements*. Report of a joint FAO/WHO/UNU expert consultation. (WHO Technical Report Series No. 724.) World Health Organization, Geneva.

WHO (1993) *World health statistics. Annual report*. World Health Organization, Geneva, 1994.

WHO (1995) *Physical status: the use and interpretation of anthropometry*. (Technical Report Series No. 854.) World Health Organization, Geneva.

WHO (2000) *Obesity: preventing and managing the global epidemic*. (WHO Obesity Technical Report Series No. 894.) World Health Organization, Geneva.

WHO/IASO/IOTF (2000) The Asia-Pacific perspective: redefining obesity and its treatment. February 2000. Full document available from: http://www.idi.org.au/obesity_report.htm.

Wilks R, McFarlane-Anderson N, Bennett F et al. (1996) Obesity in peoples of the African diaspora. In: *The origins and consequences of obesity*. Chadwick DJ, Cardew G, eds. John Wiley & Sons, New York.

Willett W, Manson J, Liu S (2002) Glycemic index, glycemic load, and risk of type 2 diabetes. *American Journal of Clinical Nutrition*, **76**:S274–280.

Willett WC, Manson JE, Stampfer MJ et al. (1995) Weight, weight change, and coronary heart disease in women: risk within the "normal" weight range. *Journal of the American Medical Association*, **273**:461–465.

Williamson DF, Pamuk ER (1993) The association between weight and increased longevity. A review of the evidence. *Annals of Internal Medicine*, **119**:731–736.

Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C (1995) Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40–64 years. *American Journal of Epidemiology*, **141**:1128–1141.

Witteman JC, Willett WC, Stampfer MJ et al. (1989) A prospective study of nutritional factors and hypertension among US women. *Circulation*, **80**:1320–1327.

Xiao-Ren Pan, Guang-wei Li, Ying-Hua Hu et al. (1997) Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes study. *Diabetes Care*, **20**:537–544.

Yajnik C (2000) Interactions of perturbations in intrauterine growth and growth during childhood on the risk of adult-onset disease. *Proceedings of the Nutrition Society*, **59**:1–9.

Yoshiike N, Matsumura Y, Zaman MM, Yamaguchi M (1998) Descriptive epidemiology of BMI in Japanese adults in a representative sample from the National Nutrition Survey 1990–1994. *International Journal of Obesity*, **22**:684–687.

Yoshiike N, Seino F, Tajima S et al. (2002) Twenty-year changes in the prevalence of overweight in Japanese adults: the National Nutrition Survey 1976–1995. *Obesity Reviews*, **3**:183–190.

Zajkas G, Biro G (1998) Data on the prevalence of obesity in Hungarian adult population between 1985–88 and 1992–94. *Zeitschrift für Ernärungswissenschaft*, **37**:S134–135.

Zhou B-F (2002) Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults—study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomedical and Environmental Sciences*, **15**:83–95.

Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L (2002) Overweight is an independent risk factor for cardiovascular disease in Chinese populations. *Obesity Reviews*, **3**:147–156.

Zimmermann MB, Hess SY, Hurrell RF (2000) A national study of the prevalence of overweight and obesity in 6–12 year old Swiss children; body mass index, body-weight perceptions and goals. *European Journal of Clinical Nutrition*, **54**:568–572.

Chapter 9

Low fruit and vegetable consumption

Karen Lock, Joceline Pomerleau, Louise Causer and Martin McKee

Summary

This analysis assessed the levels of mean dietary intakes of fruit and vegetables (excluding potatoes) measured in grams per day. The theoretical-minimum-risk distribution for fruit and vegetable intake was estimated to be 600 g/day in adults, 480 g/day in children aged 5–14 years, and 330 g/day in children aged 0–4 years. It is proposed to use set intervals of 80 g/day of fruit and vegetables (equivalent to one serving) to elaborate the distributional transition.

The effect of fruit and vegetable consumption in preventing ischaemic heart disease (IHD), cerebrovascular disease, lung cancer, stomach cancer, colon and rectum cancers and oesophageal cancer was estimated. The choice of outcomes was guided mainly by previous reviews of the literature (Law and Morris 1998; Ness and Powles 1997; World Cancer Research Fund and American Institute for Cancer Research 1997), which suggested a protective effect of fruit and vegetables for IHD, stroke and cancers of the lung and digestive tract.

Health outcomes that could be reconsidered for inclusion in the next revision of the Global Burden of Disease (GBD) study include cancers of the larynx, pancreas, bladder, ovary, endometrium, thyroid and prostate; type II diabetes; chronic obstructive pulmonary disease; and cataract.

Estimates were based primarily on representative population-based surveys of dietary intake identified using a comprehensive search of the literature and contacts with experts. Data were obtained for 26 countries from nine subregions[1] and pooled statistically within each subregion. When no survey data were available in a subregion, per capita food supply statistics were combined with estimates of the distribution of intakes by sex and age. Systematic extrapolations were made when the original data did not meet the comparative risk assessment (CRA) categories and when part of the estimates were unavailable.

Estimates of fruit and vegetable intake were highest in EUR-A, followed by WPR-A. The lowest intakes were found in AMR-B, EUR-C, SEAR-B, SEAR-D and AFR-E. Intakes varied by age groups, with children and the elderly generally having lower intakes than middle-aged adults.

Standard deviations varied considerably by subregion, sex and age group, with a median of 223 g/day. Estimates tended to be, on average, lower in women than in men (but with variations by age group), and they were generally lower in young children. In some subregions, standard deviations were also slightly smaller in the elderly.

Risk factor–disease relationships for each selected outcome were estimated based on the results of a systematic review of the literature combined with meta-analysis. The relative risk estimates derived were applied to all age groups between the ages of 15 and 70 years. To take account of age attenuation the relative risks were reduced by a quarter for ages 70–79 years, and by half for the age group ≥80 years. For those aged <15 years, a relative risk of 1 was applied.

Due to the limited information available on subregional differences in risks, constant estimates were applied to all subregions. Risks were assessed relative to the chosen theoretical-minimum-risk distribution fruit and vegetable intake.

The protective effects of fruit and vegetables were expressed as relative risk estimates associated with an 80 g/day increase in fruit and vegetable intake. The relative risk estimates were as follows: 0.90 (95% CI 0.82–0.99) for IHD, 0.94 (0.89–0.99) for ischaemic stroke, 0.96 (0.93–0.99) for lung cancer, 0.94 (0.86–1.03) for gastric cancer, 0.99 (0.97–1.02) for colorectal cancer and 0.94 (0.88–1.01) for oesophageal cancer.

CRA found that the lack of dietary fruit and vegetables contributes an important share of the worldwide disease burden. It was estimated that increasing individual fruit and vegetable consumption up to the theoretical-minimum-risk distribution could reduce the worldwide burden of disease for IHD and ischaemic stroke by about 31% (30% in men and 31% for women) and 19% (18% in men and 19% in women), respectively. For stomach and oesophageal cancer, the potential reduction in disease attributable to an increase in fruit and vegetable intake was 19% and 20%, respectively. Attributable risk fractions were lower for lung and colorectal cancer (12% and 2%). The total worldwide mortality attributable to inadequate fruit and vegetable consumption is estimated to be 2.726 million deaths or 26.662 million disability-adjusted life years (DALYs) per year.

Although these results need to be interpreted in the light of the limitations of the current methods, including the potential for residual confounding and misclassification of exposure, they clearly highlight the importance of increased fruit and vegetable consumption in improving public health worldwide.

1. Introduction

1.1 Definition of risk factor

In this chapter, the selected risk factor is the mean dietary intake of fruit and vegetables. Intake is treated as a continuous variable and is measured in grams/person per day. The estimates provided exclude potatoes in order to be consistent with current international recommendations for the intake of fruit and vegetables (WHO 1990).

1.2 Choice of exposure variable, reasons and implications

Accumulating epidemiological evidence has suggested that fruit and vegetables in the diet can reduce the risk of major diseases such as cardiovascular diseases and certain cancers, thus reducing premature deaths (Klerk et al. 1998; World Cancer Research Fund and American Institute for Cancer Research 1997). This consistent pattern of findings has led several national and international bodies to advocate an increase in intake to at least 400 g/day (excluding potatoes) (WHO 1990; World Cancer Research Fund and American Institute for Cancer Research 1997).

While the first round of the GBD study did not look explicitly at the overall impact of nutrition on the global burden of disease, an attempt was later made in Sweden to estimate the burden of disease that could be attributed to different causal factors in the European Union (EU) (National Institute of Public Health 1997). It was estimated that diet-related factors directly contributed to 8.3% of the estimated number of DALYs lost, almost half of this being attributed to low fruit and vegetable intake (3.5% compared with 3.7% for overweight and 1.1% for high saturated fat intake). However, these figures do not take account of potential interactions between the different factors. In comparison, tobacco smoking accounted for 9% of the burden of disease in the EU. These findings are similar to those of recent studies from Australia and New Zealand (Mathers et al. 1999; Tobias 2001). In these countries, it was estimated that about 3% (2.8% in Australia and 2.4% in New Zealand) of the burden of disease could be attributed to low fruit and vegetable consumption. The Australian study also reported that approximately 10% of all cancers could be due to an insufficient intake of fruit and vegetables.

1.3 Choice of theoretical-minimum-risk distribution

The CRA project estimates the effects of shifting risk factor distributions towards a counterfactual distribution, rather than the difference between "exposed" and "unexposed" groups. Fruit and vegetable consumption is unusual in the CRA project in that there is a suggested inverse risk factor–disease relationship (i.e. the potential *protective* effect of fruit and vegetables for various disease outcomes is considered). Hence, the

theoretical-minimum-risk distribution (the distribution of exposure that would yield the lowest population risk) involves estimating an upper consumption that is protective.

For this exercise, we chose limits that could be realistically attained. However, we do not know what the true *upper* intakes that would give the highest level of protection would be; they could reflect levels of intakes that are much higher than current consumption patterns. Thus, choosing a theoretical-minimum-risk distribution is currently difficult to do with certainty. Evidence has clearly shown that those in the highest categories of fruit and vegetable consumption have lower risk compared with those in the lowest consumption categories. It is not yet clear whether there is a threshold effect for fruit and vegetable consumption (although many studies have presented a linear dose–response relationship). Nor is it clear whether the same threshold would apply to all protective effects (e.g. there appears to be some evidence to suggest a lower threshold for colorectal cancer from research in individuals with very low intake) (Terry et al. 2001). However, due to the current uncertainty in this area, the same threshold was used for all selected health outcomes. Better information on threshold effects is a priority for future work.

In this project, the counterfactual was chosen to be a constant level using a minimum risk approach based on the following information.

- Most studies showing risk differences between the highest and lowest quartiles or quintiles of intakes have been performed in western Europe and North America. In the absence of other evidence, it was decided to base the counterfactual on the ranges of intakes observed in these populations.
- According to food balance sheet data, the amounts of fruit and vegetables available for consumption by the populations of these subregions range from about 300 to 1200 g/person per day (FAO 1998a). The highest availability is found in Greece where the quantity of fruit and vegetables available to consumers is 1100–1200 g/person per day. Assuming approximately 33% waste at the household level (Joffe and Robertson 2001), the mean daily intake of fruit and vegetables could be estimated to be approximately 700–800 g/person. However, dietary survey data gathered for this study showed that the mean intakes in adults of any given country rarely went above 500 g/day, and never above 550 g/day, even in countries known for their high intakes of fruit and vegetables (Israel and Italy). It was thus decided to limit the theoretical-minimum-risk distribution to 600 g/day in adults.
- As described in section 2.5, it was assumed that children consume less fruit and vegetables than adults (45% less in children aged 0–4 years and 20% less in children aged 5–14 years).

- As data gathered for this project showed almost no difference in fruit and vegetable intake between men and women (see section 2.5), it was decided to use the same theoretical-minimum-risk distribution for both sexes.
- In order to allow for slight population variability, it was decided to apply around the theoretical-minimum-risk distribution, a margin of uncertainty of 50 g/day.

The final theoretical-minimum-risk distribution levels used in this project are listed in Table 9.1.

It is proposed to use set intervals of 80 g/day of fruit and vegetables for the elaboration of the distributional transition. This amount has been estimated in nutritional studies to be equivalent to approximately one serving of fruit and vegetables and would constitute a plausible and feasible change for individuals towards the selected counterfactual level (World Cancer Research Fund and American Institute for Cancer Research 1997).

Most studies to date that have investigated the relationship between fruit and vegetable intake and risk of diseases were performed on populations that reported only a relatively narrow range of intake which in most cases did not reach the selected theoretical-minimum-risk distribution. As a result, it is not possible to know whether the same relative risks would apply in populations where high amounts are consumed. It is expected that future epidemiological studies incorporating populations with wider range of intakes, such as the European Prospective Investigation of Cancer (EPIC) study, may shed light on the impact of high fruit and vegetable intakes (higher than those investigated in current studies) on the risk of cardiovascular disease and cancer.

Table 9.1 Theoretical-minimum-risk distribution by age group

Age group (years)	*Theoretical-minimum-risk distribution and SD (fruit and vegetable intake g/person per day)*
0–4	330 ± 50
5–14	480 ± 50
15–29	600 ± 50
30–44	600 ± 50
45–59	600 ± 50
60–69	600 ± 50
70–79	600 ± 50
≥80	600 ± 50

2. Estimating risk factor levels

2.1 Methods

The methods used to obtain estimates of risk factor levels are described in the following sections.

2.2 Criteria for considering sources and studies

Potential sources of data on intake and supply

Data on dietary intake and supply of fruit and vegetables may be available at the national, household and individual level. The following subsections briefly describe these potential sources of information and whether they were used for the CRA project.

National level

The most commonly used source of information at the national level is food balance sheet data published by the Food and Agriculture Organization of the United Nations (FAO) for over 175 countries (1983). Food balance sheets provide standardized estimates of the average amount of food available per person on a daily basis. They are calculated by estimating the quantity of food produced in a given country added to the quantity of food imported (adjusted for changes in stocks), and subtracting the food exported, lost in storage, transport, and processing, fed to livestock or used for seeds and non-dietary purposes. The estimated national food supply is then divided by population size estimates to derive per capita figures (in kg/person per year). The main limitation of food balance statistics is that they tend to reflect national food availability patterns rather than actual dietary intake and are thus a reflection of both intake and wastage at the retail, food service and household levels (Kantor et al. 1997). As a result, they cannot provide information on the dietary intake of different population subgroups and they tend to overestimate food consumption, particularly in developed countries. However, time trends in food availability tend to parallel those observed with household surveys (Sekula et al. 1991), so FAO food balance sheets constitute a useful tool for international comparisons and time trend analysis.

Household level

Household-based surveys, where the unit of measurement is the household rather than the individual, are often performed to explore the diversity of food consumption patterns among communities. They can give information about dietary patterns of groups, making distinctions between geographical regions, income brackets and family structures. The most frequently used types of household surveys are the food account method, the inventory method, the household food record

method and the list-recall method (Nelson and Bingham 1997). Household surveys have several limitations: they cannot provide information on individuals; they are subject to sampling errors; they sometimes exclude foods consumed outside the home or certain food groups (e.g. sweets, alcoholic beverages, etc.); and some methods are subject to recall bias. In addition, they are available for only a limited number of countries and the diversity of the methods used make international comparisons difficult. Due to these limitations, data from household surveys were not used in this project.

Individual level

It is generally agreed that there is a considerable lack of internationally comparable data at an individual level. This is partly due to the difficulties associated with measuring the dietary intake of individuals, including potential measurement error and bias. In spite of this, data collected at the individual level provide invaluable information on the mean dietary intakes of population subgroups (e.g. stratified by age and sex) and variability in intakes. They are thus essential for stratified intake estimates.

Data on present or recent food consumption are collected using four main techniques: (i) the 24-hour recall; (ii) food records (with or without weighing of foods); (iii) food frequency questionnaires; and (iv) food history. Details of these methods and their limitations can be found elsewhere (Nelson and Bingham 1997; Willett 1998a). The choice of a method to collect data at the individual level will normally depend on the objectives of the study and on the resources available. When the main objective is to obtain the mean consumption of a large group of individuals, it is generally sufficient to use a single 24-hour recall or a one-day food record. This approach is often used in large national surveys of dietary intake as it represents a relatively small burden for the respondents and is associated with relatively low costs. The main caveat of using only one day of information is that it tends to artificially increase the standard deviation of the estimates due to large intra-individual variation in intakes (Cameron and van Staveren 1988). Thus, the observed distribution of intakes has extreme values that are higher and lower than any of the true long-term averages for any individual. Including several days of data collection for each respondent will normally dampen day-to-day variation, but it will also increase the burden on the respondents and the costs. If the objective of the study is to assess the distribution of food consumption in a group or the position of an individual's intake within the population, more complex methods such as repeated 24-hour recalls or food records, food frequency questionnaires or dietary history are needed. These approaches have been used mostly in cohort studies or smaller, more focused surveys of dietary intake; they have less frequently been used in national surveys of dietary intake.

Sources of data used in this project

Only dietary surveys with data collected at the individual level can provide information on mean intakes *and* variability in intakes (standard deviations) in population subgroups. Thus, we set out to identify data from at least one valid and representative population-based survey of dietary intake for each of the 191 countries covered by the CRA.

However, this was not realistically possible as currently only a few countries (mainly economically developed) have conducted representative national or regional surveys of dietary intake at the individual level, and a few others have performed surveys in selected sections of the population only. Conversely, for the majority of countries in the world, yearly estimates of available food supply exist in the form of the FAO food balance sheets. These food balance sheets were used to complement data collected at the individual level, when required. The methods used and the subregions to which they were applied are described in section 2.5.

Criteria for including sources of individual level data

The main criteria used for including sources of individual level data of fruit and vegetable intake were as follows:

Time frame

- The study was relatively recent—defined as having been performed since 1980.

Study sample

- The reference population was described.
- The sampling strategy was as close as possible to random sampling.
- The sample was representative of the reference population.
- The sample size was large (sample size calculation ideally included).
- As wide an age range as possible was included.
- The level of non-response was ideally documented.

Study design

- Only population-based cross-sectional studies, baseline assessment of large cohort studies (sample representative of the general population) or large interventions (sample representative of the general population) were considered for inclusion.
- Case–control studies were excluded from the selection process.

Validity of the methods

- The methods used to collect data were as free of bias as possible.

- Data were collected at the level of the individual.
- The statistical analysis of the data was appropriate.

Type of dietary information

- Data on fruit and vegetable intake had to be available as grams per day and not as frequencies (e.g. <1 serving a day, 1–2 servings a day, every day, etc.).

2.3 Search strategy for the identification of studies

Dietary intake data were identified using a comprehensive worldwide search which included computerized databases of published articles, library catalogues, hand-searching of bibliographies, an Internet search of possible sources of data, and extensive contact with experts in the field, national governments and nongovernmental organizations.

Computerized databases and library search

The following computerized sources of information were included in the search process: Medline, CAB abstracts and Embase. MESH terms used to search in Medline and HealthStar included "fruit", "vegetables", "nutrition-surveys", "diet-surveys" and "food-habits" (each term included all subheadings). Similar search terms were used in the other databases but adapted to the specific database search facilities. The search was restricted to human studies published in all languages since 1980.

Articles were rejected on initial screen if the reviewer could determine from the title and abstract that the article did not provide estimates of fruit and vegetable intake of a population or did not report data from a representative population-based survey of dietary intake. When a title or abstract could not be rejected with certainty, the full text of the article was obtained for further evaluation. Citation lists in the articles retrieved were reviewed. A second reviewer performed random checks.

The following catalogues were searched for other publications and conference proceedings that could provide appropriate data: the University of London; the British Library; the Resource Centre of the Public Health Nutrition Unit at the London School of Hygiene and Tropical Medicine; Libraries at FAO, Rome and the Ministry of Agriculture, United Kingdom of Great Britain and Northern Ireland. Food and Fisheries were also consulted. Citation lists in the documents retrieved were reviewed.

Internet searches

Internet searches (using the Google search engine—http://www.google.com) had two objectives: to locate original sources of food intake data available on the Internet, and to identify national and international organizations that could identify possible data sources including acade-

mic departments of nutrition or dietetics, food and nutrition agencies and ministries of health.

Messages requesting help in identifying data sources were also posted to four scientific mailing lists: NUTEPI@listserv.gmd.de (nutritional epidemiology); food-for-thought@jiscmail.ac.uk (nutrition); public-health@jiscmail.ac.uk (public health); and epidemio-l@cc.umontreal.ca (epidemiology).

Contacts with experts

Numerous direct contacts were made with nutrition officers from the World Health Organization (WHO) regional offices and experts for references to published or unpublished data sources or for the identification of appropriate contact persons. Experts were defined as contact authors for large population-based studies of dietary intake, or contact persons in governmental agencies or country-specific nutrition organizations (this included existing networks from WHO and the International Obesity Task Force, and other international nutritional networks).

2.4 Methods for obtaining estimates of national intake where more than one data source exists

The following hierarchy of data quality was used to select one source of data for a given country where more than one was available:

- national survey of individual dietary intake;
- large sample survey of good quality—its quality being assessed from how well the survey met the list of criteria for including sources of individual level data (section 2.2); and
- small sample survey of good quality—its quality being assessed as above.

2.5 Methods for obtaining estimates where no data source existed

Data on mean intakes not available for some age or sex groups

Attempts were made to contact the original investigators to obtain data broken down by the required age categories. However, this was not always possible and so indirect estimates were made using the following approaches.

Data not available for children

Few of the available dietary intake surveys had data for children aged <18 years. Extrapolations for the intakes of children were on the basis of two observations.

- Using data from the surveys collected for this project, it was estimated that boys and girls aged 5–14 years and those aged 0–4 years

consume, respectively, about 20% and 45% less fruit and vegetables than adults aged 30–59 years.

- Published estimates on energy requirements for infants and children (WHO 1985, 1990) suggested that girls and boys aged 5–14 years require approximately 15% and 20% less dietary energy than adult women and men, respectively. The figures for girls and boys aged 0–4 years are about 40% and 50% less than adults of the same sex, respectively. These estimates, however, may vary among countries and they depend on the true energy expenditure of the children.

Assuming that fruit and vegetable consumption decreases proportionally to energy intake in children compared with adults, the two sources of information tend to agree. Thus, the following adjustment factors were used.

- Children 5–14 years: 20% lower fruit and vegetable intake than adults aged 30–59 years.
- Children 0–4 years: 45% lower fruit and vegetable intake than adults aged 30–59 years.

Data not available for the elderly

Many surveys were only for adults up to age 60–65 years. Once again, available survey data on fruit and vegetable intakes collected for this project and published estimates of energy requirements (WHO 1985, 1990) were used to derive an adjustment factor.

- Information on fruit and vegetable intakes from survey data indicate that men and women aged 70–79 years consume daily approximately the same amount of fruit and vegetables, on average, as their counterparts aged 30–59 years, while individuals aged ≥80 years consume approximately 10% less fruit and vegetables than middle-aged adults.
- Figures based on energy requirements suggest that men and women in older age groups require approximately 10–15% less energy than middle-aged adults do.

Based on these observations, the following assumptions were made.

- Individuals aged 70–79 years consume the same amount of fruit and vegetables as individuals in the closest age group (60–69 years).
- Individuals aged ≥80 years consume 10% less fruit and vegetables than those aged 30–59 years. However, when the resulting estimates were greater than the reported intakes of survey participants aged 70–79 years, a different approach was taken: it was assumed that individuals aged ≥80 years had an intake of fruit and vegetables similar to the intake observed in the 70–79-year age group.

Cases where the age groups did not correspond to the CRA age groups

In these cases, the results available for the most similar age categories (greatest overlap of ages) were applied, weighing for population sizes when necessary.

Data on mean intakes available for only one sex or for men and women taken together

In the case of Mexico, adult data were available only for women. In the case of France, only the overall mean intakes by age group (men and women taken together) were accessible.

Using data available from the surveys gathered for this project, it was estimated that, on average, men consume approximately only 1% more fruit and vegetables than women. It was thus assumed that Mexican and French males consume similar amounts of fruit and vegetables as do their female counterparts.

Data on standard deviations not available

In some cases, survey information did not include standard deviation estimates. The authors of the studies were contacted and, for some countries, the required estimates were provided. When this was not possible, the following assumptions were made.

- When standard deviations were missing for one or more age groups and for one or more countries within a subregion (usually for children or the elderly), data were pooled based on the information available (all countries with information for these age groups).
- When standard deviations for all age groups were missing for a country, the standard deviations of the country—within the same subregion—displaying the most similar mean intakes and method of data collection were applied. For example, for the United Kingdom, the standard deviations from Germany were used. However, since data on sample size are required for the estimation of the pooled standard deviation (and its confidence interval), pooled estimates were based only on the information available from the surveys.

Data on standard deviation and sample size not available for all countries in a subregion

For two subregions (SEAR-D and EMR-B), the survey data available included only mean intakes. As a result, it was not possible to extrapolate standard deviations from other countries within the same subregion. Thus, the pooled standard deviations of the subregion displaying the closest subregional mean intakes were applied (EUR-C for SEAR-D and EUR-B for EMR-B).

Another approach for the extrapolation of missing standard deviations may have been to use the standard deviations of a subregion that

is close geographically, that has similar economic characteristics, and for which data were available. For SEAR-D, for example, a possible choice may have been to use the standard deviations of WPR-B. However, as the standard deviations obtained for WPR-B are smaller than those of EUR-C, we preferred to choose the largest standard deviations and thus keep those obtained for EUR-C. For EMR-B, there was no obvious choice among the subregions for which data were available and thus the standard deviations of EUR-B were kept.

Data on mean intakes unavailable for a subregion

When survey data were unavailable for all countries within a subregion, it was originally planned to apply the results obtained for another subregion displaying the most similar fruit and vegetable availability (from FAO food balance sheets information) and demographic and health characteristics (using data from the *World health report 2000* [WHO 2000], the World Bank classification of economies based on gross national product [World Bank 2000], and the CIA World Factbook [Directorate of Intelligence 2000]).

However, it became clear the dietary patterns and socioeconomic characteristics of the African country mortality groupings (AFR-D and AFR-E), and of the EMR-D, SEAR-B and AMR-D groupings are too different from those found in the other subregions to allow for any correct extrapolation. We have thus used FAO food balance sheet data combined with survey information to obtain *FAO-derived proxy mean intakes* by age group and sex for the five subregions for which no individual survey data were identified (as described in the next section). We concluded that this approach was likely to provide more representative estimates of mean subregional fruit and vegetable intakes than extrapolations from other subregions, as the basis of the calculations was information collected directly from within each country within the subregion, that is, country-specific FAO food balance sheet data.

Obtaining FAO-derived proxy mean intakes

Country-specific data on availability of fruit (excluding wine—FAO code 2919) and vegetables (excluding potato—FAO code 2918) and population size estimates were downloaded from the FAOstat database on the FAO web site (FAO 1998a). Three-year averages (1996–1998) were calculated in order to reduce the effect of yearly variations. These data were then used to calculate subregional population-weighted average fruit and vegetable availability in grams/person per day. For seven relatively small countries, no estimates were available (Bahrain, Bhutan, Equatorial Guinea, Oman, Qatar, Samoa, Singapore). Estimates of calculated subregional food availability (1996–1998) are listed in Table 9.2.

As mentioned in section 2.2, food balance sheets provide information on the amounts of foods available for the consumers and are thus a reflection of both intake and waste at the retail, food service and house-

Table 9.2 Fruit and vegetable availability by subregion[a]

Subregion with no available survey data	*Fruit and vegetable availability (g/person per day)*
AFR-D	291
AFR-E	194
AMR-D	317
EMR-D	323
SEAR-B	205

[a] 1996–1998 averages.

Source: FAO (2001).

hold levels. Therefore, it has been reported that the balance sheets tend to overestimate intakes in developed market economies (Joffe and Robertson 2001). In developing countries, such as those included in the five subregions for which no survey data were obtained (World Bank 2000), it has been suggested that food balance sheets are likely to underestimate food availability as they do not take account of food grown for home consumption or wild food collected. However, few studies have tested this hypothesis. In Nepal and Pakistan, the average energy consumption from intake surveys was found to be about 10% higher than that from FAO food balance sheets (FAO 1998a, 1998b).

Using survey data obtained for this project, it was estimated that food balance sheet data tend to overestimate the national mean fruit and vegetable intake by 20% in India (FAO = 252 g/day vs survey = 209 g/day), and underestimate intakes by 74% in Bangladesh (overall weighed mean = +10%). However, the results for Bangladesh were based on very small availability estimates (FAO = 59 g/day vs survey = 226 g/day) that appear peculiar. In view of these contradictory results and because of the lack of further available information, we did not apply any correction factor to the FAO estimates in our calculations of the FAO-derived proxy mean intakes for the five subregions with no available survey data.

As food balance sheets do not provide information on food intake by sex and age group, an attempt was then made to estimate how the total availability of fruit and vegetables in a subregion would be distributed among the different sex and age groups. To reach this objective, a two-step process was used.

Step 1: We calculated the proportion of total fruit and vegetable intake consumed by the different age–sex groups for each subregion with available survey data. As expected, the distributions of intakes were strongly influenced by the population structures of the subregions.

Step 2: For each subregion with no available data (AFR-D, AFR-E, AMR-D, EMR-D and SEAR-B), we then applied to the FAO availability data the calculated distributions of intakes (Step 1) of the sub-

Table 9.3 Details of subregional extrapolation of age–sex intake distribution for subregions where no survey data were available

Subregion with no available survey data	*Distribution of intakes extrapolated from*
AFR-D	EMR-B
AFR-E	EMR-B
AMR-D	EMR-B
EMR-D	EMR-B
SEAR-B	SEAR-D

Table 9.4 Details of subregional extrapolation of standard deviations for subregions where no survey data were available

Subregion using FAO-derived proxy intake estimates	*Subregion from which standard deviations were extrapolated*
AFR-D	EMR-D
AFR-E	SEAR-D
AMR-D	EMR-B
EMR-D	EMR-B
SEAR-B	SEAR-D

region displaying the most similar population structure (Table 9.3). As a result, we obtained FAO-derived proxy mean intakes by age and sex.

Obtaining standard deviation estimates for FAO-derived proxy mean intakes

In order to obtain estimates of standard deviations when FAO-derived proxy mean intakes were used, we took the following approach. We first compared proxy intakes with all other subregional mean intakes (stratified by age and sex). We then applied to AFR-D, AFR-E, AMR-D, EMR-D and SEAR-D, the standard deviations of the subregion displaying the most similar subregional intakes and closest level of socioeconomic development (see Table 9.4).

2.6 Description of studies, including methodological qualities

The 26 countries for which data were obtained are shown in Table 9.5, along with the proportion of the subregional population covered by these countries. This proportion is generally high or acceptable except for two subregions (EMR-B = 1.4%; EUR-B = 3.8%).

Details of the studies included in this project are described in Table 9.6. Twenty-two were from national surveys. For Argentina, a compila-

Table 9.5 Proportion of subregional population for which survey data were obtained

Subregion	*Countries for which survey data were available*	*% of subregional population*[a]
AFR-D	—	—
AFR-E	—	—
AMR-A	United States	87.5
AMR-B	Argentina, Mexico	32.0
AMR-D	—	—
EMR-B	Kuwait	1.4
EMR-D	—	—
EUR-A	Belgium, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Norway, United Kingdom	71.3
EUR-B	Bulgaria	3.8
EUR-C	Estonia, Kazakhstan, Latvia, Lithuania, Russian Federation	69.2
SEAR-B	—	—
SEAR-D	Bangladesh, India	93.7
WPR-A	Australia, Japan, Singapore	97.6
WPR-B	China	84.0

— No data.

[a] Percentage of subregional population covered by countries for which survey data were obtained.

tion of small representative surveys was provided—these cover the majority of the country. All but two studies were from the 1990s. Most studies used information from one 24-hour dietary recall or food diary. Other methods of data collection included multiple 24-hour recalls, 7-day weighed food records, food-frequency questionnaires and food history. The majority of the surveys attempted to provide nationally representative samples; most used multistage random sampling techniques. Sample sizes ranged from about 1000 people (Argentina) to over 22 000 (Belgium).

2.7 Characteristics of excluded studies

Due to the paucity of available information on fruit and vegetable intake at the individual level, few studies were excluded. Reasons for exclusion included the following.

- Another source of data was used for the country (e.g. more representative sample of the population or better method of data collection).
- The amounts consumed in grams per day could not be derived from the survey.

Table 9.6 Details of the dietary intake studies used

Subregion	*Country*	*Contact/ reference*	*Name of survey (if any)*	*Sample*	*Dietary data collection method*	*Data collection period*	*Sample size*	*Sex*	*Age range (years)*	*Limitation*
AMR-A	United States	J.S. Hampl, personal communication, 2001; Taylor et al. (2000)	USDA Continuing Survey of Food Intakes of Individuals	Multistage stratified random sample	Two 24-hour recall—non-consecutive days	1994–1996	15303	M+F	≥0	. . .
AMR-B	Argentina	M. Rio et al., personal communication, 2001	Collection of several dietary surveys in Argentina	Random samples in greater Buenos Aires, Province of Buenos Aires, West Areas (Mendoza)	7-day food record	1999–2000	1068	M+F	≥0	Collection of several small surveys. Very small sample size in >60 years excluded (n = 35). In West Areas (Salta), recruitment through a nutrition programme
	Mexico	Rivera Dommarco (2001); J. Rivera Dommarco et al., personal communication, 2001	National Nutrition Survey	Multistage stratified random sample		Oct 1998–March 1999	2646	F	12–49	No data on adult males. Restricted age range

continued

Table 9.6 Details of the dietary intake studies used (*continued*)

Subregion	*Country*	*Contact/ reference*	*Name of survey (if any)*	*Sample*	*Dietary data collection method*	*Data collection period*	*Sample size*	*Sex*	*Age range (years)*	*Limitation*
EMR-B	Kuwait	Sawaya et al. (1999)	Kuwait Total Diet study	Multistage sample of Kuwati nationals	One 24-hour recall	1997	6700	M+F	≥0	No standard deviations
EUR-A	Belgium	S. De Henauw, personal communication, 2001; De Henauw and De Backer (1999)	Belgian Interuniversity Research on Nutrition and Health	Random sample form voting lists in 42 out of 43 Belgian districts	One 24-hour recall	1980–1984	22 224	M+F	25–74	Restricted age range
	Denmark	Andersen et al. (1996); S. Fagt, personal communication, 2001	Dietary Habits in Denmark	Random sample from Danish civil registration system	7-day food record	Feb/March/ April 1995	3098	M+F	1–79	Restricted age range
	Finland	Findiet Study Group (1998)	Dietary survey of Finnish adults	Age-stratified random sample in 5 regions	One 24-hour recall	Jan–April 1997	3153	M+F	25–74	Restricted age range
	France	Volatier (1999)	INCA: Enquête Individuelle et Nationale sur les Consommations Alimentaires	Stratified national multistage random sample	7-day food record	Aug 1998– June 1999	3003	M+F	≥3	Means for males and females jointly. No standard deviations

Germany	G. Mensink, personal communication, 2001; Mensink et al. (1998)	German Nutrition Survey	Stratified random sample from population registries	Dietary history	Oct 1997–March 1999	4030	M+F	18–79	Restricted age range
Ireland	S. Friel, personal communication, 2001; Friel et al. (1999)	National Health and Lifestyle Survey	Two-stage sampling using Irish electoral register	Semi-quantitative food-frequency questionnaire	May–June 1998	6332	M+F	≥18	No data on children
Israel	D. Nitzan Kaluski and R. Goldberg, personal communication, 2001	First National Health and Nutrition Survey	Random sample from national population register	One 24-hour recall (in 50% 2 recalls)	1999–2001	1963	M+F	25–64	Restricted age range
Italy	A. Turrini, personal communication, 2001; Turrini et al. (2001)	INN-CA—Nation-wide Nutritional Survey of Food Behaviour of the Italian Population	Multistage random cluster stratified by region	7-day weighed food record	1994–1996	2734	M+F	≥0	. . .
Norway	L. Johansson, personal communication, 2001	National Dietary Survey	Multistage random sample	Self-administered food-frequency questionnaire	March/June/Sept/Nov 1997	4465	M+F	16–79	Restricted age range
United Kingdom	Finch (1998); Gregory (1990, 1995, 2000)	National Diet and Nutrition Survey (4 surveys)	Nationally representative random sample from postcode address files	7-day weighed record (4-days for under 5 years)	1986–2000 4 surveys	Each survey ~2000	M+F	1.5–4.5/ 4–18 16–64 >65	No SD for combined fruit and vegetable intake. Age groups different from CRA groups

continued

Table 9.6 Details of the dietary intake studies used (*continued*)

Subregion	*Country*	*Contact/ reference*	*Name of survey (if any)*	*Sample*	*Dietary data collection method*	*Data collection period*	*Sample size*	*Sex*	*Age range (years)*	*Limitation*
EUR-B	Bulgaria	S. Petrova, personal communication, 2001; Petrova et al. (2000)	National Dietary and Nutritional Survey of the population of Bulgaria	Multistage random sample stratified by region/size of settlement	One 24-hour food record	March 1998	2800	M+F	≥1	. . .
EUR-C	Estonia	J. Pomerleau, personal communication, 2001	Baltic Nutrition Survey	Random sample from the National Population Register	One 24-hour recall	Summer of 1997	2108	M+F	18–65	Restricted age range
	Kazakhstan	T. Sharmanov, personal communication, 2001	National Survey of the State of nutrition within the 1995 Kazakhstan Demographic and Health Survey	Multistage random sample	One 24-hour recall	1996	3480	M+F	15–80	No data on children
	Latvia	J. Pomerleau, personal communication, 2001	Baltic Nutrition Survey	Random sample from the National Population Register	One 24-hour recall	Summer of 1997	2308	M+F	18–65	Restricted age range

	Lithuania	J. Pomerleau, personal communication, 2001	Baltic Nutrition Survey	Random sample from the National Population Register	One 24-hour recall	Summer of 1997	2153	M+F	18–65	Restricted age range
	Russian Federation	B. Popkin, personal communication, 2001	Russian Longitudinal Monitoring Survey	Multistage random cluster sample	One 24-hour recall	Oct 1998–Jan 1999	9593	M+F	≥0	. . .
SEAR-D	Bangladesh	Ahmad and Hassan (1982)	Nutrition Survey of Rural Bangladesh	Multistage random cluster sample	One 24-hour weighed record by trained dietary investigator	1981–1982	4904	M+F	1– ≥70	No standard deviation. Age groups different from CRA groups
	India	Government of India (1998)	National Nutrition Monitoring Bureau surveys (1994) and District Nutrition Profiles (1995–1996)	Varied survey designs	One 24-hour recall	1994–1996	Compiled surveys of 18 states, 4 regions	M+F	≥1	No standard deviation. Age groups different from CRA groups
WPR-A	Australia	K. Baghurst and S. Record, personal communication, 2001	National Dietary Survey in Australia	Multistage stratified random sample	One 24-hour recall	Feb 1995–March 1996	13858	M+F	≥2	. . .

continued

Table 9.6 Details of the dietary intake studies used (*continued*)

Subregion	*Country*	*Contact/ reference*	*Name of survey (if any)*	*Sample*	*Dietary data collection method*	*Data collection period*	*Sample size*	*Sex*	*Age range (years)*	*Limitation*
	Japan	Y. Matsumura and N. Yoshiike, personal communication, 2001; Ministry of Health and Welfare (2000); S. Mizushima, personal communication, 2001	National Nutrition Survey	Multistage random cluster sample	Semi-weighed 1-day food record	Nov 1995	14240	M+F	≥1	. . .
	Singapore	M. Deurenberg-Yap et al., personal communication, 2001	National Nutrition Survey	Random sample	Food frequency questionnaire	1998	2388	M+F	18–69	Restricted age range
WPR-B	China	B. Popkin, personal communication, 2001	China Health and Nutrition Survey	Multistage random cluster sample	3 contiguous 24-hour recall	Fall of 1997	12194	M+F	≥0	. . .

- The data were not representative of the population of the country.
- Estimates included potato.

2.8 Estimates by subregion, age and sex

Obtaining subregional estimates from dietary survey data

The following approach was used to obtain subregional estimates of fruit and vegetable intake using available data from individual dietary surveys.

Obtaining estimates for subregions where data are available for two or more countries

In order to obtain subregional means and standard deviations (and obtain 95% confidence intervals for these estimates) when data were available for two or more countries within a subregion, means and standard deviations were pooled. It is assumed that each subregion is a stratified sample with the strata being countries.[2] Because of the lack of information on the shape of the distributions of intakes, it was also assumed that intakes follow a normal distribution (this assumption is discussed in more detail in section 2.8).

It is important to note that if there is substantial heterogeneity among countries in a subregion, these methods tend to underestimate the true standard error of the pooled mean and pooled standard deviation. In addition, pooling is based on only a few countries within a subregion. We have thus assumed that the *pooled* subregional mean intakes and standard deviations are representative of the *true* estimates, and that differences between the pooled estimates and estimates for which data are not available would tend to cancel each other out. Finally, using data for only a few countries may underestimate the true variation of intakes within a subregion. However, for most subregions with available data, a large proportion of the total subregional population was covered by the surveys (see Table 9.5).

Obtaining estimates for subregions where data are available for only one country

In four subregions (AMR-A, EMR-B, EUR-B and WPR-B), only one source of intake data was available. For AMR-A and WPR-B, the surveys were conducted in the United States of America and China, respectively. As these countries represent 84–88% of the total subregional population (Table 9.4), it was assumed that intake data from these countries were representative of subregional intakes. For EMR-B and EUR-B, however, the surveys were conducted in countries that represented only a very small proportion of the total subregional population (1.4% and 3.8% respectively). For this reason, a different approach based on pooling survey and FAO food balance sheet data was used.

EMR-B: First, FAO-derived proxy mean intakes for the subregion were calculated using the method described previously (when no survey data were available for a subregion). As it has been reported that FAO food balance sheet data tend to overestimate intakes in developed countries, a correction factor was applied to the subregional three-year average FAO fruit and vegetable supply. The chosen correction factor corresponded to the difference between FAO food balance sheet data and subregional intake data for AMR-A. The subregional fruit and vegetable supply in AMR-A is the closest to that observed in EMR-B. It was assumed that the age–sex subregional distribution of intakes was similar to that observed in Kuwait. Second, the FAO-derived proxy mean intakes were pooled with intake data from Kuwait to obtain mean intakes for EMR-B.

EUR-B: First, FAO-derived proxy mean intakes for the subregion was calculated using the methods described previously (when no survey data were available for a subregion). As for EMR-B, a correction factor was applied to the subregional three-year average FAO fruit and vegetable supply. The chosen correction factor corresponded to the difference between FAO food balance sheet data and pooled survey data for the subregion EUR-C (assumed to be the most similar in terms of intakes, demographic and health characteristics). It was assumed that the distribution of intakes among age–sex groups was similar to that observed in Bulgaria. Second, the FAO-derived proxy mean intakes were pooled with intake data from Bulgaria to obtain pooled mean intakes for EUR-B.

Final estimates

Estimates of fruit and vegetable intakes stratified by subregion, age and sex are given in Tables 9.8 to 9.11. Results are presented as means with 95% CI for the mean, and as standard deviations with 95% CI for the standard deviation.

Estimates of fruit and vegetable intakes were highest in EUR-A followed by WPR-A (Table 9.7). Surprisingly, reported intakes in AMR-A—the other highly economically developed subregion—are on average only 74–82% of those observed in EUR-A and WPR-A. The lowest intakes were found in AMR-B, EUR-C, SEAR-B, SEAR-D and AFR-E. As expected, intakes varied by age group, with children and the elderly generally having lower intakes than middle-aged adults. However, in a few subregions elderly individuals appeared to have higher intakes than younger adults do in our calculations. This was the case particularly for AFR-E, AFR-D and EMR-D, three groupings where FAO-derived proxy mean intakes were calculated using the distribution of total intakes from another grouping with available data. Because the true age–sex distribution of AFR-E, AFR-D and EMR-D is slightly different from that of the chosen proxy grouping, the calculation of mean intake within each

Table 9.7 Mean intake of fruit and vegetables[a] (95% CI) by subregion, sex and age

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	144 (115–173)	296 (272–320)	288 (256–319)	413 (378–448)	419 (386–452)	439 (403–476)	446 (404–488)	476 (406–546)
	Female	140 (113–167)	279 (255–304)	302 (275–328)	345 (308–381)	305 (271–340)	355 (320–390)	349 (306–392)	382 (302–462)
AFR-E	Male	94 (82–105)	193 (181–205)	192 (178–206)	278 (266–290)	294 (279–309)	325 (309–341)	333 (306–361)	380 (316–443)
	Female	91 (78–103)	181 (170–192)	201 (194–209)	236 (229–243)	214 (205–223)	257 (245–268)	244 (229–259)	245 (225–266)
AMR-A	Male	278 (265–291)	247 (235–259)	257 (240–274)	305 (288–321)	338 (321–354)	369 (349–390)	387 (361–413)	364 (323–404)
	Female	262 (251–274)	236 (224–248)	234 (221–248)	261 (248–274)	307 (292–321)	335 (318–352)	346 (325–367)	348 (316–380)
AMR-B	Male	72 (42–103)	147 (104–189)	148 (124–171)	168 (143–194)	208 (148–268)	220 (160–280)	230 (171–290)	180 (120–239)
	Female	82 (51–112)	134 (78–191)	167 (153–182)	218 (111–324)	204 (153–255)	220 (168–271)	235 (183–286)	230 (178–281)
AMR-D	Male	193 (165–222)	352 (328–376)	299 (268–330)	408 (372–443)	392 (360–425)	387 (351–424)	353 (311–395)	306 (236–377)
	Female	192 (165–220)	339 (315–363)	316 (289–342)	332 (295–368)	287 (253–321)	328 (293–363)	287 (244–330)	241 (161–322)
EMR-B	Male	218 (189–247)	335 (311–359)	296 (265–327)	368 (333–404)	374 (341–407)	392 (355–428)	350 (308–392)	334 (264–404)
	Female	218 (190–245)	327 (303–351)	323 (297–350)	362 (325–398)	346 (311–380)	392 (357–427)	336 (293–378)	319 (238–399)
EMR-D	Male	174 (145–203)	342 (318–367)	312 (281–343)	388 (353–424)	409 (376–442)	446 (410–482)	442 (400–485)	420 (350–490)
	Female	174 (147–201)	333 (308–357)	348 (322–375)	352 (316–389)	319 (284–353)	385 (350–420)	372 (329–415)	409 (329–489)

continued

Table 9.7 Mean intake of fruit and vegetables[a] (95% CI) by subregion, sex and age (*continued*)

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
EUR-A	Male	232 (204–260)	299 (274–324)	423 (401–445)	450 (433–468)	488 (467–508)	511 (487–535)	515 (473–556)	469 (407–530)
	Female	233 (211–255)	299 (279–318)	423 (406–439)	448 (435–461)	483 (469–497)	488 (467–509)	479 (451–507)	446 (411–481)
EUR-B	Male	263 (234–292)	374 (349–398)	396 (365–427)	352 (317–388)	396 (363–428)	366 (330–403)	358 (316–400)	300 (230–370)
	Female	238 (211–265)	372 (348–396)	344 (317–370)	333 (296–369)	383 (348–417)	352 (317–387)	358 (315–401)	303 (223–383)
EUR-C	Male	134 (122–146)	198 (185–210)	233 (218–247)	237 (225–249)	246 (231–261)	254 (237–270)	233 (206–260)	233 (169–297)
	Female	133 (121–146)	182 (171–193)	196 (188–204)	187 (180–194)	202 (193–211)	200 (189–211)	209 (194–224)	190 (170–211)
SEAR-B	Male	108 (96–120)	198 (185–210)	245 (231–259)	243 (232–255)	258 (243–273)	248 (231–264)	244 (217–272)	225 (161–288)
	Female	107 (94–120)	183 (172–195)	201 (194–209)	195 (188–202)	202 (193–211)	201 (190–212)	201 (187–216)	173 (153–194)
SEAR-D	Male	94 (82–106)	177 (165–190)	258 (244–272)	262 (250–274)	262 (247–277)	259 (243–275)	259 (232–286)	234 (170–298)
	Female	95 (82–108)	170 (159–182)	224 (217–232)	229 (222–236)	227 (218–236)	229 (218–240)	228 (213–243)	205 (185–226)
WPR-A	Male	264 (253–275)	345 (333–356)	366 (355–378)	376 (367–386)	450 (439–462)	491 (474–509)	446 (428–463)	415 (398–433)
	Female	232 (222–242)	342 (332–351)	352 (342–362)	383 (374–392)	486 (475–497)	485 (469–501)	440 (424–456)	386 (370–402)
WPR-B	Male	204 (187–221)	274 (266–282)	344 (336–352)	346 (338–354)	360 (350–370)	335 (320–350)	304 (285–323)	258 (221–294)
	Female	190 (170–209)	270 (261–279)	317 (308–325)	334 (326–341)	345 (336–355)	304 (292–317)	273 (257–288)	250 (221–278)

a Grams/person per day.

age–sex strata and the balance among strata was affected. This is observed particularly in the smaller age strata (particularly the elderly in these subregions). As a result, the FAO-proxy mean intakes are less reliable in population strata with relatively smaller sample size and must be interpreted with caution.

Pooled standard deviation estimates were available from only seven subregions (AMR-A, AMR-B, EUR-A, EUR-B, EUR-C, WPR-A and WPR-B). For the other subregions, we applied data from the subregion displaying the most similar intakes by age and sex, and when appropriate, method of data collection. These extrapolations need to be taken with caution, as the standard deviations of one subregion may not represent well the standard deviations of another subregion despite similarity in overall mean intakes. The results shown in Table 9.8 indicate that standard deviations varied considerably by subregion, sex and age group, with an overall median standard deviation of 223 g/day. Estimates tended to be lower in women than in men on average (but with variations by age group), and they were generally lower in young children. In some subregions, standard deviations were also slightly smaller in the elderly.

It is assumed that the reported fruit and vegetable intakes were normally distributed, due to the general lack of available information on the skewness of the distributions (except for the United States). However, this is unlikely to be true as dietary intakes are typically skewed towards higher values (Willett 1998b). Assuming a normal distribution creates the problem that some individuals will be recorded as having negative consumption when estimating impact fractions. As this is impossible, the normal distribution is truncated at zero, with all those falling below this value allocated a value of zero. The results of a sensitivity analysis, described below, based on data from the United States suggest that the approach used is likely to be conservative.

Sensitivity analysis: skewed distributions and calculation of the attributable fraction

Data from the United States were used to evaluate the possible effects of skewness in the distribution of fruit and vegetable intake on the calculation of the attributable fraction for AMR-A. The data indicated a positive skewness ranging from 1.5 to 3. To approximate this type of skewed distribution, the Weibull probability distribution function (PDF) was utilized by varying the shape and scale parameters (decreasing the shape parameter of a Weibull increases positive skewness away from a normal distribution).

Figure 9.1 illustrates a normal distribution (dashed line) with a fruit and vegetable mean intake of 300 g/day and standard deviation of 300 g/day. A significant part of the population with a normal distribution is truncated at zero consumption (approximately 10% of the population in this example). The skewed distribution (solid line) is the

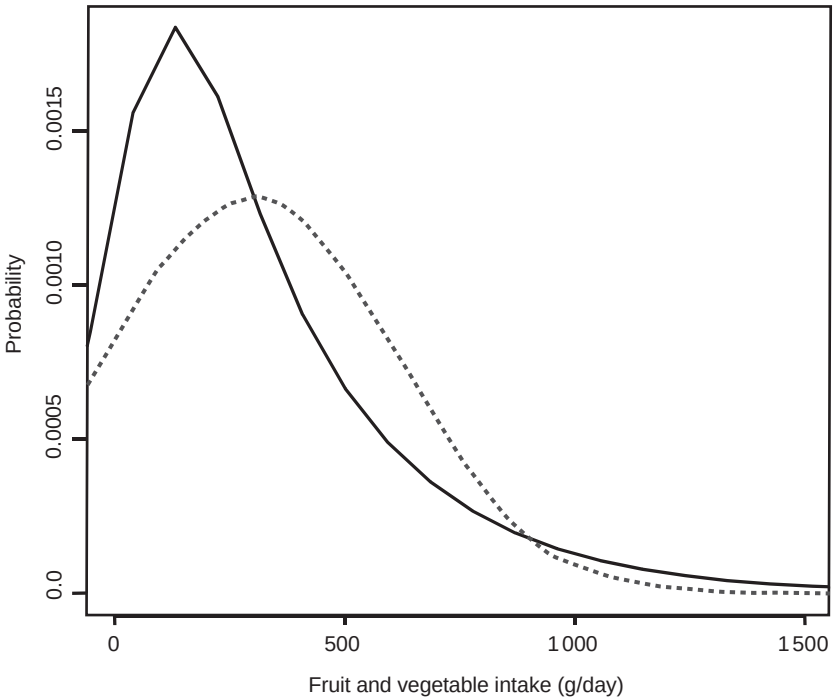
Table 9.8 Standard deviations of fruit and vegetables[a] (95% CI) by subregion, sex and age

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	175.0 (156.7–198.2)	244.8 (228.7–263.3)	293.1 (272.6–316.9)	225.0 (202.4–253.3)	220.7 (199.6–246.8)	213.4 (190.4–242.8)	235.1 (208.6–269.3)	214.6 (174.1–279.9)
	Female	163.3 (146.0–185.3)	240.8 (224.8–259.3)	247.6 (230.2–267.9)	224.5 (201.2–253.9)	237.4 (215.3–264.6)	210.5 (188.4–238.5)	251.5 (224.4–286.1)	239.0 (192.8–314.6)
AFR-E	Male	96.2 (88.6–105.3)	178.6 (170.3–187.8)	254.9 (247.5–262.7)	220.7 (214.7–227.1)	231.5 (224.3–239.3)	192.6 (183.5–202.6)	176.3 (159.9–196.4)	165.8 (130.0–228.9)
	Female	105.5 (97.3–115.3)	155.9 (148.4–164.2)	163.4 (206.3–222.2)	157.6 (189.6–202.3)	171.6 (166.9–176.5)	168.2 (161.2–175.1)	153.5 (144.2–164.1)	115.4 (102.5–132.0)
AMR-A	Male	239.0 (230.2–248.4)	221.3 (213.0–230.3)	297.0 (285.3–309.8)	299.3 (288.0–311.5)	297.8 (286.5–310.0)	295.8 (282.0–310.9)	295.8 (278.5–315.5)	318.7 (292.5–350.1)
	Female	222.5 (214.4–231.2)	209.1 (201.1–217.8)	230.4 (221.2–240.5)	236.3 (227.3–246.0)	262.4 (252.4–273.2)	243.3 (231.6–256.2)	222.8 (209.1–238.4)	243.4 (222.8–268.1)
AMR-B	Male	153.3 (134.4–178.4)	294.3 (229.8–409.4)	470.1 (438.2–507.0)	260.0 (210.9–339.2)	390.3 (312.9–518.9)	390.3 (312.9–518.9)	390.3 (312.9–518.9)	390.3 (312.9–518.9)
	Female	160.2 (141.2–185.2)	341.8 (250.2–539.1)	293.6 (272.8–317.9)	718.2 (515.0–1185.6)	260.5 (190.7–410.8)	260.5 (190.7–410.8)	260.5 (190.7–410.8)	260.5 (190.7–410.8)
AMR-D	Male	175.0 (156.7–198.2)	244.8 (228.7–263.3)	293.1 (272.6–316.9)	225.0 (202.4–253.3)	220.7 (199.6–246.8)	213.4 (190.4–242.8)	235.1 (208.6–269.3)	214.6 (174.1–279.9)
	Female	163.3 (146.0–185.3)	240.8 (224.8–259.3)	247.6 (230.2–267.9)	224.5 (201.2–253.9)	237.4 (215.3–264.6)	210.5 (188.4–238.5)	251.5 (224.4–286.1)	239.0 (192.8–314.6)
EMR-B	Male	175.0 (156.7–198.2)	244.8 (228.7–263.3)	293.1 (272.6–316.9)	225.0 (202.4–253.3)	220.7 (199.6–246.8)	213.4 (190.4–242.8)	235.1 (208.6–269.3)	214.6 (174.1–279.9)
	Female	163.3 (146.0–185.3)	240.8 (224.8–259.3)	247.6 (230.2–267.9)	224.5 (201.2–253.9)	237.4 (215.3–264.6)	210.5 (188.4–238.5)	251.5 (224.4–286.1)	239.0 (192.8–314.6)
EMR-D	Male	175.0 (156.7–198.2)	244.8 (228.7–263.3)	293.1 (272.6–316.9)	225.0 (202.4–253.3)	220.7 (199.6–246.8)	213.4 (190.4–242.8)	235.1 (208.6–269.3)	214.6 (174.1–279.9)
	Female	163.3 (146.0–185.3)	240.8 (224.8–259.3)	247.6 (230.2–267.9)	224.5 (201.2–253.9)	237.4 (215.3–264.6)	210.5 (188.4–238.5)	251.5 (224.4–286.1)	239.0 (192.8–314.6)

EUR-A	Male	347.9 (333.9–363.1)	284.7 (273.9–296.4)	350.3 (341.5–359.7)	312.2 (306.3–318.3)	345.4 (338.6–352.5)	283.7 (275.9–292.0)	344.6 (332.0–358.2)	289.7 (269.1–314.2)
	Female	280.4 (269.2–292.6)	226.2 (217.5–235.8)	290.2 (283.2–297.4)	254.2 (252.0–258.9)	262.4 (257.2–267.7)	265.8 (258.3–273.8)	317.1 (305.1–330.1)	266.6 (250.1–285.8)
EUR-B	Male	175.0 (156.7–198.2)	244.8 (228.7–263.3)	293.1 (272.6–316.9)	225.0 (202.4–253.3)	220.7 (199.6–246.8)	213.4 (190.4–242.8)	235.1 (208.6–269.3)	214.6 (174.1–279.9)
	Female	163.3 (146.0–185.3)	240.8 (224.8–259.3)	247.6 (230.2–267.9)	224.5 (201.2–253.9)	237.4 (215.3–264.6)	210.5 (188.4–238.5)	251.5 (224.4–286.1)	239.0 (192.8–314.6)
EUR-C	Male	96.2 (88.6–105.3)	178.6 (170.3–187.8)	254.9 (247.5–262.7)	220.7 (214.7–227.1)	231.5 (224.3–239.3)	192.6 (183.5–202.6)	176.3 (159.9–196.4)	165.8 (130.0–228.9)
	Female	105.5 (97.3–115.3)	155.9 (148.4–164.2)	163.4 (206.3–222.2)	157.6 (189.6–202.3)	171.6 (166.9–176.5)	168.2 (161.2–175.1)	153.5 (144.2–164.1)	115.4 (102.5–132.0)
SEAR-B	Male	96.2 (88.6–105.3)	178.6 (170.3–187.8)	254.9 (247.5–262.7)	220.7 (214.7–227.1)	231.5 (224.3–239.3)	192.6 (183.5–202.6)	176.3 (159.9–196.4)	165.8 (130.0–228.9)
	Female	105.5 (97.3–115.3)	155.9 (148.4–164.2)	163.4 (206.3–222.2)	157.6 (189.6–202.3)	171.6 (166.9–176.5)	168.2 (161.2–175.1)	153.5 (144.2–164.1)	115.4 (102.5–132.0)
SEAR-D	Male	96.2 (88.6–105.3)	178.6 (170.3–187.8)	254.9 (247.5–262.7)	220.7 (214.7–227.1)	231.5 (224.3–239.3)	192.6 (183.5–202.6)	176.3 (159.9–196.4)	165.8 (130.0–228.9)
	Female	105.5 (97.3–115.3)	155.9 (148.4–164.2)	163.4 (206.3–222.2)	157.6 (189.6–202.3)	171.6 (166.9–176.5)	168.2 (161.2–175.1)	153.5 (144.2–164.1)	115.4 (102.5–132.0)
WPR-A	Male	201.4 (190.9–213.2)	204.9 (198.7–206.7)	255.5 (249.4–261.9)	239.6 (234.2–245.3)	268.0 (261.4–275.1)	278.1 (268.1–288.8)	249.8 (237.8–263.1)	238.7 (220.0–260.9)
	Female	158.1 (149.8–167.4)	190.4 (184.6–196.7)	234.2 (228.7–240.1)	229.8 (224.8–235.1)	260.0 (253.7–266.6)	262.0 (252.9–271.7)	241.4 (231.6–252.1)	217.3 (203.7–232.8)
WPR-B	Male	110.1 (99.2–123.7)	136.1 (130.7–142.0)	161.5 (155.9–167.5)	157.3 (151.8–163.2)	167.7 (161.2–174.7)	167.1 (157.1–178.4)	141.3 (129.1–156.0)	147.1 (125.0–178.8)
	Female	107.5 (95.4–123.1)	146.0 (139.9–152.7)	150.2 (144.6–156.3)	153.2 (148.1–158.7)	161.9 (155.6–168.8)	148.4 (140.0–157.9)	130.9 (120.6–143.2)	136.2 (118.6–159.9)

a Grams/person per day.

Figure 9.1 Illustration of skewed and normal distribution based on data from the United States



approximation of what the actual intake data resemble (skewness is 2 in this illustration). Note that all data in the skewed distribution are non-zero (even though it appears that there are zero values).

The attributable fraction was then calculated, for the two different distributions, for IHD. The result for the truncated normal distribution with probability mass at zero was 35%. Incorporating a skewness value of 2 resulted in an attributable fraction of 38%, thus suggesting that our general approach is conservative.

2.9 Quantitative and qualitative sources of uncertainty in measuring dietary intake

One major source of uncertainty is that the collective term "fruit and vegetables" comprises a very heterogeneous group of foods in different countries or cultures. In a Western-type diet alone, fruit and vegetables include roots, leaves, stems, fruit and seeds from more than 40 botanical families (Lampe 1999). They can be consumed fresh or cooked in many different ways that will influence their biochemical content. Bio-

chemical composition also varies among different types of the same fruit. For example, the vitamin C content of different types of apple varies tenfold. Composition is also subject to differences in growing conditions, such as soil composition, and storage conditions, a factor of increasing importance as commodities are transported globally to ensure year-round supply in developed countries. It was decided to keep fruit and vegetables as a single entity for two main reasons. First, there remains uncertainty as to which components of fruit and vegetables would confer a protective effect. Even if the relevant effective constituents had been correctly identified, the nature of their relationship to disease risk would still need to be correctly specified. Second, obtaining intake data for specific foods (for this project) would have been even more difficult than for fruit and vegetables taken together.

Seasons also influence the amounts and variety of fruit and vegetables consumed. Indeed, evidence is emerging to link seasonality of consumption of fresh fruit and vegetables to the pattern of cardiovascular disease mortality in some countries (Powles et al. 1996). It is possible that the consequences for disease of an annual cycle of seasonal excesses and out-of-season shortages (as in the less economically developed countries of the former Soviet Union) may be quite different to the effects of consuming a similar annual level where counter-seasonal supplies ensure that there is no period of very low consumption (as in the affluent countries of north-west Europe). However, in the absence of information on national variations in fruit and vegetable intake and epidemiological evidence, it was assumed that it is the long-term annualized average of fruit and vegetable intake that best predicts disease risk. The need for caution is illustrated by the case of alcohol, where risk of cardiovascular disease appears to be more sensitive to the pattern of alcohol consumption over time as well as the total amount consumed (Kauhanen et al. 1999; Rehm et al. 2001). It is also assumed that the estimates obtained for this project represent annualized mean intakes, although some surveys collected data during only one or two seasons.

The choice of data sources may also have influenced the final estimates. It was decided that dietary surveys of representative population samples would be used as the primary source of information for this project. However, the quality and validity of individual level data depend on the ability (and willingness) of each individual to provide accurate information on his/her dietary intake (Johansson et al. 2001; Nelson and Bingham 1997). If the aim is to assess current diet, the procedure involved in measuring dietary intake may lead to changes in behaviour. If the aim is to measure past diet, then the reliability of the information provided will depend on memory and on the conceptual abilities of the respondents. The high intakes observed in AMR-A and WPR-A suggest that reported consumption could have been inflated by conscious (social desirability bias) or unconscious over-reporting of fruit and vegetable intake by the survey respondents (Hebert et al. 1995). The reported

intakes in some countries within these subregions are greater than expected. This is particularly the case for the United Kingdom and Germany where the estimated mean national fruit and vegetable consumption was higher than in Mediterranean countries such as Italy and Israel. It is possible that recent public health campaigns, such as those that took place in Finland (Puska 2000), coupled with changes in the retail trade, and thus in marketing and distribution of fruit and vegetables, have improved the dietary habits and increased the fruit and vegetable intake of these populations. This would be consistent with the striking improvements in cardiovascular mortality that they have experienced. Conversely, it is possible that the inclusion of fruit juices in the estimates of fruit and vegetable intakes made the estimates appear larger than expected. Other difficulties include the conversion of food frequencies into mean intakes in surveys that used food-frequency questionnaires, and the limitations and completeness of the various food analysis software programs used in different countries. Finally, it is possible that the survey respondents were not entirely representative of the reference populations, even though most data were from national surveys of dietary intakes.

In dietary surveys, variation as measured by standard deviations is influenced by the method used to collect data (see section 2.2). Most of the surveys used in this study were based on only one day (sometimes two days) of information. It is thus expected that standard deviations were overestimated. However, as described earlier, the method used to pool data from two or more surveys tends to underestimate the level of uncertainty surrounding the pooled standard deviation for the subregion based on a subsample of countries *if* there is substantial between-country variation.

Although we aimed to obtain dietary survey data for each country, these do not exist and thus food availability statistics were used for subregions where no or few data were available. The validity of food balance sheet statistics depends on the availability and validity of the basic national data on which they are based, including statistics of population, production, stock, import and export. These are known to vary among countries, and from one year to another, both in terms of coverage and accuracy (Kelly et al. 1991). The net availability of vegetables is affected by factors such as non-commercial production and uncertain losses to animal feed, spoilage and waste. However, the FAO performs external consistency checking using supplementary information such as household survey results as well as the application of relevant technical, nutritional and economic expertise in an attempt to eliminate these potential deficiencies. In this study we have used at least three years of FAO data in order to try to reduce the effect of potential yearly variations in coverage and accuracy. However, the current lack of information on adjustment factors to apply to FAO food balance sheet data in developing countries is a source of uncertainty. Finally, extrapolation among coun-

tries would be an important source of uncertainty, especially in the presence of inter-country heterogeneity.

3. Estimating risk factor–disease relationships

3.1 Outcomes to be assessed, evidence of causality, excluded outcomes and reasons for exclusion

Selected outcomes

The outcomes to be assessed are those for which the best evidence of a risk factor–disease relationship is available for fruit and vegetable intake. These include:

- IHD;
- cerebrovascular disease;
- lung cancer;
- stomach cancer;
- colon and rectum cancers; and
- oesophageal cancer.

Evidence of causality and excluded outcomes

A general discussion of the evidence of causality for the association of fruit and vegetable intake with health outcomes follows. Specific details of evidence for each outcome are included in section 3.7.

The choice of outcomes was guided mainly by previous reviews of the literature, including those of Ness and Powles (1997) and Law and Morris (1998) that suggested a protective effect of fruit and vegetables for IHD and stroke. The review from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) for a wide range of cancers (1997) concluded that the evidence for fruit and vegetables decreasing cancer risk was convincing for lung and digestive tract cancers. In the present study, cancers of the lung, oesophagus, stomach, colon and rectum were examined, leaving cancers of the mouth and pharynx for future work. Cancers for which the WCRF/AICR review reported only a probable association (larynx, pancreas and bladder cancers) or limited evidence of an association (cancers which may have a hormonal etiology including ovary, endometrium, thyroid and prostate) were not included in the CRA project at this stage.

Although there is also limited evidence for other health outcomes such as type II diabetes, chronic obstructive pulmonary disease and cataract (Sargeant et al. 2001; Smit et al. 1999; Tavani et al. 1996b), it was decided not to include these in the 2000 revision of the GBD

project because the number of published studies is currently too limited to draw conclusions on the size of the effect for these health problems. The evidence for these will be reconsidered in the future. Although other cardiovascular disease outcomes such as peripheral vascular disease share most risk factors with IHD and occlusive stroke, these outcomes were also excluded from the present report due to the current lack of information on a possible relationship with fruit and vegetable intake.

General discussion of causality for the selected exposure variable

Bradford Hill's criteria of causality, comprising biological plausibility, temporality, strength, consistency, dose–response, and experimental evidence, were considered in order to determine the likelihood of causality for the association of fruit and vegetable intake with the six selected health outcomes (Hill 1965).

Biological plausibility

Evidence of causality for the relationship between fruit and vegetable consumption and health can be obtained from the identification of possible biological mechanisms. A number of mechanisms have been proposed (Lampe 1999). They generally involve specific nutrient and non-nutrient constituents of fruit and vegetables, including antioxidants and various other micronutrients in fruit and vegetables. Nutrients are substances in food that the body can use to obtain energy or synthesize tissues (Insel et al. 2003). Non-nutrients are substances, which may not have a known nutrient function but are still important for biological mechanisms such as regulatory functions. Few attempts have been made to simultaneously explore a combination of potential mechanisms.

The issue of biological plausibility is thus extremely complex and evidence remains fragmentary. There are several reasons for this. First, it is very difficult, in conventional epidemiological studies, to specify precisely exposure to different types of foods or food components over a prolonged period of time. As mentioned, obtaining valid information on individual dietary intake is very difficult. Even where this is possible, it is likely that the true content of the reported foods will have varied according to variations within particular types of food (such as different brands of oranges), differences in methods of food preparation, and seasonal variation in food composition. Second, while the growth in understanding of molecular mechanisms of disease is identifying many new factors, in particular non-nutrient components of food which may be important in preventing specific diseases, in many cases their existence, let alone their possible importance, was not known at the time when cohort studies now reporting results were established (e.g. glucosinolates in brassicas [van Poppel et al. 1999] and isoflavones in soya [Messina 1999], both of which appear to reduce the incidence of some types of cancer). The incompleteness of current food composition tables is a

major limitation to the assessment of the possible effect of varying intakes of these substances.

Consequently, much of the available research for the assessment of biological mechanisms is based on studies in animals and often involves the administration of pharmacological, rather than physiological, doses of various substances. This raises important questions about the applicability of such studies to humans. These reservations must therefore be borne in mind when interpreting the evidence discussed below.

Cancer

The immediate cause of cancer is damage to DNA at some stage during the cell cycle (Weinberg 1996). At the risk of over-simplification, this can arise from one of three broad mechanisms: genetic (e.g. certain childhood cancers), cancers linked with endogenous hormonal patterns such as breast cancer and the action of exogenous carcinogens. This last group includes compounds produced from tobacco and a wide range of other chemical agents, such as asbestos or benzene, ionizing radiation, and, as is being increasingly recognized, many infectious agents (e.g. *Helicobacter pylori* as the leading cause of stomach cancer).

From this brief review it is apparent that fruit or vegetable consumption might only be expected to influence directly the risk of certain cancers and not others, and even where they do have a role, this is likely to be modulated by a wide variety of other factors, the importance of which will vary in different populations.

The substances present in fruit and vegetables that might have an impact on cancer incidence can be divided into agents that block the action of carcinogens (Table 9.9), agents that suppress carcinogenesis (Table 9.10) and antioxidants, which can prevent oxidative DNA damage. Some of these agents have both complementary and overlapping mechanisms of action.

Antioxidants include certain vitamins, such as vitamins C (Gershoff 1993) and E (Brigelius-Flohe and Traber 1999), carotenoids (Haegele et al. 2000) (including beta-carotene and other compounds such as

Table 9.9 Selected carcinogen-blocking agents present in fruit and vegetables

Component	*Fruit/vegetable*
Terpenes (Schut et al. 1997)	Citrus fruit
Organosulfides (Singh et al. 1996)	Allium vegetables: onion, leek, garlic, scallion, chives
Indoles (Oganesian et al. 1999)	Cruciferous vegetables
Flavonoids (Malaveille et al. 1996)	Onion, apple, citrus fruit, tea, coffee, cola, alcoholic beverages
Carotenoids (Sengupta and Das 1999)	Yellow and orange fruit and vegetables, green leafy vegetables

Table 9.10 Selected carcinogenesis-suppressing agents present in fruit and vegetables

Component	*Fruit/vegetable*
Protease inhibitors (Kennedy 1998)	Legumes, potato, spinach, broccoli, cucumber
Terpenes	Citrus fruit
Isothiocyanates	Cruciferous vegetables
Plant sterols (Awad et al. 2000)	Vegetables, beans, seed
Carotenoids	Yellow and orange fruit and vegetables, green leafy vegetables

flavonoids) and selenium. These act by scavenging free radicals that would otherwise damage DNA. In doing so, they would reduce the impact of certain exogenous carcinogens.

In general, any protective effect that fruit and vegetables might exert is more likely to be apparent with cancers where exogenous carcinogens play a major part. Examples include lung, stomach and colorectal cancer. Evidence from observational studies seems to support this. The WCRF/AICR review of the literature (World Cancer Research Fund and American Institute for Cancer Research 1997) concluded that the evidence for fruit and vegetables decreasing cancer risk was convincing for oral-pharyngeal, lung and digestive tract cancers; that there was a probable association for larynx, pancreas and bladder cancers; and that the evidence was limited for cancers which may have a hormonal etiology including ovary, endometrium, thyroid and prostate.

Most human research investigating cancer risk has examined either the effect of a specific compound or of overall fruit and vegetable consumption. Research into the former has yielded mixed results. While many studies have shown an association between high beta-carotene intake and reduced risk of cancer, especially lung and stomach cancer (van Poppel and Goldbohn 1995), a highly publicized study among smokers receiving vitamin supplements, including beta-carotene, found that supplementation was associated with an increased rate of lung cancer. Similarly, while a recent meta-analysis found a small reduction in the risk of breast cancer with high levels of fruit and vegetable consumption (Gandini et al. 2000), some large studies looking at vitamin supplements have found no effect (Watkins et al. 2000; Wu et al. 2000). However, the effect of dietary composition on cancers with hormonal etiologies is likely to be greatest in the pre-pubertal years, as diet during this phase of growth may influence breast cancer risk substantially via its effect on body size, age of menarche, etc.

Given the many substances potentially involved in protecting against cancer, and the diverse mechanisms involved, these mixed results have highlighted the need to look at non-nutrient components of fruit and

vegetables. More research is now investigating, among others, the potential impact of other food components such as bioactive compounds (allium compounds, dithiolthiones, isothiocyanates, terpenoids, isoflavones, protease inhibitors, phytic acid, polyphenols, glucosinolates and indoles, flavonoids, plant sterols, saponins and coumarins) (Verhagen et al. 1995).

In summary, there are many possible mechanisms by which fruit and vegetable consumption might reduce the risk of cancer. However, our knowledge is handicapped by the uncertainty with regard to the many pathways involved in carcinogenesis and the relative quantitative importance of each of the mechanisms that, on current knowledge, could plausibly be involved. However, it appears that the impact of diet is likely to be greatest for cancers caused by specific external carcinogens, such as gastrointestinal and lung cancer, and less important for cancers where endocrine factors play a greater role, such as breast and prostate cancer. Furthermore, the overall importance of diet in a given population will clearly reflect the prevalent pattern of exposure to specific carcinogens as well as differences in genetic susceptibility. Thus, an agent that acts to protect against the effects of a particular carcinogen will have less of an effect in a population where exposure to that carcinogen is rare than where it is common.

Cardiovascular disease

As with cancer, the multiple mechanisms by which fruit and vegetable consumption might act on the risk of cardiovascular disease are difficult to disentangle because of the inadequate understanding of the determinants of disease. Most research has concentrated on atherosclerosis. Other potential mechanisms by which fruit and vegetables could impact indirectly on cardiovascular risk include a link with blood pressure modulation, through the high potassium content of some fruit and vegetables (Ascherio et al. 1998; Lampe 1999), or with chronic respiratory disease (associated with fruit and vegetables—and their constituents) and vascular disease risk. For the sake of simplicity, this short review will focus on IHD, although some issues are also relevant to cerebrovascular disease.

Atheroma is thought to arise as a result of monocytes adhering to endothelial cells and migrating into the arterial intima where they become macrophages, taking up low density lipoprotein, subsequently becoming foam cells. The role of fruit and vegetable constituents in monocyte adhesion is increasingly well understood. Methionine, derived from dietary protein, is converted within cells to homocysteine. Deficiency of folic acid, vitamins B_{12} and B_6 will give rise to an elevated level of homocysteine (Chambers et al. 2001). High levels of homocysteine contribute to the generation of free radicals, and thus oxidative damage, in enthothelial cells, leading to the aggregation of monocytes and platelets, as well as vasoconstriction (Kojda and Harrison 1999). These,

in turn, promote atherogenesis. There is now compelling epidemiological evidence to link homocysteine and vascular disease. A recent meta-analysis showed that the risk of cardiovascular disease increased with plasma homocysteine, with odds ratios of 1.6 (1.4–2.3) and 1.8 (1.4–2.3) per 5 mol/l increment in plasma homocysteine in men and women, respectively. The relationship was similar for cerebrovascular disease (Boushey et al. 1995).

It has been suggested that other components of fruit and vegetables, in particular antioxidants, act at other stages in the process of atherogenesis. Such compounds could act by reducing the oxidation of low-density lipoprotein, thus reducing the formation of fatty streaks and plaques. These antioxidant compounds include vitamin C, which is involved in free radical scavenging, haemostasis and in the stabilization of lipid membranes (Witztum 1994), and beta-carotene, which neutralizes singlet oxygen molecules and prevents chain formation, so reducing oxidative processes that are important in atherogenesis (Gaziano and Hennekens 1993). Flavonoids also inhibit the oxidation of low density lipoprotein and reduce thrombotic tendencies.

Observational studies support a strong inverse association between plasma levels of vitamins C and E and cardiovascular mortality (Daviglus et al. 1997; Gale et al. 1995; Gey 1995; Manson et al. 1992; Yokoyama 2000). However, only a few studies have reported a significant inverse relationship between vitamin C specifically and cardiovascular risk (Khaw et al. 2001). Several reviews have found no significant benefit from vitamin C after controlling for other antioxidant intake or multivitamin use (Price and Fowkes 1997; Rexrode and Manson 1996). Even those that reported a benefit from vitamin C differ with regard to the point at which an effect appears and the potential magnitude of the relationship. Some studies indicated an increased risk of cardiovascular disease only at very low levels of plasma vitamin C, with no effect within the range seen in most populations. Other studies have reported a significantly reduced risk only in persons with the highest levels or with supplemental intake. However, a recent study showed a significant decrease in cardiovascular and IHD risk throughout the normal plasma range (Khaw et al. 2001). Similarly, although results from many observational studies suggest that higher serum levels of beta-carotene reduce the risk of cardiovascular disease, systematic reviews have concluded that evidence for a protective effect is inconsistent (Jha et al. 1995; Rexrode and Manson 1996).

As with studies of cancer, there is no clear evidence from intervention trials that antioxidant supplements reduce the risk of cardiovascular disease (Collins et al. 2002; Gaziano 1996; Greenberg and Sporn 1996; Hennekens et al. 1996; Lonn and Yusuf 1999). In the case of beta-carotene there is even some evidence of harm. Several trials were not, however, designed specifically to assess cardiovascular disease risk and did not provide data on non-fatal cardiovascular end-points. Some

authors have suggested that the apparent protective association found in observational studies would be due to residual confounding by differences in socioeconomic status, health behaviour and dietary intake (Ness 2001).

Many of the same challenges that arise with studies of the etiology of cancer also apply to IHD. First, if fruit and vegetables do affect atherogenesis, then their effect will be modulated by other important factors that are involved in atherogenesis and are also influenced by diet. This is particularly the case for high density and low density lipoproteins. These are determined primarily by the amount and nature of fat in the diet, but are also influenced by alcohol consumption, with the precise effect determined by the pattern of drinking. In addition, it is important to remember that atherogenesis is only one factor involved in myocardial infarction. Another is thrombosis, which may also be influenced by certain dietary factors (Chen et al. 2000).

Second, and less well recognized, cardiovascular disease embraces a wide variety of different processes. In particular, it is becoming clear that some myocardial infarctions in young people have a different etiology. Even within the more conventional understanding of IHD, there are clearly differences between those whose atheroma predominantly takes the form of plaques that are lipid-rich, and thus likely to lead to plaque rupture and so to acute infarction, and those that are predominantly fibrous, with smooth muscle proliferation, which are more likely to cause progressive angina (Kharbanda and Vallance 2001).

Experimental evidence

Trials of dietary changes

There is little experimental evidence for the health effects of increasing fruit and vegetables in the diet. Obviously foods that are part of a usual diet are not easily amenable to traditional trials in the general population. Although no trial examined just giving advice to eat more fruit and vegetables on the disease outcomes considered in this report, a few trials of dietary advice in secondary prevention of IHD have included advice to eat more fruit and vegetables (Burr et al. 1989; de Lorgeril et al. 1994, 1999; Rinzler 1968; Singh et al. 1992).

The Diet and Reinfarction Trial (DART) was set up to examine the effect of diet on the secondary prevention of myocardial infarction. Participants were randomized to receive advice or no advice on each of three dietary factors: a reduction of fat intake and an increase in the ratio of polyunsaturated to saturated fat; an increase in fatty fish intake; or an increase in cereal fibre intake. Although the fat advice arm of the trial was associated with an increased fruit and vegetable consumption of about 50 g/day, no effect on total mortality at two years was observed (RR = 1.00, 95% CI 0.77–1.30) and there was no effect on IHD events (IHD deaths plus non-fatal myocardial infarction: RR = 0.91, 95% CI

0.71–1.16) (Burr et al. 1989). It is possible, however, that the follow-up period was too short to allow for an effect to be detected or that the increase in fruit and vegetable consumption was too small to produce a detectable effect.

The Lyon Diet Heart Study investigated whether a Mediterranean-type diet compared with a prudent Western-type diet could reduce the rate of recurrence after a first myocardial infarction. Intermediate analysis showed a marked protective effect after 27 months of follow-up (73% reduction in rate of recurrence and death from cardiovascular causes; RR = 0.27, 95% CI 0.11–0.65), which was maintained for four years after infarction (RR = 0.28, 95% CI 0.15–0.53) (de Lorgeril et al. 1999). The increase in fruit and vegetable consumption in the intervention group was thought to be an important factor in risk reduction. However, as in the DART study, diet changed in a number of ways during the trial and it is thus impossible to estimate the specific influence of increased fruit and vegetable intake in either trial.

Evidence that increasing fruit and vegetable intake alone may be important as a dietary intervention in reducing cardiovascular disease risk comes from the Indian Experiment of Infarct Survival (IEIS) (Singh et al. 1992). This randomized controlled trial showed that the consumption of a low-fat diet enriched with fruit and vegetables compared with a standard low-fat diet was associated with about 40% (RR = 0.60, 95% CI 0.31–0.75) reduction in cardiac events and 45% (RR = 0.55, 95% CI 0.34–0.75) reduction in mortality in 406 men with acute myocardial infarction after one year. These findings suggest a very rapid effect of dietary change on incidence and mortality from IHD that would appear to be difficult to explain.

Some recent trials also assessed the impact of increased fruit and vegetable intake on blood pressure. In the Dietary Approaches to Stop Hypertension (DASH) trial, hypertensive participants were fed a control diet for three weeks, and then were randomized to receive for eight weeks either the control diet, a diet rich in fruit and vegetables, or a combination diet rich in fruit and vegetables, and reduced in saturated fat, fat and cholesterol (Conlin et al. 2000; Obarzanek et al. 2001). Both the combination diet and the fruit-and-vegetables diet significantly reduced systolic and diastolic blood pressure. After eight weeks, 70% of the participants on the combination diet had a normal blood pressure, 45% of those on the fruit and vegetable diet, and 23% of those on the control diet. Unsurprisingly the fruit and vegetable diet produced few changes in blood lipids and had less effect on blood pressure reduction than the combination diet. Both diets showed that they could potentially help reduce IHD risk. However, studies with a longer follow-up would be required to assess the true long-term effect of such changes.

Another trial assessed the specific effect of increased guava intake in hypertensive individuals (Singh et al. 1993b). After four weeks, the diet rich in guava (0.5–1 kg/day) was associated with 7.5/8.5 mmHg net

decrease in mean systolic and diastolic pressures compared with the control group, a significant decrease in serum total cholesterol (7.9%), triglycerides (7.0%), and an insignificant increase in high density lipoprotein (HDL) cholesterol (4.6%) with a mild increase in the ratio of total to HDL cholesterol. The authors suggested that an increased consumption of guava fruit could cause a substantial reduction in blood pressure and blood lipids without a decrease in HDL cholesterol. These changes were attributed to its high potassium and soluble fibre content, respectively. Further research is needed to confirm this hypothesis with more easily applicable dietary changes.

Nutrient supplement trials

Due to the lack of trials of increased fruit and vegetable intake on health outcomes, most data from intervention studies relate to studies of nutrient supplements. Unfortunately, these trials have generally been of small sample size and relatively short duration (Lampe 1999).

In contrast to the results of observational studies, findings from trials of antioxidant and vitamin supplementation have mostly shown no effect on mortality, cardiovascular events or cancer (Blot et al. 1995; Correa et al. 2000; Egger et al. 1998; Hooper et al. 2001; Ness et al. 1999a). There has even been some concern following two trials that showed an increased risk of lung cancer mortality with beta-carotene and vitamin A supplements in the Alpha-Tocopherol, Beta-Carotene and Cancer Prevention (ATBC) study (Anonymous 1994) and the Beta-Carotene and Retinol Efficacy Trial (CARET) (Omenn et al. 1996a, 1996b). However, the recent Heart Protection study (HPS) showed neither benefit nor harm of supplementation with antioxidant vitamins after 5.5 years follow-up. This double-blind randomized trial with a 2×2 factorial design investigated, in over 20 500 persons, the use of simvastatin and antioxidant vitamins (vitamin E, vitamin C and beta-carotene) (Collins et al. 2002).

One exception is the Linxian trial in China (Blot et al. 1995). This trial showed reduced total mortality in the group supplemented with beta-carotene, alpha-tocopherol and selenium compared with the placebo group after six years. However, it is not possible to identify which antioxidant contributed most to the trend towards lower mortality. Some trials have also suggested that vitamin E supplementation may prevent ischaemic stroke in high-risk hypertensive patients (Leppala et al. 2000).

These generally null findings, while initially surprising, are not entirely unexpected given the large number of potentially active compounds in food and the scope for interactions, both with other exogenous substances and genetic status. Given that there are very few randomized-controlled trials that investigated the association of fruit and vegetable consumption with disease outcomes, current evidence of causality is mainly based on observational studies.

Strength of association

The review of the evidence from cohort and case–control studies for this project generally supports the hypothesis that a high dietary intake of fruit and vegetables is protective for cardiovascular disease and the selected cancer (see results of the systematic review in sections 3.6 and 3.7). We consider this to be a relatively strong association for the outcomes presented in this chapter, especially taking into account the potential dilution inherent in dietary exposure measurement.

Consistency

The review of the literature performed for this project shows that most studies of fruit and vegetable consumption demonstrated a generally consistent inverse relationship with the six disease outcomes in different populations (see section 3.7). There were virtually no studies of whole foods (thus excluding nutritional supplements) that showed harmful associations, and many of the studies that reported a null association reported in fact insignificant inverse trends. The major caveat to this statement is that there have been few studies in populations from developing countries.

Temporality

It is virtually axiomatic that fruit and vegetable consumption will precede disease outcomes. The many cohort studies reviewed here that have long follow-up periods provide more convincing evidence for temporality, as they are less likely to have been affected by information bias, a major source of bias in case–control studies (e.g. recall bias).

Dose response

Evidence from the literature shows that in general, people in the highest categories of fruit and vegetable consumption have lower risk of cardiovascular disease and cancers compared with those in the lowest consumption categories. Many of the studies also reported a significant trend between the quartiles, quintiles or tertiles of consumption and disease risk, and a few studies have reported significant effects with fruit and vegetable treated as a continuous variable (see sections 3.6 and 3.7).

Summary

There are still many uncertainties with regard to the mechanisms that lead to common diseases, to the roles that fruit and vegetables could play in these mechanisms, and to the specific substances in fruit and vegetables that are particularly important. Different studies have suggested that flavonoids, carotenoids, vitamin C, folic acid, and fibre could play a protective role. However, it must be kept in mind that studies based on single food constituents may underestimate the effects of exposures such as foods, which are chemically complex. Also, single constituents can be a

marker for other active constituents (as the conflicting results between observational studies and trials have suggested for beta-carotene) (Egger et al. 1998), or even for a combination of constituents that are responsible for the protective effect. Until these mechanisms are better understood, it will not be possible to determine, with any certainty, what precise role specific components of fruit and vegetables might play. What can be said with some confidence is that there are a wide variety of substances within fruit and vegetables that appear to play a role in the etiology of cardiovascular disease and some cancers.

3.2 Overview of methods for estimating risk factor–disease relationships

The associations reported in this study were based on a systematic review of the literature. This provided evidence for the direction and size of the relationship between fruit and vegetable consumption and the selected disease outcomes. This was complemented with meta-analyses for four disease outcomes as described in section 3.7.

3.3 Criteria for identifying relevant studies

All studies that satisfied the following criteria were included in the systematic review of the literature:

- studies that measured dietary intake of fruit and/or vegetables;
- studies of vegetarians that measured food intake; and
- a special focus was placed on studies that explored associations of fruit and vegetable *intake* with diseases. However, for completeness we have also included studies that used as their exposure variable proxy measures of intake derived from the measurement of intermediate variables (such as dietary fibre) or biological markers (such as carotenoids, folate, flavonoids, vitamins A and C not due to supplements) where there was a high correlation with the specific food type.

3.4 Search strategy and inclusion criteria for the literature review

Studies were identified through a systematic review of the literature. The following databases were searched: Medline, Embase, Cochrane On-line, CABHealth and CABAbstracts using the keywords “fruit” or “vegetables” and “coronary heart disease”, “cerebrovascular disorder”, “lung”, “colorectal”, “stomach” and “esophageal”, “neoplasms” and “cancer”. All search terms were linked to MESH headings and exploded. Searches were limited to human studies in English from 1980 onwards (for the CABabstracts, however, the search was from 1987 to 2000).

The outcomes included in this systematic review were the following.

- Cardiovascular diseases: symptomatic heart disease, cerebrovascular disease and total circulatory disease. Studies of peripheral vascular

disease, all-cause mortality and cardiovascular risk factors were excluded.

- Cancer: all histological types of the site-specific cancers were included but not reviewed separately.

Relevant studies for inclusion were determined through the review of titles and abstracts. If there was any doubt regarding study relevance, the full text of the study was retrieved.

This search was complemented with a hand search of citations from books, reviews and citations of references already located. Authors who had published key studies and reviews in the field were also approached to help us identify any other studies, published or unpublished.

3.5 Characteristics of excluded studies

Studies were excluded if any one of the following criteria was satisfied.

- The measurement of risk was based solely on blood biochemical markers with no measure or estimate of dietary or nutrient intake.
- The study focus was on investigating the effect of non-dietary supplements.
- The outcome measure was prognosis, pre-cancerous lesions or pre-disease markers rather than incident cases or mortality.
- The statistical analyses of the study were not adjusted for major confounding factors such as age, sex and smoking.

3.6 Description of studies

Characteristics of included studies

A short summary of the number of studies included in the systematic review is given in Table 9.11. All studies included in the review of the literature are described in section 3.7, where the assessment of causality for each outcome is discussed. Details of the studies included for each specific outcome are provided in Tables 9.21 to 9.28.

Limitations of the studies included in the review of the literature

The studies included in the review of the literature differed in many ways, including:

- the type of study design;
- the sex, age range and ethnicity of the study population;
- the method and validity of measurement of the dietary exposure;
- the method of reporting the dietary exposure (qualitative vs quantitative);

Table 9.11 Summary of the studies included in the review of the literature

	Case–control studies		*Cohort studies*	
Outcome	*Number*	*Countries/areas covered*	*Number*	*Countries/areas covered*
Ischaemic heart disease	Not assessed	. . .	27	Japan, USA and Europe (north)
Ischaemic stroke	Not assessed	. . .	21	Japan, USA and Europe (north)
Lung cancer	32	Canada, China, Brazil, India, Japan, USA and Europe (east, north and south)	21	Japan, USA and Europe (north and south)
Colorectal cancer	33	Argentina, Australia, Canada, China, Japan, Russian Federation, Singapore, Uruguay, USA and Europe (north and south)	15	Japan, USA and Europe (north)
Gastric cancer	32	Canada, China, Japan, Mexico, Republic of Korea, Turkey, USA, Venezuela and Europe (north and south)	14	Japan, USA and Europe (north)
Oesophageal cancer	28	China, India, Japan, USA, Europe (north and south) and South America	4	China, Japan and Europe (north)

- the period of follow up;
- the outcome measured;
- the range of intake of fruit and vegetables of the study population;
- the underlying disease risk of the population (i.e. high vs low); and
- the potential confounders that were adjusted for.

These differences often made results incomparable among studies. The fact that the majority of studies came from Japan, the United States and Europe is another limitation as it restricts the generalizability of the data for use in the CRA project.

STEPS TO ASSESS AND REDUCE RANDOM ERROR

Most measures of association presented in this report include confidence intervals as a measure of uncertainty. The number of outcome events on which the measures of association are based is also given in the tables.

METHODS USED TO OBTAIN THE ESTIMATES OF RELATIVE RISKS

To date, there have been few reported meta-analyses of the association of fruit and vegetable intake with disease. In 1998, Law and Morris

reported the results of a meta-analysis of published cohort studies of the relationship of different markers of fruit and vegetable consumption, including dietary intake of fruit and vegetables, on the risk of IHD, adjusted for other factors (Law and Morris 1998). However, the results of this study were criticized by some researchers who suggested that potential residual confounding and heterogeneity among studies could have influenced the results (Ness et al. 1999b).

More recently, a group of researchers reported the results of meta-analysis of previously published case–control and cohort studies. This estimated the association of total fruit or total vegetable consumption with oesophageal, gastric and colorectal cancer (Norat et al. 2001). The methodology used had limitations: studies were included if there was information necessary for the statistical analysis, but there was no assessment of study quality or potential confounding. The studies had measured fruit and vegetable intake in a range of ways, both quantitative and qualitative. If intake data were only available as a qualitative amount (i.e. a subjective categorization into high vs low consumption), the amount of fruit and vegetables consumed in grams was estimated from average consumption in other studies or data sources, including FAO food balance sheets. The methodology used in that meta-analysis highlights the difficulties in obtaining an accurate summary measure of association for studies of fruit and vegetable intake.

Selection of studies

Considering the large variations among studies with regard to study design, study quality and measurement of both exposure and outcome, it would be methodologically inappropriate, and potentially misleading, to pool results statistically from all the separate studies identified in the systematic review to obtain summary measures of association. This view has also been taken by other researchers who believe, given the quality and heterogeneity of the evidence for fruit and vegetable consumption and the substantial potential error in the measurement of diet, that meta-analyses are not appropriate for pooling observational studies and will only serve to attenuate the error without exploring the heterogeneity which may be important in diet–disease relationships (Ness and Powles 1997, 1999; Wiseman 2002).

In this study, it was decided first to apply strict criteria to select only the best quality and most representative studies for the association of fruit and vegetable intake with each disease outcome. Only the studies meeting these criteria were then eligible for inclusion in a meta-analysis.

The following selection criteria were applied to the studies identified in the systematic review.

- Results from cohort studies were considered as more reliable evidence of association than results from case–control studies. So case–control studies were excluded from the analysis.

- The sample size of the study was large and ideally representative of the population.
- The study population ideally included a broad age range.
- The methodology for data collection and analysis was robust and clearly documented.
- The study collected data on total fruit and vegetable consumption and not just by selected groups of fruit or vegetables (e.g. citrus fruit, green leafy vegetables, raw and cooked vegetables).
- Dietary measurement had been validated and was detailed enough to quantify fruit and vegetable consumption accurately (e.g. a food frequency questionnaire having more than 40 items of fruit and vegetables is likely to be better than one that includes only four items).
- Dietary assessment performed using one 24-hour recall or food record/diary was excluded.
- The statistical analyses were adjusted for important potential confounders.
- The information was available to enable the estimation of relative risk and confidence intervals with intake treated as a continuous variable for meta-analysis.

The number of studies that met the selection criteria for each outcome is given in Table 9.12.

Data preparation

The final relative risk estimates are expressed as the unit of change in relative risk associated with an 80 g increase in fruit and vegetable consumption—this amount representing a recognized standard serving size (World Cancer Research Fund and American Institute for Cancer

Table 9.12 Number of cohort studies meeting the selection criteria for inclusion in a meta-analysis

Outcome	*Number of cohort studies reviewed*	*Number of studies meeting selection criteria*
Ischaemic heart disease	27	4
Ischaemic stroke	21	2
Lung cancer	21	4
Colorectal cancer	15	3
Gastric cancer	14	1
Oesophageal cancer	4	0

Research 1997). When data from the selected studies were not presented in this format, the following methods were used.

- Where food consumption was expressed in frequencies (e.g. number of servings per day), these were multiplied by 80 g to give daily intake in grams per day.
- Where the relative risk estimates were reported for various increments in intake (e.g. for 100 g or 1 g increase in intake), the relative risk estimates were first transformed onto a log scale and then divided by the comparison difference to give the log relative risk/gram per day; these were then multiplied by 80 to give final estimates expressed as per 80 g increase.
- Where an overall relative risk was not reported for consumption over the entire population range, two methods were used to obtain the relative risk estimates. In method 1, we estimated the additional gram per day for which the relative risks given applied (details are given later in the text for each selected study). In method 2, the method of Greenland and Longnecker (1992), implemented in Stata 7, was used to estimate the weighted regression slope over the published relative risks, allowing for correlations due to a common reference category. This method uses all the published relative risks, and should coincide approximately with method 1 if the log relative risks are linear on consumption. When there is non-linearity, the two methods will differ, with the second giving the best "average" slope over the whole consumption range, while the first gives a better estimate of slope over a smaller consumption range. Where there is a tendency for risk reduction to be less marked at higher consumption levels, method 2 will give a more conservative estimate of the relative risk per consumption increase.
- Standard errors were calculated on the log scale by taking the upper (log) confidence limit minus the (log) estimated relative risk and dividing this by 1.96; standard errors were also scaled in the same way as estimates to apply to an 80 g/day comparison difference.

Meta-analysis

Where more than one study was identified using our strict selection criteria, a meta-analysis was conducted to combine estimates and obtain a summary estimate of the relationship between fruit and vegetable intake and the selected outcome (DerSimonian and Laird 1986). Meta-analysis was performed using study log relative risks and the corresponding standard errors and implemented in Stata 7 ("meta" macro). Heterogeneity between studies was tested using the chi-squared statistic. The random-effects result was pre-specified conditional on evidence of heterogeneity. When only two studies were available, fixed-effect meta-analysis was

used. Forest plots, showing the results for individual studies, were prepared.

Extrapolations of the relative risk estimates

Subregion. For each outcome, the same relative risk estimates were applied to all subregions, assuming no interaction between the level of intake and subregion on the associations. However, it is not possible to verify whether this assumption is true, as the study populations covered by the literature reviews were from limited geographical areas, which did not allow subregional comparisons.

Sex. Another issue is the fact that several studies pooled data for men and women. Due to the limitations of the evidence for men and women separately, it was decided to apply the same relative risk estimates to both sexes for each outcome.

Age group. Many of the studies covered only limited age ranges, with most being from middle-aged or elderly populations. None of the studies included in the review were of children aged <16 years. Results from the Boyd Orr cohort suggest that childhood fruit consumption may have a long-term protective effect on cancer risk in adults (Maynard et al. 2003). This study measured intake of fruit and vegetables, energy, vitamins C and E, carotene, and retinol during a study of family diet and health in 16 rural and urban areas of England and Scotland from 1937 to 1939, and followed participants for up to 60 years. However, apart from this cohort, there are currently very few studies which have looked at the impact of childhood intake. A previous review for the New Zealand burden of disease and injury study proposed that the age-specific relative risks for fruit-and-vegetable disease associations describe an inverted u-curve, which assumes that the relative risk is one at the extremes of age (<25 years and >75 years) (Tobias 2001). The authors of the review argued that they do not expect individuals aged <25 years to be at risk given that the outcomes are chronic diseases, that such outcomes are rare in children, and that children have probably had insufficient duration of exposure. They also applied reduced relative risks to older age groups (i.e. applying a relative risk of 1 to everyone aged >75 years), as there are high competing mortality risks at these ages. In this project, it was decided to apply the same relative risks to all age groups between the ages of 15 and 69 years. It is reasonable to postulate that there may be age attenuation in the relative risks at both extremes of age. However, due to the current lack of information on how this would influence the relative risks at varying intakes of fruit and vegetables, approximate age attenuations were applied as follows: at older age groups, the excess risks were reduced by a quarter for ages 70–79 years, and by half for the age group of ≥80 years. For those

aged <15 years, a relative risk of 1 was applied as in the New Zealand study.

Steps to assess and reduce bias and to assess causality

There are a number of generic methodological issues that could lead to the introduction of bias in nutritional epidemiological studies. The following paragraphs briefly describe confounding and the major sources of measurement, recall and selection biases common to these studies, with a particular focus on issues that are specific to studying fruit and vegetables as a risk factor.

Confounding

Well-known potential confounders of the association of fruit and vegetable intake with cardiovascular disease and cancer include, among others, sex, age and smoking. It is possible that a high intake of fruit and vegetables may be associated with other healthy behaviour, for example lower consumption of saturated fat or non-smoking that also has a protective effect on the selected outcomes.

High intakes of fruit and vegetables may also displace other foods from the diet, causing reduced intake of potentially harmful substances such as saturated fat and salt. Results from the DASH trial suggested that changes in dietary fats do not necessarily accompany an increase in fruit and vegetable intake. In this trial, hypertensive participants were fed a control diet for three weeks and then randomized to receive for eight weeks either the control diet, a diet rich in fruit and vegetables, or a combination diet rich in fruit and vegetables and reduced in saturated fat, fat and cholesterol (Conlin et al. 2000; Obarzanek et al. 2001). Both the combination diet and the fruit-and-vegetables diet significantly reduced systolic and diastolic blood pressure. After eight weeks, 70% of the participants on the combination diet had a normal blood pressure, 45% of those on the fruit-and-vegetables diet did and 23% of those on the control diet did as well. The fruit- and-vegetables diet produced few changes in blood lipids but was still likely to reduce IHD risk independently. Sodium/salt is perhaps an underacknowledged potential confounder for IHD and stroke. Persons who consume more salads may consume less salt. The lack of evidence of confounding by salt mainly relates to the difficulty of measuring sodium exposure in individuals—not to its intrinsic importance.

In order to account for the potential effect of confounding on the relative risk estimates, all studies that were identified in the review of the literature must have performed some statistical adjustment for potential confounders. Most studies adjusted for the basic confounding factors, age and sex. The majority of recent studies also statistically controlled for a range of other variables including smoking, alcohol consumption, total energy intake, other foods and food constituents (including saturated fat intake for heart disease), body mass index (BMI) and vitamin

supplementation. Some studies also adjusted for socioeconomic status, educational level, ethnicity, occupation and place of residence. The potential confounders that are specific to each of the selected disease outcomes are discussed in more detail in section 3.7. It is important to note that statistical adjustment for potential confounding implies accepting that the instruments used to measure these potential confounders did this reasonably well. This may not be the case for all potential confounders (e.g. energy intake or physical activity level). In addition, even where there is a high degree of statistical control for potential confounding, the possibility remains that part of the association estimated is due to uncontrolled (residual) confounding (Ness et al. 1999b).

Selection bias

The issues related to selection bias in the studies reviewed for this project are similar to those of studies investigating other risk factor–disease relationships. For example, it is generally accepted that the selection of controls in case–control studies is likely to influence the study results. Study participation is usually high for cases but lower for controls; those who participate are more likely to be more health conscious, and thus perhaps consume more fruit and vegetables (Michels et al. 2000).

There were a variety of approaches used to reduce selection bias in the studies reviewed. For example, many studies tried to match controls to their cases as closely as possible in terms of age and sex. The generalizability of the results is also influenced by the source of controls, with population-based controls being better than hospital-based controls.

Information bias

Exposure. In the studies included in the review of the literature, data on dietary intake were collected using some form of diet history, food frequency questionnaire, 24-hour dietary recall(s) or diary/food record. Measurement of exposure will thus be influenced by the different limitations, sources of error and bias affecting each method. Some of these were described in sections 2.2 and 2.9.

Measurement error is an issue in all studies of dietary exposure (Smith-Warner et al. 1997). In general, this imprecision leads to a substantial attenuation of diet–disease associations, and an underestimation of potential thresholds in these associations (Marshall and Chen 1999). This is the case, for example when a single 24-hour recall is used as the method of dietary assessment (as in a few studies included in our review of the literature). A single 24-hour recall has a high degree of intra- to inter-individual variability and cannot accurately represent an individual's usual intake (Bingham et al. 1988). This may lead to important misclassification (likely to be non-differential) error.

Food frequency questionnaires are more commonly used in nutritional epidemiology. However, most food frequency questionnaires can be

criticized because of their limitations in collecting detailed accurate information on the intake of fruit and vegetables (Bingham et al. 1994; Michels et al. 2000). Little is known of the measurement error structure for reported fruit and vegetable intake in food frequency questionnaires. Many early estimates based on comparisons with different questionnaires or diet records had problems, underestimating both the degree of error and the correlation between the sources of errors (Day and Ferrari 2002; Thompson et al. 1997). Various problems are apparent. The level of measurement error is large compared with the true variation of intake in many study populations; there may be systematic bias in reporting at the individual level; and lack of independence of the measurement errors between the food frequency questionnaire and reference instrument (Day et al. 2001; Willett 2001). This may lead to considerably greater relative risk attenuation than has been previously realized, making modest decreases in relative risks difficult to detect (Kipnis et al. 1999). Null results of the diet–disease relationship in studies may thus be misleading, and controlling for a number of correlated dietary variables when exploring the diet–disease association of a specific dietary item can lead to uninterpretable or unpredictable results.

Other factors that can bias diet–disease relationships include the frequent assumption of unchanged dietary intake over long follow-up periods, particularly affecting long-term cohort studies, and recall bias, which is a major problem in case–control studies (Willett 1998b). In some cases, surrogate interviewees (spouses or immediate family members) are asked to provide information for the cases and controls in case–control studies; but this might also lead to misclassification bias. Another important issue to consider is the validity and reliability of extrapolating results from studies based on micronutrient intakes or status to the effect of intakes of fruit and vegetables. In this review, we have thus tried to select only studies with data based on food consumption rather than biomarkers of intakes. Where no appropriate food-exposure data existed, it was decided to include proxy nutrients (such as vitamin C from diet) when this was validated by consumption studies. This approach was necessary, as there were a large number of studies that framed their hypotheses in terms of nutrients, and reported only associations with nutrients. For example, studies such as the EPIC-Norfolk study (Bingham et al. 1997) have tried to reduce the subjective nature of dietary assessment by using biological indicators such as plasma ascorbic acid, which they correlated with food intake. The use of plasma ascorbic acid measurement is thought to represent dietary intake in the preceding few weeks and may overcome some of the issues involved with dietary assessment (Bates et al. 1991). However, biomarkers are also prone to measurement error that could also explain the lack of consistency in studies in which such biomarkers have been used. In addition, these proxy measures of intake are not ideal, as it is clear that any beneficial effect of fruit and vegetables involves many nutrient

and non-nutrient factors. They would tend to underestimate the impact of a mixed intake of fruit and vegetables.

Finally, there is substantial variability among studies in the categorization of exposure groups, not only in terms of what constitutes the "fruit and vegetables" measured, but also the actual levels of intake within these groups. Exactly what level of intake represents a high or a low intake will vary significantly among populations and will be influenced by the method of data collection. This was discussed in section 2.9. This literature review does not comment on the association of disease risk with specific fruit and vegetables, although several studies have attempted to do this in their analyses.

Outcome. The best studies reviewed for this project were those that utilized more than one method to identify cases to avoid any losses to follow up in the final analysis. The methods used included death certificates, hospital records, living relatives, self-report and cancer registries.

3.7 Structured assessment of causality for each outcome chosen

Ischaemic heart disease

A detailed description of the studies included in the review of the literature follows.

Previous reviews of the literature

Three recent reviews of the association between fruit and vegetable consumption and IHD were identified (Klerk et al. 1998; Law and Morris 1998; Ness and Powles 1997). The review by Klerk et al. (1998) concluded that high vs low consumption of fruit and vegetables (increasing from 250 to 400 g/day) is likely to reduce the risk of IHD by 20–40% in men and women; however, the methods used to derive the final estimates are unclear.

Law and Morris (1998) performed a meta-analysis of cohort studies of the relationship between IHD and markers of fruit and vegetable consumption, namely dietary intake of fruit, vegetables, carotenoids, vitamin C, fruit fibre and vegetable fibre, and serum concentration of carotenoids and vitamin C, adjusted for other factors. They estimated that the risk of IHD is about 15% lower at the 90th than at the 10th percentile of fruit and vegetable consumption.

The review by Ness and Powles (1997) identified 10 ecological, three case–control and 16 cohort studies investigating IHD. Of these, nine ecological studies, two case–control studies, and six cohort studies reported a statistically significant negative relationship between IHD and the consumption of fruit and vegetables or proxy nutrients. Ness and Powles did not attempt to arrive at a summary statistic for the association as the measures of exposure and disease varied considerably between

studies. They concluded that the results are consistent with a protective effect of fruit and vegetables for IHD.

Current review of the literature

The literature review identified 27 references of prospective studies that investigated the association of IHD risk with fruit and vegetable consumption. Details of the study characteristics are given in Table 9.13. In summary, the study populations were all from Japan, the United States and Europe (Finland, the Netherlands, Norway, Sweden and the United Kingdom). Five of the studies each gave rise to more than one report; 14 studies included men and women, nine studied men only and four studied women only. The follow-up time varied between four and 25 years. The method used to measure fruit and vegetable intake differed considerably among studies, ranging from one 24-hour dietary recall and a seven-day prospective weighed food diary to a variety of food-frequency questionnaires.

Sixteen of the 27 studies reported a statistically significant inverse association between intake of fruit and vegetables and IHD. Thirteen of these showed an association with food intake, while the other three showed an association with a proxy diet measure that was correlated with fruit and vegetable intake. Nine further studies also reported an inverse association; seven of these were not statistically significant, two others not reporting confidence intervals or measures of statistical significance. The actual relative risks for the studies included in the meta-analysis are given in Table 9.23. Relative risks for the studies in the systematic review are not given here due to the wide variation in how fruit and vegetables were reported and analysed.

Confounding

Most of the studies reviewed adjusted for some potential confounding factors shown to be associated with the risk of cardiovascular disease. All adjusted for age, and most studies adjusted for sex and smoking. Very few of the older studies had adequately addressed the issue of confounding, and this cannot be discounted as an explanation for an observed association in some studies. However, most recent studies have dealt with a comprehensive range of confounding factors, including the majority of the following: smoking, alcohol, total energy intake, saturated fat intake, cholesterol, BMI, hypertension, type II diabetes, physical activity, hormone replacement therapy, educational status or social class and nutritional supplement use. Measurement of some of these candidate confounders will potentially have substantial error (e.g. energy intake).

Summary

In summary, the review of the literature suggests that there is a strong inverse relationship between fruit and vegetable intake and

Table 9.13 Summary of cohort studies reporting association between intake of fruit and vegetables and ischaemic heart disease

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetables*	*Association with diet proxy*
Finland	Finnish Mobile Clinic Health Examination survey cohort (Knekt et al. 1994, 1996)	Males and females	30–69	5 133	Mortality (244)	14	Repeated diet history	Inverse, statistically significant	. . .
Finland	Smokers in ATBC study (Pietinen et al. 1996)	Males	50–69	21 930	Incidence (818), mortality (581)	6.1	Diet history	Inverse, statistically significant	. . .
Japan	Japanese general population survey (1965 census cohort) (Hirayama 1990)	Males and females	≥40	265 118	Mortality (NA)	16	Crude—not clear	Inverse, statistically significant (unadjusted)	. . .
Netherlands	Rotterdam study (Klipstein-Grobusch et al. 1999)	Males and females	55–95	4 802	MI (124)	4	Food frequency questionnaire	. . .	Inverse, statistically significant (beta-carotene)
Netherlands	Zutphen Elderly study (Hertog et al. 1993)	Males	65–84	805	MI (38), mortality (43)	5	Cross-check of dietary history	Inverse, not statistically significant	Inverse (flavonoids)
Sweden	Gothenburg women (Lapidus et al. 1986)	Females	38–60	1 462	MI (23), mortality (75)	12	24-hour recall	. . .	No association (vitamin C)
United Kingdom	Elderly cohort, Department of Health and Social Security survey (Gale et al. 1995)	Males and females	≥65	730	Mortality (182)	20	7-day weighed food record	. . .	Inverse, not statistically significant (vitamin C)

continued

Table 9.13 Summary of cohort studies reporting association between intake of fruit and vegetables and ischaemic heart disease (*continued*)

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetables*	*Association with diet proxy*
United Kingdom	Vegetarians and health conscious individuals study II (Mann et al. 1997)	Males and females	16–79	10 802	Mortality (64)	13.3	Food frequency questionnaire	Inverse, statistically significant	. . .
United Kingdom	Vegetarians and health conscious people (Key et al. 1996)	Males and females	≥16	10771	Mortality (350)	16.8	Crude food frequency questionnaire	Inverse, statistically significant	. . .
United Kingdom	EPIC-Norfolk (Khaw et al. 2001)	Males and females	45–79	19496	Mortality (123)	4	Food frequency questionnaire and plasma ascorbic acid analysis	. . .	Inverse, statistically significant (vitamin C)
United Kingdom	Bus and bank workers, London and south England (Morris et al. 1977)	Males	30–67	337	Mortality (26), incidence (45)	10–20	7-day weighed diary	. . .	Inverse, not statistically significant (fibre)
United Kingdom Scotland	Scottish Heart Health study (Todd et al. 1999)	Males and females	40–59	11629	Incidence (296)	6–9	60-item food frequency questionnaire	. . .	Inverse, statistically significant (vitamin C, beta-carotene in men, fibre)
United Kingdom Wales	Caerphilly Ischaemic Heart Disease study (Elwood et al. 1996; Fehily et al. 1993)	Males	45–59	2423	Incidence (148), mortality (132)	5 (10)	7-day weighed diet intake	. . .	Inverse, no CI (vitamin C, magnesium)

USA	Rancho Bernardo cohort, California (Khaw and Barrett-Connor 1987a)	Males and females	50–79	859	MI and mortality	12	24-hour recall	. . .	Positive, not statistically significant (dietary potassium)
USA	The Adventist Health study, California (Fraser et al. 1992)	Males and females	≥25	26 473	MI (134), mortality (260)	6	65-item food frequency questionnaire	Positive, not statistically significant	. . .
USA	Western Electric Company study, Chicago (Pandey et al. 1995)	Males	40–55	1 556	Mortality (231)	24	2x cross-check of diet history and food frequency questionnaire (to participant and homemaker)	. . .	Inverse, not statistically significant (vitamin C and beta-carotene)
USA	Massachusetts Health Care Panel study (Gaziano et al. 1995)	Males and females	≥66	1 299	Mortality (48)	4.75	43-item food frequency questionnaire	Inverse, statistically significant	. . .
USA	Iowa Women's Health study (Kushi et al. 1996; Yochum et al. 1999)	Females	55–69	34 486	Mortality (242)	7	127-item food frequency questionnaire	Inverse, statistically significant for some vegetables	Inverse, not statistically significant (vitamin C)
USA	NHANES I epidemiologic follow-up study (Bazzano et al. 2000)	Males and females	24–74	11 924	Mortality (793)	19	24-hour recall and food frequency questionnaire	Inverse, statistically significant	. . .
USA	NHS (Liu et al. 2000)	Females	34–59	39 876	MI (126)	5	Food frequency questionnaire	Inverse, not statistically significant	. . .
USA	HPFS (Liu et al. 2001)	Males	40–75	15 220	MI (387)	12	Food frequency questionnaire repeated twice yearly	Inverse, statistically significant	. . .

continued

Table 9.13 Summary of cohort studies reporting association between intake of fruit and vegetables and ischaemic heart disease (*continued*)

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetables*	*Association with diet proxy*
USA	HPFS (Rimm et al. 1996)	Males	40–75	43 757	MI: nonfatal (511), fatal (229)	6	Repeated food frequency questionnaire	Inverse, statistically significant	. . .
USA	NHS/HPFS (Joshipura et al. 2001)	Males Females	40–75 34–59	42 148 84 251	Incidence (1 127) Incidence (1 063)	8–14	131-item food frequency questionnaire at intervals	Inverse, statistically significant	. . .
Multiple countries	Seven Countries study, Japan, USA and Europe (Menotti et al. 1999)	Males	40–59	12 763	Mortality (1 555)	25	Weighed diet intake (1–7 day records)	Inverse, statistically significant (vegetables)	. . .

NA Not applicable.

MI Myocardial infarction.

cardiovascular disease in over half the prospective observational studies in many different populations. The relationship remains after some adjustment for confounding. This result needs to be interpreted in the light of findings with regard to the more favoured diet hypotheses. In a review of the evidence for the classic diet–heart hypothesis, Willett found a positive association with saturated fat intake in only two of the 12 cohort studies reviewed, and a positive association with cholesterol intake in two (Willett 1998b).

Ischaemic stroke

This analysis is confined to ischaemic stroke. Most of the studies in the systematic review had only considered outcomes of ischaemic stroke. Although a few studies had analysed ischaemic and haemorrhagic stroke separately, there was insufficient evidence to draw any conclusions on the association of differential outcomes with fruit and vegetable intake. As it is more biologically plausible that the relationship of fruit and vegetable protection is with ischaemic stroke, we decided to limit our analyses to this outcome. For the attributable burden calculations, stroke was divided into ischaemic and haemorrhagic using the method described in chapter 7.

Previous reviews of the literature

Three recent reviews that previously studied the association between fruit and vegetable consumption and stroke were identified (Klerk et al. 1998; Ness and Powles 1997, 1999). The review by Klerk et al. (1998) concluded that the risk of stroke is reduced by 0–25% with higher intakes of fruit and vegetables. The reviews by Ness and Powles (1997, 1999) identified five ecological, one case–control and eight cohort studies reporting measures of association between the intake of fruit and vegetables and stroke. Of these, three ecological studies and six cohort studies reported a statistically significant negative association with the consumption of fruit and vegetables or proxy nutrients. The authors concluded that the results were consistent with a strong protective effect of fruit and vegetables for stroke, but they did not calculate a summary statistic for the association as the measures of exposure and outcome varied considerably among studies.

Current review of the literature

As with IHD, evidence from case–control and ecological studies was not reviewed because the number of cohort studies identified was sufficiently high (cohort studies represent a stronger study design), and because the general pattern of findings observed was consistent among studies. Overall, the evidence suggests a strong protective effect of fruit and vegetable consumption on ischaemic stroke risk.

Twenty-one references of prospective studies of the association between stroke and the consumption of fruit and vegetables were iden-

tified. Details of the study characteristics are described in Table 9.14. In summary, the study populations were all from China, Japan, the United States or Europe (Finland, the Netherlands, Norway, Sweden and the United Kingdom). Three of the studies gave rise to more than one report. Ten studies had populations of men and women, eight studied men only and four studied women only. The follow-up period varied between five and 28 years. The method used to measure dietary intake of fruit and vegetables also varied considerably, including postal diet survey, 24-hour dietary recall, seven-day prospective weighed diet record, and various food-frequency questionnaires of differing length and quality.

Thirteen studies showed a statistically significant inverse association between the intake of fruit and vegetables and stroke. Six studies showed an association with food, while the other eight showed an association with a nutrient considered to be a proxy for fruit and vegetable intake.

Confounding

As discussed for IHD, the observed protective association for fruit and vegetables and stroke could, in theory, be explained by confounding. All studies included in the literature review adjusted for age and sex, and most recent studies reviewed also dealt with a comprehensive range of major measured confounders.

Summary

There is a strong inverse relationship between the level of fruit and vegetable consumption and stroke risk in prospective observational studies in many populations. The relationship persists after adjustment for major confounders.

Lung cancer

A detailed description of the studies included in the review of the literature follows.

Previous reviews of the literature

Five recent comprehensive reviews of the association of fruit and vegetable intake with lung cancer risk were identified. Three concluded that there was convincing evidence that a diet rich in fruit and vegetables decreases the risk of lung cancer.

One of these three reviews was that of the WCRF/AICR (1997), which reviewed seven cohort and 17 case–control studies. Of the seven cohort studies, after adjustment for smoking, all showed a protective association for some fruit or vegetable. Most of the relative risks (23 of 31) they presented were for a protective association, although not all were statistically significant. No studies showed a statistically significant increase in risk for any type of fruit or vegetable. Sixteen of the case–control studies reported statistically significant inverse associations for one or more vegetable or fruit categories. The evidence was most abundant for

Table 9.14 Summary of cohort studies reporting measures of association between intake of fruit and vegetables and stroke

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetables*	*Association with diet proxy*
China	Men in Shanghai (Ross et al. 1997)	Males	45–64	18 244	CVA mortality (245)	5–8	Food frequency questionnaire	No association	. . .
Finland	Smokers in ATBC study (Hirvonen et al. 2000)	Males	50–69	26 593	Cerebral infarction (736), haemorrhagic stroke (178)	Diet . . . 6.1	. . . questionnaire	Inverse, statistically	significant (beta-carotene)
Finland	Finnish Mobile Clinic Health Examination survey cohort (Knekt et al. 2000)	Males and females	30–69	9 208	Mortality (244)	28	Repeated diet history	. . .	Inverse, statistically significant (subgroups only)
Japan	Japanese general population survey (1965 census cohort) (Hirayama 1990)	Males and females	≥40	265 118	Mortality (NA)	16	Crude (not specified)	Positive, not statistically significant	. . .
Japan	Shibata study, rural Japan (Yokoyama 2000)	Males and females	≥40	2 121	CVA (109)	20	Food frequency questionnaire and serum vitamin C	. . .	Inverse, statistically significant (vitamin C) infarction and haemorrhagic stroke
Netherlands	Zutphen study (Keli et al. 1996)	Males	50–69	552	CVA (42)	15	Repeated cross-check of dietary history	Inverse, not statistically significant	Inverse statistically significant (flavonoids)
Norway	Norwegian dietary postal survey (Vollset and Bjelke 1983)	Males and females	45–74	16 713	Mortality (438)	11.5	Postal diet survey	. . .	Inverse, statistically significant (vitamin C)

continued

Table 9.14 Summary of cohort studies reporting measures of association between intake of fruit and vegetables and stroke (*continued*)

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetables*	*Association with diet proxy*
Sweden	Gothenburg women (Lapidus et al. 1986)	Females	38–60	1 462	CVA (13)	12	24-hour recall	. . .	No significant correlation (vitamin C)
United Kingdom	Vegetarians and health conscious people (Key et al. 1996)	Males and females	≥16	10 771	Mortality (147)	17	Crude food frequency questionnaire	Inverse, statistically significant	. . .
United Kingdom	Elderly cohort, Department of Health and Social Security survey (Gale et al. 1995)	Males and females	≥65	730	Mortality (124)	20	7-day weighed food record	. . .	Inverse, statistically significant (vitamin C)
USA	Rancho Bernardo cohort, California (Khaw and Barrett-Connor 1987b)	Males and females	50–79	859	Mortality (24)	12	24-hour recall	. . .	Inverse, statistically significant (dietary potassium)
USA	Hawaiian men of Japanese descent (Lee et al. 1988)	Males	45–68	7 591	CVA (408)	16	24-hour recall	. . .	Inverse (dietary potassium)
USA	Framingham study (Gillman et al. 1995)	Males	45–65	832	Incident stroke (97)	20	24-hour recall	Inverse, statistically significant	. . .

USA	Western Electric Company study, Chicago (Daviglus et al. 1997)	Males	40–55	1 556	CVA (222)	24	2x cross-check diet history and food frequency questionnaire (to participant and homemaker)	. . .	Inverse, not statistically significant (vitamin C and beta-carotene)
USA	Iowa Women's Health study (Yochum et al. 2000)	Females	55–69	34 492	Mortality (131)	10	127-item food frequency questionnaire	. . .	No association (flavonoids)
USA	NHANES I epidemiologic follow-up study (Bazzano et al. 2000, 2001)	Males and females	24–74	9 805	Stroke events (927)	19	24-hour recall and food frequency questionnaire	Inverse, statistically significant	Inverse, statistically significant (dietary potassium)
USA	NHS (Liu et al. 2000)	Females	34–59	39 876	CVA incidence (160)	5	Food frequency questionnaire	Inverse, not statistically significant (all CVD)	. . .
USA	HPFS (Ascherio et al. 1998, 1999)	Males	40–75	43 738	CVA (328): Ischaemic (210), haemorrhagic (70)	8	Repeated food frequency questionnaire	. . .	Inverse, statistically significant (dietary potassium); positive not significant (vitamin C)
USA	NHS/HPFS (Joshipura et al. 1999)	Males Females	40–75 34–59	38 683 75 596	Ischaemic stroke incidence: F (366), M (204)	8–14	Repeated food frequency questionnaire at intervals	Inverse, statistically significant	. . .

NA Not applicable.

CVA Cerebrovascular accident.

green vegetables and carrots. Results of an analysis of dose–response relationship between vegetable intake and risk of lung cancer estimated that the relative risk decreases by about 50% as intake increases from 150 g/day to 400 g/day. An intake of >400 g/day is always associated with a lower risk than 100 g/day or less.

In their review, Ziegler et al. (1996b) asserted that the results of observational studies of diet and lung cancer suggest strongly that an increased fruit and vegetable intake is associated with a reduced risk in men and women; in various countries; in smokers, ex-smokers, and never-smokers; and for all types of lung cancer.

The review by Klerk et al. (1998) concluded that high vs low consumption of fruit and vegetables (an average difference of 150 g/day) is likely to reduce the risk of lung cancer by 35–55% in men and women.

Koo (1997), in contrast, concluded that epidemiological studies performed over the last 20 years do not provide overwhelming evidence of an inverse association between fruit and vegetable consumption and lung cancer risk. Koo proposed the imperfect control of smoking-associated dietary correlates and "lifestyle" differences as the major problems with the perceived associations between diet and lung cancer.

Current review of the literature

The literature review identified 21 cohort and 32 case–control studies that examined the association of fruit and vegetable intake with the risk of lung cancer incidence and mortality. Details of the studies are provided in Tables 9.15 and 9.16. Overall, the evidence appears to support an inverse relationship between fruit and vegetable consumption and lung cancer risk (both incidence and mortality).

The cohort studies identified were conducted in a range of countries including Finland, Japan, the Netherlands, the United States and other southern and northern European countries included in the Seven Countries study. The study populations were not necessarily nationally representative as some studies were limited to religious groups or those with particular lifestyle characteristics (Fraser et al. 1991; Key et al. 1996), specific occupational groups (Feskanich et al. 2000; Michaud et al. 2000) or very narrow age groups such as the elderly (Shibata et al. 1992). Three studies from the United States analysed national survey data and are therefore perhaps more nationally representative. Very few studies were of young people.

It should be noted that, of the 21 cohort studies, five of the study populations were each used in more than one study. The studies differed in their analysis by reporting different risk factors (i.e. carotenoids vs fruit and vegetables) or using different outcome measures (mortality vs incidence).

Twelve studied incidence of lung cancer as the outcome measure, while eight studied lung cancer mortality. Follow-up periods varied between

Table 9.15 Summary of cohort studies reporting association between intake of fruit and vegetables and lung cancer

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetable intake*	*Association with diet proxy*
Finland	Finnish Mobile Clinic Health Examination survey cohort (Knekt et al. 1991)	Males	20–69	4538	Incidence (117)	20	100-item food frequency questionnaire	Inverse, statistically significant	. . .
Finland	Finnish Mobile Clinic Health Examination survey cohort (Knekt et al. 1997)	Males and females	15–99	9959	Incidence (151)	24	100-item food frequency questionnaire	Inverse, statistically significant	Inverse, statistically significant (flavonoids)
Finland	Smokers in ATBC study (Hirvonen et al. 2001)	Males	50–69	27110	Incidence (791)	6.1	Diet history	Inverse, statistically significant	. . .
Japan	Japanese general population survey (1965 census cohort) (Hirayama 1986, 1990)	Males and females	≥40	265118	Mortality (1917)	16	Crude—not clear	Inverse, statistically significant (men)	. . .
Netherlands	Zutphen study (Kromhout 1987; Ocke et al. 1997)	Males	40–59	561	Mortality (54)	25	Repeated cross-check of dietary history	Inverse, statistically significant	. . .
Netherlands	The Netherlands Cohort study (Voorrips et al. 2000b)	Males and females	55–69	120852	Incidence (1 074)	6.3	150-item food frequency questionnaire	Inverse, statistically significant	. . .
Norway	3 cohorts (Kvale et al. 1983)	Males and females	NA	16713	Incidence (168)	11.5	Food frequency questionnaire	Inverse, not statistically significant	. . .

continued

Table 9.15 Summary of cohort studies reporting association between intake of fruit and vegetables and lung cancer (*continued*)

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetable intake*	*Association with diet proxy*
United Kingdom	Vegetarians and health conscious people (Key et al. 1996)	Males and females	≥16	10771	Mortality (59)	16.8	Crude food frequency questionnaire	Inverse, not statistically significant	. . .
USA	National Health Interview survey (Breslow et al. 2000)	Males and females	Nationally representative	20004	Mortality (158)	8.5	59-item food frequency questionnaire	Inverse, not statistically significant	. . .
USA	Volunteers from 25 states (American Cancer Society cohort) (Wang and Hammond 1985)	Males and females		1000000	NA	11	Not clear	Inverse, not statistically significant	. . .
USA	Iowa Women's Health study (Steinmetz et al. 1993)	Females	55–69	41387	Incidence (179)	4	127-item food frequency questionnaire	Inverse, statistically significant	. . .
USA	Lutheran Brotherhood Insurance cohort (Chow et al. 1992)	Males		17818	Mortality (219)	20	Diet questionnaire	Inverse, not statistically significant	. . .
USA	Leisure World cohort, California (Shibata et al. 1992)	Males and females	50–79	11580	Incidence (164)	8	24-hour recall	Inverse, not statistically significant (women)	. . .

USA	The Adventist Health study, California (Fraser et al. 1991)	Males and females	≥25	34198	Incidence (61)	6	65-item food frequency questionnaire	Inverse, not statistically significant	...
USA	NHANES I Epidemiologic follow-up study (Yong et al. 1997)	Males and females	25–74	10068	Incidence (248)	19	24-hour recall and food frequency questionnaire	Inverse, statistically significant	...
USA	NHS (Speizer et al. 1999)	Females	34–59	121700	Incidence (593)	16	Repeated food frequency questionnaire	Inverse, statistically significant	...
USA	NHS/HPFS (Feskanich et al. 2000; Michaud et al. 2000)	Males Females	40–75 34–59	47778 77283	Incidence (793)	10–12	131-item food frequency questionnaire at intervals	Inverse, not statistically significant	Inverse, statistically significant (carotenoids)
Multiple countries	Seven Countries study, Japan, USA and Europe (Mulder et al. 2000)	Males	40–59	12763	Mortality (424)	25	Various methods in each country	Inverse, not statistically significant	...
Multiple countries	Men in Finland, Italy and Netherlands, part of Seven Countries study (Jansen et al. 2001)	Males	40–59	3108	Mortality (187)	25	Cross-check of diet history	Inverse, not statistically significant	...

NA Not applicable

Table 9.16 Summary of case–control studies reporting an association between fruit and vegetable intake and lung cancer

Country	*Study population/area (reference)*	*Sex*	*Association with fruit or vegetables*	*Association with specific risk factors only*
Brazil	Rio de Janeiro (Suzuki et al. 1994)	Males and females	Null	—
Canada	Toronto (Jain et al. 1990)	Males and females	Inverse (vegetables)	—
China	(Hu et al. 1997)	Males and females	Null	—
China	Yunnan miners (Forman et al. 1992)	Males	Null	—
China	Yunnan miners (Swanson et al. 1992)	Males	Inverse (vegetables) Null (fruit)	—
China	North-east China, women (Wu-Williams et al. 1990)	Females	Null	—
China				
Hong Kong SAR	Never-smokers (Koo 1988)	Females	Null	—
Greece	Never-smokers (Kalandidi et al. 1990)	Females	Inverse (fruit)	—
India	Kerala (Sankaranarayanan et al. 1994)	Males and females	Null	Inverse (pumpkin, onion)
Italy	Lombardy (Pisani et al. 1986)	Males and females	—	Inverse (carrot)
Japan	Nagoya (Takezaki et al. 2001)	Males and females	Inverse	—
Japan	Tokai (Gao et al. 1993)	Males and females	Inverse	—
Poland	(Pawlega et al. 1997)	Males	Inverse	Null (green vegetables)
Poland	(Rachtan and Sokolowski 1997)	Females	Inverse—no smoking adjustment	—
Spain	Barcelona (Agudo et al. 1997)	Females	Inverse (vegetables), null (fruit)	—
Sweden	Stockholm, never-smokers (Nyberg et al. 1998)	Males and females	Null	—

Sweden	West Sweden (Axelsson et al. 1996)	Males	Inverse (vegetables)	—
United Kingdom	Oxford (Harris et al. 1991)	Males	Null	—
United Kingdom	South-west England (Darby et al. 2001)	Males and females	Null	Inverse (carrot, tomato)
USA	(Pillow et al. 1997)	Males and females	Null (vegetables), inverse (fruit)	—
USA	Hawaii (Goodman et al. 1992)	Males and females	Null	—
USA	Hawaii (Le Marchand et al. 1989)	Males and females	Inverse	—
USA	Florida, female never-smokers (Candelora et al. 1992)	Females	Inverse (vegetables) Null (fruit)	—
USA	Louisiana (Fontham et al. 1988)	Males and females	Inverse	—
USA	New Jersey (Dorgan et al. 1993)	Males and females	Inverse (vegetables)	—
USA	New Jersey (Ziegler et al. 1986)	Males	Inverse	—
USA	New Jersey (Ziegler et al. 1996a)	Males and females	Inverse	—
USA	New York (Mayne et al. 1994)	Males and females	Inverse	—
USA	New York (Byers et al. 1987)	Males and females	Null (carotene)	Inverse, males only
USA	New York, Buffalo (Mettlin 1989)	Males and females	Inverse	—
USA	Texas (Bond et al. 1987)	Males	Null	—
Multiple countries	Europe, never-smokers (Brennan et al. 2000)	Males and females	Null	Inverse (tomato)

Inverse Statistically significant protective association of high vs low fruit/vegetable consumption.

Null Non-significant.

— No data.

four and 25 years, with 16 studies having follow-up periods longer than 10 years. Twelve of the studies investigated populations of men and women, seven studies had male-only cohorts and two studies were entirely female. Most studies have pooled the results for men and women, the explanation being that the number of lung cancer cases in women is too small to justify a meaningful separate analysis. Only a few studies have analysed men and women separately, usually where the entire study cohort was either men or women. More detailed characteristics of all studies are given in Table 9.15.

Eleven studies showed a statistically significant inverse association between a diet high in fruit or vegetables (one of these was significant for dietary carotenoids) and lung cancer. The remainder of the studies showed an inverse association that was not statistically significant. In some studies with non-significant results for total fruit and vegetables, subcohort analyses were reported as having significant associations.

Of particular interest are studies of lung cancer incidence and mortality that considered non-smokers, former smokers and smokers separately in the analyses. It appears that the benefit conferred through a high intake of fruit and vegetables more often reaches statistical significance in current smokers than in non-smokers (however, confidence intervals are often large and overlap). In summary, eight of the cohort studies reviewed for this project stratified the analyses by smoking status. Three of these showed a significant relationship between fruit and vegetable consumption and lung cancer incidence in smokers but not in non-smokers (but for one of these, the relative risks of both groups were similar) (Fraser et al. 1991; Knekt et al. 1991; Yong et al. 1997), while only one study showed an inverse relationship in non-smokers only (Knekt et al. 1997). The other studies showed non-significant results (Feskanich et al. 2000; Mulder et al. 2000; Steinmetz et al. 1993; Voorrips et al. 2000b) for both smokers and non-smokers. These results would tend to agree with the hypothesized biological mechanisms for the benefits of fruit and vegetables in lung cancer through late stage modification of carcinogenesis following an initial carcinogen exposure. Further research is needed to consider the current inconsistencies in findings, including exposure among non-smokers to environmental tobacco smoke and the range of other lung cancer risk factors.

The literature review identified 32 case–control studies that satisfied the inclusion criteria. These are summarized in Table 9.16. As the case–control studies were not used in the meta-analyses, fewer study details are provided here for conciseness. These studies were conducted across a range of populations including Brazil (1), Canada (13), China (4), Greece (1), India (1), Italy (1), Japan (2), Poland (2), Spain (1), Sweden (2), the United Kingdom (2) and the United States. Of the studies, 19 collected data from men and women, seven from men only and six from women only.

Eighteen found an inverse relationship between a high intake of fruit or vegetables and lung cancer. When separate associations with fruit and vegetables were analysed, there seemed to be a greater number of studies finding significant associations with vegetables as a group compared to fruit as a group. Four of the studies found significant associations only with specific types of vegetables, such as pumpkin and onion (Sankaranarayanan et al. 1994), or tomato (Brennan et al. 2000), or carrot (Pisani et al. 1986) or in specific age groups such as men aged 60–79 years (Byers et al. 1987). The results of these subgroup analyses should be treated with caution.

Of the four case–control studies that specifically collected and analysed data on non-smokers, two found no association, while two found a significant inverse association between fruit or vegetable consumption and lung cancer. But due to the inherent limitations of case–control studies, the results do not necessarily imply that dietary modification after quitting smoking is effective in reducing risk. Ex-smokers with elevated vegetable and fruit consumption could have been high consumers while they were smokers as well. However, the results of case–control studies seem consistent with the results of the cohort studies.

Although outside the criteria of this review, it is important to mention some of the evidence from experimental studies that may appear to contradict the protective relationship of fruit and vegetables on lung cancer. The CARET study (Anonymous 1994) and the ATBC study (Omenn et al. 1996b) were randomized control trials designed to investigate the effect of beta-carotene high-dose supplementation on lung cancer. The results of these trials suggested a harmful effect (increase in incidence and mortality) of beta-carotene supplementation in current smokers. This suggests that raised beta-carotene may be a marker associated with other protective factors found in foods (Lonn and Yusuf 1999), and that the status of the antioxidant hypothesis might need to be re-evaluated critically (Ness et al. 1999a).

Confounding and interactions

All studies of lung cancer adjusted for age, sex and smoking in their analyses, except for one case–control study from Poland (Rachtan and Sokolowski 1997), which did not adjust for smoking. Other potential confounders dealt with statistically included: environmental tobacco smoke; previous lung disease; occupational exposure (arsenic, asbestos, chloromethyl ethers and nickel); radon; air pollution; total energy intake; intake of other macronutrients; BMI; physical activity; and socioeconomic status (using educational level or occupation used as a proxy). The actual adjustment varied among studies.

Smoking is the most important potential confounder to consider given the strength of the association between smoking and lung cancer. There is also the possibility of smoking being an effect modifier but published

results are contradictory. The studies reviewed here have dealt with smoking in a number of ways. Some studies have not only adjusted for current smoking status, but have also considered the intensity of current smoking behaviour (as the number of cigarettes smoked per day), age of starting smoking and duration of smoking. For current non-smokers, several studies have also adjusted for time since quitting (including intensity) in ex-smokers. A couple of studies also adjusted for time since quitting for subjects who quit during follow-up.

An important issue, highlighted by Ziegler et al. (1996b), is that several studies have shown that consumption of fruit, vegetables and carotenoids is higher in non-smokers compared with current smokers, and that consumption is inversely related to smoking intensity in smokers. Thus, those studies that only considered smoking status without smoking intensity might have generated inflated estimates of the protective effect of fruit and vegetables.

The interpretation of these studies is difficult given the strong misclassification bias and the strong association between lung cancer and tobacco use, making it difficult to ensure that all the confounding effects from smoking have been removed (Boshuizen et al. 2002).

Summary

There is some evidence of an inverse relationship in many populations between lung cancer risk and fruit and vegetable consumption. There is currently not enough evidence to justify stratifying the results by smoking status.

Gastric cancer

A detailed description of the studies included in the review of the literature follows.

Previous reviews of the literature

Four recent reviews of the literature concluded that epidemiological evidence shows a consistent protective effect of fruit and vegetable intake on stomach cancer risk (Klerk et al. 1998; Kono and Hirohata 1996; Steinmetz and Potter 1996; World Cancer Research Fund and American Institute for Cancer Research 1997).

The report from the WCRF/AICR (1997) reviewed six cohort and 32 case–control studies. Three of the six cohort studies and 27 of the 32 case–control studies reported a statistically significant protective association for one or more vegetable or fruit categories. The evidence for raw vegetables, allium vegetables and citrus fruit in particular is consistent with a protective effect. Any contradictory evidence related entirely to salted and pickled vegetables. Analyses of dose–response relationships suggested that the risk of stomach cancer decreases by about 50% as fruit and vegetable intake increases from 50 g/day to 300 g/day. An intake of >150 g/day is always associated with a lower risk than 100 g/day or

less. In comparison, the review by Klerk et al. (1998) concluded that high vs low consumption of fruit and vegetables (an average difference of 150 g/day) is likely to reduce the risk of stomach cancer by 40–55% in men and women.

A recent meta-analysis by Norat et al. (2001) of previously published case–control and cohort studies examined the association of total fruit or total vegetable consumption with gastric, colorectal and oesophageal cancer. It included all studies published in English from 1973–2000 and referenced in Medline that provided data on total fruit or vegetable intake. There was no assessment of study quality, adjustment for confounders was not assessed and studies were included as long as they could provide the information necessary for the statistical analysis. For gastric cancer, 32 studies were included that analysed total fruit intake and 22 studies were included for total vegetable intake. The pooled relative risks associated with an increase of consumption of 100 g/day were 0.75 (95% CI 0.67–0.83) for fruit and 0.80 (0.74–0.86) for vegetables.

Current review of the literature

The current literature review identified 14 cohort and 32 case–control studies that investigated the association between gastric cancer risk (incidence and mortality) and the consumption of fruit and/or vegetables. Overall, the evidence seems to support an inverse association between fruit and vegetable consumption and gastric cancer risk.

The 14 cohort studies were conducted in populations from both developed and developing countries including one from China, two from Japan, two from mainland USA, three of Japanese descendants in Hawaii and six from Europe. The Asian populations had a relatively high risk of stomach cancer. The results of the studies are summarized in Table 9.17.

Of these studies, nine investigated the effect of fruit and vegetable intake on gastric cancer incidence, while the remaining five studied mortality. Two cohorts were investigated in more than one study (the Netherlands Cohort study, and Japanese descendants in Hawaii in the Honolulu Heart Program). Seven cohorts consisted of both men and women, six studies investigated men only and one study focused exclusively on post-menopausal women. Follow-up of cohorts ranged from five to 25 years.

A statistically significant inverse association between gastric cancer and fruit and vegetable intake was reported in four studies. This inverse relationship was found in populations of both European and Japanese origin. The 10 other studies showed inverse relationships, but they were not statistically significant for fruit and vegetable, or nutrient intake.

The 32 case–control studies, summarized in Table 9.18, represented a wider range of populations and geographical areas than the cohort studies. Studies were conducted in Canada and the United States (5), China (3), Japan (4), Mexico (1), Poland (1), the Republic of Korea (1),

Table 9.17 Summary of cohort studies reporting a measure of association between intake of fruit and vegetables and gastric cancer

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetables*	*Association with diet proxy*
China	Linxian Nutrition Intervention Trial cohort (Guo et al. 1994)	Males and females	NA	29 584	Incidence (539)	5	Dietary interview	Inverse, not statistically significant (fruit)	—
Finland	Smokers in ATBC study (Hirvonen et al. 2001)	Males	50–69	27 110	Incidence (111)	6.1	Food frequency questionnaire	—	Inverse, not statistically significant (flavonoids)
Japan	Japanese general population survey (1965 census cohort) (Hirayama 1986, 1990)	Males and females	≥40	265 118	Mortality (5 247)	17	Crude—not clear	Inverse, statistically significant trend	—
Japan	Rural cohort (Kato et al. 1992)	Males and females	NA	9 753	Mortality (57)	6	Food frequency questionnaire	Inverse, not statistically significant	—
Netherlands	The Netherlands Cohort study (Botterweck et al. 1998, 2000)	Males and females	55–69	120 852	Incidence (282)	6.3	150-item food frequency questionnaire	Inverse, statistically significant	Non-significant trends: inverse (vitamin C), positive (beta-carotene, retinol)
Sweden	Cohort of Swedish twins (Terry et al. 1998)	Males and females	NA	11 546	Incidence (116)	21	Crude food frequency questionnaire	Inverse, statistically significant	—

United Kingdom Wales	The Caerphilly study (Hertog et al. 1996)	Males	45–69	2 112	Mortality (45)	13.8	Food frequency questionnaire	Inverse, not statistically significant	—
USA	Iowa Women's Health study (Zheng et al. 1995)	Females	55–69	34 691	Incidence (26)	7	127-item food frequency questionnaire	Inverse, not statistically significant	—
USA	Men of German and Scandinavian origin (Kneller et al. 1991)	Males	NA	17 633	Mortality	20	Food frequency questionnaire	Inverse, not statistically significant	—
USA	Japanese residents, random survey of Hawaiian households (Galanis et al. 1998)	Males and females	≥18	11 907	Incidence (108)	14.8	Food frequency questionnaire	Inverse, statistically significant	—
USA	Cohort of Hawaiian men of Japanese Ancestry, Honolulu Heart Program (case cohort study) (Chyou et al. 1990)	Males	49–68	8 006	Incidence (111)	18	Food frequency questionnaire and 24-hour recall	Inverse, not statistically significant	—
USA	Cohort of Hawaiian men of Japanese ancestry, Honolulu Heart Program (Nomura et al. 1990)	Males	49–68	7 990	Incidence (150)	19	Food frequency questionnaire	Inverse, not statistically significant	—
Multiple countries	Seven Countries study, Japan, USA and Europe (Ocke et al. 1998)	Males	40–59	12 763	Mortality (NA)	25	Various methods (population intake)	Inverse, not statistically significant	—

NA Not applicable.

— No data.

Table 9.18 Summary of case–control studies reporting a measure of association between intake of fruit and vegetables and gastric cancer

Country	*Study population/area (reference)*	*Sex*	*Association with fruit and vegetables*	*Association with specific risk factors only*
Belgium	(Tuyns et al. 1992)	Males and females	Inverse	—
Canada	(Risch et al. 1985)	Males and females	Null	Inverse (citrus fruit)
China	(Hu et al. 1988)	Males and females	Null	Inverse (spinach)
China	North-east China (You et al. 1988)	Males and females	Inverse	—
China	Shanghai (Ji et al. 1998)	Males and females	Inverse	Null (vegetables) in females
France	(Cornee et al. 1995)	Males and females	Null	—
Germany	(Boeing et al. 1991a)	Males and females	Inverse (fruit)	—
Greece	(Trichopoulos et al. 1985)	Males and females	Inverse (vegetables), null (fruit)	—
Italy	(Buiatti et al. 1989)	Males and females	Inverse	Null (cooked vegetables)
Italy	(Munoz et al. 1997)	Males and females	Null	Inverse (citrus fruit)
Italy	Milan (La Vecchia et al. 1987)	Males and females	Inverse	—
Japan	(Hoshiyama and Sasaba 1992)	Males and females	Null	Inverse (raw vegetables)
Japan	(Kato et al. 1990)	Males and females	Null	Inverse (raw vegetables) in males
Japan	(Kono et al. 1988)	Males and females	Null	Inverse (mandarins)
Japan	(Tajima and Tominaga 1985)	Males and females	Null	Inverse (spinach, onion)
Mexico	Mexico City (Ward and Lopez-Carrillo 1999)	Males and females	Inverse	—
Poland	(Boeing et al. 1991b)	Males and females	Inverse	—

Poland	Cracow (Jedrychowski et al. 1986)	Males and females	Null (vegetables), inverse (fruit)	—
Republic of Korea	(Lee et al. 1995)	Males and females	Null	Inverse (spinach)
Spain	(Garcia-Closas et al. 1999)	Males and females	Inverse	Inverse (flavonoids)
Spain	(Gonzales et al. 1991)	Males and females	Inverse	Null (raw vegetables)
Spain	Barcelona (Ramon et al. 1993)	Males and females	Inverse	—
Sweden	(Ekstrom et al. 2000)	Males and females	Inverse (vegetables), null (fruit)	—
Sweden	(Hansson et al. 1993)	Males and females	Inverse	—
Turkey	(Demirer et al. 1990)	Males and females	Inverse	—
Turkey	(Memik et al. 1992)	Males and females	Null	—
United Kingdom	(Coggon et al. 1989)	Males and females	Inverse	—
USA	(Graham et al.1990)	Males and females	Inverse	—
USA	(Harrison et al. 1997)	Males and females	Inverse	Inverse (only for fruit)
USA	Los Angeles, California (Wu-Williams et al. 1990)	Males	Null	—
USA	Louisiana (Correa et al. 1985)	Males and females	Null (vegetables), inverse (fruit)	—
Venezuela	(Munoz et al. 2001)	Males and females	Inverse (vegetables)	Positive for fruit

Null Association not statistically significant.

Inverse Statistically significant protective association of high vs low fruit/vegetable consumption.

— No data.

Turkey (2), Venezuela (1) and northern and southern Europe (14). All but two of these studies were carried out on both men and women. Not all the populations were at high risk of stomach cancer.

Of the 32 studies, 20 reported a significant inverse association between total fruit or vegetable consumption and gastric cancer risk. A further nine studies found an inverse association only with specific food types or within a subcohort. Particular attention was placed on the consumption of allium vegetables (onion, leek, garlic and chives). One study (from Venezuela) found that the risk of gastric cancer incidence was inversely related (protective effect) with vegetable intake but directly related (harmful effect) with fruit intake. This is the only study reporting a significant positive (harmful) relationship (Munoz et al. 2001). Despite the inherent limitations of information bias in case–control studies, the evidence is strong and consistent for a protective effect from a diet high in fruit and vegetables, and supports the findings of the cohort studies.

Confounding

Most studies appear to have adjusted adequately for potential confounding factors. All adjusted for age and sex, and most studies adjusted for smoking and alcohol consumption. Other factors, considered particularly in prospective studies, were previous history of stomach illness, family history of stomach cancer, other dietary components and socioeconomic status. Protective associations remained even after adjustment for other dietary factors such as salty foods or starchy foods in some studies (Coggon et al. 1989; Hansson et al. 1993; La Vecchia et al. 1987; Lee et al. 1995; Ramon et al. 1993; Risch et al. 1985).

H. pylori infection is a major risk factor for gastric cancer, yet few studies were able to collect this information given the retrospective nature of many studies and the recent ability of testing to confirm infection.

Summary

There is an inverse relationship between fruit and vegetable intake and gastric cancer risk in both cohort and case–control studies in different populations worldwide. The relationship remains after adjustment for confounding. Some of the variations in the findings from separate studies could be due to the between-country differences in the varieties of fruit and vegetables consumed, the methods of consumption (raw or cooked), the number of specific fruit or vegetable items included in the questionnaires used or the validity of the dietary assessment methods.

Although *H. pylori* infection is an established risk factor, its relationship with fruit and vegetable consumption remains inadequately understood. A multistage model of gastric carcinogenesis is now accepted, according to which different dietary and non-dietary factors, involving genetic susceptibility, are involved at different stages in the cancer

process. A protective effect of supplementation of vitamin C and beta-carotene in the progression of pre-malignant gastric lesions was found in Latin America (Correa et al. 2000), but alpha-tocopherol and beta-carotene supplement trials in Finland showed no effect. In spite of this, results from the observational studies suggest a protective effect of diets rich in fruit and vegetables.

Colorectal cancer

A detailed description of the studies included in the review of the literature follows.

Previous reviews of the literature

Four recent comprehensive reviews of the literature investigating fruit and vegetable consumption and risk of colorectal cancer were found. They all concluded that the evidence is consistent in supporting a decreased risk of colorectal cancer with higher consumption of vegetables, and that data for an association with fruit consumption are inconsistent (Klerk et al. 1998; Norat et al. 2001; Potter 1996; World Cancer Research Fund and American Institute for Cancer Research 1997).

The review by Klerk et al. (1998) estimated that high vs low consumption of fruit and vegetables (an average difference of 150 g/day) is likely to reduce the risk of colorectal cancer by 20–45% in men and women.

The meta-analysis by Norat et al. (2001) (see description above in the section on gastric cancer) included 13 studies assessing the effect of total fruit intake and 28 studies assessing the effect of total vegetable intake. The pooled relative risks associated with an increased intake of 100 g/day were 0.94 (95% CI 0.90–0.98) for fruit and 0.90 (95% CI 0.84–0.96) for vegetables (subanalyses found similar relative risks for men and women, and for European and USA populations).

Current review of the literature

The systematic review identified 15 cohort studies and 34 case–control studies that examined the association between colorectal cancer risk (both incidence and mortality) and the consumption of fruit and vegetables. Details of these studies are given in Tables 9.19 and 9.20. Overall, the evidence supports an inverse relationship between fruit and vegetable intake and colorectal cancer risk (incidence and mortality), although it is not as strong as that for gastric cancer.

The studies investigating colorectal cancer also included a number of studies that looked separately at colon and rectal cancers. For the purposes of this review, we have combined the results of all these outcomes.

The cohort studies were conducted on a limited range of populations with most studies being from the United States (10), the others being

Table 9.19 Summary of cohort studies reporting a measure of association between intake of fruit and vegetables and colorectal cancer

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetable*	*Association with diet proxy intake*
Finland	Male smokers in ATBC study (Pietinen et al. 1999)	Males	50–69	27111	Incidence (185)	8	Food frequency questionnaire	Positive, not statistically significant	. . .
Japan	Japanese general population survey (1965 census cohort) (Hirayama 1986, 1990)	Males and females	≥40	265118	Mortality: colon (552), rectum (563)	17	Crude—not clear	Inverse (colon), positive (rectum), not statistically significant	. . .
Netherlands	The Netherlands Cohort study (Voorrips et al. 2000a)	Males and females	55–69	120852	Incidence (910)	6.3	150-item food frequency questionnaire	Inverse, not statistically significant	Non-significant trends: inverse (vitamin C), positive (beta-carotene, retinol)
Sweden	Swedish Mammography study (Terry et al. 2001)	Females	NA	61463	Incidence (460)	9.6	Food frequency questionnaire	Inverse, statistically significant	. . .
USA	NHS (Fuchs et al. 1999)	Females	34–59	88757	Incidence (787)	16	Repeated food frequency questionnaire		Inverse, not statistically significant (fibre)
USA	HPFS (Giovannucci et al. 1994)	Males	40–75	47949	Incidence (205)	6	Repeated food frequency questionnaire	Inverse (fruit), positive (vegetables), not statistically significant	. . .

USA	NHS/HPFS (Michels et al. 2000, 2002)	Males Females	40–75 30–55	88764 47325	Incidence: colon (937), rectum (244)	10–16	Repeated food frequency questionnaire	Positive, not statistically significant	...
USA	The Adventist Health study (Phillips and Snowdon 1985)	Males and females	≥16	25493	Mortality (182)	21	Food frequency questionnaire	Inverse (rectum), positive (colon), not statistically significant	...
USA	Leisure World cohort, California (Paganini-Hill et al. 1987)	Males and females	Elderly	10473	Incidence (110)	6	Food frequency questionnaire		No association (beta-carotene)
USA	Leisure World cohort, California (Shibata et al. 1992)	Males and females	Elderly	11580	Incidence (202)	9	Food frequency questionnaire	Inverse, not statistically significant (females)	...
USA	Cohort of Hawaiian men of Japanese ancestry, Honolulu Heart Program (Heilbrun et al. 1989)	Males	49–68	8006	Incidence: colon (102), rectum (60)	18	Food frequency questionnaire		Inverse, statistically significant (vitamin C)
USA	Iowa Women's Health study (Steinmetz et al. 1994)	Females	55–69	34691	Incidence (212)	5	127-item food frequency questionnaire	Inverse, not statistically significant	...
USA	New York University women's health study (Kato et al. 1997)	Females	34–65	14727	Incidence (100)	7.1	Food frequency questionnaire	Positive, not statistically significant	...
USA	American Cancer Society Prevention study, USA and Puerto Rico (Thun et al. 1992)	Males and females	≥30	764343	Mortality—colon (1150)	6	32-item food frequency questionnaire	Inverse, statistically significant	...

NA Not applicable.

Table 9.20 Summary of case–control studies reporting a measure of association between intake of fruit and vegetables and colorectal cancer

Country	*Study population (reference)*	*Sex*	*Association with fruit or vegetables*	*Association with specific risk factors*
Argentina	(Iscovich et al. 1992)	Males and females	Inverse (vegetables)	. . .
Australia	(Kune et al. 1987, 1992)	Males and females	Inverse (vegetables)	. . .
Australia	(Steinmetz and Potter 1993)	Males and females	Null	. . .
Belgium	(Tuyns et al. 1988)	Males and females	Inverse (fruit)	. . .
Canada	French Canadians (Ghadirian et al. 1997)	Males and females	Inverse (vegetables)	. . .
China	(Hu et al. 1991)	Males and females	Inverse (vegetables)	. . .
France	(Faivre et al. 1997)	Males and females	Null	. . .
France	(Macquart-Moulin et al. 1986)	Males and females	Inverse	. . .
Italy	(Bidoli et al. 1992)	Males and females	Null	Inverse (spinach)
Italy	(Franceschi et al. 1994)	Males and females	Inverse	Tomato
Italy	(Francecshi et al. 1997)	Males and females	Inverse	. . .
Italy	(Franceschi et al. 1998)	Males and females	Inverse	. . .
Italy	(La Vecchia et al. 1987)	Males and females	Inverse (vegetables)	. . .
Italy	(Negri et al. 1998)	Males and females	Inverse	. . .
Japan	(Kotake et al. 1995)	Males and females	Null	. . .
Japan	(Tajima and Tominaga 1985)	Males and females	Null	Inverse (spinach, onion, pumpkin)
Netherlands	(Kampman et al. 1995)	Males and females	Inverse (vegetables)	. . .
Russian Federation	(Zaridze et al. 1993)	Males and females	Null	Positive (dried fruit)

Singapore	(Lee et al. 1989)	Males and females	Null	...
Spain	(Benito et al. 1990)	Males and females	Null	...
Switzerland	(Levi et al. 1999)	Males and females	Inverse	...
Uruguay	(Deneo-Pellegrini et al. 1996)	Males and females	Inverse (fruit and vegetables)	...
USA	(Shannon et al. 1996)	Males	Null	...
		Females	Inverse	...
USA	(Slattery et al. 1997)	Males	Inverse (vegetables)	...
		Females	Null	...
USA	California (Peters et al. 1992)	Males and females	Null	...
USA	Hawaii (Le Marchand et al. 1997)	Males and females	Inverse	...
USA	New York University, NY (Kato et al. 1999)	Males	...	Inverse (folate)
USA	New York (western) (Freudenheim et al. 1990; Graham et al. 1988)	Males and females	Null	Inverse (tomato, pepper, celery)
USA	Utah (Slattery et al. 1988)	Males and females	Inverse (fruit)	Inverse (cruciferous vegetables)
USA	Utah (West et al. 1989)	Males	Inverse	...
		Females	Null	...
USA	Washington (Meyer and White 1993)	Males	Null	...
		Females	Inverse	...
USA	Wisconsin (Young and Wolf 1988)	Males and females	...	Inverse (cruciferous vegetables)

NA Not applicable.

Null Association not statistically significant.

Inverse Statistically significant protective association of high vs low fruit/vegetable consumption.

from Europe (3) and Japan (1). It should be noted that three of the study cohorts were common to more than one study.

The majority of studies measured cancer incidence as the outcome, with mortality being used as the study outcome in only four studies. Eight studies investigated both men and women, while three investigated men only and four looked at women only.

Although a number of the studies reported a protective effect of fruit and vegetable consumption on colorectal cancer risk, only three of the 15 showed a statistically significant inverse trend. This is summarized in Table 9.19. A further eight studies did show some inverse association between vegetable consumption and colorectal cancer risk for certain subgroup analyses of fruit, vegetables or colon or rectal cancer separately; three studies showed a statistically insignificant positive association between fruit and vegetable intake and colorectal cancer.

The case–control study populations came from a wider range of countries than those of the cohort studies. They included studies from Argentina, Australia, Belgium, Canada, China, France, Italy, Japan, the Russian Federation, Singapore, Spain, Switzerland, the United States and Uruguay. All studies collected data on both men and women. It should be noted that two of the population cohorts (Australia and New York) were each common to two studies.

Results from 21 out of the 33 populations showed an inverse association with fruit or vegetables, while three found an inverse association only with specific food types (tomato; or spinach, onion and pumpkin; or tomato, pepper and celery). This is summarized in Table 9.20.

It should be noted that although the majority of colorectal cancers are adenocarcinomas, some studies found differences depending on tumour location (proximal vs distal, colon vs rectum). This suggests that pooling of results from different anatomical sites and cell types in many of the cohort and case–control studies may have obscured a true relationship for subgroups.

Confounding and interaction

All studies adjusted for the effect of sex and age. Other confounders taken into account in the statistical analyses included total energy, meat, fat and protein intakes, BMI, smoking, alcohol consumption, physical activity, family history, dietary supplements, education and area of residence. By analogy with the evidence of lung and stomach cancer, it is conceivable that an effect might only be anticipated in those with particular genetic states (e.g. fast acetylators) that also consume significant quantities of meat. Many studies have excluded cases with strong family history of colorectal cancer or with conditions such as familial polyposis coli, and inflammatory bowel diseases such as ulcerative colitis or Crohn disease from the final analyses.

Summary

On their own, the prospective epidemiological studies have yet to produce conclusive evidence to support an association of colorectal cancer with fruit and vegetable intake. However, the hypothesis is still worthy of further consideration, as there appears to be an inverse relationship in many cohort studies and in two thirds of the case–control studies in a wide range of different populations. The relationships remained after adjustment for confounding.

The uncertainty in the studies of colorectal cancer is relatively unsurprising in view of the complex biological mechanisms involved in its etiology. The incidence can be expected to reflect a complex combination of genetic factors (including factors that affect the colonic mucosa and those that determine whether certain toxins are excreted in bile or urine), diet (both carcinogenic and protective factors) and hormonal status.

Oesophageal cancer

A detailed description of the studies included in the review of the literature follows.

Previous reviews of the literature

Three recent reviews of the literature (Cheng and Day 1996; Klerk et al. 1998; World Cancer Research Fund and American Institute for Cancer Research 1997) concluded that there is convincing evidence that diets high in fruit and vegetables decrease the risk of oesophageal cancer.

WCRF/AICR reviewed 22 case–control studies (1997). Of these, 18 showed a statistically significant protective association with at least one category of fruit or vegetables. The protective association in the studies remained after controlling for smoking and alcohol consumption. The Dutch review (Klerk et al. 1998) concluded that high vs low consumption of fruit and vegetables (an average difference of 150 g/day) is likely to reduce the risk of oesophageal cancer by 40–55% in men and women.

Finally, the meta-analysis by Norat et al. (2001) pooled the results of 10 studies assessing the effect of fruit intake and 11 studies assessing the effect of vegetable intake on oesophageal cancer (see more details of methods described in the section on stomach cancer). This estimated that an increase in food intake of 100 g/day is associated with a relative risk for oesophageal cancer of 0.79 (95% CI 0.65–0.95) for fruit; and 0.92 (95% CI 0.85–1.01) for vegetables.

Current review of the literature

This systematic review identified four cohort and 28 case–control studies investigating the association of fruit and vegetable intake with oesophageal cancer risk (incidence and mortality). Most studies looked

at oesophageal cancer mortality or at the effect of fruit and vegetable consumption on incidence and mortality considered jointly. In this review, we have also considered these outcomes together, assuming that, since oesophageal cancer survival rates are very poor, incidence is closely correlated with mortality.

The four cohort studies considered are from China (2), Japan and Norway. Details of the studies are given in Table 9.21. Both Chinese studies were based on the same population in the Linxian province, which has one of the highest incidence rates of oesophageal cancer in the world. The study population is part of a Nutrition Intervention Trial.

Three of the studies showed a statistically non-significant inverse trend with fruit and vegetable intake. One Chinese study found an inverse relationship with fresh vegetable consumption (Yu et al. 1993), while the other found an inverse relationship between the intake of both fruit and vegetables and oesophageal cancer incidence (Guo et al. 1994). The most recent study of Norwegian men also found a non-significant inverse relationship between fruit and vegetable intake and oesophageal cancer incidence, but this was based on only 22 cancer events.

Case–control studies provide the majority of evidence for the association of fruit and vegetable consumption and oesophageal cancer risk. The 28 case–control studies identified are summarized in Table 9.22.

The studies came from a wide range of populations worldwide including China (4), Hong Kong Special Administrative Region of China (Hong Kong SAR) (2), India (2), Japan (2) the United States (4), Europe (11) and South America (3). Most of these studies investigated populations of men and women, but five investigated only men and two studied only women. Not all of the study populations were from populations at a high risk of oesophageal cancer.

Of the 28 studies, 20 reported significant inverse associations between oesophageal cancer and fruit and/or vegetable consumption. Interestingly, more of these inverse associations were with fruit rather than vegetables.

Although many studies did not specifically look at the histological type of oesophageal cancer, the majority of the results presented here are likely to be limited to squamous cell cancer. There was one study, in women from the United Kingdom (Cheng et al. 2000), which focused on oesophageal adenocarcinoma. This study found an inverse association of cancer risk with a higher consumption of fruit but not vegetables.

Confounding

Most studies adjusted for age and sex. Other potential confounders considered in several studies, included smoking, total energy intake, pickled vegetable intake, BMI, marital status, occupational status, educational or socioeconomic status and ethnicity. Supplement intakes, such as vitamins, and intake of hot teas, were also considered in a few studies.

Table 9.21 Summary of cohort studies reporting a measure of association between intake of fruit and vegetables and oesophageal cancer

Country	*Study population (reference)*	*Sex*	*Age range (years)*	*Study size*	*No. of cases*	*Follow-up (years)*	*Exposure measure*	*Association with fruit or vegetable intake*
China	Linxian Nutrition Intervention Trial cohort (Guo et al. 1994)	Males and females	40–69	29584	Incidence (640)	5.25	Structured questionnaire interview	Inverse, not statistically significant
China	Linxian Nutrition Intervention Trial cohort (Yu et al. 1993)	Males and females	40–69	12693	Incidence and mortality (1162)	15	Structured questionnaire interview	Inverse, not statistically significant
Japan	Japanese general population survey (1965 census cohort) (Hirayama 1986, 1990)	Males and females	≥40	265118	Mortality (585)	17	Crude—not clear	Positive, not statistically significant
Norway	Cohort of Norwegian men (Kjaerheim et al. 1998)	Males	35–74	10960	Incidence (22)	25	32-item food frequency questionnaire	Inverse, not statistically significant

Table 9.22 Summary of case–control studies reporting a measure of association between intake of fruit and vegetables and oesophageal cancer

Country	*Study population/area (reference)*	*Sex*	*Association with fruit and vegetables group (or proxy)*	*Association with specific risk factors only*
Brazil	(Victora et al. 1987)	Males and females	Inverse (fruit)	—
China	Heilongjiang (Hu et al. 1994)	Males and females	Null	—
China	Linxian (Li et al. 1989)	Males and females	Null	—
China	Shanghai (Gao et al. 1994)	Males and females	Inverse (fruit), null (vegetables)	—
China	Shanxi (Wang et al. 1992)	Males and females	Null	Inverse (cabbage)
China, Hong Kong SAR	(Cheng et al. 1992)	Males and females	Inverse	—
China, Hong Kong SAR	Never-smokers/drinkers (Cheng et al. 1995)	Males and females	Inverse	—
France	(Tuyns et al. 1987)	Males and females	Inverse	—
France	Multicentre (Launoy et al. 1998)	Males	Inverse	—
Greece	Athens (Garidou et al. 1996)	Males and females	Null	Inverse (vegetables) in adenocarcinoma type
India	(Nayar et al. 2000)	Males and females	Null	—
India	(Notani and Jayant 1987)	Males and females	Inverse (vegetables), null (fruit)	—
Italy	(Decarli et al. 1987)	Males and females	Inverse (fruit), null (vegetables)	—

Italy	(Tavani et al. 1996a)	Males and females	Null	Inverse (fruit) in smokers
Italy	Northern Italy (Bosetti et al. 2000)	Males and females	Inverse	Null (cooked vegetables)
Italy	Milan (Negri et al. 1991)	Males and females	Inverse	—
Italy	Milan (Tavani et al. 1993)	Females	Inverse (fresh fruit), null (green vegetables)	—
Italy	Non-smokers (Tavani et al. 1994)	Males and females	Inverse	—
Japan	(Hanaoka et al. 1994)	Males	Null	—
Japan	(Takezaki et al. 2000)	Males	Inverse	—
Switzerland	(Levi et al. 2000)	Males and females	Inverse	—
United Kingdom	England; Scotland (Cheng et al. 2000)	Females	Null (vegetables), inverse (fruit)	Adenocarcinoma only
Uruguay	(DeStefani et al. 1990)	Males and females	Null	—
USA	(Brown et al. 1995)	Males and females	Inverse	—
USA	(Brown et al. 1998)	Males	Inverse	Squamous cell carcinoma only
USA	California (Yu et al. 1988)	Males and females	Inverse	—
USA	South Carolina (Brown et al. 1988)	Males	Inverse (fruit), null (vegetables)	—
Multiple countries	South America (5 countries) (Castellsague et al. 2000)	Males and females	Inverse	—

Null Association not statistically significant.

Inverse Statistically significant protective association.

— No data.

Summary

The epidemiology of oesophageal cancer shows wide geographical variation in incidence and mortality rates. Striking differences have been reported not only between regions of the world and countries, but also within smaller geographical areas (Muir and McKinney 1992; Walker et al. 2002). Oesophageal cancer risk also varies with race, ethnicity and sex. Changes in incidence patterns observed in migrant studies appear to indicate that environmental factors, among which diet may be important, play an important role in the etiology of oesophageal cancer.

The main risk factors for oesophageal cancer in Europe were previously thought to be tobacco smoking and alcohol consumption. However, time trends of oesophageal mortality from 1950–1985 in 17 European countries showed that oesophageal cancer had either decreased or increased only slightly (Cheng et al. 1992). This trend differed from that of lung cancer, cirrhosis and alcohol consumption, which had increased substantially during the same period. The results suggest that other population-wide changes in protective risk factors, such as improvements in diet after World War II, had mitigated against the effect of tobacco and alcohol and resulted in a reduction of oesophageal cancer risk. In China, which has a very high incidence of oesophageal cancer, an ecological study of 65 counties showed that oesophageal cancer mortality was significantly associated with fruit consumption, but no correlation was observed with tobacco smoking or alcohol consumption (Guo et al. 1990). There is strong evidence from ecological studies that dietary factors, especially fruit and vegetable consumption, may affect rates of oesophageal cancer.

This review of the literature showed that there are few prospective observational studies of the effect of fruit and vegetable consumption on oesophageal cancer, and that most of these show non-significant inverse associations. Evidence from supplement intervention trials is also inconclusive. Two randomized supplement intervention trials in Linxian, China tested the effect of nutrient/vitamin supplementation in a population with very high rates of oesophageal cancer (Blot et al. 1995). Modest protective effects were seen for mortality in the supplemented group in both trials, but none of the results was statistically significant for oesophageal or gastric cancer. In spite of this, evidence from case–control studies appears to support an inverse relationship between fruit and vegetable consumption and oesophageal cancer risk (incidence and mortality), although this is not as strong as that for stomach cancer.

3.8 Estimates of risk factor–disease relationships by subregion, sex and age

Estimates of relative risks

This section describes, for each selected outcome, the studies that were chosen based on the strict selection criteria for meta-analysis outlined in section 3.6, and the final estimates of relative risks derived for CRA.

Ischaemic heart disease

Details of the cohort studies that most closely met our selection criteria are given in Table 9.23. The EPIC-Norfolk study (Khaw et al. 2001) was included in spite of the fact that it presents results in relation to plasma vitamin C, because plasma vitamin C measurements (available for the whole cohort) were relatively well correlated with fruit and vegetable intake (available from a 7-day food record analysed for a subset of the cohort) and because of the high quality of the methods used to collect and analyse data.

Fruit and vegetable intake in the Nurses' Health and Health Professionals' follow-up studies (NHS/HPFS), EPIC-Norfolk and the Finnish Mobile Clinic studies were treated as continuous variables. The NHS/HPFS studies gave the relative risk in terms of one additional serving per day, which we converted as 80 g/day (assumed to be one standard serving); the EPIC-Norfolk and Finnish Mobile Clinic studies reported relative risk estimates for 50 g and 1 g increase in intake respectively. Thus, the relative risk estimates were transformed to give final estimates expressed as per 80 g/day increase.

For the Massachusetts Health Care Panel study (data analysed as quartiles of intakes), the two methods described in section 3.6 were used to estimate the relative risks. With method 1, we estimated the additional g/day for which the relative risks given applied. The study gave exposure quartiles with midpoints at 32, 88, 138 and 190 g/day (the last estimated as the lower limit, 164, plus half the previous category interval), and reported relative risks for the two latter categories compared with the first quartile. A difference of 55 g between adjacent quartiles was

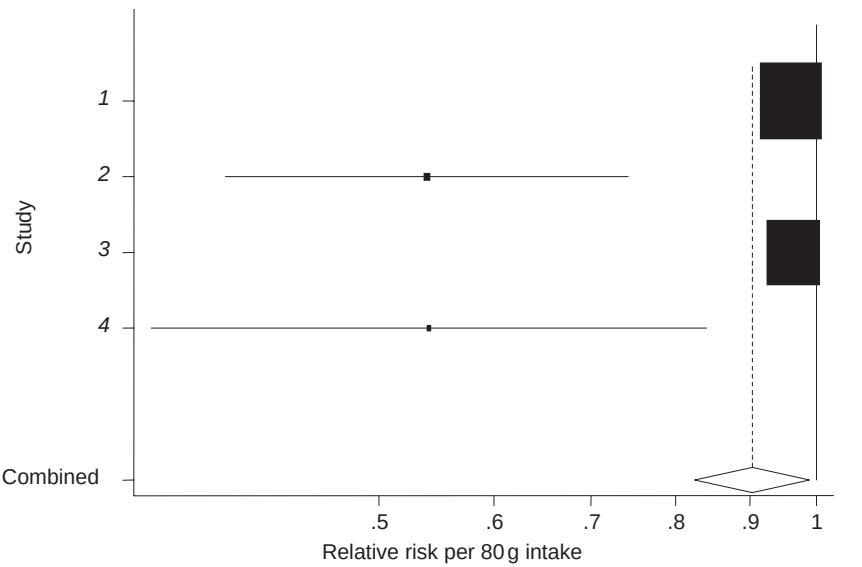
Table 9.23 Relative risk estimates for the association between ischaemic heart disease and fruit and vegetable consumption

Country	*Study population (reference)*	*Sex and age range (years)*	*Outcome*	*RR (95% CI) per 80 g/day increase in fruit and vegetable intake*
Finland	Finnish Mobile Clinic Health Examination study (Knekt et al. 1994)	Males and females (30–69)	Mortality	0.964 (0.930–0.999)
United Kingdom	EPIC-Norfolk (Khaw et al. 2001)	Males and females (45–79)	Mortality	0.54 (0.40–0.74)
USA	NHS/HPFS (Joshipura et al. 2001)	Males and females (34–75)	Myocardial infarction incidence	0.96 (0.94–0.99)
USA	Massachusetts Health Care Panel study (Gaziano et al. 1995)	Males and females (>66)	Mortality	0.54 (0.35–0.84)

assumed, which gives exposures of approximately 30, 85, 140 and 195 g/day. This approximation yielded comparable relative risks per 55 g difference whichever of the two reported relative risks was converted, and the relative risk reported for the 4th vs 1st quartile was used, which was expressed as a difference in exposure of $3 \times 55 = 165$ g/day. The method of Greenland and Longnecker (method 2) was then used to estimate the weighted regression slope over the published relative risks, allowing for correlations due to common reference category. Because of its advantages, method 2 was chosen to obtain the final estimates for inclusion in the meta-analysis.

Meta-analysis was used to pool relative risk estimates using the method described in section 3.6. The test of heterogeneity gave a chi-squared value of 19.044 ($df = 3$; $P < 0.001$). The resulting variation between studies suggests that it is inappropriate to pool estimates according to the fixed effects method. Using random effects meta-analysis, the pooled relative risk estimate was 0.903 (95% CI 0.824–0.989) for an 80 g/day increase in fruit and vegetable consumption. The random effects results are shown in Figure 9.2.

Figure 9.2 Random effects meta-analysis of the association of fruit and vegetable intake with ischaemic heart disease



Key: *1*, NHS/HPFS; *2*, EPIC-Norfolk study; *3*, Finnish Mobile Clinic Health Examination study; *4*, Massachusetts Health Care Panel study.

The figure shows that there is marked heterogeneity in the best available evidence on the effects of fruit and vegetable consumption on the risk of IHD. The sources of this heterogeneity are currently not understood scientifically, and there is, therefore, no fully satisfactory means for arriving at a summary effect estimate. The random effects model used here provides a pragmatic interim solution to summarizing this evidence, pending better scientific understanding of the underlying relationships. The derived effect size seems plausible in the light of the consistency of the study findings set out in Table 9.13, but it remains subject to substantial uncertainty—only some of that derives from the statistical uncertainty associated with the four studies included in Figure 9.2.

Ischaemic stroke

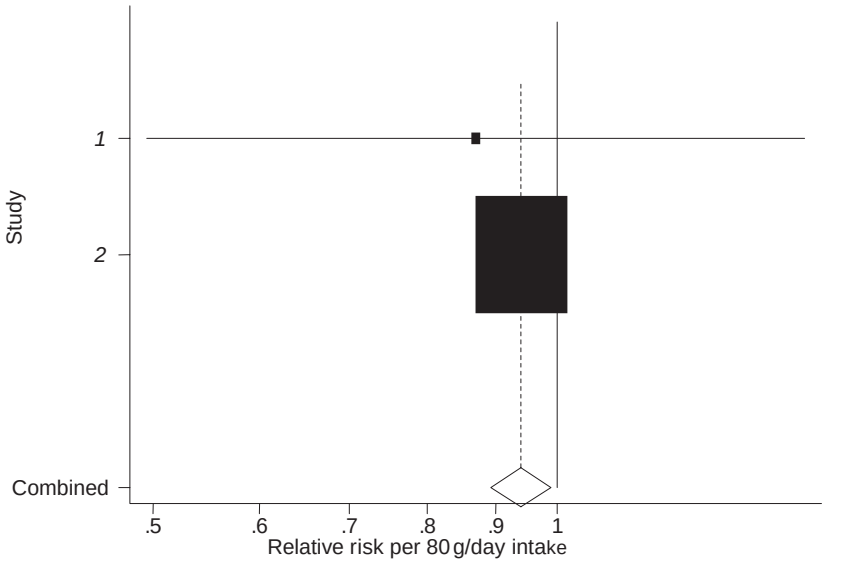
Only two cohort studies met the selection criteria for meta-analysis. These are summarized in Table 9.24.

The NHS/HPFS gave the relative risk in terms of one additional serving per day, which we converted as 80 g/day. As the Zutphen study did not give a single estimate of linear (log) relative risk per consumption, the relative risk estimates were derived using the two methods described earlier for IHD. Since vegetable and fruit consumption were separately analysed, the relative risk for vegetable consumption was used: it seems to us likely that vegetable and fruit consumption would confound each other, so that what is reported as a purely "vegetable" effect includes the effect of fruit eaten by vegetable consumers. Since a diet of only fruit is rare, the vegetable effect reported was assumed to be similar to that which would have been reported for a combined fruit and vegetable diet (although this may underestimate the effect). Method 2, of Greenland and Longnecker (1992), gave an almost identical estimate to Method 1, which used a consumption difference of the 4th vs 1st quartile (249.9 – 128.1 = 121 g/day) for the 0.82 relative risk (vegetables) as the basis for the estimate. Results based on method 2 are therefore reported here.

Table 9.24 Relative risk estimates for the association between stroke and fruit and vegetable consumption

Country	*Study population (reference)*	*Sex and age range (years)*	*Outcome*	*RR (95% CI) per 80 g/day increase in fruit and vegetable intake*
Netherlands	Zutphen study (Keli et al. 1996)	Males (50–69)	Incidence cerebrovascular accident	0.87 (0.49–1.53)
USA	NHS/HPFS (Joshipura et al. 2001)	Males and females (34–75)	Incidence ischaemic stroke	0.96 (0.94–0.99)

Figure 9.3 Fixed effects meta-analysis of the association of fruit and vegetable intake with ischaemic stroke



Key: *1*, Zupthen study; *2*, NHS/HPFS.

Relative risk estimates were combined using fixed-effect meta-analysis, as the random effects could not be estimated. The pooled relative risk estimate was 0.939 (95% CI 0.892–0.989) for an 80 g/day increase in fruit and vegetable consumption. The results are shown in Figure 9.3.

Lung cancer

Four studies met our selection criteria for meta-analysis. These are shown in Table 9.25.

Relative risks in the NHS/HPFS and the Finnish Mobile Clinic Health Examination study were available with fruit and vegetable intake treated as a continuous variable. The NHS/HPFS gave the relative risk in terms of one additional serving per day, which we converted as 80 g/day. The authors of the Finnish Mobile Clinic study provided relative risks per 1 g/day which were transformed on a log scale to give estimates expressed as an 80 g/day increase (as discussed earlier in this section).

For the Netherlands Cohort study and the National Health Interview study, data had been analysed as quintiles and quartiles of intake respectively. The method of Greenland and Longnecker (1992) was used to

Table 9.25 Relative risk estimates for the association between lung cancer and fruit and vegetable consumption

Country	*Study population (reference)*	*Sex and age range (years)*	*Outcome*	*RR (95% CI) per 80 g/day increase in fruit and vegetable intake*
Finland	Finnish Mobile Clinic Health Examination study (Knekt et al. 1991)	Males and females (55–69)	Incidence	0.92 (0.85–0.99)
Netherlands	The Netherlands Cohort study (Voorrips et al. 2000b)	Males and females (55–69)	Incidence	0.89 (0.83–0.96)
USA	National Health Interview study (Breslow et al. 2000)	Males and females (fruit)	Mortality	0.9 (0.69–1.17)
USA	NHS/HPFS (Feskanich et al. 2000)	Males and females (34–75)	Incidence	0.99 (0.91–1.08)

estimate the weighted regression slope over the published relative risks. This gave estimates of relative risks as a continuous variable.

As there was no evidence of heterogeneity (chi-squared value of 3.553, $df = 3$, $P = 0.314$), the results from fixed effect meta-analysis were used (estimates were very similar to those obtained with the random effects methods). The pooled relative risk estimate was 0.926 (0.886–0.968) for an 80 g/day increase in fruit and vegetable consumption. The forest plot of the results is shown in Figure 9.4.

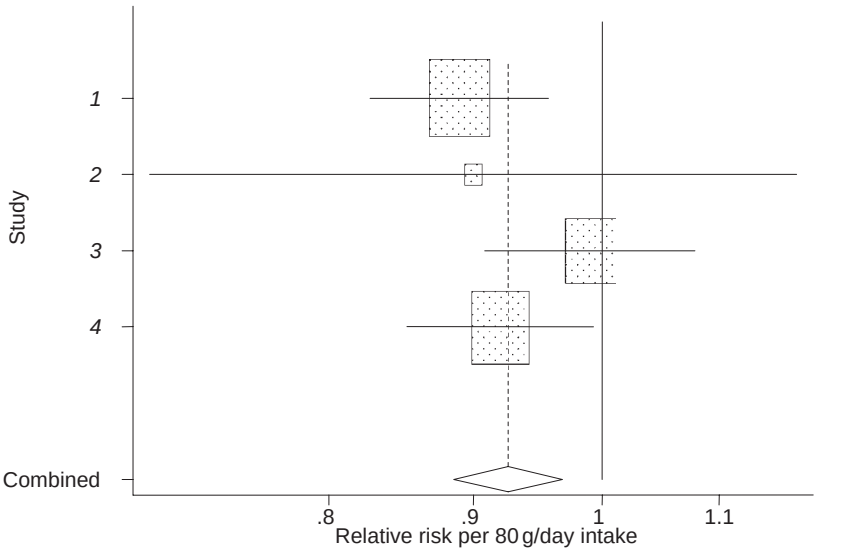
These results are consistent with those found in the only other pooled analysis for an association between lung cancer and fruit and vegetable consumption (S.A. Smith-Warner et al. personal communication, 2002). In this study, they found strong, inverse associations in the age-adjusted analyses, and analyses adjusted for education, BMI, alcohol intake and energy intake for total fruit, total vegetable, and total fruit and vegetable intakes. Associations were similar among never, past, and current smokers.

Smith-Warner et al. estimated that the pooled results for total fruit and vegetable intake gave a slightly lower reduction in lung cancer risk than the meta-analysis results for this project. Due to the potential for residual confounding, in our analysis we have decided to use the more conservative estimate of pooled relative risk which is equivalent to 0.96 (0.93–0.99) per 80 g/day increase in fruit and vegetable intake (S.A. Smith-Warner et al. personal communication, 2002). However, we should note that because of the limitations in our ability to accurately specify fruit and vegetable exposure, we might be underestimating any effect.

Gastric cancer

Only one study, the Netherlands Cohort study on diet and cancer, met our selection criteria for meta-analysis. This is shown in Table 9.26.

Figure 9.4 Fixed effects meta-analysis of the association of fruit and vegetable intake with lung cancer



Key: *1*, The Netherlands Cohort study; *2*, National Health Interview study; *3*, NHS/HPFS; *4*, Finnish Mobile Clinic Health Examination study.

Table 9.26 Relative risk estimate for the association between gastric cancer and fruit and vegetable consumption

Study population (reference)	*Sex and age range (years)*	*Outcome*	*RR (95% CI) per 80 g/day increase in fruit and vegetable intake*
The Netherlands Cohort study (Botterweck et al. 1998)	Males and females (55–69)	Incidence	0.94 (0.86–1.03)

The relative risks obtained from the Netherlands Cohort study are consistent with the effect estimates obtained from most case–control studies reviewed, but they are more conservative than the estimates of the meta-analysis from Norat et al. (2001).

Data from the Netherlands Cohort study had been analysed as quintiles of intake of fruit and vegetables. The method of Greenland and Longnecker (1992) was used to estimate the weighted regression slope over the published relative risks to estimate relative risks as a continuous variable for an 80 g/day increase in total fruit and vegetable consumption. This gave a final relative risk estimate for gastric cancer

incidence and mortality for the CRA project of 0.94 (0.86–1.03) for an 80 g/day increase in fruit and vegetable consumption.

Colorectal cancer

Three studies met our selection criteria for meta-analysis. These are shown in Table 9.27.

Relative risk in the NHS/HPFS was available with fruit and vegetable intake treated as a continuous variable. The NHS/HPFS gave the relative risk in terms of one additional serving per day, which was converted as 80 g/day.

For the Netherlands Cohort study and the Swedish Mammography study, data had been analysed as quintiles and quartiles of intake respectively. The method of Greenland and Longnecker (1992) was used to estimate the weighted regression slope over the published relative risks to give relative risks as a continuous variable.

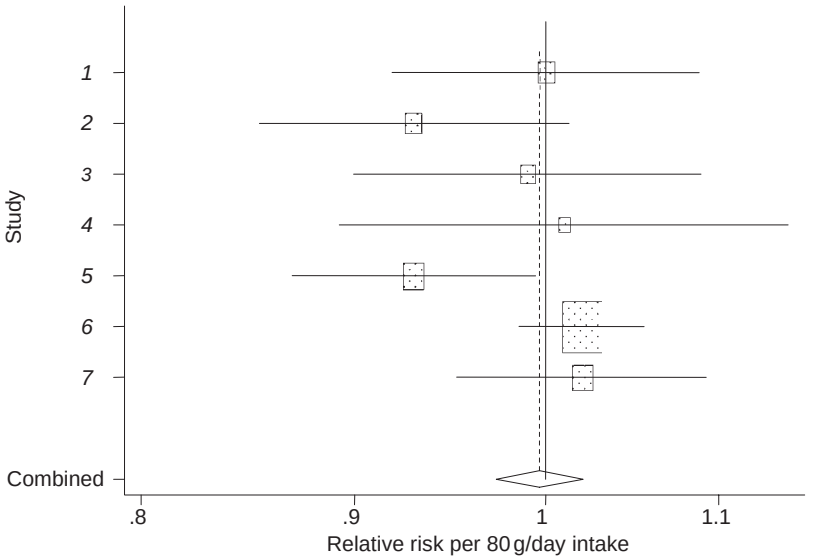
The NHS/HPFS and the Netherlands Cohort study had presented results separately for colon and rectal cancers. The Netherlands Cohort study had also analysed data for men and women separately. These subgroup analyses were combined in the meta-analysis as if they were separate studies. The test for heterogeneity gave a chi-squared value of 8.849 ($df = 6$; $P = 0.182$). As there was no evidence of heterogeneity, the fixed effects results were used (these were very similar to the results obtained with the random effects method). The pooled relative risk estimate was 0.997 (0.973–1.021) for an 80 g/day increase in fruit and vegetable consumption. The results are shown in Figure 9.5.

The Swedish Mammography study showed that the inverse association was stronger, and the dose–response more evident, among individuals who consumed the lowest amounts of fruit and vegetables. In a subgroup analysis of the population in the lowest quartile of fruit and vegetable intake, the relative risk was 0.77 (0.67–0.97) for an increase

Table 9.27 Relative risk estimates for the association between colorectal cancer and fruit and vegetable consumption

Country	*Study population (reference)*	*Sex and age range (years)*	*Outcome*	*RR (95% CI) per 80 g/day increase in fruit and vegetable intake*
Netherlands	The Netherlands Cohort study (Voorrips et al. 2000a)	Males (55–69) Females (55–69)	Incidence	Colon, 1.00 (0.92–1.09) Rectal, 0.93 (0.86–1.02) Colon, 0.99 (0.9–1.09) Rectal, 1.01 0.89–1.14)
Sweden	Swedish Mammography study (Terry et al. 2001)	Females	Incidence	Colorectal, 0.93 (0.87–0.995)
USA	NHS/HPFS (Michels et al. 2000)	Males and females (34–75)	Incidence	Colon, 1.02 (0.98–1.05) Rectal, 1.02 (0.95–1.09)

Figure 9.5 Fixed effects meta-analysis of the association of fruit and vegetable intake with colorectal cancer



Key: *1*, The Netherlands Cohort study (males, colon cancer); *2*, The Netherlands Cohort study (women, colon cancer); *3*, The Netherlands Cohort study (males, rectal cancer); *4*, The Netherlands Cohort study (females, rectal cancer); *5*, Swedish Mammography study (colorectal cancer); *6*, NHS/HPFS (males and females, colon cancer); *7*, NHS/HPFS (males and females, rectal cancer).

of one serving per day (Terry et al. 2001). It may be that individuals who consume very low amounts of fruit and vegetables have the greatest risk of colorectal cancer. This is consistent with the presence of a plateau effect and highlights the need to study populations with a wide range of dietary exposures. This finding was not replicated in the NHS/HPFS (Michels et al. 2000), although it should be noted that this study had a high reference exposure category and might not have been able to examine very low intake of fruit and vegetables as in the Swedish study.

Oesophageal cancer

None of the cohort studies of oesophageal cancer in the systematic review met our selection criteria. Studies were either of high-risk populations, had a small number of events, had a relatively short follow-up time or did not cover total fruit and vegetable intake. Very few of the case–control studies had calculated risk for total fruit and vegetable consumption, and none had estimated relative risks for quantified levels of fruit and vegetable consumption that would allow estimation of a continuous variable. Thus, it was decided to use the results of the meta-

analysis from Norat et al. (2001) to derive the final RR estimates. This meta-analysis calculated risk estimates for fruit and vegetables separately per 100 g/day intake. The pooled relative risks associated with an increase of consumption of 80 g/day were calculated. These were 0.828 (0.708–0.960) for fruit, and 0.935 (0.878–1.008) for vegetables. The results suggested risk reductions of between 17.2% and 6.5% per 80 g/day increase in fruit intake and vegetable intake, respectively. For this study, the most conservative relative risks were used, that is, those for vegetables only, 0.935 (95% CI 0.878–1.008).

Summary of the estimates of relative risks

The relative risk estimates and 95% confidence intervals are summarized in Table 9.28. Estimates are expressed as the change in relative risk associated with an 80-g increase in daily fruit and vegetable intake.

As discussed earlier, the relative risks are applied to all subregions and to both men and women. Assuming age attenuation at the extremes of age, these relative risks apply for individuals aged 15–69 years. For older adults, the relative risks were reduced by a quarter for ages 70–79 years, and by half for the age group ≥80 years. A relative risk of 1 was applied for those aged <15 years.

Estimates of risk reversibility

There is very little published evidence of risk reversibility for an increased fruit and vegetable intake, mainly due to the difficulty of conducting dietary intervention trials. Hence, the period of the latency between increased fruit and vegetable intake and risk reduction are difficult to predict.

Cardiovascular diseases

There is some limited evidence from randomized-controlled trials, which suggests that the effect of fruit and vegetables is not immediate for IHD. As was described in section 3.1, the DART study and the Lyon Diet Heart study examined the effect of dietary changes on the secondary prevention of myocardial infarction. The DART study showed no effect on mortality after two years, in the fat advice arm of the trial (advice to reduce fat intake and increase polyunsaturated to saturated fat ratio vs no advice) which was associated with an increased fruit and vegetable intake of about 50 g/day. However, the Lyon Diet Heart study showed that a Mediterranean-style diet had a marked protective effect on the rate of recurrence of myocardial infarction after 27 months, with an effect still maintained after four years of follow-up. The main disadvantage of these trials was that the interventions encompassed several dietary changes. As a result, it is not possible to estimate the specific influence of increasing fruit and vegetables intake.

Evidence for the specific benefits of an increase in fruit and vegetable intake on cardiovascular health comes from the IEIS and the DASH trial.

Table 9.28 Summary of relative risks (95% CI), for selected diseases with increased fruit and vegetable consumption by age group

	Age group (years)							
Outcome	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
Ischaemic heart disease	1.00	1.00	0.90 (0.82–0.99)	0.90 (0.82–0.99)	0.90 (0.82–0.99)	0.90 (0.82–0.99)	0.93 (0.85–1.01)	0.95 (0.87–1.03)
Ischaemic stroke	1.00	1.00	0.94 (0.89–0.99)	0.94 (0.89–0.99)	0.94 (0.89–0.99)	0.94 (0.89–0.99)	0.95 (0.91–1.00)	0.97 (0.92–1.02)
Lung cancer	1.00	1.00	0.96 (0.93–0.99)	0.96 (0.93–0.99)	0.96 (0.93–0.99)	0.96 (0.93–0.99)	0.97 (0.91–1.02)	0.98 (0.92–1.03)
Gastric cancer	1.00	1.00	0.94 (0.86–1.03)	0.94 (0.86–1.03)	0.94 (0.86–1.03)	0.94 (0.86–1.03)	0.95 (0.87–1.04)	0.97 (0.89–1.06)
Colorectal cancer	1.00	1.00	0.99 (0.97–1.02)	0.99 (0.97–1.02)	0.99 (0.97–1.02)	0.99 (0.97–1.02)	0.99 (0.97–1.02)	1.00 (0.97–1.02)
Oesophageal cancer	1.00	1.00	0.94 (0.88–1.01)	0.94 (0.88–1.01)	0.94 (0.88–1.01)	0.94 (0.88–1.01)	0.95 (0.89–1.02)	0.97 (0.91–1.04)

Note: Unit of change in risk is change per 80 g/day increase in fruit and vegetable intake.

As was described in section 3.1, the IEIS showed that after only one year, cardiac events and mortality were reduced by 40% and 45%, respectively, in a group of men who had previously suffered an acute myocardial infarction and who followed a low-fat fruit and vegetable-rich diet compared with men on a standard low-fat diet (Singh et al. 1993a). The DASH trial showed that hypertensive individuals achieved a reduction in their blood pressure after eight weeks of dietary changes (Conlin et al. 2000; Obarzanek et al. 2001). Both a diet rich in fruit and vegetables and a combination diet rich in fruit and vegetables and low in saturated fat, fat and cholesterol reduced systolic and diastolic blood pressure. After eight weeks, 70% of the participants on a combination diet rich in fruit and vegetables and low in saturated fat, fat and cholesterol, had a normal blood pressure, with 45% of those on a diet rich in fruit and vegetables, and 23% of those on a control diet. The true long-term effect of such dietary changes needs to be assessed using studies of longer duration.

Further evidence for risk reversibility of cardiovascular disease comes from time series analyses in countries of central and eastern Europe. One natural experiment in terms of rapid dietary change occurred with the reunification of Germany in 1989. After reunification, fruit and vegetable availability increased markedly, doubling between 1989 and 1992 (J.W. Powles, personal communication, 2001). But although the previous decline in vascular disease mortality accelerated, the change of trend was not noticeably greater than that in Poland and the Czech and Slovak republics where the increase in fruit and vegetable consumption was almost certainly less marked. However, the results of an ecological study performed in Poland suggested that the observed increase in supply of fresh fruit and vegetables and changes in the type of dietary fat between 1986–1990 and 1994 may have had a short-term positive effect on mortality risk (Zatonski et al. 1998). This study investigated the reasons for the decline in deaths attributed to IHD in Poland since 1991 after two decades of rising rates. For most of the potentially explanatory variables studied (i.e. alcohol consumption, cigarette smoking, socioeconomic indices and medical services) there were no corresponding changes in trend. The authors concluded that dietary changes could provide the best explanation to the reduced IHD mortality rates, with an effect noticeable within four years. While these findings cannot be dismissed, due to the limitations of ecological studies, these exploratory analyses would need to be confirmed with stronger study designs.

Cancer

The evidence for cancer outcomes is more limited and comes from one major source. The NHS/HPFS studies have both collected dietary intake data repeatedly during a long follow-up period. This enables the examination of the temporal aspects of diet–cancer associations, although this has not yet been published for all the cancer outcomes covered in this

report. For lung cancer risk, the findings support a relatively long latency period for carotenoids (used as a proxy for fruit and vegetable intake), consistent with the known natural history of the disease, and suggest that the critical period for exposure to carotenoids to maximize protection may be between four to eight years before diagnosis (Michaud et al. 2000). This may explain why some observational studies and short supplement intervention trials may not have detected a significant association.

Proposed risk reversibility for the CRA project

Assuming that the future population intake of fruit and vegetables is increased to the proposed counterfactual, we propose the following estimates of risk reduction:

- ten per cent reduction in relative risk in four years for IHD and stroke; and
- ten per cent reduction in relative risk in eight years for cancer outcomes.

Due to the current limitations of the evidence, it is assumed that risk reversibility following an increase in fruit and vegetable consumption is age independent and that it does not vary among subregions. As this may not be the case, the estimates should be seen as first approximations. Due to the high level of uncertainty, it is proposed that a ±10% range of error is included in the calculations of avoidable burden for the CRA project.

3.9 Quantitative and qualitative sources of uncertainty in measuring the diet–disease relationship

There are several sources of uncertainty in risk assessment. Some of these will be described in this section with regard to the study of the relationship between fruit and vegetable intake and health outcomes. It is likely that these underestimate the true level of uncertainty that affected the estimates presented in this report.

Little is known of the relative importance of early and late dietary exposure of fruit and vegetables for the risk of the chronic diseases examined in this report. Results from the Boyd Orr cohort suggest that fruit and vegetable intake in childhood could have a protective effect on the risk of cancer in adulthood (Maynard et al. 2003). However, we do not know whether an increased intake of fruit and vegetables is more important in young or middle age for greatest risk reversibility. Hence, it is not possible to comment on how the time trends of risk reversibility may vary among age groups.

In this project, it was assumed that there was no difference in relative risk across populations. However, it is not possible to verify whether this assumption is true as the study populations covered by the literature review were from limited geographical areas and ethnic groups. The

majority of cohort studies were from China, Japan, the United States and Europe, although there was at least one case–control study from the following countries: Australia, Brazil, China (Hong Kong SAR), India, Mexico, the Republic of Korea, Singapore, Turkey, Uruguay and Venezuela.

Relative risks in the developed world may not provide good estimates of the effect in the less developed world. For example, the impact of increasing fruit and vegetable intake may be stronger in undernourished, micronutrient-poor (e.g. vitamin A deficiency) populations in developing countries. However, this has to be considered in the wider context of nutritional requirements (energy and protein may be more important for survival in some populations) and relative causes of deaths (non-communicable diseases may not be as important killers as in developed countries).

One possibility refers to the ascertainment of exposure. There remains considerable uncertainty as to which constituents, or combination of constituents, of fruit and vegetables would confer a protective effect. Several components have been suggested, but it is unlikely that any single compound will capture the benefits, which seem to arise from a varied diet rich in fruit and vegetables. The sources of uncertainty described for exposure measurement in section 2.9 also need to be taken into account here. Errors in measurement of dietary intake mean that the strength of true associations, if they exist, is likely to be reduced. In addition, the definition of the exposure as "fruit and vegetables" introduces a substantial amount of non-specificity with the resultant potential attenuation of underlying causal relations. That is, the currently unknown active constituents contained within the category "fruit and vegetables" are likely to have a varying quantitative relationship to the less specific category of fruit and vegetables. This is especially important across food cultures with substantial differences in the make-up of foods that constitute the fruit and vegetable group, but also applies even within cultures because of differences in food composition. At a minimum, this suggests that findings of protective associations between fruit and vegetable consumption and a specific disease within one food culture may not generalize well to another culture where the fruit and vegetables in the diet are constituted by different foods—in which the causally active constituents may be present to substantially differing amounts.

Another major source of uncertainty refers to the fact that confounding is a real possibility in observational studies of the relationship between fruit and vegetable intake and health outcomes. Although the studies considered in this project have attempted to adjust for confounding, measurement error in the assessment of potential confounders and the possibility of residual confounding need to be considered.

4. Discussion of estimates of attributable burden

The results of the analysis showed that a lack of dietary fruit and vegetables contributes an important share of the worldwide disease burden. It was estimated that increasing individual fruit and vegetable consumption up to the theoretical-minimum-risk distribution could reduce the worldwide burden of disease for IHD and ischaemic stroke by about 31% (30% for men and 31% for women) and 19% (18% for men and 19% for women), respectively. For cancers of the stomach and oesophagus, the potential reduction in disease attributable to an increase in fruit and vegetable intake was 19% and 20%, respectively. Attributable risk fractions were lower for lung and colorectal cancers (12% and 2%).

There were relatively few sex and age differences in the attributable fractions of disease attributable to low fruit and vegetable consumption, mainly because relative risk estimates were assumed to be constant in all adult men and women. However, larger variations were observed in the estimates of attributable DALYs due to low fruit and vegetable intake, as this is a function of both the attributable fractions and the amount of burden of disease accounted for by each health outcome studied in the various age–sex groups, itself affected by other risk factors. The number of DALYs was generally higher in men (except for stroke). As expected for chronic diseases, it tended to be lower in young adults.

There were some subregional variations in the attributable risk fractions and number of DALYs attributable to low fruit and vegetable intake. These tended to reflect differences in exposure levels and disease patterns among subregions.

The total worldwide mortality attributable to inadequate fruit and vegetable consumption was estimated to be 2.726 million deaths or 26.662 million DALYs in 2000. These results need to be interpreted in the light of the current limitations of the methods used, as described earlier in the chapter (e.g. residual confounding, misclassification of exposure). However, they highlight that increasing fruit and vegetable consumption could play an important role in improving public health worldwide.

5. Methods for projection of future exposure

An aggregate approach based on subregional trends in fruit and vegetable availability was used to project future exposure levels. The methods used are described below.

5.1 Trends in fruit and vegetable availability over time

The projection of future fruit and vegetable consumption for the years 2000 to 2030 was based primarily on the observation of subregional

trends in fruit and vegetable availability. The FAO food balance sheet data (FAO 2001) show that there has been an overall worldwide increase in the availability of fruit and vegetables during the past decades. However, large variations exist, among subregions and countries, in the observed trends and amounts available. These variations are described below.

FAO food balance sheet statistics (1961–1999) for each country were used to calculate three-year average subregional fruit and vegetable availability. These calculations show that there has been a relatively steady increasing trend in availability in AMR-A, AMR-B, EMR-D, EUR-A, SEAR-B, SEAR-D and WPR-B between 1961 and 1999. In contrast, downward trends have been observed since the late 1970s or early 1980s in WPR-A and AFR-E. However, as the trend has been slowing down in WPR-A during the last decade, we also assumed that the downward trend would stop. Based on the observed trends in AFR-D, we also assumed that the downward trend would stop in AFR-E. Large fluctuations were observed in AFR-D between 1961 and 1981, followed by a relatively steady increase in fruit and vegetable availability. In AMR-D, the trend also was downwards between the late 1960s until the early 1990s, but this has been followed by a small recovery. In EMR-B, a steep increase was seen between the early 1970s until the mid-1980s. This was followed by a decrease in fruit and vegetable availability between about 1985 and 1990. Thereafter, the trend has been upward again. Finally, in EUR-B and EUR-C, the general increase in fruit and vegetable availability observed during the 1960s, 1970s and early 1980s was followed by a 10-year decrease in availability. This coincided with the significant political and economic changes that occurred in the subregion before and after the collapse of the former Soviet Union. Around 1993/1994, the trend then changed and a recovery was observed. The current upward trend is relatively gradual in EUR-C, but relatively steep in EUR-B.

5.2 Predicting subregional fruit and vegetable intake to 2030

In order to predict subregional fruit and vegetable intakes by age and sex between 2000 and 2030, a two-step process was used. First, the predicted subregional availability figures were obtained using linear regression analyses with fruit and vegetable availability and time (years) as the dependent and independent variables, respectively. For subregions where a relatively steadily increasing trend was observed (AMR-A, AMR-B, EMR-D, EUR-A, SEAR-B, SEAR-D and WPR-B), FAO data from 1961 onwards were used. For WPR-A and AFR-E, it was conservatively assumed that a plateau was reached during the prediction period. For the other subregions, a case-by-case approach was used based on the trends observed. For AFR-D and AMR-D, 1978 and 1992 were used as respective cut-off points for the regression analyses, as these years rep-

resented a point in time where a steep downward trend was stopped. Both EUR-B and EUR-C have experienced large fluctuations recently, and it is thus very difficult to predict future trends. For EUR-C, 1993 was selected as a cut-off since the downward trend slowed down from that point in time. The conservative increasing trend from 1993 onwards was thus used to predict future fruit and vegetable availability in that subregion. In EUR-B, a steep upward trend was observed from 1993. However, it is assumed that this trend will slow down and thus the average of the trend from 1993 onwards and the trend during the last two decades (1980+) was arbitrarily chosen. A similar approach was used for EMR-B where it is assumed that the observed trend since 1988 is too steep to reflect future projections.

The second step calculated the proportional changes in fruit and vegetable availability between 1997 (arbitrarily selected as representing the time when intake data were obtained) and 2000, 2005, 2010, 2015, 2020, 2025 and 2030. These were then applied to the intake data presented in section 2.8, assuming the same proportional increase in intakes in both genders and all age groups within each subregion.

The results obtained for AMR-D, EMR-B, EUR-B and EUR-C, which are based on smaller numbers of data points, should be treated with particular caution.

5.3 Limitations of the methods

The results obtained for the projected fruit and vegetable intakes need to be treated with caution as the approach used has several limitations. One major limitation is related to the lack of time trend data on fruit and vegetable intake around the world, and the resulting need to base the calculations on food balance sheet data. Availability statistics can be a useful tool to observe trends in food availability in the past. However, predicting availability in the future (outside the range of available data) using linear regression analysis and making the assumption that trends will not change, may lead to false conclusions as current trends may change in the next 30 years for many reasons. For example, had we undertaken this analysis for EUR-C 10 years previously, the results would have been completely different. The values obtained for EMR-B, for example, appear to be too high compared with those obtained for the other subregions. In addition, as food balance sheets reflect food availability and not food intake, it is not possible to know whether the relative changes in availability are explained by variations in intakes or by other changes such as an increase in waste at the household level.

Predicting fruit and vegetable consumption is especially difficult because of the range of factors influencing dietary intakes, including food availability, economic situation, seasons, cultural preferences, fashions and knowledge and potential interactions between these factors. To base future estimates of fruit and vegetable intake on the predicted levels of any one of these factors (e.g. predicted gross national product [GNP] of

a country in 20 years) is not justified, in part due to the lack of information on future trends in these factors themselves. Furthermore, assumptions of such relationships would overlook the multiple determinants of diet. For example, we have seen that intakes vary considerably among countries with similar GNP (e.g. Ireland, Italy and the United Kingdom). Thus, the predictions presented in this chapter simply assume a continuation of complex patterns of social, economic and agricultural development of these countries in recent years.

Acknowledgements

We would like to thank Dan Altmann, Majid Ezzati and Steve Vander Hoorn for their statistical advice. The Stata program used to implement the method of Greenland and Longnecker was written and tested by Ian White.

We also wish to thank Aileen Robertson for her contributions, and to acknowledge the help of many people worldwide who provided us with data on fruit and vegetable intake, those who helped us identify potential sources of intake data and research evidence, and all those who offered advice on methods (see list below).

We would like to thank M.E. Rio, L. Cappelen, M.C. Perez Somigliana, N.M. de Parada, N. Piazza, B. Houssay, H. Lareyna, S. Closa, K. Baghurst, S. Record, S. De Henauw, S. Petrova, S. Fagt, M. Lahti Koski, G.B.M. Mensink, S. Friel, D. Nitzan Kaluski, R. Goldberg, A. Turrini, Y. Matsumura, N. Yoshiike, T. Sharmanov, J. Rivera Dommarco, L. Johansson, M. Deurenberg-Yap, T-Bee Yian, C. Suok-Kai, J.S. Hampl and B.M. Popkin for providing us with data stratified according to the GBD age–sex categories.

Further acknowledgements go to: M.A.G. Bendech, M.K. Gabr, C. Fatoumata, F. Staubli Asobayire, P. Bovet, D. Labadarios, N. Stein, N.A. Ouedraogo, A. Pacin, L. Cappelen, M.C. Perez Somigliana, N. Marcilla, N. Piazza, H. Lareina, S. Closa, M.E. Gomez del Rio, D.R. Petteta, J. Montero, M. Esther, A. Achutti, R. Costa Ribeiro, M. Pastor, C.A. Monteiro, F. Begin, E. Boy, S. Alary, B. Choi, C. Koeune, P. Fisher, M. Houde Nadeau, S. Kirkland, C. Leinweber, L. Marrett, J. MacDonald, T. Wolever, O.F. Herran Falla, A. Rodriguez-Ojea, J. Gonzalez, F. Henry, J. Rivera Dommarco, C.P. Sanchez-Castillo, B. Popkin, T. Forrester, W. Freire, J. Potter, C. Garza, N. Scrimshaw, E. Murray, L.B. Dixon, J. Hampl, J. Hart, J. Kause, J. McClelland, S. McPherson, Lee Soo-Kyung, P. Terry, J.R. Hebert, P. Kaufmann, C. Junshi, W. Zhao, C. Chumming, J. Chen, J. Woo Wong, S. Sung, R. Gupta, H. Soori, Y. Matsumura, S. Mizushima, K. Ogawa, N.M. Al Hamad, N. Hwalla Baba, S. Jabbour, S. Reijo, J.A. Al Lawati, L.T. Cavalli-Sforza, M.O.O. Alcantara, C. Suok-Kai, M. Deurenberg-Yap, T. Bee-Yian, K. Cho-il Kim, W.H. Pan, S. Durongkadaj, P. Rawdaree, P. Chompook, L. Georgieva, S. Petrova, A. Kaic-Rak, Z. Brázdová, A.M. Beck, L. Ovesen, S. Fagt, J.

Haraldsdóttir, J.M. Lauritsen, A. Kasmel, S. Vaask, M. Lahti-Koski, R. Prattala, P. Knekt, M. Chauliac, J.L. Volatier, C. Cohidon, S. Hercberg, P. Wild, T. Norat, E. Riboli, K. Nemsadze, L. Bregvadze, G. Mensink, A. Potz, W. Sichert-Hellert, M. Thamm, G. Biro, P. Józan, J. Fodor, M. Szabo, T. Varga, G. Zajkás, J.M. Kearney, S. Friel, D. Kaluski, R. Goldsmith, F. Branca, A. Turrini, A. Ferro-Luzzi, A. Zucchi, P. Merrikin, B. Sarbayev, T.S. Sharmanov, G. Abuova, I. Pudule, M. Ellul, K .Hulshof, C.A.J. van Mierlo, H. Boshuizen, B. Blaker, L. Johansson, L. Szponar, P. Graça, P. Moreira, A.D. Deev, J. Maucec Zakotnik, B. Tivadar, A. Agudo, J. De Irala Estevez, O. Moreiras, I. López Azpiazu, K. Manderbacka, S. Hess, F.S. Asobayire, P. Bovet, E. Brunner, N. Day, A. Draper, S. Green, L. Hayes, P. James, K.T. Khaw, T. Lobstein, A. Ness, J. Powles, I. Sharp, H. Teomainen, M. Thorogood, P. Warner, T. Vos, K. Baghurst, S. Record, M. Coad, M. Anthea Magarey, E. Rutishauser Engel, I. Coles-Rutishauser, M. Watson, D. Woodward, D. Schulz, L. Andrew, K. Sladden and M. Tobias.

This work was supported by a grant from the English Department of Health. However, the English Department of Health cannot accept responsibility for any information provided or views expressed.

Notes

1 See preface for an explanation of this term.

2 Estimating the subregional mean

- *Estimation of the subregional (pooled) mean*:

  $\hat{\mu} = \dfrac{\sum N_i \times \bar{x}_i}{\sum N_i}$ where $i = 1, \ldots, k$ sampled countries, N_i is the population of the ith country and $\bar{x}_i$ is the mean of the ith country.

- *95% confidence interval (CI) for this estimator*:

  The variance of this estimator can be derived using:

  $$Var(\hat{\mu}) = \left(\frac{1}{\sum N_i}\right)^2 Var(\sum N_i \times \bar{x}_i)$$

  and assuming the means are independent

  $$= \left(\frac{1}{\sum N_i}\right)^2 \sum Var(N_i \times \bar{x}_i) = \left(\frac{1}{\sum N_i}\right)^2 \sum N_i^2 Var(\bar{x}_i)$$

  Where now:

  $Var(\bar{x}_i) = \dfrac{s_i^2}{n_i}\left(1 - \dfrac{n_i}{N_i}\right)$, with s_i the standard deviation for the ith country, sample size n_i.

  The term $\left(1 - \dfrac{n_i}{N_i}\right)$ is the finite population correction.

  The standard error of the estimator is the square root of the variance.

  The 95% CI for the subregional (pooled) mean is calculated as:

= Subregional mean ± (1.96 x standard error of this estimator)

Estimating the subregional standard deviation

- *Estimation of the subregional (pooled) variance and standard deviation*:

$$\hat{\sigma}^2 = \frac{\sum N_i \times s_i^2}{\sum N_i} = \hat{\sigma}^2 = \frac{\sum N_i \times s_i^2}{N}$$

where σ^2 = pooled variance for the subregion, $I = 1, \ldots, k$ sampled countries, N_i is the population of the ith country and s_i^2 is the variance (square of SD) of the ith country; N is the sum of the N_i, in other words the sum of the populations of the sampled countries. This is unbiased because the expected value of a sample country's variance is the subregional variance, that is, $E(s_i^2) = \sigma^2$,

then $E(\hat{\sigma}^2) = \frac{1}{N}\sum N_i E(s_i^2) = \frac{1}{N}\sigma^2 \sum N_i = \sigma^2$

- *95% CI for this estimator*:

The 95% CI for the subregional (pooled) variance $(\hat{\sigma}^2)$ is approximated using:

Lower CI = Subregional variance x $(n - 1) / \chi^2(n - 1, 0.025)$

Upper CI = Subregional variance x $(n - 1) / \chi^2(n - 1, 0.975)$

where $n = (\sum n_i)$ and n_i is the sample size for the ith country: n is thus the total size of the sample taken from the subregion.

REFERENCES

Agudo A, Esteve MG, Pallares C et al. (1997) Vegetable and fruit intake and the risk of lung cancer in women in Barcelona, Spain. *European Journal on Cancer*, **33**:1256–1261.

Ahmad K, Hassan N (1982) *Nutrition survey of rural Bangladesh*. Institute of Nutrition and Food Science, Dhaka University, Dhaka.

Andersen NL, Fagt S, Groth MV et al. (1996) *Danskernes kostvaner 1995 [Danish dietary patterns 1995]*. National Food Agency, Copenhagen. (In Danish; English summary).

Anonymous (1994) The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study group. *New England Journal of Medicine*, **330**:1029–1035.

Ascherio A, Rimm EB, Hernan MA et al. (1998) Intake of potassium, magnesium, calcium and fiber and risk of stroke among US men. *Circulation*, **98**:1198–1204.

Ascherio A, Rimm EB, Hernan MA et al. (1999) Relation of consumption of vitamin E, vitamin C and caretonoids to risk for stroke among men in the United States. *Annals of Internal Medicine*, **130**:963–970.

Awad AB, Downie A, Fink CS, Kim U (2000) Dietary phytosterol inhibits the growth and metastasis of MDA-MB-231 human breast cancer cells grown in SCID mice. *Anticancer Research*, **20**:821–824.

Axelsson G, Liljeqvist T, Andersson L, Bergman B, Rylander R (1996) Dietary factors and lung cancer among men in west Sweden. *International Journal of Epidemiology*, **25**:32–39.

Bates C, Thurnham S, Bingham S, Margetts B, Nelson M (1991) Biochemical markers of nutrient intake. In: *Design concepts in nutritional epidemiology*. Margetts B, Nelson M, eds. Oxford Medical Publications, Oxford.

Bazzano LA, He J, Ogden LG et al. (2001) Dietary potassium intake and risk of stroke in US men and women: National Health and Nutrition Examination Survey I epidemiologic follow-up study. *Stroke*, **32**:1473–1480.

Bazzano L, Ogden LG, Vupputur IS, Loria C, Meyers L, Whelton PK (2000) *Fruit and vegetable intake reduces cardiovascular disease mortality: results from the NHANES I epidemiologic follow-up study (NHEFS)*. American Heart Association, 40th Annual Conference on Cardiovascular Disease Epidemiology and Prevention. San Diego, CA.

Benito E, Obrador A, Stiggelbout A et al. (1990) A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *International Journal of Cancer*, **45**:69–76.

Bidoli E, Franceschi S, Talamini R, Barra S, La Vecchia C (1992) Food consumption and cancer of the colon and rectum in north-eastern Italy. *International Journal of Cancer*, **50**:223–229.

Bingham SA, Gill, C, Welch, A et al. (1994) Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. *British Journal of Nutrition*, **72**:619–643.

Bingham SA, Gill C, Welch A et al. (1997) Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *International Journal of Epidemiology*, **26**:S137–151.

Bingham SA, Nelson M, Paul AA, Haraldsdottir J, Løken EB, van Staveren WA (1988) Methods of data collection at an individual level. In: *Manual on methodology for food consumption studies*. Cameron ME, van Staveren WA, eds. Oxford University Press, Oxford.

Blot WJ, Li JY, Taylor PR, Guo W, Dawsey SM, Li B. (1995) The Linxian trials: mortality rates by vitamin-mineral intervention group. *American Journal of Clinical Nutrition*, **62**:S1424–1426.

Boeing H, Frentzel-Beyme R, Berger M et al. (1991a) Case-control study on diet and stomach cancer in Germany. *International Journal of Cancer*, **47**: 858–864.

Boeing H, Jedrychowski W, Wahrendorf J, Popiela T, Tobiasz-Adamczyk B, Kulig A (1991b) Dietary risk factors in intestinal and diffuse types of stomach cancer: a multicenter case-control study in Poland. *Cancer Causes and Control*, **2**:227–233.

Bond GG, Thompson FE, Cook RR (1987) Dietary vitamin A and lung cancer: results of a case-control study among chemical workers. *Nutrition and Cancer*, **9**:109–121.

Bosetti C, La Vecchia C, Talamini R et al. (2000) Food groups and risk of squamous cell esophageal cancer in northern Italy. *International Journal of Cancer*, **87**:289–294.

Boshuizen HC, Bueno-de-Mesquita HB, Altenburg HP et al. (2002) Adjustment for smoking in lung cancer analyses in the EPIC cohort. *IARC Scientific Publications*, **156**:59–61.

Botterweck AA, van den Brandt PA, Goldbohm RA (1998) A prospective cohort study on vegetable and fruit consumption and stomach cancer in the Netherlands. *American Journal of Epidemiology*, **148**:842–853.

Botterweck AA, van den Brandt PA, Goldbohm RA (2000) Vitamins, carotenoids, dietary fiber, and the risk of gastric carcinoma. *Cancer*, **88**:737–748.

Boushey CJ, Beresford SA, Omenn GS, Motulsky AG (1995) A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. *Journal of the American Medical Association*, **274**:1049–1057.

Brennan P, Fortes C, Butler J et al. (2000) A multicenter case-control study of diet and lung cancer among non-smokers. *Cancer Causes and Control*, **11**:49–58.

Breslow RA, Graubard BI, Sinha R, Subar AF (2000) Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. *Cancer Causes and Control*, **11**:419–431.

Brigelius-Flohe R, Traber MG (1999) Vitamin E: function and metabolism. *FASEB Journal*, **13**:1145–1155.

Brown LM, Blot WJ, Schuman SH et al. (1988) Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *Journal of the National Cancer Institute*, **80**:1620–1625.

Brown LM, Swanson CA, Gridley C et al. (1995) Adenocarcinoma of the esophagus: role of obesity and diet. *Journal of the National Cancer Institute*, **87**:104–109.

Brown LM, Swanson CA, Gridley et al. (1998) Dietary factors and the risk of squamous cell esophageal cancer among black and white men in the United States. *Cancer Causes and Control*, **9**:467–474.

Buiatti E, Palli D, Decarli A et al. (1989) A case-control study of gastric cancer and diet in Italy. *International Journal of Cancer*, **44**:61–616.

Burr ML, Fehily AM, Gilbert JF et al. (1989) Effects of changes in fat, fish and fibre intakes on death and myocardial infarction: diet and reinfarction trial (DART). *The Lancet*, **2**:757–761.

Byers TE, Graham S, Haughey BP, Marshall JR, Swanson MK (1987) Diet and lung cancer risk: findings from the Western New York Diet Study. *American Journal of Epidemiology*, **125**:351–363.

Cameron M, van Staveren WA (1988) *Manual on methodology for food consumption studies*. Oxford University Press, Oxford.

Candelora EC, Stockwell HG, Armstrong AW, Pickham PA (1992) Dietary intake and risk of lung cancer in women who never smoked. *Nutrition and Cancer*, **17**:263–270.

Castellsague X, Munoz N, De Stefani E, Victoria CG, Castelletto R, Rolon PA (2000) Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *International Journal of Cancer*, **88**:658–664.

Chambers JC, Seddon MD, Shah S, Kooner JS (2001) Homocysteine—a novel risk factor for vascular disease. *Journal of Royal Society of Medicine*, **94**:10–13.

Chen LY, Jokela R, Li DY et al. (2000) Effect of stable fish oil on arterial thrombogenesis, platelet aggregation, and superoxide dismutase activity. *Journal of Cardiovascular Pharmacology*, **35**:502–505.

Cheng KK, Day NE (1996) Nutrition and esophageal cancer. *Cancer Causes and Control*, **7**:33–40.

Cheng KK, Day NE, Davies TW (1992) Oesophageal cancer mortality in Europe: paradoxical time trend in relation to smoking and drinking. *British Journal of Cancer*, **65**:613–617.

Cheng KK, Day NE, Duffy SW, Lam TH, Fok M, Wong J (1992) Pickled vegetables in the aetiology of oesophageal cancer in Hong Kong Chinese. *The Lancet*, **339**:1314–1318.

Cheng KK, Duffy SW, Day NE, Lam TH (1995) Oesophageal cancer in never-smokers and never-drinkers. *International Journal of Cancer*, **60**: 820–822.

Cheng KK, Sharp L, McKinney PA et al. (2000) A case-control study of oesophageal adenocarcinoma in women: a preventable disease. *British Journal of Cancer*, **83**:127–132.

Chow WH, Schuman LM, McLaughlin JK et al. (1992) A cohort study of tobacco use, diet, occupation, and lung cancer mortality. *Cancer Causes and Control*, **3**:247–254.

Chyou PH, Nomura AM, Hankin JH, Stemmermann GN (1990) A case-cohort study of diet and stomach cancer. *Cancer Research*, **50**:7501–7504.

Coggon D, Barker DJ, Cole RB, Nelson M (1989) Stomach cancer and food storage. *Journal of the National Cancer Institute*, **81**:1178–1182.

Collins R, Peto R, Armitage J (2002) The MRC/BHF Heart Protection study: preliminary results. *International Journal of Clinical Practice*, **56**:53–56.

Conlin PR, Chow D, Miller ER 3rd et al. (2000) The effect of dietary patterns on blood pressure control in hypertensive patients: results from the Dietary Approaches to Stop Hypertension (DASH) trial. *American Journal of Hypertension*, **13**:949–955.

Cornee J, Pobel D, Riboli E, Guyader M, Hemon B (1995) A case-control study of gastric cancer and nutritional factors in Marseille, France. *European Journal of Epidemiology*, **11**:55–65.

Correa P, Fontham ET, Bravo JC et al. (2000) Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*helicobacter pylori* therapy. *Journal of the National Cancer Institute*, **92**:1881–1888.

Correa P, Fontham E, Pickle LW, Chen V, Lin YP, Haenszel W (1985) Dietary determinants of gastric cancer in south Louisiana inhabitants. *Journal of the National Cancer Institute*, **75**:645–654.

Darby S, Whitley E, Doll R, Key TJA, Silcocks P (2001) Diet, smoking and lung cancer: a case control study of 1000 cases and 1500 controls in south-west England. *British Journal of Cancer*, **84**:728–735.

Daviglus ML, Orencia AJ, Dyer AR et al. (1997) Dietary vitamin C, beta-carotene and 30-year risk of stroke: results from the Western Electric study. *Neuroepidemiology*, **16**:69–77.

Day NE, Ferrari P (2002) . Some methodological issues in nutritional epidemiology. *IARC Scientific Publications*, **156**:5–10.

Day N, McKeown N, Wong M, Welch A, Bingham S (2001) Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. *International Journal of Epidemiology*, **30**:309–317.

De Henauw S, De Backer G (1999) Nutrient and food intakes in selected subgroups of Belgian adults. *British Journal of Nutrition*, **81**:S37–42.

de Lorgeril M, Renaud S, Mamelle N et al. (1994) Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *The Lancet*, **343**:1454–1459.

de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N (1999) Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart study. *Circulation*, **99**:779–785.

Decarli A, Liati P, Negri E, Franceschi S, La Vecchia C (1987) Vitamin A and other dietary factors in the etiology of esophageal cancer. *Nutrition and Cancer*, **10**:29–37.

Demirer T, Icli F, Uzunalimoglu O, Kucuk O (1990) Diet and stomach cancer incidence. A case control study in Turkey. *Cancer*, **65**:2344–2348.

Deneo-Pellegrini PH, De Stephani E, Ronco A (1996) Vegetables, fruits, and risk of colorectal cancer: a case-control study from Uruguay. *Nutrition and Cancer*, **25**:297–304.

DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Controlled Clinical Trials*, **7**:177–188.

Directorate of Intelligence (2000) *World fact book 2000*. Central Intelligence Agency, Washington, DC.

Dorgan JF, Ziegler RG, Schoenberg JB et al. (1993) Race and sex differences in associations of vegetables, fruits and carotenoids with lung cancer risk in New Jersey (United States). *Cancer Causes and Control*, **4**:273–281.

Egger M, Schneider M, Davey Smith G (1998) Spurious precision? Meta-analysis of observational studies. *British Medical Journal*, **316**:140–144.

Ekstrom AM, Serafini M, Nyren O, Hansson LE, Ye W, Wolk A (2000) Dietary antioxidant intake and the risk of cardia cancer and noncardia cancer of the interstitial and diffuse types: a population-based case-control study in Sweden. *International Journal of Cancer*, **87**:133–140.

Elwood PC, Fehily AM, Ising H, Poor DJ, Pickering J, Kamel F (1996) Dietary magnesium does not predict ischaemic heart disease in the Caerphilly cohort. *European Journal of Clinical Nutrition*, **50**:694–697.

Faivre J, Boutron MC, Senesse P, Couillault C, Belighiti C, Meny B (1997) Environmental and familial risk factors in relation to the colorectal-carcinoma sequence: results of a case-control study in Burgundy (France). *European Journal of Cancer Prevention*, **6**:127–131.

Fehily AM, Yarnell JW, Sweetnam PM, Elwood PC (1993) Diet and incident ischaemic heart disease: the Caerphilly study. *British Journal of Nutrition*, **69**:303–314.

Feskanich D, Ziegler R, Michaud DS et al. (2000) Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *Journal of the National Cancer Institute*, **92**:1812–1823.

Finch S, Doyle, W, Lowe C, Bates C, Prentice A, Smithers G, Clarke PC (1998) *National diet and nutrition survey—people aged 65 years and over*. HMSO, London.

Findiet Study Group (1998) *Dietary survey of Finnish adults 1997*. National Public Health Institute, Helsinki.

Fontham ET, Pickle LW, Haenszel W, Correa P, Lin YP, Falk RT (1988) Dietary vitamin A and C and lung cancer risk in Louisiana. *Cancer*, **62**:2267–2273.

FAO (1983) *A comparative study of food consumption data from food balance sheets and household surveys*. Food and Agriculture Organization of the United Nations, Rome.

FAO (1998a) *Nutrition country profile: Nepal*. Food and Agriculture Organization of the United Nations, Rome.

FAO (1998b) *Nutrition country profile: Pakistan*. Food and Agriculture Organization of the United Nations, Food and Nutrition Division, Rome.

FAO (2001) *FAOSTAT*. Available at http://apps.fao.org/. Food and Agriculture Organization of the United Nations, Rome (checked February 28, 2003).

Forman MR, Yao SX, Graubard BI et al. (1992) The effect of dietary intake of fruits and vegetables on the odds ratio of lung cancer among Yunnan tin miners. *International Journal of Epidemiology*, **21**:437–441.

Franceschi S, Bidoli E, La Vecchia C, Talamini R, D'Avanzo B, Negri E (1994) Tomatoes and risk of digestive-tract cancers. *International Journal of Cancer*, **59**:181–184.

Francecshi S, Favero A, La Vecchia C et al. (1997) Food groups and risk of colorectal cancer in Italy. *International Journal of Cancer*, **72**:56–61.

Franceschi S, Parpinel M, La Vecchia C, Favero A, Talamini R, Negri E (1998) Role of different types of vegetables and fruit in the prevention of cancer of the colon, rectum and breast. *Epidemiology*, **9**:338–341.

Fraser GE, Beeson WL, Phillips RL (1991) Diet and lung cancer in California Seventh-day Adventists. *American Journal of Epidemiology*, **133**:683–693.

Fraser GE, Sabate J, Beeson WL, Strahan TM (1992) A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist health study. *Archives of Internal Medicine*, **152**:1416–1424.

Freudenheim JL, Graham S, Horvath PJ, Marshall JR, Haughey BP, Wilkinson G (1990) Risk associated with source of fiber and fiber components in cancer of the colon and rectum. *Cancer Research*, **50**:3295–3300.

Friel S, NicGabhann S, Kelleher C (1999) *The National Health and Lifestyle Survey (SLÁN)—Survey of lifestyles, attitudes and nutrition*. Health Promotion Unit/NUI Galway, Dublin.

Fuchs CS, Giovannucci, EL, Colditz GA et al. (1999) Dietary fiber and the risk of colorectal cancer and adenoma in women. *New England Journal of Medicine*, **340**:169–176.

Galanis DJ, Kolonel LN, Lee J, Nomura A (1998) Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *International Journal of Epidemiology*, **27**:173–180.

Gale CR, Martyn CN, Winter PD, Cooper C (1995) Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. *British Medical Journal*, **310**:1563–1566.

Gandini S, Merzenich H, Robertson C, Boyle P (2000) Meta–analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. *European Journal of Cancer*, **36**:636–646.

Gao C, Tajima K, Kuroishi T, Hirose K, Inoue M (1993) Protective effects of raw vegetables and fruit against lung cancer among smokers and ex-smokers: a case-control study in the Tokai area of Japan. *Japanese Journal of Cancer Research*, **84**:594–600.

Gao YT, McLaughlin JK, Gridley G et al. (1994) Risk factors for esophageal cancer in Shanghai, China. II. Role of diet and nutrients. *International Journal of Cancer*, **58**:197–202.

Garcia-Closas R, Gonzales CA, Agudo A, Riboli E (1999) Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. *Cancer Causes and Control*, **10**:71–75.

Garidou A, Tzonou A, Lipworth L, Signorello LB, Kalapothaki V, Trichopoulos D (1996) Life-style factors and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. *International Journal of Cancer*, **68**:295–299.

Gaziano JM (1996) Antioxidants in cardiovascular disease: randomized trials. *Nutrition*, **12**:583–588.

Gaziano JM, Hennekens CH (1993) The role of beta-carotene in the prevention of cardiovascular disease. *Annals of the New York Academy of Science*, **691**:148–155.

Gaziano JM, Manson JE, Branch LG, Colditz GA, Willett WC, Buring JE (1995) A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. *Annals of Epidemiology*, **5**:255–260.

Gershoff SN (1993) Vitamin C (ascorbic acid): new roles, new requirements? *Nutrition Reviews*, **51**:313–326.

Gey K (1995) Cardiovascular disease and vitamins. Concurrent correction of 'suboptimal' plasma antioxidant levels may, as important part of 'optimal' nutrition, help to prevent early stages of cardiovascular disease and cancer, respectively. *Bibliotheca Nutritio et Dieta*, **52**:75–91.

Ghadirian P, Lacroix A, Maisonneuve P et al. (1997) Nutritional factors and colon carcinoma: a case-control study involving French Canadians in Montreal, Quebec, Canada. *Cancer*, **80**:858–864.

Gillman MW, Cupples LA, Gagnon D et al. (1995) Protective effect of fruits and vegetables on development of stroke in men. *Journal of the American Medical Association*, **273**:1113–1117.

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC (1994) Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Research*, **54**:2390–2397.

Gonzales CA, Sanz JM, Marcos G et al. (1991) Dietary factors and stomach cancer in Spain: a multi-centre case-control study. *International Journal of Cancer*, **49**:513–519.

Goodman MT, Hankin JH, Wilens LR, Kolonel LN (1992) High-fat foods and the risk of lung cancer. *Epidemiology*, **3**:288–299.

Government of India (1998) *India nutrition profile*. Ministry of Human Resource Development, Delhi.

Graham S, Haughey B, Marshall J et al. (1990) Diet in the epidemiology of gastric cancer. *Nutrition and Cancer*, **65**:2344–2348.

Graham S, Marshall J, Haughey B et al. (1988) Dietary epidemiology of cancer of the colon in western New York. *American Journal of Epidemiology*, **128**:490–503.

Greenberg E, Sporn MB (1996) Antioxidant vitamins, cancer and cardiovascular disease. *New England Journal of Medicine*, **334**:1189–1190.

Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. *American Journal of Epidemiology*, **135**:1301–1309.

Gregory J (1990) *The dietary and nutritional survey of British adults a survey of the dietary behaviour, nutritional status and blood pressure of adults aged 16 to 64 living in Great Britain*. HMSO, London.

Gregory J (1995) *National diet and nutrition survey children aged 1 1/2 to 4 1/2 years*. HMSO, London.

Gregory J (2000) *National diet and nutrition survey: young people aged 4 to 18 years. Report of the diet and nutrition survey*. HMSO, London.

Guo W, Blot WJ, Li JY et al. (1994) A nested case-control study of oesophageal and stomach cancers in the Linxian nutrition intervention trial. *International Journal of Epidemiology*, **23**:444–450.

Guo WD, Li JY, Blot WJ, Hsing AW, Chen JS, Fraumeni JF Jr (1990) Correlations of dietary intake and blood nutrient levels with esophageal cancer mortality in China. *Nutrition and Cancer*, **13**:121–127.

Haegele AD, Gillette C, O'Neill C et al. (2000) Plasma xanthophyll carotenoids correlate inversely with indices of oxidative DNA damage and lipid peroxidation. *Cancer Epidemiology, Biomarkers and Prevention*, **9**:421–425.

Hanaoka T, Tsugane S, Ando N et al. (1994) Alcohol consumption and risk of esophageal cancer in Japan: A case-control study in seven hospitals. *Japanese Journal of Clinical Oncology*, **24**:241–246.

Hansson LE, Nyren O, Bergstrom R et al. (1993) Diet and risk of gastric cancer. A population-based case-control study in Sweden. *International Journal of Cancer*, **55**:181–189.

Harris RW, Key TJ, Silcocks PB, Bull D, Wald NJ (1991) A case-control study of dietary carotene in men with lung cancer and in men with other epithelial cancers. *Nutrition and Cancer*, **15**:63–68.

Harrison LE, Zhang ZF, Karpeh MS, Sun M, Kurtz RC (1997) The role of dietary factors in the intestinal and diffuse histological subtypes of gastric adenocarcinoma: a case-control study in the US. *Cancer*, **80**:1021–1028.

Hebert JR, Clemow L, Pbert L, Ockene IS, Ockene JK (1995) Social desirability bias in dietary self-report may compromise the validity of dietary intake measures. *International Journal of Epidemiology*, **24**:389–398.

Heilbrun LK, Nomura A, Hankin JH, Stemmermann GN (1989) Diet and colorectal cancer with special reference to fiber intake. *International Journal of Cancer*, **44**:1–6.

Hennekens CH, Buring JE, Manson JE et al. (1996) Lack of effect of long-term supplementation with beta-carotene on the incidence of malignant neoplasms and cardiovascular disease. *New England Journal of Medicine*, **334**: 1145–1149.

Hertog M, Bueno-de-Mesquita HB, Fehili AM et al. (1996) Fruit and vegetable consumption and cancer mortality in the Caerphilly study. *Cancer Epidemiology, Biomarkers and Prevention*, **5**:673–677.

Hertog MG, Feskens EJ, Holliman PC, Katan MB, Kromhout D (1993) Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly study. *The Lancet*, **342**:1007–1011.

Hill AB (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*, **58**:295–300.

Hirayama T (1986) Nutrition and cancer—a large scale cohort study. *Progress in Clinical and Biological Research*, **206**:299–311.

Hirayama T (1990) Diet and mortality. In: *Lifestyle and mortality*. Hirayama T, ed. Karger, Basel.

Hirvonen T, Virtamo J, Korhonen P, Albanes D, Pietinen P (2000) Intake of flavonoids, carotenoids, vitamin C and E, and risk of stroke in male smokers. *Stroke*, **31**:2301–2306.

Hirvonen T, Virtamo J, Korhonen P, Albanes D, Pietinen P (2001) Flavonol and flavone intake and the risk of cancer in male smokers (Finland). *Cancer Causes and Control*, **12**:789–796.

Hooper L, Ness AR, Smith GD (2001) Antioxidant strategy for cardiovascular diseases. *The Lancet*, **357**:1705–1706.

Hoshiyama Y, Sasaba T (1992) A case-control study of single and multiple stomach cancers in Saitama Prefecture, Japan. *Japanese Journal of Cancer Research*, **83**:937–943.

Hu J, Johnson KC, Mao Y et al. (1997) A case-control study of diet and lung cancer in northeast China. *International Journal of Cancer*, **71**:924–931.

Hu JF, Liu YY, Yu YK, Zhao TZ, Lui SD, Wang QQ (1991) Diet and cancer of the colon and rectum: a case-control study in China. *International Journal of Epidemiology*, **20**:362–367.

Hu J, Nyren O, Wolk A et al. (1994) Risk factors for oesophageal cancer in northeast China. *International Journal of Cancer*, **57**:38–46.

Hu JF, Zhang SF, Jia EM et al. (1988) Diet and cancer of the stomach: a case-control study in China. *International Journal of Cancer*, **41**:331–335.

Insel P, Turner RE, Ross D (2003) *Discovering nutrition—interactive glossary*. Jones and Bartlett Publishers, Boston, MA. http://nutrition.jbpub.com/discovering/.

Iscovich JM, L'Abbe KA, Castelleto R et al. (1992) Colon cancer in Argentina. I. Risk from intake of dietary items. *International Journal of Cancer*, **51**:851–857.

Jain M, Burch JD, Howe GR, Risch HA, Miller AB (1990) Dietary factors and risk of lung cancer: results from a case-control study, Toronto, 1981–1985. *International Journal of Cancer*, **45**:287–293.

Jansen MC, Bueno-de-Mesquita HB, Rasanen L et al. (2001) Cohort analysis of fruit and vegetable consumption and lung cancer mortality in European men. *International Journal of Cancer*, **92**:913–918.

Jedrychowski W, Wahrendorf J, Popiela T, Rachtan J (1986) A case-control study of dietary factors and stomach cancer risk in Poland. *International Journal of Cancer*, **37**:837–842.

Jha P, Flather M, Lonn E, Farkouh M, Yusuf S (1995) The antioxidant vitamins and cardiovascular disease. A critical review of epidemiologic and trial data. *Annals of Internal Medicine*, **123**:860–872.

Ji BT, Chow WH, Yang G et al. (1998) Dietary habits and stomach cancer in Shanghai, China. *International Journal of Cancer*, **76**:659–664.

Joffe M, Robertson A (2001) The potential contribution of increased vegetable and fruit consumption to health gain in the European Union. *Public Health Nutrition*, **4**:893–901.

Johansson G, Wikman A, Ahren AM, Hallmans G, Johansson I (2001) Underreporting of energy intake in repeated 24-hour recalls related to gender, age, weight status, day of interview, educational level, reported food intake, smoking habits and area of living. *Public Health Nutrition*, **4**:919–927.

Joshipura KJ, Ascherio A, Manson JE et al. (1999) Fruit and vegetable intake in relation to risk of ischemic stroke. *Journal of the American Medical Association*, **282**:1233–1239.

Joshipura KJ, Hu FB, Manson JE et al. (2001) The effect of fruit and vegetable intake on risk for coronary heart disease. *Annals of Internal Medicine*, **134**:1106–1114.

Kalandidi A, Katsouyanni K, Voropoulou N, Bastas G, Saracci R, Trichopoulos D (1990) Passive smoking and diet in the etiology of lung cancer and among nonsmokers. *Cancer Causes and Control*, **1**:15–21.

Kampman E, Verhoeven D, Sloots L, van't Veer P (1995) Vegetable and animal products as determinants of colon cancer in Dutch men and women. *Cancer Causes and Control*, **6**:225–234.

Kantor LS, Kipton K, Manchester A, Oliveria V (1997) *Estimating and addressing America's food losses*. Food Review U.S. Department of Agriculture, Economic Research Service, Washington, DC.

Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E (1997) Prospective study of diet and female colorectal cancer: the New York University Women's Health study. *Nutrition and Cancer*, **28**:276–281.

Kato I, Dnistrian, A, Schwartz M et al. (1999) Serum folate, homocysteine and colorectal cancer risk in women: a nested case-control study. *British Journal of Cancer*, **79**:1917–1922.

Kato I, Tominaga S, Ito Y et al. (1990) A comparative case-control analysis of stomach cancer and atrophic gastritis. *Cancer Research*, **50**:6559–6564.

Kato I, Tominaga S, Matsumoto K (1992) A prospective study of stomach cancer among a rural Japanese population: a 6-year survey. *Japanese Journal of Cancer Research*, **83**:568–575.

Kauhanen J, Kaplan GA, Goldberg DE, Salonen R, Salonen JT (1999) Pattern of alcohol drinking and progression of atherosclerosis. *Arteriosclerosis, Thrombosis and Vascular Biology*, **19**:3001–3006.

Keli SO, Hertog MG, Feskens EJ, Kromhout D (1996) Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. *Archives of Internal Medicine*, **156**:637–642.

Kelly A, Becker W, Helsing E (1991) Food balance sheets. In: *Food and health data. Their use in nutrition policy-making*. Becker W, Helsing E, eds. (European Series No. 34.) WHO Regional Publications, World Health Organization, Copenhagen.

Kennedy AR (1998) Chemopreventive agents: protease inhibitors. *Pharmacology and Therapeutics*, **78**:167–209.

Key TJ, Thorogood M, Appleby PN, Burr ML (1996) Dietary habits and mortality in 11 000 vegetarians and health conscious people: results of a 17-year follow-up. *British Medical Journal*, **313**:775–779.

Kharbanda R, Vallance P (2001) Coronary artery disease—from bench to bedside. *Journal of Royal Society of Medicine*, **94**:61–64.

Khaw KT, Barrett-Connor E (1987a) Dietary fiber and reduced ischemic heart disease mortality rates in men and women: a 12-year prospective study. *American Journal of Epidemiology*, **126**:1093–1102.

Khaw KT, Barrett-Connor E (1987b) Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *New England Journal of Medicine*, **316**:235–240.

Khaw KT, Bingham S, Welch A et al. (2001) Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. European Prospective Investigation into Cancer and Nutrition. *The Lancet*, **357**:657–663.

Kipnis V, Carroll RJ, Freedman LS, Li L (1999) Implications of a new dietary measurement error model for estimation of relative risk: application to four calibration studies. *American Journal of Epidemiology*, **150**:642–651.

Kjaerheim K, Gaard M, Andersen A (1998) The role of alcohol, tobacco, and dietary factors in upper aerodigestive tract cancers: a prospective study of 10 900 Norwegian men. *Cancer Causes and Control*, **9**:99–108.

Klerk M, Jansen MCJF, van't Veer P, Kok FJ (1998) *Fruits and vegetables in chronic disease prevention*. Wageningen Agricultural University, Wageningen.

Klipstein-Grobusch K, Geleijnse JM, den Breeijen JH et al. (1999) Dietary antioxidants and risk of myocardial infarction in the elderly: the Rotterdam study. *American Journal of Clinical Nutrition*, **69**:261–266.

Knekt P, Isotupa S, Rissanen H et al. (2000) Quercetin intake and the incidence of cerebrovascular disease. *European Journal of Clinical Nutrition*, **54**: 415–417.

Knekt P, Jarvinen R, Reunanen A, Maatela J (1996) Flavonoid intake and coronary mortality in Finland: a cohort study. *British Medical Journal*, **312**: 478–481.

Knekt P, Jarvinen R, Seppanen R et al. (1991) Dietary antioxidants and the risk of lung cancer. *American Journal of Epidemiology*, **134**:471–479.

Knekt P, Jarvinen R, Seppanen R et al. (1997) Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *American Journal of Epidemiology*, **146**:223–230.

Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A (1994) Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *American Journal of Epidemiology*, **139**:1180–1189.

Kneller RW, McLaughlin JK, Bjelke E et al. (1991) A cohort study of stomach cancer in a high risk American population. *Cancer*, **68**:672–678.

Kojda G, Harrison D (1999) Interactions between NO and reactive oxygen species: pathophysiological importance in atherosclerosis, hypertension, diabetes and heart failure. *Cardiovascular Research*, **43**:562–571.

Kono S, Hirohata T (1996) Nutrition and stomach cancer. *Cancer Causes and Control*, **7**:41–55.

Kono S, Ikeda M, Tokudome S, Kuratsune M (1988) A case-control study of gastric cancer and diet in northern Kyushu, Japan. *Japanese Journal of Cancer Research*, **79**:1067–1074.

Koo L (1988) Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. *Nutrition and Cancer: An International Journal*, **11**:155–172.

Koo L (1997) Diet and lung cancer 20+ years later: more questions than answers? *International Journal of Cancer*, Suppl. **10**:S22–29.

Kotake K, Koyama Y, Nasu J, Fukutomi T, Yamaguchi N (1995) Relation of family history of cancer and environmental factors to the risk of colorectal cancer: a case-control study. *Japanese Journal of Clinical Oncology*, **25**: 195–202.

Kristenson M, Zieden B, Kucinskiene Z et al. (1997) Antioxidant state and mortality from coronary heart disease in Lithuanian and Swedish men: concomitant cross sectional study of men aged 50. *British Medical Journal*, **314**: 629–633.

Kromhout D (1987) Essential micronutrients in relation to carcinogenesis. *American Journal of Clinical Nutrition*, **45**:S1361–1367.

Kune GA, Bannerman S, Watson LF (1992) Attributable risk to diet, alcohol and family history in the Melbourne Colorectal Cancer study. *Nutrition and Cancer*, **18**:231–235.

Kune S, Kune GA, Watson LF (1987) Case-control study of dietary etiological factors: the Melbourne Colorectal Cancer study. *Nutrition and Cancer*, **9**:21–42.

Kushi LH, Folsom AR, Prinaes RJ, Mink PJ, Wu Y, Bostick RM (1996) Dietary antioxidant vitamins and deaths from coronary heart disease in postmenopausal women. *New England Journal of Medicine*, **334**:1156–1162.

Kvale G, Bjelke E, Gart JJ (1983) Dietary habits and lung cancer risk. *International Journal of Cancer*, **31**:397–405.

La Vecchia C, Negri E, Decarli A, D'Avanzo B, Franceschi S (1987) A case-control study of diet and gastric cancer in northern Italy. *International Journal of Cancer*, **40**:484–489.

Lampe J (1999) Health effects of vegetables and fruits: assessing mechanisms of action in human experimental studies. *American Journal of Clinical Nutrition*, **70**:S475–490.

Lapidus L, Andersson H, Bengtsson C, Bosaeus I (1986) Dietary habits in relation to incidence of cardiovascular disease and death in women: a 12-year follow-up of the participants in the population study of women in Gothenberg, Sweden. *American Journal of Clinical Nutrition*, **44**:444–448.

Launoy G, Milan C, Day NE, Pienkowski MP, Gignoux M, Faivre J (1998) Diet and squamous-cell cancer of the oesophagus: a French multicentre case-control study. *International Journal of Cancer*, **76**:7–12.

Law M, Morris J (1998) By how much does fruit and vegetable consumption reduce the risk of ischaemic heart disease? *European Journal of Clinical Nutrition*, **52**:549–556.

Le Marchand L, Hankin JH, Wilkens LR, Kolonel LN, Englyst HN, Lyu LC (1997) Dietary fibre and colorectal cancer risk. *Epidemiology*, **8**:658–665.

Le Marchand L, Yoshizawa CN, Kolonel LN, Hankin JH, Goodman MT (1989) Vegetable consumption and lung cancer risk: a population-based case-control study in Hawaii. *Journal of the National Cancer Institute*, **81**:1158–1164.

Lee CN, Reed DM, MacLean CJ, Yano K, Chiu D (1988) Dietary potassium and stroke. *New England Journal of Medicine*, **318**:995–996.

Lee HP, Gourley L, Duffy SW, Esteve J, Lee J, Day NE (1989) Colorectal cancer and diet in an Asian population: a case-control study among Singapore Chinese. *International Journal of Cancer*, **43**:1007–1016.

Lee JK, Park BJ, Yoo KY, Ahn YO (1995) Dietary factors and stomach cancer: case-control study in Korea. *International Journal of Epidemiology*, **24**: 33–41.

Leppala JM, Virtamo J, Fogelholm R, Albanes D, Taylor PR, Heinonen OP (2000) Vitamin E and beta-carotene supplementation in high risk for stroke: a subgroup analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study. *Archives of Neurology*, **57**:1503–1509.

Levi F, Pasche C, La Vecchia C, Lucchini F, Franceschi S (1999*)* Food groups and colorectal cancer risk. *British Journal of Cancer*, **79**:1283–1287.

Levi F, Pasche C, Lucchini F et al. (2000) Food groups and oesophageal cancer risk in Vaud, Switzerland. *European Journal of Cancer Prevention*, **9**: 257–263.

Li JY, Ershow AG, Chen ZJ et al. (1989) A case-control study of cancer of the esophagus and gastric cardia in Linxian. *International Journal of Cancer*, **43**:755–761.

Liu S, Lee IM, Ajani U, Cole SR, Buring JE, Manson JE (2001) Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health study. *International Journal of Epidemiology*, **30**:130–135.

Liu S, Manson JE, Lee IM et al. (2000) Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health study. *American Journal of Clinical Nutrition*, **72**:922–928.

Lonn EM, Yusuf S (1999) Evidence-based cardiology: emerging approaches in preventing cardiovascular disease. *British Medical Journal*, **318**:1337–1341.

Macquart-Moulin G, Riboli E, Cornee J, Charnay B, Berthezene P, Day N (1986) Case-control study on colorectal cancer and diet in Marseilles. *International Journal of Cancer*, **38**:183–191.

Malaveille C, Hautefeuille A, Pignatelli B, Talaska G, Vineis P, Bartsch H (1996) Dietary phenolics as anti-mutagens and inhibitors of tobacco-related DNA adduction in the urothelium of smokers. *Carcinogenesis*, **17**:2193–200.

Mann JI, Appleby PN, Key TJ, Thorogood M (1997) Dietary determinants of ischemic heart disease in health conscious individuals. *Heart*, **78**:450–455.

Marshall JR, Chen Z (1999) Diet and health risk: risk patterns and disease-specific associations. *American Journal of Clinical Nutrition*, **69**:S1351–1356.

Mathers C, Vos T, Stevenson C (1999) *The burden of disease and injury in Australia*. Australian Institute of Health and Welfare, Canberra.

Maynard M, Gunnell D, Emmett P, Frankel S, Davey Smith G (2003) Fruit, vegetables, and antioxidants in childhood and risk of adult cancer: the Boyd Orr cohort. *Journal of Epidemiology and Community Health*, **57**:218–225.

Mayne ST, Janerich DT, Greenwald P et al. (1994) Dietary beta-carotene and lung cancer risk in U.S. nonsmokers. *Journal of the National Cancer Institute*, **86**:33–38.

Memik F, Nak SG, Gulten M, Ozturk M (1992) Gastric carcinoma in northwestern Turkey: epidemiologic characteristics. *Journal of Environmental Pathology, Toxicology and Oncology*, **11**:335–338.

Menotti A, Kromhout D, Blackburn H, Fidanza F, Buzina R, Nissinen A (1999) Food intake patterns and 25-year mortality from coronary heart disease: cross cultural correlations from the Seven Countries study. The Seven Countries study research group. *European Journal of Epidemiology*, **15**:507–515.

Mensink G, Hermann-Kunz E, Thamm M (1998) Der Ernährungssurvey. *Das Gesundheitswesen*, **60**:S83–86.

Messina MJ (1999) Legumes and soybeans: overview of their nutritional profiles and health effects. *American Journal of Clinical Nutrition*, **70**:S439–450.

Mettlin C (1989) Milk drinking, other beverage habits, and lung cancer risk. *International Journal of Cancer*, **43**:608–612.

Meyer F, White E (1993) Alcohol and nutrients in relation to colon cancer in middle-aged adults. *American Journal of Epidemiology*, **138**:225–236.

Michaud DS, Feskanich D, Rimm ED et al. (2000) Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. *American Journal of Clinical Nutrition*, **72**:990–997.

Michels KB, Giovannucci E, Joshipura KJ et al. (2000) Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *Journal of the National Cancer Institute*, **92**:1740–1752.

Michels KB, Giovannucci E, Joshipura KJ et al. (2002). Fruit and vegetable consumption and colorectal cancer incidence. *IARC Scientific Publications*, **156**:139–140.

Ministry of Health and Welfare (2000) *Annual report of the national nutrition survey in 1998*. Daiichi Publishing Co, Tokyo.

Morris JN, Marr JW, Clayton DG (1977) Diet and heart: a postscript. *British Medical Journal*, **2**:1307–1314.

Muir C, McKinney PA (1992) Cancer of the oesophagus: a global overview. *European Journal of Cancer Prevention*, **1**:259–264.

Mulder I, Jansen MC, Smit HA et al. (2000) Role of smoking and diet in the cross-cultural variation in lung cancer mortality: the Seven Countries study. Seven Countries study research group. *International Journal of Cancer*, **88**: 665–671.

Munoz N, Plummer M, Vivas J et al. (2001) A case-control study of gastric cancer in Venezuela. *International Journal of Cancer*, **93**:417–423.

Munoz SE, Ferraroni M, La Vecchia C, Decarli A (1997) Gastric cancer risk factors in subjects with family history. *Cancer Epidemiology, Biomarkers and Prevention*, **6**:137–140.

National Institute of Public Health (1997) *Determinants of the burden of disease in the EU*. National Institute of Public Health, Stockholm.

Nayar D, Kapil U, Joshi YK et al. (2000) Nutritional risk factors in esophageal cancer. *Journal of the Association of Physicians in India*, **48**:781–787.

Negri E, Franceschi S, Parpinel M, La Vecchia C (1998) Fiber intake and risk of colorectal cancer. *Cancer Epidemiology, Biomarkers and Prevention*, **7**: 667–671.

Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F (1991) Vegetable and fruit consumption and cancer risk. *International Journal of Cancer*, **48**:350–354.

Nelson M, Bingham S (1997) Assessment of food consumption and nutrient intake. In: *Design concepts in nutritional epidemiology*. Margetts BM, Nelson M, eds. Oxford University Press, Oxford.

Ness A (2001) Commentary: beyond beta-carotene-antioxidants and cardiovascular disease. *International Journal of Epidemiology*, **30**:143–144.

Ness A (2002) Is olive oil a key ingredient in the Mediterranean recipe for health? *International Journal of Epidemiology*. **31**:481–482.

Ness A, Egger M, Davey Smith G (1999a) Role of antioxidant vitamins in prevention of cardiovascular diseases. Meta-analysis seems to exclude benefit of vitamin C supplementation. *British Medical Journal*, **319**:577.

Ness A, Egger M, Powles J (1999b) Fruit and vegetables and ischaemic heart disease: systematic review or misleading meta-analysis? *European Journal of Clinical Nutrition*, **53**:900–902.

Ness AR, Powles JW (1997) Fruit and vegetables, and cardiovascular disease: a review. *International Journal of Epidemiology*, **26**:1–13.

Ness AR, Powles JW (1999) The role of diet, fruit and vegetables and antioxidants in the aetiology of stroke. *Journal of Cardiovascular Risk*, **6**:229–234.

Nomura AM, Grove JS, Stemmermann GN, Severson RK (1990) A prospective cohort study on stomach cancer and its relation to diet, cigarettes and alcohol consumption. *Cancer Research*, **50**:627–631.

Norat T, Van Bakel M, Riboli E (2001) *Fruit and vegetable consumption and risk of cancer of the digestive tract: meta-analysis of published case control and cohort studies*. European Conference on Diet and Cancer. Lyon.

Notani PN, Jayant K (1987) Role of diet in upper aerodigestive tract cancers. *Nutrition and Cancer*, **10**:103–113.

Nyberg F, Agrenius V, Svartengren K, Svensson C, Pershagen G (1998) Dietary factors and risk of lung cancer in never-smokers. *International Journal of Cancer*, **78**:430–436.

Obarzanek E, Sacks FM, Vollmer VM et al. (2001) Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) trial. *American Journal of Clinical Nutrition*, **74**:80–89.

Ocke M, Bueno-de-Mesquita HB, Feskens EJ, Kromhout D, Menotti A, Blackburn H (1998) Adherence to the European Code Against Cancer in relation to long-term cancer mortality: intercohort comparisons from the Seven Countries study. *Nutrition and Cancer*, **30**:14–20.

Ocke M, Bueno-de-Mesquita HB, Feskens EJ, van Staveren WA, Kromhout D (1997) Repeated measurements of vegetables, fruits, beta-carotene, and vitamins C and E in relation to lung cancer. The Zutphen study. *American Journal of Epidemiology*, **145**:358–365.

Oganesian A, Hendricks JD, Pereira CB, Orner GA, Bailey GS, Williams DE (1999) Potency of dietary indol-3-carbinol as a promoter of aflatoxin B1-initiated hepatocarcinogenesis: results from a 9000 animal tumor study. *Carcinogenesis*, **20**:453–458.

Omenn G, Goodman GE, Thornquist MD et al. (1996a) Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *Journal of the National Cancer Institute*, **88**:1550–1559.

Omenn GS, Goodman G, Thornquist MD et al. (1996b) Effects of a combination of beta-carotene and vitamin A on lung and cardiovascular disease. *New England Journal of Medicine*, **334**:1150–1155.

Paganini-Hill GM, Ross RK, Gray GE, Henderson BE (1987) Vitamin A, beta-carotene and risk of cancer: a prospective study. *Journal of the National Cancer Institute*, **79**:443–448.

Pandey DK, Shekelle R, Selwyn BJ, Tangney C, Stamler J (1995) Dietary vitamin C and beta-carotene and risk of death in middle-aged men. The Western Electric study. *American Journal of Epidemiology*, **142**:1269–1278.

Pawlega J, Rachtan J, Dyba T (1997) Evaluation of certain risk factors for lung cancer in Cracow (Poland)-a case-control study. *Acta Oncologica*, **36**: 471–476.

Peters RK, Pike MC, Garabrant D, Mack TM (1992) Diet and colon cancer in Los Angeles County, California. *Cancer Causes and Control*, **3**:457–473.

Petrova S, Angelova K, Ivanova L et al. (2000) National dietary and nutritional status survey of the population in Bulgaria, 1998. Food consumption. *Hygiene and Public Health*, **XLIII**:55–62.

Phillips RL, Snowdon DN (1985) Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists. *Journal of the National Cancer Institute*, **74**:307–317.

Pietinen P, Malila N, Virtene M et al. (1999) Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes and Control*, **10**:387–396.

Pietinen P, Rimm EB, Korhonen P et al. (1996) Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention study. *Circulation*, **94**:2720–2727.

Pillow PC, Hursting SD, Duphorne CM et al. (1997) Case-control assessment of diet and lung cancer risk in African Americans and Mexican Americans. *Nutrition and Cancer*, **29**:169–173.

Pisani P, Berrino F, Macaluso M, Pastorino U, Crosignani P, Baldasseroni A (1986) Carrots, green vegetables and lung cancer: a case-control study. *International Journal of Epidemiology*, **15**:463–468.

Potter JD (1996) Nutrition and colorectal cancer. *Cancer Causes and Control*, **7**:127–146.

Powles JW, Day NE, Sanz MA, Bingham SA (1996) Protective foods in winter and spring: a key to lower vascular mortality? *The Lancet*, **348**:898–899.

Price JE, Fowkes FG (1997) Antioxidant vitamins in the prevention of cardiovascular disease. The epidemiological evidence. *European Heart Journal*, **18**:719–727.

Puska P (2000) Nutrition and mortality: the Finnish experience. *Acta Cardiologica*, **55**:213–220.

Rachtan J, Sokolowski A (1997) Risk factors for lung cancer among women in Poland. *Lung Cancer*, **18**:137–145.

Ramon JM, Serra L, Cerdo C, Oromi J (1993) Dietary factors and gastric cancer risk. A case control study in Spain. *Cancer*, **71**:1731–1735.

Rehm J, Monteiro M, Room R et al. (2001) Steps towards constructing a global comparative risk analysis for alcohol consumption: determining indicators and empirical weights for patterns of drinking, deciding about theoretical minimum, and dealing with different consequences. *European Addiction Research*, **7**:138–147.

Rexrode KM, Manson JE (1996) Antioxidants and coronary heart disease: observational studies. *Journal of Cardiovascular Risk*, **3**:363–367.

Rimm EB, Ascherio A, Giovannucci E, Speigelman D, Stampfer MJ, Willett WC (1996) Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *Journal of the American Medical Association*, **275**: 447–451.

Rinzler SH (1968) Primary prevention of coronary heart disease by diet. *Bulletin of the New York Academy of Medicine*, **44**:936–949.

Risch HA, Jain M, Choi NW et al. (1985) Dietary factors and the incidence of cancer of the stomach. *American Journal of Epidemiology*, **122**:947–959.

Rivera Dommarco J, Shamah Levy T, Villalpando Hernándes S, González de Cosío T, Hernández Prado B, Sepúlveda J, eds. (2001b) *Encuesta nacional de nutrición 1999. Estado nutricio de niños y mujeres en México*. [National nutrition survey 1999. Nutritional status of women and children in Mexico.] Instituto Nacional de Salud Pública National Institute of Public Health, Cuernavaca, Mexico.

Ross RK, Yuan JM, Henderson BE, Park J, Gao YT, Yu MC (1997) Prospective evaluation of dietary and other predictors of fatal stroke in Shanghai, China. *Circulation*, **96**:50–55.

Sankaranarayanan R, Varghese C, Duffy SW, Padmakumary G, Day NE, Nair MK (1994) A case-control study of diet and lung cancer in Kerala, south India. *International Journal of Cancer*, **58**:644–649.

Sargeant LA, Khaw KT, Bingham S et al. (2001) Fruit and vegetable intake and population glycosylated haemoglobin levels: the EPIC-Norfolk study. *European Journal of Clinical Nutrition*, **55**:342–348.

Sawaya WN, al-Awadi FA, Saeed T et al. (1999) Kuwait's total diet study, dietary intake of organochlorine, carbamate, benzimidazole and pheylurea pesticide residues. *Journal of AOAC International*, **82**:1458–1465.

Schut HA, Cummings DA, Smale MH, Josyula S, Friesen MD (1997) DNA adducts of heterocyclic amines: formation removal and inhibition by dietary components. *Mutation Research*, **376**:185–194.

Sekula W, Becker W, Trichopoulou A, Zajkas G (1991) Comparison of dietary data from different sources: some examples. In: *Food and health data. Their use in nutrition policy-making*. Becker W, Helsing E, eds. (European Series No. 34.) WHO Regional Publications, World Health Organization, Copenhagen.

Sengupta A, Das S (1999) The anti-carcinogenic role of lycopene, abundantly present in tomatoes. *European Journal of Cancer Prevention*, **8**:325–330.

Shannon J, White E, Shattuck AL, Potter JD (1996) Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiology, Biomarkers and Prevention*, **5**:495–502.

Shibata A, Paganini-Hill A, Ross RK, Henderson BE (1992) Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *British Journal of Cancer*, **66**:673–680.

Singh RB, Niaz MA, Gosh S, Singh R, Rastogi SS (1993a) Effect on mortality and reinfaction of adding fruits and vegetables to a prudent diet in the Indian experiment of infarct survival (IEIS). *Journal of the American College of Nutrition*, **12**:255–261.

Singh RB, Rastogi SS, Singh NK, Ghosh S, Gupta S, Niaz MA (1993b) Can guava fruit decrease blood pressure and blood lipids? *Journal of Human Hypertension*, **7**:33–38.

Singh RR, Rastogi SS, Verma R et al. (1992) Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. *British Medical Journal*, **304**:1015–1019.

Singh SV, Mohan RR, Agarwal R et al. (1996) Novel anti-carcinogenic activity of an organosulfide from garlic: inhibition of H-RAS oncogene transformed tumor growth in vivo by diallyl disulfide is associated with inhibition of p21H-ras processing. *Biochemical Biophysical Research Communications*, **225**:660–665.

Slattery ML, Potter JD, Coates A et al. (1997) Plant foods and colon cancer: an assessment of specific foods and their related nutrients (United States). *Cancer Causes and Control*, **8**:575–590.

Slattery ML, Schumacher MC, Smith KR, West DW, Abd-Elghany N (1988) Physical activity, diet, and risk of colon cancer in Utah. *American Journal of Epidemiology*, **128**:989–999.

Smit HA, Grievink L, Tabak C (1999) Dietary influences on chronic obstructive lung disease and asthma: a review of the epidemiological evidence. *Proceedings of the Nutrition Society*, **58**:309–319.

Smith-Warner SA, Elmer PJ, Fosdick L, Tharp TM, Randall B (1997) Reliability and comparability of three dietary assessment methods for estimating fruit and vegetable intakes. *Epidemiology*, **8**:196–201.

Speizer FE, Colditz GA, Hunter DJ, Rosner B, Hennekens C (1999) Prospective study of smoking, antioxidant intake and lung cancer in middle-aged women. *Cancer Causes and Control*, **10**:475–482.

Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD (1994) Vegetables, fruits, and colon cancer in the Iowa women's health study. *American Journal of Epidemiology*, **139**:1–15.

Steinmetz KA, Potter JD (1993) Food-group consumption and colon cancer in the Adelaide Case-Control study. I. Vegetables and fruit. *International Journal of Cancer*, **53**:711–719.

Steinmetz KA, Potter JD (1996) Vegetables, fruit, and cancer prevention: a review. *Journal of the American Dietetic Association*, **96**:1027–1039.

Steinmetz KA, Potter JD, Folsom AR (1993) Vegetables, fruit, and lung cancer in the Iowa Women's Health study. *Cancer Research*, **53**:536–543.

Suzuki I, Hamada GS, Zamboni MM, de Biasi Cordeiro P, Watanabe S, Tsugane S (1994) Risk factors for lung cancer in Rio de Janeiro, Brazil: a case-control study. *Lung Cancer*, **11**:179–190.

Swanson CA, Mao BL, Li JY et al. (1992) Dietary determinants of lung cancer risk: results from a case-control study in Yunnan Province, China. *International Journal of Cancer*, **50**:876–880.

Tajima K, Tominaga S (1985) Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Japanese Journal of Cancer Research*, **76**:705–716.

Takezaki T, Hirose K, Inoue M et al. (2001) Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas. *British Journal of Cancer*, **84**:1199–1206.

Takezaki T, Shinoda M, Hatooka et al. (2000) Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). *Cancer Causes and Control*, **11**:597-608.

Tavani A, Negri E, Francesch, La Vecchia C (1993) Risk factors for esophageal cancer in women in northern Italy. *Cancer*, **72**:2531–2536.

Tavani A, Negri E, Franceschi S, La Vecchia C (1994) Risk factors for esophageal cancer in lifelong nonsmokers. *Cancer Epidemiology, Biomarkers and Prevention*, **3**:387–392.

Tavani A, Negri E, Franceschi S, La Vecchia C (1996a) Tobacco and other risk factors for oesophageal cancer in alcohol non-drinkers. *European Journal of Cancer Prevention*, **5**:313–318.

Tavani A, Negri E, La Vecchia C (1996b) Food and nutrient intake and risk of cataract. *Annals of Epidemiology*, **6**:41–46.

Taylor CA, Hampl JS, Johnston CS (2000) Low intakes of vegetables and fruits, especially citrus fruits, lead to inadequate vitamin C intakes among adults. *European Journal of Clinical Nutrition*, **54**:573–578.

Terry P, Giovanucci E, Michels KB et al. (2001) Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *Journal of the National Cancer Institute*, **93**:525–533.

Terry P, Nyren, O, Yuen J (1998) Protective effect of fruit and vegetables on stomach cancer in a cohort of Swedish twins. *International Journal of Cancer*, **76**:35–37.

Thompson FE, Moler JE, Freedman LS, Cliffors CK, Stables GJ, Willet WC (1997) Register of dietary assessment calibration-validation studies: a status report. *American Journal of Clinical Nutrition*, **65**:S1142–1147.

Thun MJ, Calle EE, Namboodiri MM et al. (1992) Risk factors for fatal colon cancer in a large prospective study. *Journal of the National Cancer Institute*, **84**:1491–1500.

Tobias M (2001) *The burden of disease and injury in New Zealand*. New Zealand Ministry of Health, Wellington.

Todd S, Woodward M, Tunstall-Pedoe H, Bolton-Smith C (1999) Dietary antioxidant vitamins and fiber in the etiology of cardiovascular disease and all-causes mortality: results of the Scottish Heart Health study. *American Journal of Epidemiology*, **150**:1073–1080.

Trichopoulos D, Ouranos G, Day N et al. (1985) Diet and cancer of the stomach: a case-control study in Greece. *International Journal of Cancer*, **36**:291–297.

Turrini A, Saba A, Perrone D, Cialfa E, D'Amicis A (2001) Food consumption patterns in Italy: the INN-CA study 1994–1996. *European Journal of Clinical Nutrition*, **55**:571–588.

Tuyns AJ, Kaaks R, Haelterman M (1988) Colorectal cancer and the consumption of foods: a case-control study in Belgium. *Nutrition and Cancer*, **11**:189–204.

Tuyns AJ, Kaaks R, Haelterman M, Riboli E (1992) Diet and gastric cancer. A case-control study in Belgium. *International Journal of Cancer*, **51**:1–6.

Tuyns AJ, Riboli E, Doornbos G, Pequignot G (1987) Diet and esophageal cancer in Calvados (France). *Nutrition and Cancer*, **9**:81–92.

van Poppel G, Goldbohm RA (1995) Epidemiologic evidence for beta-carotene and cancer prevention. *American Journal of Clinical Nutrition*, **62**: S1393–1402.

van Poppel G, Verhoeven DT, Verhagen H, Goldbohm RA (1999) Brassica vegetables and cancer prevention. Epidemiology and mechanisms. *Advances in Experimental Medicine and Biology*, **472**:159–168.

Verhagen H, Poulson HE, Loft S, van Poppel G, Willems MI, van Bladeren PJ (1995) Reduction of oxidative DNA damage in humans by brussel sprouts. *Carcinogenesis*, **16**:969–970.

Victora CG, Munoz N, Day NE, Barcelos LB, Peccin DA, Braga NM (1987) Hot beverages and oesophageal cancer in southern Brazil: a case-control study. *International Journal of Cancer*, **39**:710–716.

Volatier J (1999) *Enquête individuelle et nationale sur les consummations alimentaires*. Editions TEC et DOC, Paris.

Vollset SE, Bjelke E (1983) Does consumption of fruit and vegetables protect against stroke? *The Lancet*, **2**:742.

Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJ, van den Brandt PA (2000a) Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: the Netherlands Cohort Study on diet and cancer. *American Journal of Epidemiology*, **152**:1081–1092.

Voorrips LE, Goldbohm RA, Verhoeven DT et al. (2000b) Vegetable and fruit consumption and lung cancer risk in the Netherlands Cohort study on diet and cancer. *Cancer Causes and Control*, **11**:101–115.

Walker A, Adam F, Walker J, Walker BF (2002) Cancer of the oesophagus in Africans in sub-Saharan Africa: any hopes for its control? *European Journal of Cancer Prevention*, **11**:413–418.

Wang LD, Hammond EC (1985) Lung cancer, fruit, green salad and vitamin pills. *Chinese Medical Journal*, **98**:206–210.

Wang YP, Han XY, Su W et al. (1992) Esophageal cancer in Shanxi Province, People's Republic of China: a case-control study in high and moderate risk areas. *Cancer Causes and Control*, **3**:107–113.

Ward MH, Lopez-Carrillo L (1999) Dietary factors and the risk of gastric cancer in Mexico. *American Journal of Epidemiology*, **149**:925–932.

Watkins ML, Erickson JD, Thun MJ, Mulinare J, Heath CW Jr (2000) Multivitamin use and mortality in a large prospective study. *American Journal of Epidemiology*, **152**:149–162.

Weinberg RA (1996) How cancer arises. *Scientific American*, **275**:62–70.

West DW, Slattery, ML, Robinson, LM et al. (1989) Dietary intake and colon cancer: sex- and anatomic site-specific associations. *American Journal of Epidemiology*, **130**:883–894.

Willett W (1998a) Nature of variation in diet. In: *Nutritional epidemiology*. Willett W, ed. Oxford University Press, Oxford.

Willett W, ed. (1998b) *Nutritional epidemiology.* Oxford University Press, Oxford.

Willett W (2001) Commentary: dietary diaries versus food frequency questionnaires—a case of undigestible data. *International Journal of Epidemiology*, **30**:317–319.

Wiseman M (2002) The World Cancer Research Fund Expert Report: the next steps. *IARC Scientific Publications*, **156**:523–524.

Witztum JL (1994) The oxidation hypothesis of atherosclerosis. *The Lancet*, **344**:793–795.

World Bank (2000) *Classification of economies*. World Bank, Washington DC. Available at http://www.worldbank.org/data/databytopic/class.htm#Low_income.

World Cancer Research Fund, American Institute for Cancer Research (1997) *Food, nutrition and the prevention of cancer: a global perspective*. American Institute for Cancer Research, Washington.

WHO (1985) *Energy and protein requirements*. (Technical Report Series No. 724). World Health Organization, Geneva.

WHO (1990) *Diet, nutrition and the prevention of chronic diseases*. (Technical Report Series No. 797). World Health Organization, Geneva.

WHO (2000) *World health report 2000*. Health Systems: Improving performance. World Health Organization, Geneva.

Wu K, Helzlsouer KJ, Alberg AJ, Comstock GW, Norkus EP, Hoffman SC (2000) A prospective study of plasma ascorbic acid concentrations and breast cancer (United States). *Cancer Causes and Control*, **11**:279–283.

Wu-Williams AH, Dai XD, Blot W et al. (1990) Lung cancer among women in north-east China. *British Journal of Cancer*, **62**:982–987.

Yochum LA, Folsom AR, Kushi LH (2000) Intake of antioxidant vitamins and risk of death from stroke in postmenopausal women. *American Journal of Clinical Nutrition*, **72**:476–483.

Yochum L, Kushi, LH, Meyer K, Folsom AR (1999) Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. *American Journal of Epidemiology*, **149**:943–949.

Yokoyama T, Date C, Kokubo Y, Yoshiike N, Matsumura Y, Tanaka H (2000) Serum vitamin C concentration was inversely associated with subsequent 20-year incidence of stroke in a Japanese rural community. The Shibata study. *Stroke*, **31**:2287–2294.

Yong LC, Brown CC, Schatzkin A et al. (1997) Intake of vitamins E, C and A and risk of lung cancer. The NHANES I epidemiologic follow-up study. First National Health and Nutrition Examination Survey. *American Journal of Epidemiology*, **146**:231–243.

You WC, Blot WJ, Chang YS et al. (1988) Diet and high risk of stomach cancer in Shandong, China. *Cancer Research*, **48**:3518–3523.

Young TB, Wolf DA (1988) Case-control study of proximal and distal colon cancer and diet in Wisconsin. *International Journal of Cancer*, **42**:167–175.

Yu MC, Garabrant DH, Peters JM, Mack TM (1988) Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. *Cancer Research*, **48**: 3843–3848.

Yu Y, Taylor PR, Li JY et al. (1993) Retrospective cohort study of risk-factors for esophageal cancer in Linxian, People's Republic of China. *Cancer Causes and Control*, **4**:195–202.

Zaridze D, Filipchenko V, Kustov V, Serdyuk V, Duffy S (1992) Diet and colorectal cancer: results of two case-control studies in Russia. *European Journal of Cancer*, **29A**:112–115.

Zatonski WA, McMichael AJ, Powles JW (1998) Ecological study of reasons for sharp decline in mortality from ischaemic heart disease in Poland since 1991. *British Medical Journal*, **316**:1047–1051.

Zheng W, Sellers TA, Doyle TJ, Kushi LH, Potter JD, Folsom AR (1995) Retinol, antioxidant vitamins, and cancers of the upper digestive tract in a prospective cohort study of postmenopausal women. *American Journal of Epidemiology*, **142**:955–960.

Ziegler RG, Colavito EA, Hartge P et al. (1996a) Importance of alpha-carotene, beta-carotene, and other phytochemicals in the etiology of lung cancer. *Journal of the National Cancer Institute*, **88**:612–615.

Ziegler RG, Mason TJ, Stemhagen, A et al. (1986) Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. *American Journal of Epidemiology*, **123**:1080–1093.

Ziegler RG, Mayne ST, Swanson CA (1996b) Nutrition and lung cancer. *Cancer Causes and Control*, **7**:157–177.

Chapter 10

Physical inactivity

Fiona C. Bull, Timothy P. Armstrong, Tracy Dixon, Sandra Ham, Andrea Neiman and Michael Pratt

Summary

Physical inactivity is recognized as an important risk factor for multiple causes of death and chronic morbidity and disability.

Physical activity was chosen rather than physical fitness as the measure of exposure because it is through increases in the behaviour (physical activity) that health benefits accrue and improvements in cardiorespiratory fitness can be achieved. Moreover, there were insufficient data available worldwide to consider fitness as the exposure. Exposure was assessed as a trichotomous variable to avoid limiting the assessment of total burden to only that associated with the highest risk, namely the most inactive (a dichotomous approach). However due to a lack of data on physical inactivity, use of a more detailed (continuous) exposure variable was not possible nor was the use of a fourth category of "high activity". Therefore, our estimates of burden are likely to underestimate the total attributable burden to inactivity because of limitations with measures of exposure. Level 1 exposure (inactive) was defined as "doing no or very little physical activity at work, at home, for transport or in discretionary time". Level 2 exposure (insufficiently active) was defined as "doing some physical activity but less than 150 minutes of moderate-intensity physical activity or 60 minutes of vigorous-intensity physical activity a week accumulated across work, home, transport or discretionary domains".

We found a wide range of survey instruments and methodologies have been used for collecting, analysing and reporting data on physical activity. Most data were available for discretionary-time activity, some data were found on occupational activity and little and no national data were available for transport- and domestic-related activity, respectively. A comprehensive literature search and contact with key agencies and known researchers uncovered over 50 data sets on physical inactivity in adult populations covering 43 countries across 13 subregions.[1] However,

only 21 data sets covering 32 countries met our inclusion criteria. Hierarchical modelling techniques were used to predict discretionary-time activity using age, sex, geographic region and a measure of tertiary education. Linear regression was used to predict occupational activity and transport-related activity using two World Bank indicators (% employed in agriculture and car ownership, respectively). We used these estimates to compute the level of total inactivity for 145 countries and aggregated these data to create estimates for 14 subregions.

The final global estimate for total inactivity (level 1 exposure) was 17.1% and this ranged from 10.3% in AFR-D to 24.8% in EUR-C. Across most but not all subregions females were slightly more inactive than males and younger adults were less inactive than older adults (range 9.6–46.8% across the 12 age-sex categories). The final global estimate for insufficient activity (level 2 exposure) was 40.6% and this ranged from 31.7% in AMR-D to 51.5% in WPR-A.

The independent causal relationship between physical inactivity and ischaemic heart disease, ischaemic stroke, type II diabetes, colon cancer and breast cancer is well established; we provided new estimates of the magnitude of risk associated with inactivity. A comprehensive search of literature from 1980 onwards identified well over 100 studies assessing the relationship between physical inactivity and the set of health outcomes that met our criteria. Also, several quantitative and qualitative reviews of the association between physical inactivity and ischaemic heart disease and stoke were found but there were no quantitative meta-analyses for breast cancer, colon cancer and type II diabetes. Most of the epidemiological studies meeting our inclusion criteria measured discretionary-time activity, some studies assessed occupational activity but only a few studies incorporated transport-related activity. No study included domestic-related physical activity. Given these data and differences between previous work and our definition of exposure, we completed a series of new meta-analyses for each health outcome. To address concerns regarding measurement error associated with physical activity, an adjustment factor was incorporated into the meta-analyses. All risk estimates were attenuated for ages 70 and over. There is emerging consensus on the protective effects of activity in regards to preventing falls, osteoarthritis and osteoporosis and impaired mental health but these disease end-points did not meet our inclusion criteria.

Globally physical inactivity accounted for 21.5% of ischaemic heart disease, 11% of ischaemic stroke, 14% of diabetes, 16% of colon cancer and 10% of breast cancer. The results show small differences between males and females, due in part to differences in level of exposure and to different distribution of events between men and women. In summary, physically inactive lifestyles accounted for 3.3% of deaths and 19 million disability-adjusted life years (DALYs) worldwide. There were small, non-significant differences in the attributable fractions across subregions. Due

to our conservative methods and a number of important limitations, our global estimates are likely to be an underestimate of the true burden attributable to inactive lifestyles.

1. Introduction

Physical inactivity is associated with many of the leading causes of death, chronic morbidity and disability. The apparent protective effect of being more active, and consequently less inactive, was identified first through studies of occupational activity over 50 years ago. Subsequent research has investigated different types, duration, frequency and intensity of activity in association with various cardiovascular, musculoskeletal and mental health outcomes. Today, there is a significant amount of literature quantifying and qualifying the role of physical inactivity as a risk factor and worldwide interest and efforts to increase levels of participation.

1.1 Choice of the exposure variable—physical activity or physical fitness

There is substantial epidemiological evidence for the protective effects of both a physically active lifestyle and of various levels of physical fitness. Yet, to date, it is still not possible to determine whether one of these exposure variables is more important than the other (Blair et al. 2001). Thus, in theory, either variable could have been selected as the measure of exposure for this project. The final selection of physical activity over physical fitness was based on several reasons. Firstly, physical fitness is primarily determined by patterns of physical activity, particularly activity undertaken in recent weeks or months (Blair et al. 2001). Secondly, there is a genetic contribution to physical fitness and while of some importance, genetic makeup is likely to account for less variation than the lifestyle behaviour (Bouchard 2001). Thirdly, assessment of physical fitness in large samples of adult populations is rare across the majority of countries and infrequent in those countries in which it has been undertaken. Moreover, studies of fitness often exclude adults with certain chronic conditions. Fourthly, most national and international recommendations specify public health targets in terms of reaching thresholds of physical activity not levels of physical fitness.

It is acknowledged that one advantage of choosing physical fitness as the exposure variable would be the opportunity to use an objective, physical measure such as maximum oxygen uptake. This would be desirable for several reasons, including correspondence with many epidemiological studies assessing relative risk. Disadvantages to this approach, however, stem from the lack of nationally representative population-based estimates, which outweigh the benefits. The difficulties associated with measuring behavioural risk factors are well known and the specific

challenges pertaining to measuring physical inactivity are discussed in detail in the following sections.

Therefore, considering the scientific support, the availability of data, and consistency with public health initiatives, physical activity was selected in preference to physical fitness as the measure of exposure. Given that protective benefits come from undertaking physical activity, from here on, the risk factor is specified as *physical inactivity*. It is, however, impossible to limit the discussion of both conceptual issues and the reporting of data to solely the "absence" of physical activity. Therefore the reader is forewarned that both physical activity and physical inactivity are discussed. In places the term "physical (in)activity" is used to refer to either activity or inactivity.

1.2 Conceptual framework and definition of physical activity

The definition of the exposure of physical inactivity was determined after consideration of a number of factors. These issues included: what types of activity across what domains would be included/excluded; what cut-points between inactive and active would provide the greatest availability of data and opportunity for comparability across data sets and countries; and what cut-points would be consistent with established and emerging scientific evidence. Currently these issues are under considerable debate within the scientific community and there are no definitive answers. Thus, it is in advance of any consensus that a framework and workable definition of physical inactivity as an exposure is presented.

Traditionally, physical activity research has been interested in exercise defined as "planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness"(Caspersen and Stephens 1994). This interest focused attention towards certain types of exercise, mostly vigorous-intensity activities that were undertaken usually outside of work in recreational or discretionary time. In general terms it was acknowledged that some occupational or work-related activities could reach the threshold of vigorous-intensity and thus could potentially qualify as exercise and be beneficial to health. However, because technology and industrial development were causing a rapid decline in these occupations, particularly in developed countries, considerably less interest was invested in this direction. Moreover the opportunity to intervene was more promising outside the workplace. In essence, for those interested, particularly in developed countries, the focus was on exercise and the domain of "leisure-time". Many of the measurement instruments used today reflect this perspective.

A shift away from solely focusing on exercise started after the results from several large prospective cohort studies were published in the late 1980s and early 1990s. These studies were significant because they identified the protective effects of less intense physical activity (Blair and Jackson 2001; Blair et al. 1989, 1992, 2001). By 1996 these findings

were endorsed by several leading institutions and scientific organizations (Pate et al. 1995) and formed the primary focus of the U.S. Surgeon General's Report on Physical Activity and Health (U.S. Department of Health and Human Services 1996). Combined, the evidence and the widespread endorsement shifted the paradigm towards the benefits of moderate-intensity activity such that efforts more recently have been directed towards increasing the amount of moderate-intensity activity undertaken by all adults and children. Such activities include brisk walking (>3 mph), recreational cycling and swimming.

Some have viewed this shift as premature and raised concerns about the detrimental impact on the promotion of the known additional benefits that come from enhanced physical fitness. Furthermore, the exact nature and possible differences between the dose–response relationship between physical fitness and physical activity with various disease outcomes is still under intense debate (Bouchard 2001; Kesaniemi et al. 2001; Macera and Powell 2001). Meanwhile, the shift in focus has raised questions on the definition of "moderate-intensity", on what activities constituent moderate-intensity and on how to measure the prevalence of this broader range of activities within populations. Critically, it opened up the debate on whether activities undertaken in domains of life other than leisure-time can or should be considered beneficial and thus "counted".

The answers to these important questions are often population-specific because different types of physical activities are undertaken between and within communities that differ across social, economic, geographical and religious aspects of life. Moreover, the importance of, or necessity for, physical activity in different domains of life differs between cultures. It is these differences and the complexity of measuring physical activity that have hindered the development of any international consensus on definitions and common instruments for assessing physical inactivity. Growing concern over these issues has led to several recent initiatives and considerable progress has been made toward developing a common measurement instrument for use in the future. The International Physical Activity Questionnaire (IPAQ) is a new instrument assessing total physical activity and sedentary behaviour (time spent sitting) developed by a group of international experts and tested in collaboration with researchers from 12 countries across six continents. IPAQ has demonstrated good–very good reliability and moderate criterion validity (Craig et al. 2003). Further details are available at http://www.ipaq.ki.se.

For the purpose of this project, it was acknowledged that physical (in)activity can occur across four domains: work, domestic, transport and discretionary time (see Figure 10.1). Each domain represents a sphere of daily life that is common to most populations regardless of culture or economic development and within each domain it is possible to be more or less active. The opportunity for, and the level of, physical (in)activity in each domain for any national population is dependent on

Figure 10.1 Generic framework for four domains of physical (in)activity

Figure 10.2 Relative importance of domains of physical (in)activity in two hypothetical countries

In country A, the work, domestic and transport domains contribute very little opportunity to be active. For example, this country may have well-established and complete coverage of water and electricity supply to homes and dwellings thus reducing the demands to be physically active in the domestic domain. Extensive car ownership with poor public transportation systems may have reduced the opportunity and need for activity in the transport domain. Work may have become more sedentary due to technological innovation. Thus the discretionary (leisure) domain represents the predominate domain where the greatest opportunity to be active exists. This may be typical of a developed country.

In country B, the work, domestic and transport domains contribute the most opportunity or most necessity to be active. For example, this may represent a country that has a high proportion of the adult population employed in agriculture or heavy industry both of which may require large amounts of vigorous physical exertion. Domestic activities may still involve carrying water and/or other food preparation techniques that require moderate- or vigorous-intensity physical activity. Transportation may be dominated by walking or cycling with minimal public transport alternatives and low car ownership. Relative to the previous domains, the discretionary domain may be much less important in terms of providing opportunity or need to be active for the population of this country. This may be typical of a developing country.

economic, technological, social, cultural and religious factors interacting at the individual, community and national level. Moreover, the relative importance of each domain, in terms of either representing an opportunity or necessity to be (in)active, will vary between and within countries over time. A generic model of this framework is shown in Figure 10.1 and two hypothetical countries (a and b) are shown in Figure 10.2, each with a brief description.

Using four domains as a framework for the definition of exposure is in contrast to many previous approaches to defining and measuring physical (in)activity, which made the task of searching for and interpreting global data on physical (in)activity more complex. National data on physical activity are not readily available in many parts of the world. There is even less data available across the four domains of work, domestic, transport and discretionary-time activity. Despite this limitation, the framework was selected because it presents the exposure variable in a way that has relevance to all countries around the globe. The framework

can be applied both now and in the foreseeable future, when many countries and large numbers of people are expected to experience major transitions in economic, social and health terms (Chockalingam 2000; Reddy and Yusuf 1998). The underpinning assumptions of our framework include: that physical activity can take place in different domains; that some of this activity is of sufficient intensity and duration to provide protective effects from certain diseases; and that the pattern of physical activity in each domain is very likely to vary across countries. The measurement issues related to each domain are discussed below.

1.3 Measurement issues

Instruments

There is currently no universal or even commonly used measure or instrument for physical (in)activity. This poses a serious limitation on efforts to compare levels of exposure across populations, a problem frequently cited in the literature and by others attempting international comparisons (Caspersen and Stephens 1994; IARC 2002).

Physical (in)activity is typically assessed using a series of questions as part of a self-administered or interviewer-administered questionnaire. The wording of the questions, the examples used (if any) and the response format can and do vary. A recent compendium of instruments illustrates the diversity of approaches, many of which are more suitable to the research environment rather than public health surveillance systems (Kriska and Caspersen 1997).

We undertook a review of instruments currently used to gather data at a national or large-scale population level and found that, in general, there are five different formats for questions assessing discretionary-time and work-related activities. These range from items asking for a yes/no response regarding participation in listed activities (format 1) to detailed responses about frequency, duration and type of activity performed (format 5). The formats for questions assessing physical (in)activity in these two domains are outlined in Table 10.1, and the limitations are briefly mentioned below. Few instruments were found that assessed transport-related and domestic activity.

Measures of discretionary-time activity

Instruments vary in both their intention and ability to capture details on different aspects of discretionary-time physical activities, namely: the specific type of activity (e.g. swimming, tennis, gardening, cycling); frequency (how many times in a specified time frame); duration (usually in minutes); and intensity (e.g. light, moderate, vigorous). Moreover, they use a variety of referent time frames (e.g. last week, last month, usual week, past year).

Format 1 and format 2 (Table 10.1) are similar in assessing frequency and duration of specific types of activity (either prompted or

Table 10.1 Summary of five formats of questions assessing physical (in)activity

Format	*Question/response format*	*Example*
Discretionary (leisure) time		
1	Question presents a list of sports/activities. Response options are usually Yes/No. If yes, then frequency and duration (minutes) are usually assessed. Reference time frame vary from one week to 12 months	Europe (Institute of European Food Studies 2001) Brazil (Datafohla 1997) New Zealand (Hillary Commission 1998) Canada (C. Craig, unpublished data, 2001)
2	Question asks if any sports or activities have been undertaken but no lists are shown/provided. Selected examples may or may not have been provided. If yes, type, frequency and duration (minutes) are usually assessed. Intensity of activity may be recorded also	USA (CDC 1998)
3	A single question asking which of a set of descriptions "best describes" the respondents patterns of activity. Descriptions can cover multiple domains and/or include combinations of activities of different intensity. A variation is to present two or more questions in this format with each question specifying the domain (e.g. at work or outside of work). Responses to the latter can be combined to create a score of activity. Another variation is to present single or multiple statements about physical activity, in one or more domains, and the response scale captures frequency using a Likert scale (e.g. never through to very often), or categories or is open ended	Argentina (Instituto Gallup De La Argentina 2001) Chile (Jadue et al. 1999) Egypt (Herman et al. 1995) Estonia, Latvia, Lithuania (Pomerleau et al. 2000)
4	All activities over a specific time frame are recorded (e.g. last 24 hours or last 7 days). Responses include duration (minutes) and can be recorded by intensity and/or by domain	Ethiopia (Alemu and Lindtjorn 1995)
5	A series of questions assess participation in categories of activities usually defined by intensity (e.g. moderate-intensity or vigorous intensity). Examples usually provided. Response is usually Yes/No and if yes, frequency and duration (minutes) recorded. Walking as a specific activity can be asked either as a separate question specifying which types of walking to include (all walking, not at work, for transport) or walking is given as an example within the category of moderate-intensity activity	Australia (Armstrong et al. 2000)
Work-related		
1	Question asks respondents to indicate which description best describes their work "mostly" or "usually". Response categories are often: 1) primarily sitting/standing; 2) a lot of walking; 3) hard physical (sweat) labour	South Africa (Steyn et al. 1991)

Table 10.1 Summary of five formats of questions assessing physical (in)activity (*continued*)

Format	*Question/response format*	*Example*
2	Question asks respondents to indicate how much time spent doing specific categories of activity (e.g. sitting/standing, walking, hard physical labour). Response scale may vary and can include either hours per day or proportion of time at work	Canada (C. Craig, unpublished data, 2001) Europe (Institute of European Food Studies 2001)
3	Singular or multiple questions assess participation in categories of work activities defined by intensity (e.g. light or very light, moderate, heavy or very heavy). Examples of tasks or occupations may be provided for each category. Hours or portions of time may or may not be provided	China (North Carolina Population Center 2001b) Estonia, Latvia, Lithuania (Pomerleau et al. 2000)
4	Questions assess frequency and sometimes duration of specific tasks undertaken within a reference time period (e.g. 2–12 months) are recorded. Respondents are prompted with a list of activities	Japan (Iwai et al. 2000)
5	Occupational activity is assessed by classification of type of employment (e.g. brick layer, nurse) or occupation (e.g. professional, blue collar)	Not used by any study included in this chapter

unprompted). Format 5 assesses categories of activities defined by intensity; the number and type of examples provided can vary. Additional criteria on minimum duration may also be specified. The diary or day-by-day recall methods are grouped together as format 4. However, format 3 is the most distinct set of instruments focusing on the level of activity, rather than its type or purpose. As a group they represent instruments that present categories or descriptions and use various response options, such as: pick the best description, or a Likert scale assessing frequency or duration, or scales such as 1–3 times/week, 4–6 times/week, 1–2 times/month.

Within each of the five formats, questions can be structured to assess level of activity in the discretionary-time domain only or they can address multiple domains. The latter, of course, makes it difficult to compare results across instruments. In the former, respondents are usually instructed to limit the activities they consider. Exactly how each instrument partially or totally includes/excludes different activities can however vary, particularly in regard to the following activities: walking; gardening; domestic/yard tasks. In addition, the majority of instruments focus on assessing participation in endurance/aerobic activities, probably due to the extensive literature supporting the links to health. However, activities that build muscular strength and increase flexibility are also important and warrant further attention.

Currently there is insufficient evidence to classify any of the instruments as right or wrong, but they are clearly different and there is good evidence that different instruments will produce different estimates of particular behaviours (Pratt et al. 1999). Much research has been undertaken testing different measures of physical activity to assess their reliability and validity (Jacobs et al. 1993). The more frequently used instruments (such as the Minnesota Activity Questionnaire, Seven Day Activity Recall) have been tested for reliability and validity in more studies across diverse populations (Kriska and Caspersen 1997). However, the questions used to gather population health data are often not established instruments and often lack formal testing.

Measures of work-related activity

In recent times work-related physical activity has received less attention than discretionary-time activity. Therefore, there are sparse data on patterns of activity at work and much speculation on the accuracy of recall of work activities, especially potential discrepancies between recall and actual intensity and duration of activity (Jacobs et al. 1993; Leenders et al. 2001). In particular, there is concern about the extent of over-reporting because individuals may over-estimate intensity and/or duration of work-based activities.

The most frequently used approach to assessment in this domain is to ask about three types of activities chosen because they are common in many occupations (formats 1, 2 and 3 in Table 10.1). More specific assessment of work activity can be obtained using a detailed recall (diary) or prompted recall with a list of activities (format 4). Historically, job occupation has been used as a proxy measure for work-related physical (in)activity (format 5) but as technology and work practice differs between countries and over time this is deemed to be the least favoured approach. To date, there is little evidence on the reliability and validity of most of these instruments or approaches.

Measures of transport-related and domestic activity

Measurement of transport-related and domestic physical activities is the least well-developed area. There are few specific questions or instruments available and some activities in these domains are captured as part of questions aimed more at the discretionary or work-related domains. This confusion makes quantifying the prevalence of physical (in)activity in the transport and domestic domains very difficult.

Most of the available data on transport-related activity are from sources within the discipline of transportation. Usually these data are limited to trip origin and destination, distance, duration and mode (e.g. cycling, walking). How well they capture walking and cycling as part of multi-modal travel can vary. Also transportation surveys rarely capture the perceived intensity of the activity although a computed measure could be obtained if distance and duration were both assessed. Data on

patterns of transport are most often presented as modal split with total number of trips as the denominator; other metrics include miles of travel. Data in these formats are not readily integrated or compared with data from population health surveys on physical activity. Moreover, it is usually only in research projects that data on transport-related activities and physical activities in other domains are collected on the same individuals.

Assessment of domestic activities as a distinct domain is uncommon. If these activities are considered at all, they are usually included as examples within the structure of other questions. For example, washing floors or vacuuming can be given as examples of moderately-intense activities. However, within the field of diet and nutrition some researchers very carefully assess energy intake and energy expenditure. But for these purposes they often assess total energy expenditure using doubly-labelled water (H_2O_2), direct observation or very detailed diary methods. There is currently no suitable, valid and reliable instrument for use in assessing activity in the domestic domain. It is, therefore, evident that further instrument development is needed to advance the assessment of physical (in)activity in both transport and domestic domains.

Further issues related to measurement methodology

In addition to the use of a variety of instruments, the method of data collection can vary. Self-report instruments continue to be the most widely used method for assessing physical activity in adults (Sallis and Saelens 2000), particularly in developed countries. In these countries widespread coverage of telecommunications has led to increased use of telephone-based surveillance systems (e.g. the Behavioral Risk Factor Surveillance System in the United States of America). In contrast, household surveys remain more common in other regions (e.g. Central and South America, Asia, Africa). There is no scientific evidence to support one methodology over the other in terms of accuracy of data on physical activity. But it is possible that each method may obtain different estimates of the behaviour. If the magnitude and direction of this difference were known for different populations it would be possible to include some statistical adjustment. However, in the absence of this information the inclusion of data collected using different interview methods will be a limitation to our estimates.

Patterns of physical activity are known to vary across different climatic seasons (Pratt et al. 1999). Ideally national estimates would be based on data collected across all seasons (a 12-month period) or data collection would be limited to a specified season. Cross-country and global comparisons could then be conducted either using only data collected in comparable seasons or only data collected over all seasons. Needless to say, with the overall dearth of data on physical (in)activity it was not possible to impose seasonality criteria within this project and this feature of the data will be another limitation to our final estimates.

1.4 Quantifying levels of exposure

Once data on physical (in)activity have been collected using any one of the approaches described above, the data can be treated as either a continuous or categorical variable. There are examples of both approaches with national data from around the world. Both approaches were considered for this project but due to the availability and comparability of data we chose to treat physical inactivity as a trichotomous categorical variable. A brief description of both approaches is provided below.

Treating physical (in)activity as a continuous variable

Minutes of activity can be presented as a continuous variable either as mean minutes per specified time frame (e.g. per week or per day) or it can be used to derive an estimate of energy expenditure expressed as metabolic cost (metabolic equivalent, MET) or kilocalories/kilojoules (kcal/kJ). One MET represents the metabolic rate of an individual at rest and is set as 3.5 ml O_2/kg per minute or approximately 1 kcal/kg per hour (Kriska and Caspersen 1997). With this approach, analysts use available lists of the energy requirements of specific activities (Ainsworth et al. 2000) or standard MET values for categories of activity. For example, the following MET values are frequently, but not consistently, applied to the following categories: vigorous-intensity activities = >6 METs; moderate-intensity activities = 3–6 METs (= 4.5); walking = 3 METs (Ainsworth et al. 2000). Energy requirements of a large number of tasks across all four domains are available (Ainsworth et al. 2000).

The continuous measures were not selected as the basis for the definition of the exposure, nor were data in these formats available for use in any other way for two reasons. Firstly, these estimates were derived from different instruments, and each analysis used different criteria to compute their estimates. Thus, large variability prohibited comparability despite the seemingly similar continuous measures of risk. Secondly, data obtained as mean minutes, mean kcals or mean MET minutes of activity could not be used to compute the distribution of exposure because the relationship between these values and the pattern of inactivity in a population is not known. In contrast, the relationship between mean body mass index (BMI) and the prevalence of obesity in populations has been explored.

Treating physical (in)activity as a categorical variable

A current trend in analysing population data on physical (in)activity is to collapse the continuous data on minutes of activity into a categorical variable and report the prevalence estimates of each category. This is undertaken for each specific type of activity (e.g. walking, sports, lifting loads, climbing stairs) or more usually, the total amount of time spent doing physical activities assigned to different categories (e.g. total minutes of moderate-intensity or vigorous-intensity activity or heavy

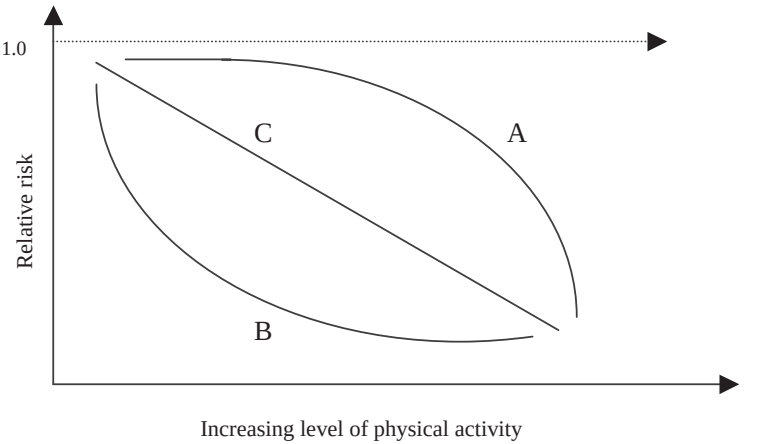
physical labour). The total of all activity can be calculated by summing all minutes of each activity or each category. However, close inspection reveals that these general approaches can include or exclude some specific physical activities or some domains depending on the investigators' purview. For example, gardening activities may be asked about but not included in calculations of activity (Armstrong et al. 2000) or work-related activity may be assessed but excluded or else reported separately from discretionary-time activity (Pomerleau et al. 2000). These specific analytic details necessitate very careful attention before comparisons between data sets can be attempted.

It has also become quite common among those dealing with national or regional surveillance data to present categorical data and to select the categories that correspond with various national public health guidelines or goals. A recent development has been the reporting of data as a measure of "recommended" or "sufficient" levels of activity in accordance with the U.S. Surgeon Generals' Report on Physical Activity and Health (U.S. Department of Health and Human Services 1996). This recommendation states that "30 minutes of moderate-intensity activity on most, if not all days of the week" is recommended for all adults. It is often, but not always interpreted and analysed as 150 minutes of moderate-intensity activity over at least five sessions or day/week. But there is still sufficient variation between the ways in which this recommendation is interpreted to make seemingly simple comparisons somewhat difficult.

1.5 Correspondence between measures of exposure used in population surveys and epidemiological research

The majority of epidemiological studies have explored the relationship between activity and disease outcomes by dividing level of activity into two or more groups. This is true whether the exposure was physical activity or physical fitness. The nature of the dose–response relationship has been explored using dichotomous categories (Morris et al. 1980), tertiles (Bijnen et al. 1998), quartiles (Folsom et al. 1985) and quintiles (Singh et al. 1998). Although continuous data are usually preferred because this maximizes the opportunity to detect associations, use of categorical data is warranted when the association may not be linear. Indeed, the nature of the curvilinear or linear relationship between physical activity and disease outcomes is a major focus of current research efforts (Blair et al. 2001; Kesaniemi et al. 2001; Williams 2001). Three possible relationships are illustrated in Figure 10.3. One contemporary view supports the presence of a threshold as shown by curve B in Figure 10.3, particularly for cardiovascular end-points. Curve B indicates that the greatest reduction in risk comes from increases at the lower levels of activity. Experts involved in a recent evidence-based symposium concluded that there is "an inverse and generally linear relationship for the rates of all-cause mortality, total cardiovascular disease, and

Figure 10.3 A schema of three possible relationships between physical inactivity and disease end-points



coronary heart disease incidence and mortality and for the incidence of type 2 diabetes mellitus", a position reflected in curve C (Kesaniemi et al. 2001).

While the debate on the exact shape of the relationship is likely to continue, the use of categorical data may be justified given the known difficulties (i.e. error) associated with both the measurement instruments used to assess physical (in)activity and respondent recall of the behaviour. Under these circumstances continuous data may present an artificial level of accuracy and specificity.

It is worth noting one additional difficulty that obscures the level of correspondence between measures and thus the accurate application of relative risk results from epidemiological studies to prevalence estimates in order to calculate population attributable risk and the burden of disease. Namely, the lack of detailed descriptions of the absolute values of activity represented by the investigators' chosen categories. For instance, it is difficult to compare the level of activity in the lowest tertile of activity from study A with study B unless the activity level is defined and reported. Likewise it is almost impossible to make accurate interpretations of tertiles and quartiles without appropriate descriptive statistics for each group. This omission necessitates qualitative judgements when comparing or pooling results across studies and may obscure the strength and nature of the disease–risk factor association.

Notwithstanding, these are important limitations; currently the greatest concordance between measures of physical activity used in epidemiological studies and population surveillance is found at the lower and

upper ends of the physical activity continuum. Application of the relative risk results for the least active group (be it tertile, quartile or quintile) to prevalence estimates for lowest level of activity in whole populations is possible. There is, however, less certainty surrounding the agreement between measures of low–mid levels and mid–upper levels of exposure.

Measurement error associated with assessing exposure to physical inactivity is a major limitation to this project. We addressed this problem in several ways. Our treatment of the exposure as a trichotomous variable avoids presenting a misleading level of accuracy. The definition of the categories corresponds with our greatest level of confidence in the accuracy of our data, particularly at the lower end. Our definitions and estimates of exposure within each domain accommodate the known or suspected direction of measurement error. Finally, as we describe in our review of epidemiology, our pooled meta-analyses included an adjustment for measurement error based on available evidence of reliability of the instruments used in each study.

1.6 Definition of exposure

In balancing the need for a conceptual framework with global relevance, concordance with the epidemiological evidence, current public health recommendations, as well as the limited availability of national data, the following definitions of a three level exposure of physical inactivity were developed:

Exposed

Level 1 Inactive:
defined as doing no or very little physical activity at work, at home, for transport or during discretionary time.

Level 2 Insufficiently active:
defined as doing some physical activity but less than 150 minutes of moderate-intensity physical activity or 60 minutes of vigorous-intensity physical activity a week accumulated across work, home, transport or discretionary domains.

Unexposed

Level 3 Sufficiently active:
defined as at least 150 minutes of moderate-intensity physical activity or 60 minutes of vigorous-intensity physical activity a week accumulated across work, home, transport or discretionary domains, which approximately corresponds to current recommendations in many countries.

In the work domain, inactive was defined as not doing any "hard" or "vigorous" physical activities at work. Where needed, we classified those that reported "mostly walking" or "mostly standing" or any equivalent category, as inactive. The effect of our definition is to potentially inflate

the proportion classified as inactive at work because some adults may perform these tasks during their work in combinations of duration and intensity sufficient to gain some health benefits. However this is perhaps counterbalanced by at least some likely misclassification of adults as active due to "heavy" activity. In the absence of data with sufficient detail and no prior evidence on which to base our classification, our definition reflects the limitations of measurement in this domain.

Inactive in the transport domain was defined as no walking or cycling trips. Therefore, a single walk or cycle trip was sufficient for an adult to be classified as active in this domain. With few data on trips per person and no data on trip intensity or duration we accepted all walking and cycling trips as activity that could provide some health benefits. In contrast to the work domain this definition is lenient and the likely effect is to overestimate transport-related activity. However, unlike walking at work, which may be performed in short bouts and undertaken intermittently, transport-related activity may be of longer duration and undertaken at moderate-intensity. Inactive in the domestic domain was defined as no moderate- or vigorous-intensity domestic-related activity. However, with no national data worldwide we were unable to include this domain of activity in our assessment.

Insufficient activity was assessed by distinguishing between those adults who met the threshold of at least 150 minutes of moderate-intensity physical activity accumulated from one or more domains from those adults who did not. Given the lack of national data using the same or equivalent definition, we used the limited available data to develop an algorithm to estimate the prevalence of this level of exposure in each country. Full details of our methods for assessing inactive (level 1) and insufficiently active (level 2) are described in section 2.

1.7 Age groups included—adults but not children

Very few data were available on levels of (in)activity in children and adolescents. Moreover, the literature on children also includes a diversity of instruments and measurement methodologies (Sallis and Saelens 2000). Therefore, due to the magnitude of the task and the project timelines, the scope of this project was limited to quantifying exposure in the adult population only. Furthermore, there is limited epidemiological evidence demonstrating the level of current risk associated with inactivity and the selected health outcomes in populations aged <18 years.

1.8 Theoretical-minimum-risk exposure distribution

For physical inactivity the theoretical-minimum-risk exposure distribution could be set as equal to the estimated proportion of the total population that would be physically unable to meet the basic requirement of "at least some activity" in at least one domain. Data from Australia (2%) and the United States (4–6%) indicate that total disability (as defined by each country) is well below 10% of the population but it is

unknown as to what proportion of this sub-population would be unable to do at least some physical activity.

Conceptually the theoretical-minimum-risk exposure is that level of activity which could *theoretically* occur if we could remove all individual, social and environmental causes of inactivity. Under such a scenario it is possible to consider a minimum that reflects all but the congenital causes of inactivity. As these are few, if any, and are likely to affect less that 1% of the whole population, we have chosen to set a theoretical minima as zero—a value that is comparable to other risk factors.

2. Estimating the prevalence of exposure

There were large gaps in the availability of nationally representative data on physical inactivity within some subregions and no data for several subregions. This was true across all four domains of activity included in the definition of exposure and both levels of exposure. To address this problem multivariate and linear regression analyses were conducted to create predicted values for missing data.

2.1 Search strategy

An extensive search was undertaken to identify studies reporting prevalence of inactivity for male and female adults (aged ≥15 years) worldwide. A particular effort was made to identify data in developing regions to avoid the need to derive estimates for these countries solely on data from developed countries.

Data were sought on physical inactivity across four domains, namely, discretionary time, work-related, transport-related and domestic. The initial search identified several studies in which population-based estimates of physical (in)activity were reported as a risk factor for specific diseases. Based upon these findings, a second search was conducted to include as keywords those diseases where physical inactivity has been shown to have a relationship, in both prevention and as a risk factor. For example, diabetes, cardiovascular disease, obesity and cancer were keywords used in the second search. Papers reporting data on physical inactivity in one or more domains were accepted for consideration. However, our search most frequently identified estimates for discretionary-time activity and rarely data on occupational, transportation or domestic (household) physical activity. Therefore separate searches for occupational and/or work, transportation and domestic domains were performed. For all searches, country names were included when global, international and/or world keywords were not used.

Publications reporting data collected between 1996 and 2000 were sought because the primary goal was to estimate prevalence of inactivity in the year 2000.

Electronic literature search

Medline, HealthStar and Chronic Disease Prevention searches were systematically conducted for studies published between 1996 and 2001 and limited to English (both United Kingdom and American English spellings) and Spanish languages. Additionally, multiple queries for each keyword were used. For example diabetes AND physical activity AND country X.

The following keywords were used:

- exercise, physical fitness, physical exercise, physical (in)activity, sedentary, energy expenditure;
- chronic disease prevention, diabetes, cancer, cardiovascular disease, hypertension, obesity;
- international, global, world, developing countries, country names;
- monograph, statistics, survey(s), prevalence;
- transportation (and physical activity/energy expenditure);
- occupation (and physical activity/energy expenditure and activity); and
- domestic (and physical activity/energy expenditure and activity).

Electronic listserve

A request for assistance in locating "gray" or fugitive literature (e.g. government and non-government agency reports) as well as unpublished data was posted on a cardiovascular listserve (procor-dialogue@healthnet.org).

Government and non-government agencies

World Health Organization (WHO) Headquarters, WHO Regional Offices, WHO collaborating centres and partner organizations worldwide were contacted to assist in identifying authors, researchers, organizations and institutions in obtaining national data on prevalence of physical activity, either at the country, regional or municipal level.

Authors of relevant papers, relevant academic institutions and experts in the field

Direct contacts were made with national governments, private and public institutions and individual authors to enquire whether unpublished or published data were available in English or other languages.

2.2 Criteria for considering sources and study inclusion

All identified studies were reviewed and included if they fulfilled the following criteria.

Time frame—data were obtained between 1996 and 2001. However, if there were no other data available for the country/region, studies reporting data collected after 1990 were considered.

Sample—studies reporting data from large, randomly selected, nationally representative samples with a wide age range were preferred. However, given this was not available in the majority of countries, studies with smaller samples, regional representative samples or narrow age ranges were considered.

Measure of exposure—the proportion of the population exposed (inactive) in one or more domains (discretionary time, occupational, domestic, transport-related) was required. In cases where data were presented as mean minutes, METs, total energy expenditure (kcals) or in any other way, the authors were contacted and asked to provide the data expressed as a proportion of the sample population. Where possible authors were asked to use our definition of exposure (overall inactivity) and/or the definition of inactivity relevant to each domain. If these data were obtained, they were considered for inclusion.

Measurement instrument—studies reported (or later provided) the instrument used to assess physical activity. As no standard measure of physical activity exists each instrument or set of questions was reviewed in this work. Those studies using previously published instruments assessing physical activity in one or more domain were accepted. Studies using questions unknown to the authors were assessed for face validity. A study was included only if it was deemed that the question(s) would provide reasonably comparable estimates.

Data collection—studies were included if data were collected by telephone survey, face-to face interview or during a physical examination.

2.3 Methods for selecting estimates where more than one data source existed

The following criteria were used to select data sources in cases where more than one source was available for a country or group of countries:

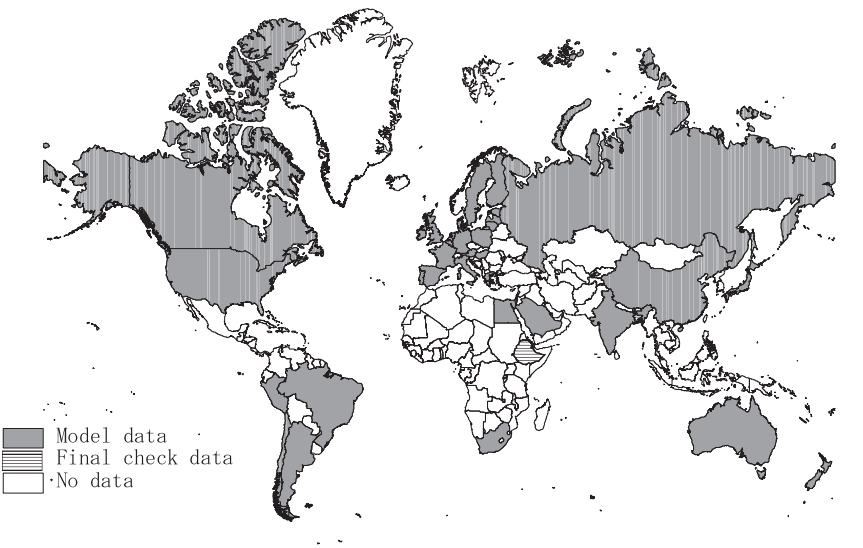
- the most recent data source—in some cases this meant the data were not yet in the public domain and specific analyses were undertaken for this project;
- nationally representative data or the study that allowed the best approximation of a national sample considering the studies representativeness and coverage of the desirable age range;

- a single study with common methods and representative population data from many countries was preferred over equal quality studies from individual countries; and
- the study providing the most comparable measure of physical inactivity as defined in this study.

2.4 Description of studies, including methodological qualities

Overall our search identified over 50 studies containing measures of physical (in)activity in one or more domain. These data covered 43 countries and 13 subregions. However, not all studies met the inclusion criteria and for some studies we were unable to obtain data in the desired format within the study time frame. Thus, our final analyses were conducted using 17 data sets for discretionary-time activity, two data sets for work-related activity and five data sets for transport-related physical activity representing 34 countries across 10 subregions. Figure 10.4 illustrates data coverage by country showing those countries that had data that met our inclusion criteria. Table 10.2 shows the proportion of the adult population for which we had data for each subregion (calculated by 12 age and sex categories).

Figure 10.4 Exposure data coverage by country[a]



[a] Reflects data found by February 2002; other data have subsequently been identified.

Table 10.2 Proportion of the adult population for which there were data on physical inactivity, by subregion

Subregion	Population in subregion (000s)	% population within subregion covered with data
AFR D	164917	0
E	192766	15
AMR A	255419	96
B	297674	48
D	44658	34
EMR B	86854	7
D	204038	21
EUR A	342220	87
B	161213	0
C	1978934	63
SEAR B	206871	0
D	818521	0
WPR A	129888	65
B	1131474	85

Table 10.3 provides an overview of the studies reviewed with details on the data source, sample characteristics and the domains of physical activity assessed by country and subregion. Overall, over 90% of the data sources comprised nationally representative samples and all data were collected using a random sampling methodology. Sample sizes ranged from 226 in Ethiopia (Alemu and Lindtjorn 1995) to 16000 in China (Du et al. 2002) with the majority of studies including between 2000 and 4000 subjects. Most data were collected as part of either national surveys or ongoing monitoring systems or as part of a research project. There is one example of data from a commercial marketing company (Instituto Gallup De La Argentina 2001) and one example of a large multi-country study (Martinez-Gonzalez et al. 2000). The foci of research studies were most often cardiovascular disease, hypertension or diabetes. All data were collected after 1990.

The majority of data were collected using a questionnaire assessing multiple lifestyle risk factors although several studies collected data on physical activity only (e.g. Australia). Only a few studies assessed occupational activity as a separate domain and typically these questions assessed prevalence of three types of occupational activity, for example "mostly walking", "mostly standing" or "mostly heavy labour". Very few data were found on transport-related activity. Specific items on transport-related activity were included in only one of the health surveys (China) (North Carolina Population Center 2001b) although several other countries included walking or cycling for transport within the context of their physical activity questions. No studies were found reporting national data on physical activity in the domestic domain

Table 10.3 Summary of sources of exposure data, by subregion

							Data obtained by domain[b]				
Subregion	*Country*	*%*[a]	*Author*	*Year of data*	*Sample size*	*Sampling frame*	*Response rate*	*L*	*O*	*T*	*D*	*M*
African Region												
AFR-E	Ethiopia[c]	18	Alemu and Lindtjorn (1995)	1991	226	Random selection of households	Not reported					✓
	South Africa	15	Steyn et al. (1991)	1990	986	Random, stratified, proportional sample of households	Not reported	✓	×			
Region of the Americas												
AMR-A	Canada	10	Health Canada (2000)	1998	6414	Random digit dial, sampling of households, stratified by region	58%	✓	×			
	USA	87	Ham (2001a)	2000	7529	Random digit dial sampling of households stratified by state	60%	✓				
	USA	87	Ham (2001b)	1995	42000 households	24-hour travel diary	Not reported			✓		
	USA	87	Macera et al. (2001)	1999–2000	7529	Random digit dial sampling of households in the 48 continuous states	. . .			✓		
AMR-B	Argentina	9	Gallup Argentina (2001)	2001	1247	Multistage random stratified sample system	Not reported	✓				
	Brazil	41	Datafohla (1997)	1997	2054	Not reported	Not reported	✓				
	Chile	4	Jadue et al. (1999)	1996–1997	3120	Random stratified sample from 4 zones in selected area	40%	✓				
AMR-D	Peru	38	Cortez et al. (2002)	1999	NA	Random sampling	Not reported	✓				

Eastern Mediterranean Region									
EMR-B	Saudi Arabia	13	al-Refaee and al-Hazzaa (2001)	2000	1333	Random selection of 3 public and 3 private institutions and random distribution to employees	75%	✓	
EMR-D	Egypt[c]	22	Herman et al. (1995)	1991–1994	4918	Systematic 1/3 of households from eight randomly selected areas within 3 chosen metro areas	81%		✓
European Region									
EUR-A	15 European countries[d]	92	Martinez-Gonzalez (2000)	Spring 1997	Median across 15 countries = 1003	Multi-stage stratified cluster sampling	Quota system —no data on respondents available	✓	
	8 European countries[e]	60	Pucher and Dijkstra (2000)	1995	Not available	Multiple sources of travel survey data which varied between countries	Not available		✓
	United Kingdom	14	Dept for Transport, Local Government and the Regions (2002)	1997–1999	Not available	Results of national travel survey	Not available		✓

continued

Table 10.3 Summary of sources of exposure data, by subregion (*continued*)

								Data obtained by domain[b]				
Subregion	*Country*	*%*[a]	*Author*	*Year of data*	*Sample size*	*Sampling frame*	*Response rate*	*L*	*O*	*T*	*D*	*M*
European Region												
EUR-C	Estonia	1	Pomerleau et al. (2000)	Summer 1997	2018	Simple random stratified sample from register	67%	✓	×			
	Latvia	1	Pomerleau et al. (2000)	Summer 1997	2303	two stage sampling	78%	✓	×			
	Lithuania	2	Pomerleau et al. (2000)	Summer 1997	2140	Simple random sample from register	73%	✓	×			
	Russian Federation	63	Cockerham and Sneed (2001)	1995	8402	Random national sample	Not available	✓				
South-East Asia Region												
SEAR-D	Bangladesh	10	Hypertension Study Group (2001)	Dec 1999–Feb 2000	723	Random multistage cluster sampling within selected site	Not reported					×
	India	82	Hypertension Study Group (2001)	Dec 1999–Feb 2000	723	Random multistage cluster sampling within selected site	Not reported					×
	India	82	Singh et al. (1998)	1997	1769 rural 1806 urban	Random multistage cluster sampling within selected sites	81% rural; 91% urban					×
	India	82	Gupta et al. (1994)	1993	1150	Random sampling	Not reported					×

Western Pacific Region										
WPR-A	Australia	12	Armstrong et al. (2000)	1999–2000	3841	Random sample of household from white pages	Not reported	✓		
	Australia	12	Transport-Travel Demand Management (2000)	1997–1998	. . .	Randomly selected households	Not reported			✓
	Australia	12	Bull et al. (2000)	1999–2000	3178	Stratified random sampling of household from white pages	46%			✓
	Japan	84	Iwai et al. (2000)	1992–1994	1893	Stratified random sample from registry of 9 rural and 4 urban selected communities	60%	✓		
	New Zealand	2	Hillary Commission (1998)	1997	5470	Multi-staged random cluster sampling of households	68%	✓		
WPR-B	China	85	Ham (2001c)	1997	16000	Multi-staged random cluster sampling of household of nine Provinces	Not available	✓	✓	✓
	China	85	Li Xiang-ru et al. (2001)	1996	8000	Multi-staged random cluster sampling	Not available	✓		

Key: ✓, data included; X, data not included; L, leisure (discretionary) time; O, occupational; T, transport; D, domestic; M, multiple domains included in one/two question(s).

[a] Percentage of the total population in each region that each country represents.

[b] Data included means data were used as presented in publication and/or data were obtained in format for comparison; data not included means data were not published and/or were unavailable in comparable format.

[c] Data used only in post hoc assessment of final predicted estimates of physical inactivity.

[d] Country (sample size): Austria (982), Belgium (1147), Denmark (979), Finland (1003), France (1159), Germany (1011), Greece (1011), Ireland (1001), Italy (1000), Luxembourg (512), Netherlands (1010), Portugal (1007), Spain (1000), Sweden (1001), United Kingdom (1490).

[e] Austria, Denmark, France, Germany, Italy, Netherlands, Sweden, Switzerland.

alone. Like transport, domestic activities were sometimes included within the context of broader questions, particularly in instruments developed for use in developing countries. Details of the questionnaire, the domains and definition of inactivity for each data set included in the analyses are provided in Tables 10.4–10.6.

Below are brief summaries of the data found and included, described by geographical region.

Africa

Finding data on physical activity from countries in the African Region was most difficult.

Several studies were found for various sub-populations in South Africa (Levitt et al. 1993, 1999; Sparling et al. 1994; Steyn et al. 1985, 1991). But these were regional studies with modest sample sizes. In the absence of a single study with a nationally representative sample, published data from the larger, more recent risk factor study in a black population (known as the Black Risk Study, BRISK) (Steyn et al. 1991) were selected to represent the black South African population. Estimates of inactivity among the white South African population were imputed from American data after a qualitative assessment (Lambert 2001) of the similarities in urban lifestyles. Given national estimates from the United States include white and non-white populations, the extrapolation to white south Africans may slightly underestimate levels of activity. This approach adds greater uncertainty to the estimates for this region and this is addressed in later sections.

Data from two small studies, one in rural Ethiopia (Alemu and Lindtjorn 1995) and the other in the United Republic of Tanzania (Aspray et al. 2000), provided a useful post hoc validity check on our final estimates of discretionary-time inactivity. Both studies assessed physical activity across multiple domains that could not be disaggregated.

No data were found to represent those countries in the AFR-D subregion. Two studies reported data from Nigeria (Ezenwaka et al. 1997; Forrest et al. 2001) and one study submitted for publication from Cameroon (Sobngwi et al. 2002) were identified but all three studies reported physical activity using different summary scores and/or units. At the time of our analyses the results from reanalysis were not available.

Americas

Data on discretionary-time physical inactivity and work-related activity from the United States and Canada were identified for the AMR-A subregion. Both countries have established surveillance systems collecting nationally representative data on patterns of physical activity (C. Craig, unpublished data, 2001; S. Ham, unpublished data, 2001a; Macera et al. 2001). Data on transport-related activity for the United States were

available from the National Personal Transportation Survey (Federal Highway Administration Research and Technical Support Center 1997) and data for Canada were found in a cross national comparison report (Pucher and Dijkstra 2000). No data were found for Cuba, the third country in this subregion.

For the AMR-B subregion national data on physical activity were found for Argentina, Brazil and Chile. In Brazil multiple data sets were found for different cities including Porto Alegre (Duncan et al. 1993) and São Paulo (Andrade et al. 2001). However data from the most recent, largest, most representative study, with sampling from 98 cities across Brazil was selected (Datafohla 1997). Data for Argentina were obtained from a recent national Gallup Poll that included one item on physical activity (Instituto Gallup De La Argentina 2001). Data for Chile were obtained from a recent published study conducted in a metropolitan area of Valparaiso. (Jadue et al. 1999) Two studies from Peru with data on work and discretionary-time activity were identified for AMR-D (E. Jacoby, unpublished data, 2000). Only the data on discretionary-time activity were available for inclusion.

Eastern Mediterranean

Only two studies were found reporting data for physical activity EMR-B and EMR-D and neither study provided national estimates. One study from Saudi Arabia reported estimates for only discretionary-time inactivity in male adults (al-Refaee and al-Hazzaa 2001). While these data are limited in both domain and are for males only, the questions were deemed comparable and due to the lack of any alternative data they were included for EMR-B. The second study reported data on physical activity from a large sample of adults in a region of Egypt (the city of Cairo and surrounding villages) (Herman et al. 1995). The measure of inactivity assessed discretionary-time, transport and work-related activity in combination. Because it was not possible to disaggregate these components these data were used only as a post hoc check of the final predictive model.

Europe

Although several individual European countries have collected data on various domains of physical activity in recent years (Hassmen et al. 2000; MacAuley et al. 1996, 1998) we selected a recent, large, multi-country study (n = 15239) assessing both discretionary-time and work-related physical activities (Institute of European Food Studies 2001). The study was selected for inclusion because it collected national representative samples from 15 countries and data were collected within a defined period of time using the same measurement instrument. The Physical and Nutrition European Union data set (known as PAN EU) provided 87% coverage of EUR-A; however these data were collected by commercial marketing companies in each country and there were no available data

on the response fraction. This concern increases uncertainty around these estimates but the data were deemed more comparable than using a larger number of country-specific estimates, collected using a variety of instruments and providing less coverage of the EUR subregions.

Data on transport-related activity are likely to exist for many European countries at either a national or regional level, often in departments of transportation or planning databases. However, these data remain difficult to locate and require translation. In lieu of obtaining these data directly we used a recent report that provided national estimates of walking and cycling for several European countries and Canada (Pucher and Dijkstra 2000).

No data were found for EUR-B. Data from the MONICA project that included two sites in Poland were considered, but were not nationally representative and were therefore excluded.

One study reported data from three countries in EUR-C, namely Estonia, Latvia and Lithuania (Pomerleau et al. 2000). Two sources were identified for data on physical activity in the Russian Federation. An unpublished research study investigated patterns of activity in an adult population in Moscow (Zabina et al. 2002) and a publication using data from the Russian Longitudinal Monitoring Survey (RLMS) (North Carolina Population Center 2001a). We were unable to complete analyses of the most recent RLMS data (1998/2000) and therefore selected the published estimates from survey six in 1995 and we were provided with additional unpublished analyses from this data set (Cockerham and Sneed 2001). Combined the two sources of data provide 63% coverage of EUR-C. No data were found on transport-related activity for EUR-C.

South-East Asia

Our search found only a few studies with data on patterns of physical activity in India (Gupta et al. 1994; Singh et al. 1998) and one study with data from Bangladesh (Hypertension Study Group 2001). Other contacts through international agencies and electronic listserve identified several studies with unpublished data although none of these included nationally representative samples (Misra et al. 2001; K. Reddy, unpublished data, 2001). One study investigated an urban slum population (A. Misra, unpublished data, 2001) and another a population selected from an industrial workforce (K. Reddy, unpublished data, 2001). Both studies provided us with additional unpublished analyses, and we attempted to create a weighted (by urban and rural) national estimate. However, the results from these studies showed no clear pattern and we had low confidence in our estimate. Therefore, these data were not used in the final analyses. The small, published study with a population of older adults from rural and urban towns in Bangladesh and India was considered for SEAR-D. However, on close inspection these data were considered insufficient for inclusion.

Western Pacific

Australia and New Zealand both have established health and population surveillance systems and from time to time conduct national surveys specifically aimed at assessing patterns of physical activity. Data from these specific surveys were selected for our analyses (Armstrong et al. 2000; Hillary Commission 1998). No national data on transportation activity were found for this region, thus we substituted data on cycling and walking for transport from a combination of two reports from Australia; one included a large survey with a representative sample of the population in Western Australia (Bull et al. 2000) and the other included data from a transportation project also undertaken in Western Australia (Travel Demand Management 1999).

Two studies published in English were found reporting data on discretionary-time physical activity in Japan (Arai and Hisamichi 1998; Kono et al. 1999) and translation of data from another source was also provided (N. Murase, unpublished data, 2001). However, we chose to include data from the larger Japanese Lifestyle Monitoring Study (Iwai et al. 2000) even though only discretionary-time physical activity was assessed in a middle-aged adult population (40–60 years). A small study in Singapore with data from women only was also found but after considering the instrument and definition of inactivity it was excluded.

Subregion WPR-B is represented by data found from China. Nine published studies were identified (Bell 2001; Hong et al. 1994; Hu et al. 1997, 2002; Matthews et al. 2001; Paeratakul et al. 1998; Pan et al. 1997; Yu and Nissinen 2000; Yu et al. 2000) but excluded in preference for recent data from the China Health and Nutrition Survey (CHNS) (North Carolina Population Center 2001b). Micro data were available online (http://www.cpc.unc.edu/) and we conducted additional analyses on physical activity across different domains (Ham 2001c). Additional data from the State Sport General Administration of China were also found and these suggested notably higher estimates of discretionary-time activity compared with CHNS. After a careful review of the two questionnaires and input from experts familiar with China, the average of the two studies was used to estimate the prevalence of inactivity in China (Wang 2002). These data provided 85% coverage of WPR-B.

2.5 Comparability of instruments assessing physical activity and estimates of exposure among included studies

Tables 10.4, 10.5 and 10.6 provide a summary of the data sets used to assess physical (in)activity in discretionary-time, work and transport domains, respectively. For each data source a brief description of the question and the definition of inactive is provided. Below is a summary on the comparability of the final selection of studies in each domain.

Table 10.4 Summary of questions used to assess discretionary-time physical (in)activity

					Discretionary-time (in)activity	
Subregion	*Country*	*Reliability*	*Validation*	*Study title/instrument (reference)*	*Method of assessment*	*Definition of inactive*
AFR-E	Ethiopia	Not available	Not available	Borana Health and Nutrition Study (Alemu and Lindtjorn 1995)	Seven-day recall via a series of close-ended questions. Participants were interviewed for 7 consecutive days every three months for one year. Activities coded as sleep (1 MET), light (1.5 METs), moderate (4 METs), hard (6 METs), very hard (10 METs)	Reported mean day EE in kcals/day and kcals/kg per day. (Reanalysis for this work defined inactive as no hard or very hard activities over a 7-day period)
	South Africa	Not available	Not available	BRISK study (Steyn et al. 1991)	Question: After working hours do you get any regular (more than twice/week) exercise? If yes, is it light or strenuous?	No exercise outside of working hours
AMR-A	Canada	Not available	Not available	1998 Physical Activity Monitor (C. Craig, unpublished data, 2001)	Prompted recall of participation in approximately 25 different activities over last 12 months. For each activity reported, number of times in last 12 months and average duration/occasion were recorded	Energy expenditure equal to or less than 0.5 KKD (kcals/kg per day)
	USA	Kappa = 0.57–0.77	Not available	National Physical Activity Survey 1999–2000 (Ham 2001a)	Question: In last month, have you participated in any physical activities or exercises such as brisk walking, bicycling, vacuuming, gardening, or anything else that causes small increases in breathing or heart rate? If yes, type, distance, usual minutes and frequency are recorded	No activities reported

AMR-B	Argentina	No	No	August Omnibus Wave-Gallup Poll (Instituto Gallup De La Argentina 2001)	Question: Do you regularly practice some type of physical activity? If yes, what (choice of 8 activities or "other")?	No practice of regular physical activity
	Brazil	No	No	Brazil – 98 Cities Project (Datafohla 1997)	Prompted recall of participation in 15 sports and activities (+ "other"). If yes, frequency during last month and pattern of participation over last 10 years was recorded	No activities reported
	Chile	Pearson correlation for leisure index 0.74–0.83	Pearson correlation r = 0.83 (VO2 Peak) 0.44–0.56 (EE from 3-day diary)	Baecke Questionnaire of Habitual Physical Activity (Jadue et al. 1999)	Participation in sports assessed in two ways. One question asked Do you play sports? If yes, type, frequency, duration recorded. Second question asked During leisure time I play sports? Response is on 5-point Likert scale (never–very often)	Persons who "never" do exercise (sports) regularly in their free (leisure) time
AMR-D	Peru	Not available	Not available	National Living Standards Measurement Survey (Cortez et al. 2002)	Question: In the last month, did you practice any sport such as soccer, volleyball, jogging or walking, among others? If yes, How many times during the last month did you participate in these activities?	No practice of physical activity in leisure time in last month
EMR-B	Saudi Arabia	Not available	Not available	Research project using original questions (al-Refaee and al-Hazzaa 2001)	Question: Do you currently do any type of physical activity in a typical week? If yes, Is it regular? How many days? For how long? What kind?	No current physical activity at all (no walking, jogging, swimming, gardening, yard work or any sporting activity)
EMR-D	Egypt	Not available	Not available	Research project using original survey (Herman et al. 1995)	One question assessed activity "outside the job" (including transportation to and from work, sporting activities, and other leisure time physical activity). Response was on a 4-point scale	No physical activity weekly

continued

Table 10.4 Summary of questions used to assess discretionary-time physical (in)activity (*continued*)

					Discretionary-time (in)activity	
Subregion	*Country*	*Reliability*	*Validation*	*Study title/instrument (reference)*	*Method of assessment*	*Definition of inactive*
EUR-A	European Union[a]	Not available	Not available	Pan-EU survey (Institute of European Food Studies 2001)	Question: At present, in an average week, which, if any of the following activities do you participate in? (Respondents prompted with list of 20 sports which included walking for 30 mins and gardening + "other"). For each activity, frequency and duration per week recorded	Zero hours of activity per week
EUR-C	Estonia, Latvia, Lithuania	Not available	Not available	Research project using original survey (Pomerleau et al. 2000)	Exact question not specified but responses coded as low, moderate (walking, cycling or other light activities >4hrs/wk), high (jogging other sports, heavy gardening >4hrs/wk) and very high (hard training/sports >1 time/wk)	Lowest category: low (i.e. reading, watching television or other sedentary activities)
	Russian Federation	. . .	Not available	Russian Longitudinal Monitoring Survey 6 (Cockerham and Sneed 2001)	Question: Which description characterizes your physical exercises best not counting at work? Seven response categories which combine intensity of activity and frequency	Published data used. Does not engage in physical activities. (Reanalysis combined lowest two categories namely "does not engage" and "light exercise for relaxation <3 times/week")

	Australia	3-day test–re-test Intra class Correlation r = 0.71–0.86	Not available	1999 National Physical Activity Survey (Armstrong et al. 2000)	Four questions assess activity: walking (for recreation/exercise or to get to or from places), vigorous gardening or heavy work around the around the yard, moderate activities (gentle swimming, social tennis, golf, etc.) and vigorous activities (jogging, cycling, aerobics, competitive tennis). Frequency and total time during the last week recorded	No participation in moderate or vigorous activities or walking. (Gardening excluded from analyses)
WPR-A	Japan	One month test–re-test: light r = 0.73; total r = 0.92	Tested against VO2 Pearson correlation r = 0.47	Japan Lifestyle Monitoring Study – (Minnesota leisure-time questionnaire) (Iwai et al. 2000)	Question: How often have you engaged in any habitual leisure-time physical activity? List of activities provided and for each activity, frequency and duration recorded	No habitual leisure-time physical activity within last 12 months
	New Zealand	Not available	Not available	1998 Sport and Physical Activity Survey (Hillary Commission 1998)	Prompted recall of activities using list of 42 activities (including walking >30 minutes, walking 10–30 minutes and gardening). Frequency over last 12 months, last 4 weeks, last 2 weeks, and last 7 days recorded. Duration for each activity over last 7 days recorded	No activity in last 4 weeks
WPR-B	China	Not available	Not available	China Health and Nutrition Survey 2001 (Ham 2001c)	Prompted recall of 5 activities (+ "other") undertaken more than 12 times in last year. Time/week for each activity recorded	No activity undertaken more than 12 times in the last year

Key: EE, energy expenditure; MET, metabolic equivalent. VO2, oxygen consumption.

[a] Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom.

Table 10.5 Summary of questions used to assess work-related physical (in)activity

					Occupational activity	
Subregion	*Country*	*Reliability*	*Validation*	*Study title (reference)*	*Method of assessment*	*Definition of active*
AFR-E	South Africa	Not available	Not available	BRISK study (Steyn et al. 1991)	Question: Does your work involve mostly: 1) primarily sitting/standing; 2) a lot of walking; 3) hard physical (sweat) work?	Category 3: hard physical (sweat) work
AMR-A	Canada	Not available	Not available	1998 Physical Activity Monitor (C. Craig, unpublished data, 2001)	One question assessed activities undertaken at home or at work like lifting boxes, carrying objects, climbing stairs or walking as part of your job or chores. Frequency was recorded. Response scale was: 1) almost all the time; 2) almost three-quarters; 3) almost half of the time; 4) about a quarter and/or almost none of the time	Category 1: almost all the time
AMR-A	USA	Not available	Not available	National Physical Activity Survey 1999–2000 (Ham 2001b; Macera et al. 2001)	Question: When you are at work which of the following best describes you: Mostly sitting or standing? Mostly walking? Mostly heavy labour?	Middle and upper category: mild physical exertion and heavy physical exertion
EUR-A	European Union[a]	Not available	Not available	Pan-EU survey (Institute of European Food Studies 2001)	One question assessed typical day's activity (either at work, college, in the office or at home). Categories of responses: 1) sitting down at work; 2) standing or walking around; 3) more physical work than any of the above. Approximate number of hours/day recorded	Category 3: more physical work than sitting down, or standing or walking around for 3–6 hours

EUR-C	Estonia, Latvia, Lithuania	Not available	Not available	Research project using original survey (Pomerleau et al. 2000)	Question not specified but responses coded as low; moderate (mixed sedentary and standing work); high (work requires a lot of walking, lifting, carrying–examples given include heavy housework); and very high (heavy manual work and example occupations given)	Categories: high (work requiring a lot of walking, lifting or carrying) or very high
WPR-A	Japan	Not available	Not available	Japan Lifestyle Monitoring Study (Iwai et al. 2000)	Frequency and average duration of various types of labour and other activities on the job, including household activities, for every two months within the last 12 months were queried. Responses were classified into 4 categories according to intensity: sedentary (1.5 METs), standing/walking (2.5 METs), moderately strenuous work (4.5 METs), strenuous work (7.5 METs). A total work activity score was calculated. Lists of activities for 5 major types of businesses were used as prompts	Strenuous work[b]
WPR-B	China	Not available	Not available	China Health and Nutrition Survey 2001 (Ham 2001c)	Time spent in three categories of activities during a work day assessed. Categories: light or very light; moderate; heavy or very heavy. Examples provided for each category	Categories: heavy or very heavy

Key: MET, metabolic equivalent.

[a] Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom.

[b] Prevalence estimates for work-related activity were not calculated and were thus unavailable for inclusion.

Table 10.6 Summary of questions used to assess transport-related physical activity

					Transport-related physical activity	
Subregion	*Country or area*	*Reliability*	*Validation*	*Study title (reference)*	*Method of assessment*	*Calculation and/or definition of active*
AMR-A	USA, Canada	Not available	Not available	1995 National Personal Transportation Survey (Ham 2001b)	Travel diary[a]	Proportion of adults reporting greater than one walk/cycle trip
EUR-A	Netherlands, Germany, England and Wales, France, Italy, Switzerland, Austria, Sweden, Denmark	Not available	Not available	Cross National Comparison (Pucher and Dijkstra 2000)	Travel diary[a]	Proportion of all trips undertaken by walking/cycling used to estimate proportion of adults walking and cycling
	United Kingdom	Not available	Not available	National Transport Survey (Department of Transport Local Government and the Regions 2002)	Travel diary[a]	Proportion of adults reporting greater than one walk/cycle trip
WPR-A	Australia	Not available	Not available	Physical Activity Levels of Western Australian Adults, 1999 (Bull et al. 2000)	Two questions asked: . . . in the last week . . . have you done continuously for ten minutes or more 1) cycle for transport; 2) walk for transport? Response was yes/no	Active defined as a yes response
	Australia	Not available	Not available	TravelSmart 2010 (Travel Demand Management 1999)	Travel diary[a]	Proportion of adults reporting greater than one walk/cycle trip
WPR-B	China	Not available	Not available	China Health and Nutrition Survey, 2001 (Ham 2001b)	Two questions assessed walking time of round trip to work, school, shopping in hour and minutes; biking time of round trip to work, school, shopping in hours and minutes	Active defined as one or more trips

[a] Typically the number of trips are recorded over a 3–7 day period in the travel diary. A trip is defined to be any "time [a person] went from one address to another in a vehicle or by walking or biking. Each stop [made] is a separate trip, including picking up or dropping off someone".

Discretionary-time (in)activity

The 17 studies providing data for 33 countries that were included in this report used 17 different measures to assess physical activity in discretionary time (Table 10.4). Seven studies assessed participation using an instrument comprising a list of specific activities (i.e. a prompted approach $n = 6$) or by asking the respondent about "any activities" and recording the type (i.e. unprompted approach $n = 1$). Both approaches assessed frequency and duration (as detailed in Table 10.1 and ascribed questionnaire format 1 and 2, respectively).

Nine studies used either a single question or a small number of questions with either open or closed response format (Table 10.1, format 3). These instruments comprised the most diverse set of questions and rarely were the reliability or validity properties of the instruments reported. Only one study used an instrument that captured time spent doing categories of activities (format 5), where categories were defined by the intensity of activity (e.g. moderate-intensity and vigorous-intensity). Only one study used a detailed recall over the past seven days (format 4).

Despite these 17 questionnaires appearing quite different, closer inspection revealed considerable similarity in what each measure attempted to assess. Moreover, the definitions of inactive (level 1 exposure) were very comparable. Three quarters of the studies ($n = 14$) used "no", "none", "never" or "zero" as part of their quantification of inactive. In one study (C. Craig, unpublished data, 2001) inactive was defined on a continuous scale (as less than 3 kcals/kg per day). Three studies used the lowest category of activity as described in their question (Cockerham and Sneed 2001; Craig 2001; Pomerleau et al. 2000).

The degree of similarity across the definitions of inactive was sufficient for these data to be included in our analyses. However, it is recognized that this comparison is not perfect. Walking and gardening were included in some studies and not others; nor were these activities always defined the same way. Furthermore, the reference time frame and definition of "regular" used in questions were not always consistent. These differences remain limitations to the comparison of data on physical activity.

Work-related (in)activity

Table 10.5 provides a summary of the questions used to assess work-related physical (in)activity in each study for which we had at least some data for consideration. Three of the seven instruments were used in formats 1 or 2 and asked about three types of work activities, namely walking, standing and hard (or heavy) physical work/labour (e.g. EU, South Africa, the United States). Three studies used an instrument (format 3) assessing different categories of intensity (e.g. light, moderate and heavy) and this was deemed comparable to format 1 and 2 instru-

ments. The remaining instrument captured frequency of different types of work-related activity (Iwai et al. 2000).

While there were clear differences in the format of the instruments used to assess this domain, the more significant problem was that "non-work" activities were also included in the wording of items and thus the physical activity prevalence estimates. For instance, Canada included "chores", and this may have been interpreted as household (domestic tasks) and Japan specifically cited "household activities". The wording and consequently broader scope of the questions severely limited the comparability of these measures of work-related physical activity—so much so that we concluded that only the questions used in the studies from the United States and China were sufficiently similar to allow comparison and thus only these data were used in subsequent analyses.

Transport-related (in)activity

Our search for data on transport-related physical activity, and more specifically patterns of cycling and walking to get to and from places, found very few national data sets. It is acknowledged that many countries collect these data as part of national or regional transportation planning and evaluation activities. However, it was beyond the scope of this project to complete an exhaustive search of these sources. Table 10.6 presents details of the six sources used in this study covering 15 countries.

Transportation data can be collected either by prompted recall during a telephone interview or from diaries completed daily over a specific time frame (usually 3–7 days). Trip origin and destination are usually recorded as well as trip mode and duration. This approach is common in developed countries and examples include the National Personal Transportation Survey in the United States (Federal Highway Administration Research and Technical Support Center 1997) and similar instruments used in several European countries (Pucher and Dijkstra 2000) and Australia (Travel Demand Management 1999). In contrast the Health and Nutrition Survey in China included very specific questions to capture the number of walk or cycle trips to a range of specific destinations.

Integrating measures of transport-related physical activity into the assessment of total physical (in)activity is at a very early stage. For this project we were limited to sources of data from three transportation surveys and one health survey. It is acknowledged that other studies previously mentioned and included under other domains may have captured all or some walking trips, either by using a distinct question or by specifying walking as an example of moderate-intensity activity (Armstrong et al. 2000). The same possibility exists for some cycling trips. However, in these cases it was not possible to disaggregate the activity into separate domains. Clearly further development of a standard set of questions for transport-related physical activity is required.

With the exception of China and the United States, all the studies used for this project presented data as "percent of trips" not as a proportion of people undertaking trips. In lieu of obtaining data in the latter format we analysed data from the United States to help derive an estimate from per cent of trips. This method is described in full detail in later sections.

Domestic-related (in)activity

No data were obtained on physical (in)activity in the domestic domain. We found several studies that did include questions to assess this domain but the data were not reported. Like transport-related activity, some domestic-related activity may have been captured because of the wording of questions or the examples provided. For instance, "housework" could be specified as a moderate-intensity activity in addition to examples of sports and recreational pursuits. In this situation, it was usually impossible to disaggregate the data and, if used, this data could potentially lead to erroneous estimates.

Due to the lack of sufficient data in this domain it was not possible to estimate the magnitude of domestic physical activity or inactivity. It is recognized that this is an important domain and therefore a significant limitation to our final estimates. Moreover, it is highly likely that there is considerable variation in levels of domestic activity between developing and developed countries, within countries, between males and females and across ages. The magnitude and direction of these differences are not well known. Some data are available from studies investigating energy intake and expenditure but these studies usually investigate very specific populations and provide too few data to generalize.

Combination measures of (in)activity across domains

Several countries used instruments that assessed physical activity across multiple domains. Often these questions presented a brief description and respondents chose a category (e.g. in Egypt) (Herman et al. 1995). In one case very detailed data were obtained via a seven-day recall instrument and the final analyses combined all activity across all domains (e.g. in Ethiopia) (Alemu and Lindtjorn 1995). Data from these approaches were excluded from our estimates in the specific domains. However, where appropriate these data were used post hoc to assess the fit of our final predicted estimates.

2.6 Treatment of data

Dealing with data reported for different age categories

Much of the data obtained was not available using the same cut-point for age categories. The first and preferred solution involved contacting the original investigators and requesting data analysed by the relevant age groups. Where this was not possible or where data were no longer

accessible, an indirect method was used to compute age-specific estimates, by assuming uniform distribution of population and exposure in one-year increments of each age category.

Where data were available for only some of the age groups included in the lower and upper age categories used in this report (e.g. 15–29 years, 60–69 years, 70–79 years) the obtained prevalence estimate was applied to all years in the category. For example if data were available for only those aged 60–65 years it was applied to our 60–69 year category, and also extrapolated to older age groups such as 70–79 or ≥80 years. The effect of this is to slightly underestimate inactivity in the older years within an age category (inactivity usually increases with age) and slightly overestimate the prevalence of inactivity within the youngest age category.

Dealing with data from non-nationally representative samples

Several data sets did not come from nationally representative samples. In these instances, descriptions of the study sample and information on the age, sex, ethnic/racial and rural/urban profile of the country were used to create adjusted weighted national estimates. For example, these steps were undertaken with data from Bangladesh and India, which were samples from older adults in urban and rural towns, and also for transport data from Australia that were weighted to form a national estimate.

Dealing with missing data by sex, age and subregion

Table 10.7 provides a summary of the amount of data identified for each of the 14 subregions according to six age groups and both sexes. Of these 168 cells, 44% were missing data. For the 14 subregions, the missing cells ranged from 0% (AMR-A and WPR-B) to 100% (SEAR-B). Across subregions, missing data cells ranged from 32% for the four age groups spanning 15–69 years, and increased to 57% and 79% for the 70–79 and ≥80 age groups, respectively. These incomplete subregional by age and sex data cells presented two tasks:

- obtaining estimates for missing age and sex categories; and
- obtaining estimates for countries/subregions where no data source exists.

One approach to solving these two issues was to select the most comparable data set available and apply these values to missing cells. For example, data from EUR-C could be substituted for EUR-B, or WPR-B (which includes China) could be used to derive estimates for SEAR-B and SEAR-D. Similarly missing data for older adults in Europe could be derived from known data from the Americas. While plausible, this approach is weak because any limitations in the data for one subregion will be extended to the other. Moreover, it makes no attempt to better represent the likely differences that exist between countries.

Table 10.7 Summary of data available by subregion, sex and age[a]

Subregion	Countries with data	Sex	Age group (years) 15–29	30–44	45–59	60–69	70–79	≥80
AFR-D		Male	0	0	0	0	0	0
		Female	0	0	0	0	0	0
AFR-E	South Africa	Male	14	18	18	16	1	1
	Ethiopia	Female	14	18	18	17	1	1
AMR-A	Canada	Male	96	96	97	97	97	88
	USA	Female	96	96	97	97	98	89
	Argentina	Male	51	54	56	17	0	0
AMR-B	Chile	Female	51	53	56	18	0	0
	Brazil	Male	36	39	40	0	0	0
AMR-D	Peru	Female	37	40	40	0	0	0
EMR-B	Saudi Arabia	Male	13	13	19	15	0	0
		Female	0	0	0	0	0	0
EMR-D	Egypt	Male	21	22	22	21	22	0
		Female	20	22	24	23	25	0
EUR-A	European Union[b]	Male	91	92	91	93	78	20
		Female	91	92	91	92	78	24
EUR-B	Estonia	Male	0	0	0	0	0	0
	Latvia	Female	0	0	0	0	0	0
EUR-C	Lithuania	Male	63	64	64	60	58	56
	Russian Federation	Female	62	64	64	61	60	61
SEAR-B		Male	0	0	0	0	0	0
		Female	0	0	0	0	0	0
SEAR-D	India	Male	0	0	0	0	0	0
	Bangladesh	Female	0	0	0	0	0	0
WPR-A	Australia	Male	15	96	98	97	10	0
	Japan							
	New Zealand	Female	16	96	98	97	9	0
	Singapore	Male	82	86	88	88	89	87
WPR-B	China	Female	82	86	87	87	88	88

[a] As % of total population in each subregion.

[b] Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom.

An alternative approach was to develop a statistical model to predict national estimates of physical inactivity. Known correlates of inactivity at the individual level could be explored for their predictive value at the national level (e.g. level of education). In addition, a range of other parameters, possibly related to inactivity, such as indicators of economic development (e.g. per capita gross national product [GNP]), could be investigated. Using this "ecological" approach represents the first stage of the epidemiological approach to identifying and understanding the determinants of physical inactivity. Such a model was used to predict

values for countries with missing data and values for missing age/sex cells in countries with only some data. This approach has the advantage of using all available, comparable data on physical inactivity to develop a statistical relationship with other indicators for which there are data available worldwide. We also had to decide whether to create a single model to predict the sum total of inactivity (i.e. inactivity across all four domains as stated in the definition of exposure) or four separate models—one for each domain. The latter approach was selected because of the complexities of the behaviour and the likelihood that different parameters may explain levels of inactivity in different domains.

2.7 Estimating prevalence of level 1 exposure (inactive) using regression analysis

Multivariate and linear regression analyses were used to create predictive models for discretionary-time, work-related and transport-related levels of inactivity. All data obtained from the worldwide search that met our inclusion criteria were considered for inclusion in this process. Only data that clearly represented a single domain were included in the domain-specific modelling exercise. Domestic physical inactivity could not be modelled due to insufficient data. Estimates from countries with measures of physical (in)activity that comprised multiple domains were used post hoc to assess the fit of predicted estimates of overall inactivity across all domains. Only one source of data per country was used.

From a practical stance it was necessary to treat all data within a domain as either values of exposed (namely % inactive) or unexposed (% active). In most cases we found it more convenient to work with a model predicting prevalence of doing some physical activity (unexposed) and in the final step to reverse the direction to inactivity (exposed). The exception was in the discretionary-time domain where the predictive model was developed for inactivity.

The modelling approach of level 1 exposure required six steps:

1. Create a predictive model to estimate discretionary-time physical inactivity, and subtract values from 100 to create estimates of physical activity.
2. Create a predictive model to estimate work-related physical activity.
3. Create a predictive model to estimate transport-related physical activity.
4. Sum the domain-specific estimates of physical activity and adjust for overlap across domains.
5. Scale estimates of physical activity and subtract values from 100 to compute final estimates of level 1 exposure (physically inactive).
6. Aggregate age by sex country-level estimates to create age by sex regional-level estimates.

Within each step estimates for each age (six categories) by sex (male/female) cell were modelled and predicted rather than working with and predicting only single point estimates to represent all persons from each country. Table 10.8 summarizes the potential parameters found from World Bank data (World Bank 1999) that were considered for inclusion in the models of (in)activity in each domain. Many of these potential parameters were highly associated including, for example, GNP and per cent of the population completing tertiary education (hereafter referred to as "% tertiary education") (correlation matrix not reported). Criteria for parameters were the following:

1. Parameters must be available on a national level for most countries across most regions.
2. Parameters must come from a reliable (reputable) source.
3. Parameters must be from recent sources consistent with our exposure variable.

Within each domain, predicted estimates were limited to the countries for which data on the selected parameters were available from the World Bank ($n = 146$). After completion of the first five steps, the final task was to aggregate the age-sex-country specific values to create age by sex

Table 10.8 Summary list of potential parameters considered for modelling level 1 exposure

Parameter categories	*Potential parameter*
Demographic	Country population Regional population Per cent urbanization Typical population density experienced by an individual
Economic	GNP per capita World Bank classification
Socioeconomic	Per cent completing tertiary education
Geographical	Subregion Latitude of the country centroid
Climatalogical	Mean annual temperature
Employment	Per cent employed in agricultural sector Per cent employed in manufacturing sector Per cent employed in service sector
Energy consumption/emissions	Cars per thousand population Carbon dioxide emissions
Data	Quality of prevalence data

regional estimates. At this point known data replaced predicted values where available. Each of the above steps undertaken to estimate the prevalence of exposure level 1 (inactive) is described in detail below.

Step 1: Estimating discretionary-time physical activity

Data by age and sex from 32 countries provided the basis for estimating the prevalence of discretionary-time physical inactivity (level 1 exposure) for 12 age-sex categories in 146 countries. A mixed model for nested, repeated measures was used to identify a model with predicted values that best approximated the data. Twelve age-sex categories were treated as repeated measures nested within each country.

The general linear mixed model is

$$Y = X\beta + Zu + e$$

where: Y = observed response variables
X = matrix of known values of covariates
β = matrix of unknown fixed-effects parameters
Z = known design matrix of random effects
u = matrix of unknown random-effects parameters
e = error.

The model assumes that the error is independent and identically distributed (iid). A mixed model was chosen as most suitable for these data because we considered the possibility of correlation within countries (e.g. clustering of age by sex prevalences). Within-country estimates are likely to cluster because the level of economic development and culture is likely to determine if any data were available and relatively small differences in use of discretionary-time within a country; in contrast, the differences in measurement instruments and protocols would be greater between countries. In addition, using a mixed model allowed for the consideration of clustering of physical activity patterns by geographic region (our strata variable) and this was deemed desirable for the analysis. Mixed models are robust to two characteristics of our prevalence data, heterogeneous variances within clusters (e.g. countries and regions) and missing and unbalanced data. It is acknowledged that missing data may not be random. The effect of missing data is most likely to increase error in subregions with less coverage and reduce error in subregions with better coverage. We compensated for the limitation due to missing data in our calculations of age by sex by subregion estimates by increasing our 95% confidence limits (described in detail later).

A simple repeated (up to 12 age by sex cells per country) measures model is

$$y_{ij} = \mu + \alpha_{ij} + d_i + e_{ij}$$

where μ and α_{ij} are fixed-effects parameters,
$d_i \sim$ iid $N(0, \sigma^2)$ is the random-effect parameter, and
$e_{ij} \sim$ iid $N(0, \sigma^2)$.

Several tasks were undertaken before the multivariate modelling. Firstly, the skewed physical inactivity data available from 32 countries were transformed to obtain a more normal distribution. Various transformations were attempted but several countries (e.g. Chile, China, the Russian Federation) which had very high estimates of inactivity (ranging 85–96%) prevented any transformation from creating a truly normal distribution. Nonetheless, the square root transformation created a more satisfactory variable with a distribution closest to normal (Figure 10.5).

Secondly, we created a variable regional strata to allow countries with data within a region to have a greater influence on the predicted values of other countries in the same region. Due to the overall lack of data across the 14 subregions, five new regional strata were developed to help our analyses. These strata were defined by considering geographical location, World Bank income classification, social, religious and cultural similarities and the availability of data on exposure. The five strata are shown in Table 10.9.

Weighting

After some preliminary attempts at modelling discretionary-time physical activity and predicting age by sex by country estimates we introduced a weighting factor for each data set. This step was in addition to using the regional strata parameter, and weighted data to the world popula-

Figure 10.5 Transformed age x sex estimates for discretionary-time physical inactivity data (n = 276) from 31 countries

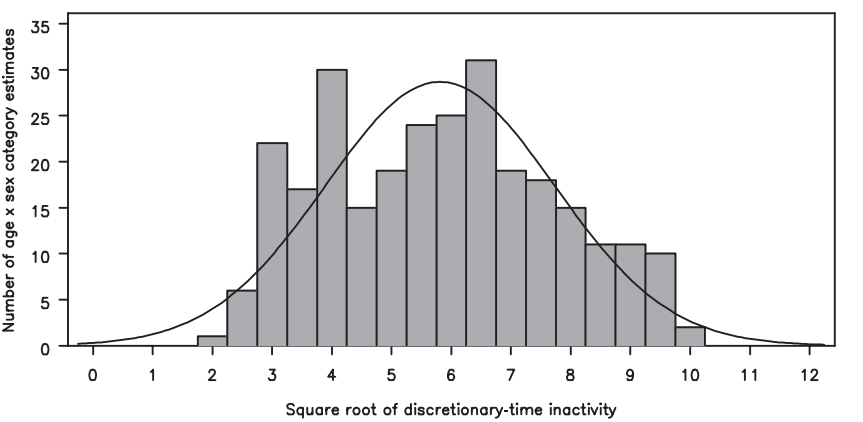


Table 10.9 Country allocation to regional strata parameter for modelling level 1 exposure

Regional strata created for model	*Countries included*
1 Western industrialized	Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, United Kingdom); North America (Canada, USA); Australia, New Zealand
2 Latin America	Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, France (Guiana), Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Netherlands, Antilles, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Suriname, Trinidad and Tobago, Uruguay, Venezuela
3 Africa	Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Côte d'Ivoire, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Somalia, South Africa, Sudan, United Republic of Tanzania, Togo, Uganda, Zambia, Zimbabwe
4 South-East Asia	Cambodia, China, Democratic People's Republic of Korea, Indonesia, Japan, Lao People's Democratic Republic, Malaysia, Mongolia, Philippines, Republic of Korea, Singapore, Sri Lanka, Thailand, Viet Nam
5 Transitional nations	Eastern Europe (Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Serbia and Montenegro, The former Yugoslav Republic of Macedonia, Turkey); Central and South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan); the Middle East (Afghanistan, Cyprus, Iran [Islamic Republic of], Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Saudi Arabia, United Arab Emirates, Yemen); North Africa (Algeria, Egypt, Morocco, Tunisia); and the Russian Federation

tion (aged ≥15 years). A weighted model should produce similar parameter estimates regardless of the number of countries, or which specific countries, were included in the model. This was an important consideration because over half of the data were from China, Europe, North America and the Russian Federation. The intent was to avoid these data dominating the model and thus the final estimates.

In practice, known data from a country were weighted to the total population (by age and sex) of the regional stratum proportional to the country population in which the data were available. The sum total population was the total population (aged ≥15 years) in the 146 countries for which the independent variable (% tertiary education) was available.

Over half of all the available data on physical inactivity were from countries in the Western industrialized stratum and within this stratum these data represented 90% of the population. In the South-East Asia stratum, data were available from China, Japan and Singapore, and China represented 77% of the stratum's population. Using the weights improved the predicted prevalence estimates by allowing China to contribute to the model approximately 1.3 times its population, while limiting the influence of data from countries in the Western industrialized countries to slightly more than their population of each country (1.1 times).

The remaining strata had fewer countries with data and thus smaller proportions of the strata population were represented. In these cases, the countries with data determined the age by sex trends of inactivity while the covariate (% tertiary education) influenced the intercept for each individual country. Individual weights are not shown because they varied for each country depending on what age by sex data were available and the age by sex population of the stratum.

Preliminary models of discretionary-time physical inactivity

All of the parameters listed in Table 10.8 were explored in univariate and multivariate models. As mentioned many of the World Bank indicators were correlated and if used in combination would cause problems of collinearity, or unreliable parameter estimates resulting from correlated covariates. Using % tertiary education was found to explain almost equal variance as GNP and provided smaller residuals that were more normally distributed. Education was reasonably normally distributed. The single point estimate of education per country was applied equally to the 12 age by sex cells.

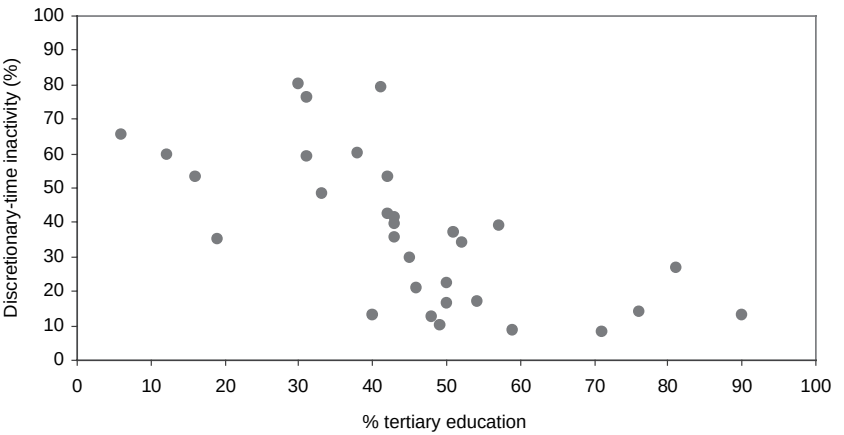
Figure 10.6 shows a plot of national estimates of discretionary-time physical inactivity by the indicator % tertiary education for 31 countries. The figure shows that countries with lower tertiary education have a higher prevalence of discretionary-time inactivity.

In addition to exploring a range of demographic, economic and development indices we tested a model that included a variable rating the "data representativeness". As discussed there is insufficient evidence on which to base judgements about different types of instruments, thus we created a variable that differentiated national sources of data from non-national (regional or metropolitan). China was coded as national because the sample was representative of 16 provinces. Including the data representativeness parameter did not, however, improve our model; thus it was removed.

Final model of discretionary-time physical inactivity

The final model parameters were education (defined as % tertiary education), age, sex, region, a three-way interaction termed age x sex x region and corresponding two-way terms. This parameter allowed trends for age to vary by sex and for each different region and it helped to

Figure 10.6 National estimates of discretionary-time physical inactivity by the indicator % tertiary education (n = 31 countries)



improve the predictive power of our analysis. Available data suggest that the trend for inactivity across age can vary by sex and by region. Education allowed inactivity for each country to be based upon an external measure known to be highly associated with a number of risk factors, including discretionary-time physical inactivity, at the individual level. Other social and economic indicators were tested and some produced good results (e.g. particularly GNP per capita), but the best model fit and distribution of the residuals was obtained using the parameter education.

Applying the simple repeated measures model to estimate discretionary-time activity, we get

$$y_{ij} = m + a_{ij} + d_i + e_{ij}$$

where y_{ij} is the response, prevalence estimates for age x sex x country categories;
m and a_{ij} are fixed-effects parameters: intercept, age, sex, region, % tertiary education, interaction parameters;
d_i is the random-effect parameter, country; and
e_{ij} is error.

The final model for predicted discretionary-time physical inactivity using data obtained from the World Bank is represented by:

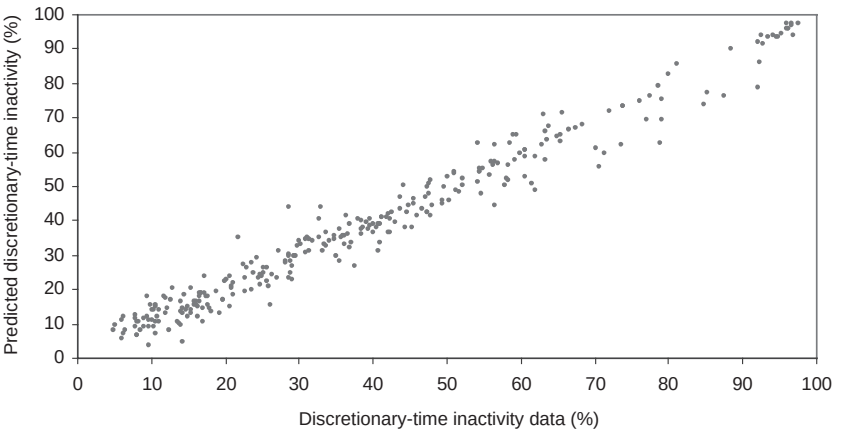
$$\begin{aligned}\text{square root(DISCRETIONARY-TIME PHYSICAL INACTIVITY)}_{\text{COUNTRY,AGE,SEX}} &= \alpha_i + \beta_1(\text{AGE}) + \beta_2(\text{SEX}) \\ &+ \beta_3(\text{REGION}) + \beta_4(\text{AGE} \times \text{SEX}) + \beta_5(\text{AGE} \times \text{REGION}) \\ &+ \beta_6(\text{SEX} \times \text{REGION}) + \beta_7(\text{AGE} \times \text{SEX} \times \text{REGION}) \\ &+ \beta_8(\%\ \text{TERTIARY EDUCATION}) + d_{\text{COUNTRY}} + e_{\text{COUNTRY,AGE,SEX}}\end{aligned}$$

where $d_{\text{COUNTRY}} \sim \text{iid } N(0, \sigma_d^2)$ is the random-effect intercept, and $e_{\text{COUNTRY,AGE,SEX}} \sim \text{iid } N(0, \sigma_d^2)$ is error.

Figure 10.7 shows a plot of the predicted estimates by actual data for 31 countries. The final model explained 52% of the within-country variance in the prevalence of physical inactivity. The remaining 48% of variance is attributed to variables not included in this model. Chile, China and the Russian Federation were identified as potential outliers and models were run including and excluding these data. The final model excluded only the Russian Federation and the predicted prevalence estimates fitted the data better by reducing the standard deviation of the residuals from 5.2 to 4.7.

Modelling was done using SAS 8.1 with the restricted maximum likelihood (REML) method and unstructured covariance structure. The REML method is a better, more conservative estimation method than least squares. We modelled within-country data as repeated measures and "countries" as a random selection of all possible countries. Various

Figure 10.7 Plot of predicted estimates against actual data for discretionary-time physical inactivity (n = 276) from 31 countries



models were compared using education and GNP with manual inclusion/exclusion of possible outlying countries. The best-fit model was assessed by minimizing the standard deviation of the residuals calculated by transforming the predicted empirical best linear unbiased predictors (EBLUPs) as well as by minimizing the –2 residual log-likelihood, Akaike's information criterion (AIC), and Schwarz's information criterion (BIC).

The model gives each country its own random-effect intercept estimate which adjusted the overall model intercepts higher or lower by a small percentage. These random-effect intercepts help the model fit the data better than a fixed-effects model by allowing each country to have a different mean value. A shortcoming in using random-effect intercepts is that the random effects are not used to adjust the intercepts for the 114 countries with no data when calculating predicted values. Therefore, the predicted values may be biased if the random-effects estimates are not randomly distributed with a mean of zero. The random-effects estimates for our model were randomly distributed within strata. Figure 10.8 presents a histogram of the distribution of the model residuals by age and sex category estimates showing a normal distribution.

Figure 10.9 shows the residuals from the final model plotted by discretionary-time physical inactivity. The plot shows an increasing trend toward positive residuals with higher estimates of physical inactivity; this is an expected effect of using skewed response data in a model that assumes normal distribution. The model underestimated high prevalence and overestimated low prevalence although the maximum absolute residual for any age-sex estimate was approximately 15%.

Figure 10.8 Distribution of residuals from final model of discretionary-time physical inactivity (n = 276)

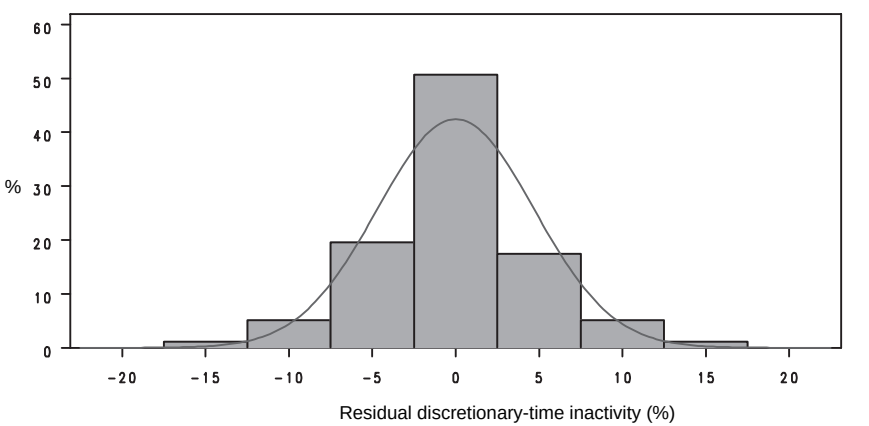


Figure 10.9 Plot of residuals for predicted age- and sex-specific estimates of discretionary-time physical inactivity (n = 276) from 31 countries

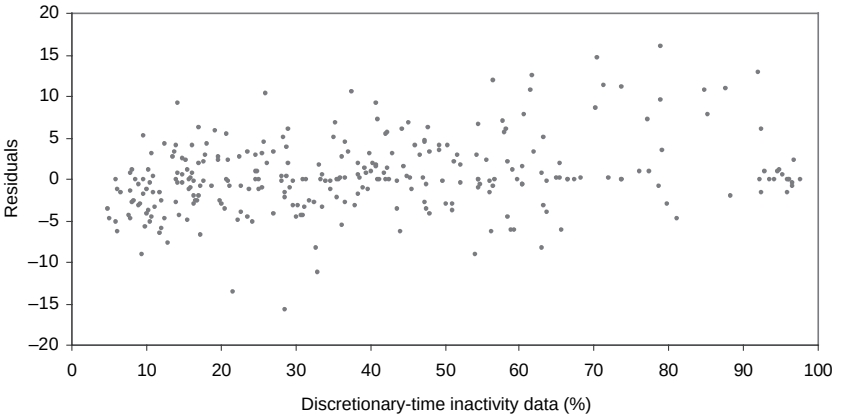


Figure 10.10 Distribution of predicted national estimates of discretionary-time physical inactivity for all countries (n = 146)

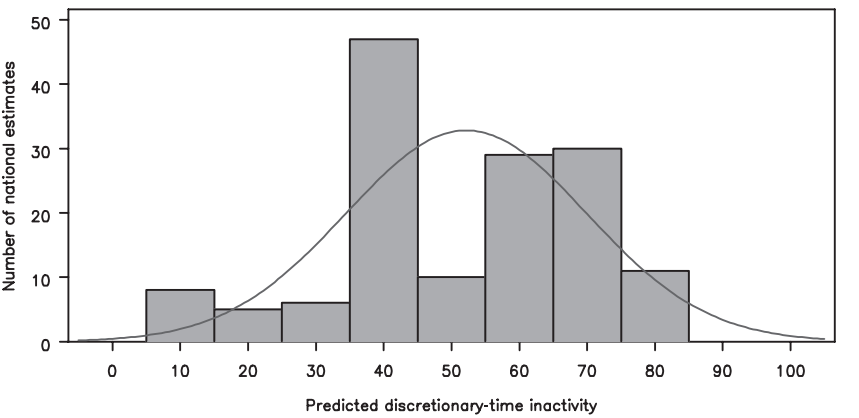
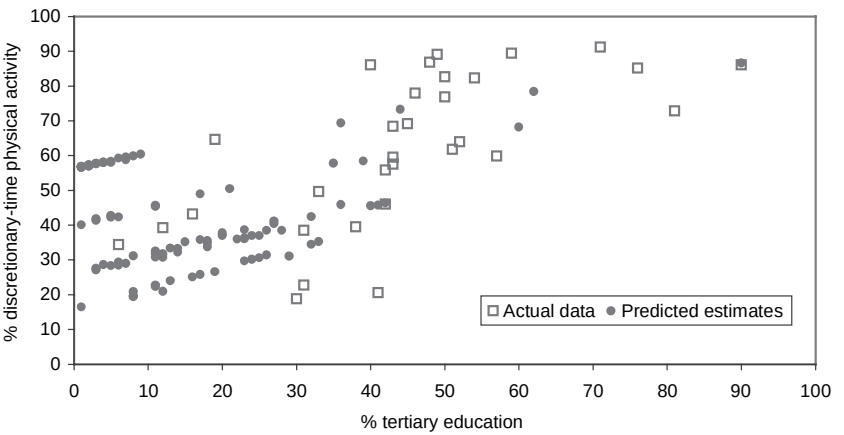


Figure 10.10 shows the distribution of predicted national estimates of discretionary-time physical inactivity from the final model for all countries (total n = 146). The plot shows about one third of the countries had estimates of discretionary-time physical inactivity around 40%. Just over one third of countries had predicted estimates ranging from 55 to 75 per cent.

Figure 10.11 Predicted national estimates of discretionary-time physical activity by the indicator % tertiary education (n = 146)



The final task in this step was to convert the model output (discretionary-time physical inactivity) to estimates of physical activity. This was easily done by subtracting the values from 100. Figure 10.11 shows a plot of the predicted national estimates of discretionary-time activity for each country by the indicator % tertiary education (n = 146). Countries with data are more developed with higher levels of tertiary education (shown by squares). The predicted values (circles) show different levels of activity for the same values of education reflecting the influence of our regional strata parameter in the predictive model.

Step 2: Estimating work-related physical activity

Although several sources of data on work-related physical (in)activity were found for a number of countries (see Table 10.5), after careful inspection and discussion with the authors, few data could be included. Specifically, we found several data sets that appeared to be limited to work-related physical activity that also included some domestic activities listed as "chores". This was true for data from Canada, Estonia, Japan, Latvia, Lithuania and the EU. Because this could inflate the prevalence estimates of work-related activity these data were excluded.

Several other countries addressed work-related activity (e.g. Egypt and Ethiopia) but these data could not be disaggregated from overall measures of physical activity. Therefore only data from China and the United States remained as distinct estimates of work-related physical activity for use in a predictive model. Fortunately these countries represent quite different societies and cultures. Moreover, because we had access to the

micro data sets, age-sex estimates for both China and the United States were computed. Only estimates for heavy physical activity at work (or its equivalent) were included.

Figure 10.12 shows the proportion of adults reporting heavy activity at work by age and sex for both China and the United States. Heavy physical activity at work declines over age and is less likely to be reported by females compared with males in both China and the United States.

A simple linear regression equation was developed using the economic development indicator of % employed in agriculture (hereafter referred to as "% agriculture"). This World Bank indicator was selected and used by making the following assumptions:

- the proportion of the population employed in agriculture would reflect the level of work-related activity undertaken in a country; and
- there is a linear relationship between the proportion of the population undertaking physical activity at work and the proportion of the total population employed in agriculture.

Figure 10.13 shows the prevalence of heavy work-related physical activity by the indicator % agriculture for males and females in China and the United States. More men were active at work than women in both China and the United States but the difference was greater in the United States (absolute difference of 12% compared with 6%).

The final model parameters used to predict prevalence of work-related physical activity were % employed in agriculture (%AGR), age, sex and

Figure 10.12 Prevalence of heavy work-related physical activity by age and sex, for China and the United States

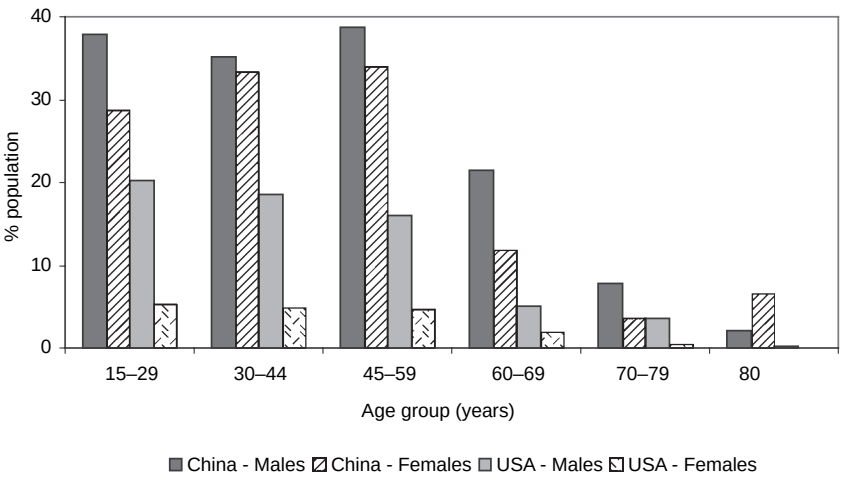
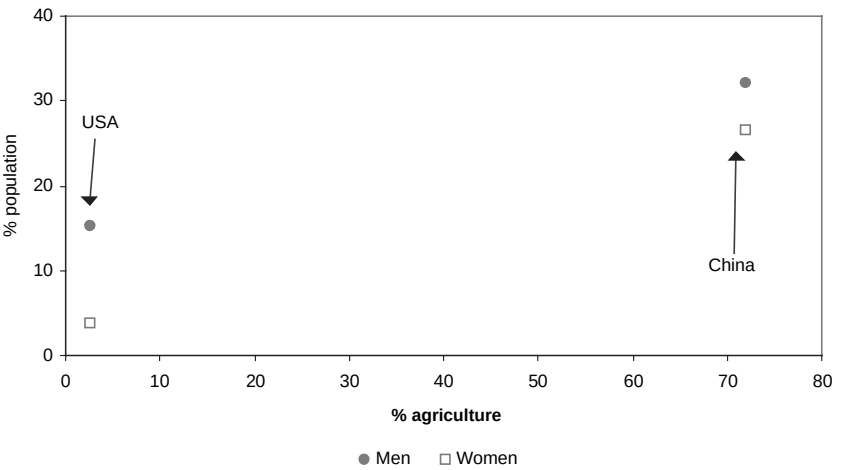


Figure 10.13 Proportion of males and females in China and the United States who undertake heavy physical activity at work, by the indicator % agriculture

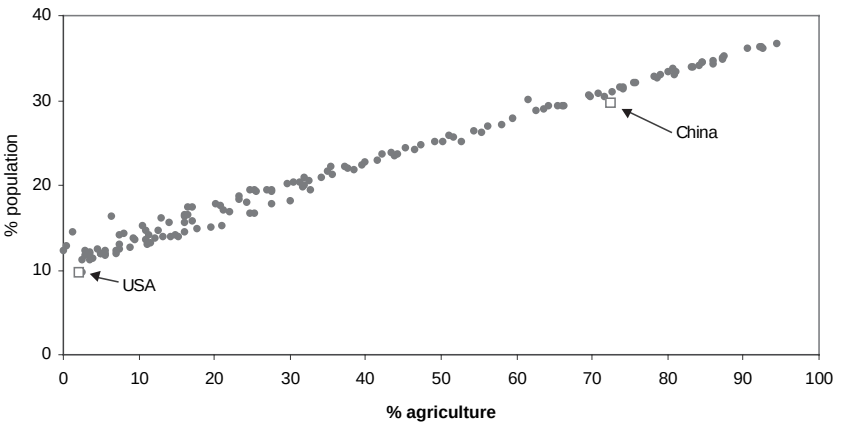


Source: China data obtained from the China Health and Nutrition Survey (Ham 2001c); United States data obtained from the NPAS (Ham 2001a) and % agriculture indicator obtained from the World Bank (1999).

an interaction term "sex by agriculture". This interaction term allowed estimates for work-related activity to vary between sex and by age as suggested by data from China and the United States (see Figure 10.12). Prevalence estimates for age categories 15–59 years were assumed to be the same because there were no clear trends by age in the data from China and the United States. However, an adjustment was introduced for age categories typically associated with retirement. Estimates for work-related activity for age categories 60–69 years, 70–79 years and ≥80 years were progressively lower than those for <60 years to account for the reduced likelihood of heavy physical work and increasing proportion of retired persons in each age group. We calculated the mean difference and reduced estimates by 13% and 19% for males and females aged 60–69 years, respectively; and by 19% and 26%, and 20% and 27% for males and females, aged 70–79 and ≥80 years, respectively (the reference estimate was 50–59 years). The magnitude of these adjustments were calculated using the mean of the differences seen between the relevant age groups in China and the United States (Figure 10.12). Additional adjustments for sex differences are described below.

Estimates for females were also adjusted to have lower values than males as suggested by the data from China and the United States (Figure

Figure 10.14 Predicted national estimates of heavy work-related physical activity by the indicator % agriculture (n = 146)



10.12) but the magnitude of difference seems to vary (range 6–12%). Thus, for the 146 countries we were working with, those countries with higher total persons employed in agriculture the difference between men and women was smallest (minimum difference set as China value namely 6%). In countries with fewer total persons employed in agriculture the difference was greatest (maximum difference set as United States value, namely 12%).

The regression equation is represented by

$$\%\ \text{heavy physical activity at work} = \alpha_i + \beta_1(\text{AGE}) + \beta_2(\text{SEX}) + \beta_3(\%\text{AGR}) + \beta_4(\%\text{AGR} \times \text{SEX})$$

Figure 10.14 shows predicted national estimates of heavy physical activity at work by the indicator % agriculture.

Step 3: Estimating transport-related physical activity

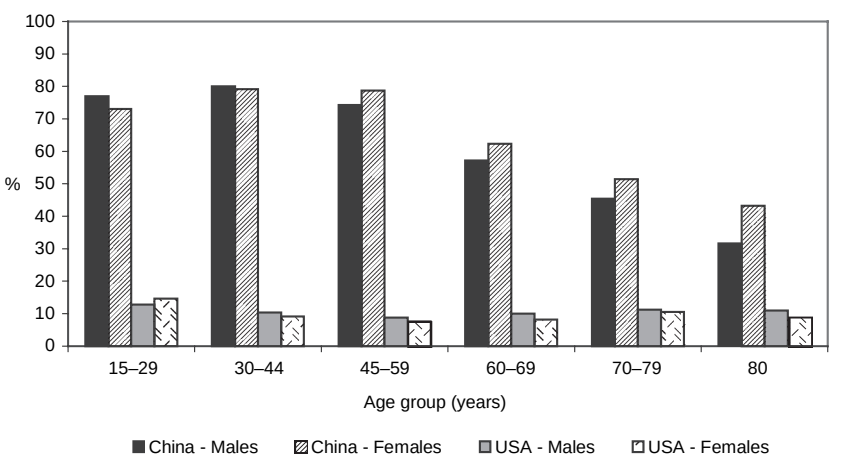
There were few data available reporting the proportion of the population undertaking transport-related physical activity, specifically cycling and walking. However some data were found reporting the per cent of "total trips" that were undertaken by bike or by foot, although even these data were not readily available from national samples.

Data used for modelling transport-related activity came from 13 countries, namely Australia (Travel Demand Management 1999), China (North Carolina Population Center 2001b), the United States (Federal Highway Administration Research and Technical Support Center 1997) and Canada and nine European countries whose data were obtained in

a report comparing trends between North America and Europe (Pucher and Dijkstra 2000). Only the data from China and the United States were available with the variable "persons" rather than "trips" as the denominator. All trip data had to be converted using available information and some adjustments. We wanted to avoid assuming that a separate individual undertook each trip (e.g. 150 trips = 150 persons) because this is highly unlikely. It is more likely that a smaller proportion of the population walks or cycles and that they account for the majority of the trips (e.g. 150 trips might equal 50 persons). To explore this further we conducted new analyses using the nationwide personal transportation survey (NPTS) database (Ham 2001b) and found that 5% of all trips were cycling and walking and that they were undertaken by just 10% of the sample population. This gives a ratio of trips to persons of 1:2. This ratio was adjusted for use with data from Australia (1:1.5) and European countries (1:1.25) based on the conservative assumption that more individuals undertake more trips in these countries compared with the United States.

Figure 10.15 shows the prevalence of active transport (walk and cycle trips) undertaken by males and females in China and the United States. There was little difference between men and women in both China and the United States but considerable difference between the two countries. However, one notable difference is car ownership. This parameter was explored as a potential predictor of activity in this domain.

Figure 10.15 Proportion of adults undertaking transport-related physical activity (cycling or walking) by age and sex, in China and the United States



A simple linear regression equation was developed using the economic development indicator of cars per thousand population (see Figure 10.16). The underlying assumption is that the prevalence of cycling and walking declines as car ownership increases.

The final regression equation is represented by

$$\begin{aligned}\text{TRANSPORT-RELATED PHYSICAL ACTIVITY} &= \alpha_i + \beta_1(\text{CARS}) \\ &= \text{TRANSPORT-RELATED PHYSICAL ACTIVITY} \\ &= 73.69 - (0.063.\text{CARS})\end{aligned}$$

Figure 10.17 shows the predicted estimates (shown in circles) as well as actual country estimates (shown in squares) for transport-related physical activity data.

China had the lowest ownership of cars and the highest proportion of the population walking and cycling for transport. In contrast, the European countries had much higher car ownership and lower levels of active transport. Australia, Canada, New Zealand and the United States do not fit this model well. They have high estimates of car ownership, with values similar to European countries, but notably lower levels of active transport. This may be due to the degree to which these geographically large countries have developed public transportation infrastructure and the quality of these systems. It is also possible that the mean distance to work (or other destinations) is greater reflecting "sprawling" communities or particular land use patterns that may differ

Figure 10.16 Age-sex estimates of transport-related physical activity for 13 countries, by the indicator cars per thousand population (n = 156)

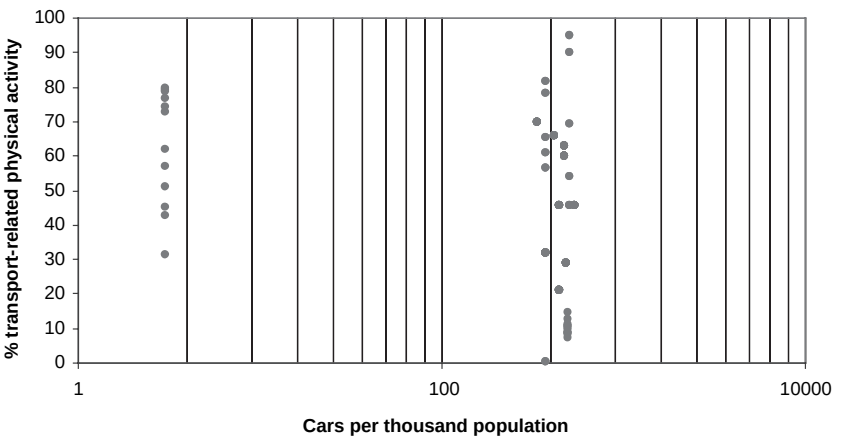
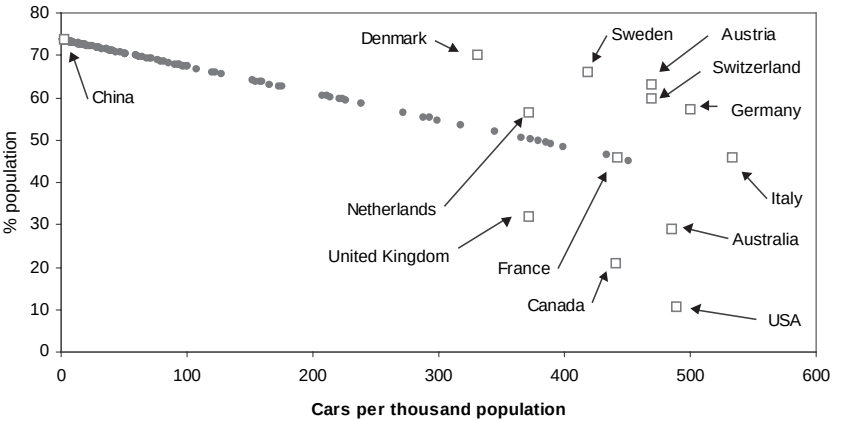


Figure 10.17 Predicted estimates and actual country data for transport-related physical activity (cycling and walking) by the indicator cars per thousand population (n = 146 countries)



between Australia, Europe and the United States. It is likely that a more sophisticated multivariate model, including average miles driven, would better describe and predict active transport. However in the absence of available data on these other possible parameters we limited our model to cars per thousand population.

Four countries had transport data by age and sex, but the pattern differed for each country (China, Germany, the Netherlands and the United States), therefore a model ignoring age and sex was developed. Australia and the United States were identified as outliers and excluded from the linear regression. In subsequent steps of the analyses the actual values for these countries, as well as from China, were used.

Step 4: Summation of domain estimates and adjustment for overlap

Estimates of total physical activity were obtained by combining the estimates of physical activity in each of the sub-domains (with the exception of the domestic domain). A simple summation of the estimates of activity in three domains produced country-level estimates ranging from 41% to 178% (mean 120, median 122, SD 20). High estimates of activity in more than one domain produced values well over 100%. This was anticipated because it is known that at least some individuals are active in more that one domain and a simple summation would fail to take this into account. However, the magnitude of the overlap between different domains, and for men and women, across age is not well established.

In the absence of published data we explored the pattern of activity in multiple domains using data from China and the United States (Ham

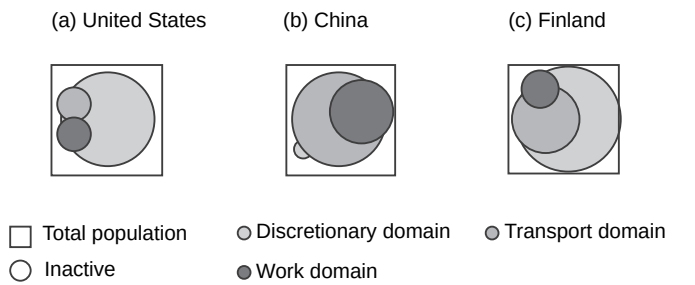
2001a, 2001b, 2001c). It was observed that 6.2% of adults in the United States were active in both work and discretionary domains, 7.1% were active in discretionary and transport domains, and 0.2% were active in both work and transport domains. These relationships are shown schematically in Figure 10.18(a).

Similar analyses were repeated with data from China and are shown in Figure 10.18(b). In China, 29% of adults were active at work and in the transport domain; 5% were active in both the discretionary and transport domains but zero per cent were active in both work and discretionary domains. Therefore the pattern of overlap is quite different compared with the United States.

Finally, data on physical activity across multiple domains were found for Finland and considered in a similar way (Luoto et al. 1998). However, without the exact data on the overlap only a hypothesized relationship between domains is shown for Finland in Figure 10.18(c). Finbalt Health Monitor data indicate that over 90% of Finnish adults are active in their discretionary time, 50% are active in transport and 13% are active at work. Accepting these values as reasonable estimates, there must be a large overlap between domains and this is shown schematically in Figure 10.18(c).

Figure 10.18 illustrates that quite different patterns of activity across different combinations of domains are possible and they are likely to vary across different countries around the world, and may vary for men and women and across age. Without additional information on these relationships it was necessary to develop a standard adjustment to our raw sum total of activity (i.e. the sum of the estimates of discretionary-time, transport-related and work-related activity), and apply this to all countries.

Figure 10.18 Schematic representation of national data for three countries showing the proportion of activity in single and multiple domains



Source: USA: Ham (2001a); China: Ham (2001b); Finland: Finbalt data (Luoto et al. 1998).

Adjustment of raw domain-specific estimates

Adjustment could be made to the estimates in each of the domains (n = 3) in an attempt to reduce the absolute magnitude of the prevalence estimate of total inactivity. It was also possible to consider an additional adjustment (upward) to accommodate the missing data on activity in the domestic domain. The latter was rejected because there were insufficient data to guide such an adjustment across age, sex or country. Undertaking three separate adjustments was also rejected in favour of a single adjustment and the estimate of transport-related activity was selected as our focus. Our estimate of transport-related activity was selected for the adjustment for overlapping domains for no better reason than it was judged to be the weakest data (both in quality and quantity).

With only data on physical activity across multiple domains from China and the United States (Figure 10.18 [a and b]) we were unable to identify a clear relationship, and therefore selected to reduce the raw estimate of transport-related physical activity by 60%. This gross adjustment was further refined for each country by choosing to scale the magnitude of the adjustment to a range of 50–70% based on each country's GNP. The underlying assumption was that those countries with the lowest GNP were more likely to have more active transport (cycling and walking), and therefore a smaller adjustment was appropriate (i.e. 30% reduction in absolute value of the predicted estimate). In contrast, those countries with the highest GNP were likely to have less walking and cycling so they had a larger adjustment (50% reduction in absolute value of the predicted estimate).

These functions are represented below:

$$\text{Adjusted TRANSPORT-RELATED PHYSICAL ACTIVITY} = \alpha_i + \beta_1(\text{CARS}) + \beta_2(\text{GNP}) + \beta_3(\text{CARS})(\text{GNP})$$

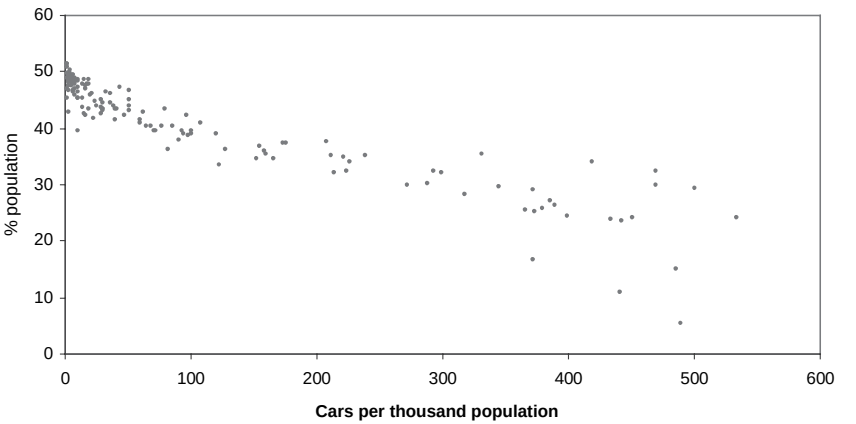
$$\text{Adjusted TRANSPORT-RELATED PHYSICAL ACTIVITY} = (73 - 0.06\,\text{CARS})(85 - 3.35\,\text{GNP}/100)$$

Adjusted estimates for transport-related physical activity by the indicator cars per thousand population are shown in Figure 10.19 and this can be compared to the previous unadjusted data shown in Figure 10.17.

Step 5: Scaling and computation of final estimates of exposure

The age- and sex-specific estimates for discretionary-time activity, work-related activity and adjusted transport-related activity were summed to create a sum total of physical activity for each age by sex cell for each of the 146 countries. Using the adjusted transport scores, the sum totals had a range of 45–135, a mean of 95 (SD = 20.2) and median of 97. The distribution of both the adjusted and unadjusted sum totals is shown in Figure 10.20. Despite the adjustment described in Step 4, the sum total for some age by sex categories exceeded 100%. Given these values are

Figure 10.19 Adjusted estimates for transport-related physical activity (cycling and walking) by the indicator cars per thousand (n = 147 countries)



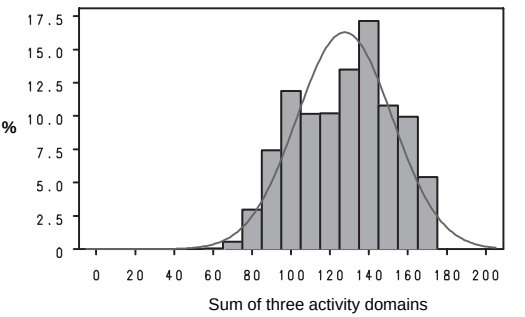
impossible some form of recalibration of at least the upper values was necessary. Scaling offered one way to address this final problem, which in itself is deemed to be primarily a result of insufficient data on levels of exposure within and between domains.

Once again, known data were used to guide this computation. Specifically, 12 age- and sex-specific estimates of total physical activity were available for both China and the United States ($n = 24$). These data were used to investigate what value to set as the mean to enable z-scores to be calculated and the data to be scaled. In addition, we set the maximum value for any age by sex cell for total activity as 98%. This was derived from United States data on disability that suggests approximately 2% of the whole population may not be able to achieve any physical activity in any domain. Using a maximum value of 98% and exploring various values for the mean we identified the model of best fit for the 24 age-sex category data for China and the United States. Predicted estimates of total physical activity from the best fit model are shown against actual data in Figure 10.21.

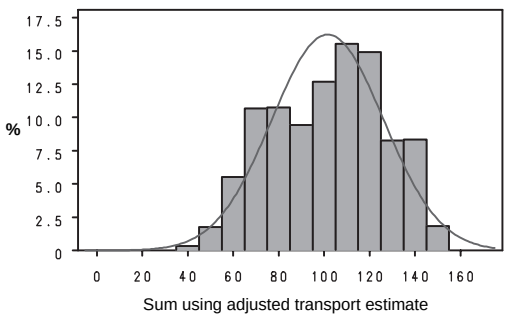
The final step was to scale the scores from Step 4 to create age x sex estimates within the range of 0–100. We calculated the z-scores by setting the mean at 82% and maximum at 98% and these parameters determined the SD to be 4.33. We chose to only scale estimates above the mean using the following formula:

$$\text{If TOTAL SUM SCORE} > 82 \text{ then } 82 + z\text{-score} \times \text{SD of desired distribution } (= 4.33).$$

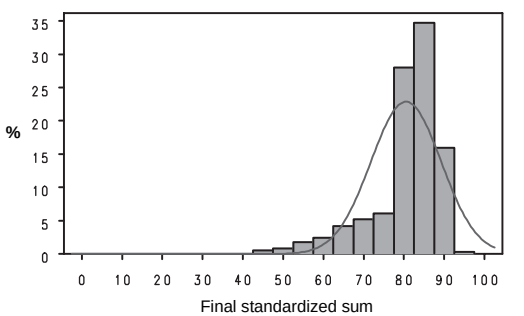
Figure 10.20 Distribution of estimates of total physical activity (a) before adjustment to transport, (b) after adjustment and (c) after standardizing scores above the mean



(a) Distribution of estimated prevalence scores of total physical activity for each age x sex cell before adjustment to transport-related activity



(b) Distribution of estimated prevalence scores of total physical activity for each age x sex cell after adjustment to transport-related activity

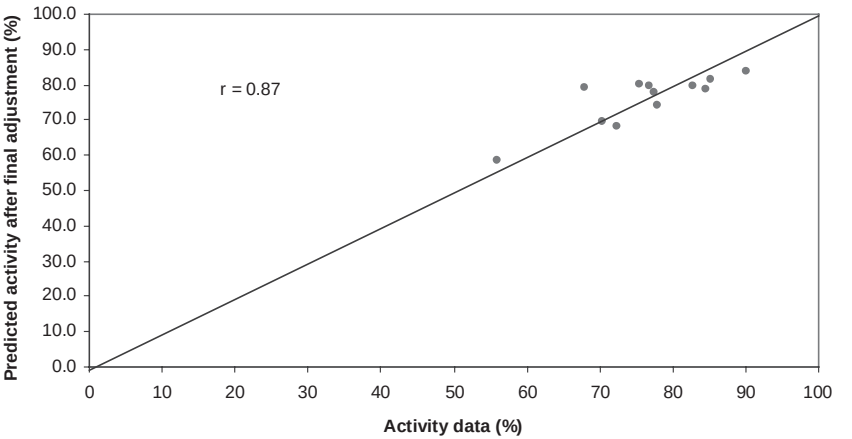


(c) Distribution of final estimated prevalence scores of total physical activity for each age x sex cell after standardization of cells with very high levels of activity

Predicted estimates that fell below 82% were not scaled. The final distribution of estimates of total activity is shown in Figure 10.20(c).

In addition to using data from China and the United States, available prevalence estimates of total physical activity (covering at least three domains) from Egypt and the United Republic of Tanzania were used to provide a check on the face validity of our final predicted estimates

Figure 10.21 Predicted and actual age x sex estimates of total physical activity for the USA (n = 12)



derived from the adjusted (for activity in multiple domains i.e. Step 4) and now scaled (Step 5) model.

Step 6: Aggregation of country estimates to create regional estimates

The penultimate step was to create prevalence estimates in terms of the exposure variable physical inactivity by subtracting physical activity scores from 100. In order to create age- and sex-specific estimates for 14 subregions, each age by sex by country prevalence estimate was weighted to the age by sex population of the country. The final estimates for each subregion were obtained by calculating the mean level of activity for each age category for males and females. Actual data were substituted for predicted estimates where available.

Estimates of exposure to physical inactivity by subregion, sex and age are shown in Table 10.10 and graphically in Figure 10.22(a). Figure 10.22(b) depicts physical activity by domain and subregion.

2.8 Estimating prevalence of level 2 exposure (insufficiently active)

Consistent with our estimates of level 1 exposure, we attempted to consider all domains in our computation of level 2 exposure. We used the results of our literature search described earlier to identify those studies with data that matched or closely corresponded to our definition of level 2 exposure, those undertaking some physical activity but not sufficient amounts to meet the Centers for Disease Control and Prevention and the American College of Sports Medicine (CDC/ACSM) public health

Table 10.10 Exposure estimates by subregion, sex and age[a]

Subregion	Sex	Exposure category	Age group (years)					
			15–29	30–44	45–59	60–69	70–79	≥80
AFR-D	Male	Inactive	10	12	13	15	17	18
		Insufficient	48	48	48	46	44	43
		Recommended	42	40	40	39	39	39
	Female	Inactive	12	11	12	15	18	19
		Insufficient	45	52	51	48	46	45
		Recommended	43	37	37	37	36	36
AFR-E	Male	Inactive	9	11	11	14	16	16
		Insufficient	50	51	50	49	47	46
		Recommended	41	38	38	37	38	38
	Female	Inactive	11	10	10	13	15	15
		Insufficient	47	56	55	51	50	50
		Recommended	42	35	35	35	35	35
AMR-A	Male	Inactive	16	18	19	20	21	31
		Insufficient	44	47	44	40	40	35
		Recommended	40	35	36	40	39	34
	Female	Inactive	21	22	20	26	30	40
		Insufficient	36	41	40	38	36	31
		Recommended	43	37	40	37	34	29
AMR-B	Male	Inactive	16	17	18	22	25	28
		Insufficient	42	44	41	39	36	35
		Recommended	42	39	40	39	39	37
	Female	Inactive	22	26	27	36	39	41
		Insufficient	33	32	31	30	30	29
		Recommended	45	41	42	33	31	30
AMR-D	Male	Inactive	16	18	18	22	27	29
		Insufficient	38	38	33	32	30	29
		Recommended	46	45	49	46	43	42
	Female	Inactive	21	25	29	39	45	47
		Insufficient	28	26	24	24	22	22
		Recommended	51	48	47	38	32	31
EMR-B	Male	Inactive	14	18	18	21	24	26
		Insufficient	41	39	38	36	32	32
		Recommended	44	43	43	42	44	42
	Female	Inactive	18	20	20	24	30	32
		Insufficient	36	36	35	32	31	30
		Recommended	46	45	45	44	40	38
EMR-D	Male	Inactive	13	17	18	20	22	25
		Insufficient	42	38	36	35	32	31
		Recommended	45	45	46	45	46	44
	Female	Inactive	17	19	19	22	28	30
		Insufficient	36	36	35	32	31	30
		Recommended	47	45	46	45	41	39
EUR-A	Male	Inactive	13	15	16	18	20	21
		Insufficient	52	57	55	52	50	47
		Recommended	35	29	30	30	30	32
	Female	Inactive	17	18	18	22	24	28
		Insufficient	47	51	51	45	45	42
		Recommended	37	31	31	33	31	30

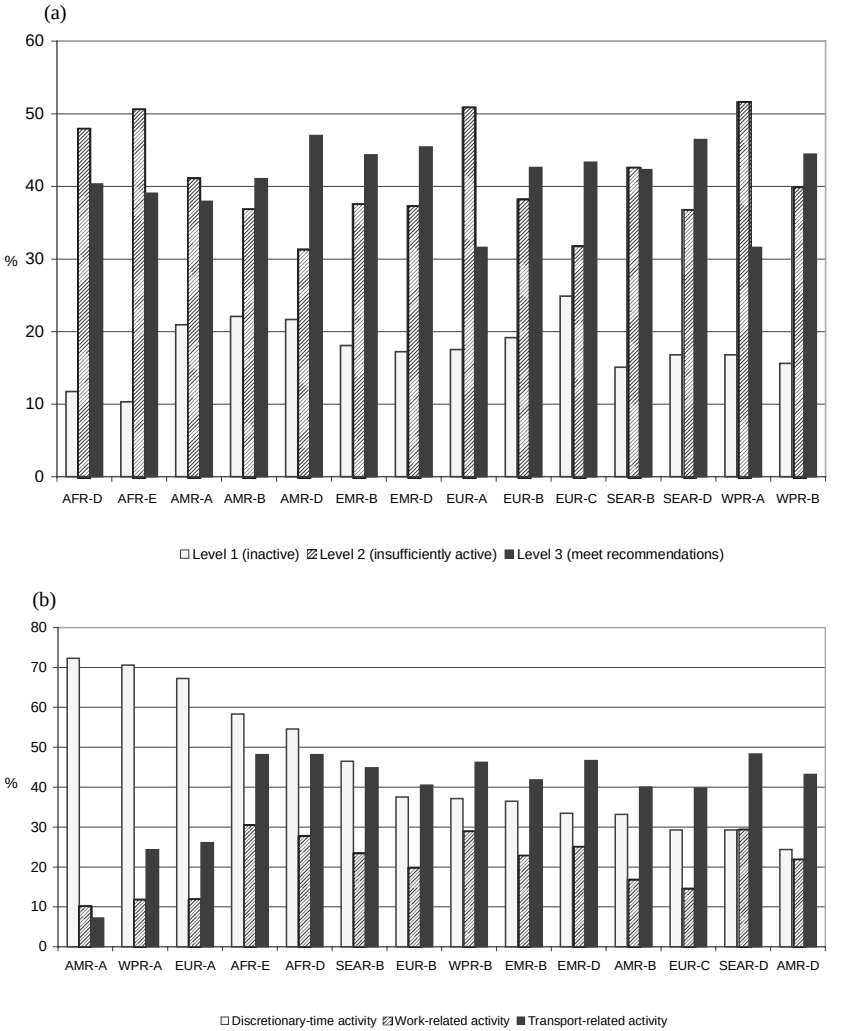
Table 10.10 Exposure estimates by subregion, sex and age[a] (*continued*)

Subregion	Sex	Exposure category	Age group (years) 15–29	30–44	45–59	60–69	70–79	≥80
EUR-B	Male	Inactive	15	18	19	22	25	28
		Insufficient	43	40	38	36	34	33
		Recommended	42	42	43	42	41	39
	Female	Inactive	18	20	21	26	31	32
		Insufficient	37	37	36	33	32	32
		Recommended	44	42	43	40	37	36
EUR-C	Male	Inactive	17	18	21	30	36	38
		Insufficient	38	34	32	30	28	28
		Recommended	45	48	47	39	35	34
	Female	Inactive	20	26	27	38	39	40
		Insufficient	32	31	30	27	27	26
		Recommended	48	43	43	34	34	34
SEAR-B	Male	Inactive	13	15	15	15	14	14
		Insufficient	43	43	43	47	52	52
		Recommended	44	42	42	38	34	34
	Female	Inactive	14	17	17	17	16	16
		Insufficient	41	41	41	45	50	50
		Recommended	44	42	42	38	34	34
SEAR-D	Male	Inactive	13	16	17	20	22	20
		Insufficient	42	38	36	34	32	31
		Recommended	45	46	47	46	47	49
	Female	Inactive	17	18	19	22	24	26
		Insufficient	36	35	34	32	30	30
		Recommended	47	47	47	47	46	44
WPR-A	Male	Inactive	14	15	16	18	17	17
		Insufficient	50	56	53	52	56	55
		Recommended	35	29	30	30	27	28
	Female	Inactive	16	19	18	20	17	17
		Insufficient	48	49	50	49	55	54
		Recommended	36	32	32	31	28	28
WPR-B	Male	Inactive	13	15	15	17	18	20
		Insufficient	41	40	41	41	44	41
		Recommended	46	44	45	41	38	38
	Female	Inactive	15	16	17	20	20	19
		Insufficient	40	39	38	38	41	38
		Recommended	45	45	45	42	39	42

[a] As % of total population.

recommendation of 150 minutes of moderate-intensity physical activity per week or equivalent. We found some data for the discretionary-time domain but no specific data on the level of insufficient activity in the transport- and occupation-related domains. Thus, with only a modest amount of empirical evidence we constructed a method to differentiate between those adults doing some activity but not meeting the recommended amount (i.e. level 2 exposure) and those adults meeting the current recommendations (level 3).

Figure 10.22 Prevalence of exposure by (a) subregion and (b) prevalence of physical activity by domain and subregion

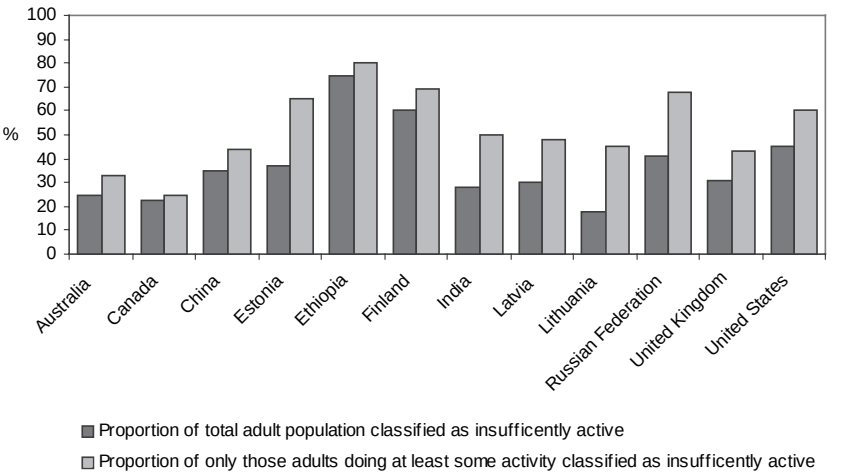


METHODS FOR ESTIMATING LEVEL 2 EXPOSURE BY DOMAIN

Discretionary-time domain

Countries with some data on levels of insufficient activity in the discretionary-time domain were Australia, Canada, China, Estonia, Ethiopia, Finland, India, Latvia, Lithuania, the Russian Federation, the United Kingdom of Great Britain and Northern Ireland and the United States. Figure 10.23 presents the country-level estimates of % insufficient

Figure 10.23 Prevalence of insufficiently active as a proportion of total adult population and insufficiently active as a proportion of adults who do at least some activity, in 12 countries[a]



[a] Definitions of insufficiently active are similar but not identical in each country; comparisons should therefore be made with caution.

for these 12 countries. We emphasize that these data are not exactly comparable due to different instruments and calculations as well as slightly different definitions. With the exception of Ethiopia, these data represent levels of insufficient activity in the discretionary-time domain only.

Figure 10.23 shows that there was no clear pattern across this set of countries. For instance, Canada and Australia had similar prevalence estimates of insufficiently active, namely 23% and 25% respectively, but this represented 25% of the "active" Canadian population and 33% in Australia. In contrast, 45% of the adult population in the United States was classified as insufficient and this was 63% of the active population. Finland had a very high proportion of adults doing at least some activity (90%) but of these, 63% did not meet the current recommendations. This was similar in Ethiopia. In the absence of any pattern in the proportion of adults classified as inactive with data ranging from 25–80%, we assumed that 50% of adults who were doing some activity were not active enough to meet recommendations. This rule was applied to our calculations of insufficient for all countries, male and females and all ages except the lowest age category (15–29 years). Available data indicate that younger adults are more likely to meet recommended levels of activity; therefore for this age group we assumed only 40% of those active were insufficiently active.

Transport domain

The data on physical activity in the transport domain are generally of poor quality. Some data from Europe suggest that approximately half of all walk and cycle trips are less than 3km. Using this information, we estimated that 50% of adults classified as active in the transport domain would be classified as insufficient because at a moderate-intensity (walking pace) 3km would take approximately 30 minutes). It is likely that trips may be longer in duration in developing countries; therefore we scaled our algorithm such that 60% of adults identified as active in countries defined as "high income" (World Bank 1999) were classified as insufficient compared with 50% and 40% of adults in "upper middle income" and the combined group of "lower middle" and "lower income", respectively. We applied no additional adjustment to account for likely age and sex differences.

Work domain

Data on work-related physical activity are not often reported in terms of hours of different intensity activities. Our search found few data assessing this activity in this domain alone, and only data from China were reported in hours. It is suspected that there is a large degree of measurement error in self-reporting of heavy physical activity at work; therefore some proportion of those adults reporting heavy activity may be misclassified. We decided to assume that 30% of those identified as doing heavy physical activity at work in countries defined as "high income" (World Bank 1999) did not meet recommendations. In "upper middle", "lower middle" and "lower income" countries we adjusted this assumption to 15% thus allowing more work activity "to count" as recommended. We did no further adjustments based on age or sex. Moreover, we did not attempt to estimate the proportion of adults misclassified as inactive when they should have been classified as insufficient.

Summing across domains and final adjustment of estimates

We used our age-sex-country estimates of level 1 exposure (inactive) within in each domain (discretionary, transport and work) to compute the prevalence of adults doing at least some activity for each age x sex x country category within each domain. This was simply 100 – % inactive. The algorithms described above were used to compute the prevalence of insufficient in each domain, which in turn were summed to derive an overall estimate for level 2 exposure.

We reviewed these data and noted the absence of any difference between males and females. In contrast, limited available data in the discretionary-time domain suggest women are less likely to be undertaking the recommended level of activity (level 3, sufficient). In addition, there is evidence of a trend over age, with older adults more likely to be insuf-

ficient compared with younger adults who are more likely to be undertaking recommended levels. We therefore developed and imposed an age and sex adjustment which resulted in the best fit between our age-sex-country estimates and available data. It was, however, not possible to get a good fit; but the results appear to reflect the regional variations even though certain individual countries may be poorly described. Computed estimates of level 2 exposure by subregion, sex and age are reported in Table 10.10.

2.9 Sources of uncertainty

Given the paucity of existing data in each of the domains of physical (in)activity and the complexity of the approach taken to predict estimates of exposure, there is a large degree of uncertainty around the final data. Both quantitative and qualitative approaches were taken to estimate the magnitude of this error and these steps are outlined below.

Methods used to estimate uncertainty and compute standard error and 95% confidence intervals

Level 1—Inactive

Subregions were categorized according to the level of estimate uncertainty by considering both the quantity and quality of available data within each subregion. Quantity of data was assessed using the proportion of the total subregional population represented by data. Subregions with fewer data from fewer countries were deemed to have much greater uncertainty than those subregions with more data from more countries. Quality of data was assessed by considering the source of data (national or non-national samples). The subregions were classified into four levels of uncertainty.

- AFR-D, EUR-B, SEAR-B, SEAR-D — highest uncertainty;
- AFR-E, EMR-B, EMR-D — high uncertainty;
- AMR-B, AMR-D — moderate–high uncertainty;
- AMR-A, EUR-A, EUR-C, WPR-A, WPR-B — lowest uncertainty.

The predicted estimates within each domain (discretionary-time, work-related and transport-related), the missing data on domestic inactivity and the modelling procedures all represent sources of uncertainty. To account for these an adjustment factor was calculated for each age-sex-subregion estimate. The magnitude of the adjustment was proportional to the level of uncertainty surrounding the data and was a sliding scale inverse to the grading of data quality. The maximum adjustment was chosen to elicit a maximum coefficient of variation of approximately 30% for the least certain estimates. To achieve this the adjustment factor

was greatest for prevalence estimates in the subregions with the highest uncertainty (25%) and smallest for those subregions with the lowest uncertainty (10%). The adjustment factor for high uncertainty and moderate–high uncertainty were 20% and 15%, respectively. The resulting uncertainty ranges for level 1 exposure are shown in Table 10.11.

The lack of data on older adults would add greater uncertainty to these estimates across all subregions. Furthermore, the omission of data (actual or predicted) on domestic-related activity may add differential levels of uncertainty to the final estimates of women compared with men and between subregions.

Level 2—Insufficiently active

Overall there is more uncertainty around the estimates of level 2 exposure than for level 1 due to the paucity of data and the heterogeneity among the existing data. Therefore, larger rather then smaller confidence limits were used. We computed uncertainty ranges by calculating a 25% upper and lower margin of error around each age-sex-subregion predicted estimates (Table 10.11). Given a mean level of insufficient exercise of approximately 40% this produces a range of ±10 prevalence estimate points.

3. Estimating physical inactivity–disease relationships

3.1 Selection of health outcomes

There is a large body of scientific evidence linking physical inactivity with a wide range of cardiovascular, musculoskeletal and mental health outcomes. All potential disease end-points were considered; however, for inclusion the following criteria had to be met:

1. the disease outcome is included in the Global Burden of Disease (GBD) disease list;
2. there was strong evidence for a causal association between physical inactivity and an increase in risk;
3. biologically plausible mechanisms exist to explain (at least partly) the association; and
4. sufficient information was available to allow quantification of hazard.

The disease end-points initially considered for inclusion were cardiovascular disease, specifically ischaemic heart disease and stroke, several site-specific cancers (colon, rectal, breast, prostate), type II diabetes, various musculoskeletal conditions (namely lower back pain, osteoarthritis, osteoporosis), falls and mental health outcomes (specifically depression). Literature pertaining to each of these was reviewed to

Table 10.11 Range of uncertainty associated with estimates for level 1 and 2 exposure by subregion, sex and age

			Age group (years)					
Subregion	*Sex*	*Exposure category*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	Inactive	4.03–15.23	5.18–19.38	5.28–19.80	6.58–23.70	7.43–27.03	7.54–28.86
		Insufficient	29.31–67.10	29.29–67.05	28.93–66.23	28.03–64.16	26.60–60.90	26.05–59.64
	Female	Inactive	4.99–18.97	4.25–18.63	4.49–18.95	6.06–24.56	6.36–28.96	6.51–31.63
		Insufficient	27.39–62.70	31.50–72.12	31.10–71.21	29.09–66.59	28.17–64.49	27.37–62.67
AFR-E	Male	Inactive	4.51–12.51	6.00–16.00	6.15–16.33	7.70–19.82	8.83–22.29	9.18–22.96
		Insufficient	30.48–69.79	31.00–70.98	30.65–70.17	29.76–68.13	28.40–65.03	27.98–64.07
	Female	Inactive	5.68–15.52	5.04–14.36	5.32–14.94	7.37–19.59	8.34–21.22	8.73–21.97
		Insufficient	28.79–65.91	33.78–77.34	33.17–75.94	31.21–71.46	30.51–69.85	30.20–69.14
AMR-A	Male	Inactive	11.93–19.95	12.68–23.60	13.12–25.70	14.65–25.07	13.91–28.25	20.09–41.77
		Insufficient	26.57–60.83	28.46–65.16	26.91–61.61	24.45–55.99	24.08–55.13	21.50–49.22
	Female	Inactive	14.03–27.45	13.65–30.29	11.90–28.62	14.87–36.69	18.66–41.50	24.15–55.43
		Insufficient	22.01–50.39	25.08–57.43	24.44–55.96	22.89–52.40	21.64–49.53	18.73–42.89
AMR-B	Male	Inactive	10.53–21.07	11.56–23.24	11.93–24.93	12.90–31.20	14.02–35.98	15.92–39.72
		Insufficient	25.75–58.95	26.51–60.70	25.18–57.65	23.47–53.72	22.09–50.58	21.42–49.05
	Female	Inactive	13.88–30.84	15.87–37.03	15.25–39.17	21.31–51.55	23.32–55.40	24.21–57.71
		Insufficient	19.92–45.61	19.56–44.78	18.77–42.97	18.50–42.35	18.08–41.39	17.56–40.20
AMR-D	Male	Inactive	10.27–21.61	11.48–23.92	11.99–24.35	14.16–28.84	15.18–39.44	16.02–42.68
		Insufficient	22.92–52.48	22.97–52.58	19.95–45.66	19.63–44.94	18.13–41.52	17.72–40.56
	Female	Inactive	13.18–28.60	13.93–36.47	15.09–43.05	21.97–55.65	26.43–64.39	27.65–65.99
		Insufficient	17.12–39.19	16.01–36.66	14.74–33.74	14.40–32.96	13.62–31.17	13.34–30.54
EMR-B	Male	Inactive	7.94–20.96	10.03–25.67	10.25–26.31	11.20–31.46	10.86–36.16	12.62–39.74
		Insufficient	25.21–57.73	23.67–54.18	23.29–53.32	22.06–50.50	19.70–45.11	19.19–43.95
	Female	Inactive	10.23–25.95	11.13–28.27	11.19–28.83	10.85–36.77	15.37–44.09	17.05–47.09
		Insufficient	21.88–50.10	21.67–49.62	21.31–48.79	19.43–44.49	18.69–42.79	18.30–41.90
EMR-D	Male	Inactive	6.78–20.18	8.65–25.27	9.01–26.43	10.54–30.06	10.94–33.36	12.29–39.74
		Insufficient	25.29–57.91	23.22–53.17	22.15–50.71	20.98–48.04	19.48–44.60	18.89–43.24
	Female	Inactive	8.60–25.74	8.91–28.51	9.12–28.94	10.62–34.06	13.35–43.65	13.87–46.59
		Insufficient	21.94–50.24	21.90–50.15	21.47–49.16	19.62–44.92	18.81–43.05	18.53–42.41

continued

Table 10.11 Range of uncertainty associated with estimates for level 1 and 2 exposure by subregion, sex and age (*continued*)

			Age group (years)					
Subregion	*Sex*	*Exposure category*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
EUR-A	Male	Inactive	10.02–16.76	10.81–18.47	11.32–19.76	13.07–22.85	13.72–25.62	14.99–27.41
		Insufficient	31.56–72.25	34.57–79.14	33.33–76.31	31.82–72.85	30.61–70.08	28.68–65.65
	Female	Inactive	12.19–21.05	12.97–22.65	13.02–23.28	15.29–29.63	16.08–31.66	18.39–36.95
		Insufficient	28.39–65.00	31.17–71.37	30.84–70.62	27.25–62.39	27.19–62.26	25.82–59.11
EUR-B	Male	Inactive	6.69–21.85	8.40–27.00	8.92–28.38	10.11–31.75	10.84–38.98	11.87–43.05
		Insufficient	26.17–59.92	24.49–56.07	23.30–53.36	22.09–50.57	20.59–47.15	20.16–46.16
	Female	Inactive	8.58–27.62	9.47–30.11	9.80–30.92	11.15–40.51	12.82–48.68	13.36–50.64
		Insufficient	22.77–52.14	22.73–52.04	22.15–50.72	20.32–46.52	19.59–44.85	19.32–44.24
EUR-C	Male	Inactive	11.50–21.54	13.51–22.49	14.88–27.98	18.45–42.51	21.16–51.62	21.64–54.24
		Insufficient	23.11–52.92	20.64–47.26	19.38–44.36	18.34–41.98	17.22–39.43	16.94–38.78
	Female	Inactive	14.39–25.89	16.90–36.06	17.02–37.08	22.04–54.54	21.33–56.49	22.26–57.94
		Insufficient	19.34–44.29	18.78–42.99	18.43–42.19	16.62–38.05	16.27–37.25	15.91–36.42
SEAR-B	Male	Inactive	5.73–20.03	6.82–23.70	6.83–23.71	7.02–23.90	6.40–21.78	6.59–22.31
		Insufficient	26.18–59.93	25.96–59.44	25.95–59.41	28.47–65.18	31.73–72.65	31.57–72.29
	Female	Inactive	6.41–22.57	7.60–26.52	7.53–26.29	7.73–26.43	7.09–24.25	7.28–24.72
		Insufficient	25.22–57.74	24.63–56.38	24.85–56.89	27.39–62.71	30.70–70.28	30.56–69.96
SEAR-D	Male	Inactive	6.34–19.36	8.17–24.73	8.49–25.95	9.50–30.38	9.57–33.43	9.46–30.96
		Insufficient	25.38–58.10	22.96–52.56	21.87–50.07	20.81–47.64	19.33–44.24	18.88–43.23
	Female	Inactive	8.11–24.91	9.10–27.58	9.23–28.03	10.11–33.21	10.94–36.94	11.50–41.28
		Insufficient	21.94–50.23	21.26–48.67	20.84–47.72	19.17–43.89	18.38–42.08	18.02–41.25
WPR-A	Male	Inactive	10.31–18.25	11.15–19.07	12.05–20.37	13.65–21.97	12.86–20.80	12.61–21.35
		Insufficient	30.60–70.06	34.00–77.84	32.46–74.33	31.79–72.79	33.91–77.65	33.70–77.16
	Female	Inactive	11.72–20.60	13.40–24.08	13.36–23.00	15.30–23.84	12.98–21.36	12.49–22.29
		Insufficient	28.93–66.24	29.80–68.22	30.59–70.03	30.06–68.81	33.44–76.55	33.13–75.85
WPR-B	Male	Inactive	10.07–16.44	11.91–18.93	11.53–18.07	13.22–21.62	13.51–23.27	14.49–26.19
		Insufficient	24.93–57.07	24.39–55.83	24.65–56.44	25.13–57.53	26.55–60.79	25.14–57.56
	Female	Inactive	11.28–18.34	12.76–19.90	13.08–20.58	15.09–25.27	14.88–25.98	14.42–24.56
		Insufficient	24.30–55.64	23.64–54.13	23.05–52.77	23.19–53.09	24.83–56.85	23.14–52.99

Table 10.12 Health outcomes considered in this analysis

Health outcome	*GBD classification system outcome*	*Causal*	*Biological plausibility*	*Risk data*	*Inclusion/Exclusion*
Ischaemic heart disease	Yes	Yes	Yes	Yes	Included
Stroke	Yes	Yes[a]	Yes[a]	Yes	Included[a]
Type II diabetes	Yes	Yes	Yes	Yes	Included
Breast cancer	Yes	Yes	Yes	Yes	Included
Colon cancer	Yes	Yes	Yes	Yes	Included
Prostate cancer	Yes	Uncertain	Uncertain	Limited	Excluded
Rectal cancer	Yes	Uncertain	Uncertain	Limited	Excluded
Low back pain	Yes	Some	Some	Limited	Excluded
Osteoporosis	No	Some	Some	Limited	Excluded
Osteoarthritis	No	No	No	Limited	Excluded
Falls	No	Some	No	Limited	Excluded
Depression	Yes	No	Uncertain	Limited	Excluded
Obesity	No	Yes	Yes	No	Excluded

[a] For ischaemic stroke only.

identify the level of evidence on causality. For several outcomes there is a considerable level of interest and a large number of studies, particularly in recent years, but insufficient support for the biological mechanism associated with physical inactivity. In these cases the disease outcomes were excluded but any future attempts at assessing attributable burden should update our review. Below is a brief summary of the evidence and proposed biological mechanisms associated with physical inactivity for each disease end-point considered. These are summarized in Table 10.12.

Cardiovascular diseases

Ischaemic heart disease

The strongest evidence for the benefits of physical activity pertains to the reduction of risk of mortality and morbidity from cardiovascular disease, particularly acute myocardial infarction and other forms of ischaemic heart disease (Berlin and Colditz 1990; Powell et al. 1987). These associations are generally strong and independent of the definition of physical activity used. Biologically plausible mechanisms for the effects of moderate and/or vigorous intensity physical activity on ischaemic heart disease have been identified through clinical and observational studies. The mechanisms or pathways include advantageous effects on athero-

sclerosis, lipid profile, ischaemia, blood pressure, thrombosis and fibrinolytic activity (Hardman and Stensel 2003).

A number of studies have shown physical activity directly and indirectly reduces the effects of excess cholesterol and other atherosclerotic agents (Durstine and Haskell 1994; Kramsch et al. 1981; Leon 1991). Participation in physical activity can improve total blood cholesterol levels (McMurray et al. 1998) and improve high density lipoprotein (HDL) subfraction profiles (Moore 1994). An increase in HDL is desirable because HDL transports cholesterol to the liver for elimination in the bile, and thus has an "anti-atherosclerotic" function. Physical activity has also been shown to increase the activity of lipoprotein lipase, which is involved in the removal of cholesterol from the blood (Stefanick and Wood 1994). There may be, however, a threshold for the relationship between physical activity and improvements in the HDL subfraction of cholesterol, with prolonged or intensive physical activity being more beneficial for HDL to cholesterol ratios (Kokkinos and Fernhall 1999).

Decreased risk of ischaemia may be due to positive adaptations in coronary circulation from structural adaptations following physical activity (Laughlin 1994; Tomanek 1994). Acute coronary events may be reduced by a reduction in thromboses by an increase in enzymatic (fibrinolytic) breakdown of blood clots and a decrease in platelet aggregation (Leon 1991).

Vigorous physical activity has been shown to decrease systolic and diastolic blood pressures (Arroll and Beaglehole 1992; Kelley and McClellan 1994; McMurray et al. 1998; Mensink et al. 1999). Moreover there is some evidence that participation in more moderate-intensity activity may achieve similar or even greater effects than vigorous activity (Hagberg et al. 1989; Marceau et al. 1993; Matsusaki et al. 1992; Moreau et al. 2001). The proposed mechanisms by which blood pressure is lowered is via the immediate and temporary dilation of the peripheral blood vessels during physical activity and the ongoing effect of a reduction in sympathetic nervous system activity (Fagard and Tipton 1994).

Stroke

A recent review of the dose–response relationship between physical activity and risk of stroke suggests current evidence remains equivocal (Kohl 2001). Only six studies from a total of 15 showed evidence of a dose–reponse relationship; eight did not and two studies suggested a "U" shaped distribution (Kohl 2001). While this presents an unclear picture, it is notable that many studies did not differentiate between the two different types of stroke: ischaemic and haemorrhagic, as we describe in detail below.

The biological mechanisms for the association between physical activity and ischaemic stroke and ischaemic heart disease are thought to be

similar, namely atherosclerosis and hypertensive disease (Kohl 2001). However, the biological pathway for haemorrhagic stroke is less clear. Given potentially different pathophysiological pathways, it follows that physical activity may be differentially related to one type (ischaemic) and not the other (haemorrhagic). In general, studies show a decrease in the risk of ischaemic stroke with increasing levels of physical activity (Ellekjaer et al. 2000; Wannamethee and Shaper 1999) but studies with separate risk by sub-type show no or smaller associations with varying levels of activity for haemorrhagic stroke (Hu et al. 2000).

Given the evidence is mixed for an association between overall stroke and physical inactivity and sufficient evidence on causality and burden exists only for ischaemic stroke, for this study, only ischaemic stroke was included.

Type II diabetes

A recent review (Ivy et al. 1999) showed that the benefits of physical activity in the prevention of type II diabetes are strongly supported by current research, especially among people already at risk (Kelley and Goodpaster 2001). In general, prospective observational studies show a lower incidence of type II diabetes in more active people compared with the least active in the population. Both moderate- and vigorous-intensity physical activity reduce the risk of type II diabetes in women (Hu et al. 1999), and the benefits appear to accrue also for males and in diverse populations (Folsom et al. 2000; Okada et al. 2000). Reduction in risk of type II diabetes appears to occur only from regular, sustained physical activity.

The biological mechanisms for this protection have not been clearly identified, but are likely to occur at systemic, tissue and cellular levels. Numerous studies and reviews have described either a short- and/or a long-term effect from participation in physical activity on glucose tolerance and carbohydrate metabolism. In general, physical activity increases sensitivity to insulin, improves glucose metabolism, reduces atherosclerosis risk, and reduces intra-abdominal fat distribution (Kelley and Goodpaster 2001). Physical inactivity appears to relate to increased risk of type II diabetes by two possible pathways, which are described in detail by Katzmarzyk et al. (1996). Briefly, one pathway involves the relationship between physical inactivity, a positive energy balance, and an increase in adiposity. The resulting insulin resistance leads to a reduction in plasma free fatty acid (FFA) clearance. Elevated blood FFA levels have detrimental effects on blood glucose, which result in increased pancreatic β cell insulin secretion and hyperinsulinaemia in order to control blood glucose levels. The increased requirement for insulin causes β cell impairment and reduced blood insulin levels, which increases the insulin resistant state, further reduces clearance of FFA from the blood, increases glucose levels and results in type II diabetes (Katzmarzyk et al. 1996).

A second mechanism suggests that a physically inactive lifestyle exposes a genetic predisposition in skeletal muscle, which can result in muscular insulin resistance. This results in increases in β cell insulin secretion and hyperinsulinaemia to control blood glucose concentrations. One result of hyperinsulinaemia is a suppression of fatty acid oxidation and increases of triglyceride storage, and adipose cell hypertrophy. Adipose cells then become insulin resistant and there is a reduced ability to remove FFA from the blood. This results in an increase in glucose output from the liver and further development of muscle insulin resistance. Ultimately, the increased reliance on insulin to control blood glucose concentration results in β cell impairment and development of type II diabetes.

The physiological adaptations that are responsible for the protective effects of physical activity subside within a short period of the cessation of physical activity, within two weeks of inactivity (Arciero et al. 1999; Dela et al. 1993; Rogers et al. 1990). Therefore physical activity must be undertaken regularly to provide benefits in terms of risk reduction.

The evidence for a causative association between physical inactivity and increased risk of type II diabetes was strong enough for inclusion.

Cancers

Colon cancer

Numerous studies have shown the protective effect of physical activity on risk of colon cancer (Colditz et al. 1997; IARC 2002; Thune and Furberg 2001) and on the prevention of precancerous polyps in the large bowel (Neugut et al. 1996; Slattery et al. 1997). However, no definitive biological mechanisms have been identified to explain the relationship between physical inactivity and increased risk of colon cancer although several mechanisms have been proposed, which link physical activity and changes in physiologic measures.

One possible mechanism is the effect of prostaglandins on colon mucosal cell proliferation. Physical activity produces an increase in prostaglandin F2 alpha that increases intestinal motility, and a decrease in prostaglandin E2, which stimulates colon cell proliferation (Thor et al. 1985; Tutton and Barkla 1980). Further support for this possible mechanism comes from laboratory studies on rats and evidence in humans that aspirin and nonsteroidal anti-inflammatory drugs, also inhibitors of prostaglandin synthesis, reduce risk of colon cancer (Tomeo et al. 1999). A second mechanism relates physical inactivity and abdominal obesity and proposes that obesity may increase the risk of colon cancer via its influence on insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding proteins (IGFBP). Since insulin is a growth factor for colon mucosal cells this may promote cancerous cell production. Thus, it is possible that activity exerts its protective effect through reduced insulin levels, because physical activity has been shown

to reduce insulin levels in both obese individuals and those of healthy weight (Giovannucci et al. 1995; McKeown-Eyssen 1994; Tomeo et al. 1999). Insulin-like growth factor is associated with colon cancer risk (Giovannucci et al. 2000; Ma et al. 1999), and IGF is influenced by caloric intake and physical activity. Thus higher levels of physical activity may down-regulate IGF by increasing the production of the binding protein (IGFBP3). The nature of the evidence for an association between physical inactivity and colon cancer was sufficient to meet criteria for inclusion.

Rectal cancer

There is less evidence for a significant causal association between physical inactivity and rectal (or colorectal) cancer. A recent review of studies in which separate risk estimates for colon and rectal cancers were provided found no association between physical activity and rectal cancer in 80% of studies included in their review (Thune and Furberg 2001). The authors suggest that the apparent protective effect of physical activity on colorectal cancer may be derived, in the main, from the association between physical activity and colon cancer (Thune and Furberg 2001). On the basis of this review rectal (or colorectal) cancer was not included in this study.

Breast cancer

The majority of studies investigating the benefits of physical activity and breast cancer report a reduction in the risk of breast cancer among physically active women (Gammon et al. 1998; Latikka et al. 1998; Verloop et al. 2000). There is substantial evidence that discretionary-time and/or occupational physical activity is associated with approximately a 30% reduction in the risk of breast cancer in pre-, peri- and post-menopausal women (Thune and Furberg 2001). Increased number of lifetime ovulatory cycles and cyclic estrogen has been proposed as a risk factor for breast cancer (Henderson et al. 1985). The impact of regular physical activity on the secretion, metabolism, and excretion of the sex hormones estradiol and progesterone provides a biologically plausible causal mechanism for the reduction of risk for breast cancer among physically active women. However, elevated relative and absolute estrogen levels may increase the risk of breast cancer (McTiernan et al. 1996). The strength and nature of the evidence for an association between physical inactivity and risk of breast cancer meets criteria for inclusion.

Prostate cancer

There is limited evidence showing vigorous activity may provide a protective effect against prostate cancer in men (Giovannucci et al. 1998) and other researchers have not found such a relationship (Liu et al. 2000). A recent review of 24 studies found that 14 suggested an inverse association of physical activity on prostate cancer, six showed no asso-

ciation, and an increased risk of prostate cancer was observed among the most physically active men in four other studies (Friedenreich and Thune 2001). Given these equivocal results prostate cancer was not included in this project.

Musculoskeletal conditions

Participation in physical activity throughout the course of life can increase, maintain or reduce the decline of musculoskeletal health that generally occurs with ageing in sedentary people (Brill et al. 2000). Participation by older adults can help maintain strength and flexibility, resulting in an ability to continue to perform daily activities (Brill et al. 2000; Huang et al. 1998; Simonsick et al. 1993). Furthermore, participation can reduce the risk of falling and hip fractures in older adults. (Grisso et al. 1997; Lord 1995) Evidence for associations between physical inactivity and low back pain, osteoporosis and falls, and oesteoarthritis are examined below.

Low back pain

Low back pain is a term applied to a group of conditions or symptoms where there is pain, muscle tension and/or stiffness in the lower back. Low back pain may or may not include sciatica and other "nerve" discomfort. Physical activity is associated with both increased and decreased risk for low back pain. Certain specific activities such as heavy physical work, lifting, twisting, pulling, pushing that generally occur in occupational or during some specific discretionary-time activities (e.g. certain sports, heavy yard work) can increase the risk of low back pain (Picavet and Schouten 2000; Vuori 2001). However, participation in certain types of exercise may also reduce risk of low back pain. Four potential mechanisms for the protective effects of specific types of physical activities were proposed by Suni (2000), namely: increased abdominal and back muscle strength; better mobility and flexibility of trunk; increased endurance of trunk muscles assisting in the maintenance of motor control and stability; and increased capacity for appropriate motor skills.

Although there is some evidence from randomized controlled trials to show that low back pain can be prevented by participation in specific exercises, the evidence on participation in general physical activity and reduction on risk of low back pain is neither consistent nor strong (Vuori 2001). The outcomes are often poorly defined in many studies and this is in part due to the problematic nature of the term "low back pain", which is used for a collection of conditions with various International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) codes (M45–48). Further, the type of physical activity associated with a reduced risk of low back pain has yet to be fully elucidated. Since participation in specific types of activity can not be identified at a population level there is insufficient information on which to

quantify hazard. Low back pain therefore was not included as a health outcome in this project.

Osteoporosis and falls

Osteoporosis is characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased risk of fractures. The development of osteoporosis has been shown to be associated with physical inactivity (Drinkwater 1994). The biological mechanism proposed for the benefits of physical activity is via the impact on bone density. Put simply, bone cells respond to mechanical loading by increasing bone mass through improvements between bone formation and bone resorption (Lanyon 1993) and this process is mediated by glucose-6-phosphate, prostaglandins and nitric oxide (Pitsillides et al. 1995; Tang et al. 1995; Turner et al. 1995). Cross-sectional studies show that participation in weight-bearing physical activity is positively associated with bone density (Gutin and Kasper 1992). Undertaking weight-bearing activity is particularly important in the development of peak bone density for adolescents (Welten et al. 1994) and for middle-aged women (Zhang et al. 1992).

Although this mechanism is strongly supported by the American College of Sports Medicine (ACSM), their position statement on osteoporosis states the types of activity most effecting such change are still not clear (1995). A recent review came to similar conclusions (Vuori 2001).

Systematic reviews of the literature have identified the beneficial role of physical activity in reducing the risks of falls in the elderly (Gillespie and McMurdo 1998; Kujala et al. 2000). Participation in physical activity is likely to be beneficial through an increase in bone strength, muscle strength, balance and coordination (Gregg et al. 2000). Currently osteoporosis is not listed as an outcome in the GBD classification system for diseases and injuries, but rather is grouped with "other musculoskeletal conditions". Given we were unable to classify what proportion of other musculoskeletal conditions are attributable to osteoporosis, or quantify the proportion of osteoporosis attributable to physical inactivity, falls were excluded from this project. Excluding osteoporosis and falls is based upon application of the specific criteria of this report, and does not indicate that physical activity is not important in fall prevention, or that there is not evidence suggesting a causal relationship.

Osteoarthritis

Physical activity appears to be beneficial for controlling the symptoms of osteoarthritis and maintaining the health of joints. However there is limited evidence that physical activity itself can prevent osteoarthritis.

Conversely, there is evidence that certain types of physical activity, such as sustained participation in training and competition in elite sports, can lead to injuries and may increase the risk of osteoarthritis (Kujala

et al. 1994, 1995; U.S. Department of Health and Human Services 1996). However, these studies are often based on extremely small samples and specific populations and this limits their generalization to whole populations. Moreover, participation in recreational running, as opposed to competitive athletics, over a long period was not shown to increase risk of osteoarthritis (Lane 1995). Due to a lack of evidence for a causal association, and the absence of clear biologically plausible mechanisms, osteoarthritis was excluded from this review.

Depression

Observational studies demonstrate that participation in discretionary-time and/or occupational physical activity can reduce symptoms of depression and possibly stress and anxiety (Dunn et al. 2001; Glenister 1996; Hassmen et al. 2000; Paffenbarger et al. 1994). Physical activity may also confer other psychological and social benefits that impact on health. For example, participation by individuals can help build self-esteem (Sonstroem 1984), social skills among children (Evans and Roberts 1987), positive self-image among women (Maxwell and Tucker 1992) and improve quality of life among children and adults (Hassmen et al. 2000; Laforge et al. 1999; Morans and Mohai 1991). These benefits are probably due to a combination of participation in the activity itself and from the social and cultural aspects that can accompany physical activity.

However, interpretation of the evidence on how physical activity might improve mental health is difficult due to less than ideal methodology and inconsistencies in study designs. Often studies involve small samples and use different definitions and measures of mental health outcomes. Thus, although the literature supports a beneficial effect on relieving symptoms of depression and anxiety, and as a treatment modality, there is currently limited evidence that physical activity can reduce the risk of depression and no clear evidence for a causal association. Exclusion of depression does not indicate that physical activity is not considered important for mental health; it indicates rather that the current evidence does not provide sufficient information for compliance with the inclusion criteria for this project.

Obesity

There is considerable interest in the role of physical activity on weight. The available literature comprises a large body of observational studies showing that habitual physical activity over a lifetime can attenuate the increase in weight normally associated with increasing age, and participation in appropriate amounts of activity can lead to weight maintenance, or even weight loss (Grundy et al. 1999). The latter is especially true if physical activity is combined with a restriction of dietary energy intake. There are several proposed biological mechanisms for the association between physical inactivity and obesity (Hill and Melanson

1999). The most simple being that obesity occurs when energy intake (dietary intake) exceeds total energy expenditure (including the contribution of physical activity).

In this book, obesity is assessed as a risk factor (see Chapter 8). Moreover, it is currently not listed as a condition in the GBD classification system, instead it is included within the group "endocrine disorders". For these reasons obesity did not meet our inclusion criteria. Like depression, osteoporosis and other excluded disease end-points, exclusion does not imply the lack of any identified association with physical activity nor any lack of importance. Indeed, for obesity there is an urgent need for research and public health interventions to control and reverse the epidemic. Many health outcomes mediated through obesity are also among those considered above.

3.2 Search strategies for data sources

Medline and manual searches were conducted to identify review articles, individual studies and published meta-analyses of studies on the relationship between physical activity and the selected disease outcomes. The search was limited to studies published in English from 1980 to 2001. Keywords used were *physical activity* or *exercise*, along with at least one of the relevant disease outcomes listed below.

Coronary heart disease OR cardiovascular disease

Overall our search identified a total of seven quantitative or qualitative reviews on the relationship between physical activity and ischaemic heart disease. These were: a qualitative review by Powell et al. (1987); a quantitative replication of Powell et al. by Berlin and Colditz (1990); a qualitative review undertaken as part of the 1996 U.S. Surgeon General's report on physical activity and health (U.S. Department of Health and Human Services 1996); a quantitative meta-analysis of 12 cohort studies by Eaton in 1992; a review of the dose–response relationship by Kohl (2001); a review of physical fitness vs physical activity by Blair et al. (2001); and a recent quantitative meta-analysis of all studies included in the U.S. Surgeon General's report along with any subsequent papers by Williams (2001).

Stroke OR cardiovascular disease

Studies included in the recent reviews by Kohl (2001), Blair et al. (2001) and the U.S. Surgeon General's report (U.S. Department of Health and Human Services 1996) were obtained. Medline and manual searches revealed only a small number of additional articles not included in these documents, and these were obtained as well.

Colon cancer OR breast cancer

Recent reviews by Thune and Furberg (2001) and McTiernan et al. (1998) provided a comprehensive coverage of the literature. We found

and obtained only a limited number of additional articles with at least one of the exposure titles (physical activity or exercise) which had not been included in either of these reviews.

Non-insulin-dependent diabetes OR NIDDM OR type II diabetes mellitus

A recent review by Kelley and Goodpaster (2001) provided a list of relevant papers. Our search revealed only one additional review and a small number of articles with at least one of the exposure titles (physical activity or exercise).

3.3 Criteria for study inclusion

The following criteria were established for inclusion of studies in the meta-analyses:

- timing of exposure (level of physical inactivity) preceded the health outcome;
- at least two categories of physical activity were included;
- the health outcome(s) of interest were defined separately (specifically, ischaemic heart disease could be separated from cardiovascular disease and ischaemic and heamorrhagic stroke were treated separately);
- the instrument used to measure physical activity was described;
- if the exposure variable was part of a larger intervention (e.g. effect of a combined diet and exercise programme), the physical inactivity component alone could be estimated;
- demographic information was provided on the study population;
- sample size was provided;
- loss during follow up was less than 20% (if applicable);
- relative risks were published or it was possible to calculate them; and
- confidence intervals or standard errors were published or could be computed.

In addition to the above criteria, if there were multiple publications concerning the same outcome from a single cohort or trial, only the most recent publication that satisfied the inclusion criteria was selected.

3.4 Description of included studies, including methodological qualities

Ischaemic heart disease

The search identified 43 papers on physical activity and ischaemic heart disease outcomes, representing 30 cohorts. After critically reviewing each of the papers against the inclusion criteria 20 papers were retained covering 18 separate cohorts. These studies are summarized in Table 10.13.

Six of the 23 excluded papers used fitness measures rather than a measure of physical activity (Blair et al. 1989; Ekelund et al. 1988; Hein et al. 1992; Lie et al. 1985; Mundal et al. 1987; Peters et al. 1983). Of the remainder, four presented total cardiovascular disease as the outcome (LaCroix et al. 1996; Sherman et al. 1994a, 1994b, 1999), nine were reports covering cohorts which were already included (Donahue et al. 1988; Johansson et al. 1988; Morris et al. 1980; Paffenbarger et al. 1984; Seccareccia and Menotti 1992; Shaper et al. 1991; Slattery and Jacobs 1988; Stampfer et al. 2000; Yano et al. 1984), in one case a relative risk could not be calculated (Pomrehn et al. 1982), and in three cases standard errors could not be determined (Garcia-Palmieri et al. 1982; Kannel et al. 1986; Lindsted et al. 1991).

Sample sizes were generally of the order of a several thousand people, with the median sample size around 8000, but ranged from 636 to 99 029. Most studies adjusted for confounding factors notably age, sex and smoking. Many studies adjusted for the intermediate factors identified as being in the causal pathway, namely blood pressure and blood cholesterol.

Mortality was ascertained by linkage or review of state, municipal or national death records. Incident cases were identified through hospital discharge lists, linkage with health registers, self-report (with and without verification by hospital records), or by abstraction and examination of hospital records.

Twelve studies were conducted in western Europe and eight studies were from North America. No studies were found from Africa, Asia or the Eastern Mediterranean. Study populations were generally of middle socioeconomic status and mostly Caucasians, an exception being men of Japanese ancestry (Rodriguez et al. 1994).

Estimates of relative risk *with* and *without* an adjustment for blood pressure and cholesterol were extracted for meta-analyses where available (see Table 10.13). The total effect of physical inactivity, not the independent effect, is required to calculate the estimates of disease burden.

Ischaemic stroke

Over 30 papers were considered for inclusion into our meta-analysis for ischaemic stroke. Only eight studies met our criteria, all of which had

Table 10.13 Summary of included studies relating to ischaemic heart disease

Subregion	*Study (year)*	*Name*[a]	*n*	*Cases*	*Sex*	*Age (years)*	*Outcome*	*Follow-up (years)*	*Adjustment*[b]	*RR*[c]	*Approximate SE*	*95% CI*	*PA measure*[d]
AMR-A	Folsom et al. (1997)*	ARIC	7852	97	Female	45–64	IHD incidence[e]	4–7	1,2,3,4,5,6	1.39 (1.64)	0.34	0.71–2.70	Sports index
										1.56 (1.79)	0.33	0.82–2.98	Leisure index
			6188	223	Male					1.20 (1.43)	0.20	0.81–1.78	Sports index
										1.12 (1.32)	0.21	0.74–1.70	Leisure index
	Lee et al. (2000)	Harvard Alumni	7307	482	Male	Mean 66.1	IHD incidence	5	1,2,4,6	1.51	0.22	1.05–2.48	DTPA + walking + stairs
	Lee and Skerrett (2001)*	Women's Health	39372	244	Female	≥45	IHD incidence	4–7	1,2	1.82	0.20	1.23–2.69	DTPA + walking + stairs
	Leon et al. (1987)	MRFIT	12138	225	Male	35–57	IHD mortality	6–8	1,2,4,5	1.49 (1.56)	0.16	1.09–2.04	DTPA
	Manson et al. (1999)*	US Nurses' Health	72488	645	Female	40–65	IHD mortality or AMI	8	1,2,3,4,5,6	1.52 (1.85)	0.15	1.13–2.03	DTPA + walking + stairs
	Rodriguez et al. (1994)	Honolulu Heart Program	8006	789	Male	45–68	IHD incidence	23	1,2,3,4,5,6	1.05 (1.22)	0.09	0.88–1.26	All PA

	Sesso et al. (2000)*	Harvard Alumni	12516	2135	Male	39–88	IHD incidence	16	1,2,3,4,6	1.23 (1.37)	0.07	1.07–1.41	Sports + walking + stairs
	Slattery et al. (1989)	US Railroad	2548		Male	22–79	IHD mortality	17–20	1,2,4,5	1.28 (1.39)	0.13	0.99–1.63	DTPA
EUR-A	Bijnen et al. (1998)	Zutphen Elderly	802	90	Male	64–84	IHD mortality	10	1,2	1.18 (1.18)	0.26	0.71–1.96	DTPA
	Haapanen et al. (1997)*	. . .	953	75	Female	35–63	IHD incidence	10	1,2	1.25	0.28	0.72–2.15	DTPA
			754	108	Male	35–63	IHD incidence	10		1.98	0.25	1.18–3.15	DTPA
	Kaprio et al. (2000)*	Finnish Twins	8177	723	Male	25–68	IHD incidence	2–20	1,2,3,4,6	1.47 (1.92)	0.16	1.07–2.01	DTPA
	Lakka et al. (1994)*	Kuopio	1166	42	Male	42–60	AMI	2–8	1,2,3,4,5,6	2.63 (2.94)	0.51	0.97–7.15	DTPA
	Menotti and Seccareccia (1985)	Italian Railroad	99029	614	Male	40–59	AMI mortality	5	None	1.97	0.12	1.56–2.49	OPA
	Morris et al. (1990)	British Civil Servants	9376	474	Male	45–64	IHD incidence	10	None	1.32	0.15	0.98–1.77	DTPA
	Pekkanen et al. (1987)	Seven Countries	636	106	Male	45–64	IHD mortality	20	1,2,4,5	1.30 (1.40)	0.19	0.89–1.89	All PA
	Rosengren and Wilhelmsen (1997)	Goteborg	7142	584	Male	47–55	IHD mortality	20	1,2,3,4,5,6	1.35 (1.45)	0.14	1.03–1.78	DTPA

continued

Table 10.13 Summary of included studies relating to ischaemic heart disease (*continued*)

Subregion	*Study (year)*	*Name*[a]	*n*	*Cases*	*Sex*	*Age (years)*	*Outcome*	*Follow-up (years)*	*Adjustment*[b]	*RR*[c]	*Approximate SE*	*95% CI*	*PA measure*[d]
	Salonen et al. (1982)	North Karelia	3688	63	Female	30–59	AMI	6	1,2,3,4,5	1.50 (1.70) 2.40 (2.70)	0.31 0.23	0.82–2.75 1.53–3.77	DTPA OPA
			3978	89	Male	30–59	IHD mortality	6		1.40 (1.60) 1.6 (1.70)	0.23 0.19	0.89–2.20 1.10–2.32	DTPA OPA
	Salonen et al. (1988)	North Karelia	15088	102	Male and female	30–59	IHD mortality	6	1,2,3,4,5,7	1.30	0.11	1.13–1.74	All PA
	Shaper et al. (1994)	British Regional	5694	311	Male	40–59	IHD incidence	9.5	1,2,3,5	2.50	0.22	1.64–3.85	DTPA
	Sobolski et al. (1987)	Belgian Fitness	2106	62	Male	40–55	IHD incidence	5	none	0.76	0.35	0.38–1.51	All PA

Key: SE, standard error (of log relative risk); CI, confidence interval; PA, physical activity; IHD, ischaemic heart disease; AMI, acute myocardial infarction.

[a] Name refers to the common name of the cohort study.

[b] Adjusted for: 1 = age, 2 = smoking, 3 = BMI or waist/hip ratio, 4 = blood pressure, 5 = cholesterol, 6 = type II diabetes, 7 = sex.

[c] Relative risk estimate with adjustment as indicated in footnote b. Figure in brackets indicates relative risk estimate NOT adjusted for blood pressure and cholesterol and some other factors.

[d] DTPA refers to discretionary-time activity; Sports index refers to organized sporting activities; Leisure index refers to DTPA excluding organized sports; OPA refers to occupational-related activity.

[e] Incidence includes both morbidity and mortality.

* Indicates data from study used to calculate summary relative risk for level 2 exposure (insufficiently active).

been published since 1990 (Table 10.14). The majority of studies were excluded because they did not separate the subtypes of stroke; instead they reported risk estimates for the combined outcome of ischaemic and heamorrhagic stroke. The studies included covered both males and females and the age range of 40–74 years. Seven of the eight studies were from North America (Abbott et al. 1994; Evenson et al. 1999; Gillum et al. 1996; Hu et al. 2000; Kiely et al. 1994; Lee et al. 1999; Sacco et al. 1998) and one study was conducted in Europe (Sweden) (Harmsen et al. 1990). Median sample size was811 1473.

For stroke, cases were identified through hospital discharge lists, linkage with health registers, self-report (in some cases verified by hospital records) or by abstraction and examination of hospital records. Deaths were identified through linkage with national, state or municipal registries.

Details of each study and relative risk estimates are presented in Table 10.14.

Cancers

Over 100 papers published since 1980 were identified for the two site-specific cancer types, namely, colon and breast cancer. For both types of cancer, the majority of cases were identified through hospital discharge lists, cancer registries or by direct hospital recruitment (for case–control studies). In a small number of studies, self-reported data were used, but in all but one study these data were verified by review of hospital records. Deaths were identified via linkage with national, municipal or state records.

Sample sizes varied greatly, with a median sample size of 1844 for breast cancer and 1472 for colon cancer. The studies of breast cancer included only females, a single study looking at male breast cancer was excluded. Colon cancer studies appeared to cover both sexes equally. The majority of studies controlled for various important confounding or intermediary factors including age, smoking, family history of cancer and BMI. In addition, parity, use of hormone replacement therapy, use of oral contraceptives and menopausal status were controlled for in studies on breast cancer, and alcohol consumption, caloric intake and dietary factors (such as fat and fibre intake) were considered in studies on colon cancer.

The majority of studies for both types of cancer were conducted in North America, western Europe and the Western Pacific (e.g. China and Japan) (Kato et al. 1990; Matthews et al. 2001). Details of the 43 studies on breast cancer and 30 studies on colon cancer are shown in Tables 10.15 and 10.16.

Type II diabetes

Twenty-two recent studies (see Table 10.17) were identified addressing the relationship between physical inactivity and type II diabetes. A

Table 10.14 Summary of included studies relating to ischaemic stroke

Subregion	Study (year)	n	Cases	Sex	Age (years)	Outcome	Follow-up (years)	Adjustment[a]	RR[b]	Approximate SE	95% CI	PA measure[c]
AMR-A	Abbott et al. (1994)*	1854	110	Male	55–68	Incidence[d]	22	1,4,5,6,7	1.80 (2.00)	0.26	1.10–3.10	All PA (non-smokers)
		1257	116						1.20 (3.7)	0.21	0.80–1.80	All PA (smokers)
	Evenson et al. (1999)	14575	189	Male and female	45–64	Incidence	7.2	1,2,3,4,6,7	1.22	0.23	0.78–1.91	Sport PA
									1.11	0.15	0.83–1.49	DTPA (non-sports)
									1.43	0.21	0.95–2.16	OPA
	Gillum et al. (1996)*	1285	60	Male	45–64	Incidence	10–16	1,2,3,4,5,6,8	1.10 (1.10)	0.36	0.54–2.23	DTPA
		1083	186		65–74				1.34 (1.49)	0.20	0.90–2.00	DTPA
		1473	48	Female	45–64				2.89 (3.05)	0.61	0.87–9.55	DTPA
		1240	179		65–74				1.47 (1.6)	0.26	0.88–2.44	DTPA
		771	94	Male and female	45–74				1.43 (1.43)	0.37	0.70–2.94	DTPA
	Hu et al. (2000)*	72488	258	Female	40–65	Incidence	8	1,2,3,4,5,6	1.20 (1.45)	0.18	0.85–1.71	All PA
	Kiely et al. (1994)*	1228	107	Male	28–62	Incidence	18	1,2,3,4,5,6,8	1.89 (2.27)	0.23	1.20–2.96	All PA
		1676	127	Female					0.83 (1.05)	0.25	0.51–1.35	All PA
	Lee et al. (1999)*	21823	437	Male	40–84	Incidence	11.1	1,2,3,4,5,6,7,8	1.05	0.13	0.82–1.36	DTPA
	Sacco et al. (1998)	284[e]	163	Male	≥40	Incidence		1,2,3,4,6,7,8	2.78	0.29	1.57–4.90	DTPA
		394[e]	206	Female					2.94	0.35	1.48–5.84	DTPA
EUR-A	Harmsen et al. (1990)	7495	69	Male	47–55	Mortality	11.8	None	1.20	0.27	0.70–2.00	All PA

Key: SE, standard error (of log relative risk); PA, physical activity.

[a] Adjusted for: 1 = age, 2 = smoking, 3 = BMI or waist/hip ratio, 4 = blood pressure, 5 = cholesterol, 6 = type II diabetes, 7 = sex, 8 = history of cardiovascular disease.

[b] Relative risk estimate with adjustment as indicated in footnote a. Figure in brackets indicates relative risk estimate NOT adjusted for blood pressure and cholesterol and some other factors.

[c] Sports PA refers to organized sporting activities; DTPA refers to discretionary-time activity; OPA refers to occupational-related activity.

[d] Incidence includes both morbidity and mortality.

[e] Case–control study. *"n"* is number of controls.

* Indicates data from study used to calculate summary relative risk for level 2 exposure (insufficiently active).

Table 10.15 Summary of studies relating to breast cancer

Subregion	Study (year)	n		Age (years)	Follow-up (years)	Adjustment[a]	RR[b]	Approximate SE	95% CI	PA measure[c]
		Cases	Controls							
AMR-A	Albanes et al. (1989)*	122	7407[e]	25–74	7–13	1	1.00	0.25	0.61–1.63	DTPA
							1.11	0.31	0.60–2.04	OPA
	Bernstein et al. (1994)	545	545	≤40		3,4,5,7,8	1.25	0.20	0.84–1.85	DTPA
	Breslow et al. (2001)	138	6160	≥50	8–10	Yes	3.03	0.45	1.25–7.32	DTPA
	Calle et al. (1998)	1780	563395[d]	≥29	9	Yes	0.91	0.07	0.79–1.04	OPA
	Carpenter et al. (1999)	1123	904	55–64		1,3,5,8	1.14	0.10	0.93–1.38	DTPA
	Cerhan et al. (1998)*	46	1806	65–102	11	Yes	5.00	0.74	1.17–21.32	DTPA
	Chen et al. (1997)	747	961	21–45		1,3,4,5,8	1.05	0.13	0.82–1.36	DTPA
	Coogan et al. (1997)	4863	6783	17–74		1,3,4,5,8	1.16	0.06	1.03–1.31	OPA
	Coogan and Aschengrau (1999)	233	670	All ages		1	1.25	0.30	0.69–2.25	OPA (ever held job with at least moderate activity)
	Dorgan et al. (1994)	117	2307[d]	≥35	28	1,4,5,9	0.77	0.31	0.42–1.41	All PA
	Fraser and Shavlik (1997)	218	20341[d]	≥24	6	1,3,4,5,6,8,9	1.27	0.14	0.97–1.67	All PA
	Friedenreich et al. (2001)*	462	475	<80		1,2,3,6,8	0.87	0.20	0.59–1.29	All PA (pre-menopausal)
		771	762	<80			1.33	0.15	0.99–1.79	All PA (post-menopausal)
	Frisch et al. (1987)	69	5398[d]	18–22	56	1,2,3,4,6,7,8	1.86	0.32	1.00–3.47	DTPA (college athletics)
	Gammon et al. (1998)	1668	1505	<45		3,9	0.98	0.10	0.81–1.19	DTPA

continued

Table 10.15 Summary of studies relating to breast cancer (*continued*)

Subregion	Study (year)	n		Age (years)	Follow-up (years)	Adjustment[a]	RR[b]	Approximate SE	95% CI	PA measure[c]
		Cases	Controls							
	Gilliland et al. (2001)*	171	210	30–74		1,4,5,6,7	2.70	0.36	1.33–5.47	DTPA (post-menopausal Hispanic)
		228	224			1,4,5,6,7	2.04	0.29	1.16–3.60	DTPA (post-menopausal non-Hispanic)
		128	152			1,4,5,6	2.04	0.40	0.93–4.47	DTPA (pre-menopausal Hispanic)
		115	183			1,4,5,6	0.69	0.39	0.32–1.49	DTPA (pre-menopausal non-Hispanic)
	Lee et al. (2001b)*	411	39322	≥45	4	1,3,4,5,6,7,8,9	1.16	0.15	0.87–1.56	EE of DTPA + stairs (all women)
		261	21482			1,3,4,5,6,7,8	1.28	0.19	0.88–1.86	EE of DTPA + stairs (post-menopausal)
	Marcus et al. (1999)	790	864	20–74		Not specified	1.25	0.13	0.97–1.61	DTPA (at age 12)
	McTiernan et al. (1996)*	537	492	50–64		1	1.67	0.21	1.10–2.52	DTPA
	Mittendorf et al. (1995)	6888	9539	17–74		Yes	1.00	0.10	0.80–1.20	DTPA (at age 14–22)
	Moore et al. (2000)*	1380	37105[d]	55–69	12	1,3,5,6,8,9	1.09	0.09	0.91–1.30	DTPA
	Rockhill et al. (1998)	372	116671[d]	25–42	16	Yes	0.91	0.18	0.64–1.29	DTPA in adolescence
	Rockhill et al. (1999)*	3137	121701[d]	30–55	16	1,3,4,5,6,8,9	1.12	0.05	1.02–1.24	DTPA
	Sesso et al. (1998)	109	1566[d]	≥40	31	1,3	0.56	0.43	0.24–1.29	DTPA (pre-menopausal)
							2.04	0.29	1.16–3.60	DTPA (post-menopausal)
	Shoff et al. (2000)	4614	5817	20–74		3,4,5,8,9	1.08	0.08	0.92–1.26	DTPA
	Steenland et al. (1995)	163	14407[e]	25–74	13–17	Yes	1.11	0.30	0.62–2.00	All PA

	Sternfeld (1992)	254	201	All ages		Not specified	0.45	0.34	0.23–0.88	DTPA
	Taioli et al. (1995)	195	191	≥25		1,3,4	1.11	0.51	0.41–3.02	DTPA (pre-menopausal)
		421	337				0.77	0.47	0.31–1.93	DTPA (post-menopausal)
	Wyrwich and Wolinsky (2000)	77	3131	70–98	7	1,3	2.38	0.41	1.07–5.32	All PA
	Wyshak and Frisch (2000)	175	3940[e]	21–80	15	1,2,3,4,6,7,8	1.65	0.16	1.21–2.26	DTPA (college athletics)
		12		21–44	15	1,2,3,4,7,8	6.10	0.69	1.58–23.59	DTPA (college athletics)
EUR-A	Fioretti et al. (1999)	1041	1002	15–79		1,3,6,7	1.18	0.31	0.64–2.16	All PA (pre-menopausal)
							1.35	0.26	0.81–2.45	All PA (post-menopausal)
	Levi et al. (1999)*	245	371	27–74		1,4,5,8,9	2.00	0.25	1.23–3.26	DTPA (at 30–39 years)
							1.96	0.34	1.01–3.82	OPA (at 30–39 years)
	Mezzetti et al. (1998)*	989	841	18–74		1,3	1.39	0.22	0.91–2.13	OPA (pre-menopausal)
		1577	1745				1.61	0.17	1.16–2.23	OPA (post-menopausal)
	Moradi et al. (2000)	3347	3455	50–74		Yes	1.25	0.06	1.11–1.41	DTPA recently
	Moradi et al. (1999)	22840	982270[d]	All ages	19	1	1.18	0.05	1.07–1.30	OPA
	Pukkala et al. (1993)	228	10038[d]	18–22	24		1.43	0.07	1.25–1.64	DTPA
	Thune et al. (1997)	98	25624[d]	20–69	14	1,3,4	1.30	0.26	0.78–2.16	DTPA (pre-menopausal)
		98					1.00	0.17	0.72–1.40	DTPA (post-menopausal)
		248					1.22	0.25	0.75–1.99	OPA (pre-menopausal)
		248					1.15	0.18	0.81–1.64	OPA (post-menopausal)
	Verloop et al. (2000)	918	918	20–54		1,2,3,4,8	1.45	0.16	1.06–1.98	DTPA
EUR-B	Dosemeci et al. (1993)	241	244	≥18		1,2	0.71	0.63	0.21–2.46	OPA

continued

Table 10.15 Summary of studies relating to breast cancer (*continued*)

Subregion	Study (year)	n		Age (years)	Follow-up (years)	Adjustment[a]	RR[b]	Approximate SE	95% CI	PA measure[c]
		Cases	Controls							
WPR-A	Friedenreich and Rohan (1995)	110	110	20–74		Yes	1.67	0.35	0.84–3.31	DTPA (pre-menopausal)
		258	258				1.37	0.26	0.82–2.28	DTPA (post-menopausal)
	Hirose et al. (1995)	606	14864	All ages		Not specified	1.35	0.13	1.05–1.74	DTPA (pre-menopausal)
		439	6170				1.39	0.15	1.04–1.87	DTPA (post-menopausal)
	Hu et al. (1997)	87	202	All ages		Yes	0.99	0.32	0.53–1.85	DTPA (pre-menopausal)
		67	159				1.89	0.53	0.67–5.33	DTPA (post-menopausal)
	Ueji et al. (1998)	148	296	26–69		3,4,5,8	3.33	0.59	1.05–10.59	DTPA (pre-menopausal)
							2.00	0.71	0.50–8.04	DTPA (post-menopausal)
							1.67	0.62	0.49–5.62	OPA (pre-menopausal)
							1.43	0.57	0.47–4.37	OPA (post-menopausal)
WPR-B	Matthews et al. (2001)	1459	1556	25–64		1,5,8,9	2.13	0.14	1.62–2.80	DTPA (all ages)

Key: SE, standard error (of log relative risk); PA, physical activity; EE, energy expenditure.

[a] Adjusted for: 1 = age, 2 = smoking, 3 = BMI or waist/hip ratio, 4 = parity, 5 = age at first birth, 6 = use of hormone replacement therapy, 7 = use of oral contraceptives, 8 = family history of breast cancer, 9 = menopausal status.

[b] Relative risk estimate with adjustment as indicated in footnote a.

[c] DTPA refers to discretionary-time activity; OPA refers to occupational-related activity.

[d] Cohort/cross-sectional study – number of controls is total sample size.

* Indicates data from study used to calculate summary relative risk for level 2 exposure (insufficiently active).

Table 10.16 Summary of studies relating to colon cancer

Subregion	Study (year)	n		Sex	Age (years)	Follow-up (years) (cohort)	Adjustment[a]	RR[b]	Approximate SE	95% CI	PA measure[c]
		Cases	Controls								
AMR-A	Ballard-Barbash et al. (1990)*	79	2308[d]	Female	30–62	28	1,2,3,4	1.11	0.28	0.64–1.82	All PA
		73	1906[d]	Male				1.78	0.29	1.02–3.18	All PA
	Brownson et al. (1989)*	1993	9965	Male	≥20		1	1.43	0.16	1.00–1.90	OPA
	Brownson et al. (1991)*	1838	14497	Male	≥20		1,2	1.20	0.10	1.00–1.50	OPA
	Garabrant et al. (1984)	2950		Male	20–64		1	1.67	0.07	1.46–1.92	OPA
	Giovannucci et al. (1995)*	203	47723[d]	Male	40–75	6	1,2,3,4,6,8	1.06	0.20	0.72–1.57	DTPA
	Lee et al. (1991)	225	17148[d]	Male	30–79	23	1	1.92	0.31	1.05–3.53	DTPA
	Lee et al. (1997)	217	21807[d]	Male	40–84	10.9	1,3,4	0.83	0.18	0.59–1.19	DTPA
	Longnecker et al. (1995)*	163	703	Male	≥31		1,2,3,4,5,6,8	1.27	0.40	0.58–2.78	OPA
								2.78	0.60	0.86–9.01	DTPA
	Marcus et al. (1994)	536	2315	Female	<75		1,3,8	1.02	0.11	0.82–1.27	All PA (at age 14–22)
	Markowitz et al. (1992)*	308	1164	Male	All ages		1	2.00	0.25	1.23–3.26	OPA
	Martinez et al. (1997)*	161	67802[d]	Female	30–55	16	1,2,3,4,6,8	1.28	0.22	0.83–1.97	DTPA
	Severson et al. (1989)*	192	8006[d]	Male	46–68	18–21	1,3	1.41	0.17	1.01–1.97	All PA
	Slattery et al. (1999)*	1993	2410	Male and female			1,2,3,6	1.35	0.13	1.05–1.74	DTPA (males)
								1.41	0.14	1.07–1.86	DTPA (females)
	Slattery et al. (1988)*	110	180	Male	40–79		1,3,5,6	1.10	0.32	0.61–2.13	All PA
		119	204	Female				1.14	0.29	0.62–1.94	All PA

continued

Table 10.16 Summary of studies relating to colon cancer (*continued*)

Subregion	Study (year)	n		Sex	Age (years)	Follow-up (years) (cohort)	Adjustment[a]	RR[b]	Approximate SE	95% CI	PA measure[c]
		Cases	Controls								
	Thun et al. (1992)	611	2073	Male			1,3,6,8	1.67	0.37	0.81–3.44	All PA
		539	2081	Female				1.11	0.41	0.50–2.48	All PA
	Vena et al. (1985)	210	1431	Male	30–79		1	1.97	0.18	1.38–2.80	OPA (time in sedentary job)
	White et al. (1996)*	251	233	Male	30–62		1	1.27	0.20	0.86–1.87	All PA
		193	194	Female				1.49	0.32	0.80–2.79	All PA
	Whittemore et al. (1990)	61	255	Male	20–79			1.59	0.20	1.07–2.35	DTPA
								2.50	0.43	1.08–5.81	OPA
		46	198	Female				2.00	0.26	1.20–3.33	DTPA
								1.20	0.51	0.44–3.27	OPA
EUR-A	Clemmensen (1998)	88	5248[d]	Male	40–59	15	Not specified	2.00	0.25	1.23–3.26	All PA
	Gerhardsson et al. (1986)	5100	1055715[d]	Male	20–64	19	1	1.3	0.07	1.13–1.49	OPA
	Gerhardsson et al. (1988)	121	16477[d]	Male and female	42–82	14	1,7	3.6	0.52	1.3–9.8	All PA
	Gerhardsson et al. (1990)	163	624	Male	40–79		1,3,5,6	2.33	0.50	0.64–4.52	All PA
		189	624	Female				1.69	0.48	0.91–5.96	All PA
	Lynge and Thygesen (1988)		2000000[d]	Male	20–64	11	1	1.38	0.16	1.01–1.89	OPA
				Female				1.73	0.24	1.06–2.68	OPA

	Tavani et al. (1999)*	688	2073	Male	19–74		1,4,5	1.41	0.16	1.03–1.93	OPA at age 30–39
		537	2081	Female	19–74			2.04	0.20	1.38–3.02	OPA at age 30–39
	Thune and Lund (1996)	236	53242[d]	Male	40–54	16.3	1,3	1.03	0.22	0.67–1.59	All PA
		99	28274[d]	Female				1.59	0.25	0.97–2.59	All PA
EUR-B	Dosemici et al. (1993)	93	486	Male	All ages		1,2	1.67	0.09	1.40–1.99	OPA
WPR-A	Fraser and Pearce (1993)	1651	Population	Male	All ages		Not specified	1.25	0.08	1.07–1.46	OPA
	Kato et al. (1990)	1716	16600	Male	≥20		1,2,4,8	1.92 (proximal)	0.17	1.38–2.67	OPA
								1.52 (distal)	0.12	1.19–1.94	OPA
	Kato et al. (1990)	132	528	Male and female			Not specified	1.67	0.28	0.96–2.89	DTPA
								2.00	0.28	1.16–3.46	OPA
WPR-B	Tang et al. (1999)	71	71	Female	33–80		1,2,4,6	5.26	0.64	0.45–5.56	DTPA
		92	92	Male				1.59	0.70	1.33–20.74	DTPA
	Whittemore et al. (1990)	81	567	Male	20–79		Not specified	0.85	0.40	0.39–1.87	DTPA
								1.41	0.46	0.57–3.47	OPA
		66	305	Female				2.50	0.47	1.00–6.28	DTPA
								1.69	0.57	0.55–5.18	OPA

Key: SE, standard error (of log relative risk); PA, physical activity.

[a] Adjusted for: 1 = age, 2 = smoking, 3 = BMI or waist/hip ratio, 4 = alcohol consumption, 5 = caloric intake, 6 = other dietary factors (e.g. fat, fibre), 7 = sex, 8 = family history of colon cancer.

[b] Relative risk estimate with adjustment as indicated in footnote a.

[c] OPA refers to occupational-related activity; DTPA refers to discretionary-time activity.

[d] Cohort/cross-sectional study – number of controls is total sample size.

* Indicates data from study used to calculate summary relative risk for level 2 exposure (insufficiently active).

Table 10.17 Summary of studies relating to type II diabetes

Subregion	Author (year)	n		Sex	Age (years)	Follow-up (years) (cohort)	Adjustment[a]	RR[b]	Approximate SE	95% CI	PA measure[c]
		Cases	Controls								
AFR-D	Dowse et al. (1991)*	288	2362[d]	Male	25–74		1,3,6	4.31	0.24	1.07–2.69	All PA
		314	2669[d]	Female				1.70	0.75	1.00–18.61	All PA
AFR-E	Levitt et al. (1999)	69	974[d]	Male and female	≥15		1,3,6,7	1.75	0.25	1.07–2.86	DTPA
AMR-A	Folsom et al. (2000)*	1997	34257[d]	Female	55–69	12	1,2,3,6	1.27	0.06	1.13–1.43	DTPA
	Fulton-Kehoe et al. (2001)*	167	1100	Male and female	20–74		1,3,6,7	1.39	0.30	0.77–2.50	All PA
	Gurwitz et al. (1994)	185	2737[d]	Male and female	≥65	6	1,4,7	1.5	0.19	1.03–2.18	DTPA
	Helmrich et al. (1994)	202	5990[d]	Male		14	1,3,4,6	1.32	0.1	1.09–1.61	DTPA
	Hu et al. (1999)*	1419	70102[d]	Female	40–65	12	1,2,3,4,5,6	1.30	0.09	1.09–1.55	DTPA
	Hu et al. (2001)*	1058	37918[d]	Male	40–75	10	1,2,3,6	1.45	0.12	1.15–1.83	DTPA
	James et al. (1998)*	78	916[d]	Male and female	30–55	5	1,3,7	2.86	0.54	1.00–8.16	DTPA
	Kriska et al. (1993)	131	353[d]	Male and female	37–59		1,3,7	2.17	0.26	1.30–3.61	DTPA before age 35
	Leonetti et al. (1989)	78	79	Male	Mean 61		1,3,6	1.69	0.22	1.10–2.60	DTPA age 15–20
	Manson et al. (1991)	1303	87253[d]	Female	34–59	8	1,3,6	1.20	0.06	1.07–1.35	DTPA
	Manson et al. (1992)	285	21271[d]	Male	40–84	5	1,2,3,4,5	1.43	0.14	1.09–1.88	DTPA

EUR-A	Baan et al. (1999)*	69	503[d]	Male	55–75		1,2,3,6	1.39	0.38	0.66–2.93	DTPA
		49	513[d]	Female				2.56	0.48	1.00–6.56	DTPA
	Haapanen et al. (1997)*	64	891[d]	Male	35–63	10	1,2	1.54	0.31	0.83–2.84	DTPA
		54	973[d]	Female				2.64	0.37	1.28–5.45	DTPA
	Lynch et al. (1996)		897[d]	Male	Middle aged		1,3,6	2.27	0.35	1.14–4.51	DTPA
	Perry et al. (1995)	194	7735[d]	Male	40–59	11–13	1,2,3,4,5	2.50	0.35	1.26–4.96	DTPA
	Tuomilehto et al. (2001)	27	265[d]	Male and female	40–65	Mean 3.3	3	3.33	0.5	1.25–8.87	DTPA
	Wannamethee et al. (2000)*	196	5159[d]	Male	40–59	16.8	1,2,3,4,5	1.61	0.29	0.91–2.85	DTPA
WPR-A	Okada et al. (2000)	444	6013[d]	Male	35–60	6–16	1,2,3,4,6	1.33	0.11	1.07–1.65	DTPA
	Todoroki et al. (1994)*	48	1113[d]	Male	49–56		2,3,6	2.00	0.46	0.81–4.93	DTPA
WPR-B	Pan et al. (1997)	2731	11028[d]	Male and female	25–64		1,3,4,6,7	1.18	0.05	1.07–1.30	OPA
	Taylor et al. (1984)		640[d]	Male	≥20		1,3	2.50	0.44	1.06–5.92	All PA (Melanesians)
			595[d]					2.10	0.25	1.29–3.43	All PA (Indians)

Key: SE, standard error (of log relative risk); PA, physical activity.

* Indicates data from study used to calculate summary relative risk for level 2 exposure (insufficiently active).

[a] Adjusted for: 1 = age, 2 = smoking, 3 = BMI or waist/hip ratio, 4 = blood pressure, 5 = cholesterol, 6 = family history of type II diabetes, 7 = sex.

[b] Relative risk estimate with adjustment as indicated in footnote a.

[c] DTPA refers to discretionary-time activity; OPA refers to occupational-related activity.

[d] Cohort/cross-sectional study – number of controls is total sample size.

diverse range of populations have been studied from the regions of Africa (Mauritius, South Africa and the United Republic of Tanzania), Asia (China), the Western Pacific (Japan and Fiji) as well as North America and western Europe.

For type II diabetes, cases in all case–control studies were identified using oral glucose tolerance tests (OGTT). In the majority of cohort studies, identification was by OGTT or fasting plasma glucose tests at follow-up, or by self-report, validated by physician or medical record review. In only one case was unverified self-reported data used.

Sample sizes ranged widely with a median sample size of 1113. All studies adjusted for a variety of important confounding or intermediary factors including age, BMI, blood pressure, cholesterol and family history of diabetes.

3.5 Methods for meta-analysis

Our general method for meta-analyses was similar to that used by Berlin and Colditz (1990) and Eaton (1992) and combined estimates of the log relative risks using an inverse-variance weighting scheme (Berlin and Colditz 1990; Eaton 1992). This method gives relatively more importance to studies with a larger number of cases and produces a wider confidence interval for the pooled relative risk estimate than would be obtained by other methods (such as the Mantel-Haenszel method). Confidence intervals for the summary risks were derived using a pooled standard error.

For ischaemic heart disease and ischaemic stroke we conducted two different meta-analyses. Firstly, we pooled risk estimates derived from analyses which *had* adjusted for two intermediary variables (blood pressure and cholesterol) and secondly, we pooled estimates of risk *without* adjustment for these intermediary variables. The former (with adjustment) removes the effect due to other factors and identifies the independent risk due to physical inactivity. Estimates of risk *without* adjustment for other variables in the causal pathway indicate the total effect of exposure to inactivity. The first method partials out the contribution of inactivity to various disease end-points while the second is useful in calculating the total effect of removing exposure to inactivity (Greenland 1987). We report both results to enable comparison with results from previous meta-analyses, all of which used adjusted data, and to allow computation of avoidable burden of disease (which required the unadjusted analyses). For type II diabetes and breast and colon cancer, estimates of risk were computed using only adjusted data as noted in Tables 10.15–10.17.

The problems associated with measurement of behavioural risk factors are well known and to date few satisfactory solutions are available. Given the difficulties associated with assessing a complex exposure variable like physical inactivity and the heterogeneity among the instruments used across the epidemiological studies, one approach is to intro-

duce an adjustment at the analytical stage. Adjustment for measurement error within the meta-analysis has been previously applied to other risk factors (Bashir and Duffy 1997). We employed this technique in our analyses and present the results both adjusted for measurement error and unadjusted for measurement error.

Overall three separate analytical approaches were conducted to derive summary estimates of relative risk, as summarized below.

- *Adjusted for intermediary variables*: This method was undertaken for all disease outcomes and used pooled relative risk estimates from studies in which the analyses *had* controlled for the intermediate factors (blood cholesterol and blood pressure). These results have not incorporated the adjustment for measurement error and so can be compared to other published results that have controlled for intermediaries.
- *Adjusted for intermediary variables AND adjusted for measurement error*: This method is the same as above with the addition of a statistical adjustment for measurement error. This method was conducted for all disease outcomes and represents an extension of the above method.
- *Unadjusted for intermediary variables AND adjusted for measurement error*: This method pooled relative risk estimates from studies in which the analyses *had not* controlled for blood pressure and cholesterol. It was conducted for only ischaemic heart disease and ischaemic stroke and, for those studies without unadjusted risk estimates, the adjusted risk estimates were included.

Measurement error

The major sources of error arise from the variability in the measurement and/or definitions of the health outcome and the exposure variable (i.e. physical inactivity). A further source of variability may be due to the timing of the exposure. These will be discussed in turn below.

Error due to variable measures of exposure

In general, measurement error is a product of the different ways in which physical inactivity is measured and/or categorized. Using different measures and definitions can result in quite different estimates of the level of exposure to physical inactivity. We identified three main sources of potential measurement error for exposure.

Firstly, the questionnaires used in the epidemiological studies included in our meta-analyses vary in their attempt to measure physical activity undertaken in different domains. The studies included for ischaemic heart disease mostly evaluated discretionary-time physical activity (Haapanen et al. 1997; Lakka et al. 1994; Leon et al. 1987; Rosengren and Wilhelmsen 1997; Shaper et al. 1994; Slattery et al. 1989), although in

some studies this was defined as "sport" and "leisure activities" (Folsom et al. 1997) and in other studies it was extended to include other activities such as walking and stair climbing (Lee and Skerrett 2001; Lee et al. 2000; Manson et al. 1999). In the Harvard Alumni study "sports" activity plus walking and stair climbing were assessed (Sesso et al. 2000). In several studies "all" physical activity was evaluated but the exact meaning and coverage of domains required a careful inspection of the specific instruments (Morris et al. 1990; Pekkanen et al. 1987; Rodriguez et al. 1994; Salonen et al. 1988; Sobolski et al. 1987). Only one study included in our meta-analysis provided an estimate of risk based on only occupational physical activity and one other study provided separate relative risk estimates for occupational and discretionary-time activity (Menotti and Seccareccia 1985; Salonen et al. 1982). It is notable that the majority of studies published post 1980 focus more on discretionary-time activity whereas literature published between 1958–1980 is dominated by studies of work-related activity.

Pooling results from studies with measures of exposure across discretionary time, sports, walking, stair climbing and "all" activity could have a marked affect on the overall estimates of risk. One solution, previously used by Berlin and Colditz (1990), is to separately pool results from studies assessing different domains (e.g. occupation only, discretionary time only). However, in this study the pooled summary relative risk estimates were applied to prevalence estimates of exposure in which multiple domains had been considered. We therefore considered the inclusion of studies with diverse definitions of activity, possibly across more than one domain as acceptable. Nonetheless, this source of heterogeneity among the literature is noted, as is the desirability for much greater comparability of measures of exposure between studies.

A second source of measurement error could arise from the different instruments used to assess exposure in the various domains. Five of the 19 included cohort studies used the Minnesota Leisure Time Physical Activity questionnaire and three used the Harvard Alumni instrument, but the remaining 11 studies used different and sometimes unspecified survey tools. Different questionnaires have different properties and concomitant variation in the level of validity and reliability. The instruments used in the studies included in our meta-analyses assessed physical activity over differing referent time periods (e.g. the previous year, last week or usual week) and used various response formats (Folsom et al. 1997; Lakka et al. 1994; Lee and Paffenbarger 2000). To address this concern we included an adjustment for measurement error in our meta-analyses using information on the reliability of each instrument. The rationale and methodology are described below.

A third potential source of error relating to the exposure variable may result from the different ways in which physical activity data are categorized. For instance, different studies have used different methods of categorization (e.g. tertiles, quartiles, quintiles, sextiles) (Folsom et al.

1997; Lee and Paffenbarger 2000; Leon et al. 1987; Rodriguez et al. 1994; Rosengren and Wilhelmsen 1997; Sesso et al. 2000; Shaper et al. 1994), but not all studies provide a full description of the level of activity in each category to facilitate between-study comparison. In addition to the variability between studies there is also likely to be within-category variability (Blair and Jackson 2001). Indeed, Berlin and Colditz (1990) discussed this problem and concluded that this could explain why some studies failed to show a protective affect due to physical activity.

We attempted to reduce the error from pooling results from different studies using different categories by identifying from each study the categories of activity most consistent with our definitions of exposure. We selected the "sedentary" or lowest category from each study as the "most exposed" group and this was deemed most comparable to our level 1 exposure (inactive). Similarly, the categories of activity within each study were reviewed to identify the most comparable group(s) for our level 2 exposure (insufficient activity). Finally, and most importantly, we extracted from each study the estimate of relative risk pertaining to a referent group equivalent to our level 3 exposure, namely, a level of activity equal to at least 150 minutes of moderate-intensity activity per week (at least 2.5 hours of activity per week or an energy expenditure of at least 4000 kJ/week). Some studies did not clearly define this group and in these cases we carefully reviewed each category within the study and made a subjective assessment. In this regard, our meta-analysis differs from previous reviews which have chosen to assess the relative risk of inactivity using a referent group defined as the "most active" or "vigorous activity" or "high fitness".

Error due to measures of disease end-points

Another possible source of measurement error arises from different definitions or classifications of the disease end-points, particularly when disease subtypes exist within a health outcome. For example, studies with ischaemic heart disease as an outcome may include mortality and/or morbidity from all types of ischaemic heart disease (including angina pectoris), only myocardial infarction or myocardial infarction and sudden death combined. However, the etiology of these conditions may differ, as may the contribution of physical inactivity.

In assessing ischaemic heart disease, Berlin and Colditz (1990) undertook separate meta-analyses for acute myocardial infarction, ischaemic heart disease incidence and for ischaemic heart disease mortality. They found no difference in the relative risk estimates from the analysis of each outcome separately, although the strength of association (defined by the range of confidence intervals) was greater for mortality than morbidity. Eaton (1992) examined the differences between pooled estimates from studies using ischaemic heart disease mortality and those using clinical ischaemic heart disease as health outcomes and also found no dif-

ference in the size or the strength of the association. Therefore, given no evidence to the contrary, we combined ischaemic heart disease mortality and morbidity in our meta-analyses.

There appears to be no association between physical activity and hemorrhagic stroke. As a result in studies assessing stroke, misclassification of subtypes may have led to null associations between physical activity level and disease outcome (Kohl 2001). Therefore, for inclusion in our meta-analyses, only studies that clearly differentiated and reported results for ischaemic stoke were included.

For type II diabetes, colon cancer and breast cancer there is a paucity of information on the level of any misclassification and the effect on relative risk estimates. However, any misclassification of colon cancer (i.e. colon, colorectal and rectal cancers) would, if random, most likely underestimate the relationship between physical activity and risk for colon cancer. The positive effect of physical activity would be diluted because of null associations included due to misclassification.

Error due to timing and duration of exposure

Epidemiological data may also be inconsistent due to the timing of the exposure, in this case physical inactivity. However it is simpler to consider the timing of physical activity and ask when during the life course is activity required for risk reduction? For ischaemic heart disease and type II diabetes the activity is required to be regular and recent for risk reduction. However, for other conditions (e.g. breast cancer, colon cancer) activity during childhood or adolescence may be important to reduce risk.

Among the studies included in the meta-analyses a range of follow-up periods can be seen—for example, from 2 to 23 years for ischaemic heart disease, from 8 to 22 years for ischaemic stroke and from 4 to 56 years for breast cancer. Measurement error associated with assessing long-term physical activity patterns by a questionnaire administered only at baseline is likely to be important. It was, however, not possible to account for this in our meta-analyses but it is highly recommended that this issue be explored in future research.

Adjustment for measurement error

We considered the issue of measurement error associated with self reported recall of physical (in)activity and concluded that such error could lead to an underestimate of the association between physical activity and disease end-points. Thus, an adjustment for measurement error was made to each estimate of relative risk extracted from the individual studies based on the reliability of the instrument used to measure exposure. Specifically, the adjustment involved multiplying the beta coefficients (log relative risks) by the inverse of the study-specific test–retest correlation coefficient as previously used with other risk factors (Bashir

and Duffy 1997), although we found no prior evidence of its use with physical inactivity.

The test–retest coefficient for each instrument was obtained in the first instance from the article as cited by the authors of the epidemiological study. When this was not available we searched the published literature including a compendium of instruments which contained an excellent summary of test–retest reliability data for many instruments (Pereira et al. 1997). If no information was found for a specific instrument but a sufficiently detailed description was available, we assigned a test–retest coefficient based on the correspondence between characteristics of the instrument as described by the authors and other known instruments. In those cases where little or no information on the instrument was provided the average score of known instruments was applied. This process was undertaken for all studies included for each of the disease outcomes. Table 10.18 reports the test–retest coefficient for the instruments used in studies addressing ischaemic heart disease.

Heterogeneity

Although the fixed-effects model gives relatively more importance to bigger studies than smaller studies in the summary relative risk estimate, the effect of any heterogeneity not accounted for by study size remains. Despite our study inclusion criteria heterogeneity among the studies was significant for all conditions, except for ischaemic heart disease, as we describe below. No attempt to identify the sources of heterogeneity was undertaken. However, it is probable that differences in study design such as combining studies with different types of physical activity, different measurement instruments, different follow-up time, and differences in disease outcomes contributed to the heterogeneity (Berlin and Colditz 1990). Tests of heterogeneity and bias were conducted to assess the quality of the data as well as to reveal any evidence of heterogeneity and/or publication bias. The extent of bias was assessed by regressing the standard errors to the relative risk estimates and testing whether the regression coefficient was equal to zero (Sterne and Egger 2001).

Heterogeneity was assessed using funnel plots by drawing 95% confidence limits around the summary risk estimate for various values of the standard error. In the absence of heterogeneity, 95% of the point estimates should lie within these limits.

3.6 Attenuation for age

The relative risk associated with physical activity and some disease endpoints has been shown to be lower for older age groups compared with younger age groups (Sesso et al. 2000). This is consistent with an age attenuation seen in other intermediate risk factors such as systolic blood pressure and cholesterol (MacMahon et al. 1990). It is desirable for any calculation of attributable burden to include an attempt to better represent the differential risk across age. However, overall there were too few

Table 10.18 Test–re-test reliability for instruments used in studies on ischaemic heart disease

Authors	*Year*	*Study name*	*Instrument*	*Test–re-test reliability*
Sesso et al.	2000	Harvard Alumni	Harvard Alumni	0.72
Morris et al.	1990	British Civil Servants	(No specific name)	0.75
Rodriguez et al.	1994	Honolulu	Framingham	0.45
Menotti and Seccareccia	1985	Seven Counties Italian Railroad	(No specific name)	0.70
Rosengren and Wilhelmsen	1997	Goteborg Primary Prevention	(No specific name)	0.75
Lee and Paffenbarger	2000	Harvard Alumni	Harvard Alumni	0.72
Lee et al.	2001a	US Women's Health	Harvard Alumni	0.72
Leon et al.	1987	MRFIT	Minnesota LTPA	0.92
Lakka et al.	1994	Kuopio	Minnesota LTPA	0.92
Sobolski et al.	1987	Belgian Fitness	Minnesota LTPA	0.92
Shaper et al.	1994	British Regional	Minnesota LTPA	0.92
Folsom et al.	1997	ARIC	Baecke Physical Activity	0.93
Salonen et al.	1988 1982	North Karelia (two cohorts)	(No specific name)	0.75
Slattery et al.	1989	US Railroad	Minnesota LTPA (Early version)	0.82
Pekkanen et al.	1987	Finish Cohort	(No specific name)	0.75
Haapanen et al.	1997	Finish Cohort	(No specific name)	0.80
Manson et al.	1999	US Nurses' Health	(No specific name)	0.79
Kaprio et al.	2000	Finnish Twins	(No specific name)	0.75
Bijnen et al.	1998	Zutphen Elderly	Zutphen Elderly	0.93

data on physical inactivity by age to compute age-specific estimates of relative risks.

In lieu of this, the summary relative risk estimates from our meta-analyses were applied to the age categories 30–44 years, 45–59 years and 60–69 years on the basis that this age range was well represented by the studies included in our analyses. In addition, the summary estimate was applied to the 15–29-year age group for all disease end-points except breast cancer. In this case there was sufficient evidence to support differential relative risk estimates for pre-/peri- and postmenopausal women and we classified these groups as 15–44 years, and ≥45 years, respectively.

Reviewing data from two studies on ischaemic heart disease in which older age cohorts were examined (Bijnen et al. 1998; Sesso et al. 2000)

we found older adults had around half the excess of the average risk estimate from all other studies combined. This formed the basis of age attenuation estimates. Specifically, 25% of the excess risk was used to estimate risk for the 70–79-year age group and 50% of the excess risk was used for the age group ≥80 years. These algorithms were used to compute age attenuated estimates for all other disease end-points. It is possible that there is no attenuation across age for increased risk of cancer, employing the age attenuation described may have added to the likely underestimation of burden.

3.7 Extrapolation of hazard estimates

In general, there was a paucity of data on the effects of physical activity and reduction in risk of disease among populations not of European decent. For ischaemic heart disease and ischaemic stroke, the majority of studies were conducted with men of primarily European descent. For colon and breast cancer the population base was broader but still mostly of North American and European origin. Studies on type II diabetes included data from a much wider range of regions and the reduction in risk was in the same direction across different population groups. Like previous reviews (Powell and Blair 1994), we found no established reasons to suggest that the association between physical inactivity and chronic diseases would differ across diverse populations. Thus, in the absence of evidence to the contrary, we assume that the relative risk estimates for all conditions can be applied across all populations.

3.8 Estimated hazards

Where possible, separate relative risks for males and females were used to derive the summary estimates. If studies provided specific risk estimates for various age groups and/or for different domains of activity in addition to an overall summary risk, the estimate across all age groups and/or across all domains was extracted for our analyses (e.g. Morris et al. 1990). If no summary score was presented, the age/domain specific estimates were included as one study in the meta-analysis (e.g. Gillum et al. 1996).

Ischaemic heart disease

Table 10.19 reports the summary risk estimates from meta-analyses undertaken with and without an adjustment for measurement error. Funnel plots showed little evidence of bias but some heterogeneity in these meta-analyses (Figure 10.24). The regression test showed no evidence of bias ($P = 0.34$).

Ischaemic stroke

The analyses described above for ischaemic heart disease were repeated for ischaemic stroke and the results are reported in Table 10.20. Funnel plots (Figure 10.25) showed some evidence of heterogeneity and large

Table 10.19 Summary relative risk estimates for ischaemic heart disease[a] for level 1 (inactive) and level 2 (insufficiently active) exposure, by age and sex

	NO adjustment for measurement error[b]		*WITH adjustment for measurement error*[b]	
Level 1 (inactive)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	1.47 (1.39–1.56)	1.47 (1.39–1.56)	1.71 (1.58–1.85)	1.71 (1.58–1.85)
30–44	1.47 (1.39–1.56)	1.47 (1.39–1.56)	1.71 (1.58–1.85)	1.71 (1.58–1.85)
45–59	1.47 (1.39–1.56)	1.47 (1.39–1.56)	1.71 (1.58–1.85)	1.71 (1.58–1.85)
60–69	1.47 (1.39–1.56)	1.47 (1.39–1.56)	1.71 (1.58–1.85)	1.71 (1.58–1.85)
70–79	1.34 (1.26–1.42)	1.34 (1.26–1.42)	1.50 (1.38–1.61)	1.50 (1.38–1.61)
≥80	1.21 (1.14–1.29)	1.21 (1.14–1.29)	1.30 (1.21–1.41)	1.30 (1.21–1.41)
Level 2 (insufficiently active)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	1.31 (1.21–1.41)	1.31 (1.21–1.41)	1.44 (1.28–1.62)	1.44 (1.28–1.62)
30–44	1.31 (1.21–1.41)	1.31 (1.21–1.41)	1.44 (1.28–1.62)	1.44 (1.28–1.62)
45–59	1.31 (1.21–1.41)	1.31 (1.21–1.41)	1.44 (1.28–1.62)	1.44 (1.28–1.62)
60–69	1.31 (1.21–1.41)	1.31 (1.21–1.41)	1.44 (1.28–1.62)	1.44 (1.28–1.62)
70–79	1.22 (1.13–1.32)	1.22 (1.13–1.32)	1.31 (1.17–1.48)	1.31 (1.17–1.48)
≥80	1.14 (1.06–1.24)	1.14 (1.06–1.24)	1.20 (1.07–1.35)	1.20 (1.07–1.35)

NA Not applicable.

[a] Incidence and mortality.

[b] Summary risk estimates computed using estimates adjusted for confounding variables (e.g. age, sex) but NOT adjusted for blood pressure and cholesterol. If these were unavailable from any study the available overall adjusted relative risk estimate was used.

bias in these analyses (regression $P < 0.001$). We were unable to account for this bias, however publication bias (i.e. preferential publication and increased citation of studies with significant results) and the restriction to studies published in English may have contributed.

Breast cancer

Summary risk estimates were computed for pre- and peri-menopausal women combined and for post-menopausal women. These estimates

Figure 10.24 Funnel plot of studies used in ischaemic heart disease meta-analysis for ischaemic heart disease, level 1 exposure (inactive)

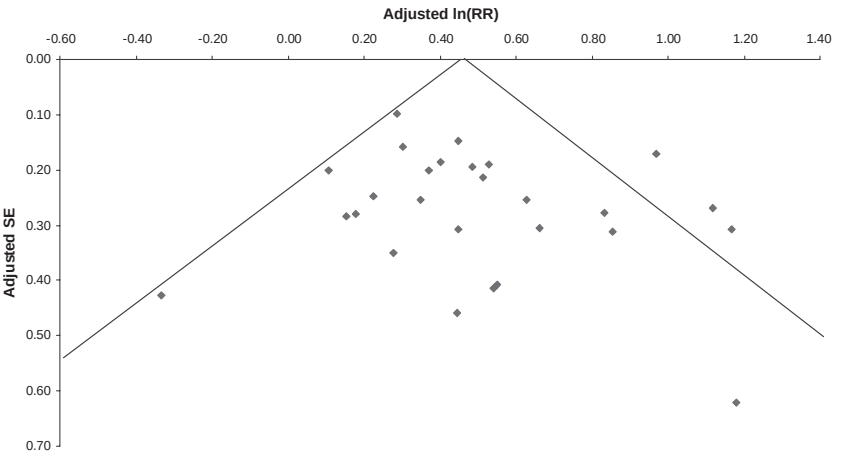


Figure 10.25 Funnel plot of studies used in ischaemic stroke meta-analysis for ischaemic heart disease, level 1 exposure (inactive)

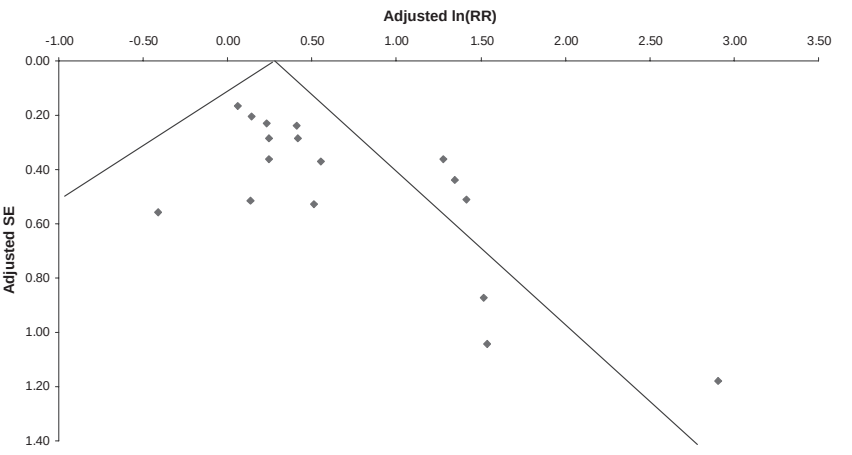


Table 10.20 Summary relative risk estimates for ischaemic stroke[a] for level 1 (inactive) and level 2 (insufficiently active) exposure, by age and sex

	NO adjustment for measurement error[b]		*WITH adjustment for measurement error*[b]	
Level 1 (inactive)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	1.39 (1.24–1.56)	1.39 (1.24–1.56)	1.53 (1.31–1.79)	1.53 (1.31–1.79)
30–44	1.39 (1.24–1.56)	1.39 (1.24–1.56)	1.53 (1.31–1.79)	1.53 (1.31–1.79)
45–59	1.39 (1.24–1.56)	1.39 (1.24–1.56)	1.53 (1.31–1.79)	1.53 (1.31–1.79)
60–69	1.39 (1.24–1.56)	1.39 (1.24–1.56)	1.53 (1.31–1.79)	1.53 (1.31–1.79)
70–79	1.28 (1.14–1.44)	1.28 (1.14–1.44)	1.38 (1.18–1.60)	1.38 (1.18–1.60)
≥80	1.18 (1.05–1.33)	1.18 (1.05–1.33)	1.24 (1.06–1.45)	1.24 (1.06–1.45)
Level 2 (insufficiently active)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	0.97 (0.87–1.15)	0.97 (0.87–1.15)	1.10 (0.89–1.37)	1.10 (0.89–1.37)
30–44	0.97 (0.87–1.15)	0.97 (0.87–1.15)	1.10 (0.89–1.37)	1.10 (0.89–1.37)
45–59	0.97 (0.87–1.15)	0.97 (0.87–1.15)	1.10 (0.89–1.37)	1.10 (0.89–1.37)
60–69	0.97 (0.87–1.15)	0.97 (0.87–1.15)	1.10 (0.89–1.37)	1.10 (0.89–1.37)
70–79	0.97 (0.87–1.15)	0.97 (0.87–1.15)	1.08 (0.87–1.33)	1.08 (0.87–1.33)
≥80	0.97 (0.87–1.15)	0.97 (0.87–1.15)	1.05 (0.85–1.30)	1.05 (0.85–1.30)

NA Not applicable.

[a] Incidence and mortality.

[b] Summary risk estimates computed using estimates adjusted for confounding variables (e.g. age, sex) but NOT adjusted for blood pressure and cholesterol. If these were unavailable from any study the available overall adjusted relative risk estimate was used.

were applied to the 15–29- and 30–44-year age groups and those groups of women aged ≥45 years, respectively. The results shown in Table 10.21 indicate a somewhat stronger association between level 1 exposure and breast cancer for post-menopausal women (1.34) compared to pre- and peri-menopausal women (1.25). This relationship is also evident for level 2 exposure. Funnel plot (Figure 10.26) revealed some evidence of bias and heterogeneity. The regression test showed significant bias among studies of post-menopausal women ($P = 0.002$) but not among pre- and peri-menopausal women ($P = 0.23$).

Table 10.21 Summary relative risk estimates for breast cancer[a] for level 1 (inactive) and level 2 (insufficiently active) exposure, by age and sex

	Adjusted for confounding variables but NO adjustment for measurement error		*Adjusted for confounding variables WITH adjustment for measurement error*	
Level 1 exposure (inactive)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	NA	1.13 (1.04–1.22)	NA	1.25 (1.20–1.30)
30–44	NA	1.13 (1.04–1.22)	NA	1.25 (1.20–1.30)
45–59	NA	1.13 (1.04–1.22)	NA	1.34 (1.29–1.39)
60–69	NA	1.13 (1.04–1.22)	NA	1.34 (1.29–1.39)
70–79	NA	1.09 (1.01–1.18)	NA	1.25 (1.21–1.30)
≥80	NA	1.06 (0.98–1.15)	NA	1.16 (1.11–1.20)
Level 2 exposure (insufficiently active)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	NA	1.09 (1.03–1.16)	NA	1.13 (1.04–1.22)
30–44	NA	1.09 (1.03–1.16)	NA	1.13 (1.04–1.22)
45–59	NA	1.09 (1.03–1.16)	NA	1.13 (1.04–1.22)
60–69	NA	1.09 (1.03–1.16)	NA	1.13 (1.04–1.22)
70–79	NA	1.07 (1.01–1.13)	NA	1.09 (1.01–1.18)
≥80	NA	1.04 (0.98–1.11)	NA	1.06 (0.98–1.15)

NA Not applicable.

[a] Incidence and mortality.

Colon cancer

Table 10.22 reports the results of risk associated with colon cancer for men and women. Separate analyses by sex were conducted but showed a non-significant difference, thus pooled estimates are provided (data not shown). Funnel plots showed some evidence of bias but little heterogeneity (see Figure 10.27), however the regression test revealed a significant bias (P <0.001). This bias would appear to be attributable to the inclusion of three studies which each had relatively large estimates of risk and small standard errors (Gerhardsson et al. 1988; Longnecker et al. 1995; Tang et al. 1999). Excluding these studies resulted in a regression test p-value of 0.30 and had no effect on the summary risk estimates.

Figure 10.26 Funnel plot of studies used in breast cancer meta-analysis for ischaemic heart disease, level 1 exposure (inactive)

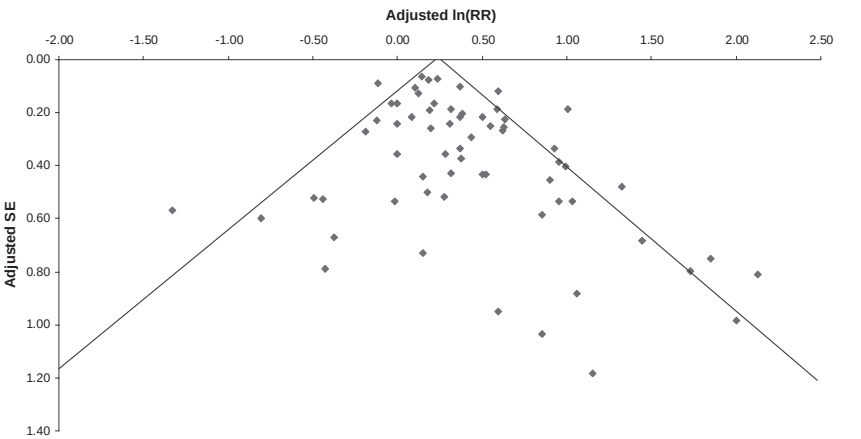
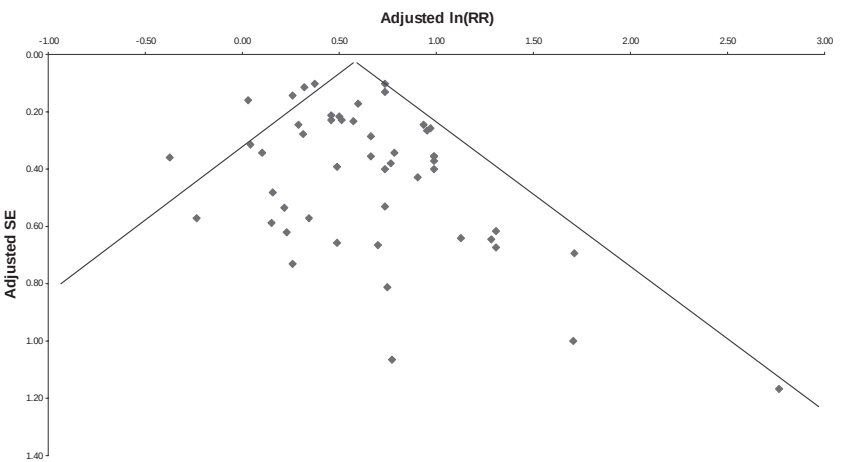


Figure 10.27 Funnel plot of studies used in colon cancer meta-analysis for ischaemic heart disease, level 1 exposure (inactive)



TYPE II DIABETES

The risk of type II diabetes associated with level 1 exposure was 1.45 and 1.31, with and without the adjustment for measurement error, respectively (see Table 10.23). Level 2 exposure was associated with a relative risk of 1.24 (with measurement adjustment) and 1.17 (without

Table 10.22 Summary relative risk estimates for colon cancer[a] for level 1 (inactive) and level 2 (insufficiently active) exposure, by age and sex

	Adjusted for confounding variables but NO adjustment for measurement error		*Adjusted for confounding variables WITH adjustment for measurement error*	
Level 1 exposure (inactive)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	1.43 (1.38–1.49)	1.43 (1.38–1.49)	1.68 (1.55–1.82)	1.68 (1.55–1.82)
30–44	1.43 (1.38–1.49)	1.43 (1.38–1.49)	1.68 (1.55–1.82)	1.68 (1.55–1.82)
45–59	1.43 (1.38–1.49)	1.43 (1.38–1.49)	1.68 (1.55–1.82)	1.68 (1.55–1.82)
60–69	1.43 (1.38–1.49)	1.43 (1.38–1.49)	1.68 (1.55–1.82)	1.68 (1.55–1.82)
70–79	1.31 (1.26–1.36)	1.31 (1.26–1.36)	1.48 (1.36–1.60)	1.48 (1.36–1.60)
≥80	1.20 (1.15–1.24)	1.20 (1.15–1.24)	1.30 (1.20–1.40)	1.30 (1.20–1.40)
Level 2 exposure (insufficiently active)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	1.11 (1.03–1.20)	1.11 (1.03–1.20)	1.18 (1.05–1.33)	1.18 (1.05–1.33)
30–44	1.11 (1.03–1.20)	1.11 (1.03–1.20)	1.18 (1.05–1.33)	1.18 (1.05–1.33)
45–59	1.11 (1.03–1.20)	1.11 (1.03–1.20)	1.18 (1.05–1.33)	1.18 (1.05–1.33)
60–69	1.11 (1.03–1.20)	1.11 (1.03–1.20)	1.18 (1.05–1.33)	1.18 (1.05–1.33)
70–79	1.08 (1.00–1.17)	1.08 (1.00–1.17)	1.13 (1.01–1.27)	1.13 (1.01–1.27)
≥80	1.05 (0.97–1.14)	1.05 (0.97–1.14)	1.08 (0.97–1.22)	1.08 (0.97–1.22)

NA Not applicable.

[a] Incidence and mortality.

measurement adjustment). Age attenuation was applied to the age groups of 70–79 years and ≥80 years.

The funnel plot showed no evidence of heterogeneity (Figure 10.28) but strong evidence of bias for these analyses (regression test $P < 0.001$). We were unable to account for this bias, however it is possible that publication bias may have contributed.

Discussion of relative risk estimates

Overall the results from our set of meta-analyses are similar to previous reports. For instance, the summary estimate of the independent effect of inactivity (1.38) is similar to previous findings of Eaton (1992) and the

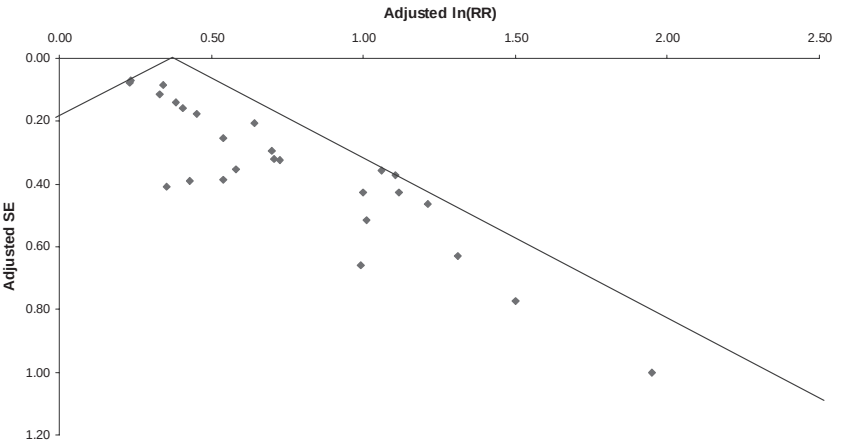
Table 10.23 Summary relative risk estimates for type II diabetes for level 1 (inactive) and level 2 (insufficiently active) exposure, by age and sex

	Adjusted for confounding variables but NO adjustment for measurement error		*Adjusted for confounding variables WITH adjustment for measurement error*	
Level 1 exposure (inactive)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	1.31 (1.24–1.39)	1.31 (1.24–1.39)	1.45 (1.37–1.54)	1.45 (1.37–1.54)
30–44	1.31 (1.24–1.39)	1.31 (1.24–1.39)	1.45 (1.37–1.54)	1.45 (1.37–1.54)
45–59	1.31 (1.24–1.39)	1.31 (1.24–1.39)	1.45 (1.37–1.54)	1.45 (1.37–1.54)
60–69	1.31 (1.24–1.39)	1.31 (1.24–1.39)	1.45 (1.37–1.54)	1.45 (1.37–1.54)
70–79	1.22 (1.15–1.30)	1.22 (1.15–1.30)	1.32 (1.25–1.40)	1.32 (1.25–1.40)
≥80	1.14 (1.08–1.21)	1.14 (1.08–1.21)	1.20 (1.14–1.28)	1.20 (1.14–1.28)
Level 2 exposure (insufficiently active)				
Age group (years)	*Males*	*Females*	*Males*	*Females*
0–4	NA	NA	NA	NA
5–14	NA	NA	NA	NA
15–29	1.17 (1.08–1.27)	1.17 (1.08–1.27)	1.24 (1.10–1.39)	1.24 (1.10–1.39)
30–44	1.17 (1.08–1.27)	1.17 (1.08–1.27)	1.24 (1.10–1.39)	1.24 (1.10–1.39)
45–59	1.17 (1.08–1.27)	1.17 (1.08–1.27)	1.24 (1.10–1.39)	1.24 (1.10–1.39)
60–69	1.17 (1.08–1.27)	1.17 (1.08–1.27)	1.24 (1.10–1.39)	1.24 (1.10–1.39)
70–79	1.12 (1.04–1.22)	1.12 (1.04–1.22)	1.18 (1.04–1.32)	1.18 (1.04–1.32)
≥80	1.08 (1.00–1.17)	1.08 (1.00–1.17)	1.11 (0.99–1.25)	1.11 (0.99–1.25)

NA Not applicable.

recent findings reported by Williams (2001). Eaton (1992) found an association between physical inactivity and ischaemic heart disease of 1.37 (1.27–1.48) from a set of 14 studies that assessed discretionary time and/or well-defined occupational physical activity, with ischaemic heart disease mortality or morbidity as disease end-points. More recently, Williams (2001) pooled results from 16 cohorts with measures of discretionary-time physical activity or "all physical activity" and ischaemic heart disease end-points. The author reported pooled relative risk estimates against percentiles of activity and showed relative risks of between 0.65–0.75 for the 70th percentile and above of activity compared with the referent group of zero activity. Inverting his result to allow comparison with this study produced a relative risk of about 1.4.

Figure 10.28 Funnel plot of studies used in type II diabetes meta-analysis for ischaemic heart disease, level 1 exposure (inactive)



Our results are also consistent with earlier reviews undertaken by Powell et al. (1987) and Berlin and Colditz (1990) when the differences in protocols are reviewed. Powell et al. (1987) pooled 47 studies with diverse methodological properties and included studies with exposure of either fitness or physical activity. Their qualitative summary estimate of relative risk was 1.9 but the authors noted the magnitude of this association ranged from 1.5–2.4. Berlin and Colditz (1990) replicated the work of Powell et al. with the addition of any subsequent published work, and reported several estimates of relative risk specific to occupational physical activity and non-occupational activity, and for separate cardiovascular disease outcomes. Also, they undertook separate analyses for studies with two and with three levels of exposure. Using only those studies included by Powell et al., they computed a summary estimate of risk for discretionary-time inactivity and ischaemic heart disease (morbidity) of 1.6 with a confidence interval of 1.3–1.8 (see published paper Table 4, analysis B) (Berlin and Colditz 1990). This did not change substantially when additional studies were added (RR=1.5, 95% CI 1.4–1.7, see published paper Table 5, analysis B).

Berlin and Colditz refined their analyses by separating studies based on epidemiological criteria and classified studies as "satisfactory" and "unsatisfactory". Including only the former studies, relative risk estimates ranged from 1.3 (0.7–2.6) to 1.9 (1.0–3.6) for ischaemic heart disease mortality (see published paper Table 6). Thus, comparing our

results with the intricate set of analyses of Berlin and Colditz and other previous work of Powell et al. (1987), and Eaton (1992) revealed our results are similar and well within the range of published confidence limits.

We found a weaker relationship for the effect of physical activity on ischaemic stroke than on ischaemic heart disease, the relative risk estimate for the inactive group being 1.53. The existence of a dose–response relationship between physical activity and stroke is not yet established (Kohl 2001) and there is no evidence of a dose–response effect seen in this study, with the relative risk of the insufficiently active group being no different from 1.

The relative risk of physical inactivity associated with developing type II diabetes was 1.45 (1.37–1.54) and this was applied to men and women. Previous studies have reported a differential protective effect across sex, however we found only modest evidence for level 1 exposure and no evidence for level 2 exposure. Any apparent difference may have been due to the large degree of heterogeneity among studies. A dose–response relationship across levels of exposure was observed and this is consistent with a recent review of the benefits of physical activity in preventing or delaying the development of diabetes (Kelley and Goodpaster 2001).

The relative risk associated with colon cancer was 1.68 (1.55–1.82) for inactive adults compared with those who are reaching recommended levels of activity. The insufficiently active group had a lower relative risk of 1.18 (1.05–1.33) compared to the referent group. These results indicate a dose–response relationship across exposure and this is consistent with previous research (Thune and Furberg 2001). No previous quantitative meta-analyses have been undertaken on physical inactivity and colon cancer, although the recent review by Thune and Furberg (2001) concluded that the majority of studies showed an independent protective effect ranging in magnitude of between 10% and 70% (2001).

We found the relative risks associated with breast cancer were 1.25 (1.20–1.30) for women aged 15–44 years and 1.34 (1.29–1.39) for women aged 45–69 years. These results are consistent with a previously published qualitative review that showed a 30% reduction in risk of breast cancer among pre-, peri- and post-menopausal women, with a graded dose- response seen in around half of the studies reviewed (Thune and Furberg 2001). Evidence of a dose–response effect was observed with the relative risk of 1.13 (1.04–1.22) associated with the insufficiently active group.

In summary, our estimates of risk of ischaemic heart disease are consistent with previous research, given a careful inspection of the study inclusion criteria and treatment of the data. There are less data by which to compare our results on ischaemic stroke and no previous quantitative reviews addressing type II diabetes and breast and colon cancers. Across

all health outcomes, except ischaemic stroke, a dose–response relationship was observed, with the most inactive (level 1 exposure) associated with having the greatest risk. There is considerable heterogeneity across studies aimed at answering apparently similar questions. This is a notable limitation to conducting meta-analyses. This field of research would benefit from improved measures of exposure; and greater consistency in the reporting of results between studies would advance this field.

3.9 Risk reversibility and temporal aspects of the risk factor–disease relationship

There is little direct evidence on risk reversibility associated with increases in levels of physical activity. This is primarily due to the lack of randomized controlled trials and the fact that a long period between exposure to physical inactivity and disease outcomes is required for assessment. Further, the few data that are available mostly relate to risk reduction in all-cause mortality and ischaemic heart disease and predominantly among white men from middle to upper socioeconomic groups. Despite these limitations, we reviewed the available literature and attempted to estimate the magnitude and time lag associated with change in level of activity and change in risk. Our conclusions for each health outcome are summarized below.

Ischaemic heart disease and ischaemic stroke

Increase in levels of physical activity can reduce the risk of ischaemic heart disease (Paffenbarger et al. 1994). Among Harvard alumni, physically inactive men who started a moderate–vigorous physical activity routine reduced risk of ischaemic heart disease mortality by 41% compared with men who remained inactive (Paffenbarger et al. 1993). This is consistent with findings on the benefits of changes in cardiorespiratory fitness, which although not included in this review may help inform the potential nature of risk reversibility due to physical inactivity (Blair et al. 1995). Blair et al. (1995) reported a reduction in risk of ischaemic heart disease due to improvements in cardiorespiratory fitness. They found that men classified as unfit at their initial examination and fit at their subsequent examination had a 44% reduction in risk of ischaemic heart disease mortality than did men who were unfit at both examinations (Blair et al. 1995). Furthermore, these associations were independent of other potentially confounding factors (e.g. smoking, BMI, systolic blood pressure, cholesterol) (Blair et al. 1995, 1996). Moreover, there is evidence to suggest that recent participation in physical activity, rather than activity performed in the past, is required for reduction in risk of ischaemic heart disease (Paffenbarger et al. 1978).

Although there is limited empirical support, there are indications that reversibility for ischaemic heart disease could be complete, and could occur within a relatively short period of time following reversal of exposure, perhaps as short as several months or up to two years. This assump-

tion is based on the available evidence pertaining to changes in physical inactivity, indirect evidence from studies using fitness parameters, and known acute effects of physical activity on elements of the physiological pathways which reduce cardiovascular risk.

There is little evidence to guide the estimates of risk reversibility for ischaemic stroke following changes in exposure to physical inactivity. As the biological pathways are considered to be the same as those for ischaemic heart disease, it is possible that there may be a similar relationship for a reduction in risk.

Breast cancer and colon cancer

There are no data to help quantify what degree of risk reduction may occur over what time frame for breast cancer. The paucity of data on physical activity and risk reduction required us to use indicative information on which to base such estimates. Studies on the cessation of postmenopausal hormone replacement therapy and breast cancer rates provide indirect estimates, as the biological pathways (i.e. through hormone levels, as described in section 1) are considered to be similar to that assumed for physical activity's impact on breast cancer.

Major reviews of the epidemiological evidence suggest complete reversibility. That is, women who stop postmenopausal hormone replacement therapy generally revert to the same breast cancer rates as women who had never had hormone replacement therapy, over a period of two to five years (Collaborative Group on Hormonal Factors in Breast Cancer 1997; La Vecchia et al. 2001). There is, however, debate on the biological plausibility and mechanisms of this observed reduction in risk (Bieber and Barnes 2001).

Again there are few data to indicate what the magnitude of risk reduction may be over time for colon cancer. Lee et al. (1991) suggested that although a lifetime or at least consistent participation during adulthood in physical activity is required for greatest protection from risk of colon cancer, some reduction (13% over 11–15 years) is seen in men who become active after being inactive.

Type II diabetes

There are two sources of information to help with risk reversibility for type II diabetes. Data from the Nurses' Health Study show that women who increased their physical activity levels over six years experienced 29% lower rates of type II diabetes than those who remained inactive over the same period (RR = 0.71) (Hu et al. 1999). However, women who were active at the beginning and remained active over the six years still had lower rates of type II diabetes than those who became active (RR = 0.59). Recently, the Diabetes Prevention Program Research Group (2002) showed that, among people who had impaired glucose tolerance, a lifestyle intervention combining moderate amounts of physical activity

with a controlled diet resulted in a 58% reduction in the incidence of type II diabetes over 2 to 5 years. Since this risk reduction resulted from a combined lifestyle intervention with a population already at increased risk, the effect of only changes in physical activity in the general population is assumed to be less. These estimates suggest a risk reversibility of 25% over five years for sedentary adults becoming sufficiently active and 35% over four years for insufficiently active adults becoming sufficiently active.

4. Burden of disease attributable to physical inactivity

The fraction of burden (mortality and morbidity combined) attributable to physical inactivity for each disease end-point is shown in Figure 10.29. Globally physical inactivity contributed to an estimated 22% of ischaemic heart disease, 11% of ischaemic stroke, 14% of type II diabetes, 16% of colon cancer and 10% of breast cancer. The results show small differences between males and females, due in part to differences in the level of exposure and to the different distribution of events between the sexes. There were small, non-significant differences in the attributable fractions across subregions (data not shown). For ischaemic heart disease the subregional differences ranged from 21% (SEAR-D, EMR-D and WPR-B) to 23% (AMR-B, EUR-C and WPR-A). A slightly wider range was seen for ischaemic stroke 9% (AFR-D) to 14% (EUR-C).

The number of deaths and number of DALYs were computed for each disease outcome (Figures 10.30 and 10.31, respectively). Over one

Figure 10.29 Attributable burden of disease due to physical inactivity for ischaemic heart disease, ischaemic stroke, type II diabetes, colon cancer and breast cancer

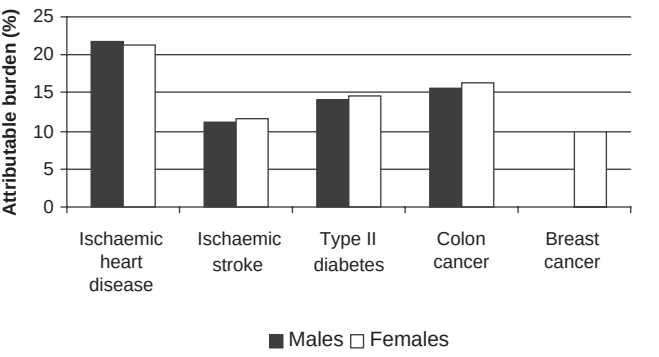


Figure 10.30 Attributable mortality due to physical inactivity for ischaemic heart disease, ischaemic stroke, type II diabetes, colon cancer and breast cancer

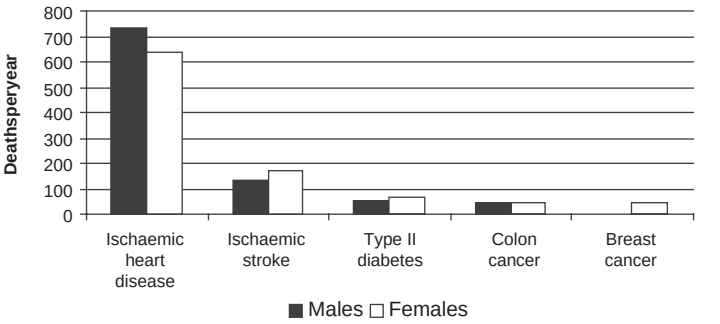
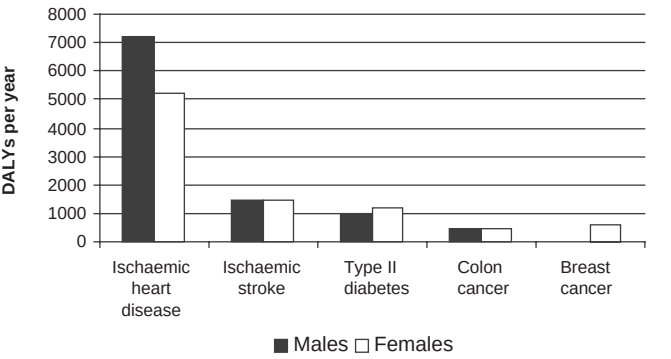


Figure 10.31 Attributable DALYs due to physical inactivity for ischaemic heart disease, ischaemic stroke, type II diabetes, colon cancer and breast cancer



million deaths due to ischaemic heart disease were attributable to physical inactivity (730 000 males and 634 000 females). Another 308 000 deaths from ischaemic stroke were also attributable to inactive and insufficiently active lifestyles. Combined with deaths from type II diabetes (116 000), colon cancer (90 000) and breast cancer (45 000) a total of 1.92 million deaths could be prevented from increasing levels of physical activity (Figure 10.30). Similarly inactive lifestyles contributed to a loss of 19 million DALYs worldwide.

5. Discussion

The attributable fraction for ischaemic heart disease morbidity and mortality (22%) is slightly lower than previous estimates that range from 23% (Hahn et al. 1990) to 35% (Powell and Blair 1994). This variation is explained by differences in the estimates used for prevalence and relative risk. Previous attempts have used rounded estimates of risk (1.9) (Powell and Blair 1994). We estimated relative risks that are consistent but marginally lower than previous reports because we only accepted data from studies reporting an exposure of physical activity not physical fitness; risk of exposure was computed relative to the current public health recommendations not a referent group of "high level of activity" or "vigorously active"; an adjustment for attenuation of risk over age was included; and, perhaps most importantly, we used a trichotomous not continuous measure of exposure. We acknowledge that no attempt was made to account for the additional benefit associated with being highly active and/or engaging in activities of vigorous intensity.

Furthermore, past estimates of exposure have been based on only one domain, namely discretionary time. Single domain estimates will overestimate exposure by not including activity undertaken in other domains. Another important difference with previous estimates is in the number of categorical levels used in the analyses. We created a trichotomous measure; in contrast previous work had used four levels of exposure (Powell and Blair 1994). Estimates of level 2 exposure should be interpreted with great caution. Available data were the most difficult to compare and we acknowledge our assumptions will inevitably include some misclassification. Our global estimate of insufficiently active was 41%, although data show that in different countries it can range from 20% to 70%. For both level 1 and level 2 there is greatest uncertainty around prevalence estimates for Africa, Asia and the Eastern Mediterranean and across all subregions for adults aged >60 years. There is a corresponding high level of uncertainty around the estimates of disease burden for these subregions and age groups. A difference of ±10% in prevalence estimates would make a considerable difference in the estimated magnitude of the disease burden.

Given the noted differences between our input variables and those used in previous reports, our global estimates of attributable fraction appear consistent, but we suggest that they too are likely to underestimate the true burden due to inactive lifestyles. Moreover, a number of the limitations combine to make it more difficult to compare with other continuously measured risk factors such as blood pressure and cholesterol.

In summary, the multiple model of exposure provided a useful platform for these analyses of attributable burden but recent, comparable country-level data on inactivity would be far more preferable. This would require, however, having more countries systematically collect

data on the distribution of physical inactivity. Well developed, culturally appropriate measurement instruments should be used to collect comparable data. While there are examples of progress in this area (Craig et al. 2003), with few exceptions, instruments to assess exposure across the diverse cultures of Africa, Asia and the Eastern Mediterranean have yet to be well tested or widely used.

Emerging evidence is pointing towards the important role of physical activity in avoiding outcomes (e.g. falls, poor mental health) as well as other disease end-points (e.g. osteoarthritis and osteoporosis) that did not meet our inclusion criteria. Future replications of this work should review the evidence to ensure a complete a picture as possible is obtained on the burden attributable to inactivity. Across these outcomes as well as those included, the exact nature of the dose–response relationship across all disease end-points is not well defined. Moreover, the heterogeneity across studies is notable and represents a limitation to conducting meta-analyses in this field. Researchers are encouraged to pursue this research agenda systematically to maximize the expedient pooling of data and furthering of our knowledge.

Physically inactive lifestyles account for 3.3% of deaths and morbidity worldwide. Successful promotion of more active lifestyles would prevent at least 2 million premature deaths and almost 20 million DALYs worldwide. Success in prevention requires greater commitment through policy development and resource allocation at the national and local level. Diverse challenges face developed and developing countries as they consider the current and future rapid changes in patterns of activity by domain.

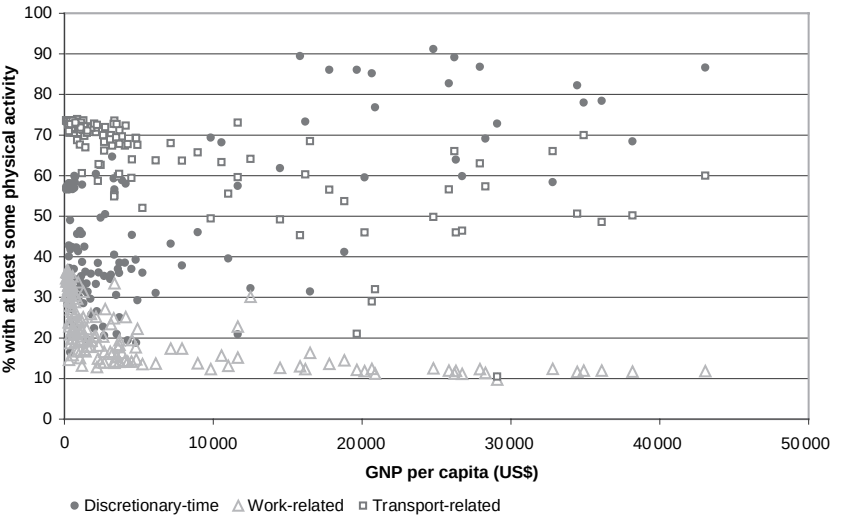
6. Projected estimates of future exposure

Calculation of the avoidable burden of disease requires predicated estimates of exposure in the future. Estimates are usually based on trends and patterns seen over past years adjusted based on assumptions and models of factors likely to influence exposure in the future. We looked for data on patterns of activity over time for predicting level 1 and level 2 exposure in 2010, 2020 and 2030. Our search found few trend data and those available were mostly from developed countries and had similar limitations regarding their comparability as previously discussed.

6.1 Methods

In the absence of data on trends to guide our calculations of future exposure we considered the factors that might influence inactivity in the next 30 years. Considering each domain separately and in combination, we proposed that economic development was a central factor to changes in the level of physical activity undertaken in the work place, at home, through transportation and in leisure time. As economies develop, new mechanical, computer and biological technologies will reduce the

Figure 10.32 Predicted[a] estimates of physical activity for 145 countries in 2000, by domain and GNP per capita

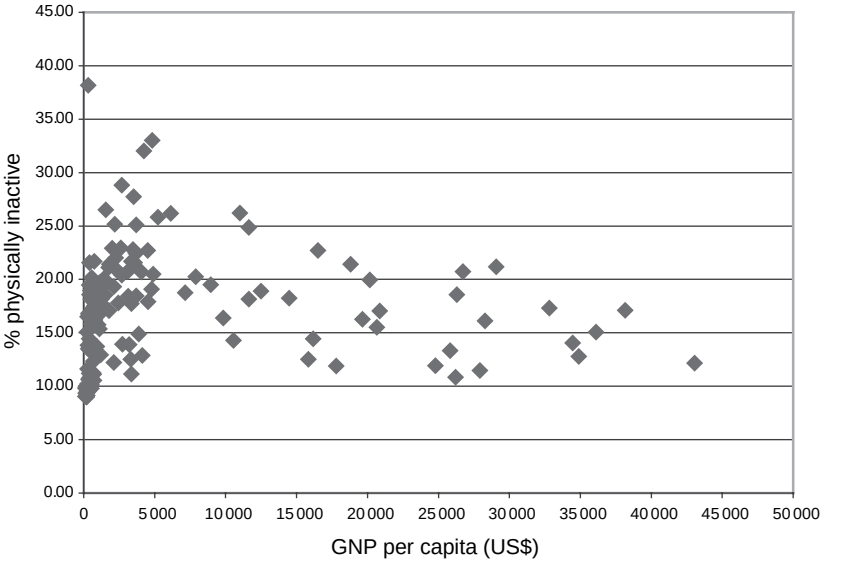


[a] Actual physical activity estimates for countries were used when available.

demand for physical tasks in the work place as well as drive the shift in employment from agriculture to manufacturing and service industries. Both factors will result in lower levels of physical activity in the occupational domain. Furthermore, as economies develop and individuals have higher incomes, there will be a shift in travel behaviour, specifically walking and cycling will decrease in favour of modes of personal transportation (motor vehicle) and to a lesser extent public transit. Discretionary time is likely to increase as economies develop and there is a higher level of wealth. While there is more time for discretionary physical activity there also will be more alternative options, many of which will require low levels of physical activity, for example, computer-based entertainment and television. Figure 10.32 shows our predicted estimates for physical activity in 2000 by domain and GNP.

We also considered whether the changes in physical activity within each domain over time could have a lag effect, such that increases in available leisure time would result some time after the shifts in the work place and changes in transportation. However, we had insufficient data to model future change in each domain separately or to explore our hypothetical time lag. Instead we used the net effect or the summary estimate of physical inactivity and GNP (shown in Figure 10.33) to model the association based on current (year 2000) levels. We then used dif-

Figure 10.33 Per cent physically inactive (level 1 exposure) for 145 countries by GNP per capita



ferentiation to compute the change in inactivity associated with a change in GNP over time and predicted estimates of GNP to solve the equation and compute estimates for physical inactivity in 2010, 2020 and 2030. This method is described in detail below.

Methods for the projection of future estimates of level 1 exposure

Prevalence of inactivity was related to GNP per capita for each country and prevalence of malnutrition (at the regional level rather than country level) as below. Malnutrition (as measured by childhood underweight) was included in the model along with GNP because preliminary regression analyses using per cent childhood mortality improved the model fit substantially for developing countries. However, future predictions for child mortality were not available therefore malnutrition was used as a proxy measure. Because country level estimates of malnutrition also did not exist, predicted estimates at the regional level were used (see chapter 2).

$$\log(\%\ \text{Inactivity}_{2000}) = B_1(\text{GNP per capita}_{2000}) + B_2(\%\ \text{malnutrition}_{2000})$$

Linear regression was used to estimate B_1 and B_2. The relationship between GNP per capita in 2000 and the prevalence of inactivity for

Table 10.24 Mean (range) GNP per capita and % malnourished for years 2000 and 2030

World Bank income classification	*GNP per capita (US$ 1000)*		*% children malnourished*	
	2000	*2030*	*2000*	*2030*
Low/Middle income	3.6 (0.5–14.9)	8.2 (0.9–53.8)	18.8 (2.3–45.9)	18.4 (0.0–50.7)
High income	22.7 (12.3–33.6)	59.6 (31.9–105.9)	3.1 (2.3–8.1)	0.0 (0.0–0.5)

2000 showed that inactivity increased with GNP per capita when GNP was less than US$ 5000 and decreased when GNP was greater than US$ 5000 (Figure 10.33). Therefore, we divided countries into two groups using World Bank income classification: a low/middle-income group, and high-income group (including Organisation for Economic Co-operation and Development [OECD] and non-OECD countries). The two groups were modelled separately to give two sets of parameter estimates for B_1 and B_2. Inactivity (%) was log-transformed and all variables were centred to reduce collinearity and to set the regression intercepts to zero by using mean % inactivity equal to zero. Change in physical inactivity over time was computed using predicted changes in GNP per capita (from World Bank estimates) and predicted change in malnutrition (World Bank 1999; chapter 2).

The assumption that the relationship seen in year 2000 would continue to characterize countries in year 2030 is examined in Table 10.24. Mean GNP increases in both groups between year 2000 and 2030 with a considerable increase in the ranges with only a small overlap between groups. Malnutrition, predicted at the regional level and aggregated to create a group estimate showed only a very small decrease over time in the low/middle-income group reflecting the worsening conditions predicted for some regions (e.g. Africa). For high-income countries malnutrition is predicted to approach zero by 2030 (chapter 2).

Methods for the projection of future estimates of level 2 exposure

Age by sex estimates of level 2 exposure (insufficiently active) were computed by holding constant our predicted values for year 2000 and applying these uniformly for 2010, 2020 and 2030. We chose this simple approach based on evidence that changes in the population distribution of physical (in)activity occur between levels of both inactive and insufficiently active, as well as between insufficiently active and sufficient (level 3 unexposed). We had no data on which to estimate the magnitude of the shift between level 2 and level 3. Thus, our predicted values of level 2 exposure are based on the assumption that the changes calculated for level 1 (predicted based on changes in economic development as described above) are equal to the change from level 2 to level 3—the net result of which is that level 2 estimates remain unchanged over time.

This approach is clearly limited but without more data from different populations on both current trends and patterns over time it was the only feasible approach.

6.2 Results

The parameter estimates for the model used to estimate future level 1 exposure show the different relationship between physical inactivity estimates in 2000 and GNP per capita and % malnutrition for each group (see Figure 10.33). Final age by sex estimates for 14 subregions for 2010, 2020 and 2030 are shown in Tables 10.25, 10.26 and 10.27, respectively. These data indicate an increasing physical inactivity in all subregions, for males and females and across all age groups. The magnitude of increase in level 1 exposure was of the order of 3–4%. We did not model any change in level 2 exposure. Recent evidence suggests these data are likely to grossly underestimate change in exposure. Between 1999 and 2002, Western Australia experienced a 4% decline in the proportion of the population meeting recommended levels of physical activity (McCormack et al. 2003). These data may be more indicative of the possible magnitude of negative change to expect in developed market economies in coming years if no action is undertaken. Taken in combination with the changing patterns of lifestyle people will experience in developing economies, the future burden of disease attributable to inactivity may be considerable.

Table 10.25 Projected estimates (%) of physical inactivity in year 2010

		Males						Females					
Subregion	*Exposure level*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Inactive	11	13	14	16	18	19	13	12	13	16	19	20
	Insufficient	48	48	48	46	44	43	45	52	51	48	46	45
	Recommended	41	39	38	38	38	38	42	36	36	36	35	35
AFR-E	Inactive	9	12	12	15	16	17	12	11	11	14	16	16
	Insufficient	50	51	50	49	47	46	47	56	55	51	50	50
	Recommended	41	37	38	36	37	37	41	33	34	35	34	34
AMR-A	Inactive	17	19	20	21	22	32	22	23	21	27	31	41
	Insufficient	44	47	44	40	40	35	36	41	40	38	36	31
	Recommended	39	34	36	39	38	33	42	36	39	35	33	28
AMR-B	Inactive	17	18	20	23	26	29	23	28	28	38	40	42
	Insufficient	42	44	41	39	36	35	33	32	31	30	30	29
	Recommended	41	38	39	38	38	36	44	40	41	32	30	29
AMR-D	Inactive	17	19	19	23	28	30	22	26	30	40	46	48
	Insufficient	38	38	33	32	30	29	28	26	24	24	22	22
	Recommended	45	43	48	45	42	41	50	48	46	36	32	30
EMR-B	Inactive	16	19	19	22	25	27	19	21	21	25	31	33
	Insufficient	41	39	38	36	32	32	36	36	35	32	31	30
	Recommended	43	42	43	42	43	41	45	43	44	43	38	37
EMR-D	Inactive	15	18	19	21	23	26	18	20	20	23	30	31
	Insufficient	42	38	36	35	32	31	36	36	35	32	31	30
	Recommended	43	44	45	44	45	43	46	44	45	45	39	39

continued

Table 10.25 Projected estimates (%) of physical inactivity in year 2010 (*continued*)

		Males						*Females*					
Subregion	*Exposure level*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
EUR-A	Inactive	14	15	16	19	21	22	17	19	19	23	25	29
	Insufficient	52	57	55	52	50	47	47	51	51	45	45	42
	Recommended	34	28	29	29	29	31	36	30	30	32	30	29
EUR-B	Inactive	15	19	20	22	26	28	19	40	38	36	34	33
	Insufficient	43	40	38	36	34	33	37	37	36	33	32	32
	Recommended	42	41	42	42	40	39	44	23	26	31	34	35
EUR-C	Inactive	18	19	23	32	37	39	21	28	28	39	40	41
	Insufficient	38	34	32	30	28	28	32	31	30	27	27	26
	Recommended	44	47	45	38	35	33	47	41	42	34	33	33
SEAR-B	Inactive	14	16	16	17	15	16	16	18	18	18	17	17
	Insufficient	43	43	43	47	52	52	41	41	41	45	50	50
	Recommended	43	41	41	36	33	32	43	41	41	37	33	33
SEAR-D	Inactive	14	18	18	21	23	21	18	20	20	23	25	28
	Insufficient	42	38	36	34	32	31	36	35	34	32	30	30
	Recommended	44	44	46	45	45	48	46	45	46	45	45	42
WPR-A	Inactive	15	16	17	19	18	18	17	19	19	20	18	18
	Insufficient	50	56	53	52	56	55	48	49	50	49	55	54
	Recommended	35	28	30	29	26	27	35	32	31	31	27	28
WPR-B	Inactive	14	17	16	19	20	21	16	17	18	21	22	21
	Insufficient	41	40	41	41	44	41	40	39	38	38	41	38
	Recommended	45	43	43	40	36	38	44	44	44	41	37	41

Table 10.26 Projected estimates (%) of physical inactivity in year 2020

		Males						Females					
Subregion	*Exposure level*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Inactive	11	13	13	16	18	19	13	12	13	16	19	20
	Insufficient	48	48	48	46	44	43	45	52	51	48	46	45
	Recommended	41	39	39	38	38	38	42	36	36	36	35	35
AFR-E	Inactive	9	12	12	15	16	17	11	11	11	14	16	16
	Insufficient	50	51	50	49	47	46	47	56	55	51	50	50
	Recommended	41	37	38	36	37	37	42	33	34	35	34	34
AMR-A	Inactive	17	19	20	21	22	32	21	23	21	27	31	41
	Insufficient	44	47	44	40	40	35	36	41	40	38	36	31
	Recommended	39	34	36	39	38	33	43	36	39	35	33	28
AMR-B	Inactive	17	19	20	23	26	29	24	28	28	38	41	42
	Insufficient	42	44	41	39	36	35	33	32	31	30	30	29
	Recommended	41	37	39	38	38	36	43	40	41	32	29	29
AMR-D	Inactive	17	19	19	23	28	31	22	26	30	40	47	48
	Insufficient	38	38	33	32	30	29	28	26	24	24	22	22
	Recommended	45	43	48	45	42	40	50	48	46	36	31	30
EMR-B	Inactive	16	19	19	22	25	27	19	21	21	25	31	33
	Insufficient	41	39	38	36	32	32	36	36	35	32	31	30
	Recommended	43	42	43	42	43	41	45	43	44	43	38	37
EMR-D	Inactive	15	18	19	21	23	26	18	20	20	24	30	31
	Insufficient	42	38	36	35	32	31	36	36	35	32	31	30
	Recommended	43	44	45	44	45	43	46	44	45	44	39	39

continued

Table 10.26 Projected estimates (%) of physical inactivity in year 2020 (*continued*)

		Males						*Females*					
Subregion	*Exposure level*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
EUR-A	Inactive	14	15	16	19	20	22	17	19	19	23	25	28
	Insufficient	52	57	55	52	50	47	47	51	51	45	45	42
	Recommended	34	28	29	29	30	31	36	30	30	32	30	30
EUR-B	Inactive	15	19	20	22	26	28	19	21	21	27	32	33
	Insufficient	43	40	38	36	34	33	37	37	36	33	32	32
	Recommended	42	41	42	42	40	39	44	42	43	40	36	35
EUR-C	Inactive	18	19	23	32	38	39	14	17	17	17	16	16
	Insufficient	38	34	32	30	28	28	32	31	30	27	27	26
	Recommended	44	47	45	38	34	33	54	52	53	56	57	58
SEAR-B	Inactive	14	17	17	17	16	16	16	19	18	19	17	17
	Insufficient	43	43	43	47	52	52	41	41	41	45	50	50
	Recommended	43	40	40	36	32	32	43	40	41	36	33	33
SEAR-D	Inactive	14	18	19	21	23	22	18	20	20	23	25	28
	Insufficient	42	38	36	34	32	31	36	35	34	32	30	30
	Recommended	44	44	45	45	45	47	46	45	46	45	45	42
WPR-A	Inactive	15	16	17	18	17	17	17	19	19	20	18	18
	Insufficient	50	56	53	52	56	55	48	49	50	49	55	54
	Recommended	35	28	30	30	27	28	35	32	31	31	27	28
WPR-B	Inactive	15	17	16	19	20	22	16	18	18	22	22	21
	Insufficient	41	40	41	41	44	41	40	39	38	38	41	38
	Recommended	44	43	43	40	36	37	44	43	44	40	37	41

Table 10.27 Projected estimates (%) of physical inactivity in year 2030

		Males						Females					
Subregion	*Exposure level*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Inactive	11	13	13	16	18	19	13	12	13	16	19	20
	Insufficient	48	48	48	46	44	43	45	52	51	48	46	45
	Recommended	41	39	39	38	38	38	42	36	36	36	35	35
AFR-E	Inactive	9	12	12	15	16	17	11	10	11	14	16	16
	Insufficient	50	51	50	49	47	46	47	56	55	51	50	50
	Recommended	41	37	38	36	37	37	42	34	34	35	34	34
AMR-A	Inactive	17	19	20	20	22	32	21	23	21	26	31	40
	Insufficient	44	47	44	40	40	35	36	41	40	38	36	31
	Recommended	39	34	36	40	38	33	43	36	39	36	33	29
AMR-B	Inactive	17	19	20	23	26	29	24	28	29	38	41	42
	Insufficient	42	44	41	39	36	35	33	32	31	30	30	29
	Recommended	41	37	39	38	38	36	43	40	40	32	29	29
AMR-D	Inactive	17	19	19	23	29	31	22	26	30	40	47	48
	Insufficient	38	38	33	32	30	29	28	26	24	24	22	22
	Recommended	45	43	48	45	41	40	50	48	46	36	31	30
EMR-B	Inactive	16	19	20	23	25	27	19	21	21	25	31	33
	Insufficient	41	39	38	36	32	32	36	36	35	32	31	30
	Recommended	43	42	42	41	43	41	45	43	44	43	38	37
EMR-D	Inactive	15	18	19	22	23	26	18	20	20	24	30	32
	Insufficient	42	38	36	35	32	31	36	36	35	32	31	30
	Recommended	43	44	45	43	45	43	46	44	45	44	39	38

continued

Table 10.27 Projected estimates (%) of physical inactivity in year 2030 (*continued*)

		Males						*Females*					
Subregion	*Exposure level*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
EUR-A	Inactive	14	15	16	19	20	22	17	18	19	23	24	28
	Insufficient	52	57	55	52	50	47	47	51	51	45	45	42
	Recommended	34	28	29	29	30	31	36	31	30	32	31	30
EUR-B	Inactive	15	19	20	22	26	29	19	21	22	27	32	33
	Insufficient	43	40	38	36	34	33	37	37	36	33	32	32
	Recommended	42	41	42	42	40	38	44	42	42	40	36	35
EUR-C	Inactive	18	19	23	32	38	39	21	28	28	40	40	41
	Insufficient	38	34	32	30	28	28	32	31	30	27	27	26
	Recommended	44	47	45	38	34	33	47	41	42	33	33	33
SEAR-B	Inactive	15	17	17	17	16	16	16	19	19	19	18	18
	Insufficient	43	43	43	47	52	52	41	41	41	45	50	50
	Recommended	42	40	40	36	32	32	43	40	40	36	32	32
SEAR-D	Inactive	14	18	19	22	23	22	18	20	20	23	26	28
	Insufficient	42	38	36	34	32	31	36	35	34	32	30	30
	Recommended	44	44	45	44	45	47	46	45	46	45	44	42
WPR-A	Inactive	15	15	16	18	17	17	16	19	18	20	17	18
	Insufficient	50	56	53	52	56	55	48	49	50	49	55	54
	Recommended	35	29	31	30	27	28	36	32	32	31	28	28
WPR-B	Inactive	15	17	16	19	20	22	16	18	18	22	22	21
	Insufficient	41	40	41	41	44	41	40	39	38	38	41	38
	Recommended	44	43	43	40	36	37	44	43	44	40	37	41

Acknowledgements

The authors wish to extend their sincere thanks to all the colleagues and researchers worldwide who assisted in either providing existing data, re-analysing data and/or providing contacts. The generous contributions of the following people helped us complete this project: Erinaldo Adrande, Ahmed al-Hashemi, Hazzaa al-Hazzaa, Jawad al-Lawati, Wahid al-Kharus, Terry Aspray, Adrian Bauman, Angèle Beaulieu, Pascal Bovet, Steve Blair, Clareann Bunker, Nick Cavill, L. Cavalli-Sforza, Beatriz Champagne-Marcet, Dr Chandran, Constanza Cilley, William Cockerham, Cora Craig, Catherine Cross, Constanza Cilley, Maximilian de Courten, Kathy Douglas, Michael Engelgau, Ted Forbes, Gauden Galea, Bill Haskill, Louise Hayes, Francisco Holway, Frank Hu, Toni Hunt, Enrique Jacoby, Konrad Jamrozik, Andrea Kriska, Darwin Labarthe, Vicky Lambert, I-Min Lee, N Mallick, Beatriz Champagne Marcet, Miguel Martinez-Gonzalez, Sandra Matsudo, Victor Matsudo, Willem Van Mechelen, Abdulrahman Musaiger, Norio Murase, Anoop Misra, Pekka Oja, Andrzej Pajak, Rimma Potemkina, Joceline Pomerleau, Barry Popkin, Antonio Prista, Jasem Ramadan, Srinath Reddy, Vikram Singh, Christine Snead, Eugene Sobngwi, Soeharsono Soemantri, Michael Sjöström, Elena Subirats, Roger Vaughan, Guijing Wang, Dr Yang, C. Yajnik, Helena Zabina.

In addition, the authors wish to extend particular thanks to Barbara Ainsworth, David Buchner and Carl Caspersen for their internal review and to the anonymous external reviewers who provided valuable comments on the methods and assumptions. Finally, the authors thank colleagues leading the CRA project Majid Ezzati, Alan Lopez, Anthony Rodgers and Steve Vander Hoorn for their support and technical assistance.

Note

1 See preface for an explanation of this term.

References

Abbott RD, Rodriguez BL, Burchfiel CM, Curb JD (1994) Physical activity in older middle-aged men and reduced risk of stroke: The Honolulu Heart Program. *American Journal of Epidemiology*, **139**:881–893.

Ainsworth BE, Haskell WL, Whitt MC et al. (2000) Compendium of physical activities: an update of activity *codes* and MET intensities. *Medicine and Science in Sports and Exercise*, **32**:S498–504.

al-Refaee SA, al-Hazzaa HM (2001) Physical activity profile of Saudi adult males: implications for health. *Saudi Medical Journal*, **22**:784–789.

Albanes D, Blair A, Taylor P (1989) Physical activity and risk of cancer in the NHANES I population. *American Journal of Public Health,* **79**:744–750.

Alemu T, Lindtjorn B (1995) Physical activity, illness and nutritional status among adults in a rural Ethiopian community. *International Journal of Epidemiology*, **24**:977–983.

American College of Sports Medicine (1995) ACSM position stand on osteoporosis and exercise. *Medicine and Science in Sports and Exercise*, **27**:i–vii.

Andrade E, Matsudo V, Andrade D, Araujo T, Oliveira L, Braggion GRV (2001) *Level of physical activity in adults, including and excluding walking, according to the knowledge of Agita Sâo Paulo Program*. American College of Sports Medicine Scientific Conference, St Louis, MO.

Arai Y, Hisamichi S (1998) Self-reported exercise frequency and personality: a population-based study in Japan. *Perceptual and Motor Skills*, **87**:1371–1375.

Arciero PJ, Vukovich MD, Holloszy JO, Racette SB, Kohrt WM (1999) Comparison of short-term diet and exercise on insulin action in individuals with abnormal glucose tolerance. *Journal of Applied Physiology*, **86**: 1930–1935.

Armstrong TP, Bauman A, Davies J (2000) *Physical activity patterns of Australian adults—results of the 1999 National Physical Activity survey*. Australian Institute of Health and Welfare, Canberra.

Arroll B, Beaglehole R (1992) Does physical activity lower blood pressure? A critical review of the clinical trials. *Journal of Clinical Epidemiology*, **45**:419–428.

Aspray TJ, Mugusi F, Rashid S et al. (2000) Rural and urban differences in diabetes prevalence in Tanzania: the role of obesity, physical inactivity and urban living. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **94**:637–644.

Baan CA, Stolk RP, Grobbee DE, Witteman JC, Feskens EJ (1999) Physical activity in elderly subjects with impaired glucose tolerance and newly diagnosed diabetes mellitus. *American Journal of Epidemiology*, **149**:219–227.

Ballard-Barbash R, Schatzkin A, Taylor P, Kahle L (1990) Association of change in body mass with breast cancer. *Cancer Research*, **50**:2152–2155.

Bashir SA, Duffy SW (1997) The correction of risk estimates for measurement error. *Annals of Epidemiology*, **7**:154–164.

Bell ACG (2001) Weight gain and its predictors in Chinese adults. *International Journal of Obesity and Related Metabolic Disorders*, **25**:1079–1086.

Berlin JA, Colditz G (1990) A meta-analysis of physical activity in the prevention of coronary heart disease. *American Journal of Epidemiology*, **132**: 612–628.

Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK (1994) Physical exercise and reduced risk of breast cancer in young women. *Journal of the National Cancer Institute*, **86**:1403–1408.

Bieber E, Barnes R (2001) Breast cancer and HRT—what are the data? *International Journal of Fertility and Women's Medicine*, **46**:73–78.

Bijnen F, Caspersen C, Feskens E, Saris W, Mosterd W, Kromhout D (1998) Physical activity and 10-year mortality from cardiovascular diseases and all causes. The Zutphen Elderly Study. *Archives of Internal Medicine*, **158**:1499–1505.

Blair S, Kampert J, Kohl H et al. (1996) Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *Journal of American Medical Association*, **276**:205–210.

Blair S, Kohl H, Barlow C, Paffenbarger RS Jr, Gibbons L, Macera C (1995) Changes in physical fitness and all-cause mortality. *Journal of American Medical Association*, **273**:1093–1098.

Blair SN, Cheng Y, Holder JS (2001) Is physical activity or physical fitness more important in defining health benefits? *Medicine and Science in Sports and Exercise*, **33**:S379–399.

Blair SN, Jackson AS (2001) Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Medicine and Science in Sports and Exercise*, **33**:762–764.

Blair SN, Kohl HW, Gordon NF, Paffenbarger RS Jr (1992) How much physical activity is good for health? *Annual Review of Public Health*, **13**:99–126.

Blair SN, Kohl HW, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW (1989) Physical fitness and all-cause mortality. A prospective study of healthy men and women. *Journal of American Medical Association*, **262**:2395–2401.

Bouchard C (2001) Physical activity and health: introduction to the dose–response symposium. *Medicine and Science in Sports and Exercise*, **33**:347–350.

Breslow RA, Ballard-Barbash R, Munoz K, Graubard BI (2001) Long-term recreational physical activity and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up study. *Cancer Epidemiology, Biomarkers and Prevention*, **10**:805–808.

Brill P, Macera C, Davis D, Blair S, Gordon N (2000) Muscular strength and physical function. *Medicine and Science in Sports and Exercise*, **32**:412–416.

Brownson R, Chang J, Davis J, Smith C (1991) Physical activity on the job and cancer in Missouri. *American Journal of Public Health*, **81**:639–642.

Brownson RC, Zahm SH, Chang JC, Blair A (1989) Occupational risk of colon cancer. An analysis by anatomic subsite. *American Journal of Epidemiology*, **130**:675–687.

Bull FC, Milligan R, Rosenberg M, MacGowan H (2000) *Physical activity levels of Western Australian adults, 1999*. The Health Department of Western Australia and the Ministry of Sport and Recreation, Perth, Western Australia. (Available at http://www.ausport.gov.au/fulltext/2001/wa/PActivity.pdf).

Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW Jr (1998) Occupation and breast cancer mortality in a prospective cohort of US women. *American Journal of Epidemiology*, **148**:191–197.

Carpenter CL, Ross RK, Paganini-Hill A, Bernstein L (1999) Lifetime exercise activity and breast cancer risk among post-menopausal women. *British Journal of Cancer*, **80**:1852–1858.

Caspersen CJ, Stephens T (1994) The demography of physical activity. In: *Physical activity, fitness and health*. Bouchard C, Shepard R, Stephens T, eds. Human Kinetics, Champaign, IL.

CDC (1998) *Behavioral risk factor surveillance system questionnaire*. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/brfss/questionnaires/pdf-ques/98brfss.pdf.

Cerhan JR, Chiu BC-H, Wallace RB et al. (1998) Physical activity, physical function, and the risk of breast cancer in a prospective study among elderly women. *Journals of Gerontology,* **53A**:M351–356.

Chen CL, White E, Malone KE, Daling JR (1997) Leisure-time physical activity in relation to breast cancer among young women (Washington, United States). *Cancer Causes and Control* **8**:77–84.

Chockalingam A (2000) Let's not make the same mistakes. *The Lancet*, **356**:S9.

Clemmensen IH (1998) *Physical activity and cancer.* [Dissertation.] University of Copenhagen, Denmark.

Cockerham WC, Sneed C (2001) *Reanalysis of data from the Russian Longitudinal Monitoring Study Survey 6*. Department of Sociology, University of Alabama at Birmingham, AL (unpublished). Data set available from the University of North Carolina http://www.cpc.unc.edu/rlms/.

Colditz G, Cannuscio C, Frazier A (1997) Physical activity and reduced risk of colon cancer: implications for prevention. *Cancer Causes and Control*, **8**: 649–667.

Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative re-analysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *The Lancet*, **350**:1047–1059.

Coogan PF, Newcomb PA, Clapp RW, Trentham-Dietz A, Baron JA, Longnecker MP (1997) Physical activity in usual occupation and risk of breast cancer (United States). *Cancer Causes and Control*, **8**:626–631.

Coogan PF, Aschengrau A (1999) Occupational physical activity and breast cancer risk in the upper Cape Cod cancer incidence study. *American Journal of Industrial Medicine,* **36**:279–285.

Cortez R, Jacoby ER, Alarcrón G (2002) Determinantes de la obesidad y el sobrepeso en el Perú [Determinants of obesity and overweight in Peru]. In: *Salud, equidad y pobreza en el Perú: teoría y nuevas evidencias [Health, equity and poverty in Perú: theory and new evidence]*. Cortez R, ed. Centro de Investigación de la Universidad del Pácifico, Lima.

Craig C. (2001) *Data from the 1998 physical activity monitor*. Unpublished document available at http://www.cflri.ca.

Craig CL, Marshall AL, Sjöström M et al. (2003) International physical activity questionnaire: 12-country reliability and validity. *Medicine and Science in Sports and Exercise,* **35**:1381–1395.

Datafohla (1997) *Pesquisa de prática de atividades físicas no Brasil. [Research on physical activity practices in Brazil]*. Relatório Datafolha, Brasil. Available at http://www1.folha.uol.com.br/folha/datafolha.

Dela F, Handberg A, Mikines K, Vinten J, Galbo H (1993) GLUT 4 and insulin receptor binding and kinase activity in trained human muscle. *Journal Physiology London*, **469**:615–624.

Department of Transport Local Government and the Regions (2002) *UK National Travel survey.* The Stationery Office, London.

Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine*, **346**:393–403.

Dishman RK, Buckworth J (1996) Increasing physical activity: a quantitative synthesis. *Medicine and Science in Sports and Exercise*, **28**:706–719.

Donahue RP, Abbott RD, Reed DM, Yano K (1988) Physical activity and coronary heart disease in middle-aged and elderly men: the Honolulu Heart Program. *American Journal of Public Health*, **78**:683–685.

Dorgan JF, Brown C, Barrett M et al. (1994) Physical activity and risk of breast cancer in the Framingham Heart study. *American Journal of Epidemiology*, **139**:662–669.

Dosemeci M, Hayes RB, Vetter R et al. (1993) Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. *Cancer Causes and Control*, **4**:313–321.

Dowse GK, Zimmet PZ, Gareeboo H et al. (1991) Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. *Diabetes Care*, **14**:271–282.

Drinkwater B (1994) 1994 C. H. McCloy research lecture: does physical activity play a role in preventing osteoporosis. *Research Quarterly for Exercise and Sport*, **65**:197–206.

Du S, Lu B, Zhai F, Popkin BM (2002) The nutrition transition in China: a new stage of the Chinese diet. In: *Nutrition transition: diet and disease in the developing world.* Caballero B, Popkin BM, eds. Academic Press, San Diego, CA.

Duncan BB, Schmidt MI, Achutti AC, Polanczyk CA, Benia LR, Maia AA (1993) Socioeconomic distribution of noncommunicable disease risk factors in urban Brazil: the case of Porto Alegre. *Bulletin of the Pan American Health Organization*, **27**:337–349.

Dunn AL, Trivedi MH, O'Neal HA (2001) Physical activity dose–response effects on outcomes of depression and anxiety. *Medicine and Science in Sports and Exercise*, **33**:S587–597.

Durstine J, Haskell W (1994) Effects of exercise training on plasma lipids and lipoproteins. *Exercise and Sport Sciences Reviews*, **22**:477–521.

Eaton CB (1992) Relation of physical activity and cardiovascular fitness to coronary heart disease, Part I: a meta-analysis of the independent relation of physical activity and coronary heart disease. *Journal of the American Board Family Practice*, **5**:31–42.

Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS (1988) Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up study. *New England Journal of Medicine*, **319**:1379–1384.

Ellekjaer H, Holmen J, Ellekjaer E, Vatten L (2000) Physical activity and stroke mortality in women. Ten-year follow-up of the Nord-Trondelag health survey, 1984–1986. *Stroke*, **31**:14–18.

Evans J, Roberts G (1987) Physical competence and the development of children's peer relations. *Quest*, **39**:23–25.

Evenson K, Rosamond W, Cai J et al. (1999) Physical activity and ischaemic stroke risk. The Atherosclerosis Risk in Communities study. *Stroke*, **30**:1333–1339.

Ezenwaka CE, Akanji AO, Akanji BO, Unwin NC, Adejuwon CA (1997) The prevalence of insulin resistance and other cardiovascular disease risk factors in healthy elderly southwestern Nigerians. *Atherosclerosis*, **128**:201–211.

Fagard R, Tipton C (1994) Physical activity, fitness and hypertension. In: *Physical activity, fitness and health*. Bouchard C, Shephard R, Stephens T, eds. Human Kinetics, Champaign, IL.

Federal Highway Administration Research and Technical Support Center (1997) *Nationwide Personal Transportation survey.* U.S. Department of Transportation, Washington, DC. Available at http://www-cta.orn/gov/npts.

Fioretti F, Tavani A, Bosetti C et al. (1999) Risk factors for breast cancer in nulliparous women. *British Journal of Cancer*, **79**:1923–1928.

Folsom AR, Arnett DK, Hutchinson RG, Liao F, Clegg LX, Cooper LS (1997) Physical activity and incidence of coronary heart disease in middle-aged women and men. *Medicine and Science in Sports and Exercise*, **29**:901–909.

Folsom AR, Caspersen CJ, Taylor HL et al. (1985) Leisure time physical activity and its relationship to coronary risk factors in a population-based sample. The Minnesota Heart Survey. *American Journal of Epidemiology*, **121**:570–579.

Folsom AR, Kushi LH, Hong CP (2000) Physical activity and incident diabetes mellitus in postmenopausal women. *American Journal of Public Health*, **90**:134–138.

Forrest KY, Bunker CH, Kriska AM, Ukolif A, Huston SL, Markovic N (2001) Physical activity and cardiovascular risk factors in a developing population. *Medicine and Science in Sports and Exercise*, **33**:1598–1604.

Fraser G, Pearce N (1993) Occupational physical activity and risk of cancer of the colon and rectum in New Zealand males. *Cancer Causes and Control,* **4**:45–50.

Fraser G, Shavlik D (1997) Risk factors, lifetime risk, and age at onset of breast cancer. *Annals of Epidemiology,* **7**:375–382.

Friedenreich CM, Courneya KS, Bryant HE (2001) Relation between intensity of physical activity and breast cancer risk reduction. *Medicine and Science in Sports and Exercise,* **33**:1538–1545.

Friedenreich CM, Rohan TE (1995) Physical activity and risk of breast cancer. *European Journal of Cancer Prevention*, **4**:145–151.

Friedenreich CM, Thune I (2001) A review of physical activity and prostate cancer risk. *Cancer Causes and Control*, **12**:461–475.

Frisch RE, Wyshak G, Witschi J, Albright N, Albright T, Schiff I (1987) Lower lifetime occurrence of breast cancer and cancers of the reproductive system among former college athletes. *International Journal of Fertility*, **32**:217–225.

Fulton-Kehoe D, Hamman RF, Baxter J, Marshall J (2001) A case-control study of physical activity and non-insulin dependent diabetes mellitus (NIDDM). The San Luis Valley Diabetes study. *Annals of Epidemiology*, **11**:320–327.

Gammon MD, Schoenberg JB, Britton JA et al. (1998) Recreational physical activity and breast cancer risk among women under age 45 years. *American Journal of Epidemiology*, **147**:273–280.

Garabrant GH, Peters JM, Mack TM, Bernstein L (1984) Job activity and colon cancer risk. *American Journal of Epidemiology*, **119**:1005–1014.

Garcia-Palmieri MR, Costas RJ, Cruz-Vidal M, Sorlie PD, Havlik RJ (1982) Increased physical activity: a protective factor against heart attacks in Puerto Rico. *American Journal of Cardiology*, **50**:749–755.

Gerhardsson M, Floderus B, Norell SE (1988) Physical activity and colon cancer risk. *International Journal of Epidemiology*, **17**:743–746.

Gerhardsson M, Norell SE, Kiviranta H, Pedersen NL, Ahlbom A (1986) Sedentary jobs and colon cancer. *American Journal of Epidemiology*, **123**: 775–780.

Gerhardsson de Verdier M, Steineck G, Hagman U, Rieger A, Norell SE (1990) Physical activity and colon cancer: a case-referent study in Stockholm. *International Journal of Cancer*, **46**:985–989.

Gillespie ND, McMurdo M (1998) Falls in old age: inevitable or preventable? *Scottish Medical Journal*, **43**:101–103.

Gilliland F, Yu-Fen L, Baumgartner K, Crumley D, Samet J (2001) Physical activity and breast cancer risk in Hispanic and non-Hispanic white women. *American Journal of Epidemiology*, **154**:442–450.

Gillum R, Mussolino M, Ingram D (1996) Physical activity and stroke incidence in women and men. *American Journal of Epidemiology*, **143**:860–869.

Giovannucci E, Ascherio A, Rimm EB, Colditz G, Stampfer MJ, Willett WC (1995) Physical activity, obesity, and risk for colon cancer and adenoma in men. *Annals of Internal Medicine*, **122**:327–334.

Giovannucci E, Leitzmann M, Spiegelman D et al. (1998) A prospective study of physical activity and prostate cancer in male health professionals. *Cancer Research*, **58**:5117–5122.

Giovannucci E, Pollak M, Platz E et al. (2000) A prospective study of plasma insulin-like growth factor-I and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiology, Biomarkers and Prevention*, **9**:345–349.

Glenister D (1996) Exercise and mental health: a review. *Journal of the Royal Society of Health*, **116**:7–13.

Gregg E, Pereira M, Caspersen CJ (2000) Physical activity, falls, and fractures among older adults: a review of the epidemiologic evidence. *Journal of the American Geriatrics Society*, **48**:883–893.

Greenland S. (1987) Quantitative methods in the review of epidemiologic literature. *Epidemiologic Reviews*, **9**:1–30.

Grisso JA, Kelsey JL, O'Brien LA et al. (1997) Risk factors for hip fracture in men. hip fracture study group. *American Journal of Epidemiology*, **145**: 786–793.

Grundy SM, Blackburn G, Higgins M, Lauer R, Perri MG, Ryan D (1999) Physical activity in the prevention and treatment of obesity and its comorbidities: evidence report of independent panel to assess the role of physical activity in the treatment of obesity and its comorbidities. *Medicine and Science in Sports and Exercise*, **31**:1493–1500.

Gupta R, Gupta HG, Keswani P, Sharma A, Gupta VP, Gupta KD (1994) Coronary heart disease and coronary risk factor prevalence in rural Rajasthan. *Journal of Applied Physiology International*, **42**:24–26.

Gurwitz JH, Field TS, Glynn RJ et al. (1994) Risk factors for non-insulin-dependent diabetes mellitus requiring treatment in the elderly. *Journal of the American Geriatrics Society*, **42**:1235–1240.

Gutin B, Kasper M (1992) Can vigorous exercise play a role in osteoporosis prevention? A review. *Osteoporosis International*, **2**:55–69.

Haapanen N, Miilunpalo S, Vuori I, Oja P, Pasanen M (1997) Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. *International Journal of Epidemiology*, **26**:739–747.

Hagberg J, Montain S, Martin WI, Ehsani A (1989) Effect of exercise training in 60- to 69-year-old persons with essential hypertension. *American Journal of Cardiology*, **64**:348–353.

Hahn R, Teutsch S, Rothberg R, Marks J (1990) Excess deaths from nine chronic diseases in the United States, 1986. *Journal of American Medical Association*, **264**:2654–2659.

Ham S (2001a) *Unpublished analysis of National Physical Activity Survey (NPAS) 1999-2000 data*. Available from author at Epidemiology Section, Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Atlanta, GA.

Ham S (2001b) *Unpublished analysis of the 1995 U.S. National Personal Transportation Survey data*. Details available from author at Epidemiology Section, Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Atlanta, GA. Data set available at http://www-cta.ornl.gov/npts/1995/doc/index.shtml.

Ham S (2001c) *Unpublished analysis of the China Health and Nutrition survey*. Details available from author at Epidemiology Section, Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Atlanta, GA. Data set available at http://www.cpc.unc.edu/.

Hardman A, Stensel D (2003) *Physical activity and health: the evidence explained*. Routledge, London.

Harmsen P, Rosengren A, Tsipogianni A, Wilhelmsen L (1990) Risk factors for stroke in middle-aged men in Goteborg, Sweden. *Stroke*, **21**:223–229.

Hassmen P, Koivula N, Uutela A (2000) Physical exercise and psychological well-being: a population study in Finland. *Preventive Medicine*, **30**:17–25.

Hein HO, Suadicani P, Gyntelberg F (1992) Physical fitness or physical activity as a predictor of ischaemic heart disease? A 17-year follow-up in the Copenhagen Male study. *Journal of Internal Medicine*, **232**:471–479.

Helmrich SP, Ragland DR, Paffenbarger RS Jr (1994) Prevention of non-insulin-dependent diabetes mellitus with physical activity. *Medicine and Science in Sports and Exercise,* **26**:824–830.

Henderson B, Ross R, Judd H, Krailo M, Pike M (1985) Do regular ovulatory cycles increase breast cancer risk? *Cancer*, **56**:1206–1208.

Herman WH, Ali MA, Aubert RE et al. (1995) Diabetes mellitus in Egypt: risk factors and prevalence. *Diabetic Medicine*, **12**:1126–1131.

Hill J, Melanson E (1999) Overview of the determinants of overweight and obesity: current evidence and research issues. *Medicine and Science in Sports and Exercise*, **33**:S515–521.

Hillary Commission (1998) *Fitness and leisure report: a discussion paper by the Physical Activity Taskforce*. Hillary Commission for Sport, Wellington, New Zealand. Accessed in 2001 from: www.hillarysport.org.nz. Details now available at http://www.sparc.org.nz.

Hillsdon M, Cavill N, Nanchahal K, Diamond A, White IR (2001) National level promotion of physical activity: results from England's ACTIVE for LIFE Campaign. *Journal of Epidemiology and Community Health*, **55**: 755–761.

Hillsdon M, Thorogood M, Anstiss T, Morris J (1995) Randomised controlled trials of physical activity promotion in free living populations: a review. *Journal of Epidemiology and Community Health*, **49**:448–453.

Hirose K, Tajima K, Hamajima N et al. (1995) A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Japanese Journal of Cancer Research*, **86**:146–154.

Hong Y, Bots ML, Pan X et al. (1994) Physical activity and cardiovascular risk factors in rural Shanghai, China. *International Journal of Epidemiology*, **23**:1154–1158.

Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WA, Rimm EB (2001) Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Archives of Internal Medicine*, **161**:1542–1548.

Hu FB, Sigal RJ, Rich-Edwards JW et al. (1999) Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *Journal of American Medical Association*, **282**:1433–1439.

Hu FB, Stampfer MJ, Colditz G et al. (2000) Physical activity and risk of stroke in women. *Journal of American Medical Association*, **283**:2961–2967.

Hu G, Pekkarinen H, Hanninen O, Yu Z, Guo Z, Tian H (2002) Commuting, leisure-time physical activity, and cardiovascular risk factors in China. *Medicine and Science in Sports and Exercise,* **34**:234–238.

Hu YH, Nagata C, Shimizu H, Kaneda N, Kashiki Y (1997) Association of body mass index, physical activity, and reproductive histories with breast cancer: a

case-control study in Gifu, Japan. *Breast Cancer Research and Treatment*, **43**:65–72.

Huang Y, Macera C, Blair S, Brill P, Kohl H, Kronenfeld J (1998) Physical fitness, physical activity, and functional limitation in adults aged 40 and older. *Medicine and Science in Sports and Exercise*, **30**:1430–1435.

Hypertension Study Group (2001) Prevalence, awareness, treatment and control of hypertension among elderly in Bangladesh and India: a Multicentre study. *Bulletin of the World Health Organization,* **79**:490-500.

Institute of European Food Studies (2001) *A Pan-EU survey on consumer attitudes to physical activity, body-weight and health—a report by the Institute of European Food Studies*. Trinity College, Dublin.

Instituto Gallup De La Argentina (2001) *Results from a national survey of physical activity in Argentine*. Unpublished document available at http://www.gallup-international.com/scripts/member.asp?id=2.

IARC (2002) *Weight control and physical activity*. IARC Handbook of Cancer Prevention (Vol. 6). International Agency for Research on Cancer Press, Lyon.

Ivy J, Zderic T, Fogt D (1999) Prevention and treatment of non-insulin-dependent diabetes mellitus. In: *Exercise and sport sciences reviews*. Holloszy J, ed. Lippincott Williams and Wilkins, Philadelphia, PA.

Iwai N, Yoshiike N, Saitoh S, Nose T, Kushiro T, Tanaka H (2000) Leisure-time physical activity and related lifestyle characteristics among middle-aged Japanese. Japan Lifestyle Monitoring Study Group. *Journal of Epidemiology*, **10**:226–233.

Jacobs DR, Ainsworth BE, Hartman TJ, Leon AS (1993) A simultaneous evaluation of 10 commonly used physical activity questionnaires. *Medicine and Science in Sports and Exercise*, **25**:81–91.

Jadue L, Vega J, Escobar MC et al. (1999) Risk factors for non communicable diseases: methods and global results of the CARMEN program basal survey. *Revista Medica de Chile*, **127**:1004–1013.

James SA, Jamjoum L, Raghunathan TE, Strogatz DS, Furth ED, Khazanie PG (1998) Physical activity and NIDDM in African-Americans. The Pitt County study. *Diabetes Care*, **21**:555–562.

Johansson S, Rosengren A, Tsipogianni A, Ulvenstam G, Wiklund I, Wilhelmsen L (1988) Physical inactivity as a risk factor for primary and secondary coronary events in Goteborg, Sweden. *European Heart Journal*, **9**:S8–19.

Kannel WB, Belanger A, D'Agostino R, Israel I (1986) Physical activity and physical demand on the job and risk of cardiovascular disease and death: the Framingham study. *American Heart Journal*, **112**:820–825.

Kaprio J, Kujala UM, Koskenvuo M, Sarna S (2000) Physical activity and other risk factors in male twin-pairs discordant for coronary heart disease. *Atherosclerosis*, **150**:193–200.

Kato I, Tominaga S, Ikari A (1990) A case-control study of male colorectal cancer in Aichi Prefecture, Japan: with special reference to occupational activity level, drinking habits and family history. *Japanese Journal of Cancer Research*, **81**:115–121.

Katzmarzyk PT, Leonard WR, Stephen MA, Berti PR, Ross AG (1996) Differences between observed and predicted energy costs at rest and during exercise in three subsistence-level populations. *American Journal of Physical Anthropology*, **99**:537–545.

Kelley D, Goodpaster B (2001) Effects of exercise on glucose homeostasis in type 2 diabetes mellitus. *Medicine and Science in Sports and Exercise*, **33**: S495–501.

Kelley G, McClellan P (1994) Antihypertensive effects of aerobic exercise: a brief meta-analytic review of randomized controlled trials. *American Journal of Hypertension*, **7**:115–119.

Kesaniemi YA, Danforth EJ, Jensen MD, Kopelman PG, Lefebvre P, Reeder BA (2001) Dose–response issues concerning physical activity and health: an evidence-based symposium. *Medicine and Science in Sports and Exercise*, **33**:S351–358.

Kiely DK, Wolf PA, Cupples LA, Beiser AS, Kannel WB (1994) Physical activity and stroke risk—the Framingham study. *American Journal of Epidemiology*, **140**:608–620.

Kohl HW (2001) Physical activity and cardiovascular disease: evidence for a dose response. *Medicine and Science in Sports and Exercise*, **33**:S472–483.

Kokkinos P, Fernhall B (1999) Physical activity and high density lipoprotein cholesterol levels: what is the relationship? *Sports Medicine*, **28**:307–314.

Kono S, Handa K, Hayabuchi H et al. (1999) Obesity, weight gain and risk of colon adenomas in Japanese men. *Japanese Journal of Cancer Research*, **90**:805–811.

Kramsch D, Aspen A, Abramowitz B, Kreimendahl T, Hood WJ (1981) Reduction of coronary atherosclerosis by moderate conditioning exercise in monkeys on an atherogenic diet. *New England Journal of Medicine*, **305**: 1483–1489.

Kriska AM, Caspersen CJ (1997) Introduction to a collection of physical activity questionnaires. *Medicine and Science in Sports and Exercise*, **29**:S5–9.

Kriska AM, LaPorte RE, Pettitt DJ et al. (1993) The association of physical activity with obesity, fat distribution and glucose intolerance in Pima Indians. *Diabetologia*, **36**:863–869.

Kujala U, Kaprio J, Kannus P, Sarna S, Koshenvuo M (2000) Physical activity and osteoporotic hip fracture risk in men. *Archives of Internal Medicine*, **160**:705–708.

Kujala U, Kaprio J, Sarna S (1994) Osteoarthritis of weight bearing joints of lower limbs in former elite male athletes. *British Medical Journal*, **308**: 231–234.

Kujala UM, Kettunen J, Paananen H et al. (1995) Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. *Arthritis and Rheumatology*, **38**:539–46I.

La Vecchia C, Brinton L, McTiernan A (2001) Menopause, hormone replacement therapy and cancer. *Maturitas*, **39**:97–115.

LaCroix AZ, Leveille SG, Hecht JA, Grothaus LC, Wagner EH (1996) Does walking decrease the risk of cardiovascular disease hospitalizations and death in older adults? *Journal of American Geriatrics Society*, **44**:113–120.

Laforge RG, Rossi JS, Prochaska JO, Velicer WF, Levesque DA, McHorney CA (1999) Stage of regular exercise and health-related quality of life. *Preventive Medicine*, **28**:349–360.

Lakka TA, Venäläinen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT (1994) Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. *New England Journal of Medicine*, **330**:1549–1554.

Lane N (1995) Exercise: a cause of osteoarthritis. *Journal of Rheumatology*, **43**:S3–6.

Lanyon L (1993) Osteocytes, strain detection, bone modelling and remodelling. *Calcified Tissue International*, **53**:S102–107.

Latikka P, Pukkala E, Vihko V (1998) Relationship between the risk of breast cancer and physical activity. *Sports Medicine*, **26**:133–143.

Laughlin M (1994) Effects of exercise training on coronary circulation: introduction. *Medicine and Science in Sports and Exercise*, **26**:1226–1229

Lee I-M, Skerrett P-J (2001) Physical activity and all-cause mortality: what is the dose–response relation? *Medicine and Science in Sports and Exercise*, **33**:S459–471.

Lee I-M, Hennekens C, Berger K, Buring J, Manson J (1999) Exercise and risk of stroke in male physicians. *Stroke*, **30**:1–6.

Lee I-M, Manson JE, Ajani U, Paffenbarger RS Jr, Hennekens CH, Buring JE (1997) Physical activity and risk of colon cancer: the Physicians' Health study (United States). *Cancer Causes and Control*, **8**:568–574.

Lee I-M, Paffenbarger RS Jr (2000) Associations of light, moderate and vigorous intensity physical activity with longevity. *American Journal of Epidemiology*, **151**:293–299.

Lee I-M, Paffenbarger RS Jr, Hsieh C (1991) Physical activity and risk of developing colorectal cancer among college alumni. *Journal of the National Cancer Institute*, **83**:1324–1329.

Lee I-M, Rexrode KM, Cook NR, Manson JE, Buring JE (2001a) Physical activity and coronary heart disease in women: is "no pain, no gain" passé? *Journal of the American Medical Association*, **285**:1447–1454.

Lee I-M, Rexrode KM, Cook NR, Hennekens CH, Buring JE (2001b) Physical activity and breast cancer risk: the Women's Health study. *Cancer Causes Control*, **12**:137–145.

Lee I-M, Sesso HD, Paffenbarger RS Jr (2000) Physical activity and coronary heart disease risk in men: does the duration of exercise episodes predict risk? *Circulation*, **102**:981–986.

Leenders NY, Sherman WM, Nagaraja HN, Kien CL (2001) Evaluation of methods to assess physical activity in free-living conditions. *Medicine and Science in Sports and Exercise*, **33**:1233–1240.

Leon AS, Connett J, Jacobs D, Rauramaa R (1987) Leisure-time physical activity levels and risk of coronary heart disease and death. The Multiple Risk Factor Intervention Trial. *Journal of American Medical Association*, **258**:2388–2395.

Leon A (1991) Effects of exercise conditioning on physiological precursors of coronary heart disease. *Journal of Cardiopulmonary Rehabilitation*, **11**:46–57.

Leonetti DL, Fujimoto WY, Wahl PW (1989) Early-life background and the development of non-insulin-dependent diabetes mellitus. *American Journal of Physical Anthropology*, **79**:345–355.

Levi F, Pasche C, Lucchini F, La Vecchia C (1999) Occupational and leisure time physical activity and the risk of breast cancer. *European Journal of Cancer*, **35**:775–778.

Levitt NS, Katzenellenbogen JM, Bradshaw D, Hoffman MN, Bonnici F (1993) The prevalence and identification of risk factors for NIDDM in urban Africans in Cape Town, South Africa. *Diabetes Care*, **16**:601–607.

Levitt NS, Steyn K, Lambert EV et al. (1999) Modifiable risk factors for type 2 diabetes mellitus in a peri-urban community in South Africa. *Diabetic Medicine*, **16**:946–950.

Lie H, Mundal R, Erikssen J (1985) Coronary risk factors and incidence of coronary death in relation to physical fitness. Seven-year follow-up study of middle-aged and elderly men. *European Heart Journal*, **6**:147–157.

Lindsted KD, Tonstad S, Kuzma JW (1991) Self-report of physical activity and patterns of mortality in Seventh-Day Adventist men. *Journal of Clinical Epidemiology*, **44**:355–364.

Liu S, Lee I, Linson P, Ajani U, Buring JE, Hennekens C (2000) A prospective study of physical activity and risk of prostate cancer in US physicians. *International Journal of Epidemiology*, **29**:29–35.

Li Xiang-ru et al. (2001) Status quo and the strategies of the implementation of the national fitness program in urban communities in China [in Chinese]. *Sport Science*, **21**:1–6.

Longnecker MP, Gerhardsson le Verdier M, Frumkin H, Carpenter CL (1995) A case-control study of physical activity in relation to risk of cancer of the right colon and rectum in men. *International Journal of Epidemiology*, **24**:42–50.

Lord S (1995) The effect of a 12 month exercise trial on balance, strength and falls in older women. *Journal of American Geriatrics Society*, **43**: 1198–1206.

Luoto R, Prattala R, Uutela A, Puska P (1998) Impact of unhealthy behaviours on cardiovascular mortality in Finland, 1978–1993. *Preventive Medicine*, **27**:93–100.

Lynch J, Helmrich SP, Lakka TA et al. (1996) Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Archives of Internal Medicine*, **156**:1307–1314.

Lynge E, Thygesen L (1988) Use of surveillance systems for occupational cancer: data from the Danish National system. *International Journal of Epidemiology*, **17**:493–500.

Ma J, Pollak M, Giovannucci E (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3. *Journal of the National Cancer Institute*, **91**:620–625.

MacAuley D, Mc C, Stott G et al. (1998) Levels of physical activity, physical fitness and their relationship in the Northern Ireland Health and Activity Survey. *International Journal of Sports Medicine*, **19**:503–511.

MacAuley D, McCrum EE, Stott G et al. (1996) Physical activity, physical fitness, blood pressure, and fibrinogen in the Northern Ireland health and activity survey. *Journal of Epidemiology and Community Health*, **50**:258–263.

Macera C, Ham S, Jones D, Kimsey D, Ainsworth BE, Neff L (2001) Limitations on the use of a single screening question to measure sedentary behaviour. *American Journal of Public Health*, **91**:2010–2012.

Macera CA, Powell KE (2001) Population attributable risk: implications of physical activity dose. *Medicine and Science in Sports and Exercise*, **33**: S635–639.

MacMahon S, Peto R, Cutler J et al. (1990) Blood pressure, stroke and coronary heart disease. Part I, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *The Lancet*, **335**:765–774.

Manson J, Hu F, Rich-Edwards J et al. (1999) A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *New England Journal of Medicine*, **341**:650–658.

Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH (1992) A prospective study of exercise and incidence of diabetes among US male physicians. *Journal of the American Medical Association*, **268**:63–67.

Manson JE, Rimm EB, Stampfer MJ et al. (1991) Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *The Lancet*, **338**: 774–778.

Marceau M, Kouame N, Lacourciere Y, Cleroux J (1993) Effects of different training intensities on 24-hour blood pressure in hypertensive subjects. *Circulation*, **88**:2803–2811.

Marcus PM, Newcomb PA, Storer BE (1994) Early adulthood physical activity and colon cancer risk among Wisconsin women. *Cancer Epidemiology, Biomarkers and Prevention*, **3**:641–644.

Marcus PM, Newman B, Moorman PG et al. (1999) Physical activity at age 12 and adult breast cancer risk (United States). *Cancer Causes and Control*, **10**:293–302.

Markowitz S, Morabia A, Garibaldi K, Wynder E (1992) Effect of occupational and recreational activity on the risk of colorectal cancer among males: a case-control study. *International Journal of Epidemiology*, **21**:1057–1062.

Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA (1997) Leisure-time physical activity, body size, and colon cancer in

women. Nurses' Health Study Research group. *Journal of the National Cancer Institute*, **89**:948–955.

Martinez-Gonzalez MA, Martinez JA, Hu FB, Gibney MJ, Kearney J (1999) Physical inactivity, sedentary lifestyle and obesity in the European Union. *International Journal of Obesity and Related Metabolic Disorders*, **23**: 1192–1201.

Matsusaki M, Ikeda M, Tashiro E, Koga M, Miura S, Ideishi M (1992) Influence of workload on the antihypertensive effect of exercise. *Clinical and Experimental Pharmacology and Physiology*, **19**:471–479.

Matthews CE, Shu XO, Jin F et al. (2001) Lifetime physical activity and breast cancer risk in the Shanghai Breast Cancer Study. *British Journal of Cancer*, **84**:994–1001.

Maxwell K, Tucker L (1992) Effects of weight training on the emotional well-being and body image of females: predictors of greatest benefit. *American Journal of Health Promotion*, **6**:338–344.

McCormack G, Milligan R, Giles-Corti B, Clarkson JP (2003) Physical activity levels in Western Australian Adults 2002: results from the adult physical activity survey and pedometer study. Western Australian Government, Perth, Western Australia.

McKeown-Eyssen G (1994) Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiology, Biomarkers and Prevention*, **3**:687–695.

McMurray RG, Ainsworth BE, Harrell JS, Griggs TR, Williams OD (1998) Is physical activity or aerobic power more influential on reducing cardiovascular disease risk factors? *Medicine and Science in Sports and Exercise*, **30**:1521–1529.

McTiernan A, Stanford JL, Weiss NS, Daling JR, Voigt LF (1996) Occurrence of breast cancer in relation to recreational exercise in women age 50–64 years. *Epidemiology*, **7**:598–604.

McTiernan A, Ulrich C, Slate S, Potter J (1998) Physical activity and cancer etiology: associations and mechanisms. *Cancer Causes and Control*, **9**: 487–509.

Menotti A, Seccareccia F (1985) Physical activity at work and job responsibility as risk factors for fatal coronary heart disease and other causes of death. *Journal of Epidemiology and Community Health*, **39**:325–329.

Mensink GBM, Ziese T, Kok FJ (1999) Benefits of leisure-time physical activity on the cardiovascular risk profile at older age. *International Journal of Epidemiology*, **28**:659–666.

Mezzetti M, La-Vecchia C, Decarli A, Boyle P, Talamini R, Franceschi S (1998) Population attributable risk for breast cancer: diet, nutrition, and physical exercise. *Journal of the National Cancer Institute*, **90**:389–394.

Misra A, Sharma R, Pandey RM, Khanna N (2001) Adverse profile of dietary nutrients, anthropometry and lipids in urban slum dwellers of northern India. *European Journal of Clinical Nutrition*, **9**:727–734.

Mittendorf R, Longnecker MP, Newcomb PA et al. (1995) Strenuous physical activity in young adulthood and risk of breast cancer (United States). *Cancer Causes and Control,* **6**:347–353.

Moore DB, Folsom AR, Mink PJ, Hong CP, Anderson KE, Kushi LH (2000) Physical activity and incidence of postmenopausal breast cancer. *Epidemiology*, **11**:292–296.

Moore S (1994) Physical activity, fitness and atherosclerosis. In: *Physical activity, fitness and health: international proceedings and consensus statement*. Bouchard C, Shepherd R, Stephens T, eds. Human Kinetics, Champaign, IL.

Moradi T, Adami HO, Bergstrom R et al. (1999) Occupational physical activity and risk for breast cancer in a nationwide cohort study in Sweden. *Cancer Causes and Control*, **10**:423–430.

Moradi T, Nyren O, Zack M, Magnusson C, Persson I, Adami HO (2000) Breast cancer risk and lifetime leisure-time and occupational physical activity (Sweden). *Cancer Causes and Control*, **11**:523–531.

Morans R, Mohai P (1991) Leisure resources, recreation activity and the quality of life. In: *Benefits of leisure*. Driver B, Brown P, Peterson G, eds. Venture Publishing, Philadelphia, PA.

Moreau K, Degarmo R, Langley J et al. (2001) Increasing daily walking lowers blood pressure in postmenopausal women. *Medicine and Science in Sports and Exercise*, **33**:1825–1831.

Morris JN, Clayton DG, Everitt MG, Semmence AM, Burgess EH (1990) Exercise in leisure time: coronary attack and death rates. *British Heart Journal*, **63**:325–334.

Morris JN, Everitt MG, Pollard R, Chave SP, Semmence AM (1980) Vigorous exercise in leisure-time: protection against coronary heart disease. *The Lancet*, **2**:1207–1210.

Mundal R, Erikssen J, Rodahl K (1987) Assessment of physical activity by questionnaire and personal interview with particular reference to fitness and coronary mortality. *European Journal of Applied Physiology and Occupational Physiology*, **56**:245–252.

Murray CJL, Lopez AD, eds. (1996a) Quantifying the burden of disease and injury attributable to ten major risk factors. In: *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, vol. 1. Murray CJL, Lopez AD, eds. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJL, Lopez AD, eds. (1996b) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, vol. 1. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Neugut A, Terry M, Hocking G, Mosca L, Garbowski G, Forde K (1996) Leisure and occupational physical activity and risk of colorectal adenomatous polyps. *International Journal of Cancer*, **68**:744–748.

North Carolina Population Center (2001a) *Russian Longitudinal Monitoring survey*. Unpublished document available at http://www.cpc.unc.edu/rlms/.

North Carolina Population Center (2001b) *China Health and Nutrition survey*. Unpublished document available at http://www.cpc.unc.edu/.

Okada K, Hayashi T, Tsumura K, Suematsu C, Endo G, Fujii S (2000) Leisure-time physical activity at weekends and the risk of type 2 diabetes mellitus in Japanese men: the Osaka Health Survey. *Diabetic Medicine*, **17**:53–58.

Paeratakul S, Popkin BM, Keyou G, Adair LS, Stevens J (1998) Changes in diet and physical activity affect the body mass index of Chinese adults. *International Journal of Obesity and Related Metabolic Disorders*, **22**:424–431.

Paffenbarger RS Jr, Hyde RT, Wing AL, Steinmetz CH (1984) A natural history of athleticism and cardiovascular health. *Journal of American Medical Association*, **252**:491–495.

Paffenbarger RS Jr, Kampert JB, Lee I-M, Hyde RT, Leung RW, Wing AL (1994) Changes in physical activity and other lifeway patterns influencing longevity. *Medicine and Science in Sports and Exercise*, **26**:857–865.

Paffenbarger RS Jr, Hyde R, Wing A, Jung D, Kampert J (1993) The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *New England Journal of Medicine*, **328**:538–545.

Paffenbarger RS Jr, Wing AL, Hyde RT (1978) Physical activity as an index of heart attack risk in college alumni. *American Journal of Epidemiology*, **108**:161–175.

Pan XR, Yang WY, Li GW, Liu J (1997) Prevalence of diabetes and its risk factors in China, 1994. National Diabetes Prevention and Control Cooperative Group. *Diabetes Care*, **20**:1664–1669.

Pate RR, Pratt M, Blair SN, Macera C, Bouchard C, Buchner D et al. (1995) Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of American Medical Association*, **273**:402–407.

Pekkanen J, Nissinen A, Marti B, Tuomilehto J, Punsar S, Karvonen MJ (1987) Reduction of premature mortality by high physical activity: a 20-year follow-up of middle-aged Finnish men. *The Lancet*, **1**:1473–1477.

Pereira MA, FitzerGerald SJ, Gregg EW et al. (1997) A collection of physical activity questionnaires for health-related research. *Medicine and Science in Sports and Exercise*, **29**:S1–205.

Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG (1995) Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *British Medical Journal*, **310**:560–564.

Peters RK, Cady LD, Bischoff DP, Bernstein L, Pike MC (1983) Physical fitness and subsequent myocardial infarction in healthy workers. *Journal of American Medical Association*, **249**:3052–3056.

Picavet H, Schouten J (2000) Physical load in daily life and low back problems in the general population—The MORGEN study. *Preventive Medicine*, **31**:506–512.

Pitsillides A, Rawlenson S, Suswillo R, Bourrin S, Zaman G, Lanyon L (1995) Mechanical strain-induced NO production by bone cells: a possible role in adaptive bone (re)modelling. *Journal of the Federation of American Societies for Experimental Biology*, **9**:1614–1622.

Pomerleau J, McKee M, Robertson A et al. (2000) Physical inactivity in the Baltic countries. *Preventive Medicine*, **31**:665–672.

Pomrehn PR, Wallace RB, Burmeister LF (1982) Ischaemic heart disease mortality in Iowa farmers. The influence of life-style. *Journal of American Medical Association*, **248**:1073–1076.

Powell K, Blair S (1994) The public health burdens of sedentary living habits: theoretical but realistic estimates. *Medicine and Science in Sports and Exercise*, **26**:851–856.

Powell KE, Thompson PD, Caspersen CJ, Kendrick JS (1987) Physical activity and the incidence of coronary heart disease. *Annual Review of Public Health*, **8**:253–287.

Pratt M, Macera CA, Blanton C (1999) Levels of physical activity and inactivity in children and adults in the United States: current evidence and research issues. *Medicine and Science in Sports and Exercise*, **31**:S526–533.

Pucher J, Dijkstra L (2000) Making walking and cycling safer: lessons from Europe. *Transportation Quarterly*, **54**:2–33.

Pukkala E, Poskiparta M, Apter D, Vihko V (1993) Life-long physical activity and cancer risk among Finnish female teachers. *European Journal of Cancer Prevention*, **2**:369–376.

Reddy KS, Yusuf S (1998) Emerging epidemic of cardiovascular disease in developing countries. *Circulation*, **97**:596–601.

Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Colditz GA (1999) A prospective study of recreational physical activity and breast cancer risk. *Archives of Internal Medicine*, **159**:2290–2296.

Rockhill B, Willett WC, Hunter DJ et al. (1998) Physical activity and breast cancer risk in a cohort of young women. *Journal of the National Cancer Institute*, **90**:1155–1160.

Rodriguez BL, Curb JD, Burchfiel CM et al. (1994) Physical activity and 23-year incidence of coronary heart disease morbidity and mortality among middle-aged men. The Honolulu Heart Program. *Circulation*, **89**:2540–2544.

Rogers MA, King DS, Hagber JM, Ehsani AA, Holloszy JO (1990) Effect of 10 days of physical inactivity on glucose tolerance in master athletes. *Journal of Applied Physiology*, **68**:1833–1837.

Rosengren A, Wilhelmsen L (1997) Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the primary prevention study in Goteborg. *Annals of Epidemiology*, **7**:69–75.

Sacco R, Gan R, Boden-Albala B et al. (1998) Leisure-time physical activity and ischaemic stroke risk. The Northern Manhattan Stroke Study. *Stroke*, **29**:380–387.

Sallis J, Owen N (1999) *Physical activity and behavioural medicine*. Sage Publications, Thousand Oaks, CA.

Sallis JF, Saelens BE (2000) Assessment of physical activity by self-report: status, limitations, and future directions. *Research Quarterly for Exercise and Sport*, **71**:S1–14.

Salonen JT, Puska P, Tuomilehto J (1982) Physical activity and risk of myocardial infarction, cerebral stroke and death: a longitudinal study in eastern Finland. *American Journal of Epidemiology*, **115**:526–537.

Salonen JT, Slater JS, Tuomilehto J, Rauramaa R (1988) Leisure time and occupational physical activity: risk of death from ischaemic heart disease. *American Journal of Epidemiology*, **127**:87–94.

Seccareccia F, Menotti A (1992) Physical activity, physical fitness and mortality in a sample of middle aged men followed-up 25 years. *Journal of Medicine and Physical Fitness*, **32**:206–213.

Sesso HD, Paffenbarger RS Jr, Lee I-M (1998) Physical activity and breast cancer risk in the College Alumni Health Study (United States). *Cancer Causes and Control*, **9**:433–439.

Sesso HD, Paffenbarger RS Jr, Lee I-M (2000) Physical activity and coronary heart disease in men: The Harvard Alumni Health study. *Circulation*, **102**:975–980.

Severson R, Nomura A, Grove J, Stemmermann G (1989) A prospective analysis of physical activity and cancer. *American Journal of Epidemiology*, **130**: 522–529.

Shaper A, Wannamethee G, Walker M (1994) Physical activity, hypertension and risk of heart attack in men without evidence of ischaemic heart disease. *Journal of Human Hypertension*, **8**:3–10.

Shaper AG, Wannamethee G, Weatherall R (1991) Physical activity and ischaemic heart disease in middle-aged British men. *British Heart Journal*, **66**:384–394.

Sherman SE, D'Agostino RB, Cobb JL, Kannel WB (1994a) Does exercise reduce mortality rates in the elderly? Experience from the Framingham Heart study. *American Heart Journal*, **128**:965–972.

Sherman SE, D'Agostino RB, Cobb JL, Kannel WB (1994b) Physical activity and mortality in women in the Framingham Heart Study. *American Heart Journal*, **128**:879–884.

Sherman SE, D'Agostino RB, Silbershatz H, Kannel WB (1999) Comparison of past versus recent physical activity in the prevention of premature death and coronary artery disease. *American Heart Journal*, **138**:900–907.

Shoff S, Newcomb P, Trentham-Dietz A et al. (2000) Early-life physical activity and postmenopausal breast cancer: effect of body size and weight change. *Cancer, Epidemiology, Biomarkers and Prevention*, **9**:591–595.

Simonsick EM, Lafferty ME, Phillips CL et al. (1993) Risk due to inactivity in physically capable older adults. *American Journal of Public Health*, **83**:1443–1450.

Singh RB, Bajaj S, Niaz MA, Rastogi SS, Moshiri M (1998) Prevalence of type 2 diabetes mellitus and risk of hypertension and coronary artery disease in rural and urban population with low rates of obesity. *International Journal of Cardiology*, **66**:65–72.

Slattery ML, Edwards SL, Boucher KM, Anderson K, Caan BJ (1999) Lifestyle and colon cancer: an assessment of factors associated with risk. *American Journal of Epidemiology*, **150**:869–877.

Slattery ML, Jacobs D (1988) Physical fitness and cardiovascular disease mortality. The US Railroad study. *American Journal of Epidemiology*, **127**:571–580.

Slattery ML, Jacobs D, Nichaman MZ (1989) Leisure time physical activity and coronary heart disease death. The US Railroad study. *Circulation*, **79**:304–311.

Slattery ML, Potter J, Caan B et al. (1997) Energy balance and colon cancer–beyond physical activity. *Cancer Research*, **57**:75–80.

Slattery ML, Schumacher MC, Smith KR, West DW, Abd-Elghany N (1988) Physical activity, diet, and risk of colon cancer in Utah. *American Journal of Epidemiology*, **128**:989–999.

Sobngwi E, Mbanya JN, Unwin et al. (2002) Physical activity and its relationship with obesity, hypertension and diabetes in urban and rural Cameroon. *International Journal of Obesity and Related Metabolic Disorders*, **26**: 1009–1016.

Sobolski J, Kornitzer M, De Backer G et al. (1987) Protection against ischaemic heart disease in the Belgian Physical Fitness Study: physical fitness rather than physical activity? *American Journal of Epidemiology*, **125**:601–610.

Sonstroem R (1984) Exercise and self-esteem. *Sport Science Review*, **12**:123–155.

Sparling PB, Noakes TD, Steyn K et al. (1994) Level of physical activity and CHD risk factors in black South African men. *Medicine and Science in Sports and Exercise*, **26**:896–902.

Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC (2000) Primary prevention of coronary heart disease in women through diet and lifestyle. *The New England Journal of Medicine*, **343**:16–22.

Steenland K, Nowlin S, Palu S (1995) Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiology, Biomarkers and Prevention*, **4**: 807–811.

Stefanick M, Wood PD (1994) Physical activity, lipid and lipoprotein metabolism, and lipid transport. In: *Physical activity, fitness and health: International proceedings and consensus statement*. Bouchard C, Shephard R, Stephens T, eds. Human Kinetics, Champaign, IL.

Sterne JA, Egger M (2001) Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *Journal of Clinical Epidemiology*, **54**: 1046–1055.

Sternfeld B (1992) Cancer and the protective effect of physical activity: the epidemiological evidence. *Medicine and Science in Sports and Exercise*, **24**:1195–1209.

Steyn K, Jooste PL, Bourne L et al. (1991) Risk factors for coronary heart disease in the black population of the Cape Peninsula. The Black Risk study. *South African Medical Journal*, **79**:480–485.

Steyn K, Jooste PL, Langenhoven ML et al. (1985) Coronary risk factors in the coloured population of the Cape Peninsula. *South African Medical Journal*, **67**:619–625.

Suni J (2000) *Health-related fitness test battery for middle-aged adults with emphasis on musculoskeletal and motor tests*. [Dissertation.] University of Jyväskylä, Finland.

Taioli E, Barone J, Wynder E (1995) A case-control study on breast cancer and body mass. The American Health Foundation—Division of Epidemiology. *European Journal of Cancer*, **31A**:723–728.

Tang L, Raab-Cullen M, Yee J, Jee WD (1995) Prostaglandin E2 increases skeletal response. *Journal of Bone and Mineral Research*, **10**:S256.

Tang R, Wang JY, Lo SK, Hsieh LL (1999) Physical activity, water intake and risk of colorectal cancer in Taiwan: a hospital-based case-control study. *International Journal of Cancer*, **82**:484–489.

Tavani A, Braga C, La Vecchia C et al. (1999) Physical activity and risk of cancers of the colon and rectum: an Italian case-control study. *British Journal of Cancer*, **79**:1912–1916.

Taylor R, Ram P, Zimmet P, Raper LR, Ringrose H (1984) Physical activity and prevalence of diabetes in Melanesian and Indian men in Fiji. *Diabetologia*, **27**:578–582.

Thor P, Konturek J, Konturek S, Anderson J (1985) Role of prostaglandins in control of intestinal motility. *American Journal of Physiology*, **248**: G353–359.

Thun MJ, Calle EE, Namboodiri MM et al. (1992) Risk factors for fatal colon cancer in a large prospective study. *Journal of the National Cancer Institute*, **84**:1491–1500.

Thune I, Brenn T, Lund E, Gaard M (1997) Physical activity and the risk of breast cancer. *New England Journal of Medicine,* **336**:1269–1275.

Thune I, Furberg A-S (2001) Physical activity and cancer risk: dose–response and cancer, all sites and site-specific. *Medicine and Science in Sports and Exercise*, **33**:S530–550.

Thune I, Lund E (1996) Physical activity and risk of colorectal cancer in men and women. *British Journal of Cancer*, **73**:1134–1140.

Todoroki I, Shinchi K, Kono S, Imanishi K (1994) Lifestyle and glucose tolerance: a cross-sectional study of Japanese men. *Annals of Epidemiology*, **4**:363–368.

Tomanek R (1994) Exercise-induced coronary angiogenesis: a review. *Medicine and Science in Sports and Exercise*, **26**:1245–1251.

Tomeo CA, Colditz G, Willett WC et al. (1999) Harvard Report on Cancer Prevention. Volume 3: prevention of colon cancer in the United States. *Cancer Causes Control*, **10**:167–180.

Travel Demand Management (1999) *TravelSmart 2010: a 10-year plan*. Department of Transport, Perth, Western Australia. Available at http://www.dpi.wa.gov.au/travelsmart/index.html.

Tuomilehto J, Lindstrom J, Eriksson JG et al. (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*, **344**:1343–1350.

Turner C, Owan I, Takano Y, Madali S, Murrell G (1995) Nitric oxide plays a role in bone mechanotransduction. *Journal of Bone and Mineral Research*, **10**:S235.

Tutton P, Barkla D (1980) Influence of prostaglandin analogues on epithelial cell proliferation and xenograft growth. *British Journal of Cancer*, **41**:47–51.

Ueji M, Ueno E, Osei-Hyiaman D, Takahashi H, Kano K (1998) Physical activity and the risk of breast cancer: a case-control study of Japanese women. *Journal of Epidemiology*, **8**:116–122.

U.S. Department of Health and Human Services (1996) *Physical activity and health: a report of the Surgeon General*. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, The Presidents' Council on Physical Fitness and Sports, Atlanta, GA.

U.S. Department of Health and Human Services (2001) *Increasing physical activity: a report on recommendations of the task force on community preventive services*. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5018a1.htm.

Vena JE, Graham S, Zielezny M, Swanson MK, Barnes RE, Nolan J (1985) Lifetime occupational exercise and colon cancer. *American Journal of Epidemiology*, **122**:357–365.

Verloop J, Rookus MA, van der Kooy K, van Leeuwen FE (2000) Physical activity and breast cancer risk in women aged 20–54 years. *Journal of the National Cancer Institute*, **92**:128–135.

Vuori I (2001) Dose–response of physical activity and low back pain, osteoarthritis, and osteoporosis. *Medicine and Science in Sports and Exercise*, **33**:S551–586.

Wang G (2002) *personal correspondence on data on physical activity in China—results published by the Ministry of Sport* [in Chinese]. Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Atlanta, GA.

Wannamethee S, Shaper A (1999) Physical activity and the prevention of stroke. *Journal of Cardiovascular Risk*, **6**:213–216.

Wannamethee SG, Shaper AG, Alberti KG (2000) Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. *Archives of Internal Medicine*, **160**:2108–2116.

Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN (1999) The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Annals of Internal Medicine*, **130**:89–96.

Welten D, Kemper H, Post G et al. (1994) Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. *Journal of Bone and Mineral Research*, **9**:1089–1096.

White E, Jacobs EJ, Daling JR (1996) Physical activity in relation to colon cancer in middle-aged men and women. *American Journal of Epidemiology*, **144**:42–50.

Whittemore A, Wu-Williams A, Lee M et al. (1990) Diet, physical activity, and colorectal cancer among Chinese in North America and China. *Journal of the National Cancer Institute*, **82**:915–126.

Williams P-T (2001) Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Medicine and Science in Sports and Exercise*, **33**: 754–761.

World Bank (1999) *World development indicators 1999*. World Bank, Development Data Group, Washington, DC.

Wyrwich KW, Wolinsky FD (2000) Physical activity, disability, and the risk of hospitalization for breast cancer among older women. *Journals of Gerontology*, **55**:M418–421.

Wyshak G, Frisch R (2000) Breast cancer among former college athletes compared to non-athletes: a 15-year follow-up. *British Journal of Cancer*, **82**:726–730.

Yano K, Reed DM, McGee DL (1984) Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to biologic and lifestyle characteristics. *American Journal of Epidemiology*, **119**:653–666.

Yu Z, Nissinen A (2000) Associations between socioeconomic status and, cardiovascular risk factors in an urban population in China. *Bulletin of the World Health Organization*, **78**:1296–1305.

Yu Z, Nissinen A, Vartiainen E, Song G, Guo Z, Tian H (2000) Changes in cardiovascular risk factors in different socioeconomic groups: seven year trends in a Chinese urban population. *Journal of Epidemiology and Community Health*, **54**:692–696.

Zabina H, Schmid T, Potemkina R, Glasunov I, Deev A (2002) *Evaluation of physical activity levels in Russia based on the international physical activity questionnaire (IPAQ)*. American College of Sports Medicine, 49th annual meeting, May 2002, St. Louis, MO.

Zhang J, Feldblum P, Fortney J (1992) Moderate physical activity and bone density among perimenopausal women. *American Journal of Public Health*, **82**:736–738.

Chapter 11

Smoking and oral tobacco use

Majid Ezzati and Alan D. Lopez

Summary

Smoking has been causally associated with increased mortality from several diseases. This chapter provides global and regional estimates of premature mortality and disease burden in 2000 caused by tobacco use, including an analysis of uncertainty. It also describes a method for estimating the future burden of disease that could be avoided through smoking cessation or prevention.

Comparable data, especially age-specific data, on the prevalence of smoking are often unavailable or inaccurate. More importantly, current prevalence of smoking is a poor proxy for cumulative hazards of smoking, which depend on factors such as age at which smoking began, duration of smoking, the number of cigarettes smoked per day, cigarette characteristics such as tar and nicotine content or filter type, and smoking behaviour such as degree of inhalation. We used the smoking impact ratio (*SIR*) as a marker for accumulated smoking risk. *SIR* uses lung cancer mortality in excess of never-smokers as a biological marker for accumulated hazards of smoking. Lung cancer mortality data were from the Global Burden of Disease (GBD) mortality database. Never-smoker lung cancer mortality rates were estimated based on the household use of coal in unvented stoves for each subregion.[1] Age–sex-specific *SIR* was divided into three categories: zero, medium ($0 < SIR \leq 0.5$), and high ($0.5 < SIR \leq 1.0$).

Estimates of mortality and disease burden due to smoking were made for lung cancer, upper aerodigestive cancer, all other cancers, chronic obstructive pulmonary disease (COPD), other respiratory diseases, cardiovascular diseases and selected other medical causes. All diseases for which no plausible physio-biological causal mechanism is currently known were excluded from the analysis of the category "other medical causes", as were the impacts of maternal smoking during pregnancy. No estimates were made for non-medical causes (injuries). Estimates were

limited to ages 30 years and above. The American Cancer Society Cancer Prevention Study, Phase II (CPS-II), with follow-up for the years 1982–88, was the reference population and provided data on exposure-disease relationships. For China, the exposure-disease relationship was estimated from the retrospective proportional mortality analysis of Liu et al. (1998). Relative risks were corrected for confounding and extrapolation to other regions using conservative correction factors for groups of diseases. For non-fatal outcomes, we assumed that the same attributable fraction as mortality applied to all cancers and COPD (i.e. smoking changes mortality by changing incidence) and used only one half of this value for other health outcomes (i.e. assumed smoking changes mortality by changing incidence and severity/case fatality).

Estimates of reduction in risk after smoking cessation were obtained from the re-analysis of CPS-II, with follow-up for the years 1982–98, for lung cancer, COPD and cardiovascular diseases. To obtain the estimates of exposure under a "business-as-usual" scenario, we assigned male and female populations of countries to one of the ten main or transitional stages of a descriptive model of the smoking epidemic based on available prevalence data. This model was used to divide per capita tobacco consumption data into age–sex-specific estimates. Historical consumption and mortality trends were used to project lung cancer mortality and *SIR* under the business-as-usual scenario.

Quantitative analysis of uncertainty was conducted for five input parameters: population lung cancer mortality, never-smoker lung cancer mortality, reference population smoker and never-smoker lung cancer mortality, relative risks and relative risk correction factors. Uncertainty in population lung cancer was based on a critical review of the quality of country mortality reporting. Uncertainty in never-smoker mortality rates was based on the likely presence of other risk factors for lung cancer, and uncertainty in reference population lung cancer mortality and in relative risk estimates was estimated from the statistical uncertainty in CPS-II data and data from the Chinese retrospective proportional mortality analysis of Liu et al. (1998). Uncertainty in the correction factor was based on the potential and measured confounding of smoking hazard estimates due to other risk factors. Three other sources of uncertainty were discussed qualitatively: uncertainty associated with the use of *SIR* as the exposure variable, uncertainty associated with exposure to environmental tobacco smoke (ETS), and uncertainty in the estimates of non-fatal conditions.

In the year 2000, there were an estimated 4.83 (95% CI 3.94–5.93) million deaths in the world attributable to smoking. Of these, 2.41 (95% CI 1.80–3.15) million deaths were in developing countries and 2.43 (95% CI 2.13–2.78) million deaths in industrialized countries. There were 3.84 million global smoking-attributable deaths among men (2.02 million in developing countries and 1.81 million in industrialized countries) and 1.00 million among women (0.38 million in developing

countries and 0.61 million in industrialized countries). The leading causes of death due to smoking were cardiovascular diseases with 1.69 million deaths, COPD with 0.97 million deaths and lung cancer with 0.85 million deaths. In addition to those cases shared with smokers, there were an estimated 60 000 deaths from oral tobacco use in SEAR-D.

Smoking and oral tobacco use accounted for 4.1% of healthy life years lost in the world in 2000. Given the demographic and epidemiological transitions and current smoking patterns in the developing world, the health loss from smoking will grow even larger unless effective interventions and policies that reduce smoking among males and prevent increases among females in developing countries are implemented.

1. Introduction

Tobacco is cultivated in many regions of the world and can be legally purchased in all countries. The dried leaf of the plant *nicotiana tabacum* is used for smoking, chewing or as snuff. Smoking has been causally associated with substantially increased risk of premature mortality from lung cancer as well as other medical causes (Doll et al. 1994; Liu et al. 1998; U.S. Department of Health and Human Services 1989; Zaridze and Peto 1986). As a result, in populations where smoking has been common for many decades, tobacco use accounts for a considerable proportion of premature mortality, as illustrated by estimates of smoking-attributable deaths in industrialized countries (Peto et al. 1992).

There have been large increases in smoking in developing countries, especially among males, over the last part of the twentieth century (Corrao et al. 2000; WHO 1997). The first estimates of the health consequences of smoking in China and India have also shown substantially increased risk of mortality and disease among smokers (Dikshit and Kanhere 2000; Gupta and Mehta 2000; Liu et al. 1998; Niu et al. 1998; Gajalakshmi et al. 2003). This chapter provides estimates of premature mortality and morbidity caused by smoking in all regions of the world, with complete description of methods and data sources, including quantitative estimates of uncertainty. It also describes a method for estimating the future burden of disease due to smoking that could be avoided through cessation or prevention.

It is well-known that the accumulated hazards of smoking depend on factors such as the age at which smoking began, the number of cigarettes smoked per day, cigarette characteristics such as tar and nicotine content or filter type, and smoking behaviour such as degree of inhalation (Fletcher and Peto 1977; Liu et al. 1998; Peto 1986). Current prevalence of smoking alone is therefore an insufficient indicator of accumulated risk from smoking. Although such pattern variables have been studied in a few industrialized countries (Nicolaides-Bouman et al. 1993), few data are available elsewhere. This lack of knowledge about important parameters of smoking patterns and history, coupled with the fact that

smoking is currently increasing in many developing countries, motivates using an exposure variable that better describes accumulated risk in populations with varying smoking histories.

Peto et al. (1992) used data on absolute lung cancer mortality to obtain the proportions of mortality from lung cancer as well as various other diseases attributable to smoking. We extended this method for indirect estimation of excess mortality due to smoking to all regions of the world and also included analysis of morbidity and uncertainty. The large retrospective proportional mortality analysis in China (Liu et al. 1998) and newer studies from India provided a means for calibrating and verifying the method for developing countries using direct estimates from the world's largest countries.

1.1 Evidence for causality

Smoking has been one of the most extensively studied human health risks, with detailed epidemiological research dating back to the 1930s (Doll and Hill 1950; Levin et al. 1950; Mills and Porter 1950; Muller 1939; Schairer and Schoniger 1943; Schrek et al. 1950; Wassink 1948; Wynder and Graham 1950) (see Table 1 in Doll 1986 for a summary of early studies). The sample size and details of data and methods have grown in subsequent studies in a number of countries, leading to a growing list of more than 60 000 publications on the hazards of smoking (Lopez 1999). The evidence for the causal relationship between smoking and all-cause and cause-specific mortality, as well as the mechanisms of disease causation have been extensively reviewed (Doll 1986, 1998b; U.S. Department of Health and Human Services 1989). Added to these are a number of recent studies, especially from developing countries such as China and India (Doll et al. 1994; Gajalakshmi et al. 2003; Gupta and Mehta 2000; Lam et al. 2001; Liu et al. 1998; Niu et al. 1998). We provide a brief summary of this evidence.

Randomized controlled trials of smoking and health, with randomization of exposure to cigarette smoking, would be impossible for ethical and logistical reasons. Therefore, research on the health impacts of smoking has been based on observational epidemiology and statistical adjustment. The first evidence for the causal relationship between smoking and mortality was from case–control studies. After the initial evidence from case–control studies, numerous prospective cohort studies were initiated to establish the relationship between smoking and mortality. These included studies in the United Kingdom of Great Britain and Northern Ireland (Male British Doctors) (Doll and Peto 1976; Doll et al. 1994), the United States of America (Males in 25 States, Males in 9 States, U.S. Veterans, California Occupations, the American Cancer Society Cancer Prevention Study Phases I and II) (Dunn et al. 1960; Garfinkel 1985; Hammond 1966; Hammond and Horn 1958; Kahn 1966; Peto et al. 1992; Thun et al. 1997a, 1997b), Japan (Hirayama 1977), Canada (Canadian Veterans) (Best et al. 1961), Sweden (Cederlof et al. 1975),

and more recently India (Gupta and Mehta 2000) and a number of other countries. Evidence for the relationship between smoking and total mortality or cause-specific mortality has been consistent among the studies. The causes of mortality from smoking include lung cancer and cancer of various other sites, cardiovascular diseases, COPD and other respiratory diseases, gastric ulcer and a number of other causes.

In addition to establishing the basic causal relationship between smoking and mortality, the results from all these studies exhibit the features and criteria that have been considered important in establishing causality:

1. consistently large risks relative to life-long non-smokers—more than a 20-fold increase in risk for some diseases;
2. existence of a dose–response relationship that shows increasing risk with increasing number of cigarettes smoked and duration of smoking (Doll 1986; Peto 1986; Thun et al. 1997b; U.S. Department of Health and Human Services 1989);
3. consistency of mortality (in particular for lung cancer) with smoking characteristics and cigarette type (such as tar and nicotine yield) across sexes and populations (Doll 1986);
4. risk reduction with smoking cessation, and a decreasing risk gradient with increasing time since smoking cessation (Doll 1986; U.S. Department of Health and Human Services 1989); and
5. biological plausibility. Cigarette smoke contains a number of known human carcinogens and other toxics (Hecht 2003). The toxic (in particular carcinogenic) properties of cigarette smoke have also been established in studies with laboratory animals (U.S. Department of Health and Human Services 1989). More recently, the pathophysiological mechanisms for some non-cancer effects such as COPD and cardiovascular diseases have also been studied and established (see U.S. Department of Health and Human Services 1989 for a summary).

2. Methods and data

2.1 Exposure variable

Lung cancer mortality as an indicator of accumulated smoking hazard

Peto et al. (1992) observed that the level of lung cancer mortality compared with never-smokers is an indicator of the accumulated hazard of smoking and the "maturity" of the smoking epidemic in a population. The relationship between cumulative smoking and lung cancer from various populations confirm this relationship (Peto 1986; Yamaguchi

et al. 2000). Based on this observation, the smoking impact ratio (*SIR)* is defined as population lung cancer mortality in excess of never-smokers, relative to excess lung cancer mortality for a known reference group of smokers. Formally, the ratio in Equation 1 measures the *absolute* excess lung cancer mortality due to smoking in the study population, relative to the *absolute* excess lung cancer mortality in life-long smokers of the reference population.

$$SIR = \frac{C_{LC} - N_{LC}}{S^*_{LC} - N^*_{LC}} \tag{1}$$

C_{LC}: (age–sex-specific) lung cancer mortality rate in the study population (e.g. country of analysis)

N_{LC}: (age–sex-specific) lung cancer mortality rate of never-smokers in the same population

S^*_{LC} and N^*_{LC}: (age–sex-specific) lung cancer mortality rates for smokers and never-smokers in a reference population

Liu et al. (1998) found that in China, the relative risk of mortality from lung cancer as a result of smoking is approximately constant in different cities and villages whose non-smoker lung cancer mortality rates varied by a factor of 10 (see Figure 4 in Liu et al. 1998). A constant relative risk means that smoking results in a larger absolute excess mortality (i.e. the numerator of Equation 1) where never-smoker lung cancer mortality is higher (and smaller absolute excess mortality where never-smoker lung cancer mortality is lower). Therefore, to be converted to an indictor of the maturity of the smoking epidemic, the numerator and denominator of Equation 1 need to be normalized with the respective never-smoker lung cancer mortality rates. We defined the background-adjusted *SIR* by the following relationship:

$$SIR = \frac{C_{LC} - N_{LC}}{S^*_{LC} - N^*_{LC}} \times \frac{N^*_{LC}}{N_{LC}} \tag{2}$$

where C_{LC}, N_{LC}, S^*_{LC}, and N^*_{LC} are defined as above.

Following Peto et al. (1992), we used the CPS-II study population (described below) as the reference population. This is because, among the numerous studies of smoking and cause-specific mortality (U.S. Department of Health and Human Services 1989), CPS-II is one of the very few with follow-up conducted when the smoking epidemic was at its highest levels, especially for men. Therefore, the vast majority of (male) CPS-II current-smokers had been lifelong cigarette smokers. Further, the estimates of increased risk of mortality among smokers were available for both men and women and in smaller age groups than in other studies of smoking and mortality, such as the Male British Doctors cohort (Doll et al. 1994).

It is straightforward to show that *SIR* equals the proportion of reference-population (i.e. CPS-II) smokers in a mix of smokers and never-smokers, which has the same lung cancer mortality rate as the study population (Peto et al. 1992).[2] This provides a convenient interpretation of *SIR*: using excess lung cancer mortality over never-smokers, *SIR* captures the accumulated hazards of smoking by converting the smokers in the study population into equivalents of smokers in the reference population where hazards for other diseases have been measured (Peto et al. 1992).

SIR values were calculated for individual countries and then averaged (population-weighted) across the 14 reporting subregions by age group and sex. The age groups used in the analysis were 0–4, 5–14, 15–29, 30–44, 45–59, 60–69, 70–79, and ≥80, which are the reporting age groups used in the GBD study. No deaths before the age of 30 years were attributed to smoking. Peto et al. (1992) used 35 as the lowest age for considering the impacts of smoking. Because of the GBD age grouping, we also included the 30–34 age group. The number of deaths attributed to smoking among people between 30 and 34 years of age is likely to be very small.

SIR values larger than 1.0 were set to 1.0. This occurred in the case of males in the 30–44 age group in 17 European countries and one Western Pacific island, and in the 45–59 age group in three countries in eastern Europe. Relatively low lung cancer mortality in younger ages can lead to unstable *SIR* values. This is particularly the case if the never-smoker rates are estimated with error, which is more likely in younger ages when lung cancer is relatively rare. Further, although a *SIR* larger than 1.0 may seem to imply that a population which consists of some smokers and some never-smokers had higher lung cancer mortality than CPS-II life-long smokers, factors such as the type and number of cigarettes or the age at which smoking began can result in such a pattern, especially where prevalence of smoking is high. The age of smoking initiation is particularly important for *SIR* values in earlier ages such as those affected in this analysis. For example, historical lung cancer mortality data show *SIR* larger than 1.0 among British males aged <60 years in some years between 1950 and 1970 and American males between 1968 and 1976. We nonetheless set the *SIR* for these groups to 1.0 to avoid any potential overestimation of risk.

Exposure categories

SIR is a measure of exposure in the population, vs the individual. In fact, since *SIR* is based on the lung cancer mortality rate, it cannot be defined at the level of an individual. It is nonetheless possible to divide a population into subgroups with different *SIR*s subject to the constraint that the overall population *SIR* should remain unchanged.

Suppose that a population with a specific *SIR* is divided into three subgroups with SIR_1, SIR_2 and SIR_3. Then

$$SIR = a_1 SIR_1 + a_2 SIR_2 + a_3 SIR_3 \tag{3}$$

and

$$a_1 + a_2 + a_3 = 1.0 \tag{4}$$

where a_1, a_2, and a_3 are the fractions of the population in the three subgroups. The above system of equations is under-determined for any division of more than two subgroups. If one considers never-smokers as one of the subgroups (subgroup 1) then, by definition of the smoking impact ratio, $SIR_1 = 0$ and

$$SIR = a_2 SIR_2 + a_3 SIR_3 \tag{5}$$

If p denotes the fraction of the population who have been smokers at some stage of their lives: $a_1 = 1 - p$ and $a_2 + a_3 = p$.

After some manipulation, it can be shown that

$$a_2 = \frac{SIR - pSIR_3}{SIR_2 - SIR_3} \tag{6a}$$

and

$$a_3 = \frac{SIR - pSIR_2}{SIR_3 - SIR_2} \tag{6b}$$

But prevalence data (p) are often unavailable or inaccurate, because of both differences in the definition of "ever-smoker" (someone who has smoked at least one cigarette in their life) and data collection complexity. In this work, the additional requirement for age-specific information makes the existing prevalence data—which are often defined for youth and adults only—even less useful. Therefore, in dividing the population into subgroups, the calculation of the fraction of the population in each subgroup is subject to the constraint that the overall *SIR* remains unchanged.

The specific categories that were used correspond to $SIR_1 = 0$, $0 < SIR_1 \leq 0.5$, and $0.5 < SIR_3 \leq 1.0$. For the last two categories, the midpoints (0.25 and 0.75) were used in estimating the fraction of population in the two categories (a_2 and a_3), once again subject to the constraint that the overall *SIR* be equal to the original population *SIR*. The analysis was conducted to divide each age-sex-subregion *SIR* value into three categories.

Theoretical-minimum-risk exposure distribution

Because the harmful effects of smoking outweigh the potential health benefits for a small number of diseases (such as parkinsonism) by many

orders of magnitude (Doll 1986, 1998a), the dose–response relationships for smoking and overall mortality and burden of disease are monotonically increasing. Therefore, the minimum risk from smoking would occur in a population in which no one had ever smoked. Further, although such a population may not be achievable in practice, there are no physical limits to reduction of smoking. Therefore, the theoretical minimum exposure distribution was chosen as a population with a *SIR* of zero.

Population and lung cancer mortality statistics

The age–sex-specific population estimates for the 191 WHO Member States were from the United Nations Population Division, and mortality statistics from WHO's GBD database. GBD mortality statistics are divided by country, sex, age (five-year age groups up to 85 and then ≥85), and more than 150 causes of death. The sources of mortality data include vital registration and sample registration, population laboratories, and epidemiological studies. Details of mortality data and cause-of-death analysis methods are described elsewhere (Mathers et al. 2002) and are summarized below where relevant.

The reliability of the *SIR* is determined by the reliability of lung cancer mortality estimates. In countries with good vital registration and medical certification of deaths (approximately 75 countries), lung cancer mortality is diagnosed with a high degree of accuracy. For example, microscopic confirmation of diagnosis against the cause reported on death certificates has suggested a 95% or higher confirmation rate in these settings (Percy and Muir 1989; Percy et al. 1990). In approximately another 50 countries, vital registration of mortality is incomplete and medical certification of the cause much less reliable. Standard demographic techniques (Bennett and Horiuchi 1984; Hill 1981; Preston et al. 2000) are used in the GBD project to correct all-cause death rates by age for these populations, and lung cancer rates are adjusted accordingly. Finally, for countries without vital registration, overall age-specific death rates were first determined using model life-tables (Lopez et al. 2002). Total cancer death rates are then estimated based on regional information about proportionate cancer mortality. Within this death rate, the distribution by site is based on regional incidence patterns from cancer registries reporting to the International Agency for Research on Cancer, IARC (Parkin et al. 1992, 1997). This indirect procedure is likely to entail considerable uncertainty, as we describe below.

2.2 Risk factor–disease relationships

American Cancer Society Cancer Prevention Study (ACS CPS-II)

The American Cancer Society's Cancer Prevention Study, phase II (CPS-II) is a prospective study of smoking and death in more than one million Americans aged >30 years when they completed a questionnaire in 1982,

with the latest follow-up in 1998. A complete description of the study is provided elsewhere and summarized below (Garfinkel 1985; Peto et al. 1992; Thun et al. 1995, 1997a, 1997b, 2000). In 1992, when the first six-year (1982–1988) results were obtained, mortality follow-up was virtually complete for the first two years, and about 98–99% complete for the next four. Because some conditions that cause death in the first two years may have affected smoking habits at entry (e.g. those diagnosed with lung cancer may have stopped smoking because of their disease or related symptoms), analysis was restricted to years 3–6 inclusive (1984–1988) (Peto et al. 1992). The analysis related deaths (subdivided by cause, sex and five-year age groups at the time of death) to person-years (with accounting for incompleteness) for those who in 1982 had never smoked regularly, and for those who were then current cigarette smokers (Peto et al. 1992). Most of the CPS-II current-smokers were life-long cigarette smokers with a mean consumption of about 20 cigarettes per day. Relative risks for cause-specific mortality among smokers in the CPS-II population are provided in Table 11.1.

Retrospective proportional mortality study in China

In a retrospective study of one million deaths in 24 urban centres and 74 rural areas of China, Liu et al. (1998) used proportional mortality analysis to obtain relative risks for three groups of diseases (neoplastic, respiratory and cardiovascular diseases). As explained in Liu et al. (1998), proportional mortality analysis cannot estimate excess mortality for these causes of death in the reference group. Therefore, in this study (Liu et al. 1998) the attributable fraction for causes other than the above three groups was considered to be zero. At the same time, since a few of the deaths in the reference group were also due to smoking, this method would underestimate (as zero) the proportion of mortality due to the causes in the reference group. The relative risks and attributable fractions of cause-specific mortality from Liu et al. (1998) are summarized in Table 11.2.

Disease outcomes and hazard size

Lung cancer mortality attributable to smoking was obtained as the difference between population lung cancer mortality and that of never-smokers (i.e. the numerator of Equation 1). For all other diseases, the relative risks from CPS-II (Table 11.1) were used. To obtain mortality from other causes, a "mixture" of CPS-II smokers and non-smokers was taken to give a *SIR* equal to that of the study population (as described above, the proportion of smokers in this mixture equals the *SIR* of the study population). This mixture was then used together with the cause-specific relative risks from CPS-II (Table 11.1) to estimate population attributable fractions (PAF) in the study population for different diseases.

Table 11.1 Selected relative risks for cause-specific mortality for years 3–6 inclusive of ACS CPS-II prospective study of one million American adults

Cause (ICD-9 code)	*Male*	*Female*
Lung cancer (162)[a]	24.22	12.50
Upper aerodigestive cancer (mouth, oropharynx or oesophagus) (140–150 and 161)	7.87	6.95
Other cancer (rest of 140–209)	1.69	1.20
Chronic obstructive pulmonary disease (490–492, 496)	13.82	14.21
Other respiratory diseases (460–466, 480–487, 381–382)[b]		
35–59	3.05	2.69
60–64	2.31	2.68
65–69	2.09	2.52
70–74	2.00	2.00
≥75	1.54	1.44
Infectious and parasitic diseases (001–139, 320–323, 614–616 with the exception of those above), maternal and perinatal conditions (630–676, 760–779), neuro-psychiatric conditions (290–319, 324–359), cirrhosis of the liver (571), congenital anomalies (740–759), and non-medical causes (injuries) (E800–999)[c]	NA	NA
Other medical causes (rest of 000–799)		
35–59	3.05	2.69
60–64	2.31	2.68
65–69	2.09	2.52
70–74	2.00	2.00
≥75	1.54	1.44

NA Not applicable.

[a] For lung cancer, the population attributable fraction was obtained by direct subtraction of population lung cancer mortality from that of non-smokers.

[b] This category also includes tuberculosis (010–018, 137) for which there are separate estimates of relative risk in China.

[c] Peto et al. (1992) included medical (non-injury) causes of death in this category with the category "other medical causes". We assumed that none of the deaths in this category were attributable to smoking because of lack of established causal pathways.

Source: Peto et al. (1992).

The use of relative risk models in estimating tobacco-attributable mortality has been criticized in the past (Lee 1996). While both additive and multiplicative risk models have been used in epidemiology (Moolgavkar and Venzon 1987), the use of a relative risk approach for common risk factors for common diseases is standard in epidemiological literature based on its ability to capture the "risk magnification" role of most risk factors. In the particular case of smoking, Liu et al. (1998) found that in China, the relative risks for mortality from lung cancer and other major diseases are approximately constant in different cities and

Table 11.2 Selected relative risks and attributable fractions of mortality from the retrospective mortality analysis of one million deaths in China

Cause (ICD-9 code)	Ages 35–69 years		Ages ≥70 years	
	Weighted mean relative risks (SE)	% deaths attributable to smoking	Weighted mean relative risks (SE)	% deaths attributable to smoking
Male				
Malignant neoplasm (140–208)	1.51 (0.02)	24.4	1.39 (0.03)	18.7
Lung cancer (162)	2.72 (0.05)	52.3	2.47 (0.07)	46.6
Oesophageal cancer (150)	1.61 (0.04)	27.9	—	18.2
Stomach cancer (151)	1.35 (0.03)	18.1	—	9.1
Liver cancer (155)	1.40 (0.03)	20.2	—	14.7
Mouth, pharynx, larynx, pancreas or bladder (140–9, 161, 157, 188)	1.51 (0.05)	24.6	—	19.1
Other malignant neoplasm	1.24 (0.03)	13.1	—	—
Respiratory	1.31 (0.02)	17.2	1.54 (0.02)	24.6
Chronic obstructive pulmonary disease (ICD 490–492, 496, 416–417)	1.43 (0.03)	22.6	1.63 (0.03)	27.4
Respiratory tuberculosis (011, 012, 018)	1.20 (0.04)	11.3	—	24.5
Other respiratory (rest of 460–519)	1.07 (0.05)	4.2	—	—
Cardiovascular (390–415, 418–459)	1.15 (0.02)	8.5	1.06 (0.02)	3.4
Stroke (430–439)	1.17 (0.02)	10.0	—	4.2
Ischaemic heart disease (410–414)	1.28 (0.03)	14.7	—	2.8
Other cardiovascular diseases (all cardiovascular except 430–439, 410–414, 416–417)	0.94 (0.03)	NA	—	—
Other causes (reference group)	1.00	NA	1.00	NA
Female				
Malignant Neoplasm (140–208)	1.37 (0.04)	4.0	1.37 (0.03)	4.7
Lung cancer (162)	2.64 (0.08)	19.4	2.50 (0.09)	20.1
Oesophageal cancer (150)	1.34 (0.08)	2.8	—	4.3
Stomach cancer (151)	1.17 (0.06)	1.7	—	2.3
Liver cancer (155)	1.22 (0.06)	2.4	—	4.2
Mouth, pharynx, larynx, pancreas, or bladder (140–9, 161, 157, 188)	1.53 (0.09)	6.4	—	9.1
Other malignant neoplasm	1.04 (0.04)	0.5	—	—
Respiratory	1.61 (0.05)	7.5	1.59 (0.03)	7.4
Chronic obstructive pulmonary disease (ICD 490–492, 496, 416–417)	1.72 (0.05)	9.3	1.70 (0.03)	8.6
Respiratory tuberculosis (011, 012, 018)	1.29 (0.08)	2.8	—	6.7
Other respiratory (rest of 460–519)	1.14 (0.09)	1.5	—	—

continued

Table 11.2 Selected relative risks and attributable fractions of mortality from the retrospective mortality analysis of one million deaths in China (*continued*)

	Ages 35–69 years		*Ages ≥70 years*	
Cause (ICD-9 code)	*Weighted mean relative risks (SE)*	*% deaths attributable to smoking*	*Weighted mean relative risks (SE)*	*% deaths attributable to smoking*
Cardiovascular (390–415, 418–459)	1.01 (0.03)	0.2	1.02 (0.02)	0.2
Stroke (430–439)	0.97 (0.03)	NA	—	—
Ischaemic heart disease (410–414)	1.30 (0.05)	4.1	—	2.0
Other cardiovascular diseases (all cardiovascular except 439–439, 410–414, 416–417)	0.94 (0.05)	NA	—	—
Other causes (reference group)	1.00	NA	1.00	NA

— Values not reported in Liu et al. (1998).

NA Not applicable.

Source: Liu et al. (1998), Tables 1 and 5.

villages where background (non-smoker) mortality rates for the same disease varied significantly. This finding also has been confirmed in studies which stratified on serum cholesterol for cardiovascular diseases (Jee et al. 1999).

The exception to the use of CPS-II relative risks was tobacco-attributable mortality in China, for which direct estimates of the fraction of cause-specific mortality due to smoking from 1990 were available. For China, attributable fractions for diseases other than lung cancer were obtained using relative risks from Liu et al. (1998). Since smoking has been increasing in China over the past few decades, we used *SIR* estimates to capture the impact of this trend. The relative risks for each smoker from Liu et al. (1998) were converted to relative risks for each unit of *SIR* (i.e. equivalent to life-long CPS-II smoker) by back-calculation in 1990 and used with 2000 *SIR* estimates. The upper aerodigestive cancer category was constructed from oesophageal cancer and cancers of five minor sites (mouth, pharynx, larynx, pancreas and bladder) by using weights based on the number of deaths in each disease category. Relative risks per unit of *SIR* for China (which correspond to the same level of accumulated smoking hazard as Table 11.1 for CPS-II life-long smokers), are provided in Table 11.3.

Although smokers are found to have increased mortality due to causes other than those in Table 11.1, none of the deaths from non-medical causes (injuries) and the following medical causes (for which there are no known pathways of causality) were attributed to smoking: infectious and parasitic diseases (with the exception of those in the category "other respiratory disease" for which there were estimates of hazard), maternal

Table 11.3 Relative risks for each unit of *SIR*[a] for China obtained by back-calculation from 1990 estimates of attributable mortality from Table 11.2

	Male		*Female*[b]	
Cause	*35–69 years*	*≥70 years*	*35–69 years*	*≥70 years*
Lung cancer	20.97	35.76	14.19	15.06
Upper aerodigestive cancer	7.71	9.90	2.78	3.89
Other cancer	4.39	5.12	1.56	2.30
Chronic obstructive pulmonary disease	6.32	16.03	6.62	6.26
Tuberculosis	3.32	7.32	2.58	2.49
Other respiratory diseases	1.80	3.14	1.83	1.79
Cardiovascular diseases	2.69	2.40	1.11	1.11
Other causes (reference category)[c]	1.00	1.00	1.00	1.00

[a] Equivalent to a CPS-II life-long smoker in Table 11.1.

[b] Relative risks for females are likely to be unstable due to low prevalence of female smoking in China.

[c] Since the proportional mortality method used by Liu et al. (1998) does not allow obtaining attributable mortality for causes in the reference group, the relative risks were estimated as one. At the same time, since some deaths in this category are also due to smoking the relative risks from CPS-II were used for these causes.

and perinatal conditions (see below for discussion), neuro-psychiatric conditions, cirrhosis of the liver and congenital anomalies.

There is increasing evidence of an association between smoking and tuberculosis (Dhillon et al. 2000; Gajalakshmi et al. 2003; Lam et al. 2001; Liu et al. 1998). The role of air pollutants in increased risk of infectious pulmonary disease has also been suspected to be through weakening of lung function and defence mechanisms (Thomas and Zelikoff 1999). At the same time tuberculosis is a highly communicable disease whose transmission dynamics are affected by a number of factors. Further, progress from infection to disease and mortality is highly dependent on control and treatment mechanisms. Because of this crucial role of cofactors in tuberculosis incidence and mortality, and their concentration in specific sectors of society, we did not extrapolate relative risks for this disease from one setting to another. We considered tuberculosis as a separate cause of mortality due to smoking only in China where published direct estimates on the relationship were available. We grouped tuberculosis with the category "other respiratory diseases", which have a lower relative risk, in all other countries. Not including tuberculosis as a separate cause of death for the rest of the world is a conservative assumption. This is particularly true in the case of India where recent evidence indicates risks larger than those in China (Dhillon et al. 2000; Gajalakshmi et al. 2003).

Many deaths from burns and other injuries due to fires are also attributable to smoking. For example, pooled studies from Australia, the

United Kingdom and the United States show an attributable fraction of 0.23 for fire-related injuries due to smoking (English et al. 1995). The number of fire-related deaths and injuries are highly dependent on local circumstances including population density, housing, the availability of emergency services, etc. A relative risk approach would, therefore, be unsuitable for their analysis, which is better conducted using injury registries. Given the large burden of injuries due to fires, excluding nonmedical causes undoubtedly results in an underestimation of the health impacts of tobacco.

There has also been growing evidence of the impact of maternal smoking on maternal and child health. Specific outcomes include still births and neonatal deaths, perinatal mortality, low birth weight, primary and secondary infertility, ectopic pregnancy and spontaneous abortion and a number of other child and maternal conditions (U.S. Department of Health and Human Services 1989, 2001). Despite the evidence for the relationship, there has been little quantification of the impact of maternal exposure on child disease and mortality, especially in settings with high background levels of child and maternal mortality. Further, these estimates would require estimating what fraction of female smokers continues to smoke during pregnancy. Not including quantitative estimates of the health hazards for maternal and child health also underestimates the burden of disease due to smoking.

Before using the relative risks from CPS-II, we reduced the excess risk attributed to smoking using constant correction factors as described below. As explained by Peto et al. (1992), a constant correction factor, although arbitrary, avoids overestimating mortality due to confounding in the ACS CPS-II relative risk estimates (which were adjusted for age and sex only) as well as extrapolation of relative risk values from this population to other populations, where exposure to other risk factors that could modify the effects of smoking in a non-multiplicative way may be different. The issue of the confounding of the CPS-II risk estimates used by Peto et al. (1992) and the arbitrary nature of the correction factor were used to challenge the indirect estimates of mortality due to this risk factor (Lee 1996; Sterling et al. 1993).

In studies other than CPS-II, the overall impact of confounding due to diet on the estimates of excess risk of mortality from smoking has been found to be considerably less than half of the excess risk for cardiovascular diseases (such as those studies reviewed as a part of the meta-analysis of ETS and ischaemic heart disease [IHD] by Law et al. 1997 or in analysis of multiple cardiovascular disease risk factors in Japan Hirayama 1990). Alcohol consumption and smoking are correlated in many populations, including in the United States where the ACS CPS-II, which was used to obtain relative risks, was conducted. Alcohol may affect cardiovascular disease (in particular IHD) in both beneficial and harmful ways depending on the patterns of consumption (Britton and McKee 2000; Puddey et al. 1999; chapter 12 in this book). Alcohol

was associated with a reduction in cardiovascular disease mortality risk in CPS-II (Thun et al. 1997c). But the overall death rates were lowest among men and women reporting about one drink daily and increased with heavier drinking, particularly among adults aged <60 years with lower risk of cardiovascular disease (Thun et al. 1997c). It may also have been the case that CPS-II smokers had more harmful drinking patterns, which would confound the relative risk estimates for cardiovascular disease. At the same time, given that the beneficial impacts of alcohol in this cohort persisted even at higher consumption levels, any possible confounding effect on estimates of smoking hazard size is likely to be considerably less than one half of the excess risk. In the Nurses' Health Study, Kawachi et al. (1997) found that the relative risk for cardiovascular diseases as a result of smoking after adjustment for multiple covariates (3.74) was larger than the unadjusted relative risk (3.47); the change was not statistically significant. The reduction in cardiovascular disease excess risk due to adjustment for age, community, history of hypertension and diabetes, consumption of alcohol, systolic blood pressure, and frequency of walking in a study of the relationship between smoking and mortality in three United States communities was 20% for men (2.0 to 1.8). Adjustment resulted in an increase in female relative risk (from 1.7 to 1.8) (LaCroix et al. 1991); neither change was statistically significant.

Among cancers, upper aerodigestive cancers are the diseases for which confounding due to alcohol consumption may be most important. There is evidence from studies in different parts of the world on the interaction (excess over multiplicative) between alcohol and tobacco for various upper aerodigestive cancers (Flanders and Rothman 1982; Kinjo et al. 1998). As described by Flanders and Rothman (1982), this interactive effect as well as the correlation between exposure to these two risk factors, would imply larger risks from smoking than would be the case in the absence of interaction and correlation. Therefore, reduction of risk by one half is likely to not only account for potential confounding but also result in conservative estimates.

In response to the criticism about the lack of empirical evidence for confounding correction, CPS-II data were re-analysed together with adjustment for potential confounders (Malarcher et al. 2000; Thun et al. 2000). Malarcher et al. (2000) found that adjusting for multiple covariates (age, education, alcohol use, hypertension status and diabetes status) only marginally changed the fraction of mortality attributable to smoking in the United States, as shown in Table 11.4. As seen in the table, except for cerebrovascular disease (CVD) among men, adjustment for confounding had no or little effect, or even resulted in a slight increase, on the smoking-attributable mortality.

In a more detailed re-analysis of CPS-II data, Thun et al. (2000) adjusted for age, race, education, marital status, occupation ("blue collar" worker) and total weekly consumption of citrus fruits and vegetables in estimat-

Table 11.4 Effect of adjustment for confounding on the fraction of cause-specific mortality attributable to smoking

	Male		*Female*	
	Age-adjusted	*Fully-adjusted*	*Age-adjusted*	*Fully-adjusted*
Lung cancer	0.91 (0.89–0.92)	0.89 (0.87–0.91)	0.71 (0.68–0.74)	0.77 (0.71–0.80)
COPD	0.85 (0.82–0.88)	0.88 (0.83–0.92)	0.70 (0.65–0.74)	0.68 (0.61–0.76)
IHD	0.23 (0.20–0.26)	0.24 (0.21–0.27)	0.08 (0.06–0.10)	0.10 (0.06–0.13)
CVD	0.16 (0.09–0.22)	0.10 (0.02–0.19)	0.10 (0.07–0.12)	0.09 (0.05–0.12)

Source: Malarcher et al. (2000).

ing the relative risk of mortality due to a range of neoplasms, cardiovascular diseases and respiratory diseases. In addition, the analysis for cardiovascular diseases adjusted for current aspirin use or alcohol consumption, body mass index (BMI), physical activity at work or leisure and weekly consumption of fatty foods. For lung cancer and COPD, the analysis also adjusted for occupational exposure to asbestos. Similar to the analysis of Malarcher et al. (2000), with the exception of stroke among men, whose relative risk declined from 2.9 (95% CI 2.3–3.7) to 2.4 (95% CI 1.8–3.0) for the 35–64-year age group and from 1.8 (95% CI 1.6–2.2) to 1.5 (95% CI 1.2–1.8) for those aged >64 years, excess risks increased, stayed unchanged or decreased by small amounts. As in the case of Malarcher et al. (2000), the largest decrease was in the case of stroke for males (17% decrease in excess risk for the 35–64-year age group and 38% for those aged ≥65 years). Overall, Thun et al. (2000) concluded that adjustment for confounding reduced their estimates of mortality attributable to smoking in the United States by approximately 1%.

Finally, the Chinese retrospective study provides some evidence that background disease rates do not change the proportion of mortality attributable to smoking (Figures 4 and 5 in Liu et al. 1998). In extrapolating hazard size from industrialized to developing countries, one would have to deal with availability of health services (such as medical care for cardiovascular disease patients) if extrapolation were based on absolute risk (i.e. number of deaths) because the number of fatal cases would vary based on available treatment. If extrapolation is made based on risk of mortality for smokers *relative* to non-smokers, however, availability of health services would not bias the estimates if smokers and non-smokers have similar access to these services.

Based on this evidence of the robustness of CPS-II relative risk estimates to adjustment for confounding and extrapolation across settings with different background mortality rates, we modified the choice of correction factor from that used by Peto et al. (1992). We used a correction factor of 30%, approximately equal to the largest reduction in excess risk due to confounding seen in the re-analysis of CPS-II data, to reduce

the excess risk for all cause-specific relative risks (see also discussion of uncertainty). This choice continues to be conservative to account for any potential residual confounding or any other potential sources of overestimation arising from extrapolation across regions. For the category, "other medical causes", where the extent of confounding is still not known, we continued to attribute only one half of the excess mortality estimated by CPS-II.

The excess risk for China was reduced by 5%. Confounding due to other risk factors is likely to have been negligible in China because of the more homogenous level of exposure to other risk factors (e.g. diet, alcohol, and indoor air pollution from coal) in the population compared to the CPS-II population (R. Peto, personal communication, 2001). The proportional mortality method used by Liu et al. (1998) also is not affected by confounding due to any risk factor that increases mortality in the study and reference disease categories (such as effects of alcohol on cancer and liver cirrhosis). Finally, since the relative risks are used for China only, effect modification due to other risk factors is not a concern. The 5% reduction of excess risk was used to account for the potential small level of residual confounding.

Assessment of morbidity

Virtually all causes of mortality (diseases) that are affected by smoking are chronic diseases due to long-term exposure. Therefore, a reasonable assumption would be that smoking increases mortality by increasing disease incidence, rather than modifying case fatality among those who would already be affected by the disease. Since the non-fatal component of disability-adjusted life years (DALYs) (i.e. years lived with disability or YLD) is based on incidence, this assumption would imply that the relative risks for mortality and incidence are equal. Among the causes of mortality considered, the most obvious exception to this assumption may be asthma and respiratory infections, where smoking may affect incidence, case fatality or both. For these diseases we assumed that one half of the morbidity obtained from the above approach is due to smoking. To provide conservative estimates, we also considered that for those diseases where medical interventions may reduce case fatality (such as some cardiovascular diseases) and those for which smokers have a smaller excess risk compared to non-smokers (such as the "other medical conditions" category), the increased risk of mortality may be partially due to increased case fatality. Therefore, for these diseases also, we assumed that one half of the above attributable fraction was due to smoking. In summary, the attributable fraction of morbidity due to smoking was assumed to be the same as mortality for all cancers and COPD, and one half of the latter for all other causes.

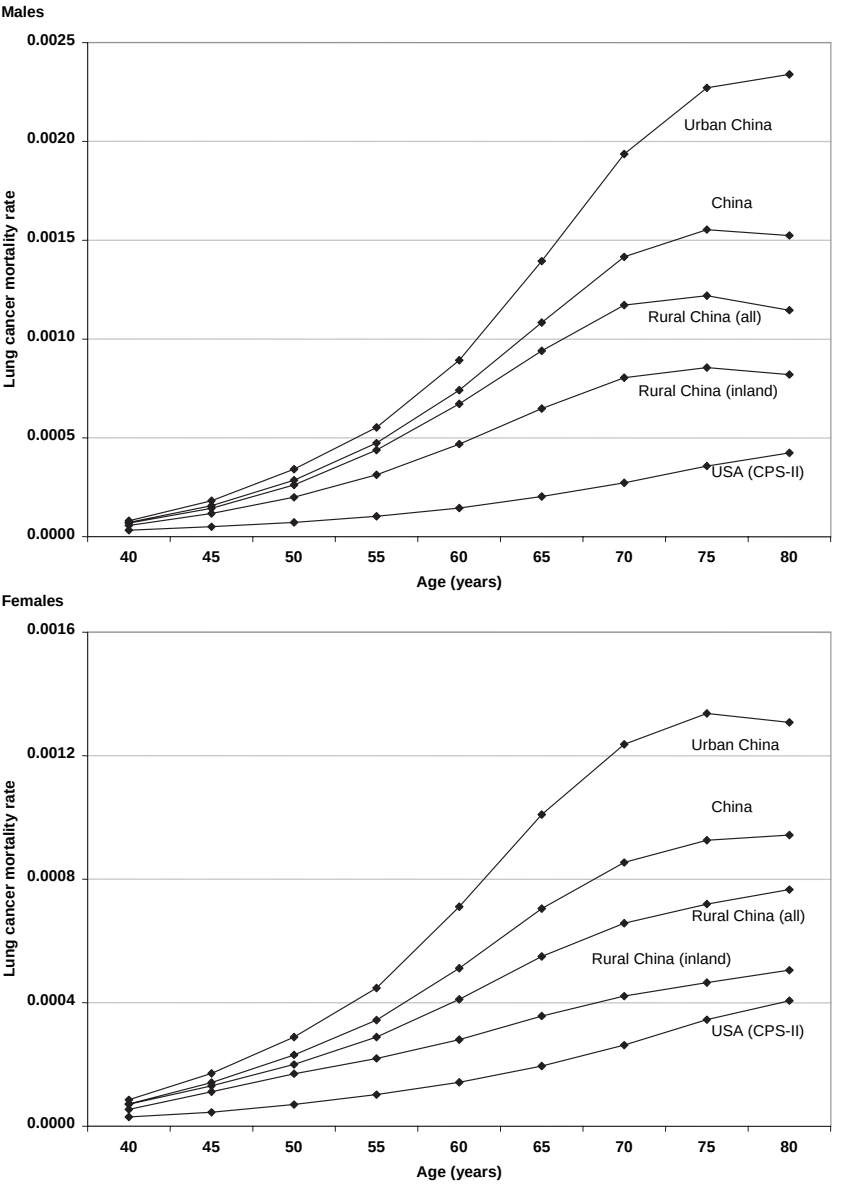
2.3 Choice of never-smoker lung cancer mortality in the study population

In Equation 2, C_{LC} is from the GBD mortality database and S^*_{LC} and N^*_{LC} directly from CPS-II. The only parameter to be estimated indirectly is N_{LC}, since direct estimates of never-smoker lung cancer mortality are known for very few countries. Figure 11.1 shows non-smoker lung cancer mortality for the United States (from CPS-II) and China (from Liu et al. 1998). The detailed data in Liu et al. (1998) further allow dividing the Chinese rates into urban and rural areas, and the latter into coastal and inland rural.

As seen in Figure 11.1, age-specific non-smoker lung cancer mortality is considerably higher in China than in the United States for both males and females. In China itself, there are also marked differences between different parts of the country with urban areas having the highest non-smoker lung cancer mortality rates and inland rural areas the lowest (also seen in Figure 4 in Liu et al. 1998). The difference between the non-smoker lung cancer mortality rates for the United States and China, and between urban and rural regions of China is explained by the Chinese patterns of household energy use over the past few decades. Coal is a common household fuel in China, often burned in stoves and buildings without adequate ventilation (Du et al. 1996; Liu et al. 1998; Smith et al. 1993; Wang et al. 1996). Exposure to coal smoke and cooking fumes has been associated with increased lung cancer incidence in China (Du et al. 1996; He et al. 1991; Wang et al. 1996). In inland rural regions of China, where incomes are the lowest, biomass (including crop residues and wood) has been the dominant household fuel compared with coastal villages and cities where coal has been more commonly used.

The relationship between biomass fuels and lung cancer has been absent or considerably smaller than that between coal and lung cancer (Bruce et al. 2000; Ko et al. 1997; Smith and Liu 1993; Sobue 1990) as seen also in chapter 18. Although urban air pollution has been linked to increased lung cancer mortality in some studies, the size of the risk is considerably smaller than the effects of smoking or direct exposure to coal smoke (Doll 1978; Jedrychowski et al. 1990; Nyberg et al. 2000; Pope et al. 2002; Vena 1982). Further, the impact of ambient air pollution on lung cancer has been found to be smaller among non-smokers than among smokers, with one study finding increased risk of lung cancer as a result of urban air pollution among smokers only (Jedrychowski et al. 1990; Vena 1982). For example, exposure to high levels of urban air pollution, even in regions where coal was used extensively, was found to increase the risk of mortality from lung cancer by approximately 14% among non-smokers (vs 40% among smokers) (Jedrychowski et al. 1990). Coupled with the fact that only small fractions of national populations live in the most polluted urban areas,

Figure 11.1 Non-smoker mortality from lung cancer in different populations



Note: Chinese rates correspond to 1990. Note that the scales on the female and male charts are different to maintain the resolution for females.

Source: Ezzati and Lopez (2003).

overall population lung cancer mortality is not expected to be greatly affected by urban air pollution. For example, the lung cancer mortality rate among non-smoking American women remained constant at approximately 12 per 100 000 between 1960 and 1986 despite changes in exposure to urban air pollution (U.S. Department of Health and Human Services 1989).

Based on the pattern of background lung cancer mortality rates, and the underlying risk factors for increased lung cancer mortality in China and its various regions, background (never-smoker) lung cancer rates for the different subregions were based on the estimated use of coal for domestic energy in unvented stores as provided in chapter 18. We used Chinese non-smoker rates for China, a weighted average of Chinese and CPS-II non-smoker for SEAR-D where coal is also used for household fuel (with weights for Chinese rates equal to the prevalence of coal use), and CPS-II non-smoker rates for the remaining countries of the world where domestic coal use in unvented stoves is negligible. The remaining risk factors with potential effects on lung cancer mortality (ambient air pollution, occupational hazards, indoor air pollution from radon or biomass smoke, etc.) affect all populations in varying degrees. The net impacts of these other risk factors are considered as sources of uncertainty in extrapolating never-smoker lung cancer mortality from one setting to another.

2.4 Risk reversibility

Estimating the burden of disease that might be avoidable as a result of exposure removal requires knowledge of risk reversibility (the decline in risk after exposure is removed) for those who are current smokers.[3] For those who never begin to smoke, of course, the entire disease burden as a result of smoking is avoided. The benefits of smoking cessation for reduction of mortality risk have been reported in a number of studies (Best et al. 1961; Doll and Hill 1956; Doll and Peto 1976; Doll et al. 1994; Dunn et al. 1960; Hammond 1966; Kahn 1966; U.S. Department of Health and Human Services 1990c). Many studies have also considered the reduction in risk with time since cessation. Most of these studies have focused on the reduction in the risk of lung cancer and cardiovascular causes since cessation. Although the estimates of risk reduction time have varied among different studies, possibly due to different smoking histories and other differences (such as age at which cessation occurred) among the study populations, the benefits of cessation have been consistently demonstrated.

To capture the history and accumulated hazards of smoking, we continued to use smoking impact ratio (*SIR*) as the exposure variable in considering risk reversibility. We first estimated risk reversibility for lung cancer to obtain estimates of reduction in *SIR* values after cessation. For diseases other than lung cancer, we estimated the reduction in disease risk per unit of *SIR*—our exposure variable—using the studies on risk

reversibility. Together with the *SIR* estimates after cessation, these provided estimates of avoidable mortality for causes other than lung cancer, which also took into consideration the full history of smoking before cessation.

Lung cancer

The reduction in lung cancer risk with smoking cessation has been demonstrated in a number of studies (Alderson et al. 1985; Higgins et al. 1988; Kahn 1966; Lubin et al. 1984; Pathak et al. 1986; Peto and Doll 1984; Peto et al. 2000; Sobue et al. 1991; U.S. Department of Health and Human Services 1990a). Peto et al. (2000) provided an analysis of risk reduction for those who would have been life-long smokers but stopped smoking at various ages using two case–control studies for lung cancer, and national lung cancer mortality statistics in 1950 and 1990 (see Figure 3 in Peto et al. 2000). Table 11.5 shows the reduction in risk, relative to those who continue to smoke, as a function of time since cessation. The results are presented for all ages to increase statistical stability (S. Darby, personal communication, 2001). The large difference between male and female estimates of reversibility in this study is because female estimates were based on relatively few cases of ex-smokers with lung cancer (S. Darby, personal communication, 2001). Also, because the smoking epidemic for females lagged the male epidemic in the United Kingdom, as elsewhere, the comparison of 1950 and 1990 lung cancer mortality rates was likely to have included few females who had stopped smoking after the peak of the epidemic.

These estimates of decline in risk are consistent with those from a number of prospective cohort studies (summarized in Table 3 in U.S. Department of Health and Human Services 1990a) including Male British Doctors, United States Veterans, and American Cancer Society CPS-I and CPS-II. When all subjects are considered, these prospective

Table 11.5 Decline in the risk of lung cancer mortality with time since smoking cessation

Smoking status	*Male*	*Female*
Current smoker	1.00	1.00
Years since cessation among former smokers		
0–9	0.66	0.69
10–19	0.42	0.21
20–29	0.18	0.05
≥30	0.08	—

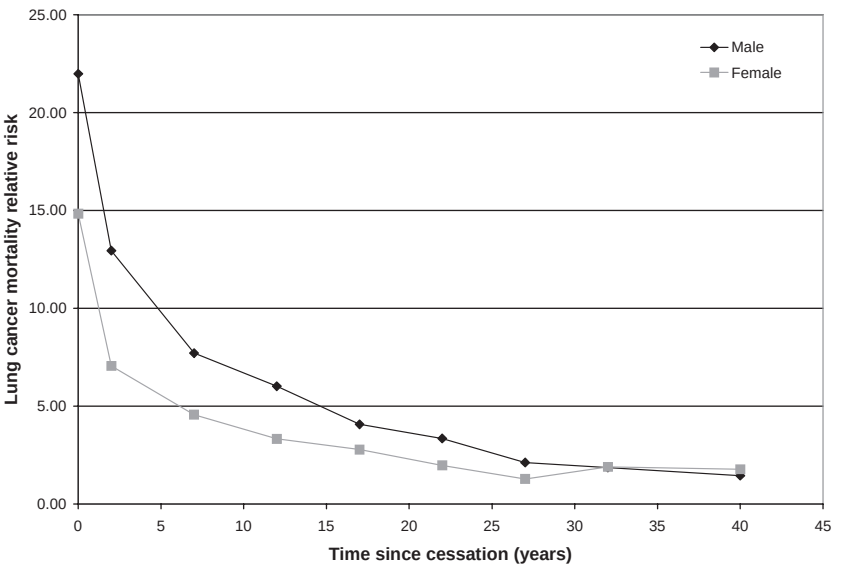
— Value not reported.

Source: Peto et al. (2000).

studies show a consistent increase in relative risk in the first five years from the date of cessation (U.S. Department of Health and Human Services 1990a). This can be attributed to selection bias, as those who die in the first few years after cessation are likely to have stopped smoking because they had been diagnosed with a disease. This is confirmed in the separate analysis of those with and without history of chronic disease in CPS-II. In this analysis, those without a history of chronic disease have a consistent declining trend in lung cancer mortality risk compared to all respondents (Figure 11.2). To estimate lung cancer risk reversibility with cessation, we used a re-analysis of CPS-II data (1998 follow-up) excluding those subjects with a history of chronic disease (lung cancer, COPD, cardiovascular diseases) (Figure 11.2).

Despite some remaining differences, the male and female reversibility estimates in Figure 11.2 are much more similar than those in Table 11.5. With better estimates of reversibility among females, we took sex-specific estimates of reversibility to be consistent with the sex-specific smoker and non-smoker lung cancer mortality rates used in the definition of *SIR*. For the last two cessation periods (30–34 and ≥35 years)

Figure 11.2 Relative risk of lung cancer among former smokers (compared with lifelong non-smokers) with time since cessation



Note: Zero years represent current smokers. The estimates at 40 years represent cessation of more than 35 years in the subjects. Data are from ACS CPS-II 1998 follow-up.

Source: American Cancer Society, unpublished data, 2002.

female estimates show a slight increase in risk compared to the 25–29 year cessation period. This anomaly, which is not statistically significant, is probably due to a small number of events in these groups, itself caused by the more recent maturity of the female smoking epidemic in the United States compared to men. Too few women would have stopped smoking so long ago to have had more than 35 years of cessation and a large number of lung cancer events. For these two cessation periods, we simply assumed that the declining trend observed between the 20–24 and 25–29 year periods would continue.

Avoidable lung cancer mortality can be estimated from the difference between lung cancer risk as it would have been without cessation and the risk that results from cessation. If, as above, we denote smoker and non-smoker lung cancer mortality rates in the reference cohort as S^*_{LC} and N^*_{LC}, and lung cancer mortality rates for those who stopped smoking x years ago as $S^*_{LC,x}$, then for this cohort of former smokers $S^*_{LC,x} - N^*_{LC}$ is the mortality attributable to past smoking, and $S^*_{LC} - S^*_{LC,x}$ is the mortality avoidable because they stopped smoking x years ago. If RR and RR_x are the relative risks for life-long smokers without and with cessation respectively, then $S^*_{LC} = RR \times N^*_{LC}$ and $S^*_{LC,x} = RR_x \times N^*_{LC}$. Attributable and avoidable mortality x years after cessation is then $N^*_{LC} \times (RR_x - 1)$ and $N^*_{LC} \times (RR - RR_x)$. Of course, for those who never begin to smoke, $S^*_{LC,x} = N^*_{LC}$ and no mortality is attributed to this risk factor and $S^*_{LC,x} - N^*_{LC}$ (i.e. the whole excess mortality due to smoking) is avoidable. In Table 11.5, for example, for males who stop smoking, 34%, 58% and 82% of lung cancer mortality would be avoided within 10, 20 and 30 years from cessation, respectively, compared to what would have happened had they continued to smoke. The remaining 66%, 42% and 18% of mortality in these time periods is still attributable to their past smoking, despite cessation.

So far, by using CPS-II estimates of risk reversibility, we have implicitly addressed risk reversibility among those who have smoked since youth and stop smoking at a given age (because ACS smokers were life-long smokers, including at cessation time). We argued earlier, however, that such information is rare and unreliable, and that the only measure of accumulated history of smoking is the *SIR*. We also showed earlier that for each population, *SIR* is the equivalent prevalence of life-long smokers. Therefore, to obtain estimates of avoidable burden in each cohort, a fraction of whom have smoked for some period, the estimates of attributable and avoidable mortality x years after cessation are given by $SIR \times (S^*_{LC,x} - N^*_{LC}) = SIR \times N^*_{LC} \times (RR_x - 1)$ and $SIR \times (S^*_{LC} - S^*_{LC,x}) = SIR \times N^*_{LC} \times (RR - RR_x)$ respectively where, *SIR* is measured at the time of cessation (say in 2000 for estimates of avoidable burden as a result of cessation in 2000). We emphasize that this estimation, like all other uses of *SIR*, is based on the assumption that the equivalence of *SIR* with life-long smokers holds in estimating the benefits of cessation.

Finally, to apply this information to populations with different background (non-smoker) mortality rates, we used the results of Liu et al. (1998) who found that in China the relative risk for mortality from lung cancer was approximately constant in different cities where the non-smoker lung cancer mortality varies by a factor of 10. Therefore for populations whose background mortality is N_{LC}, the attributable burden due to past smoking x years after cessation is given by $SIR \times N_{LC} \times (RR_x - 1)$ and the avoidable burden as a result of cessation by $SIR \times N_{LC} \times (RR - RR_x)$.

SIR after cessation

To estimate the decline in risk for other diseases, while accounting for the pre-cessation history of smoking, we needed to also estimate the value of *SIR* after cessation. Once again noting that *SIR* is the equivalent of life-long smokers in the population, the lung cancer mortality rate in the population as a whole, C_{LC}, can be re-written as:

$$C_{LC} = SIR \times RR \times N_{LC} + (1 - SIR) \times N_{LC}$$

If the same number of life-long smokers continue to smoke, *SIR* will remain more or less constant for the cohort and in each time period their new *SIR* will be given by the same relationship, with *RR* referring to the age-specific relative risk. On the other hand, if the smokers stop smoking, after x years their relative risk will decrease to RR_x a value less than *RR* at any time after cessation (Table 11.5). In this case, the new (post-cessation) lung cancer mortality rate, $C_{LC,x}$, is given by:

$$C_{LC,x} = SIR \times RR_x \times N_{LC} + (1 - SIR) \times N_{LC}$$

Replacing this value for $C_{LC,x}$ in Equation 2 to obtain the post-cessation smoking impact ratio, SIR_x, gives:

$$SIR_x = \frac{SIR \times RR_x \times N_{LC} + (1 - SIR) \times N_{LC} - N_{LC}}{S^*_{LC} - N^*_{LC}} \times \frac{N^*_{LC}}{N_{LC}}$$

with some algebraic simplification and noting that $S^*_{LC,x} = RR \times N^*_{LC}$,

$$SIR_x = SIR \frac{RR_x \times N_{LC} - N_{LC}}{RR \times S^*_{LC} - N^*_{LC}} \times \frac{N^*_{LC}}{N_{LC}}$$

or

$$SIR_x = SIR \times \frac{RR_x - 1}{RR - 1}$$

In other words, smoking cessation after x years results in scaling down the population *SIR* values relative to what they would be if smoking continued, with the scaling factor equal to the ratio of excess lung cancer risk after cessation to excess lung cancer risk if cessation did not occur.[4]

Diseases other than lung cancer

The decline of relative risk for cardiovascular diseases as a function of time since cessation has been estimated in a number of studies, resulting in a range of estimates for the rate of decline (Cook et al. 1986; Dobson et al. 1991; Kawachi et al. 1997; LaCroix et al. 1991; Rogot and Murray 1980; Rosenberg et al. 1985, 1990; U.S. Department of Health and Human Services 1990c). Kawachi et al. (1997) also considered the decline in the risk of other causes of mortality, including all cancers and external causes.

To convert the estimates of relative risk reduction from the time of cessation for diseases other than lung cancer to the estimates of relative risk per unit of *SIR* we used the following notation: Let RR and RR' be the age-specific risks of lung cancer and disease A respectively for life-long smokers in the absence of cessation; RR_x and RR'_x the age-specific relative risks at some specific time, x, after cessation; and RR'_{SIR} and $RR'_{SIR,x}$ the relative risks of disease A per unit of *SIR* without and with cessation respectively. In all cases, $RR'_{SIR} = RR'$ since in the absence of cessation, the relative risks for life-long smokers (from CPS-II for example) would apply. It is $RR'_{SIR,x}$ that we are interested in, which, with the decline in *SIR* as outlined above, is now the risk of disease A "per unit of former life-long smoker". Four scenarios are possible.

1. If the rate of decline in relative risk for cause A is the same as the rate of decline in relative risk for lung cancer, then the relative risk per unit of *SIR* would stay constant at the pre-cessation level (except for age effects). This is because, in this case, all the benefits of cessation for both disease A and lung cancer (which move together) would be captured in the decline of *SIR* (to SIR_x). Therefore, in this case $RR'_{SIR,x} = RR'$.

2. If there had been no decline in lung cancer risk (i.e. $RR_x = RR$ and $SIR_x = SIR$) but there was a decline in the risk of disease A (i.e. $RR'_x < RR'$), then the relative risk per unit of *SIR* would decline at the same rate as the decline in relative risk for disease A after cessation. This is because, in this case, none of the benefits of cessation would be captured by decline in *SIR*, and therefore they need to be included in the estimates of relative risk per unit of *SIR*. In this case $RR'_{SIR,x} = RR'_x$.

3. If disease A is an acute condition, such as an injury or death (or possibly an acute respiratory infection) due to smoking-caused fires then cessation would result in complete removal of the risk for A, and $RR'_{SIR,x} = 1$.

4. If cessation results in lowering of the risk for both lung cancer and disease *A*, but at different rates, then the relative risk of disease *A* per unit of *SIR* after cessation, is given by the following relationship:

$$RR'_{SIR,x} = 1 + (RR'_x - 1) \times \frac{RR'_x - 1}{RR' - 1} \times \frac{RR - 1}{RR_x - 1}$$

The product of the terms $\frac{RR'_x - 1}{RR' - 1}$ and $\frac{RR - 1}{RR_x - 1}$ captures the relative drop in excess risk for disease *A* (first term) compared to lung cancer (second term). If the risk of disease *A* declines faster than lung cancer, then the relative risk per unit of *SIR* will decline to capture the additional benefits of cessation for disease *A*, compared to lung cancer. On the other hand, if the risk of disease *A* declines more slowly than lung cancer, then the relative risk per unit of *SIR* will rise to capture the reduced benefits of cessation for disease *A*, compared to lung cancer.[5] Scenarios 1–3 above are special cases of this general relationship.

The estimates of RR and RR_x (for lung cancer) can be obtained from Figure 11.2 for different times since cessation. To estimate RR' and RR'_x for COPD and cardiovascular diseases, we used CPS-II data. In the analysis of risk reversibility for cardiovascular diseases for the first six-year follow up (1988), the estimates for those who had quit for less than one year showed inconsistent patterns (Table 11.6) even though subjects with cancer, heart disease and stroke were excluded at baseline (U.S. Department of Health and Human Services 1990b). This has been attributed to both high incidence of smoking resumption and the possible inclusion of subjects who stopped smoking as a result of symptoms from undiagnosed illness (U.S. Department of Health and Human Services 1990b).

Table 11.6 Decline in the risk of cardiovascular disease mortality with time since smoking cessation

	RR (Male)		*RR (Female)*	
Smoking status	*≤20 cig/day*	*>20 cig/day*	*≤20 cig/day*	*>20 cig/day*
Current smoker	1.93	2.02	1.76	2.27
Years since cessation among former smokers				
<1	1.43	2.56	2.13	1.41
1–2	1.61	1.57	0.87	1.16
3–5	1.49	1.41	1.31	0.96
6–10	1.28	1.63	0.74	1.88
11–15	0.99	1.16	1.2	1.37
≥16	0.88	1.09	1.17	1.12

Source: U.S. Department of Health and Human Services (1990b).

The rate of decline in relative risk and the unstable behaviour in the early years since cessation were nonetheless consistent with other studies (see Table 2 in U.S. Department of Health and Human Services 1990b and the estimates [Kawachi et al. 1997] from the Nurses' Health Study).

Re-analysis of ACS CPS-II data (1998 follow up) with more stringent exclusion of subjects with a history of chronic disease (lung cancer, COPD, vascular diseases) shows a more consistent pattern of risk reversibility, especially if the first cessation period is considered as 2 years, which reduces the likelihood of high smoking resumption rates. Figure 11.3 shows the estimates of relative risk for COPD and cardiovascular disease with time since cessation for males and females using this re-analysis. To apply risk reversibility with cessation to the CPS-II and Chinese baseline relative risk estimates in Tables 11.1 and 11.3, we estimated the *relative* decline in relative risks after x years of cessation (i.e. the ratio of relative risk x years after cessation to current smokers in Figure 11.3) and applied this to CPS-II or Chinese relative risks (i.e. RR') to obtain RR'_x.

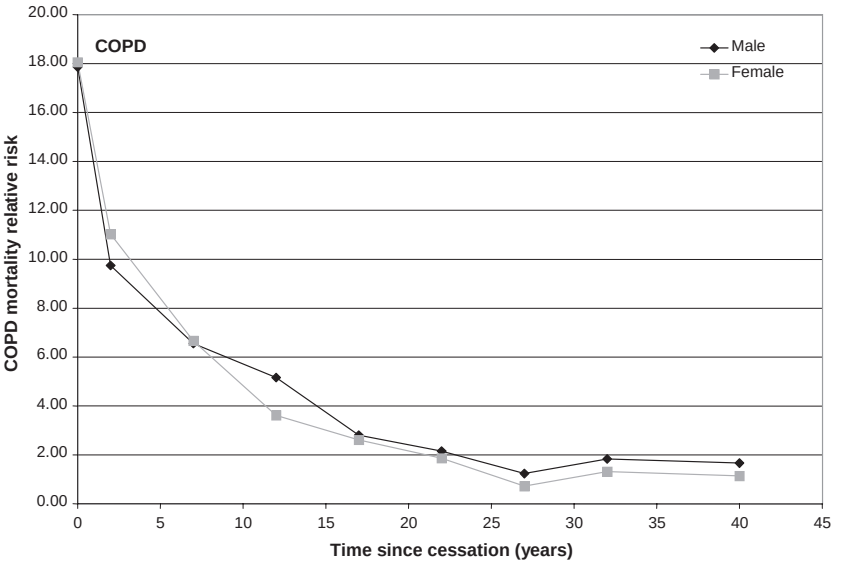
For cardiovascular disease among men, former smokers with long cessation periods have lower risk than never-smokers (statistically not significant). This pattern, however, is implausible and is likely to be due to unobserved confounders that have affected the behaviour of former smokers (e.g. the same factor may have motivated cessation and change in diet or physical activity) and hence, lowered their risk. To account for this, we re-adjusted the values for the 25–29 and 30–34-year cessation periods based on the trends between the 20–24 and ≥35 periods. For females, the estimates for cessation beyond 10 years were re-adjusted based on the male trends to asymptotically reach 1 for the longest cessation periods. The re-adjusted values are shown as dotted lines in Figure 11.3.

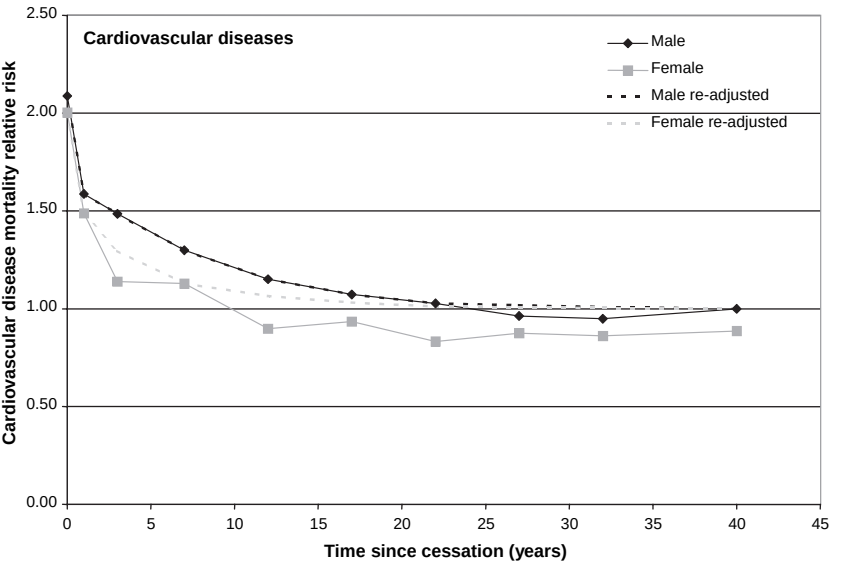
Given the potentially similar biological mechanisms of carcinogenesis, we assumed that all other cancers had the same rate of decline in relative risk as lung cancer. This is also seen in estimates of relative risk since smoking cessation for cancers including and excluding lung cancer analysed by Kawachi et al. (1997). Therefore, as described in scenario 1 above, the relative risk per unit of *SIR* remains constant for these diseases and the benefits of cessation in terms of avoidable mortality are fully captured by the decline in *SIR*. For all other disease categories, we used scenario 4 to estimate the risk per unit of *SIR* after cessation. We assumed that these diseases, for which reversibility data were not available, followed the same time pattern of decline as cardiovascular diseases, which decline more rapidly than lung cancer.

2.5 Analysis of uncertainty

In one taxonomy, uncertainty in quantitative risk assessment can be divided into *parameter uncertainty* and *model uncertainty* (Finkel 1990; National Research Council 1994). Parameter uncertainty includes the

Figure 11.3 Relative risk of chronic obstructive pulmonary disease (COPD) and cardiovascular diseases among former smokers





Note: Zero years represent current smokers. The estimates at 40 years represent cessation of more than 35 years in the subjects. Data are from ACS CPS-II 1998 follow up.

Source: American Cancer Society, unpublished data, 2003.

uncertainty quantifiable using random-variable methods such as that in a risk factor distribution, the magnitude of the risk factor–disease relationship, and burden of disease estimates. Model uncertainty is defined as uncertainty due to gaps in scientific theory (Finkel 1990; National Research Council 1994). In other words, model uncertainty occurs in those aspects of the analysis which are not currently quantifiable using a random-variable statistical methodology. In risk assessment, model uncertainty, broadly defined, also includes cases where exposure distributions or exposure–response relationships for populations are not known and are extrapolated from others. The uncertainty reported here is the 95% range of the combined distribution. In the following sections we describe the sources of uncertainty and the approach for quantifying parameter uncertainty.

Parameter uncertainty

Uncertainty for each of the variables and parameters in the analysis was estimated separately. These include population lung cancer mortality and never-smoker lung cancer mortality for each subregion, lung cancer mortality for smokers and never-smokers in the reference population, and relative risks. The first four parameters are those needed for the estimation of *SIR* which, when combined with the relative risk of mortality, gives the fraction of cause-specific mortality due to smoking. Estimates of uncertainty for individual parameters were combined in a simulation using Latin hypercube sampling to obtain overall uncertainty for *SIR* and relative risk values, and eventually the fraction of mortality or morbidity due to smoking. The parameter-specific uncertainty estimates were obtained as follows:

1. *Population lung cancer mortality*: The GBD estimates of mortality do not currently include complete analysis of uncertainty. To obtain uncertainty estimates for population lung cancer mortality, we assigned each country into one of four uncertainty categories based on the quality of available mortality data, as we described earlier. Lung cancer mortality information for the four country categories were assigned uncertainty ranges equal to 10%, 20%, 40% and 80% of the best-estimate, with a triangular distribution. Since for countries with good vital registration, 95% or higher confirmation rates of the cause reported on death certificates have been found (Percy et al. 1990; Percy and Muir 1989), 10% is more than double the observed uncertainty and a conservative estimate of true uncertainty. Eighty per cent uncertainty for the least certain countries, i.e. those with no established mortality reporting, implies that we have allowed nearly all of lung cancer mortality to be due to misclassification. Given that zero lung cancer mortality is implausible, higher levels of uncertainty could occur only on the upper side of these estimates, making this a conservative assumption for lung cancer mortality and *SIR*. Countries with less complete and/or less reliable data were

Table 11.7 Uncertainty (as % of best-estimate) assigned to reported or estimated country level lung cancer mortality

Uncertainty	*Country*[a]
10%	AMR-A – all; AMR-B – Chile, Costa Rica, Dominica, Uruguay; EMR-B – Bahrain; EUR-A – all except Croatia; EUR-B – Poland, Slovakia; EUR-C – Estonia, Hungary, Latvia, Lithuania, Russian Federation; WPR-A – all except Brunei Darussalam
20%	AMR-B – Argentina, Bahamas, Barbados, Colombia, Mexico, Panama, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and Grenadines, Trinidad and Tobago, Venezuela; EMR-B – Kuwait; EUR-A – Croatia; EUR-B – Armenia, Bosnia and Herzegovina, Bulgaria, Romania, The former Yugoslav Republic of Macedonia, Serbia and Montenegro; EUR-C – Belarus, Republic of Moldova, Ukraine; WPR-A – Brunei Darussalam; WPR-B – China
40%	AFR-D – Mauritius; AFR-E – South Africa; AMR-B – Antigua and Barbuda, Belize, Brazil, Grenada, Jamaica, Suriname; EMR-D – Egypt; EUR-B – Albania, Georgia, Kyrgyzstan, Tajikistan, Uzbekistan; EUR-C – Kazakhstan; SEAR-B – Thailand; WPR-B – Fiji, Malaysia, Marshall Islands, Republic of Korea
80%	AFR-D – all except Mauritius; AFR-E – all except South Africa; AMR-B – Dominican Republic, El Salvador, Guyana, Honduras, Paraguay; AMR-D – all; EMR-B – all except Bahrain and Kuwait; EMR-D – all except Egypt; SEAR-B – Indonesia, Sri Lanka; SEAR-D – all; WPR-B – all except China, Fiji, Malaysia, Marshall Islands, Republic of Korea

[a] By subregion.

assumed to have 20% or 40% uncertainty around the best-estimate of lung cancer mortality. Table 11.7 shows the countries assigned to each uncertainty category.

2. *Never-smoker lung cancer mortality*: For China, estimates of the uncertainty for never-smoker lung cancer mortality rates from the proportional mortality study were used (Liu et al. 1998). For all other countries, where non-smoker lung cancer mortality rates were assumed to be those of CPS-II, we assumed an uncertainty of 15% around CPS-II estimates plus the statistical uncertainty of the CPS-II estimates themselves. Fifteen per cent is approximately equivalent to the whole (non-smoker) population being exposed to the highest levels of air pollution, such as that in the centre of the industrial city of Cracow, Poland, which resulted in a 14% increase in lung cancer mortality over the period 1980–1985 (Jedrychowski et al. 1990) or the whole (never-smoker) population being exposed to more than 10 $\mu g/m^3$ of $PM_{2.5}$ (particulates below 2.5 microns in diameter) (Pope et al. 2002). Because the net difference between accumulated exposure to additional lung cancer risk factors (radon, urban air pollution, biomass smoke) in any two countries is less than the whole population, 15% is a relatively large uncertainty range for never-smoker lung cancer mortality.

3. *Reference population smoker and never-smoker lung cancer mortality*: We used statistical uncertainty of the CPS-II population since the reference population is constant in all regions of the world and the excess mortality of the reference population of smokers is simply a normalizing factor.

4. *Relative risk*: Uncertainties in relative risks were obtained directly from the CPS-II and Chinese mortality studies as well as the decline in risk due to cessation.

5. *Confounding and extrapolation of relative risk and correction factor*: To avoid overestimation of risk as a result of confounding in CPS-II relative risks, as well as from the extrapolation of relative risk to other regions, we have reduced the relative risk values by 30% to 50% for various diseases. To account for uncertainty in the level of the correction factor, we assumed that the 30% correction factor could vary between 10% and 50% with a triangular distribution. The lower end of this range corresponds to the typical amount of reduction in excess risk seen after adjustment for covariates in the re-analysis of CPS-II data (Thun et al. 2000) and seen in other studies such as the magnitude of confounding due to diet found by Law et al. (1997). The upper end is the conservative correction used by Peto et al. (1992) before the level of confounding was known and larger than those in the CPS-II re-analysis (Thun et al. 2000). The 50% correction factor used for the "other medical causes" group was assumed to be highly uncertain and in the range of 10% to 90% with a triangular distribution. We also assumed that the 5% correction factor for estimates of relative risk for China were in the range of 0–10% with a triangular distribution.

Model uncertainty

Although lung cancer mortality provides a biological marker for accumulated exposure to the hazards of smoking in general, the question remains whether it equally represents the accumulated hazards for each of the diseases considered in this analysis. Two factors may reduce the accuracy of excess lung cancer and *SIR* as markers of accumulated hazard:

1. *If the cigarette smoke characteristics that cause lung cancer are not fully correlated with those that cause the other hazard*: While the carcinogens in cigarette smoke are the cause of cancer, the concentration or size distribution of respirable particles or other pollutants may be a better indicator of some of the other health effects. The validity of the *SIR* method compared to direct estimates in the United States was estimated by Peto et al. (1992). Comparisons with other (largely direct) methods for other countries also show consistent results (Bronnum-Hansen and Juel 2000; Valkonen and van Poppel 1997).

2. *If the time-to-hazard* (or hazard accumulation function as described in chapter 1) *is different for lung cancer and other diseases caused by smoking*: Lung cancer is caused by exposure and hazard accumulated over an extended period of time spent smoking. This property may be shared by some other outcomes of smoking, such as other cancers and COPD. Some of the other health effects of smoking, such as acute respiratory diseases, may occur after immediate exposure, and others, such as cardiovascular disease, are determined by a period of exposure that may be somewhat shorter than that of lung cancer. With these differences, when smoking is on the rise, an indicator based on excess lung cancer—which generally occurs later—would underestimate the impacts of those diseases that occur earlier. On the other hand some time after smoking begins to decline, an indicator based on excess lung cancer would overestimate the impacts of those diseases, where risk declines faster with cessation than lung cancer.[6] Since smoking has been increasing in most regions of the world over the past two or three decades, the net effect of this would be an underestimation of current global mortality due to cardiovascular and some other diseases in our analysis.

In addition to the uncertainty in the use of *SIR* as exposure variable, the following other sources of uncertainty have not been quantified:

3. *The impact of environmental tobacco smoke on SIR estimates*: The carcinogenic effects of cancer agents are likely to apply at low levels without a threshold (Peto 1978). Therefore exposure to environmental tobacco smoke (ETS) is a likely cause of lung cancer. This relationship, as well as the impact of ETS on cardiovascular disease, has also been established in epidemiological studies (Australia National Health and Medical Research Council 1997; Environmental Protection Agency 1992; Hackshaw et al. 1997; Law et al. 1997; UK Department of Health Scientific Committee on Tobacco and Health 1998). Although we did not conduct a separate analysis of the burden of disease due to ETS, because of its relationship to lung cancer, ETS exposure affects *SIR* estimates.

Of the four variables in the *SIR* relationship (C_{LC}, N_{LC}, S^*_{LC}, and N^*_{LC} in Equation 2), the effects of ETS are smallest on life-long smokers (S^*_{LC}) who are almost completely affected by direct smoking. The lung cancer mortality of the population as a whole (C_{LC}) is also affected more by direct smoking but nonetheless captures the effects of both direct and indirect exposure to tobacco smoke. The effects of ETS are largest on never-smokers (N_{LC} and N^*_{LC}) who would otherwise not be exposed to tobacco smoke. Therefore, both N_{LC} and N^*_{LC} are larger in the presence of ETS than they would be in its absence. Since C_{LC} is almost always smaller than S^*_{LC}, increasing non-smoker lung cancer rates will result in

a larger relative reduction (through subtraction) in the numerator of Equation 1 compared to the denominator, and therefore an underestimation of *SIR* values.

4. *Estimates of non-fatal health outcomes*: To obtain relative risks for non-fatal effects of these diseases, we have assumed that smoking increases mortality by increasing disease incidence (rather than modifying case fatality) for cancers and COPD. We have assumed a potential change in either the incidence or the severity/case fatality for all other causes. Given that most of the diseases affected by smoking are chronic diseases as a result of chronic exposure, this is a conservative assumption and requires further investigation using epidemiological studies on the relationship between smoking and disease incidence.

5. *Future exposure and risk reversibility*: Estimates of avoidable burden are possibly the most uncertain component of a risk assessment exercise because of the number of assumptions that, by definition, are needed for estimates of future burden. These include estimates of the "business-as-usual" trends of smoking and lung cancer and estimates of risk reversibility (reduction in relative risk) for those current smokers who stop smoking.

The future estimates of lung cancer mortality and *SIR* (see below) are based on a number of assumptions. These include the descriptive model of the tobacco epidemic and its parameters, the estimates of total tobacco consumption, and the statistical model used for estimating lung cancer based on consumption. As we discussed under risk reversibility, the estimates of decline in the relative risk for lung cancer, and more importantly for other diseases, after smoking cessation are derived from a limited number of studies and extrapolated to people of different ages, sexes and smoking histories. At the same time it may be possible that the benefits of cessation are more dependent on the specific history of smoking such as duration of smoking and age at cessation, than the current accumulated risk (which is captured by *SIR*) as also seen in the comparison between male and female reductions in lung cancer risk in Table 11.5. In this case, the use of *SIR* as the indicator of pre-cessation history would create an additional source of uncertainty. At the same time, after a few decades, the potential health benefits of smoking reduction occur among those who would be prevented from smoking altogether. In this case, the longer-term estimates of avoidable burden would be less dependent on the specifics of risk reversibility and depend only on the estimates of risk among life-long smokers, which are known with much greater certainty.

2.6 Additional oral cancer mortality due to oral tobacco use

Oral tobacco use, in the form of chewing of betel-quid with tobacco, is common in many parts of south Asia, and in particular in the Indian sub-continent (Bhonsle et al. 1992). Although oral tobacco use has been associated with increased risk of all-cause mortality (Gupta and Mehta 2000), we focus here on the risk of oral cancer which is the most-widely known and studied outcome of this risk behaviour (Gupta et al. 1982; International Agency for Research on Cancer (IARC) 1984; U.S. Department of Health and Human Services 1986), and a leading form of cancer mortality in the region (Parkin et al. 1997). Smoking in India is much more common among men than women whereas the prevalence of tobacco chewing is of comparable magnitude, although still higher among men (Corrao et al. 2000; Gupta 1996; WHO 1997). Given the correlation between smoking and oral tobacco use, many cases of oral cancer are likely to be affected by both habits. To report the total burden of disease due to both forms of tobacco use, we made estimates of only those cases of oral cancer that are caused by tobacco chewing *in addition* to smoking. The estimates were applied to SEAR-D only. Oral tobacco use is common throughout the region, whose mortality estimates are nonetheless dominated by those from India.

We obtained estimates of the fraction of total chewers who do not smoke (p_c) and the fraction of total smokers who do not chew (p_s) using a survey of tobacco habits in various ethnic and religious groups in India (Gupta 1996). The estimates of oral cancer for smokers who do not chew (p_s) are included in those from the application of the *SIR* method. Those who both smoke and chew (p_{sc} as a fraction of total smokers), have a higher risk than smokers-only, by a factor $RR_{(chewing+smoking)/smoking}$, because of their additional chewing habit. We used $RR_{(chewing+smoking)/smoking}$ to increase the CPS-II relative risk estimates for the upper-aerodigestive cancer category for this group,[7] and applied these increased risk estimates to oral cancer mortality. The difference between these new estimates of oral cancer (using increased relative risk) and those using the CPS-II risk estimate, are the *additional* deaths due to oral tobacco use over and above those accounted for by smoking, among those who both chew and smoke. Finally, for those who chew only (p_c), we used the corresponding relative risk, $RR_{(chewing\ and\ not\ smoking)}$, to obtain estimates of oral cancer mortality, which are independent from those obtained using the *SIR* method. For this group, we directly used the estimated prevalence of chewing. Although oral cancer as a result of tobacco chewing is also dependent on accumulated exposure, the relative risk estimates from recent literature are directly applicable because they were used in the same time period and region where epidemiological studies took place.

For males, we used the estimate that 20% of all smokers also chew (WHO 1997), which is close to the largest overlap of any ethnic or reli-

gious group found in a study of socio-demographic characteristics of tobacco users (Gupta 1996). Assuming a 40% prevalence of smoking and a 65% prevalence of total tobacco use, this implies that 32% of adult males smoke only, 8% of adult males both smoke and chew, and another 25% chew only, consistent with other estimates (WHO 1997). For females, we used a 33% prevalence of total tobacco use and a 3% prevalence of smoking (Corrao et al. 2000; WHO 1997). We also assumed that all female smokers also chew tobacco (Gupta 1996), hence 30% of adult females are chewers-only.

A review of studies prior to 1982 that estimated the relative risk of oral cancer due to tobacco chewing is provided by Gupta et al. (1982). We did not use these estimates since the definitions of cancer sites or control for covariates were not consistent with more recent studies. All these studies nonetheless show statistically significant increased risk of oral cancer due to tobacco chewing. A number of recent studies have estimated the relative risks for oral cancer (or one of its sub-types) based on stratification by smoking and tobacco chewing, all finding a significant increase in the risk of oral cancer among chewers regardless of their smoking habits (Balaram et al. 2002; Dikshit and Kanhere 2000; Rao et al. 1994; Sankaranarayanan et al. 1989a, 1989b, 1990). A description of recent studies and their estimates of relative risk (or odds ratio) of oral cancer due to chewing tobacco among smokers and non-smokers is provided in Table 11.8. Those studies that provided separate analysis according to the frequency of chewing also consistently show an increasing dose–response relationship. Note that in some of the studies, those who both chew and smoke tobacco had lower risk than those who used oral tobacco only. This may be because smokers chewed less tobacco than those whose only habit was tobacco chewing. We used a relative risk of 3.64 for chewing only and 1.7 for those who both chew and smoke relative to smokers. These values, which are lower than almost all other studies, are from non-drinkers in the study of Rao et al. (1994) to avoid confounding due to alcohol consumption, an important risk factor for oral cancer.

3. Results

3.1 Exposure (*SIR*) estimates

Figure 11.4 shows *SIR* estimates for females and males in developing and industrialized countries. We have also shown in the figure legend the best estimate of adult smoking prevalence for each subregion. As discussed above, prevalence estimates are uncertain and based on data from a limited number of countries. At the same time, as discussed by Jha et al. (2002), despite uncertainties in country-level and age-specific estimates, they provide a reasonable indication of current smoking status among adults in each subregion. The subregion WPR-B includes China.

Table 11.8 Summary of studies on the relationship between tobacco chewing, smoking and oral cancer[a]

Study location (reference)	*Cancer site (ICD code)*	*Number of cases and control choice*	*Covariate adjustment*	*Effect size*
Kerala (Sankaranarayanan et al. 1989a)	Oral tongue and the floor of the mouth (ICD 141.1–141.4 and 144)	228 cases; 453 hospital-based controls matched for age, sex and religion	Age	$RR_{chewing} = 6.13$; $RR_{smoking} = 4.98$; $RR_{chewing+smoking} = 7.02$[b]
Kerala (Sankaranarayanan et al. 1989b)	Gingiva (ICD 143.0 and 143.1)	187 cases; 895 hospital-based controls with respiratory, intestinal, and genito-urinary infections, excluding malignancy in sites other than head and neck	Age	$RR_{chewing} = 11.76$; $RR_{smoking} = 4.21$; $RR_{chewing+smoking} = 16.48$[b]
Kerala (Sankaranarayanan et al. 1990)	Buccal and labial mucosa (ICD 145.0, 145.1, and 145.6–140.3 and 140.4)	414 cases; 895 hospital-based controls with non-malignant conditions	Age, religion	$RR_{chewing} = 14.28$; $RR_{smoking} = 4.21$; $RR_{chewing+smoking} = 21.46$[b]
Bangalore (Nandakumar et al. 1990)	Oral cavity (140–141 and 143–145 excluding 141.0)	348 cases; 348 hospital-based controls with non-malignant conditions matched for age, sex and residence	Age, sex, religion and diet	$RR_{chewing} = 10.2$; $RR_{smoking} = 3.5$; $RR_{chewing+smoking} = 9.2$[b]

continued

Table 11.8 Summary of studies on the relationship between tobacco chewing, smoking and oral cancer[a] (*continued*)

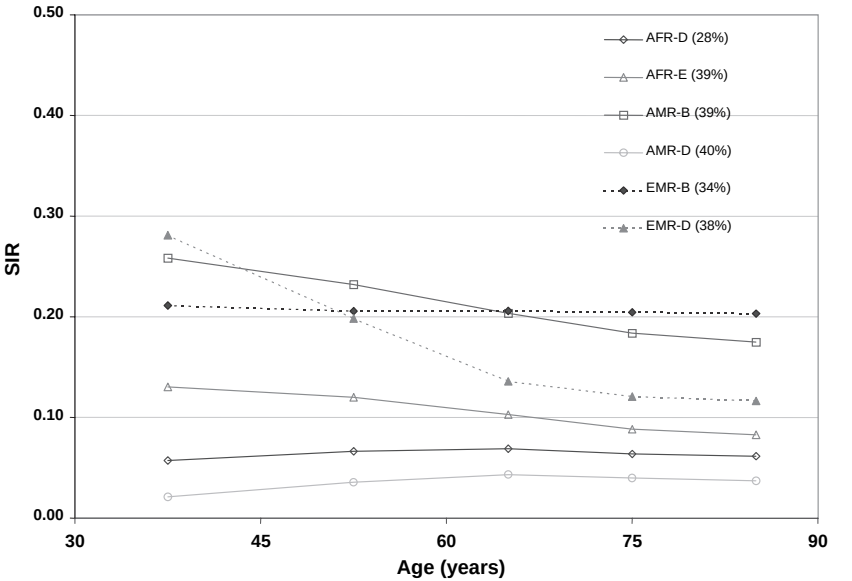
Study location (reference)	*Cancer site (ICD code)*	*Number of cases and control choice*	*Covariate adjustment*	*Effect size*
Bombay (Rao et al. 1994)	Oral (excluding 141.0 and 145.3)	713 male cases; 635 male hospital-based controls without cancer, benign tumour and infectious disease	Age and area of residence	Non-drinkers: $RR_{chewing} = 3.64$; $RR_{smoking} = 1.69$; $RR_{chewing+smoking} = 2.93$ Drinkers: $RR_{chewing} = 4.32$; $RR_{smoking} = 2.44$; $RR_{chewing+smoking} = 8.88$
Bhopal (Dikshit and Kanhere 2000)	Oral cavity (140.0–144.9, 145.0–145.2, 145.5–145.9)	148 male cases; 260 controls randomly selected from a survey of tobacco habits	Age	$OR_{chewing} = 10.6$; $OR_{smoking}$ (<10 cig/day) = 1.0; $OR_{smoking}$ (≥20 cig/day) = 4.9; $OR_{chewing+smoking}$ (<20 cig/day) = 8.4; $OR_{chewing+smoking}$ (≥20 cig/day) = 16.3
Southern India (Balaram et al. 2002)	Oral	591 cases; hospital-based controls matched by medical centre, age and sex	Age, sex, medical centre, education and alcohol	$OR_{chewing} = 9.19$; $OR_{smoking}$ (<20 cig/day) = 1.78; $OR_{smoking}$ (≥20 cig/day) =3.69; $OR_{chewing+smoking}$ (<20 cig/day) = 8.86; $OR_{chewing+smoking}$ (≥20 cig/day) = 6.69[b]

[a] All studies were case–control and took place in India.

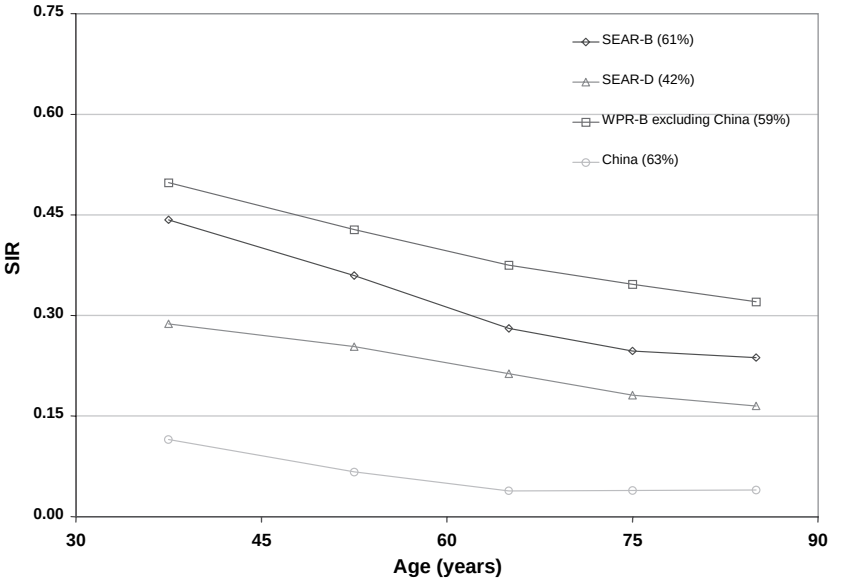
[b] The effect estimates are for males only since none or few of the female cases smoked.

Figure 11.4 Estimates of smoking impact ratio (*SIR*) by age, sex and subregion

(a) Developing countries (male) I



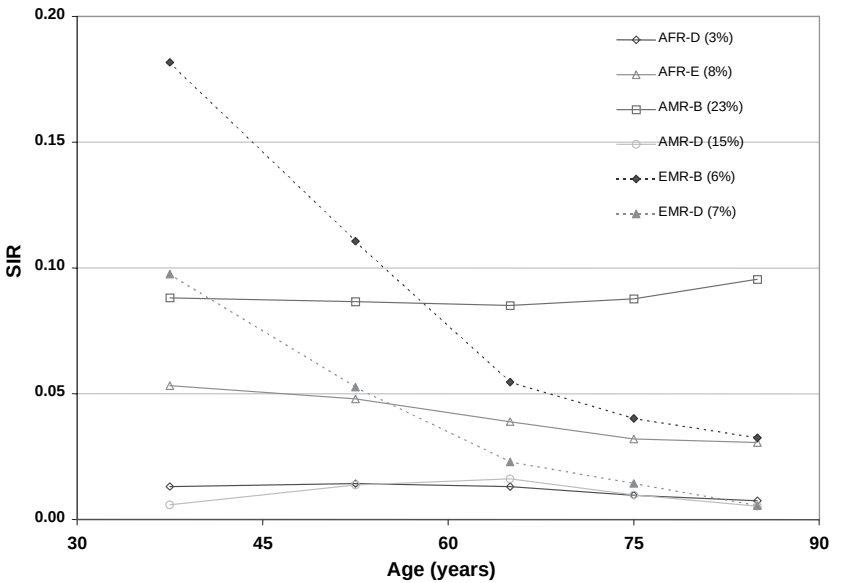
(b) Developing countries (male) II



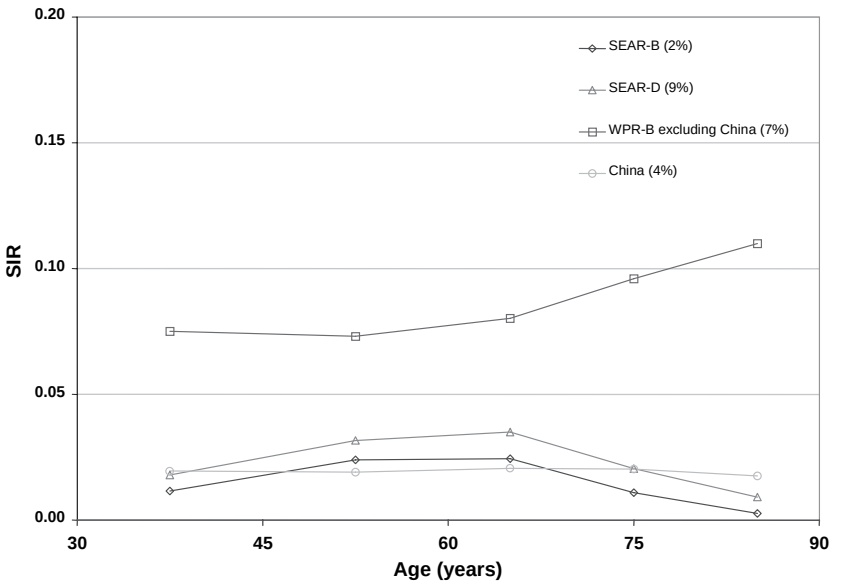
continued

Figure 11.4 Estimates of smoking impact ratio (*SIR*) by age, sex and subregion (*continued*)

(c) Developing countries (female) I



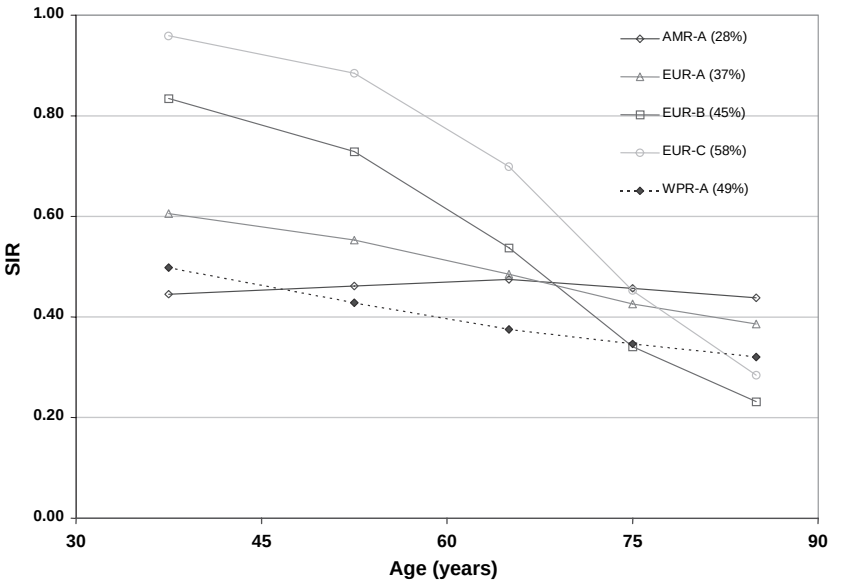
(d) Developing countries (female) II



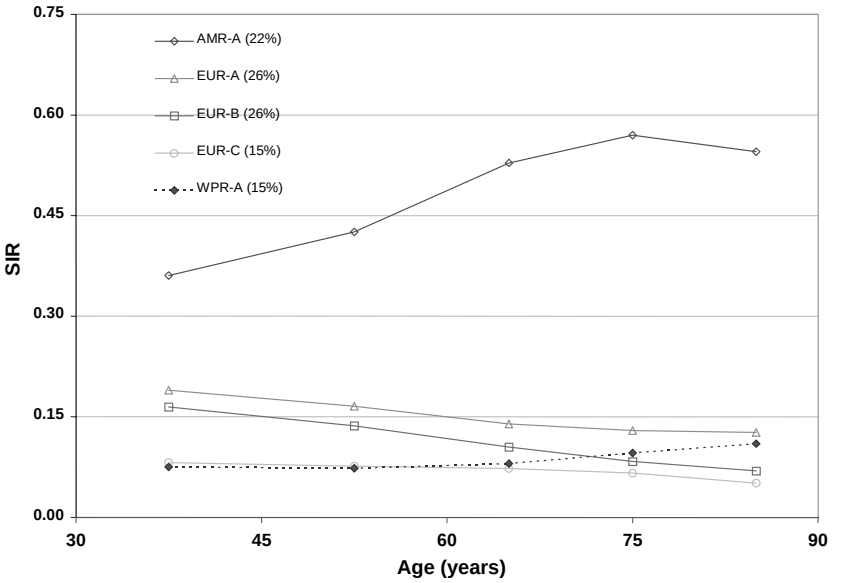
continued

Figure 11.4 Estimates of smoking impact ratio (*SIR*) by age, sex and subregion (*continued*)

(e) Industrialized countries (male)



(f) Industrialized countries (female)



Note: The vertical axis scales are different in the different panels of the figure to increase resolution. The figures in parentheses next to the legend indicate estimates of the subregional prevalence.

Source: Ezzati and Lopez (2003).

Hence the aggregate estimates for this subregion are dominated by the Chinese data. This division allows the characteristics of the other countries in the subregion to also be considered, in particular given the role of higher background lung cancer mortality in China. Table 11.9 provides the *SIR* distribution, divided as defined earlier.

A number of important features of the global smoking epidemic can be seen in the different panels of Figure 11.4:

1. The largest accumulated risk of smoking for males aged <70 years in the countries of eastern Europe and the former Soviet Union (EUR-B and EUR-C). For older males (aged ≥70 years), North America and western European countries have the largest accumulated risk. These two results are consistent with the very high current and recent prevalence of smoking among eastern European men which has been sustained for several decades, and the longer history of smoking among North American and western European men.

The accumulated hazards of smoking among men were lowest in AMR-D, AFR-D and AFR-E. In these subregions, the rise in smoking has been a recent phenomenon. The results for China (WPR-B) are particularly important and instructive. The background-adjusted *SIR* values for China were still fairly low, despite high lung cancer mortality in this country. At the time of the Liu et al. (1998) study (in 1990) the relative risk of lung cancer for a Chinese smoker was less than 3.0 because of the more recent start of the epidemic in this country. Over the next few decades, increasing accumulated exposure to smoking may well result in rising lung cancer mortality in China to levels comparable to populations with life-long smokers (such as those in North America and western Europe where the relative risks for lung cancer are approximately 20). Together with the finding of Liu et al. (1998) that smoking acts to "amplify" the high background rates of lung cancer, this increase in accumulated hazard will result in enormous lung cancer (and other) mortality in China.

Examining prevalence and *SIR* patterns simultaneously also emphasizes the importance of considering accumulated risks. For example, the current prevalence of smoking among adult men in AMR-A was equal to AFR-D and lower than all other subregions in the developing world. At the same time, the *SIR* values for AMR-A males were larger than those of most developing subregions because of the histories of smoking. In AMR-A, smoking has been declining and current prevalence would underestimate the current impacts of smoking. In developing countries, on the other hand, smoking has been rising in recent decades with current prevalence being comparable to AMR-A, but the accumulated hazards were still lower.

2. For women, AMR-A had the single highest accumulated risk from smoking. Although women in many countries in western Europe

Table 11.9 Prevalence of exposure by subregion, age and sex

		Prevalence of exposure (%)															
		0–4 years[b]		*5–14 years*[b]		*15–29 years*[b]		*30–44 years*		*45–59 years*		*60–69 years*		*70–79 years*		*≥80 years*	
Subregion	*Exposure variable*[a]	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
AFR-D	1	NA	NA	NA	NA	NA	NA	75	96	75	96	75	96	75	96	75	96
	2	NA	NA	NA	NA	NA	NA	25	4	23	3	23	4	25	4	25	4
	3	NA	NA	NA	NA	NA	NA	0	0	2	1	2	1	0	0	0	0
AFR-E	1	NA	NA	NA	NA	NA	NA	55	88	55	88	55	88	55	88	55	88
	2	NA	NA	NA	NA	NA	NA	40	7	43	8	45	10	45	12	45	11
	3	NA	NA	NA	NA	NA	NA	5	5	2	4	0	2	0	0	0	0
AMR-A	1	NA	NA	NA	NA	NA	NA	56	66	55	59	50	45	55	39	72	78
	2	NA	NA	NA	NA	NA	NA	0	0	0	0	0	0	0	0	0	0
	3	NA	NA	NA	NA	NA	NA	44	34	45	41	50	55	45	61	28	22
AMR-B	1	NA	NA	NA	NA	NA	NA	60	75	60	75	60	75	60	75	60	75
	2	NA	NA	NA	NA	NA	NA	4	20	15	21	18	20	24	22	25	17
	3	NA	NA	NA	NA	NA	NA	35	5	25	4	22	5	16	3	15	8
AMR-D	1	NA	NA	NA	NA	NA	NA	61	84	61	84	61	84	61	84	61	84
	2	NA	NA	NA	NA	NA	NA	39	16	39	16	39	16	39	16	39	16
	3	NA	NA	NA	NA	NA	NA	0	0	0	0	0	0	0	0	0	0
EMR-B	1	NA	NA	NA	NA	NA	NA	66	77	66	94	66	94	66	94	66	94
	2	NA	NA	NA	NA	NA	NA	8	0	13	0	8	0	12	0	11	3
	3	NA	NA	NA	NA	NA	NA	27	23	22	6	26	6	23	6	24	3
EMR-D	1	NA	NA	NA	NA	NA	NA	63	92	63	92	63	92	63	92	63	100
	2	NA	NA	NA	NA	NA	NA	0	0	25	7	29	7	33	8	33	0
	3	NA	NA	NA	NA	NA	NA	37	8	13	1	8	1	4	0	5	0
EUR-A	1	NA	NA	NA	NA	NA	NA	37	74	45	74	52	74	63	74	63	74
	2	NA	NA	NA	NA	NA	NA	0	0	0	5	0	13	0	12	0	14
	3	NA	NA	NA	NA	NA	NA	63	26	55	20	48	13	37	14	37	12

continued

Table 11.9 Prevalence of exposure by subregion, age and sex (*continued*)

		Prevalence of exposure (%)															
		0–4 years[b]		5–14 years[b]		15–29 years[b]		30–44 years		45–59 years		60–69 years		70–79 years		≥80 years	
Subregion	Exposure variable[a]	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
EUR-B	1	NA	NA	NA	NA	NA	NA	12	74	25	74	55	74	55	74	55	74
	2	NA	NA	NA	NA	NA	NA	0	2	0	12	0	18	5	21	30	2
	3	NA	NA	NA	NA	NA	NA	88	23	75	14	45	8	40	4	15	0
EUR-C	1	NA	NA	NA	NA	NA	NA	2	85	7	85	42	85	42	85	42	85
	2	NA	NA	NA	NA	NA	NA	0	6	0	7	0	10	0	7	46	15
	3	NA	NA	NA	NA	NA	NA	98	9	93	8	58	5	58	9	12	0
SEAR-B	1	NA	NA	NA	NA	NA	NA	40	97	40	97	40	97	40	97	40	100
	2	NA	NA	NA	NA	NA	NA	0	3	24	0	35	0	43	2	43	0
	3	NA	NA	NA	NA	NA	NA	60	0	36	3	25	3	17	0	17	0
SEAR-D	1	NA	NA	NA	NA	NA	NA	55	91	55	91	55	91	55	91	55	91
	2	NA	NA	NA	NA	NA	NA	6	9	19	6	24	6	33	9	35	9
	3	NA	NA	NA	NA	NA	NA	39	0	26	3	21	4	12	0	10	0
WPR-A	1	NA	NA	NA	NA	NA	NA	51	85	51	85	51	85	51	84	51	85
	2	NA	NA	NA	NA	NA	NA	28	8	37	6	25	4	4	0	0	0
	3	NA	NA	NA	NA	NA	NA	20	7	12	9	23	9	45	16	49	15
WPR-B (excluding China)	1	NA	NA	NA	NA	NA	NA	31	90	31	90	31	90	31	90	31	90
	2	NA	NA	NA	NA	NA	NA	0	0	26	2	27	0	34	0	42	0
	3	NA	NA	NA	NA	NA	NA	69	10	43	8	42	10	35	9	27	10
China	1	NA	NA	NA	NA	NA	NA	37	96	37	96	37	96	37	96	37	96
	2	NA	NA	NA	NA	NA	NA	63	1	63	2	63	1	63	1	63	3
	3	NA	NA	NA	NA	NA	NA	0	2	0	1	0	3	0	2	0	1

NA Not applicable.

[a] The exposure variable is smoking impact ratio (*SIR*), divided into three categories: 1) $SIR = 0$; 2) $0 < SIR \leq 0.5$; 3) $0.5 < SIR \leq 1.0$ as described earlier.

[b] No risk is estimated for those aged <30 years.

(EUR-A) have smoked for a long time (in particular in the United Kingdom), smoking is a more recent phenomenon in the southern parts of the continent, and therefore the overall *SIR* is still lower than in AMR-A. *SIR* values for women were consistently low in developing countries except for younger and middle-aged women in AMR-B (Latin America and the Caribbean) and young adult women in EMR-B. Once again, comparing *SIR* values for females in AMR-A, whose current prevalence of smoking is 22% (reflecting recent declines in female smoking in North America), with those for males in many subregions of the developing world, who have higher current prevalence but lower *SIR*, illustrates the inadequacy of current prevalence as a marker for smoking risk.[8]

3. Age patterns of *SIR* estimates for the different subregions also provide information about the state of the smoking epidemic. For each age–sex group, *SIR* is excess lung cancer, relative to the same age–sex group of American smokers in the 1980s. Among men in industrialized countries, the *SIR* values were relatively constant across ages in AMR-A, but decline with age in other industrialized regions, with EUR-A being closest to the constant pattern. These inter-subregional and intra-subregional age patterns imply that, when compared to the same age group of American smokers in the 1980s, age patterns of smoking have been relatively constant in North America whereas smoking has been more concentrated among younger and middle-age men in Europe and the Western Pacific, especially in the former Soviet Union (EUR-C). In the developing countries of Latin America and the Caribbean, the Eastern Mediterranean, and sub-Saharan Africa, smoking also seems to have had fairly constant effects across ages, when each is compared to the same age group of American smokers in the 1980s. In Asia, on the other hand, smoking had a greater impact on younger and middle-aged male cohorts than at older ages when compared to the same age group of American smokers in the 1980s.

Overall, the age patterns of *SIR* were less variant among women in both developing and industrialized countries compared to men. In AMR-B, EMR-B, EMR-D, and the EUR subregions there is more smoking among younger and middle-age women than at older ages, when each is compared to the same age group of female American smokers in the 1980s. In Asia, female smoking seems to peak among the middle-aged cohorts, which may reflect social factors that would prevent smoking among many young women. In North America, the distribution was more towards older age groups when compared to the same age group of female American smokers in the 1980s.

3.2 Mortality and disease burden due to smoking

Tables 11.10 and 11.11 provide the estimated number of smoking-attributable deaths and DALYs for males and females in developing and industrialized countries. Table 11.12 divides the estimates of global mortality

due to smoking into broad causes and age groups. Although the results were estimated for the eight age groups described in Table 11.9 (assumed to be zero for the first three age groups <30 years), they are reported in two age groups (30–69 and ≥70 years) to be comparable with previous estimates of mortality due to smoking, such as those in Peto et al. (1992). The distribution of mortality and DALYs by broad disease groups is given in Figures 11.5 and 11.6.

The 4.83 (95% CI 3.94–5.93) million deaths due to smoking accounted for 12% of total global adult (aged ≥30 years) mortality.[9] The shares of adult male and female total mortality due to smoking were 18% and 5%, respectively. Of these deaths, 2.69 million were among those aged 30–69 years, resulting in a larger number of life years lost to premature mortality, and 2.14 million among those aged >69 years. As seen in a comparison of Tables 11.10 and 11.11, although developing and industrialized countries accounted for virtually equal numbers of global mortality, the burden of disease associated with this risk factor

Table 11.10 Mortality (in millions) due to smoking in developing and industrialized countries, 2000

	Male	*Female*	*Total*
Developing[a]	2.02 (1.56–2.50)[c]	0.38 (0.25–0.65)[c]	2.41 (1.80–3.15)[c]
Industrialized[b]	1.81 (1.62–2.02)[c]	0.61 (0.52–0.75)[c]	2.43 (2.13–2.78)[c]
Total	3.84 (3.17–4.53)[c]	1.00 (0.76–1.40)[c]	4.83 (3.94–5.93)[c]

[a] Developing countries include those in AFR, AMR-B, AMR-D, EMR, SEAR and WPR-B subregions.

[b] Industrialized countries include those in AMR-A, EUR and WPR-A.

[c] Numbers in parentheses are 95% confidence intervals.

Table 11.11 Loss of healthy life years (in thousands of DALYs) due to tobacco-caused mortality and morbidity in developing and industrialized countries, 2000

	Male	*Female*	*Total*
Developing[a]	28015 (4.4%)[c]	4962 (0.8%)[c]	32977 (2.7%)[c]
Industrialized[b]	20162 (17%)[c]	5942 (6.2%)[c]	26104 (12%)[c]
Total	48177 (6.3%)[c]	10904 (1.6%)[c]	59081 (4.1%)[c]

[a] Developing countries include those in AFR, AMR-B, AMR-D, EMR, SEAR and WPR-B subregions.

[b] Industrialized countries include those in AMR-A, EUR and WPR-A.

[c] Figures in parentheses indicate the proportion of overall disease burden in each category attributable to smoking.

Table 11.12 Global mortality due to smoking by cause, sex and age, 2000

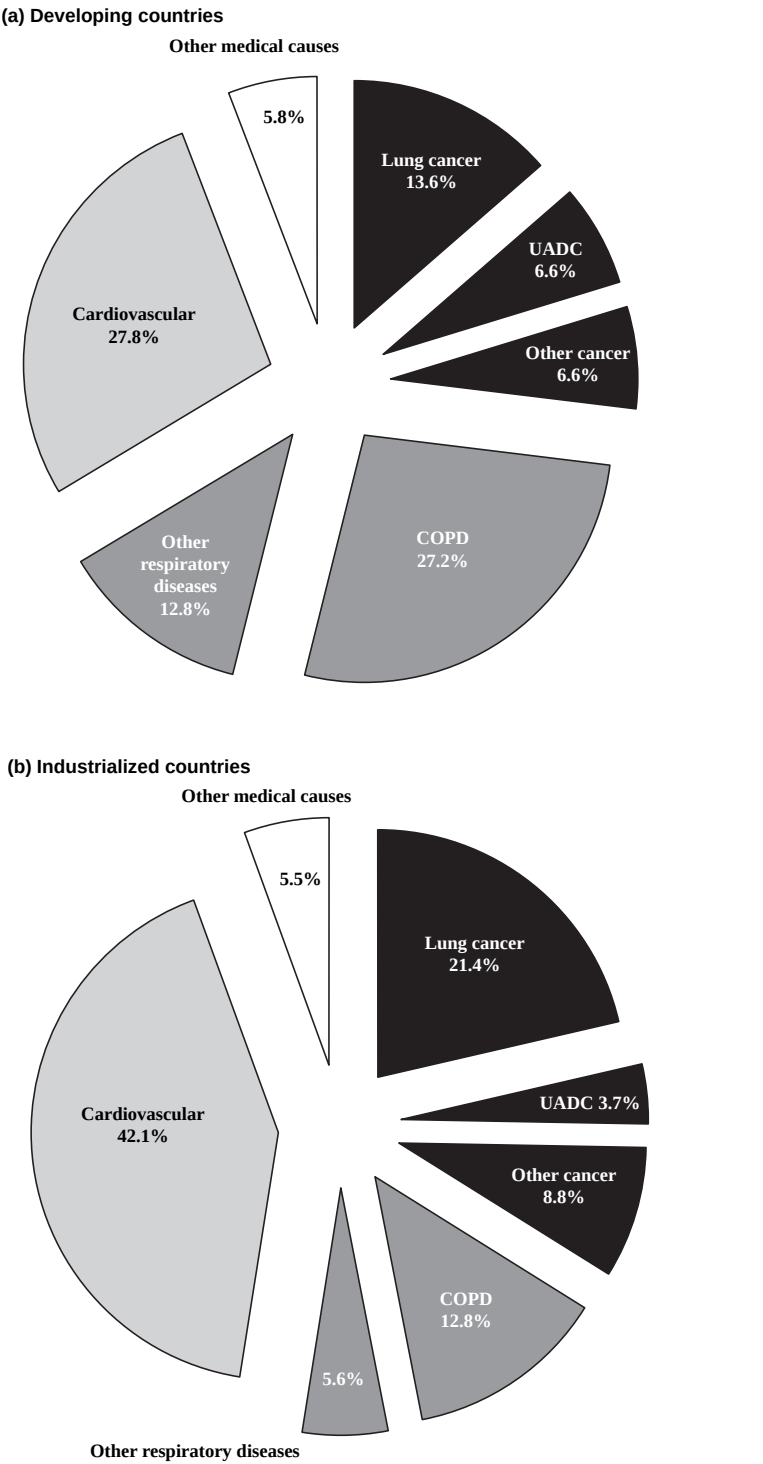
	Male				*Female*			
	No. of deaths (000s)	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*
Cause[a]	*30–69 years*		*≥70 years*		*30–69 years*		*≥70 years*	
Lung cancer	398	77	294	82	77	44	79	54
Upper aerodigestive cancer[b]	152	46	66	42	17	12	15	13
Other cancer[b]	195	15	135	13	17	1	24	2
COPD[c]	269	54	433	52	86	24	178	19
Other respiratory diseases	274	22	93	11	34	5	32	4
Cardiovascular diseases	848	24	476	12	143	6	223	4
Other attributable medical causes	0	0	0	0.0	0	0	0	0
Other medical causes	145	17	57	8	36	5	35	4
Total medical	2 280	22	1 556	18	410	6	587	5
Non-medical (accidents and injuries)	0	0	0	0.0	0	0	0	0
Total mortality	2 280	19	1 556	18	410	5	587	5

[a] See Table 11.1 for details on causes of death.

[b] The estimates of mortality for upper aerodigestive cancer include only ICD codes 140–150. ICD code 161 is included with other cancers.

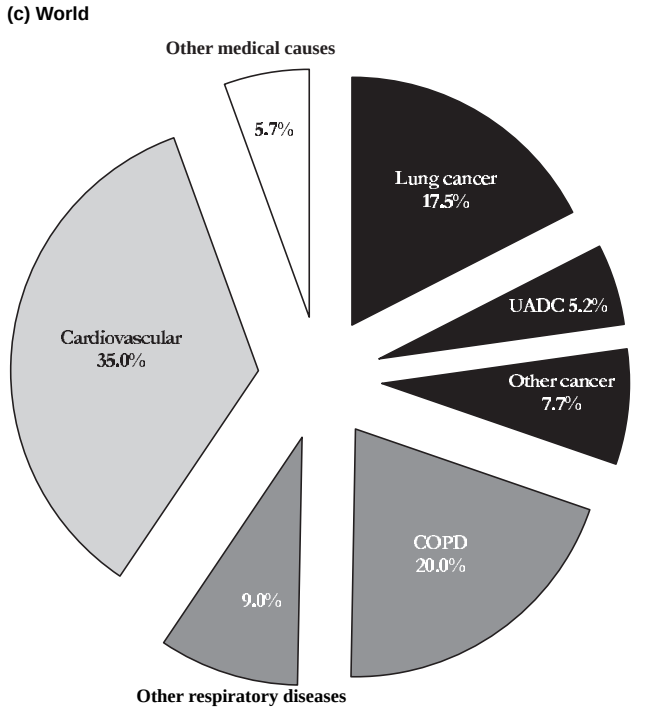
[c] The estimates also include ICD 495, which was not included in the CPS-II relative risk estimates, due to GBD grouping; normally this cause would have been included with other medical causes.

Figure 11.5 Distribution of mortality due to smoking by cause and development group, 2000



continued

Figure 11.5 Distribution of mortality due to smoking by cause and development group, 2000 (*continued*)



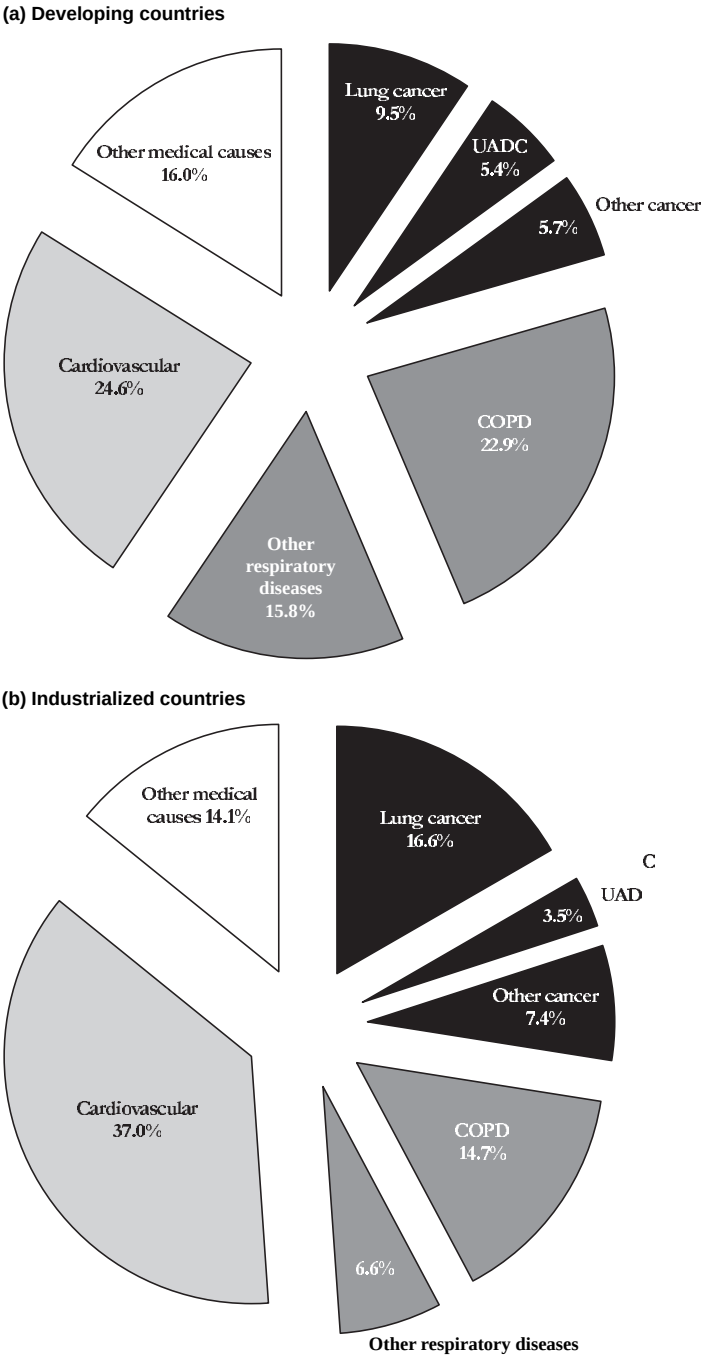
UADC Upper aerodigestive cancer.

Note: See Table 11.1 for details on causes of death.

was much higher in the former. As discussed below, this is because in general smoking-caused mortality in developing countries occurs at earlier ages than in industrialized nations accounting for a larger loss of life from premature mortality. Further, a comparison of Figures 11.5 and 11.6 indicates that the relative share of cancers in terms of the total burden of disease is lower than their comparative role in mortality because of the shorter morbidity associated with cancers compared to the other categories.

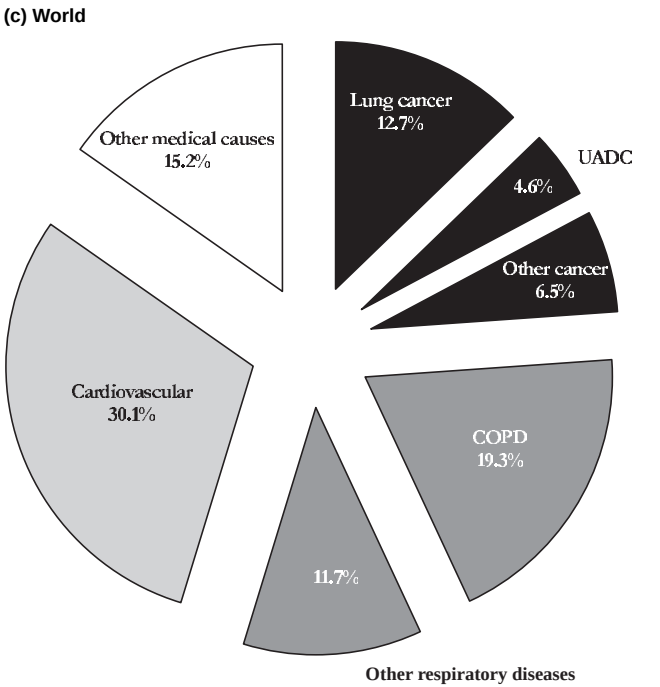
Lung cancer was the disease with the highest fraction attributable to smoking. Seventy-one per cent of all lung cancers or 0.85 million deaths (79% or 0.69 million deaths among men and 48% or 0.16 million deaths among women) were attributable to smoking. However, cardiovascular diseases were the largest cause of death due to smoking in terms of number of deaths. One million six hundred and ninety thousand cardiovascular disease deaths (1.37 million among men and 0.32 million

Figure 11.6 Distribution of DALYs due to smoking by cause and development group, 2000



continued

Figure 11.6 Distribution of DALYs due to smoking by cause and development group, 2000 (*continued*)



UADC Upper aerodigestive cancer.

Note: See Table 11.1 for details on causes of death.

among women) were due to smoking, accounting for 35% of all smoking-attributable deaths (35% among men and 37% among women). Overall, 11% of all cardiovascular deaths in the world were attributable to smoking (17% among men and 4% among women). Only when all cancers are considered together did they approach cardiovascular diseases as the largest cause of death due to smoking. One million four hundred and seventy thousand neoplasm deaths (22% of all cancer deaths; 1.24 million or 33% of all adult male cancer deaths and 0.23 million or 8% of all adult female cancer deaths) were due to smoking, accounting for 30% of all smoking-attributable deaths (32% among men and 23% among women).

3.3 Mortality in industrialized countries

Table 11.13 provides the details of mortality due to smoking in industrialized countries by age, sex and causes of death. In the year 2000,

smoking caused an estimated 2.43 (95% CI 2.13–2.78) million deaths in industrialized countries for people aged >30 years, accounting for 19% of adult mortality. One million eight hundred and ten thousand (95% CI 1.62–2.02) deaths were among men (28% of total mortality of adult males) and 0.61 (95% CI 0.52–0.75) million among women (10% of total mortality of adult females). The magnitude of the years of life lost due to premature mortality becomes more obvious when we note that 1.19 million, or approximately one half, of these deaths were among those aged 30–69 years.

In industrialized countries, smoking-caused deaths accounted for 33% of total mortality among males between the ages of 30 and 69 years (1.00 million deaths), 24% of total mortality among males aged >70 years (0.81 million deaths), 12% of total mortality among females between the ages of 30 and 69 years (0.19 million deaths), and 9% of total mortality among females aged >70 years (0.42 million deaths).

The fraction of smoking-attributable mortality among men was highest in the EUR-C and AMR-A subregions, causing 0.55 million and 0.35 million smoking-attributable male deaths, respectively. These were 32% and 28% of all adult male deaths (36% and 24% of all deaths for 30–69 and ≥70 age groups in EUR-C; 31% and 26% of all deaths for 30–69 and ≥70 age groups in AMR-A reflecting the fact that the two subregions are at different stages of the tobacco epidemic). Among women the highest fraction of smoking-attributable mortality was in AMR-A where 0.29 million deaths (22% of all mortality) (27% and 20% of all deaths for the 30–69- and ≥70-year age groups, respectively), were caused by smoking. The lowest fraction of smoking-attributable mortality among men in the industrialized world was in WPR-A (22% of all deaths; 18% and 24% of all deaths for 30–69- and ≥70-year age groups, respectively) and among women in EUR-C (4% of all deaths; 6% and 4% of all deaths for 30–69- and ≥70-year age groups, respectively) and EUR-B (6% of all deaths; 10% and 5% of all deaths for the 30–69- and ≥70-age groups, respectively).

For both males and females in all subregions and age groups, lung cancer was the cause of death with the largest fraction attributable to smoking, ranging from a low of 45% among females aged ≥30 years in EUR-C to a high of 91–94% among males aged ≥30 years in AMR-A, EUR-A, EUR-B and EUR-C. Overall 92% of all lung cancer deaths among adult (≥30 years) males (0.40 million lung cancer deaths) and 71% of all lung cancer deaths among adult (≥30 years) females (0.12 million lung cancer deaths) in industrialized countries were caused by smoking.

Despite the predominance of smoking as a cause, lung cancer accounted for only 22% (0.40 million) of smoking-attributable deaths among men and 19% (0.12 million) among women in industrialized countries. In fact, in terms of the fraction of all causes of death due

Table 11.13 Mortality due to smoking in industrialized countries by cause, sex and age, 2000

	Male				*Female*			
	No. of deaths (000s)	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*
Cause[a]	*30–69 years*		*≥70 years*		*30–69 years*		*≥70 years*	
Lung cancer	216	91	187	92	50	70	67	72
Upper aerodigestive cancer[b]	52	72	24	66	5	39	9	41
Other cancer[b]	97	21	88	16	11	2	18	3
COPD[c]	63	84	142	77	20	62	86	61
Other respiratory diseases	67	44	38	16	9	15	23	8
Cardiovascular diseases	455	40	298	17	77	13	192	7
Other attributable medical causes	55	32	33	13	17	14	28	7
Other medical causes	0	0	0	0	0	0	0	0
Total medical	1005	39	810	24	189	13	423	9
Non-medical (accidents and injuries)	0	0	0	0	0	0	0	10
Total mortality	1005	33	810	24	189	12	423	9

[a] See Table 11.1 for details on causes of death.

[b] The estimates of mortality for upper aerodigestive cancer include only ICD codes 140–150. ICD code 161 is included with other cancers.

[c] The estimates also include ICD 495, which was not included in the CPS-II relative risk estimates, due to GBD grouping; normally this cause would have been included with other medical causes.

to smoking, cardiovascular diseases led the grouping used in Table 11.1 and accounted for 42% and 44% of deaths caused by smoking among men and women, respectively (0.75 million male deaths and 0.27 million female deaths from cardiovascular diseases due to smoking). When all cancers are considered together, however, the numbers approached cardiovascular diseases for men. Neoplasm deaths accounted for 37% and 26% of all smoking caused deaths among men and women, respectively, in industrialized countries (0.66 million male deaths and 0.16 million female deaths from all cancers due to smoking accounting for 43% and 13% of all cancers among men and women, respectively).

3.4 Mortality in developing countries

Table 11.14 provides the details of mortality due to smoking in developing countries by age, sex and cause of death in 2000. The number of deaths attributable to smoking among people aged >29 years in developing countries in 2000 was 2.41 (95% CI 1.80–3.15) million accounting for 9% of total adult mortality in these countries. Of the smoking-attributable deaths, 2.02 (95% CI 1.56–2.50) million were among men (14% of total adult male mortality) and 0.38 (95% CI 0.25–0.65) million among women (3% of total adult female mortality). About twice as many—1.5 million deaths—deaths were among those between 30 and 69 years compared with 0.91 million among those aged >69 years.

In developing countries also, lung cancer was the disease with the highest fraction due to smoking. Fifty-five per cent of all lung cancers or 0.33 million deaths (67% or 0.29 million deaths among men and 25% or 39 000 deaths among women) were attributable to smoking. But lung cancer accounted for only 14% of all smoking-attributable mortality (14% among men and 10% among women) vs 21% in industrialized countries. As in the industrialized countries, cardiovascular diseases were the largest cause of death due to smoking, followed very closely by COPD. Six hundred and seventy thousand cardiovascular deaths (0.57 million among men and 97 000 among women) were due to smoking, accounting for 28% of all smoking-attributable deaths (28% among men and 25% among women). Six hundred and fifty thousand COPD deaths (0.50 million among men and 0.16 million among women) were due to smoking accounting for 27% of all smoking-attributable deaths (25% among men and 41% among women). This high contribution from COPD is consistent with direct observations of Liu et al. (1998) in China, where the high background (non-smoker) rates of COPD mortality due to other risk factors result in an even larger mortality due to smoking from this cause. Further, the lower contribution of cardiovascular diseases to smoking-caused mortality compared to the 42% in industrialized countries is likely to be due to lower overall cardiovascular disease mortality in these populations. Future changes in dietary risk factors and

Table 11.14 Mortality due to smoking in developing countries by cause, sex and age, 2000

	Male				*Female*			
	No. of deaths (000s)	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*	*No. of deaths (000s)*	*Fraction of total mortality (%)*
Cause[a]	*30–69 years*		*≥70 years*		*30–69 years*		*≥70 years*	
Lung cancer	181	65	108	69	27	26	12	22
Upper aerodigestive cancer[b]	100	38	42	35	12	10	6	7
Other cancer[b]	98	11	48	9	7	1	6	1
COPD[c]	206	49	290	45	65	20	93	12
Other respiratory diseases	207	18	55	9	26	4	9	1
Cardiovascular diseases	393	17	178	8	66	4	31	1
Other attributable medical causes	90	14	25	5	19	3	7	0
Other medical causes	0	0	0	0	0	0	0	3
Total medical	1 275	16	746	14	221	4	164	3
Non-medical (accidents and injuries)	0	0	0	0	0	0	0	0
Total mortality	1 275	14	746	14	221	3	164	3

[a] See Table 11.1 for details on causes of death.

[b] The estimates of mortality for upper aerodigestive cancer include only ICD codes 140–150. ICD code 161 is included with other cancers.

[c] The estimates also include ICD 495, which was not included in the CPS-II relative risk estimates, due to GBD grouping; normally this cause would have been included with other medical causes.

increased exposure to other cardiovascular disease risks in developing countries, even with similar attributable fractions, would result in a rise in tobacco-caused mortality in these subregions. As for the global total and in industrialized countries, when all cancers are considered together, they approach cardiovascular diseases and COPD as the largest cause of death due to smoking. Six hundred and fifty thousand neoplasm deaths (16% of all cancer deaths; 0.58 million or 26% of all adult male cancer deaths and 69 000 or 4% of all adult female cancer deaths) were due to smoking, accounting for 27% of all smoking-attributable deaths (29% among men and 18% among women).

In general, there was larger variation in mortality due to smoking among different subregions of developing countries than industrialized countries, because of the variability in the stages of the smoking epidemic. In the sections below, we discuss the estimates for different areas of developing countries, including comparisons with direct estimates where available.

China

Liu et al. (1998) estimated that smoking caused 0.6 million deaths in China in 1990 and expected this number to rise to 0.8 million in 2000 if the fraction of mortality due to smoking remained unchanged. Since smoking had been rising rapidly in China since the 1970s, the fraction of deaths due to smoking was expected to rise, resulting in more deaths than the 0.8 million estimate. The 2000 estimates were based on a projected total adult (≥35 years) mortality of 9 million in China in 2000.[10]

In fact, total adult mortality in China in 2000 from the GBD mortality database was 7.5 million deaths, reflecting recent health gains in China. Applying the 1990 cause-specific mortality and total mortality attributable fractions from Liu et al. (1998) to the 2000 mortality estimates in China would result in approximately 0.6 million smoking-attributable deaths, with 0.51 million male deaths and 0.09 million female deaths. Actual mortality is expected to be higher, in particular among men, because of the rising trend of smoking (Corrao et al. 2000; WHO 1997). Further, since the proportional mortality analysis of Liu et al. (1998) cannot estimate mortality from those causes in the reference group, smoking-attributable mortality is underestimated (to zero) for these causes, to the extent that smoking caused some deaths from these diseases.

As described above in the section on methods, in estimating smoking-attributable mortality in China, we converted the 1990 relative risks for smoking estimated in Liu et al. (1998) to relative risks per unit of *SIR*. We then estimated the *SIR* for in China in 2000 to capture the impacts of the more recent increase in smoking. Mortality was then estimated by applying the relative risk estimates from 1990 (with some correction for potential confounding) to 2000 *SIR* estimates. The

exception is for diseases in the category "other medical causes" in Table 11.1, for which proportional mortality analysis does not estimate relative risks. For these causes, we used the relative risks of CPS-II from Table 11.1.

Using this method for China we estimated that smoking caused 0.59 million deaths, 0.49 million of which are among men (13% of total adult male mortality) and the remaining 0.10 million among women (3% of total adult female mortality). In China, deaths caused by smoking accounted for 11% of total mortality among males between the ages of 30 and 69 years (0.22 million deaths), 15% of total mortality among males aged >69 years (0.27 million deaths), 2% of total mortality among females between the ages of 35 and 69 years (32 000 deaths), and 3% of total mortality among females aged >69 years (66 000 deaths).

The relatively small fraction of mortality among women due to smoking remained constant between 1990 and 2000, reflecting the stable, low prevalence of smoking among Chinese women. The fraction of mortality among men dropped for the 35–69-year age group from 13% to 11%, and increased from 12% to 15% for the ≥70-year age group. The increase among the older men is due to demographic shifts in smoking patterns. Tobacco consumption in China increased between 1970 and 1990 and then stabilized (Corrao et al. 2000; WHO 1997). Therefore, while many of the younger smokers in 1990 and in 2000 had started smoking around the same age, those in older age groups in 2000 are likely to have smoked for a longer time than those of similar age in 1990. This slight increase in the fraction of mortality attributable to smoking among the older age cohorts with the maturity of the smoking epidemic is consistent with historical trends in age-specific attributable fractions in Canada, the United Kingdom and the United States. The decline among the younger age groups was partially due to the 5% correction factor applied to the hazards for this country.

Lung cancer accounted for 20% and 18% of smoking-attributable mortality among men and women, respectively, in China, resulting in 98 000 male deaths and 17 000 female deaths. The fractions of smoking-attributable mortality from all cancers were 44% (215 000 deaths) for males and 29% (28 000 deaths) for females. This suggests that the contribution of smoking to mortality from cancers other than lung cancer is larger in China than in industrialized countries (Lopez 1998). In China, COPD also accounted for a large fraction of smoking-attributable mortality with 33% (163 000 deaths) and 61% (60 000 deaths) of smoking-caused mortality among men and women respectively.

India and SEAR-D[11]

Seven hundred and fifty thousand deaths among adult men and 110 000 among adult women were attributable to smoking in SEAR-D accounting for 18% and 3% of total mortality, respectively. Six hundred and thirty thousand of these deaths occured before the age of 70 (13%

of total mortality) and the remaining 230 000 among those aged ≥70 years (8% of total mortality).

Adult male lung cancer mortality, 82% of which (84 000 deaths) in this subregion is caused by smoking, accounted for 11% of smoking-attributable male mortality, the lowest fraction among males in any subregion. The 6000 lung cancer deaths among females attributed to smoking (26% of all female lung cancer deaths) was likewise the smallest fraction (6%) of smoking-attributable deaths compared with other subregions. When all cancers are considered together, smoking caused 0.18 million neoplasm deaths in SEAR-D in 2000 (160 000 among men and 14 000 among women). Cardiovascular diseases, with 0.28 million deaths (240 000 or 16% of all cardiovascular deaths among men and 34 000 or 2% of all cardiovascular deaths among women), were the cause of death with the highest number due to smoking and accounted for 33% of all smoking-attributable deaths (33% among men and 31% among women), reflecting the large contribution of this cause to adult male mortality in this subregion.

No *direct* nationally representative study of mortality due to smoking was available from India or other countries in SEAR-D at the time of writing. Estimates from specific regions within India as well as indirect national estimates, however, are available and can be used for comparison with our results. Gupta and Mehta (2000) estimated that the relative risk for mortality from all causes in a mixed cohort of male smokers and non-smokers aged >34 years in India relative to non-users of tobacco is approximately 1.63. Assuming, as in the case of CPS-II relative risks, that 30% of the excess risk is due to confounding (because of covariates such as chewing tobacco, diet, etc.) this relative risk and a smoking prevalence of 40–50% imply that 15–18% of all male mortality is due to smoking, a result consistent with our estimate of 18% of male mortality attributable to tobacco. Applying the relative risk of 2.1 obtained by Gajalakshmi et al. (2003) with the same correction factor will result in an even higher attributable fraction (23–28%) than ours. The estimates of total mortality in this chapter are lower than those by Gupta (1989) who attributes at least 19% of adult male mortality and 4% of adult female mortality to tobacco use, as well as those in a recent case–control study that finds an unadjusted attributable fraction of approximately 20% for all adult deaths among Indian men (Gajalakshmi et al. 2003).

Additional oral cancer mortality due to oral tobacco use

Using the methods described above, we estimated that there were 60 000 additional cases of oral cancer due to oral tobacco use (tobacco chewing) in SEAR-D, accounting for an additional 50% of oral cancers in the subregion. Of these, 39 000 were among men (48% of male oral cancer deaths) and 22 000 among women (54% of female oral cancer

deaths). We emphasize that these estimates are those cases of oral cancer that are caused by tobacco chewing *in addition* to smoking. Since many cases of oral cancer are likely to be affected by both habits, the overall effects of tobacco chewing are larger. Important sources of uncertainty in the estimates are the prevalence of oral tobacco use and relative risk estimates as well as the extent of overlap between tobacco smoking and chewing, especially for men.

Other developing countries

The fraction of total adult mortality due to smoking ranged from a low of 2–4% in AFR-D, AMR-D and AFR-E to a high of 11% in SEAR-B and 18% in WPR-B (excluding China). For males the lowest fraction of total mortality due to smoking was in AMR-D (3%), AFR-D (5%) and AFR-E (6%), reflecting the more recent smoking epidemic in these subregions. Given that the current prevalence of smoking among adult men is approximately 25–30% in AFR-D and 35–45% in AFR-E, this finding emphasizes the fact that current prevalence is a poor marker of accumulated smoking risks (see also Figure 11.4).

The highest fractions of adult male mortality due to smoking were in WPR-B (excluding china) (26%), SEAR-B (19%), EMR-B (15%) and AMR-B (15%). For females, the fraction of total mortality due to smoking in 2000 was equal to or below 2% in AFR-D, AFR-E, AMR-D, EMR-D and SEAR-B. The highest fractions of female mortality were in AMR-B (6%) and WPR-B (excluding China) (8%), reflecting more recent increases in female smoking in these subregions, especially with increasing urbanization and economic development.

4. Discussion

We applied the indirect method of Peto et al. (1992), which uses absolute lung cancer mortality in a population as a marker for accumulated hazards of smoking, to estimate the mortality and disease burden due to smoking in different subregions of the world. We chose the parameters of the model, such as relative risks and non-smoker lung cancer mortality, based on direct estimates or by extrapolation from other subregions based on best available evidence, explicitly stating the assumptions and reasons for each choice.

Using this method, we estimated that in 2000, approximately 4.83 (95% CI 3.94–5.93) million deaths worldwide were due to smoking, accounting for 12% of global adult mortality. Of these deaths, 2.41 (95% CI 1.80–3.15) million were in developing countries, marking a transition to an era in which smoking killed as many people in developing countries as in industrialized nations. In fact, even in the earlier stages of the tobacco epidemic, more men died from smoking in developing countries than in the industrialized nations (2.02 million vs 1.81

million). In addition to those cases shared with smokers, there were an estimated 60 000 deaths from oral tobacco use in SEAR-D. Premature mortality and morbidity caused by smoking accounted for an estimated 4.1% of the global burden of disease.

As we discussed under sources of uncertainty, using lung cancer—which has a longer lag than cardiovascular diseases—as the marker for accumulated smoking hazard, would result in an overestimation of hazard where there has been sharp drops in smoking and underestimation of hazard where there has been large increases in smoking. The former is most likely to apply to North America and among males in some countries in western Europe where smoking has declined (partially or fully offset by a continued choice of conservative relative risk estimates). On the other hand, the underestimation scenario would be applicable to most developing countries where smoking has been on the rise in the past few decades.

Total male mortality in terms of numbers of deaths was considerably higher than female mortality—3.0 fold in industrialized nations and 5.3 fold in developing countries. The decline of the male-to-female mortality ratio from 3.6 to 3.0 in industrialized countries between 1990 and 2000, however, reflects the recent relative increases in female smoking in these countries. 2.69 million deaths, more than one-half of the all global deaths due to smoking, were in the 30–69-year age group.

Due to differences in methodology and presentation, the estimates reported here are not fully comparable with those for previous years. The existing estimates of consumption, prevalence and mortality, however, generally indicate that mortality due to smoking (in terms of the fraction of cause-specific or all-cause mortality) has been relatively stable in industrialized countries over the past ten years. Some countries in the established market economies category have seen a small decline in male mortality while in most of these countries female mortality has increased, reflecting differential time trends in male and female smoking. Industrialized countries also have seen a small decline in the fraction of mortality in the 30–69-year age group and an increase in the ≥70-year group, confirming that in these countries as a whole, the smoking epidemic may be shifting with the effects increasingly being felt among the older age groups. There were, nonetheless, subregional differences, and the share of mortality at ages 30–69-years is in fact rising among females in some subregions including AMR-A and EUR-A.

Mortality and disease burden attributable to smoking, including its share of total mortality and sex or age patterns, varied importantly among different geographical regions of developing countries. This interregional variation, which is larger than that observed in industrialized countries, occurs because the nature and maturity of the smoking epidemic is highly affected by the varying economic and cultural determinants of smoking in these populations. A few general statements can nonetheless be made about the health effects of smoking in developing

countries. First, current hazards of smoking in these populations are highly concentrated among men. Given that the prevalence of smoking among women is still low in developing countries (with the exception of Latin America and the Caribbean and some countries in Asia), the current level of male mortality should provide an indicator of the large health losses that may well occur if female smoking increases over the next few decades. Second, relative to industrialized countries, developing countries have a higher proportion of smoking-attributable mortality in the 30–69 age group than in the ≥70 group (62% in developing countries vs 49% in industrialized countries). Coupled with the 1990–2000 trends in mortality for the two age groups in China, this suggests that as people (mostly men) who began smoking over the past three decades in developing countries become older, mortality due to smoking will continue to rise as a share of cause-specific mortality; and almost inevitably as a share of total mortality.

Smoking prevalence in some developing countries appears to have stabilized, albeit at very high levels. In others, it is still rising. Given the gradually shifting disease patterns and because most of the growth in global population is expected to take place in the developing world, the health effects of smoking, already one of the most important global health hazards, will continue to rise unless effective interventions and policies that curb and reduce smoking among males and prevent increases among females in these countries are implemented.

5. Projected future exposure

Many diseases caused by smoking, in particular various malignant neoplasms and COPD, occur after long delays. This motivated using *SIR* as the exposure variable for estimating the accumulated hazards of smoking. Disease burden due to smoking in the next few decades will depend on both past and future smoking patterns. There is therefore a need to link estimates of accumulated current exposure, which are in the form of *SIR* estimates, with future exposure, which is often in the form of projections of prevalence of smoking or tobacco consumption (whether under the business-as-usual scenario or some counterfactual). Further, the combination of past and projected future exposure must be presented in the form of a single exposure variable which accounts for hazard accumulation. We used the following steps to estimate future smoking prevalence and tobacco consumption and convert these to estimates of lung cancer mortality and *SIR*.

1. We estimated past and current age–sex-specific smoking prevalence under the business-as-usual scenario based on a descriptive model of the smoking epidemic (Lopez et al. 1994), calibrated to regional characteristics of the epidemic for different subregions. The tobacco epidemic was divided into five stages (early, rising, peak or maturity, declining and late)

as well as five transitional stages as seen in Figure 11.7. Historical evidence from multiple industrialized countries consistently shows that the youngest and oldest age groups at any stage of the epidemic have lower smoking prevalence (Gajalakshmi et al. 2000; Nicolaides-Bouman et al. 1993), the former probably because of economic and social constraints and the latter because of a higher mortality rate among smokers. The prevalence distribution is also based on the observation that in the rising stages of the epidemic, younger adults begin to smoke more than the older adults but as the epidemic matures the age-pattern becomes more stable (Gajalakshmi et al. 2000). Finally, as observed in historical data we assumed that the prevalence of female smoking is lower than that of males at every stage of the epidemic.

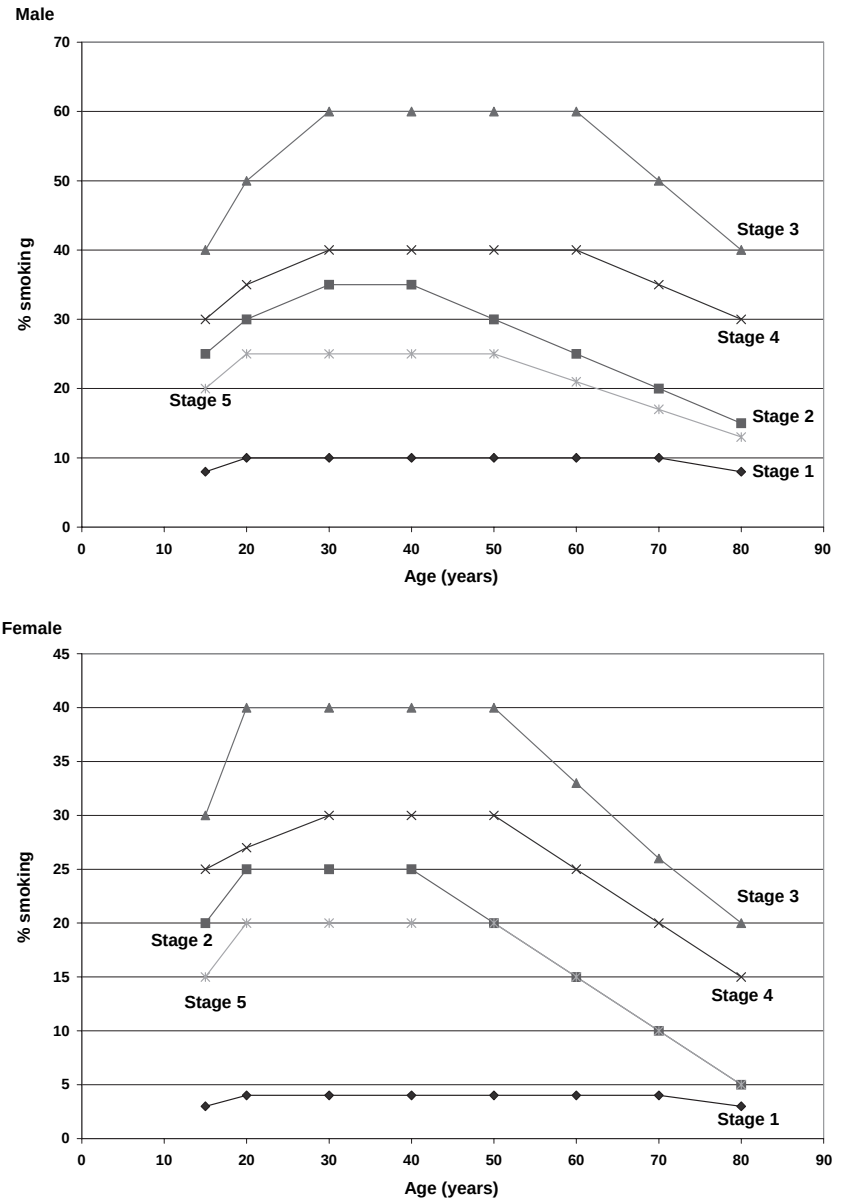
In calibrating the level of the prevalence curves for different regions, we used the available comparative data on current and historical smoking prevalence (Corrao et al. 2000; Gajalakshmi et al. 2000; WHO 1997). Recent data on smoking prevalence show that the male epidemic has peaked at lower levels in Latin America and the Caribbean as well as in sub-Saharan Africa compared to North America, Europe and Asia, possibly because of the economic crises in these regions in the last two decades of the 20th century. Although for most regions female smoking is still in the early stages of the epidemic, we assumed that the peak of the epidemic would be lower in developing countries than what was observed in industrialized countries in the past. This assumption was because in those developing countries where female smoking has been on the rise, prevalence is lower than levels previously observed at similar stages in industrialized countries.

In each country, males and females were assigned to one stage of the epidemic in 2000 (Table 11.15) based on the best available data on smoking patterns in recent years (Corrao et al. 2000; WHO 1997).

2. We divided country-level per capita consumption data into age–sex-specific per capita consumption of smoking based on the above estimates of prevalence. The Tobacco Free Initiative (TFI) of WHO provides time-series estimates of tobacco consumption based on production, export, and import data from the Food and Agriculture Organization of the United Nations (FAO). The consumption numbers are reported as equivalent cigarettes per adult (aged ≥15 years) for each country. We used the above estimates of prevalence to divide the past and current country-level per capita consumption numbers (corrected for smuggling and other sources of error whenever possible) into age–sex-specific per capita consumption.

In addition to differences in prevalence, male smokers smoke more cigarettes per day than female smokers (Gajalakshmi et al. 2000; Nicolaides-Bouman et al. 1993). Differences between age groups also exist (Gajalakshmi et al. 2000; Nicolaides-Bouman et al. 1993). The

Figure 11.7 Descriptive model for the main stages of the tobacco epidemic based on the parameter values in industrialized countries



Note: For some developing regions, lower peak values were chosen based on observed prevalence data. The vertical axis scales are different for males and females to increase resolution. The number next to each curve indicates the epidemic stage. An additional transitional stage is also assumed between each pair. With appropriate policies, one can assume declining prevalence even beyond stage 5. We assumed that the business-as-usual scenario would not include this achievement, which is considered as a part of our counterfactuals.

Table 11.15 Status of the tobacco epidemic in 2000 among (a) males and (b) females

(a)

Epidemic stage[a]	*Country*[b]
0.5–1	NA
1.5–2	AFR-D – all except Algeria, Mauritius, Seychelles; AFR-E – all except South Africa; EMR-B – Iran (Islamic Republic of); EMR-D – Afghanistan, Djibouti, Somalia, Sudan; EUR-B – Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan
2.5–3	AFR-D – Algeria, Mauritius, Seychelles; AFR-E – South Africa; AMR-A – Cuba; AMR-B – all except Argentina, Brazil, Chile; AMR-D – all; EMR-B – all except Iran (Islamic Republic of); EMR-D – Egypt, Iraq, Morocco, Pakistan, Yemen; EUR-A – Croatia, Czech Republic, Greece, Portugal, Slovenia; EUR-B – all except Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan; EUR-C – all; SEAR-B – all; SEAR-D – all; WPR-A – Brunei Darussalam, Japan; WPR-B – all
3.5–4	AMR-B – Argentina, Brazil, Chile; EUR-A – Andorra, Austria, Denmark, France, Germany, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, San Marino, Spain, Switzerland
4.5–5	AMR-A – Canada, USA; EUR-A – Belgium, Finland, Iceland, Netherlands, Norway, Sweden, United Kingdom; WPR-A – Australia, New Zealand, Singapore

(b)

Epidemic stage[a]	*Country*[b]
0.5–1	AFR-D – all except Seychelles; AFR-E – all except South Africa; AMR-B – Antigua and Barbuda, Bahamas, Barbados, Belize, Dominica, Grenada, Guyana, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and Grenadines, Suriname; EMR-B – all except Cyprus, Jordan, Lebanon, Syrian Arab Republic; EMR-D – all except Morocco; Albania, Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan; SEAR-B – Indonesia, Sri Lanka; SEAR-D – all except Myanmar, Nepal; WPR-A – Singapore; WPR-B – Cambodia, China, Malaysia, Mongolia, Republic of Korea, Viet Nam
1.5–2	AFR-D – Seychelles; AFR-E – South Africa; AMR-B – Colombia, Costa Rica, Dominican Republic, El Salvador, Honduras, Jamaica, Mexico, Panama, Trinidad and Tobago, Uruguay, Venezuela; AMR-D – all; EMR-B – Cyprus, Jordan, Lebanon, Syrian Arab Republic; Morocco; EUR-A – Croatia, Czech Republic, Greece, Israel, Malta, Portugal, San Marina, Slovenia; EUR-B – all except Albania, Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan; EUR-C – all; SEAR-B – Thailand; SEAR-D – Myanmar, Nepal; WPR-A – Brunei Darussalam, Japan; WPR-B – Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Philippines, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu
2.5–3	AMR-A – Cuba; AMR-B – Argentina, Brazil, Chile; EUR-A – Andorra, Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Monaco, Spain, Switzerland; WPR-B – Papua New Guinea
3.5–4	AMR-A – Canada, USA; EUR-A – Belgium, Iceland, Netherlands, Norway, United Kingdom; WPR-A – Australia, New Zealand
4.5–5	EUR-A – Sweden

NA Not applicable.

[a] The stages of the epidemic refer to those in Figure 11.7.

[b] By subregion.

Table 11.16 Ratios of number of cigarettes smoked per day for various demographic groups from historical data in industrialized countries

	Ratios of number of cigarettes smoked	
Age group (years)	*Male*	*Female*
15–19	1.00	1.00
20–29	1.22	1.15
30–39	1.42	1.24
40–49	1.37	1.34
50–59	1.26	1.21
60–69	1.15	1.04
70–79	1.15	1.04
≥80	1.15	1.04
Male	1.0	
Female	1/1.25 (stages 4 and 5);[a] 1/1.5 (stage 3); 1/1.75 (stages 1 and 2)	

[a] The stages of the epidemic refer to those in Figure 11.7.

ratios for the number of cigarettes smoked per day between different age groups and men and women have been estimated for industrialized countries (Gajalakshmi et al. 2000) and are presented in Table 11.16. We assumed a lower female-to-male ratio in the earlier stages of the female epidemic.

We emphasize that because the prevalence estimates from the descriptive model are used to *divide* existing total per capita consumption into age–sex-specific estimates, it is only the various male-female and age *ratios* that affect the estimates, rather than the absolute values. Therefore, the age–sex-specific consumption estimates are not sensitive to the level of the prevalence curve or assumptions about the stage of the epidemic, provided that male-to-female and age ratios are close to actual values (i.e. under- or over-estimating male and female prevalence by the same factor would not affect the consumption estimates).

3. We projected age–sex-specific lung cancer mortality based on consumption projections and a statistical model of the relationship between lung cancer mortality and lagged consumption (Girosi and King 2002). Finally, the projections of lung cancer mortality were converted to the projections of *SIR* using the definition of *SIR* above.

Acknowledgements

We thank R. Peto and J. Boreham for discussions on methodology and for providing data from the Chinese retrospective proportional mortal-

ity study; M. Thun and J. Henley for discussions on methodology and for additional re-analysis of data from the American Cancer Society CPS-II cohort; S. Darby for data on lung cancer risk reversibility in the United Kingdom; E. Guindon and P. Jha for data on the prevalence of smoking and tobacco consumption; and P. Gupta for discussions on methods and data for oral tobacco use risk. The generous assistance of these individuals and their organizations greatly improved the data sources used in this chapter. The participants in the comparative risk assessment (CRA) project review meetings and anonymous reviewers provided valuable comments on methods and assumptions.

Notes

1 See preface for an explanation of this term.

2 If the fraction of smokers in the mixture is x, then the lung cancer mortality for the mixture is $xS^*_{LC} + (1 - x)N^*_{LC}$. Since the *SIR* of the mixture has to equal that of the population, excess lung cancer mortality in the mixture has to be equal to that of the study population. Therefore $xS^*_{LC} + (1 - x)N^*_{LC} - N^*_{LC} = C_{LC} - N_{LC}$. Solving this equation gives $x = \dfrac{C_{LC} - N_{LC}}{S^*_{LC} - N^*_{LC}}$ which is equal to *SIR* when the study and reference populations have the same non-smoker lung cancer rates. When non-smoker lung cancer rates are not the same in the study and reference populations, the same result can be obtained with algebraic manipulation of Equation 2, accounting for differences in never-smoker rates.

3 The discussion in this section is based on age-specific risk estimates. In other words, a decline in risk as a result of cessation does not necessarily imply that risk stops rising in absolute terms. Rather, it implies that at all ages after cessation, relative risk is less than it would be if smoking continued.

4 These estimates also assume no new smokers in the cohort.

5 No disease with this latter characteristic is known.

6 Note that this applies only to current exposure and not to future exposure (avoidable risk) since the difference in decline time is accounted for in estimating risk reversibility, as described earlier.

7 Note that the estimates of oral cancer for smokers are based on *SIR* as the exposure variable to capture the accumulated hazards of smoking and not on prevalence. Therefore the fraction of smokers who also chew ($p_{sc} = 1 - p_s$) was applied to *SIR* estimates rather than direct prevalence. Estimating chewing-caused oral cancer by increasing the relative risk for this condition in the *SIR* framework implicitly assumes that the accumulated hazards of the two habits are similar. If oral tobacco use has a longer history in the region, this would result in an underestimation of accumulated hazards.

8 Given that *SIR* values are estimated relative to reference populations of the same sex and age, female and male estimates are not directly comparable. At the same time, the large differences are illustrative of the relative magnitudes.

9 All fractions are based on mortality in the respective age groups 30–69, ≥70, and ≥30 years.

10 Mortality estimates for China were combined with the remaining countries in WPR-B to obtain subregional estimates.

11 Eighty-three per cent of the population of SEAR-D lives in India. Therefore the estimates for the subregion are dominated by, and comparable in terms of fractions with, those from India.

References

Alderson MR, Lee PN, Wang R (1985) Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarettes smoked. *Journal of Epidemiology and Community Health,* **39**:286–293.

Australia National Health and Medical Research Council (1997) *The health effects of passive smoking*. Commonwealth Department of Health and Family Services, Canberra.

Balaram P, Sridhar H, Rajkumar T et al. (2002) Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *International Journal of Cancer,* **98**:440–445.

Bennett NG, Horiuchi S (1984) Mortality estimation from registered deaths in less developed countries. *Demography,* **21**:217–234.

Best EWR, Josie GH, Walker CB (1961) A Canadian study of mortality in relation to smoking habits: a preliminary report. *Canadian Journal of Public Health,* **52**:99–106.

Bhonsle RB, Murti PR, Gupta PC (1992) Tobacco habits in India. In: *Control of tobacco related cancers and other diseases*. Gupta PC, Hamner JE, Murti PR, eds. Oxford University Press, Bombay.

Britton A, McKee M (2000) The relationship between alcohol and cardiovascular disease in eastern Europe: explaining the paradox. *Journal of Epidemiology and Community Health,* **54**:328–332.

Bronnum-Hansen H, Juel K (2000) Estimating mortality due to cigarette smoking: two methods, same result. *Epidemiology,* **11**:422–426.

Bruce N, Perez-Padilla R, Albalak R (2000) Indoor air pollution in developing countries: a major environmental and public health challenge. *Bulletin of the World Health Organization,* **78**:1078–1092.

Cederlof R, Friberg L, Hrubec Z, Lorich U (1975) *The relationship of smoking and some social covariables to mortality and cancer morbidity*. Department of Environmental Hygiene, Karolinska Institute, Stockholm.

Cook DG, Pocock SJ, Shaper AG, Kussick SJ (1986) Giving up smoking and the risk of heart attacks: a report from the British Regional Heart Study. *The Lancet,* **ii**(8520):1376–1380.

Corrao MA, Guindon GE, Sharma N, Shokoohi DF, eds. (2000) *Tobacco control: country profiles*. American Cancer Society, Atlanta, GA.

Dhillon I, Gupta PC, Asma S (2000) *Evidence for a causal link between smoking and tuberculosis: summary of the proceedings of the international scientific*

expert meeting on the possible causality between smoking and tuberculosis. TATA Institute of Fundamental Research (with World Health Organization and Centers for Disease Control and Prevention). Thiruvanathapuram, Kerala.

Dikshit RP, Kanhere S (2000) Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. *International Journal of Epidemiology,* **29**:609–614.

Dobson AJ, Alexander HM, Heller RF, Lloyd DM (1991) How soon after quitting smoking does risk of heart disease decline? *Journal of Clinical Epidemiology,* **44**:1247–1253.

Doll R (1978) Atmospheric pollution and lung cancer. *Environmental Health Perspectives,* **22**:23–31.

Doll R (1986) Tobacco: an overview of health effects. In: *Tobacco: a major international health hazard*. (IARC Scientific Publication No. 74.) Zaridze DG, Peto R, eds. International Agency for Research on Cancer, Lyon.

Doll R (1998a) Diseases with lower risks in smokers. In: *Report of the Scientific Committee on Tobacco and Health*. UK Department of Health. HMSO, London.

Doll R (1998b) Uncovering the effects of smoking: historical perspective. *Statistical Methods in Medical Research,* **7**:87–117.

Doll R, Hill AB (1950) Smoking and carcinoma of the lung. *British Medical Journal,* **ii**:739.

Doll R, Hill AB (1956) Lung cancer and other causes of death in relation to smoking. *British Medical Journal,* **ii**:1071–1081.

Doll R, Peto R (1976) Mortality in relation to smoking: 20 years' observation on male British doctors. *British Medical Journal,* **ii**:1525–1536.

Doll R, Peto R, Wheatly K, Gray R, Sutherland I (1994) Mortality in relations to smoking: 40 years' observation on male British doctors. *British Medical Journal,* **309**:901–911.

Du YX, Cha Q, Chen XW et al. (1996) An epidemiological study of risk factors for lung cancer in Guangzhou, China. *Lung Cancer,* **14**:S9–S37.

Dunn JE, Linden G, Brelow L (1960) Lung cancer mortality experience of men of certain occupations in California. *American Journal of Public Health,* **50**:1475–1487.

English DR, Holman CDJ, Milne E et al. (1995) *The quantification of drug caused morbidity and mortality in Australia, Part 2*. Commonwealth Department of Human Services and Health, Canberra.

Environmental Protection Agency (1992) *Respiratory health effects of passive smoking: lung cancer and other disorders*. (EPA/600/6-90/006F.) U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC.

Ezzati M, Lopez AD (2003) Measuring the accumulated hazards of smoking: global and regional estimates for 2000. *Tobacco Control*, **12**:79–85.

Finkel A (1990) *Confronting uncertainty in risk management: a guide for decision makers*. Resources for the Future, Washington, DC.

Flanders WD, Rothman KJ (1982) Interaction of alcohol and tobacco in laryngeal cancer. *American Journal of Epidemiology,* **115**:371–379.

Fletcher CM, Peto R (1977) The natural history of chronic airflow obstruction. *British Medical Journal,* **i**:1645–1648.

Gajalakshmi CK, Jha P, Ranson K, Nguyen SN (2000) Global patterns of smoking and smoking-attributable mortality patterns. In: *Tobacco control in developing countries*. Jha P, Chaloupka FJ, eds. Oxford University Press, Oxford.

Gajalakshmi V, Peto R, Kanaka TS, Jha P (2003) Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43 000 adult deaths and 35 000 controls. *Lancet*, **363**:507–515.

Garfinkel L (1985) Selection, follow-up, and analysis in the American Cancer Society prospective studies. In *Selection, follow-up, and analysis in prospective studies: a workshop*. (NCI Monograph 67.) Garfinkel L, Ochs O, Mushinkski M, eds. National Cancer Institute, Bethesda, MD.

Girosi F, King G (2002) *Time series cross-sectional analysis with different explanatory variables in each cross-section*. Center for Basic Research in the Social Sciences, Harvard University, Cambridge, MA.

Gupta PC (1989) An assessment of excess mortality caused by tobacco usage in India. (Proceedings of the UICC workshop "Tobacco or health".) In: *Tobacco and health: the Indian scene*. Sanghavi LD, Notani P, eds. Tata Memorial Centre, Bombay.

Gupta PC (1996) Survey of sociodemographic characteristics of tobacco use among 99 598 individuals in Bombay, India using handheld computers. *Tobacco Control,* **5**:114–120.

Gupta PC, Mehta HC (2000) Cohort study of all-cause mortality among tobacco users in Mumbai, India. *Bulletin of the World Health Organization,* **78**:877–883.

Gupta PC, Pindborg JJ, Mehta FS (1982) Comparison of carcinogenecity of betel quid with and without tobacco: an epidemiological review. *Ecology of Disease,* **1**:213–219.

Hackshaw AK, Law MR, Wald NJ (1997) The accumulated evidence on lung cancer and environmental tobacco smoke. *British Medical Journal,* **315**:980–988.

Hammond EC (1966) Smoking in relation to the death rates of one million men and women. In: *Epidemiological approaches to the study of cancer and other chronic disease*. (National Cancer Institute Monograph No. 19.) Haenszel W, ed. National Cancer Institute, Bethesda, MD.

Hammond EC, Horn D (1958) Smoking and death rates: report of forty-four months of follow-up of 187 783 men. *Journal of American Medical Association,* **166**:1159–1172 and 1294–1308.

He XZ, Chen W, Liu ZY, Chapman RS (1991) An epidemiological study of lung cancer in Xuan Wei county, China: current progress. Case-control study on lung cancer and cooking fuel. *Environmental Health Perspectives,* **94**:9–13.

Hecht SS (2003) Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nature Reviews Cancer*, **3**:733–744.

Higgins ITT, Mahan CM, Wynder EL (1988) Lung cancer among cigar and pipe smokers. *Preventive Medicine,* **17**:116–128.

Hill K (1981) Estimating census and death registration completeness. *Asian and Pacific Population Forum,* **1**:8–13.

Hirayama T (1977) *Smoking and cancer: a prospective study on cancer epidemiology based on census population in Japan*. Health Consequences, Education, Cessation Activities, and Governmental Action. Smoking and Health II. (Proceedings of the Third World Conference on Smoking and Health.) DHEW Publication No. [NIH] 77-1413. U.S. Government Printing Office, Washington, DC.

Hirayama T (1990) *Life-style and mortality: a large-scale census-based cohort study in Japan,* Karger, Tokyo.

International Agency for Research on Cancer (1984) *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosomines*. International Agency for Research on Cancer, Lyon, France.

Jedrychowski W, Becher H, Wahrendorf J, Basa-Cierpialek Z (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. *Journal of Epidemiology and Community Health,* **44**:114–120.

Jee SH, Suh I, Kim IS, Appel LJ (1999) Smoking and atherosclerotic cardiovascular disease in men with low levels of serum cholesterol: the Korea Medical Insurance Corporation study. *Journal of the American Medical Association,* **282**:2149–2155.

Jha P, Ranson MK, Nguyen SN, Yach D (2002) Estimates of global and regional smoking prevalence in 1995 by age and gender. *American Journal of Public Health,* **92**:1002–1006.

Kahn HA (1966) The Dorn study of smoking and mortality among U.S. veterans: report on eight and one half years of observation. In: *Epidemiological approaches to the study of cancer and other chronic disease*. (National Cancer Institute Monograph No. 19.) Haenszel W, ed. National Cancer Institute, Bethesda, MD.

Kawachi I, Colditz GA, Stampfer MJ et al. (1997) Smoking cessation and decreased risks of total mortality, stroke, and coronary heart disease incidence among women: a prospective cohort study. In: *Changes in cigarette-related disease risks and their implications for prevention and control.* (Smoking and Tobacco Control Monograph No. 8.) National Cancer Institute, ed. National Cancer Institute, Bethesda, MD.

Kinjo Y, Cui Y, Akiba S et al. (1998) Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *Journal of Epidemiology,* **8**:235–243.

Ko YC, Lee CH, Chen MJ et al. (1997) Risk factors for primary lung cancer among non-smoking women in Taiwan. *International Journal of Epidemiology,* **26**:24–31.

LaCroix AZ, Lang J, Scherr P et al. (1991) Smoking and mortality among older men and women in three communities. *New England Journal of Medicine,* **324**:1619–1625.

Lam TH, Ho SY, Hedley AJ, Mak KH, Peto R (2001) Mortality and smoking in Hong Kong: Case-control study of all adult deaths in 1998. *British Medical Journal,* **323**:361–363.

Law MR, Morris JK, Wald NJ (1997) Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *British Medical Journal,* **315**:973–980.

Lee PN (1996) Mortality from tobacco in developed countries: are indirect estimates reliable? *Regulatory Toxicology and Pharmacology,* **24**:60–68.

Levin ML, Goldstein H, Gerhardt PR (1950) Cancer and tobacco smoking. *Journal of American Medical Association,* **143**:336–338.

Liu BQ, Peto R, Chen ZM et al. (1998) Emerging tobacco hazards in China: 1. Retrospective proportional mortality study of one million deaths. *British Medical Journal,* **317**:1411–1422.

Lopez AD (1998) Counting the dead in China. *British Medical Journal,* **317**:1399.

Lopez AD (1999) Alcohol and smoking as risk factors. In: *Health and mortality: issues of global concern*. (Proceedings of the United Nations Symposium on Health and Mortality, Brussels, 19–22 November, 1997.) Chamie J, Cliquet RL, eds. United Nations Population Division, New York.

Lopez AD, Ahmad OB, Guillot M et al. (2002) *World mortality in 2002: life tables for 191 countries*. World Health Organization, Geneva.

Lopez AD, Collishaw NE, Piha T (1994) A descriptive model of the cigarette epidemic in developed countries. *Tobacco Control,* **3**:242–247.

Lubin JH, Blot WJ, Berrino F et al. (1984) Modifying risk of developing lung cancer by changing habits of cigarette smoking. *British Medical Journal,* **288**:1953–1956.

Malarcher AM, Schuman J, Epstein LA et al. (2000) Methodological issues in estimating smoking-attributable mortality in the United States. *American Journal of Epidemiology,* **152**:573–584.

Mathers CD, Stein C, Ma Fat D et al. (2002) The global burden of disease 2000: version 2, methods and results. (GPE Discussion Paper No. 50.) World Health Organization, Global Programme on Evidence for Health Policy, Geneva. (Available at http://www.who.int/evidence).

Mills CA, Porter MM (1950) Tobacco smoking habits and cancer of the mouth and respiratory system. *Cancer Research,* **10**:539–542.

Moolgavkar SH, Venzon DJ (1987) General relative risk regression models for epidemiologic studies. *American Journal of Epidemiology,* **126**:949–961.

Muller FH (1939) Tobacco abuse and carcinoma of the lung. *Zeitschrift fur Krebsforschung,* **49**:57–85.

Nandakumar A, Thimmasetty KT, Sreeramareddy NM et al. (1990) A population-based case-control investigation on cancers of the oral cavity in Bangalore, India. *British Journal of Cancer,* **62**:847–851.

National Research Council (1994) *Science and judgment in risk assessment,* National Academy Press, Washington, DC.

Nicolaides-Bouman A, Wald N, Forey B, Lee P, eds. (1993) *International smoking statistics: a collection of historical data from 22 economically developed countries*. The Wolfson Institute of Preventive Medicine and Oxford University Press, London and Oxford.

Niu SR, Yang GH, Chen ZM et al. (1998) Emerging tobacco hazards in China: 2. Early mortality results from a prospective study. *British Medical Journal,* **317**:1423–1424.

Nyberg F, Gustavsson P, Jarup L et al. (2000) Urban air pollution and lung cancer in Stockholm. *Epidemiology,* **11**:487–495.

Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J, eds. (1992) *Cancer incidence in five continents: Volume VI*. (IARC Scientific Publications No. 120.) International Agency for Research on Cancer (IARC), Lyon.

Parkin DM, Whelan SL, Ferlay J, Black RJ, eds. (1997) *Cancer incidence in five continents: Volume VII*. (IARC Scientific Publications No. 143.) International Agency for Research on Cancer, Lyon.

Pathak DR, Samet JM, Humble CG, Skipper BJ (1986) Determinants of lung cancer risk in cigarette smokers in New Mexico. *Journal of the National Cancer Institute,* **76**:597–604.

Percy C, Miller BA, Gloeckler Reis LA (1990) Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. *Annals of New York Academy of Sciences,* **609**:87–97.

Percy C, Muir C (1989) The international comparability of cancer mortality data: results of an international death certificate study. *American Journal of Epidemiology,* **129**:934–946.

Peto R (1978) Carcinogenic effects of chronic exposure to very low levels of toxic substances. *Environmental Health Perspectives,* **22**:155–159.

Peto R (1986) Influence of dose and duration of smoking on lung cancer rates. In: *Tobacco: a major international health hazard*. Zaridze D, Peto R, eds. (IARC Scientific Publication No. 7) International Agency for Research on Cancer, Lyon.

Peto R, Darby S, Silcocks P, Whitley E, Doll R (2000) Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *British Medical Journal,* **321**:323–329.

Peto R, Doll R (1984) Keynote address: the control of lung cancer. In: *Lung cancer: causes and prevention*. Mizell M, Correa P, eds. Verlag Chemie International, Deerfield Beach, FL.

Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr (1992) Mortality from tobacco in developed countries. *The Lancet,* **339**:1268–1278.

Pope CA, III, Burnett RT, Thun MJ et al. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *Journal of American Medical Association,* **287**:1132–1141.

Preston SH, Heuveline P, Guillot M (2000) *Demography: measuring and modelling population processes*. Blackwell, Oxford.

Puddey IB, Rakic V, Dimmitt SB, Beilin LJ (1999) Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors: a review. *Addiction,* **94**:649–663.

Rao DN, Ganesh B, Rao RS, Desa PB (1994) Risk assessment of tobacco, alcohol, and diet in oral cancer: a case-control study. *International Journal of Cancer,* **58**:469–473.

Rogot E, Murray JL (1980) Smoking and causes of death among U.S. Veterans: 16 years of observation. *Public Health Reports,* **95**:213–222.

Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S (1985) The risk of myocardial infarction after quitting smoking in men under 55 years of age. *New England Journal of Medicine,* **313**:1511–1514.

Rosenberg L, Palmer JR, Shapiro S (1990) The risk of myocardial infarction among women who stop smoking. *New England Journal of Medicine,* **322**:213–217.

Sankaranarayanan R, Duffy SW, Day NE, Nair MK, Padmakumary G (1989a) A case-control investigation of cancer of the oral tongue and the floor of the mouth in southern India. *International Journal of Cancer,* **44**:617–621.

Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Nair MK (1990) Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. *Journal of Epidemiology and Community Health,* **44**:286–292.

Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Padmanabhan TK (1989b) Tobacco chewing, alcohol, and nasal snuff in cancer of the gingiva in Kerala, India. *British Journal of Cancer,* **60**:638–643.

Schairer E, Schoniger E (1943) Lung cancer and tobacco use. *Zeitschrift fur Krebsforschung,* **54**:261–269.

Schrek R, Baker LA, Ballard GP, Dolgoff S (1950) Tobacco smoking as an etiologic factor in disease. *Cancer Research,* **10**:49–58.

Smith KR, Liu Y (1993) Indoor air pollution in developing countries. In: *Epidemiology of lung cancer: lung biology in health and disease*. Samet J, ed. Marcel Dekker, New York.

Smith KR, Shuhua G, Kun H, Daxiong Q (1993) One hundred million improved cookstoves in China: How was it done? *World Development,* **21**:941–961.

Sobue T (1990) Association of indoor air pollution and lifestyle with lung cancer in Osaka, Japan. *International Journal of Epidemiology,* **19**:S62–66.

Sobue T, Suzuki T, Fujimoto I et al. (1991) Lung cancer risk among ex-smokers. *Japanese Journal of Cancer Research,* **82**:273–279.

Sterling TD, Rosenbaum WL, Weinkam JJ (1993) Risk attribution and tobacco-related deaths. *American Journal of Epidemiology,* **138**:128–139.

Thomas P, Zelikoff J (1999) Air pollutants: moderators of pulmonary host resistance against infection. In: *Air pollution and health*. Holgate ST, Samet JM, Maynard RL, Koren HS, eds. Academic Press, San Diego, CA.

Thun MJ, Apicella LF, Henley SJ (2000) Smoking vs other risk factors as the cause of smoking-attributable mortality. *Journal of American Medical Association,* **284**:706–712.

Thun MJ, Day-Lally CA, Calle EE, Flanders WD, Heath CW Jr (1995) Excess mortality among cigarette smokers: changes in a 20-year interval. *American Journal of Public Health,* **85**:1223–1230.

Thun MJ, Day-Lally CA, Myers DG et al. (1997a) Trends in tobacco smoking and mortality from cigarette use in cancer prevention studies I (1959 through 1965) and II (1982 through 1988). In: *Changes in cigarette-related disease risks and their implications for prevention and control.* (Smoking and Tobacco Control Monograph No. 8.) National Cancer Institute, ed. National Cancer Institute, Bethesda, MD.

Thun MJ, Myers DG, Day-Lally C et al. (1997b) Age and exposure-response relationships between cigarette smoking and premature death in cancer prevention study II. In: *Age and exposure-response relationships between cigarette smoking and premature death in cancer prevention study II*. National Cancer Institute, Bethesda.

Thun MJ, Peto R, Lopez AD et al. (1997c) Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *New England Journal of Medicine,* **337**:1705–1714.

U.S. Department of Health and Human Services (1986) *The health consequences of using smokeless tobacco. A report of the advisory committee to the Surgeon General.* (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.

U.S. Department of Health and Human Services (1989) *Reducing the consequences of smoking: 25 years of progress. A report of the Surgeon General, 1989*. (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.

U.S. Department of Health and Human Services (1990a) Chapter 4: smoking cessation and respiratory cancers. In: *The health benefits of smoking cessation. A report of the Surgeon General, 1990*. U.S. Department of Health and Human Services, ed. USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.

U.S. Department of Health and Human Services (1990b) Chapter 6: Smoking cessation and cardiovascular disease. In: *The health benefits of smoking cessation. A report of the Surgeon General, 1990*. U.S. Department of Health and Human Services, ed. USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.

U.S. Department of Health and Human Services (1990c) *The health benefits of smoking cessation. A report of the Surgeon General, 1990*. (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.

U.S. Department of Health and Human Services (2001) *Women and smoking. A report of the Surgeon General*. (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention. Office on Smoking and Health, Bethesda, MD.

UK Department of Health, Scientific Committee on Tobacco and Health (1998) *Report of the scientific committee on tobacco and health*. UK Department of Health, London.

Valkonen T, van Poppel F (1997) Smoking. The contribution of smoking to sex differences in life expectancy. *European Journal of Public Health,* **7**:302–310.

Vena JE (1982) Air pollution as a risk factor in lung cancer. *American Journal of Epidemiology,* **116**:42–56.

Wang TJ, Zhou BS, Shi JP (1996) Lung cancer in nonsmoking Chinese women: a case control study. *Lung Cancer,* **14**:S93–98.

Wassink WF (1948) Onstaansvoorwarden voor Longkanker [Etiology of lung cancer]. *Tijdschrift voor Geneeskunde,* **92**:3732–3747.

WHO (1997) *Tobacco or health: a global status report*. World Health Organization, Geneva.

Wynder EL, Graham EA (1950) Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *Journal of American Medical Association,* **143**:329–336.

Yamaguchi N, Mochizuki-Kobayashi Y, Utsunomiya O (2000) Quantitative relationship between cumulative cigarette smoking and lung cancer mortality in Japan. *International Journal of Epidemiology,* **29**:963–968.

Zaridze D, Peto R, eds. (1986) *Tobacco: a major international health hazard*. (IARC Scientific Publication No. 7.) International Agency for Research on Cancer, Lyon.

Chapter 12

Alcohol use

Jürgen Rehm, Robin Room, Maristela Monteiro, Gerhard Gmel, Kathryn Graham, Nina Rehn, Christopher T. Sempos, Ulrich Frick and David Jernigan

Summary

Alcohol has long been known as a risk factor for disease. The 1990 Global Burden of Disease (GBD) study (Murray and Lopez 1996a, 1996b) identified alcohol as one of the major global risk factors, accounting for 1.5% of global deaths, 2.1% of years of healthy life lost owing to premature mortality, 6.0% of years of life lost owing to disability and 3.5% of disability-adjusted life years (DALYs).

Based on the epidemiological literature, and modelling the relationship between alcohol exposure and disease, two dimensions of alcohol consumption were defined as exposure variables:

- average volume of alcohol consumption; and
- pattern of drinking.

Average volume of consumption was estimated using both existing estimates of country-specific adult per capita consumption (based on production and sales data) and self-reported alcohol consumption from general population surveys. Country-specific patterns of drinking were defined using indicators of high-volume drinking occasions and types of drinking situation (e.g. drinking with meals). These indicators were drawn from key informant surveys and general population surveys, where available. Optimal scaling procedures were used to determine whether drinking patterns formed a single dimension and the relative impact of the underlying indicators on the pattern value.

The relationship between exposure and various disease categories was estimated by the following methods. Estimates of the relationship between categories of average volume of alcohol consumed and chronic disease were based on disease-specific meta-analyses. Estimates of the relationship between average volume of alcohol consumption and acute disease were based on alcohol-attributable fractions (AAFs) published in the literature. To estimate the impact of patterns of drinking on the risk

of ischaemic heart disease (IHD) and injuries, multilevel modelling with random intercept and random slope was used.

Effects of alcohol on someone other than the drinker were either included in the AAFs of the literature (e.g. alcohol-related injury) or were modelled indirectly (e.g. in the case of the effect of alcohol on the newborn).

Both average volume of alcohol consumption and patterns of drinking varied markedly across subregions.[1] Average volume of drinking was highest in EUR-A, EUR-C and AMR-A, and lowest in EMR-B, EMR-D and SEAR-D. Patterns were most detrimental in EUR-C, EUR-B, AMR-D and AFR-E. Patterns were least detrimental in EUR-A and WPR-A.

Existing research indicates causal relationships between average volume of consumption and more than 60 International Statistical Classification of Diseases and Related Health Problems (ICD) codes, including both chronic diseases (malignant neoplasms, neuro-psychiatric conditions, cardiovascular diseases, gastrointestinal conditions) and injuries (intentional and unintentional). Although most of these relationships involve a detrimental impact of alcohol, there are beneficial relationships between alcohol and IHD, cerebrovascular disease and type II diabetes for certain combinations of average volume of consumption and patterns of drinking. Patterns of drinking were also associated with the level of injury burden from alcohol, although no pattern of drinking had beneficial effects on injury.

The present analysis found that alcohol-related burden of disease is considerable: 3.2% of global mortality and 4.0% of the global burden of disease measured in DALYs. In terms of alcohol-related mortality, almost half of the global burden is related to acute causes, i.e. unintentional and intentional injuries, particularly unintentional injuries. The next most important category comprises malignant neoplasms with 20% of the overall alcohol-related mortality burden, followed by cardiovascular diseases (15% of all alcohol-attributable deaths) and other noncommunicable diseases, primarily liver cirrhosis (13%). However, although the overall proportion of cardiovascular deaths attributable to alcohol reflects a net result of 15%, this figure does not give a clear picture of the underlying structure of the relationship between alcohol consumption and cardiovascular disease. In particular, although alcohol was estimated to cause a total of almost 600 000 cardiovascular deaths in the year 2000, exceeding even the alcohol-related deaths of unintentional injuries, this figure was partly "offset" by the beneficial effects of alcohol on IHD and stroke. Across all diseases, more males than females die from the effects of alcohol, with a ratio of about 10 : 1.

In terms of DALYs, 4.0% of the overall global disease burden was attributable to alcohol. The biggest differential effect of alcohol on mortality vs morbidity was for neuro-psychiatric diseases. Neuro-psychiatric diseases are often disabling, but not fatal, and this is reflected in the markedly higher proportion of overall disease burden caused by

this category compared to alcohol-attributable mortality (38% of alcohol-attributable DALYs vs 6% of alcohol-attributable deaths). As with alcohol-related mortality, males have more than five times the alcohol-related disease burden in terms of DALYs than females.

Alcohol-attributable disease burden is expected to further increase in the future. This is due partly to increases in consumption in developing and emerging economies in south-east Asia and partly to shifting patterns of morbidity and mortality, in particular the increased significance of chronic diseases and injuries related to alcohol. This trend, however, could be reversed quickly, as much of the disease burden of alcohol is almost immediately preventable (40% of the overall alcohol-attributable burden is from acute conditions). While a total ban on alcohol is not realistic, there are other alcohol policy measures that could be implemented to reduce the resulting disease burden.

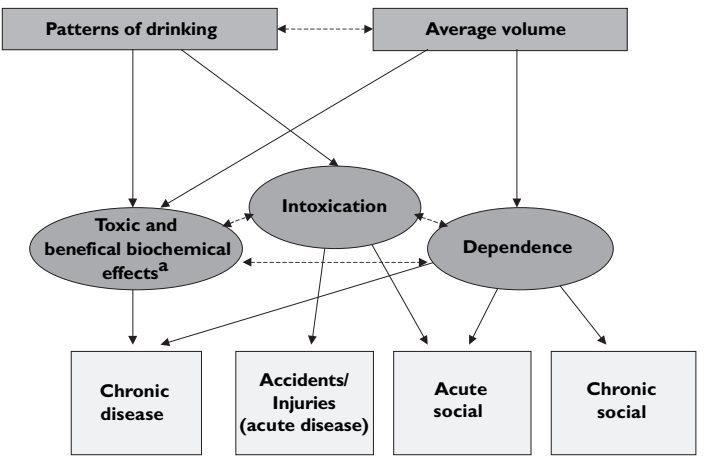
1. Introduction

1.1 Definition of alcohol as a risk factor

The relationship between alcohol consumption and health and social outcomes[2] is complex and multidimensional. Figure 12.1 gives an overview.

Alcohol consumption is linked to long-term biological and social consequences through three intermediate outcomes: intoxication,

Figure 12.1 Model of alcohol consumption, intermediate outcomes and long-term consequences



[a] Independent of intoxication or dependence.

dependence and direct biochemical effects. Examples of such biochemical effects are the promotion of blood clot dissolution and direct toxic effects on acinar cells triggering pancreatic damage.[3] Figure 12.1 shows only the main causal pathways. Intoxication may, for example, lead to chronic social consequences (e.g. when a drunken driver kills somebody and thereafter loses his or her job and social standing). Most of the consequences of intoxication are nonetheless covered by acute health and social consequences.

- *Direct biochemical effects* of alcohol consumption may influence chronic disease, either beneficially or in a harmful way. Beneficial effects include the influence of moderate drinking on IHD by reducing plaque deposits in arteries, protecting against blood clot formation and promoting blood clot dissolution (Zakhari 1997). Examples of harmful effects include increasing the risk of high blood pressure, direct toxic effects on acinar cells triggering pancreatic damage (Apte et al. 1997) and hormonal disturbances (Emanuele and Emanuele 1997). The term "direct toxic and beneficial effects" is used to summarize all the biochemical effects of alcohol on body functions other than intoxication and dependence.
- *Intoxication* is a powerful mediator, mainly for acute outcomes such as accidents, intentional injuries or deaths, domestic conflict and violence, although episodes of intoxication can also be implicated in chronic health and social problems. The effects of alcohol on the central nervous system mainly determine the subjective feeling of intoxication. These effects are felt and can be measured even at consumption levels that are light to moderate (Eckardt et al. 1998).
- *Alcohol dependence* is a disorder in itself, but is also a powerful mechanism sustaining alcohol consumption and mediating its impact on both chronic and acute physiological and social consequences (Drummond 1990).

Biological mechanisms have historically been the most important criteria in establishing the causal link between alcohol consumption and health outcomes (English et al. 1995; Hill 1965; Rothman and Greenland 1998a).

Total consumption or average volume of consumption has been the usual measure of exposure linking alcohol to disease (Bruun et al. 1975). Average volume was linked to more than 60 disease conditions in a series of recent meta-analyses (English et al. 1995; Gutjahr et al. 2001; Ridolfo and Stevenson 2001; Single et al. 1999a).

As shown in Figure 12.1, average volume of consumption as a risk factor works mainly through biochemical effects or through dependence to produce long-term consequences. Although average volume is somewhat correlated with intoxication, this correlation is not of sufficient strength to adequately predict acute effects of alcohol related to injury

and death. Such effects are much better predicted by patterns of drinking (Rehm et al. 1996). For example, the same overall average volume of alcohol can be consumed in small quantities regularly with meals (e.g. two drinks a day with meals) or in large quantities on few occasions (e.g. two bottles of wine on a single occasion every Friday). Data on the influence of patterns of drinking are less available than data on overall consumption, but evidence is accumulating that patterns of drinking affect the link between alcohol and disease (Bondy 1996; Puddey et al. 1999; Rehm et al. 1996, 2003) and between alcohol and mortality (Rehm et al. 2001d). In other words, the impact of an average volume of consumption on mortality or morbidity is partly moderated by the way alcohol is consumed by the individual, which in turn is influenced by the social context (Room and Mäkelä 2000). It should be noted that patterns of drinking have been linked not only to acute health outcomes such as injuries (Greenfield 2001; Rossow et al. 2001) but also to chronic diseases such as IHD and especially sudden cardiac death (Britton and McKee 2000; Chadwick and Goode 1998; Puddey et al. 1999; Trevisan et al. 2001a, 2001b).

1.2 Choice of exposure variable

To determine the impact of alcohol on burden of disease, both average volume of consumption and pattern of drinking have to be considered and included in the analysis. Unfortunately, average volume of consumption and pattern of drinking are not independent at the level of the individual drinker, because average volume is often determined by heavy drinking occasions (Rehm and Gmel 2000a). Consider someone who drinks eight drinks per day. This person has by definition both a high average volume of consumption and many heavy drinking occasions. On the aggregate level, however, the two dimensions can be statistically independent, as described below in section 2.3.

Average volume of drinking is a relatively simple concept, at least on a theoretical level. It is more difficult to conceptualize patterns of drinking on a worldwide scale. For the comparative risk assessment (CRA) project (see also WHO 2002), aspects of drinking patterns likely to contribute to consequences were identified as a first step in this process (see also Rehm et al. 2001a, 2001b). Table 12.1 provides an overview of the results of this exercise.

1.3 Choice of theoretical minimum

Because the relationship between alcohol and disease or injury stems from two potentially interrelated dimensions—average volume of alcohol consumption and drinking pattern—the theoretical minimum or other counterfactual scenarios that provide a reference for hypothetical risk reduction should take both dimensions into account. One obvious and important counterfactual would be total abstinence from alcohol. If all effects of alcohol on health were negative, this would obviously be

Table 12.1 Patterns of drinking relevant to CRA

Pattern indicators	*Link to disease*
Proportion of the adult population who abstain from alcohol	The same adult consumption per capita will have more detrimental effects in countries where drinking is concentrated among fewer people. *This variable was later dropped from the pattern analyses, as it has been incorporated into the average drinking categories*
Heavy drinking occasions[a] High usual quantity of alcohol per occasion Proportion of drinkers who drink daily or nearly daily Proportion of drinking occasions when drinkers get drunk Festive drinking common—at fiestas or community celebrations	The fewer occasions on which a given amount of alcohol is consumed, the more detrimental the consequences (Puddey et al. 1999; Room et al. 2002; Walsh and Rehm 1996). Heavy drinking occasions lead to an increase in injuries. Also, heavy drinking occasions have been shown to lead to detrimental cardiovascular outcomes
Drinking with meals—how common to drink with meals	Drinking with meals has been shown in epidemiological and biological research to be less detrimental than drinking at other times (Gentry 2000; Ramchandani et al. 2001; Trevisan et al. 2001a)
Drinking in public places—how common to drink in public places	Drinking in public often requires transportation, and thus has been linked to traffic accidents and injuries (Fahrenkrug and Rehm 1994)
Drinking linked to violence	Alcohol-related violence is an important cause of injuries. *This variable confounds exposure and a potential consequence and was thus dropped in subsequent analyses*

[a] This is often termed "binge drinking". However, the definition of binge drinking varies widely (e.g. from heavy festive drinking with intoxication lasting more than one day to having five or more drinks on one occasion). It was therefore decided not to use the term in this work.

the ideal theoretical minimum. However, it has been shown that alcohol, if consumed in a regular pattern of light to moderate doses, has protective effects against IHD and potentially other ischaemic diseases (Ashley et al. 2000; Puddey et al. 1999).

The cardioprotective effect has the most relevance to countries with established market economies, which tend to have the longest life expectancy and the highest proportion of deaths from ischaemic disease (Murray and Lopez 1996a). In addition, the pattern of light regular drinking associated with this protective effect, when it occurs, is found mainly in these countries. Drinking to intoxication, heavy drinking occasions and other more detrimental drinking patterns, on the other hand, are often the prevalent drinking style outside established market economies[4] (see Table 12.3 for an overview of country-by-country drinking patterns). Economic development and patterns of drinking are correlated to a higher degree than volume of alcohol consumption and economic development (Pearson correlation of 0.6 between patterns and per capita gross national product [GNP] on the 2001 data set of the CRA

with 89 countries, where the correlation between average volume of consumption and GNP is 0.2; see Rehm et al. 2001a, 2001b). Unfortunately, insufficient research has been carried out to identify the causal determinants of this relationship.

It is proposed to establish the following counterfactual scenarios for measuring the effects of alcohol consumption:

- total abstinence, which would mean an increase in the disease burden of some cardiovascular categories for established market economies and countries with a general pattern of light to moderate drinking;
- as a sensitivity analysis, the current status in patterns of drinking with different scenarios for volume of drinking;
- as a sensitivity analysis, the current status in average consumption with different values for patterns of drinking; and
- changing both average volume of consumption and drinking patterns towards light, regular drinking.

The overall attributable burden of disease should be calculated using abstainers as the comparison group, as this provides the *global* theoretical minimum. Owing to the large contribution of neuropsychological disease and injuries, neither of which benefits from alcohol consumption, it is also likely that at the population level in every subregion except AMR-A, EUR-A and WPR-A abstinence results in the lowest population risk. The cardioprotective effect will be included in established market economies with light to moderate drinking patterns by using relative risks smaller than 1, thus subtracting "prevented burden" from the burden of disease for these countries.

2. Estimating risk factor levels

2.1 Measuring average volume of alcohol consumption and patterns of drinking

To quantify the effects of alcohol on population health, it is necessary to measure the two key exposure variables, average volume of alcohol consumption and patterns of drinking, at the population level around the world.

Average volume of alcohol consumption

There have been a number of attempts to gather country-level data on average volume of alcohol consumption, most recently by the World Health Organization (WHO) in the *Global status report on alcohol* (1999). Most attempts have tried to arrive at an aggregate figure per country, i.e. per capita consumption or adult per capita consumption (i.e. per capita consumption for all inhabitants aged >15 years). For several reasons, however, this aggregate figure is insufficient for health impact

assessment. First, as a global figure, this approach does not allow disaggregation into different groups (e.g. as defined by sex and age), which is needed for valid estimates of burden of disease. Second, per capita consumption estimates are usually based on production figures or sales data, and thus do not include consumption of home-made or illegally imported alcohol (see discussion of unrecorded consumption in Giesbrecht et al. 2000; Leifman 2001; Summer 2000).

On the positive side, the production and trade or sales data required to calculate per capita consumption have traditionally been collected by various sources (including the alcoholic beverage industry and international agencies such as the Food and Agriculture Organization of the United Nations [FAO]) and are available for most countries of the world. FAO collects production and trade data for different alcoholic beverages, mainly from ministries of agriculture and customs departments. For some countries, estimates include data on alcoholic beverages outside the usual beer, wine and spirits categories (e.g. palm wine and sorghum beer) but they do not systematically include home production or illicit production.

To use per capita consumption data for detailed risk analysis, we combined this source with survey data from various countries. Survey data are especially important in determining the proportion of abstainers in a country, as well as in dividing the overall volume into drinking categories by sex and age groups. In addition, some surveys can be used to estimate unrecorded consumption (e.g. Kühlhorn et al. 1999; and the current WHO-supported efforts in Brazil, China, India and Nigeria).[5]

Although survey data are essential for refining per capita estimates, they also have problems that preclude them from being used as the single source of data. In particular, survey data from many established market economies considerably underestimate total volume (Midanik 1988; Midanik and Harford 1994; Rehm 1998a; de Vries et al. 1999).[6] In addition, survey data are less available than per capita consumption data on an international level (Rehm and Gmel 2000b; WHO 1999). Nevertheless, by combining both kinds of information one may arrive at disaggregated estimates. In this combination, the per capita estimates based on production and sales (combined with data on unrecorded consumption where available) are taken as the overall value. Surveys are then used to estimate the distribution of this overall volume among various groups, as defined by abstinence and different levels of drinking, and by sex and age.

Patterns of drinking

Existing general population surveys cover some of the patterns of drinking listed in Table 12.1, but rarely would one find all features in one representative survey in a particular country. Moreover, not all surveys on drinking patterns are recent. Therefore, to develop drinking pattern estimates for the 14 subregions used in the CRA, key informant question-

Table 12.2 Countries with returned key informant questionnaires

Subregion	*Countries that returned questionnaires in at least one phase*	*Total no. of countries in subregion*
AFR-D	Burkina Faso, Nigeria, Seychelles	26
AFR-E	Congo, Namibia, South Africa, Zambia	20
AMR-A	Canada, USA	3
AMR-B	Argentina, Brazil, Costa Rica, Mexico, Trinidad and Tobago	26
AMR-D	Peru	6
EMR-B	None	13
EMR-D	None	9
EUR-A	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Malta, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, United Kingdom	26
EUR-B	Armenia, Bulgaria, Poland, Slovakia, The former Yugoslav Republic of Macedonia	16
EUR-C	Belarus, Estonia, Hungary, Latvia, Lithuania, Russian Federation	9
SEAR-B	Sri Lanka, Thailand	3
SEAR-D	India	7
WPR-A	Australia, Japan, New Zealand, Singapore	5
WPR-B	China, Fiji, Malaysia, Micronesia, Palau, Papua New Guinea, Philippines, Republic of Korea, Solomon Islands	22
Total		191

naire studies were undertaken in early 2000 (Rehm et al. 2001b; for the key informant questionnaire see Appendix 1 in European Addiction Research 2001) and repeated in 2001, using a slightly modified questionnaire.[7] In 2000, 61 questionnaires were sent out, 52 of which were returned, and in 2001 another 155 were sent out, 40 of which were returned. Table 12.2 lists, by subregion, the countries for which key informant surveys were received. Together with survey data, the responses from the survey on patterns provided sufficient data for a first estimate of patterns of drinking for all subregions.

SUMMARY OF DATA SOURCES USED

The following country level measures of alcohol consumption were used in the analysis:

- adult per capita consumption based on sales data or production and trade data;
- unrecorded consumption based on various estimates;
- survey data on abstinence, average volume consumed in different sex and age groups, and patterns of drinking; and

- key informant information on various aspects of patterns of drinking.

Data for all years after 1998 were considered. Data were checked for consistency across time and for internal consistency (e.g. survey vs per capita estimates of average volume of consumption).

2.2 Data sources for average volume of alcohol consumption

Data on adult per capita and unrecorded consumption were taken from the *Global status report on alcohol* (WHO 1999) and from the WHO Global Alcohol Database, created by the Marin Institute for the Prevention of Alcohol and Other Drug Problems and currently maintained by the Swiss Institute for the Prevention of Alcohol Problems. Surveys were also collected from this database, but additional surveys were accessed based on individual contacts (including several experts from each subregion) and by announcing this project on a specific WHO listserve and at the Annual Alcohol Epidemiology Symposia of the Kettil Bruun Society for Social and Epidemiological Research on Alcohol. Data on drinking patterns were collected from researchers and health officials known to WHO who had the knowledge to serve as key informants for their countries or regions. Key informant information was collected by surveys in early 2000 and in mid 2001.

Categorical levels for average volume of alcohol per day in relating consumption to chronic disease were selected to be consistent with previous meta-analyses (English et al. 1995; Gutjahr et al. 2001; Ridolfo and Stevenson 2001; Single et al. 1999a; for a discussion of the background to these categories see English et al. 1995; Holman et al. 1996) and were defined as follows:

- *abstainer*: a person not having had a drink containing alcohol within the last year;
- *average volume drinking category I*: for females 0–19.99 g pure alcohol daily; for males 0–39.99 g pure alcohol daily;
- *average volume drinking category II*: for females 20–39.99 g pure alcohol daily; for males 40–59.99 g pure alcohol daily; and
- *average volume drinking category III*: for females 40 g or more pure alcohol daily; for males 60 g or more pure alcohol daily.[8]

This categorization of average drinking, rather than using a continuous measure of consumption, makes it possible to derive different shapes of risk curve (linear, J-shape, threshold, etc.) while, at the same time, allowing inclusion of data from studies in which only categorical information on levels of alcohol consumption were collected. Using per capita consumption data derived from production and trade or sales data plus unrecorded consumption as the first estimate of overall alcohol con-

sumption, the following strategy was adopted to generate age- and sex-specific prevalence rates.

- For each subregion, the average adult per capita consumption, including unrecorded consumption for the population aged ≥15 years, was estimated as a population-weighted average of country-specific per capita consumption data. All entries per country after 1998 were taken and averaged to obtain a stable estimate for 2000. The weights were derived from the average population aged ≥15 years in each country for the years after 1998, on the basis of United Nations population data. Country-specific adult per capita data were estimated for 132 countries (see Table 12.3). Per capita consumption was known and adult per capita consumption could be calculated for more than 90% of the world's population. Survey information on abstinence was available for 69 countries, in particular from almost all countries with population larger than 100 million resulting in more than 80% of the world population with available survey data. This means that more than 50% of the countries for which data were available on per capita consumption also had survey data available.
- Country-specific survey data of the ratio of male to female consumption were used to allocate proportionally the overall adult per capita consumption to adult male and adult female per capita consumption.
- Based on surveys, the age-specific prevalence of drinking was calculated on the assumption that the average per capita consumption and the proportions of male and female abstainers were correct.

2.3 Data sources for patterns of drinking

Initial estimates of drinking patterns across a range of countries were based on two surveys of key informants selected by WHO staff, conducted in early 2000 and mid 2001. The surveys covered relevant drinking characteristics within different countries or regions. In most cases, respondents had access to national or regional survey data, although these data had not always been published in the international literature. In addition, the informants provided a confidence rating for their responses (i.e. whether based on surveys or just best guesses). This information was used for decisions about inclusion of data when conflicting information existed. As listed in Table 12.1, the survey considered five main areas of drinking patterns that might be expected to affect the impact of volume of drinking: proportion of abstainers, heavy drinking occasions, drinking with meals, drinking in public places and drinking linked to violence (later dropped from analyses because of its interference with outcome measures).

The key informant ratings were analysed using optimal scaling analysis (Bijleveld et al. 1998, chapter 2). This analysis is similar to factor analysis, but permits the simultaneous inclusion of ordinal and categor-

ical data. As with factor analysis, this statistical technique allows the analyst to determine the number of underlying dimensions and the relation of items to each dimension. In the analysis of patterns of drinking, one global dimension was identified and labelled as detrimental impact (for details see Rehm et al. 2001b).

The results of the optimal scaling analysis were very similar to a score derived simply by summing the ratings of the key informant survey (Pearson correlation: 0.93). To further simplify the pattern values into robust general categories based on these scale values, the countries were placed in four categories and assigned values from 1 to 4. By the time the final pattern values were constructed, additional survey data were available as well as the second wave of key informant data, allowing refinement and corrections of estimates. Also, the proportion of abstainers was no longer included as one of the parameters of pattern weights, because rates of abstinence were taken into account separately as one of the average volume of consumption categories. The underlying variables and the scoring pattern can be found in Appendix A.

To apply pattern values to estimate the burden of disease attributable to alcohol, countries with missing data on drinking pattern values were assigned the same category as that of neighbouring countries, taking into consideration geographical and cultural proximity. The pattern values for more than 130 countries worldwide can be seen in Table 12.3.[9]

Patterns of drinking thus defined were found to be unrelated to volume: the overall Pearson correlation between pattern values and per capita consumption for the countries included is –0.126 and the more appropriate Spearman correlation is –0.072. Both correlations do not achieve statistical significance; that is, they are not significantly different from zero (both correlations based on 132 countries with data on both variables). This suggests that drinking pattern may provide important unique information about the risks of drinking alcohol beyond that captured by per capita consumption.

Although this procedure allowed us to derive drinking pattern values from a combination of empirical data and expert judgement, these patterns still needed to be validated empirically to demonstrate that they were, in fact, related to outcomes. In other words, pattern values serve as a description of one aspect of exposure that is theoretically postulated to be related to harm, but such a relation still has to be empirically established. In addition, the degree of influence of patterns on harm (i.e. how much weight to assign to drinking pattern in calculating the burden of disease attributable to alcohol) had to be estimated. Moreover, the weight to be assigned to drinking pattern may vary by type of outcome, sex and age. A later section of this chapter describes how these weights were developed.

2.4 Methods for obtaining estimates where more than one data source exists

For estimating overall consumption, clear hierarchies were used for integrating per capita data into the WHO Global Alcohol Database and subsequently into this work.

- Scientifically derived and well documented local estimates (e.g. from the National Drug Research Institute in Australia, see Catalano et al. 2001) were given first priority.
- Production/sales data were used, such as the annual data on per capita consumption published by the alcohol industry (e.g. Productschap voor Gedistilleerde Dranken 1999, 2000).
- FAO production and trade data were used where other data were not available.

If more than one data point existed for the time after 1998 (e.g. per capita estimates for 1998 and 1999), data points were averaged. With respect to survey data, if more than one representative survey with more than 2000 persons existed, the most recent survey estimates were used. Survey data were always given priority over key informant estimates in estimating pattern values.

2.5 Methods for obtaining estimates where no data source exists

Most regions had sufficient data for estimating prevalence of average volume of drinking, based on per capita consumption (including unrecorded consumption) plus the sex-specific ratio of abstinence derived from surveys. Survey data on abstinence were available for 69 countries (52.3% of all 132 countries included), and were additionally estimated for 39 countries (29.5% of all the countries). Estimation was based on abstinence rates in adjoining countries. Survey data on abstinence were available for many of the countries with large populations: Brazil, China, India, Mexico, Nigeria, the Russian Federation, South Africa, the United States of America and the major (western) European countries. These surveys were taken as indicators for the respective subregions. Regional numbers are to a large degree influenced by a limited number of highly populated countries. Thus, it is important to get the numbers for these countries correct by investing limited resources in estimating alcohol consumption for these countries, rather than attempting to improve the data for all countries in the world.[10]

Data were scarcer with respect to patterns of drinking. Only 44 countries (33.3% of 132 countries) had sufficient information on patterns to compute a pattern score. For another 88 countries (66.6%), data on patterns had to be estimated. Clearly, it is a priority for future estimates that more data on drinking patterns be collected for use in these analyses (see

also Rehm and Gmel 2000b). As with per capita consumption, ratings on drinking patterns for countries for which no data were available were based on social and cultural factors (Muslim vs non-Muslim country, type of drinking culture, etc.) and on drinking patterns in surrounding countries.

2.6 Description of databases, including methodological qualities

A description of the WHO Global Alcohol Database can be found in the *Global status report on alcohol* (WHO 1999). The Swiss Institute for the Prevention of Alcohol Problems constantly updates and expands the Database, which includes both adult per capita and survey data. In addition, many surveys were directly sent to the first author of this work, especially from countries that also supplied key informant information. Additional surveys from developing countries can be found in a WHO collection (WHO 2001). The data in the WHO Database are selected and scrutinized according to set criteria. The data from established market economies are usually based on more reliable sales data and better-quality surveys than those from developing countries.

2.7 Characteristics of excluded studies/databases

Studies were excluded only if better survey information was available for the same country. Better survey information was defined in terms of how recently the survey had been conducted, the availability of a probability sample of at least 2000 respondents, or other quality criteria (e.g. a representative survey based on probabilistic sampling of the whole country vs a non-representative survey or regional survey; better alcohol measures, such as quantity–frequency measure vs frequency-only measure; or larger survey at the same time).

2.8 Estimates of country data and exposure dimensions by subregion, age and sex

Table 12.3 provides country-specific information on alcohol consumption, drinking patterns, percentage abstainers and validity ratings for estimates. Also shown are the relevant subregion and the population aged ≥15 years in 2000.

Table 12.4 gives estimates of the proportion of population in each of the four categories of average alcohol consumption described above by subregion, sex and age. The CRA required two age groups for people aged >70 years: 70–79 years and ≥80 years. With a lack of evidence to differentiate between these two age categories, both were assumed to have the same prevalence and risk relations.

These figures assume no alcohol consumption leading to harm for young people under the age of 15 years. This is certainly not true for young people in established market economies, where drinking starts early and where alcohol-related harm can be found (though not with a

Table 12.3 Per capita alcohol consumption, patterns of drinking and abstinence in selected countries after 1998

Country	*Subregion*	*Adult per capita alcohol consumption*[a]	*Unrecorded consumption*[b]	*Pattern value*[c]	*Validity pattern value*[d]	*Percentage male abstainers*[e]	*Percentage female abstainers*[f]	*Validity of abstinence*[g]	*Population aged ≥15 years (000s)*
Albania	EUR-B	4.77	3.00	3	0	12.0	36.0	0	2195.8
Algeria	AFR-D	0.47	0.16	3	0	80.0	98.0	0	19 939.8
Argentina	AMR-B	16.30	1.00	2	1	7.0	21.0	1	26766.9
Armenia	EUR-B	2.88	1.44	2	1	9.9	60.0	1	2656.9
Australia	WPR-A	9.19	0.00	2	1	15.8	24.0	1	14988.4
Austria	EUR-A	13.90	1.00	1	0	13.0	33.0	1	6814.9
Azerbaijan	EUR-B	2.86	1.43	3	0	12.0	36.0	0	5520.9
Barbados	AMR-B	7.43	–0.50	2	0	29.0	70.4	0	213.6
Belarus	EUR-C	12.22	4.90	4	0	2.0	4.0	1	8322.3
Belgium	EUR-A	11.45	0.50	1	0	9.6	20.5	1	8420.4
Belize	AMR-B	6.35	2.00	4	0	24.0	44.0	0.5	145.0
Bolivia	AMR-D	5.74	3.00	3	0	23.8	44.6	1	5028.6
Bosniaand Herzegovina	EUR-B	7.65	3.00	3	0	12.0	36.0	0	3223.8
Botswana	AFR-E	5.33	3.00	3	0	37.0	70.0	0	938.4
Brazil	AMR-B	8.59	3.00	3	1	36.4	57.0	1	121 038.8
Bulgaria	EUR-B	13.08	5.00	2	1	8.0	16.0	1	6890.0
Burkina Faso	AFR-D	3.81	3.32	3	0	—	—	—	6287.6
Burundi	AFR-E	7.42	4.75	3	0	—	—	—	3591.1
Cambodia	WPR-B	0.36	0.12	3	0	74.4	96.0	0	6603.7
Cameroon	AFR-D	4.35	2.62	3	0	—	—	—	8524.9

continued

Table 12.3 Per capita alcohol consumption, patterns of drinking and abstinence in selected countries after 1998 (*continued*)

Country	*Subregion*	*Adult per capita alcohol consumption*[a]	*Unrecorded consumption*[b]	*Pattern value*[c]	*Validity pattern value*[d]	*Percentage male abstainers*[e]	*Percentage female abstainers*[f]	*Validity of abstinence*[g]	*Population aged ≥15 years (000s)*
Canada	AMR-A	9.43	1.00	2	1	17.3	28.0	1	25248.1
Central African Republic	AFR-E	3.01	1.00	3	0	—	—	—	2078.4
Chile	AMR-B	8.34	1.00	3	0	31.4	46.5	1	10883.1
China	WPR-B	4.83	1.00	2	1	15.9	70.7	1	960300.9
Colombia	AMR-B	8.30	2.00	3	0	31.4	46.5	0.5	28470.8
Costa Rica	AMR-B	6.70	2.00	3	0	45.0	75.0	1	2721.4
Croatia	EUR-A	18.39	4.50	3	0	12.0	36.0	0	3709.2
Cuba	AMR-A	5.66	2.00	2	0	29.0	70.4	0	8823.4
Cyprus	EMR-B	9.29	1.00	1	0	1.2	15.4	0	603.0
Czech Republic	EUR-A	15.02	1.00	2	1	3.1	8.1	1	8547.7
Democratic People's Republic of Korea	SEAR-D	5.14	1.00	3	0	—	—	—	17399.1
Denmark	EUR-A	14.32	2.00	1	1	2.0	4.0	1	4341.6
Djibouti	EMR-D	.66	0.22	3	0	—	—	—	373.4
Dominican Republic	AMR-B	5.71	1.00	2	0	29.0	70.4	0	5687.8
Ecuador	AMR-D	5.49	3.66	3	0	20.0	40.0	0.5	8368.2
Egypt	EMR-D	0.92	0.46	2	0	70.0	98.0	0.5	44274.2
El Salvador	AMR-B	4.64	2.00	4	0	8.7	37.7	0	4041.9
Eritrea	AFR-E	2.55	0.85	3	0	—	—	—	2151.5
Estonia	EUR-C	11.70	5.00	3	0	5.0	10.0	1	1152.4

Ethiopia	AFR-E	1.68	0.84	3	0	—	—	—	33690.1
Fiji	WPR-B	2.95	1.00	3	0	74.3	97.5	1	561.3
Finland	EUR-A	11.69	2.00	3	1	8.0	10.0	1	4239.6
France	EUR-A	15.62	1.00	1	1	7.3	11.3	1	48032.9
Gabon	AFR-D	7.34	4.00	3	0	—	—	—	733.5
Georgia	EUR-B	7.36	2.00	2	0	12.0	36.0	0	3868.9
Germany	EUR-A	14.40	1.00	1	1	4.2	5.4	1	69469.4
Ghana	AFR-D	3.64	1.82	3	0	—	—	—	11489.3
Greece	EUR-A	11.39	2.00	2	1	1.2	15.4	1	9051.8
Guatemala	AMR-D	3.71	2.00	4	0	45.0	62.0	0.5	6420.1
Guyana	AMR-B	12.07	2.00	3	0	20.0	40.0	0	604.3
Haiti	AMR-D	5.38	0.00	2	0	58.0	62.0	0.5	4874.7
Honduras	AMR-B	4.22	2.00	4	0	8.7	37.7	0	3784.3
Hungary	EUR-C	17.35	4.00	3	0	6.6	21.4	1	8329.4
Iceland	EUR-A	6.41	1.00	3	0	9.1	13.3	0	215.4
India	SEAR-D	2.00	1.65	3	1	75.0	96.0	1	676054.8
Indonesia	SEAR-B	0.58	0.50	3	0	74.4	96.0	0	147181.7
Iraq	EMR-D	0.48	0.00	2	0	80.0	98.0	0	13558.9
Ireland	EUR-A	15.21	1.00	3	1	9.0	16.0	1	2938.4
Israel	EUR-A	2.91	1.00	2	1	21.0	48.7	1	4492.5
Italy	EUR-A	10.34	1.50	1	1	14.7	30.2	1	49133.0
Jamaica	AMR-B	4.28	1.00	2	0	29.0	70.4	0	1780.9
Japan	WPR-A	8.47	2.00	1	1	12.0	23.0	1	107949.3

continued

Table 12.3 Per capita alcohol consumption, patterns of drinking and abstinence in selected countries after 1998 (*continued*)

Country	*Subregion*	*Adult per capita alcohol consumption*[a]	*Unrecorded consumption*[b]	*Pattern value*[c]	*Validity pattern value*[d]	*Percentage male abstainers*[e]	*Percentage female abstainers*[f]	*Validity of abstinence*[g]	*Population aged ≥15 years (000s)*
Jordan	EMR-B	0.28	0.14	2	0	74.0	98.0	0	3871.8
Kazakhstan	EUR-C	10.11	6.90	4	0	10.0	27.0	0	11751.4
Kenya	AFR-E	6.83	5.00	3	0	45.0	65.0	0	17137.1
Kyrgyzstan	EUR-B	5.89	4.00	3	0	60.0	80.0	0	3054.5
Lao People's Democratic Republic	WPR-B	5.82	2.00	3	0	—	—	—	3044.4
Latvia	EUR-C	16.48	7.00	3	0	15.0	46.2	1	1940.2
Lebanon	EMR-B	5.60	2.00	3	0	—	—	—	2208.6
Lesotho	AFR-E	3.16	1.58	3	0	—	—	—	1294.2
Liberia	AFR-D	4.54	2.00	3	0	—	—	—	1824.6
Lithuania	EUR-C	11.41	4.90	3	0	15.0	46.2	0	2964.8
Luxembourg	EUR-A	17.32	–2.00	1	0	1.0	4.0	0.5	352.9
Malaysia	WPR-B	4.26	3.40	3	0	35.1	63.5	1	14678.4
Mauritius	AFR-D	15.62	11.00	3	0	22.0	53.0	1	865.2
Mexico	AMR-B	8.15	4.00	4	1	15.8	46.5	1	66105.2
Mongolia	WPR-B	4.45	2.00	3	0	20.2	62.7	0	1740.8
Morocco	EMR-D	1.16	0.58	3	0	—	—	—	19121.7
Myanmar	SEAR-D	0.62	0.42	2	0	45.0	93.5	0	32887.4
Namibia	AFR-E	5.40	1.80	3	1	60.9	47.1	1	1008.5
Netherlands	EUR-A	10.39	0.50	1	1	14.0	26.5	1	12926.5

New Zealand	WPR-A	11.32	0.50	2	1	10.0	14.0	1	2986.5
Nicaragua	AMR-D	3.71	1.00	4	0	8.7	37.7	0	2905.3
Nigeria	AFR-D	6.94	3.50	2	1	46.2	54.9	1	63465.7
Norway	EUR-A	7.50	2.00	3	1	8.0	17.0	1	3588.2
Pakistan	EMR-D	0.23	0.20	3	0	90.0	99.0	0	91048.8
Papua New Guinea	WPR-B	0.88	0.50	3	1	22.0	86.5	1	2948.4
Paraguay	AMR-B	9.55	1.50	3	0	18.0	38.0	0.5	3323.7
Peru	AMR-D	5.43	1.00	3	1	16.6	23.6	1	17094.4
Philippines	WPR-B	6.40	3.00	3	1	10.0	70.0	1	48096.9
Poland	EUR-B	12.64	5.00	3	1	11.6	25.7	1	31240.1
Portugal	EUR-A	15.06	1.00	1	0	14.8	48.8	1	8261.3
Republic of Korea	WPR-B	14.20	7.00	3	1	7.1	14.2	1	36775.6
Republic of Moldova	EUR-C	29.36	12.00	4	0	9.0	18.0	0	3360.7
Romania	EUR-B	16.27	4.00	3	0	23.0	53.0	0	18364.0
Russian Federation	EUR-C	16.39	5.85	4	1	9.0	8.0	1	120255.0
Rwanda	AFR-E	6.36	4.32	3	0	—	—	—	4224.2
Saudi Arabia	EMR-B	0.21	0.14	2	0	95.0	99.0	0	12848.8
Senegal	AFR-D	1.26	0.84	3	0	—	—	—	5244.9
Seychelles	AFR-D	11.00	5.16	3	1	10.0	45.0	1	69.0
Sierra Leone	AFR-D	4.22	2.41	3	0	—	—	—	2716.7
Singapore	WPR-A	3.14	1.00	2	0	74.4	96.0	0	2778.7
Slovakia	EUR-B	19.30	7.00	3	1	5.1	21.6	1	4326.7

continued

Table 12.3 Per capita alcohol consumption, patterns of drinking and abstinence in selected countries after 1998 (*continued*)

Country	*Subregion*	*Adult per capita alcohol consumption*[a]	*Unrecorded consumption*[b]	*Pattern value*[c]	*Validity pattern value*[d]	*Percentage male abstainers*[e]	*Percentage female abstainers*[f]	*Validity of abstinence*[g]	*Population aged ≥15 years (000s)*
Slovenia	EUR-A	13.42	5.20	3	1	31.2	55.4	1	1669.0
South Africa	AFR-E	12.41	2.20	3	1	55.3	83.1	1	26236.4
Spain	EUR-A	13.28	1.00	1	1	7.0	24.0	1	33863.3
Sri Lanka	SEAR-B	0.57	0.38	3	0	74.4	96.0	1	13912.4
Sudan	EMR-D	0.69	0.46	3	0	—	—	—	17863.6
Suriname	AMR-B	5.96	0.00	3	0	30.0	55.0	0.5	290.0
Swaziland	AFR-E	7.89	4.05	3	0	—	—	—	574.6
Sweden	EUR-A	9.07	2.00	3	1	7.0	12.0	1	7288.2
Switzerland	EUR-A	12.49	0.50	1	1	11.0	27.0	1	6097.3
Syrian Arab Republic	EMR-B	0.70	0.36	2	0	—	—	—	9546.7
Tajikistan	EUR-B	5.23	3.95	3	0	60.0	80.0	0	3692.5
Thailand	SEAR-B	11.70	2.00	3	1	30.5	71.7	1	45909.9
The former Yugoslav Republic of Macedonia	EUR-B	8.56	3.20	3	1	20.0	40.0	1	1559.4
Trinidad and Tobago	AMR-B	2.36	0.00	2	1	29.0	70.4	1	970.9
Tunisia	EMR-B	1.80	0.50	2	0	70.0	95.0	0	6677.8
Turkey	EUR-B	4.30	2.70	3	0	35.0	55.0	0	47742.9
Turkmenistan	EUR-B	2.85	1.00	3	0	35.0	55.0	0	2780.1

Uganda	AFR-E	13.30	10.71	3	0	45.0	67.0	0.5	10877.2
Ukraine	EUR-C	8.00	4.00	3	1	12.0	36.0	0	41487.6
United Arab Emirates	EMR-B	3.68	1.00	2	0	—	—	—	1757.7
United Kingdom	EUR-A	11.88	2.00	2	1	8.0	14.0	1	47761.2
United Republic of Tanzania	AFR-E	6.47	2.00	3	0	—	—	—	18291.2
United States	AMR-A	9.47	1.00	2	1	28.1	42.6	1	218586.3
Uruguay	AMR-B	9.54	2.00	3	0	7.0	21.0	0	2509.7
Uzbekistan	EUR-B	2.92	1.90	3	0	60.0	80.0	0	15211.3
Venezuela	EUR-C	9.59	2.00	3	0	30.0	55.0	0.5	15942.8
Viet Nam	WPR-B	2.26	1.00	3	0	—	—	—	53320.3
Zambia	AFR-E	3.96	1.00	4	1	35.0	70.0	1	4837.4
Zimbabwe	AFR-E	12.65	9.00	4	0	7.0	36.0	0.5	6847.3

— No data.

[a] Average annual per capita consumption by adults (≥15 years) after 1998 in litres of pure alcohol, including estimates of unrecorded consumption (average of available years).

[b] Estimated annual per capita unrecorded consumption by adults (≥15 years) after 1998 in litres of pure alcohol (based in part on the *Global status report on alcohol*). Negative values reflect where estimated cross-border shopping by non-residents and drinking by tourists exceeds any estimated unrecorded consumption by residents.

[c] 1 denotes the least detrimental pattern value and 4 denotes the most detrimental. Pattern values are assumed to be relatively stable and were derived for the 1990s.

[d] 0 = imputed based on regional and cultural similarities, or based on data from the *Global status report on alcohol*; 1 = questionnaire available with sufficient non-missing values to allow optimal scaling.

[e] Proportion of adult males who were abstainers for the year before the survey.

[f] Proportion of adult females who were abstainers for the year before the survey.

[g] 0 = imputed based on regional and cultural similarities; 0.5 = based on survey but only for subsections of the country or not differentiated for sex; 1 = survey data, differentiated for sex.

high prevalence) before the age of 15 years (Hibell et al. 2000). However, as data for this age group are scarce and as the prevalence rates for drinking and harm are low, the conservative approach of estimating no alcohol-related harm for this age group was adopted. The decision to model alcohol-related harm at zero for people's own drinking does not mean that there will be no alcohol-related harm estimated in this age group altogether. Rather, owing to the nature of effects, we must deviate from the standard epidemiological model and include effects of drinking on other externalities. To give just one example of this type of harm, a drunken driver may kill innocent bystanders or passengers driving in his car who are younger than 15 years, and this would be a fatality caused by alcohol.

The following distribution data were based on survey-based information on abstainers for 69 countries. For distributional information on drinkers, the following sources were considered:

- AFR-D, Nigeria (Mustonen et al. 2001 and newer survey data reported in the key informant questionnaire from I. Obot/O. Gureje);
- AFR-E, South Africa (Department of Health 1998, South African Demographic and Health Survey);
- AMR-A, Canada and the United States (surveys provided by E. Adlaf for Canada and T. Greenfield for the United States);
- AMR-B, Brazil (São Paulo) (Galduróz et al. 2000) and Mexico (surveys provided by the Mexican Institute of Psychiatry); see also WHO (2001) for country reports on Costa Rica and Mexico, and Jutkowitz and Hongsook (1994);
- AMR-D (survey data for Peru and Jutkowitz and Hongsook 1994);
- EMR-B and EMR-D (only per capita information and general distribution information as approximately log-normal[11] with some data on abstinence);
- EUR-A (based on the average of many country surveys);
- EUR-B, Poland (based on survey information provided by key informants);
- EUR-C, the Russian Federation (published national and regional survey data from Bobak et al. 1999; Malyutina et al. 2001);
- SEAR-B, Sri Lanka and Thailand (survey estimates provided by key informants);
- SEAR-D, India (regional survey data provided by key informants);
- WPR-A, Australia and New Zealand (survey data, see English et al. 1995; Ridolfo and Stevenson for Australia and http://www.aphru.ac.nz/projects/Larger for New Zealand); and

- WPR-B, China (Wei et al. 1999 and additional information by the first author).

The numbers in Table 12.4 are given as a proportion of the age–sex-specific population. Thus, for females aged 15–29 years in WPR-B, 67.4% are estimated to abstain, 32.6% are estimated to drink the equivalent of between 0 g and 20 g pure alcohol per day, 0.1% are estimated to drink between 20 g and 40 g, and less than 0.05% are estimated to drink more than 40 g. In the oldest age group, 89.8% of females are estimated to abstain, 10.2% to drink the equivalent of up to 20 g pure alcohol per day, and less than 0.05% to drink more.

Currently, pattern values assigned to each country and then computed as a population-weighted average for each subregion are not specific by sex and age (see Table 12.5). This may change in the future when survey data on patterns become more available.

2.9 Quantitative and qualitative sources of uncertainty

Uncertainty analysis

As described, alcohol consumption as a risk factor has two dimensions: average volume and patterns. It is thus proposed to base the uncertainty analysis on the weighted average of the available information for both dimensions for each subregion. Uncertainty analysis is undertaken to give an indication on uncertainty, based on different characteristics such as the source or variability of the estimated data. It will also be used to calculate the confidence intervals (CIs) of the alcohol-related burden. Classically, CIs for prevalence are determined by sample size, assuming that the underlying individual data are representative of the subregion. For some subregions, however, we do not have probabilistic samples. As alcohol consumption is a social activity and can vary markedly from one country to another within a region, one cannot automatically assume that the countries without surveys would have the same alcohol distribution as the countries with surveys. Thus, the procedure based on sample size cannot be used here. Moreover, prevalence was derived from both aggregate- (per capita consumption) and individual-level data in a triangulation of information, for which there is no statistical theory for readily deriving CIs.

The algorithms specified below were developed after extensive discussions with experts in the field. They are intended to reflect the quantity and quality of the underlying data sources. Aggregate-level data exist for all countries. To estimate average volume of alcohol consumption, we propose to base uncertainty analysis on the amount of survey information available in a subregion. The procedure allowed the estimation of lower or upper limits, even if no survey information existed. In Pakistan, for example, per capita alcohol consumption set clear upper boundaries for the highest drinking categories, since some values would

Table 12.4 Estimated proportions of population in average volume of consumption categories by sex, age and subregion, in 2000[a]

Subregion	Sex	Average volume of consumption category[b]	Age group (years)					
			15–29	30–44	45–59	60–69	70–79	≥80
AFR-D	Male	Abstinence	0.510	0.462	0.514	0.565	0.616	0.616
		D I	0.420	0.447	0.396	0.354	0.323	0.323
		D II	0.063	0.073	0.072	0.063	0.044	0.044
		D III	0.007	0.018	0.018	0.018	0.016	0.016
	Female	Abstinence	0.746	0.697	0.697	0.746	0.796	0.796
		D I	0.234	0.267	0.265	0.237	0.191	0.191
		D II	0.019	0.030	0.029	0.010	0.010	0.010
		D III	0.001	0.007	0.010	0.007	0.003	0.003
AFR-E	Male	Abstinence	0.432	0.375	0.428	0.482	0.536	0.536
		D I	0.431	0.430	0.403	0.368	0.354	0.354
		D II	0.125	0.161	0.135	0.116	0.082	0.082
		D III	0.012	0.034	0.034	0.033	0.029	0.029
	Female	Abstinence	0.715	0.664	0.664	0.715	0.766	0.766
		D I	0.243	0.277	0.271	0.237	0.203	0.203
		D II	0.036	0.046	0.046	0.036	0.025	0.025
		D III	0.006	0.012	0.018	0.012	0.006	0.006
AMR-A	Male	Abstinence	0.240	0.221	0.268	0.374	0.431	0.431
		D I	0.522	0.583	0.577	0.525	0.498	0.498
		D II	0.164	0.146	0.105	0.095	0.064	0.064
		D III	0.074	0.050	0.050	0.006	0.006	0.006
	Female	Abstinence	0.360	0.331	0.409	0.584	0.633	0.633
		D I	0.563	0.620	0.548	0.382	0.337	0.337
		D II	0.050	0.033	0.027	0.025	0.023	0.023
		D III	0.027	0.016	0.016	0.008	0.007	0.007
AMR-B	Male	Abstinence	0.220	0.203	0.172	0.199	0.358	0.358
		D I	0.671	0.674	0.711	0.714	0.605	0.605
		D II	0.035	0.045	0.045	0.031	0.025	0.025
		D III	0.074	0.078	0.072	0.056	0.012	0.012
	Female	Abstinence	0.463	0.444	0.444	0.488	0.538	0.538
		D I	0.464	0.475	0.486	0.450	0.429	0.429
		D II	0.028	0.028	0.026	0.030	0.020	0.020
		D III	0.046	0.053	0.044	0.032	0.013	0.013
AMR-D	Male	Abstinence	0.298	0.264	0.304	0.398	0.498	0.498
		D I	0.677	0.712	0.672	0.585	0.494	0.494
		D II	0.017	0.016	0.016	0.013	0.008	0.008
		D III	0.008	0.008	0.008	0.004	0.001	0.001
	Female	Abstinence	0.431	0.393	0.487	0.548	0.628	0.628
		D I	0.536	0.572	0.483	0.428	0.356	0.356
		D II	0.024	0.025	0.021	0.019	0.012	0.012
		D III	0.009	0.009	0.008	0.005	0.004	0.004
EMR-B	Male	Abstinence	0.789	0.838	0.838	0.887	0.976	0.976
		D I	0.191	0.149	0.149	0.107	0.024	0.024
		D II	0.013	0.010	0.010	0.004	0.000	0.000
		D III	0.006	0.003	0.003	0.001	0.000	0.000

Table 12.4 Estimated proportions of population in average volume of consumption categories by sex, age and subregion, in 2000[a] (*continued*)

Subregion	Sex	Average volume of consumption category[b]	Age group (years)					
			15–29	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
	Female	Abstinence	0.937	0.968	0.968	0.998	1.000	1.000
		D I	0.052	0.027	0.027	0.002	0.000	0.000
		D II	0.008	0.005	0.005	0.000	0.000	0.000
		D III	0.003	0.000	0.000	0.000	0.000	0.000
EMR-D	Male	Abstinence	0.898	0.898	0.898	0.947	0.987	0.987
		D I	0.101	0.102	0.102	0.052	0.013	0.013
		D II	0.001	0.000	0.000	0.000	0.000	0.000
		D III	0.000	0.000	0.000	0.000	0.000	0.000
	Female	Abstinence	0.975	0.990	0.990	1.000	1.000	1.000
		D I	0.024	0.010	0.010	0.000	0.000	0.000
		D II	0.001	0.000	0.000	0.000	0.000	0.000
		D III	0.001	0.000	0.000	0.000	0.000	0.000
EUR-A	Male	Abstinence	0.074	0.074	0.093	0.139	0.186	0.186
		D I	0.748	0.721	0.701	0.723	0.717	0.717
		D II	0.087	0.102	0.096	0.069	0.042	0.042
		D III	0.091	0.102	0.110	0.069	0.055	0.055
	Female	Abstinence	0.138	0.138	0.173	0.259	0.346	0.346
		D I	0.698	0.726	0.662	0.635	0.571	0.571
		D II	0.123	0.103	0.124	0.085	0.065	0.065
		D III	0.041	0.033	0.041	0.021	0.017	0.017
EUR-B	Male	Abstinence	0.237	0.284	0.284	0.331	0.379	0.379
		D I	0.653	0.606	0.625	0.598	0.582	0.582
		D II	0.054	0.054	0.049	0.038	0.016	0.016
		D III	0.056	0.056	0.042	0.033	0.024	0.024
	Female	Abstinence	0.410	0.461	0.512	0.614	0.614	0.614
		D I	0.507	0.449	0.414	0.328	0.339	0.339
		D II	0.068	0.069	0.053	0.047	0.037	0.037
		D III	0.016	0.021	0.021	0.010	0.010	0.010
EUR-C	Male	Abstinence	0.088	0.088	0.110	0.164	0.219	0.219
		D I	0.602	0.662	0.584	0.629	0.669	0.669
		D II	0.188	0.159	0.185	0.132	0.067	0.067
		D III	0.123	0.091	0.121	0.075	0.045	0.045
	Female	Abstinence	0.140	0.140	0.175	0.263	0.351	0.351
		D I	0.719	0.743	0.683	0.645	0.588	0.588
		D II	0.115	0.096	0.116	0.079	0.051	0.051
		D III	0.026	0.020	0.026	0.013	0.011	0.011
SEAR-B	Male	Abstinence	0.631	0.561	0.701	0.841	0.981	0.981
		D I	0.359	0.410	0.295	0.156	0.018	0.018
		D II	0.007	0.024	0.003	0.002	0.000	0.000
		D III	0.002	0.006	0.001	0.001	0.000	0.000
	Female	Abstinence	0.885	0.914	0.914	0.943	0.953	0.953
		D I	0.103	0.078	0.078	0.052	0.047	0.047
		D II	0.009	0.008	0.008	0.005	0.000	0.000
		D III	0.002	0.000	0.000	0.000	0.000	0.000

continued

Table 12.4 Estimated proportions of population in average volume of consumption categories by sex, age and subregion, in 2000[a] (*continued*)

Subregion	Sex	Average volume of consumption category[b]	Age group (years)					
			15–29	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
SEAR-D	Male	Abstinence	0.717	0.637	0.796	0.956	1.000	1.000
		D I	0.276	0.338	0.201	0.044	0.000	0.000
		D II	0.006	0.020	0.002	0.001	0.000	0.000
		D III	0.002	0.005	0.001	0.000	0.000	0.000
	Female	Abstinence	0.937	0.968	0.968	0.998	1.000	1.000
		D I	0.051	0.028	0.028	0.002	0.000	0.000
		D II	0.007	0.004	0.004	0.000	0.000	0.000
		D III	0.005	0.000	0.000	0.000	0.000	0.000
WPR-A	Male	Abstinence	0.095	0.095	0.119	0.179	0.238	0.238
		D I	0.834	0.849	0.812	0.776	0.730	0.730
		D II	0.033	0.028	0.032	0.023	0.013	0.013
		D III	0.037	0.028	0.037	0.023	0.018	0.018
	Female	Abstinence	0.163	0.163	0.204	0.306	0.408	0.408
		D I	0.806	0.812	0.766	0.675	0.578	0.578
		D II	0.023	0.019	0.023	0.015	0.011	0.011
		D III	0.008	0.006	0.008	0.004	0.003	0.003
WPR-B	Male	Abstinence	0.153	0.153	0.153	0.204	0.256	0.256
		D I	0.769	0.761	0.761	0.719	0.684	0.684
		D II	0.055	0.053	0.053	0.051	0.040	0.040
		D III	0.022	0.032	0.032	0.026	0.020	0.020
	Female	Abstinence	0.674	0.674	0.674	0.786	0.898	0.898
		D I	0.326	0.326	0.326	0.214	0.102	0.102
		D II	0.001	0.000	0.000	0.000	0.000	0.000
		D III	0.000	0.000	0.000	0.000	0.000	0.000

[a] Prevalences are rounded to full percentages. Thus, a value of zero does not necessarily indicate that there are no people in a certain category, but may indicate a prevalence of less than 0.005 or 0.5%.

[b] **Drinking categories are defined as follows:**

Risk factor: alcohol—first dimension: average volume of consumption.

Units: grams of pure alcohol per day.

Definitions of categories of risk factor levels

Level 1:	Abstinence	abstainer
Level 2:	D I	drinking category I: women >0–<20 g; men >0–<40 g
Level 3:	D II	drinking category II: women 20–<40 g; men 40–<60 g
Level 4:	D III	drinking category III: women >40 g; men >60 g

not be physically possible within the overall volume consumed in this country.

In operationalizing these principles, the validity of the abstainer category was selected (for values in individual countries see Table 12.3). This variable was aggregated using the population aged ≥15 years as a

Table 12.5 Patterns of drinking by subregion

Subregion	*Pattern value*[a]	*Validity of pattern value*
AFR-D	2.48	0.52
AFR-E	3.09	0.24
AMR-A	2.00	0.97
AMR-B	3.14	0.77
AMR-D	3.10	0.38
EMR-B	2.01	0.00
EMR-D	2.35	0.00
EUR-A	1.34	0.92
EUR-B	2.93	0.31
EUR-C	3.62	0.75
SEAR-B	2.50	0.22
SEAR-D	2.95	0.93
WPR-A	1.16	0.98
WPR-B	2.15	0.93

[a] Pattern values were defined as follows:

Risk factor: alcohol—second dimension: patterns of drinking.

Units: range between 1 and 4; originally derived from optimal scaling and then based on addition of values of each pattern component (see Appendix A for details); subregional averages are population-weighted country averages.

Definitions of categories of risk factor levels

Level 1: based on score of initial pattern components, with values in the lowest quartile reflecting least detrimental patterns of drinking such as least heavy drinking occasions, drinking with meals, no fiesta drinking and least drinking in public places.

Level 2: based on score of initial pattern components, with values in the second lowest quartile.

Level 3: based on score of initial pattern components, with values in the second highest quartile.

Level 4: based on score of initial pattern components, with values in the highest quartile reflecting detrimental patterns such as many heavy drinking occasions, drinking outside meals, high level of fiesta drinking and drinking in public places.

weight. The resulting values were treated in the uncertainty analysis as follows:

For aggregated validity values of 0	Base prevalence estimate on full range from 0 to twice the point estimate (i.e. point estimate plus 100% of the point estimate).
For aggregated validity values >0 and <0.5	Point estimate ±50% of point estimate of prevalence.
For aggregated validity values ≥0.5 and <0.75	Point estimate ±25% of point estimate of prevalence.

For aggregated validity values ≥0.75	Point estimate ±10% of point estimate of prevalence.

This applies to both sexes, as most surveys include both males and females. Further corrections were made based on per capita consumption for subregions where certain distributions were not plausible because the known per capita consumption could not be derived with less than a certain proportion of abstainers (for EMR-B: maximum CI for abstainers ±15%, minimum: ±1%; for EMR-D: maximum ±10%, minimum: ±1%; for SEAR-B: maximum ±10%, minimum: ±1%; for SEAR-D and WPR-B: minimum: ±0.2%). The results can be seen in Table 12.6.

Similarly, for constructing CIs around patterns of drinking (see Table 12.7), the validity of the underlying pattern values was used. Again, using the weighted average on the validity ratings of the pattern value (see Table 12.3 for the underlying country data), the following uncertainty ranges were proposed:

For validity of pattern value of 0	Uncertainty analysis on full range of pattern values (i.e. using pattern values 1 and 4 as bounds).
For validity of pattern value ranging from >0 and <0.5	Point estimate ± 1.
For validity of pattern value ranging from ≥0.5 and <0.75	Point estimate ± 0.5.
For validity of pattern value ranging from ≥0.75	Point estimate ± 0.25.

The validity of pattern value ranged from 0 (e.g. only expert judgements for pattern in EMR-B and EMR-D with no underlying data) to values above 0.95 for several subregions (theoretically 1 if all the pattern values of constituent countries were derived from survey estimates).

The suggested procedure clearly reflects our range of knowledge. For example, we have no knowledge about patterns in EMR-B and EMR-D, where the uncertainty estimates consequently varied between 1 (best possible pattern) and 4 (most detrimental pattern), whereas we have good data for many other subregions (e.g. all the A mortality strata subregions), where the uncertainty estimates vary by only ± 0.25 (e.g. EUR-A, between 1.09 and 1.59).

Overall evaluation of quality for exposure data

Data on production and trade or sales required for estimating adult per capita consumption have been collected systematically for decades in most countries. In this sense, alcohol as a risk factor for global health is privileged compared to some other risk factors, where exposure data are

Table 12.6 Estimated uncertainty range (±%) around point estimate for prevalence of average volume of consumption categories

Subregion	Sex	Average volume of consumption category	Age group (years)					
			15–29	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	Abstinence	5.10	4.62	5.14	5.65	6.16	6.16
		D I	4.20	4.47	3.96	3.54	3.23	3.23
		D II	0.63	0.73	0.72	0.63	0.44	0.44
		D III	0.07	0.18	0.18	0.18	0.16	0.16
	Female	Abstinence	7.46	6.97	6.97	7.46	7.96	7.96
		D I	2.34	2.67	2.65	2.37	1.91	1.91
		D II	0.19	0.30	0.29	0.10	0.10	0.10
		D III	0.01	0.07	0.10	0.07	0.03	0.03
AFR-E	Male	Abstinence	10.80	9.37	10.71	12.05	13.39	13.39
		D I	10.77	10.75	10.08	9.21	8.84	8.84
		D II	3.12	4.03	3.36	2.91	2.05	2.05
		D III	0.31	0.85	0.84	0.83	0.72	0.72
	Female	Abstinence	17.88	16.61	16.61	17.88	19.16	19.16
		D I	6.07	6.93	6.78	5.92	5.07	5.07
		D II	0.90	1.16	1.16	0.90	0.63	0.63
		D III	0.15	0.30	0.45	0.30	0.15	0.15
AMR-A	Male	Abstinence	2.40	2.21	2.68	3.74	4.31	4.31
		D I	5.22	5.83	5.77	5.25	4.98	4.98
		D II	1.64	1.46	1.05	0.95	0.64	0.64
		D III	0.74	0.50	0.50	0.06	0.06	0.06
	Female	Abstinence	3.60	3.31	4.09	5.84	6.33	6.33
		D I	5.63	6.20	5.48	3.82	3.37	3.37
		D II	0.50	0.33	0.27	0.25	0.23	0.23
		D III	0.27	0.16	0.16	0.08	0.07	0.07
AMR-B	Male	Abstinence	2.20	2.03	1.72	1.99	3.58	3.58
		D I	6.71	6.74	7.11	7.14	6.05	6.05
		D II	0.35	0.45	0.45	0.31	0.25	0.25
		D III	0.74	0.78	0.72	0.56	0.12	0.12
	Female	Abstinence	4.63	4.44	4.44	4.88	5.38	5.38
		D I	4.64	4.75	4.86	4.50	4.29	4.29
		D II	0.28	0.28	0.26	0.30	0.20	0.20
		D III	0.46	0.53	0.44	0.32	0.13	0.13
AMR-D	Male	Abstinence	7.46	6.60	7.60	9.96	12.45	12.45
		D I	16.93	17.80	16.80	14.62	12.34	12.34
		D II	0.41	0.39	0.39	0.31	0.19	0.19
		D III	0.20	0.20	0.20	0.10	0.02	0.02
	Female	Abstinence	10.79	9.83	12.17	13.70	15.70	15.70
		D I	13.40	14.31	12.09	10.70	8.90	8.90
		D II	0.60	0.63	0.53	0.48	0.31	0.31
		D III	0.22	0.23	0.21	0.12	0.09	0.09
EMR-B	Male	Abstinence	15.00	15.00	15.00	15.00	15.00	15.00
		D I	19.55	15.25	15.25	11.00	2.65	2.65
		D II	1.21	1.00	1.00	1.00	1.00	1.00
		D III	1.00	1.00	1.00	1.00	1.00	1.00

continued

Table 12.6 Estimated uncertainty range (±%) around point estimate for prevalence of average volume of consumption categories (*continued*)

Subregion	Sex	Average volume of consumption category	Age group (years)					
			15–29	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
	Female	Abstinence	15.00	15.00	15.00	15.00	15.00	15.00
		D I	5.40	2.87	2.87	1.00	1.00	1.00
		D II	1.00	1.00	1.00	1.00	1.00	1.00
		D III	1.00	1.00	1.00	1.00	1.00	1.00
EMR-D	Male	Abstinence	10.00	10.00	10.00	10.00	10.00	10.00
		D I	5.07	5.09	5.09	2.61	1.00	1.00
		D II	1.00	1.00	1.00	1.00	1.00	1.00
		D III	1.00	1.00	1.00	1.00	1.00	1.00
	Female	Abstinence	10.00	10.00	10.00	10.00	10.00	10.00
		D I	1.18	1.00	1.00	1.00	1.00	1.00
		D II	1.00	1.00	1.00	1.00	1.00	1.00
		D III	1.00	1.00	1.00	1.00	1.00	1.00
EUR-A	Male	Abstinence	0.74	0.74	0.93	1.39	1.86	1.86
		D I	7.48	7.21	7.01	7.23	7.17	7.17
		D II	0.87	1.02	0.96	0.69	0.42	0.42
		D III	0.91	1.02	1.10	0.69	0.55	0.55
	Female	Abstinence	1.38	1.38	1.73	2.59	3.46	3.46
		D I	6.98	7.26	6.62	6.35	5.71	5.71
		D II	1.23	1.03	1.24	0.85	0.65	0.65
		D III	0.41	0.33	0.41	0.21	0.17	0.17
EUR-B	Male	Abstinence	5.92	7.10	7.10	8.28	9.47	9.47
		D I	16.34	15.14	15.63	14.94	14.55	14.55
		D II	1.35	1.36	1.23	0.96	0.39	0.39
		D III	1.39	1.40	1.05	0.82	0.59	0.59
	Female	Abstinence	10.24	11.52	12.80	15.36	15.36	15.36
		D I	12.66	11.22	10.35	8.20	8.47	8.47
		D II	1.70	1.73	1.32	1.18	0.91	0.91
		D III	0.39	0.53	0.53	0.26	0.26	0.26
EUR-C	Male	Abstinence	2.19	2.19	2.74	4.11	5.48	5.48
		D I	15.05	16.55	14.60	15.72	16.72	16.72
		D II	4.69	3.98	4.63	3.29	1.68	1.68
		D III	3.07	2.27	3.03	1.88	1.12	1.12
	Female	Abstinence	3.51	3.51	4.39	6.58	8.77	8.77
		D I	17.97	18.58	17.07	16.12	14.69	14.69
		D II	2.88	2.40	2.90	1.97	1.27	1.27
		D III	0.64	0.51	0.64	0.33	0.27	0.27
SEAR-B	Male	Abstinence	10.00	10.00	10.00	10.00	10.00	10.00
		D I	17.96	20.48	14.73	7.80	1.00	1.00
		D II	0.37	1.18	1.00	1.00	1.00	1.00
		D III	1.00	1.00	1.00	1.00	1.00	1.00
	Female	Abstinence	10.00	10.00	10.00	10.00	10.00	10.00
		D I	5.16	3.88	3.88	2.62	2.36	2.36
		D II	0.46	0.41	0.41	1.00	1.00	1.00
		D III	1.00	1.00	1.00	1.00	1.00	1.00
SEAR-D	Male	Abstinence	7.17	6.37	7.96	9.56	10.00	10.00
		D I	2.76	3.38	2.01	0.44	0.20	0.20
		D II	0.20	0.20	0.20	0.20	0.20	0.20
		D III	0.20	0.20	0.20	0.20	0.20	0.20

Table 12.6 Estimated uncertainty range (±%) around point estimate for prevalence of average volume of consumption categories (*continued*)

Subregion	Sex	Average volume of consumption category	Age group (years)					
			15–29	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
	Female	Abstinence	9.37	9.68	9.68	9.98	10.00	10.00
		D I	0.51	0.28	0.28	0.20	0.20	0.20
		D II	0.20	0.20	0.20	0.20	0.20	0.20
		D III	0.20	0.20	0.20	0.20	0.20	0.20
WPR-A	Male	Abstinence	0.95	0.95	1.19	1.79	2.38	2.38
		D I	8.34	8.49	8.12	7.76	7.30	7.30
		D II	0.33	0.28	0.32	0.23	0.13	0.13
		D III	0.37	0.28	0.37	0.23	0.18	0.18
	Female	Abstinence	1.63	1.63	2.04	3.06	4.08	4.08
		D I	8.06	8.12	7.66	6.75	5.78	5.78
		D II	0.23	0.19	0.23	0.15	0.11	0.11
		D III	0.08	0.06	0.08	0.04	0.03	0.03
WPR-B	Male	Abstinence	1.53	1.53	1.53	2.04	2.56	2.56
		D I	7.69	7.61	7.61	7.19	6.84	6.84
		D II	0.55	0.53	0.53	0.51	0.40	0.40
		D III	0.22	0.32	0.32	0.26	0.20	0.20
	Female	Abstinence	6.74	6.74	6.74	7.86	8.98	8.98
		D I	3.26	3.26	3.26	2.14	1.02	1.02
		D II	0.20	0.20	0.20	0.20	0.20	0.20
		D III	0.20	0.20	0.20	0.20	0.20	0.20

Table 12.7 Uncertainty analysis for patterns of drinking, by subregion

Subregion	Pattern value	Validity of pattern value	Lower boundary for uncertainty	Upper boundary for uncertainty
AFR-D	2.48	0.52	1.98	2.98
AFR-E	3.09	0.24	2.09	4.00
AMR-A	2.00	0.97	1.75	2.25
AMR-B	3.14	0.77	2.89	3.39
AMR-D	3.10	0.38	2.10	4.00
EMR-B	2.01	0.00	1.00	4.00
EMR-D	2.35	0.00	1.00	4.00
EUR-A	1.34	0.92	1.09	1.59
EUR-B	2.93	0.31	1.93	3.93
EUR-C	3.62	0.75	3.37	3.87
SEAR-B	2.50	0.22	1.50	3.50
SEAR-D	2.95	0.93	2.70	3.20
WPR-A	1.16	0.98	1.00	1.66
WPR-B	2.15	0.93	1.90	2.40

available only in established market economies, if at all. Unfortunately, adult per capita consumption figures *per se,* as described above, cannot be used as exposure data for global burden of disease because these figures do not give any specification about who consumed alcohol, when and in what quantities. This can only be specified by using representative surveys of the general population. Thus, for the current exercise, adult per capita figures had to be supplemented by survey data and, where such data were not available, by expert judgements. This procedure may have introduced errors at different points.

- *Errors in adult per capita consumption estimates.* Because per capita estimates are derived mainly from production and trade or sale, other sources (home brewing, cross-border smuggling, illegal production, etc.) are often ignored. There is a long tradition of trying to estimate this *unrecorded* consumption, but mainly in established market economies where the proportion of unrecorded to recorded is low relative to other parts of the world. For example, see the recent European Comparative Alcohol Study (ECAS) estimates for Europe (http://www.fhi.se/pdf/ECAS_2.pdf; Leifman 2001) compared to the estimates of unrecorded consumption for sub-Saharan Africa given below. In addition, estimation of unrecorded consumption is particularly difficult in regions where alcohol is prohibited for religious reasons. In summary, although these sources of error exist, the global aggregate estimates on adult per capita consumption are among the best and most reliable sources for global risk factors.

Adult per capita consumption figures then were used to derive prevalence rates for specific drinking categories for different age–sex groups. This derivation was based on survey data with the following potential sources of error.

- *Survey measurement error.* Alcohol surveys are subject to measurement errors that apply generally to surveys (for an overview see Groves 1989). However, the most important sources of error relating to estimating alcohol consumption include non-probabilistic sampling, sampling schemes that exclude groups with a high alcohol consumption, and measurement bias. The major problem with survey estimates of alcohol consumption is that surveys generally account for 66% or less of alcohol produced or sold (Midanik 1988; Midanik and Harford 1994; Rehm 1998a; de Vries et al. 1999). However, combining survey and aggregate (i.e. per capita) estimates may ameliorate the problem of underreporting that is characteristic of survey estimates.
- *Errors in combining adult per capita and survey data.* Although combining survey and aggregate data can rectify the underreporting of survey data, other sources of error may be created by this procedure. This is especially true if the difference in overall adult consumption between aggregate and survey estimates is large. There are theoreti-

cally several ways in which the survey estimates could be used to arrive at the per capita figures. For example, the prevalence of all drinking categories could be proportionally increased to cover the difference between survey and per capita estimates. This is not possible, however, as the rate of abstainers would automatically change as well. Thus, a procedure must be selected to keep the proportion of abstainers from the survey fixed and proportionally increase the higher consumption categories at the expense of the middle category. Even if this procedure is plausible it may introduce error, such as when survey underreporting differs for different age–sex groups. Nevertheless, the overall benefits of combining surveys and adult per capita data seem to outweigh this disadvantage.

There are other potential sources of error in the exposure estimates.

- *Errors in estimating missing survey data.* Survey data are available for only some countries, so that regional figures had to be estimated from selected countries where surveys were available. This introduces error, and overall the lack of data for some countries is probably the most important source of error for exposure estimates. The more survey data are lacking, the more severe is this problem. Thus it is least severe for those who abstain from alcohol, because even when survey data on the amount of alcohol consumed were not available, many countries had survey data in which respondents were asked whether or not they consumed alcohol. The problem of error in estimating missing survey data was most severe for estimates of drinking patterns, where expert judgements had to be used to supplement survey results, and where no production and trade or sale estimates were available for triangulation.

Overall, this listing of sources for potential errors and biases clearly indicates that the results of CRA, while based on the best available sources, are accompanied by large uncertainties, only some of which could be quantified.

3. Estimating risk factor–disease relationships

3.1 Outcomes to be assessed, evidence of causality and exclusions

Average volume of alcohol consumption has been related to more than 60 categories of the ninth revision of the ICD (ICD-9). This review restricts itself to categories that have already been identified in systematic meta-analyses, together with depression, which we describe in more detail below. Specifically, the following meta-analytical reviews were used: Gutjahr et al. 2001; English et al. 1995; Ridolfo and Stevenson 2001; Single et al. 1996, 1999a.

The categories that have been selected in modelling the impact of patterns of drinking are based on our own literature reviews. The analyses involving drinking patterns include the two main ICD categories for which sufficient evidence of a causal link to drinking patterns has been established: IHD and injuries. In addition, we restricted modelling of the protective effects of moderate regular drinking on type II diabetes and stroke to established market economies with the best drinking patterns (AMR-A, EUR-A and WPR-A), as there is evidence that patterns influence these diseases as well (for detailed reasoning, see below).

Assessment of causality

Following the procedure described by English et al. (1995), the evidence of causality between alcohol consumption and disease outcomes (including both harmful and protective effects for particular diseases) is assessed in accordance with the Australian National Health and Medical Research Council's (NHMRC) *Guidelines for the development, implementation and evaluation of clinical practice guidelines*, which are the most used in the alcohol field and close to the criteria of Hill (1965). Sufficient evidence of causality includes outcomes for which the evidence indicates that an association (positive or negative) exists between alcohol consumption and the disease or injury and that chance, confounding variables and other bias can with reasonable confidence be ruled out as factors in this association. This judgement was made using the usual criteria for establishing causality in epidemiology (Hill 1965; Rothman and Greenland 1998a), with the most weight placed on the following four criteria:

- consistency across several studies;
- established experimental biochemical evidence of mediating processes, or at least physiological plausibility;
- strength of the association (effect size); and
- temporality (i.e. cause before effect).

Two examples of judgements regarding somewhat controversial outcomes may illustrate this process. For lung cancer, meta-analysis showed a consistent effect with a relatively large effect size (English et al. 1995; but see the meta-analysis of Bagnardi et al. 2001, which came to a different conclusion), after adjusting for smoking in at least some studies. However, evidence for the possible biological mechanisms is not conclusive at present (Bandera et al. 2001) and residual confounding from smoking cannot be excluded as an alternative explanation. Thus, consistent with a recent review of the epidemiological evidence, the evidence for alcohol causing lung cancer was not judged sufficient to establish causality according to the criteria listed above (Bandera et al. 2001), and thus lung cancer was excluded as an alcohol-related disease outcome in this work.

On the other hand, although English et al. (1995) concluded that there was not sufficient evidence linking alcohol consumption and breast cancer, recent advances both in biological and epidemiological research have changed this evaluation (especially Smith-Warner et al. 1998; Singletary and Gapstur 2001; see below for detailed reasoning), so that breast cancer now is included in the list of alcohol-related outcomes.

It was concluded that there was limited evidence of causality when an association (positive or negative) was observed between alcohol consumption and the disease or injury for which a causal interpretation was considered to be credible, although chance, confounding variables or other bias cannot be ruled out with reasonable confidence. These diseases were not included in determining either alcohol-related mortality or burden of disease.

It was concluded that there was inadequate evidence of causality when the available studies were of insufficient quantity, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal connection.

It was concluded that there was evidence suggesting lack of causality when several adequate studies, covering the full range of levels of alcohol consumption in the population, indicated a lack of a relationship (positive or negative) between alcohol consumption and the disease or injury. This conclusion is inevitably limited to diseases and injuries, levels of consumption and lengths of observations covered by the available studies, and the possibility of very small risks at the levels of exposure studied can never be excluded.

Excluded outcomes and reasons for exclusion

A list of outcomes considered and excluded can be found in English et al. (1995). Some of these outcomes had been reconsidered in subsequent reviews (Gutjahr et al. 2001; Ridolfo and Stevenson 2001; Single et al. 1999a) and we followed Gutjahr et al. (2001) for the final selection of outcomes. Otherwise, the only restriction was one of age. Outcomes for people under 15 years of age *who had been drinking themselves* and subsequent alcohol-related consequences were excluded for two reasons:

- there are not enough global data on drinking in these age groups; and
- the epidemiological basis linking drinking to health outcomes is scarce.

Based on these considerations, the conservative choice was made not to include these outcomes.

As stated above, this does not mean that no alcohol-related outcomes are calculated for the age group under 15 years. On the contrary, so-called second-hand effects of alcohol (somebody else's drinking causing alcohol-related harm to a person) are included in the estimation.

3.2 Overview of methods

Meta-analyses on average volume of drinking and disease

Meta-analyses were the bases for estimating the risk relationships between average volume of alcohol consumption and chronic disease. In alcohol epidemiology, there is a tradition of conducting such meta-analyses as part of social cost studies (English et al. 1995; Gutjahr et al. 2001; Ridolfo and Stevenson 2001; Single et al. 1999a). We used the results of the most recent existing meta-analyses (Gutjahr et al. 2001) for most outcomes, and Ridolfo and Stevenson (2001) for breast cancer and the subtypes of stroke. Details such as inclusion and exclusion of studies are described below.

Multilevel modelling to determine pattern weights

For estimating the contribution of patterns of drinking applied to IHD and injuries, a new methodology had to be developed. Details of this method are described and discussed in Rehm and Gmel (2000b) and Gmel et al. (2001). It consists of combining multilevel[12] models with pooled cross-sectional time series models, and aims at maximizing methodological rigour and practical feasibility for the data available to undertake such an analysis. The principal variables for the present study are time series of adult per capita alcohol consumption and mortality for different countries, and one value measuring drinking patterns in a country. One could imagine conducting time series analyses separately for each country and then relating the patterns measured with the different estimates obtained for the relationship between alcohol consumption and mortality. However, time series data on both mortality and alcohol consumption for any single country are commonly too short (Rehm and Gmel 2001a) to perform reliable estimation and hypothesis testing, and there are no time-specific data on patterns of drinking within a country to determine pattern weights in this manner. Even for established market economies, there are at most 40 consecutive years of data from the same source (see e.g. Table 12.12 for the length of time series on IHD mortality and adult per capita consumption). In many developing and emerging economies, however, if data are available at all, they cover less than 10 consecutive years. Similarly, for many countries, owing to social and political changes (e.g. the countries of the former Soviet Union), longer time series inherently do not exist.

A common strategy to overcome such data shortcomings for parameter estimation is pooling of data across countries[13] to increase overall sample size, and to set constraints for several parameters (Greene 2000). Examples of such constraints could be to assume similar (i.e. differences statistically not significant) error variances (homoscedasticity) across countries, or to estimate the same regression parameters across all countries, or to assume a distribution for varying parameters (e.g. fixed vs random).

The approach adopted for the present study consists of pooling time series of differing lengths across countries and conducting multilevel analysis. For this approach, statistical problems arise from three major sources.

1. Pooling of data may violate the independence assumption in regression analysis. This concerns at least two aspects. First, the variability of measurements made in different countries is usually much greater than the variability of measurements within one country. Thus, data points are not independent of each other. In addition, within-country variability itself may differ among countries (heteroscedastic variances). Second, as countries provide different numbers of disease and consumption data points, countries with more data points (mainly established market economies) would have a higher impact on an overall estimate of the association between alcohol consumption and mortality than countries for which fewer data points exist (mainly developing and emerging economies). Such a disproportionate contribution to an overall regression estimate would be aggravated by the fact that the population sizes of countries would be often inversely related to the number of data points contributed to the regression analysis by such countries. For IHD mortality, for example, Switzerland (31 data points) and Norway (33 data points) would far outweigh the more populous South Africa (3 data points) and the Russian Federation (8 data points), even though they do not contribute substantially to the global burden of disease.
2. The estimation of time series needs further attention as regards to stationarity (stochastic or deterministic trends in the data) and the correlation of residuals within a country over time (autocorrelation).
3. The use of pooled cross-sectional time series analysis complicates estimation compared to a single time series alone, as errors (or residuals, both are used synonymously in this chapter) may co-vary across sections, and the degree of stationarity or autocorrelation may vary across sections (see below).

It should be noted that it was not possible to estimate all potential effects simultaneously. Either estimation of parameters failed to converge (potential explanations will be discussed below), the available standard software did not include the estimation of more complex models, or estimation of models was not applicable in the present context. To give an example of the latter, the estimation of cross-sectional correlation of errors would need time series that are equal in length (so-called balanced panels), at least with the available software used for estimation (Shazam: Whistler et al. 2001; STATA: StataCorp 1999; HLM: Bryk et al. 1996; MLWin: Yang et al. 1999). It was not possible to test models that include

cross-sectional autocorrelation in the present context, since balanced panel data are not available.

As not all potential shortcomings and drawbacks of multilevel and pooled cross-sectional time series models could be considered in one single model, sensitivity analysis was performed in two phases.

In phase 1, to determine pattern weights, multilevel analyses were conducted using a pilot sample of 29 European countries[14] for which data were available for at least three consecutive years in the 1990s on each of the following variables: adult per capita alcohol consumption, standardized mortality and per capita GNP (level-1 variables) and an estimate of patterns of drinking (level-2 variable assumed to be time-invariant). Calendar year was used to control for omitted variable bias and the time structure (Gmel et al. 2001);[15] per capita GNP was included to control for economic strength as a potential confounder. The analyses to elucidate pattern weights for IHD and injuries have, for the present work, used the same methodology (for details see Gmel et al. 2001). For the sensitivity analysis and for the final pattern weights to calculate burden of disease in this chapter, data were taken from the following sources.

- Mortality data (either all-cause mortality in the sensitivity analysis or IHD/injury) were obtained from the WHO Mortality Database and age-standardized using United Nations population estimates. Direct standardization of mortality rates was performed using the latest WHO world standard population (Ahmad et al. 2000). The reference population is quite "young" with regard to the age distributions of populations in established market economies, but better reflects developing and emerging economies. On the other hand, the new WHO standard takes into account the reduced mortality rates in the older age groups nowadays, which have made the distribution a little "older" than the formerly widely used SEGI standard (Segi 1960).
- Adult per capita alcohol consumption data were again taken from WHO Global Alcohol Database described above.
- Per capita GNP data were taken from World Bank statistics, which used the Atlas method to arrive at standardized, de-inflated values in US dollars for the year 2000.

For all countries in this phase, time series data were collected from 1962 onwards on the four level-1 variables—standardized mortality (either all-cause mortality in the sensitivity analyses or IHD and injury in the final estimates), calendar year, adult per capita alcohol consumption and per capita GNP.

In phase 2, different models were run to especially take into account the cross-sectional time series structure, i.e. to assess the impact of eventually violating statistical assumption in hierarchical multilevel models.

For this exercise, data on countries where a long time series exists were used to try to estimate effects such as heteroscedasticity and error structure (autocorrelation) with some precision. Per capita consumption and data on all-cause mortality for 15 countries were obtained from ECAS, and are extensively described in the February 2001 supplement to *Addiction* (e.g. Norström 2001). Briefly, per capita alcohol consumption, measured in litres of pure alcohol per inhabitant aged ≥15 years, was obtained from the Brewers Association of Canada (1997). Age-specific data on all-cause mortality were obtained from the WHO Mortality Database and standardized to the WHO 1998 standard population (Ahmad et al. 2000). For all countries, time series were available for a time span of at least 40 years. Worldwide, few if any countries exist that would be able to provide longer time series (say 60 or more years) of annual data.

Sensitivity analysis, phase 1: multilevel models

The main difference between multilevel models and simple regression models is that the association between the outcome (mortality) and the independent variables (adult per capita consumption; calendar year as a control variable) is not fixed but varies across cross-sections (i.e. countries). Therefore, multilevel modelling analytically takes into account the lack of independence stemming from a potentially lower variability of data within a country compared to the variability between countries.

Essentially, this problem is the same as in cluster sampling, where variation between clusters is usually also higher than variation within clusters. Two approaches to account for cluster sampling have been suggested (see Lehtonen and Pahkinen 1994). One, the design-based approach, treats cluster sampling and the effect of it on parameter estimates as a nuisance. The information on variation across different clusters and variation within clusters is not included in the model. The estimation of CIs for relevant parameters (e.g. slopes and intercepts in regression analysis) without considering cluster sampling, however, is usually biased. Commonly, standard errors of parameters are underestimated, i.e. CIs are estimated to be narrower than they really are. The design-based approach accounts for these effects by adjusting the standard errors for the impact of the design, e.g. the cluster sampling, but does not model the effects explicitly. The other approach, the model-based approach, treats the different variability across clusters as one parameter of interest in the study and explicitly models this variability. For this approach, multilevel (random coefficient) models are used. Comparison of the two approaches has shown that they yield similar results, but that the model-based (random coefficient) approach yields additional information as it is partly able to model the variability of estimates, and therefore to explain it (Skinner et al. 1989).

Our modelling is one variant of the model-based random coefficient approach. The rationale of multilevel models in the present context is described in detail by Rehm and Gmel (2000b); see also Bryk and Raudenbush (1992); Hox (1995); Kreft and de Leeuw (1998). Briefly, intercept and slopes are assumed to vary randomly[16] across sections. In a two-level analysis this variation can be predicted by variables at the level of the cross-sections (e.g. per subregion). In the present study the variation in the slopes of adult per capita consumption to predict mortality will be explained by drinking patterns per country. Thus, it is assumed that drinking patterns moderate the association between adult per capita consumption and mortality. The corresponding model (without control variables) can be described as follows:

$$\text{mortality\_rate}_{tc} = \beta_{0c} + \beta_{1c} \times \text{alcohol}_{tc} + \varepsilon_{tc} \quad (1)$$

where t = index of time
c = index of countries

The coefficients β_{0c} and β_{1c} symbolize random variables, which vary across countries. Therefore, the simplest way to model this random variation is given by the following equation:

$$\beta_{00} = \gamma_{0c} + \mu_{0c} \quad (2)$$

where γ_{00} = global intercept of mortality rate
μ_{0c} = country-specific variation of intercepts of mortality rates

similarly $\beta_{1c} = \gamma_{10} + \mu_{1c}$

where γ_{10} = global slope of impact of alcohol (level-2 intercept of alcohol)
μ_{1c} = country specific variation of alcohol impact

Influences of country-specific drinking patterns on the slopes of per capita consumption can then be modelled as:

$$\text{pattern\_weight} = \beta_{1c} = \gamma_{10} + \gamma_{11} \times \text{pattern\_value}_{c} + \mu_{1c} \quad (3)$$

The impact of one unit of per capita consumption on mortality is thus assumed constant in time but specific for each country, and is denoted by β_{1c}. This impact itself (throughout this chapter called "pattern weight") is regarded both as a dependent variable and as a predictor variable, for which the value not only varies across countries but also systematically depends on drinking pattern (i.e. pattern value) observed in the respective country.

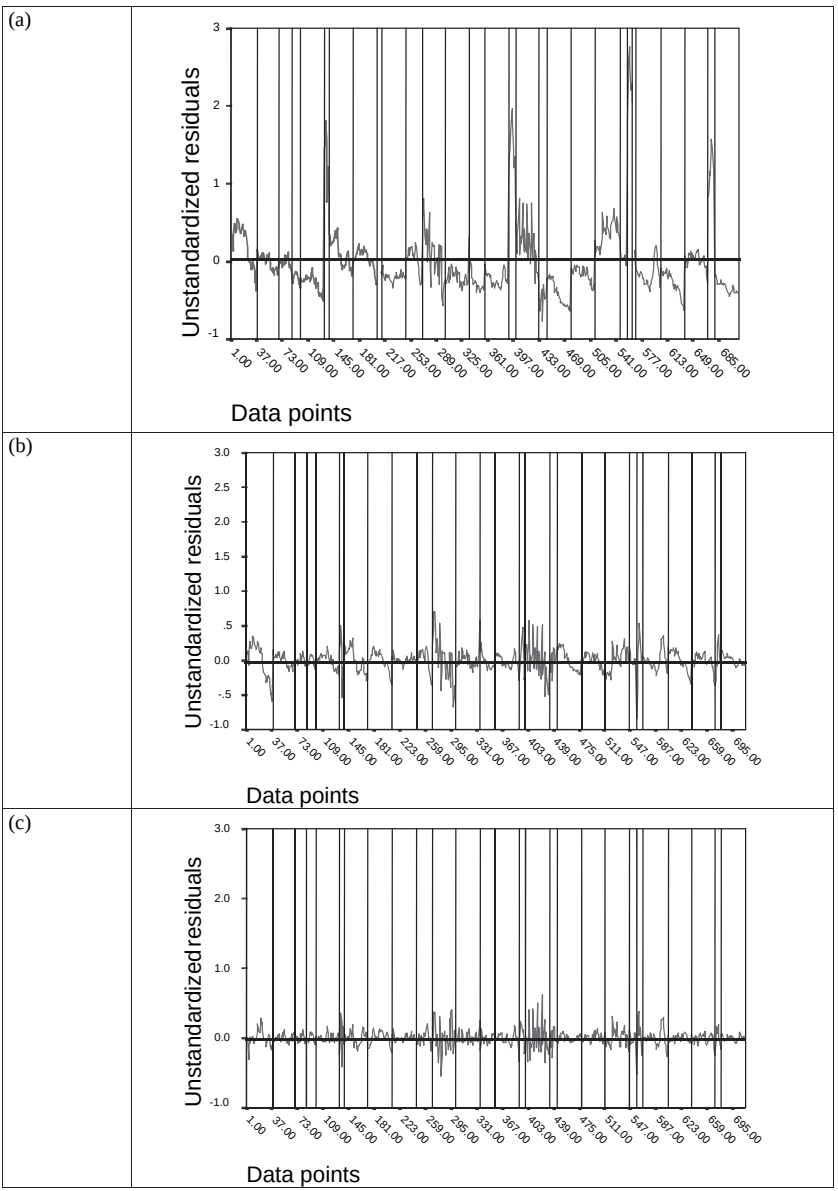
The coefficient γ_{10} can be regarded as a baseline measure for the impact of per capita consumption on mortality.[17] The country-specific deviations

are introduced by the patterns of drinking in the country and a country specific error term μ_{1c}.

Note that if we estimated, in a simple one-level analysis, a global coefficient β_1 (not varying across countries), this measure would not necessarily be the same as γ_{10} in a random coefficients model including level-2 variables. The coefficient γ_{11} can be regarded as the contribution of drinking patterns to modifying the detrimental effects of per capita consumption on mortality. This modifying effect per unit of drinking patterns is treated as being the same for all countries. But clearly drinking patterns vary between countries, and therefore the impact on mortality β_{1c} is specific to each country. There may remain unexplained variation in these country-specific impact coefficients. This is expressed by the level-2 error term μ_{1c}.

Figure 12.2 shows the modifications in residuals for different models. Figure 12.2(a) reflects a simple regression model in which all countries were simply pooled into one data set and analysis was performed without any multilevel modelling (i.e. standard multiple regression; in terms of multilevel modelling this would be a model with constant intercepts and constant slopes). Vertical lines in Figure 12.2 separate residuals within a country from those in other countries. It can be seen that residuals (ε_{tc}) are clearly not independent, as for some countries all residuals were greater than zero whereas for other countries all residuals were below zero. In addition, residuals within a country clearly exhibit trends over time, which also violates the independence assumption. In Figure 12.2(b), a random intercept model was used. This means that for each country a separate intercept was estimated but the association between alcohol consumption and mortality was constant (i.e. it was estimated that the global level of mortality differed across countries, but the association between alcohol consumption and mortality was assumed to be the same across all countries). In this model residuals were more clustered around zero (owing to the random intercept), although there were still trends in the residuals. In the final model also, slopes were allowed to vary across countries (i.e. the association between alcohol consumption and mortality could vary across countries). In addition, control for confounding (GNP as constant slope term) and for omitted variable bias and potential deterministic trend stationarity (calendar year as a random slope term) was included in the multilevel model. The residuals of such a model (Figure 12.2[c]) look very much as they should, as they exhibit neither visible trends nor autocorrelation. Thus, such a model not only turned out to be feasible but it also seemed to account for most of the undesirable aspects of residuals in time series analysis, such as nonstationarity and autocorrelated residuals. Nevertheless, the variability of errors still seems to be different across countries (heteroscedasticity).

Figure 12.2 Level-1 residuals of multilevel models: a) constant intercept and constant alcohol slope; b) random intercept and constant alcohol slope; c) random intercept and random slope (including control for confounding, i.e. constant slope for GNP and random slope for calendar year)



Unstandardized residuals are the raw residuals as indicated by formula 1 above.

Sensitivity analysis, phase 2: pooled cross-sectional time series models

The models discussed above could also be seen as pooled cross-sectional time series models in so far as data used consisted of time series. The models discussed here, however, include special features to deal with the structure of residuals, namely correlations in time. For the models discussed above, the order of data points in time within a country is not taken into account and could be randomly rearranged within each country. In time series analysis, however, it is often assumed that (within each country) values that are closer in time may be more correlated than values that are more separated in time. Thus, the time span between two values must be taken into account. This could not be done by the multilevel modelling, only indirectly by including calendar year into the models.

The sensitivity analyses of different pooled cross-sectional time series models used data on 15 countries from the ECAS project. As a starting point we analysed the data with multilevel models as outlined for Figure 12.2(c), using three different estimation techniques with three different statistical software packages (2-stage OLS with STATA; iterative GLS with MLWin; restricted ML with HLM). Parameter estimates across the three models were comparable and differed less than those from models discussed below (for details of findings see Gmel et al. 2001; for details of differences in estimators see Kreft and de Leeuw 1998).

The simplest model of a pooled time series design, called the "constant coefficient model" (Sayrs 1989) or "population-averaged model with independent errors" (StataCorp 1999), would stack all observations across time points and cross-sections into one data file and analyse the combined data by standard regression techniques (e.g. OLS regression for an interval-scaled dependent variable). Such a model would assume that observations across time and cross-sections are completely independent of each other. This model equals a "multilevel" model with a single fixed intercept and a single fixed slope. This means that neither the ordering in time nor the grouping within cross-sections (countries) must be obeyed and, hence, that there is no association between the time points within a cross-section or between time points over cross-sections, and that there is no relationship between the cross-sections within a time point or between time points. The constant coefficient model often serves as a reference model only. It could be written as follows.

1. Zero expectation of errors for all cross-sections:

   $E(\varepsilon_{ct}) = 0$ for all c, t

2. Constant error variance for all cross-sections:

   $V(\varepsilon_{ct}) = \sigma^2$ for all c, t

3. Uncorrelatedness of errors within and across cross-sections:

   $COV(\varepsilon_{it}, \varepsilon_{jt}) = 0$ for any i, j, t

where t = index of time
c, i, j = index of countries, where it ≠ jt

Assumptions 1 and 2 would be violated when, for example, mortality in a country is always higher than the overall prediction across all countries and all time points. For such a country all errors would be positive. Similarly, the error variances may vary across countries (heteroscedasticity) owing to the fact that, for example, mortality is measured with different reliability in different countries. Typical for time series data, errors may be correlated within a country (autocorrelation within cross-section) but also at the same time point across countries, which would violate assumption 3. An example of such a pattern may be seen in the Nordic countries, where there are similar alcohol policies.

Related to the corresponding procedures in STATA (StataCorp 1999) two sets of models were run. The first set uses GEE estimation (Liang and Zeger 1986) and allows different descriptions of the correlation matrix within cross-sections, subject to the constraint that the same correlation matrix applies to all cross-sections. The following models were used, with $R_{t,s}$ being the t,s element of the correlation matrix, where t and s describe time points (here, years).

1. The independence structure (i.e. $R_{t,s} = 1$ for t = s and 0 otherwise) is equivalent to a model for which all observations are pooled into one file and analysed as if all data come from the same underlying population.

2. The autoregressive (AR) structure (i.e. for an autoregressive structure of order 1, $R_{t,s} = 1$ for t = s and $\rho^{|t-s|}$ otherwise) models an exponentially decaying correlation in time within a cross-section, hence assuming that the less observations are correlated the more they are separated in time.

3. The stationary structure (i.e. for stationarity of order 1, $R_{t,s} = 1$ for t = s, ρ for |t−s| = 1, and 0 otherwise) permits a correlation only between two consecutive time points.

4. The nonstationary structure (i.e. for nonstationarity of order g, $R_{t,s} = 1$ for t = s, ρ_{ts} for g ≥|t−s| >0) permits correlations for all observations separated by up to g time points. The correlation may differ with the number of time points between two observations, and with the location in time (i.e. a different correlation between 1950 and 1951 and between 1974 and 1975). A completely unconstrained correlation matrix would be a nonstationary structure with g = n – 1 (number of time points).

The second set of models uses GLS estimation. Compared with the GEE models, this method relaxes the restrictions of sameness within cross-section correlation matrices. Hence, it permits the estimation of heteroscedastic variances across sections, and the estimation of cross-

sectional specific autoregression (i.e. each country is allowed to have its own error variance and its own magnitude of autocorrelation). The models are restricted to autoregressive models of order 1.

Thus, the GEE models in STATA permit a greater flexibility in estimating error structures, but assume that these structures are constant for all countries. On the other hand, the GLS models in STATA allow the coefficients of autocorrelated residuals and the error variance to vary across countries, but are restricted to an autocorrelation of order 1 only. None of these models allows for testing of random coefficient models. Thus, the association between alcohol consumption and mortality is assumed to be constant across all countries. The same is true of variables to adjust for confounding, omitted variable bias and time trends (GNP and calendar time). Models were used with and without inclusion of calendar time.

The findings can be summarized as follows.

- Measurements within countries are highly correlated in such a way that accounting for correlations only at lags 1 or 2 were not sufficient (e.g. models with stationary or nonstationary structure up to order 2). Thus, the correlations of higher order remained significant. Better fits were obtained, for example, under the assumption of an autoregressive structure, i.e. exponentially decaying correlations with increasing time span between measurements. In general, point estimates of coefficients for the alcohol–mortality association increased with better control of this autoregressive structure, indicating that insufficient control would bias estimates of this association downwards.

- The inclusion of calendar time as a constant coefficient control variable acted in the same direction as controlling for autoregression and clearly performed better than controlling for nonstationarity alone; controlling for nonstationarity did not further improve the estimation of the alcohol coefficient when used in addition to calendar time. As a conclusion, the use of calendar time as a continuous variable is at least as good as other methods (e.g. differencing) to account for nonstationarity in the present context. However, inclusion of autoregression further improved estimation even when calendar time was included.

- Whether the autoregressive structure was estimated to be constant across countries or to be country-specific resulted in smaller differences than those between an autoregressive structure and a structure restricted to low-order lag correlations (nonstationary or stationary). It should be noted, however, that the estimation of higher order (>2) nonstationary structures (which allow more flexibility of the correlation matrix) did not converge to a solution. This was probably because of the number of parameters that needed estimation. For a

model with an autoregressive structure (e.g. of order 1), although correlations for higher lags can be significant, only 1 parameter must be estimated as it is assumed that correlations of time points with higher lag orders follow an exponentially decaying function of the correlation at lag 1. In nonstationary models, correlations with a higher lag order can vary freely and must be estimated separately.

- The inclusion of heteroscedasticity (unequal variances) did not improve models, or did so only marginally.

As already mentioned, it appeared that the better the error structure of time series was captured, the higher were the point estimates for the relationship between alcohol consumption and mortality. In none of these models, however, could varying coefficients for this relationship across countries be modelled. The underlying assumption of these pooled cross-sectional models is that there is a constant relationship and that pooling is used to increase sample size for efficient estimation, while adjusting for a more complex error structure than independence. However, tests for constant coefficients showed that there is significant variation across countries for both the coefficient of alcohol consumption and for calendar year, pointing to geographically differing and not altogether changing associations. Although the autocorrelated error structure could not be accounted for, random coefficient models yielded the highest association for alcohol consumption, pointing to the possibility that the use of random coefficient models better captured the data and the error structure than constant coefficient models accounting for autocorrelated residuals, by estimating a constant effect of alcohol consumption and a constant effect of calendar time. Clearly, random coefficient models including the autoregressive error structure may further improve estimation.

There is software that can in principle handle autocorrelation and heteroscedasticity in multilevel models (Bryk et al. 1996; Yang et al. 1999). It should be noted, however, that in the present study the inclusion of autocorrelated disturbances failed to converge. The possible reason for the nonconvergence might be that the model was already well specified with the inclusion of random coefficient time trends, and the additional inclusion of further parameters might therefore have resulted in colinearity problems. This seems to be a general problem in analysis of aggregate data in the alcohol field, where relatively low variability within series is coupled with relatively short series. It is, however, not likely that the omission of autocorrelated disturbances in random coefficient models may have greatly distorted the findings. Although including autocorrelation of errors resulted in further improvement, this improvement was relatively minor in pooled cross-sectional time series models with constant alcohol coefficients that adjusted for a constant coefficient of calendar time, compared to the improvement from random coefficients models. In addition, in random coefficient models without including autocorrelation

the impact of calendar year was not estimated as being constant across all countries, and might therefore further account for autocorrelation, as it separately adjusted in each country and therefore better captured the country-specific confounding than a country-averaged model.

The advantage of random coefficient models was that not only could the association between consumption and mortality vary across countries, but so could the associations with the control variable time. Thus, the adjustment of time could be analysed in a country-specific manner. Finally, none of the pooled cross-sectional time series models could analyse variations in the relationship between alcohol consumption and mortality as being moderated by patterns.

In conclusion, all sensitivity analysis performed indicated that multilevel modelling outperformed pooled cross-sectional time series models, although the autocorrelated error structure could not be taken into account directly. As estimation of such a structure was not feasible even for the longer time series in the field, there was no hope that this could be done when more countries with relatively short series (fewer than 10 data points) were added. On the contrary, adding other countries would increase the cross-country variability and reduce the impact of autocorrelation within country, especially as this may have little impact given the few data points.

3.3 Criteria for identifying relevant studies

The criteria listed in Table 12.8 apply to all meta-analyses used to estimate the relationship between per capita consumption and specific diseases (English et al. 1995).

Alcohol-related consequences were thus identified by reviewing and evaluating large-scale epidemiological studies on alcohol and health, including epidemiological input into major reviews (Collins and Lapsley 1991; Corrao et al. 1999; Devlin et al. 1997; English et al. 1995; Gurr 1996; Harwood et al. 1998; Klingeman and Gmel 2001; Rice et al. 1991; Ridolfo and Stevenson 2001; Single et al. 1996, 1999a, 1999b; Stinson et al. 1993; U.S. Department of Health and Human Services 2000). Papers were collected primarily from the peer-reviewed international literature. As indicated above under the discussion on causality, we followed the accepted guidelines established in the first major review (English et al. 1995). All conditions for which evidence of a causal relationship was conclusive were included in the final list. Discussion of disease conditions where causality was not judged to be sufficient can be found in section 3.5.

3.4 Description of studies, including methodological qualities

More than 6000 studies were included in the different analyses on which the estimates for this chapter were based. For further descriptions we refer to the original publications of the meta-analyses (English et al.

Table 12.8 Exclusion criteria for studies used in determining the relationship between average volume of consumption and mortality/morbidity in CRA

Reason for exclusion	*Explanation and/or examples*
Restricted study population	The study was carried out in a sample that was difficult to generalize for the entire population (for example, a cohort of persons suffering from a particular disorder)
Inappropriate comparison group	The control group was contaminated by a high exposure to the risk factor under consideration or other factors related to the condition
No quantitative exposure measure	Exposure was alcohol dependence rather than alcohol consumption, or alcohol consumption was undefined or had poorly defined nominal categories (for example, "regular" vs "non-regular" drinkers) or was limited to frequency of consumption (without considering quantity) or was measured in a manner not representative of general exposure (for example, with meals or in the last 24 hours)
Duplication of study	A study was reported in more than one paper, and was already included in the review. A second important way in which a study may be duplicated is when it has already been included in the earlier review conducted by members of the project team. These studies are included in the review but not re-examined in detail
Sample size too small	There was an insufficient number of cases (n <20 deaths or outcomes)
Inadequate control for confounding variables	An important confounding variable was not controlled for in the study (for example, smoking not controlled for when examining impact on heart disease, or only bivariate relationships and relative risks presented)
Results not usable	Data were presented in a manner that precludes their use (for example, data only presented in graphs that are difficult to read)
No age- or sex-specific data presented	This was done where unacceptable (i.e. where the condition under review is strongly related to age or sex)

1995; Gutjahr et al. 2001; Ridolfo and Stevenson 2001; Single et al. 1999a). Nevertheless, we provide here a general methodological description of the studies used and their assumptions.

Most studies reviewed used either a cohort or case–control design (Rothman and Greenland 1998b). For epidemiological studies on alcohol consumption using these designs, the following limitations generally apply.

- Alcohol use is mostly measured by only a few questions, either separating frequency of drinking and quantity per occasion or combining them into one modified frequency question in the tradition of nutritional epidemiology (e.g. Rehm 1998a, 1998b for further descriptions and a critique). Research has shown that such questions may lead to underestimates of true consumption. Also, data on the relationship

between patterns of drinking and health outcomes are limited, as typical questions in epidemiological surveys cannot be used to measure drinking patterns (Rehm 2000). Studies with more complete alcohol assessment are mostly cross-sectional, or the baseline assessment was carried out very recently so that no longitudinal results can yet be reported.

- The relationships between alcohol consumption and chronic disease outcomes are often based on outcomes assessed at follow-up, regressed on several variables from the baseline assessment. These procedures assume that the baseline variables are stable over time, or that they are somehow good indicators of the postulated theoretical relationship (e.g. Rehm et al. 1996). For example, in assessing the relationship between volume of consumption and liver cirrhosis, it must be assumed that heavy consumption persists after baseline and is a good indicator for overall tissue exposure, which is the theoretical determinant (Lelbach 1975, 1976). Work on the regression dilution bias has shown that the size of the real effect is often underestimated by using only the baseline assessment (Clarke et al. 1999) if the exposure is somewhat constant or preserves rank order over time. Moreover, there is evidence from longitudinal studies that individual drinking patterns are not stable over time (Fillmore 1988; Vaillant and Hiller-Sturmhofel 1996), which may obscure the apparent relationship even further.
- The relationship between alcohol consumption and outcomes must be assumed to be fairly constant across settings, in that results of epidemiological studies from a few countries are applied to others. While this may be justified with biologically based relationships (e.g. alcohol and breast cancer),[18] such an assumption is more problematic with casualties and injuries as outcomes, since these are much more context-dependent.

All of these points indicate that the results of the meta-analyses on which our estimates are based will have limits with regard to precision. These limits are not captured by the CI for combined relative risks.

3.5 Relative risks and attributable fractions

Some conditions, such as alcoholic psychosis or alcohol dependence syndrome, are by definition causally related and wholly attributable to alcohol (i.e. they would not exist in the absence of alcohol consumption) (Table 12.9). For most conditions, however, alcohol is a contributory rather than a sufficient cause (Rothman and Greenland 1998a). Pooling of risk estimates for these diseases from individual studies was performed by means of precision-based weighting (English et al. 1995). Methods and results of the pooling procedure (meta-analysis) have been described in more detail elsewhere (Gutjahr and Gmel 2001).

In contrast, the alcohol-attributable fractions (AAFs) for acute consequences such as injuries are usually directly determined from the blood alcohol concentration (BAC) at the time of the injury. For example, road accidents are attributed to alcohol according to whether the driver responsible for the accident tested positive for alcohol and to what degree (e.g. BAC ≥0.05%).[19] In the case of traffic accidents we have relative risk estimates, based on case–control studies, for different levels of BAC (Ridolfo and Stevenson 2001; see also McLeod et al. 1999). But relative risk estimates are usually rare for acute consequences other than traffic injuries. Thus, for the purpose of the present study, AAFs from the international literature were used (English et al. 1995; Gutjahr and Gmel 2001; Ridolfo and Stevenson 2001; Single et al. 1996; Stinson et al. 1993).

To structure the presentation and discussion of results, alcohol-related health consequences will be categorized as follows.

1. Chronic harmful effects of alcohol consumption, excluding depression and IHD:
   - wholly alcohol-attributable outcomes;
   - cancers (neoplasms);
   - cardiovascular diseases;
   - liver cirrhosis;
   - effects of prenatal alcohol exposure;
   - neuropsychological conditions; and
   - other chronic diseases.
2. Chronic beneficial effects of alcohol consumption, excluding IHD:
   - ischaemic stroke; and
   - other conditions (type II diabetes, gallstones).
3. IHD as a chronic condition where alcohol has harmful and beneficial consequences:
   - depression; and
   - acute adverse effects:
     — unintentional injuries (motor vehicle accidents, poisonings, falls, drownings, other unintentional injuries)
     — intentional injuries (self-inflicted injuries, homicide, other intentional injuries).

Table 12.9 Disease conditions that are by definition fully alcohol-attributable (AAF = 1)

ICD-9 code	*Disease*
291	Alcoholic psychoses
303	Alcohol dependence
305.0	Alcohol abuse
357.5	Alcoholic polyneuropathy
425.5	Alcoholic cardiomyopathy
535.3	Alcoholic gastritis
571.0–571.3	Alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of liver, unspecified alcoholic liver damage
790.3	Elevated blood alcohol level
980.0, 980.1	Toxic effect of ethyl alcohol, toxic effect of methyl alcohol

3.6 Chronic harmful effects of alcohol consumption, excluding depression and IHD

Wholly alcohol-attributable diseases

A number of diseases are by definition fully attributable to alcohol (AAF = 1). These are listed in Table 12.9.

Diseases with a contributory role

Cancer

Oropharyngeal, oesophageal and liver cancers. Alcohol has consistently been related to the risk of cancer of the mouth (lip, tongue), pharynx, larynx, hypopharynx, oesophagus and liver (Corrao et al. 1999; English et al. 1995; Gurr 1996; Single et al. 1999; U.S. Department of Health and Human Services 2000; WHO 2000). The relationship between average volume of alcohol consumed and cancer incidence is usually characterized as increasing almost monotonically (Bagnardi et al. 2001), but this may partially be an artefact of the methods used (Single et al. 1999). Evidence for the role of alcohol in these cancers has accumulated from case–control and cohort studies. Recently, much emphasis has been placed on investigating biochemical mechanisms in laboratory studies to explain the carcinogenic behaviour of alcohol (U.S. Department of Health and Human Services 2000).[20]

Female breast cancer. Much research has been conducted over the last decade on breast cancer. Prior to 1995, it was usually concluded that evidence of a causal relationship with alcohol was insufficient (English et al. 1995; Rosenberg et al. 1993; Schatzkin and Longnecker 1994). Recent studies and reviews have shown, however, that not only haz-

ardous or harmful drinking but also even moderate alcohol consumption can cause female breast cancer (Single et al. 1999a). A meta-analysis by Smith-Warner et al. (1998) found a clear linear relationship over the whole continuum of consumption. Other original studies supported this finding (Bowlin et al. 1997; Corrao et al. 1999; Nasca et al. 1994; Royo-Bordonada et al. 1997; Swanson et al. 1997; Van den Brandt et al. 1995; Wingo et al. 1997). In contrast to the weight of evidence, Zhang et al. (1999) concluded from their investigation that moderate intake did not increase the risk of breast cancer, and that a low level of drinking was associated with a protective effect. This finding, however, appears to be a notable outlier (Longnecker 1999) and, so far, has not been corroborated. Recent studies have focused on plausible biological mechanisms, including alcohol's effect on hormones and tissue, its contribution to the initiation, progression and promotion of breast cancer, and its interaction with nutritional factors (for an overview see Singletary and Gapstur 2001; Soler et al. 1998; U.S. Department of Health and Human Services 2000).

Cancers of the stomach, pancreas, colon, rectum and prostate. Many recent research projects have investigated whether these cancers are alcohol-related. Overall, evidence for a causal relationship between alcohol and cancer of these sites, if any was found, was weak and inconclusive (Bode and Bode 1997; Boutron et al. 1995; De Stefani et al. 1998; Gapstur et al. 1994; Harnack et al. 1997; Ji et al. 1996; Longnecker and Enger 1996; Lundberg and Passik 1997; Piette et al. 1998; Sarles et al. 1996; Seitz et al. 1998a, 1998b; Singborg 1998; Soler et al. 1998). On prostate cancer, again most studies did not report observing an increased risk (Breslow and Weed 1998; Ellison et al. 1998; Hiatt et al. 1994; Tavani et al. 1994), whereas two cohort studies (Ajani et al. 1998; Putnam et al. 1998) and one case–control study (Hayes et al. 1996) reported a small increased risk in men who consume even moderate amounts of alcohol. In conclusion, evidence for a causal relationship between alcohol and cancer of the stomach, pancreas, colon, rectum and prostate has not so far produced consistent results, especially with regard to physiological pathways. Thus, we did not include these cancers, even though some of them showed significantly elevated risks in a recent meta-analysis (Bagnardi et al. 2001).

Cancer of salivary glands, ovary, endometrium, bladder. It has been hypothesized that alcohol might constitute a risk factor for cancer of the major salivary glands (Horn-Ross et al. 1997; Muscat and Wynder 1998), ovary, endometrium (Bradley et al. 1998; Longnecker and Enger 1996; Newcomb et al. 1997; Parazzini et al. 1995) and bladder (Bruemmer et al. 1997; Donato et al. 1997; Longnecker and Enger 1996; Yu et al. 1997). For each of these sites, results were scarce or conflicting, and

the effects, if any, were not statistically significant. Moreover, there is no knowledge of physiological pathways for these sites.

There is an almost linear dose–response relationship between volume of drinking and the relative risk of alcohol-related cancers. Although there have been speculations about the impact of patterns of drinking, especially for breast cancer (Kohlmeier and Mendez 1997), the current state of knowledge does not suggest that these play an important role in the etiology of cancer.[21] Thus, the alcohol-attributable burden for cancer will be modelled exclusively on average volume.

Cardiovascular disease

The role of alcohol, as both a risk and protective factor for cardiovascular disease, has been studied extensively in the past decade. IHD has been the focus of most research and is discussed separately below. Most studies suggest that low-level consumption also offers some protection against ischaemic stroke, and this condition is therefore also discussed in the section below on the beneficial effects of alcohol.

In contrast, hypertension and other cardiovascular disorders such as cardiac arrhythmias, heart failure and ill-defined descriptions and complications of heart disease are adversely affected by alcohol (see e.g. Friedman 1998; Klatsky 1995; Puddey et al. 1999; Rosenqvist 1998; U.S. Department of Health and Human Services 1997; Wood et al. 1998). The weight of evidence suggests that daily consumption of more than 30 g pure alcohol for men (and presumably lower levels for women) causes hypertension (Beilin et al. 1996; Curtis et al. 1997; English et al. 1995; Grobbee et al. 1999; Keil et al. 1997; Klatsky 1996). Low-level intake, however, was not associated with hypertension in men, and may even confer a small protective effect in women (English et al. 1995). There are some indications that hypertension may be related to the pattern of heavy drinking occasions (Murray et al. 2002; Puddey et al. 1999; Wannamethee and Shaper 1991).

For haemorrhagic stroke, the weight of evidence suggests an increase in risk for males even at low levels of consumption (Berger et al. 1999; Jackson 1994; Sacco et al. 1999; You et al. 1997). For females, the most recent meta-analyses of Ridolfo and Stevenson (2001) suggested a protective effect for drinking categories I and II but an 8-fold increased risk for drinking the equivalent of more than 40 g pure alcohol daily (see Table 12.10). Patterns of drinking not only play a role in any protective effects of alcohol on IHD but are also relevant for risk of stroke (Hillbom et al. 1998) and sudden cardiovascular death or cardiovascular death in general (Kauhanen et al. 1997a, 1997b; Kosarevic et al. 1982; Poikolainen et al. 1983; Wannamethee and Shaper 1992), with heavy drinking occasions and intoxication resulting in increased risk. Patterns of drinking should therefore be included in future estimates of harmful cardiovascular outcomes.

Liver cirrhosis

Alcohol consumption has been identified as the leading cause of liver cirrhosis in established market economies (Corrao et al. 1997, 1998; English et al. 1995). Whereas the association with alcoholic liver cirrhosis is clear, with all cases being attributable to alcohol, debate remains as to whether this equally applies to unspecified liver cirrhosis. Several authors contend that, empirically, it is extremely difficult to separate alcoholic from unspecified liver cirrhosis, and that the term "unspecified liver cirrhosis" is applied when no specific etiological factor is reported or identified (English et al. 1995). Research in the United States and in Central and South American countries has indicated that an appreciable proportion of deaths from cirrhosis without mention of alcohol was in fact attributable to alcohol (Haberman and Weinbaum 1990; Puffer and Griffith 1967; Room 1972).[22]

On the other hand, applying AAFs of liver cirrhosis to other countries can be extremely misleading. In many countries (e.g. China and India), liver cirrhosis is mainly caused by other factors such as viral infections. The corresponding AAFs have been shown to vary between less than 10% (China) and 90% (Finland) (WHO 2000).

The relationship between alcohol consumption and liver cirrhosis seems to depend mainly on volume of drinking and is independent of pattern of drinking (Lelbach 1975, 1976). However, some research also indicates a potential effect of occasions of heavy drinking (Rhodés et al. 1993). Moreover, there is some indication that spirits are especially harmful in causing liver cirrhosis (Gruenewald and Ponicki 1995; Kerr et al. 2000; Longnecker et al. 1981; Schmidt 1991). The problem with this research is that it is almost entirely based on ecological studies and thus describes only correlations, which may have other causes (Morgenstern 1998; Rehm and Gmel 2001a).

Effects of prenatal alcohol exposure

Today, there is ample evidence that alcohol consumption during pregnancy is related to various risks to the fetus, which include gross congenital anomalies and fetal alcohol syndrome (FAS) (Alvear et al. 1998; Church et al. 1997; Faden et al. 1997; Habbick and Snyder 1997; Larkby and Day 1997; Larroque and Kaminski 1996; Mattson et al. 1997; Passaro and Little 1997; Passaro et al. 1996; Polygenis et al. 1998; Roebuck et al. 1998; Shu et al. 1995; Windham et al. 1995). FAS has been characterized as a continuum, with minor physical malformations at one end and serious neurobiological dysfunctions, including mental retardation, at the other (Connor and Streissguth 1996). The prenatal teratogenic effects of alcohol also include lethal outcomes comprising spontaneous abortion, low birth weight, fetal damage, prematurity and intrauterine growth retardation (Abel 1997; Bradley et al. 1998; Windham et al. 1997). These can occur even at low average

volumes of consumption, particularly during the first trimester of pregnancy.

Mental conditions

The co-morbidity of alcohol dependence with other mental conditions is high, both in clinical and in general population samples (e.g. Grant and Harford 1995; Merikangas et al. 1998). The crucial question in this respect is about causation. We have included depression in this review only where we believe the evidence to be sufficient to conclude a causal role for alcohol. Since this relationship is controversial, it is discussed below in a separate section.

Other chronic conditions

Other risks of alcohol consumption currently discussed in the literature include epilepsy (see e.g. Jallon et al. 1998; Leone et al. 1997; Martin et al. 1995), acute and chronic pancreatitis and psoriasis. Whereas for pancreatitis the causal role of alcohol seems to be clear, Amman et al. (1996) and Skinazi et al. (1995) contend that the discrimination between acute and chronic pancreatitis is not justifiable, since the overwhelming majority of patients presenting with acute pancreatitis at the same time have an underlying chronic pancreatitis (Robles-Diaz and Gorelick 1997; Thakker 1998). On psoriasis, our search did not yield any recent studies. English et al. (1995) found that the results of the pooled estimates were consistent with a moderately strong and statistically significant effect of average volume of consumption.

Table 12.10 summarizes the relative risks at different levels of consumption for alcohol-related chronic consequences.

3.7 Beneficial health effects of alcohol consumption on disease

Ischaemic stroke

Cerebrovascular disease (stroke) consists of several subtypes, the most common being ischaemic stroke and haemorrhagic stroke, which are affected differently by alcohol. For ischaemic stroke (the predominant type) the weight of evidence, including biological mechanisms, suggests effects similar to those for IHD, namely that low to moderate consumption may offer some protection (Beilin et al. 1996; Hillbom 1998; Keil et al. 1997; Kitamura et al. 1998; Knuiman and Vu 1996; Sacco et al. 1999; Thun et al. 1997; Yuan et al. 1997; Wannamethee and Shaper 1996). It seems that this protective effect is more pronounced in females (Table 12.11).

Other beneficial health effects

Alcohol consumption may offer some protection against type II diabetes and cholelithiasis (gallstones) (see also Ashley et al. 2000 for a recent

Table 12.10 Relative risks for chronic harmful alcohol-related disease for different drinking categories (relative to abstainers)

		Relative risk					
		Drinking category I		*Drinking category II*		*Drinking category III*	
Disease or condition	*ICD-9 codes*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
Lip and oropharyngeal cancer	140, 141, 143–146, 148, 149, 230.0	1.45	1.45	1.85	1.85	5.39	5.39
Oesophageal cancer	150, 230.1	1.80	1.80	2.38	2.38	4.36	4.36
Liver cancer	155, 230.8	1.45	1.45	3.03	3.03	3.60	3.60
Laryngeal cancer	161, 231.0	1.83	1.83	3.90	3.90	4.93	4.93
Female breast cancer, <45 years	174, 233.0	NA	1.15	NA	1.41	NA	1.46
Female breast cancer, ≥45 years		NA	1.14	NA	1.38	NA	1.62
Epilepsy	345	1.23	1.34	7.52	7.22	6.83	7.52
Hypertension[a]	401–405	1.40	1.40	2.00	2.00	4.10	2.00
Cardiac arrhythmias	427.0, 427.2, 427.3	1.51	1.51	2.23	2.23	2.23	2.23
Heart failure and ill-defined complications of heart disease[b]	428, 429						
Haemorrhagic stroke	430–432	1.27	0.59	2.19	0.65	2.38	7.98
Oesophageal varices	456.0–456.2	1.26	1.26	9.54	9.54	9.54	9.54
Gastro-oesophageal haemorrhage[c]	530.7	NA	NA	NA	NA	NA	NA
Unspecified liver cirrhosis	571.5–571.9	1.26	1.26	9.54	9.54	13.00	13.00
Acute and chronic pancreatitis[a]	577.0, 577.1	1.30	1.30	1.80	1.80	3.20	1.80
Spontaneous abortion	634	NA	1.20	NA	1.76	NA	1.76
Low birth weight	656.5	1.00	1.00	1.40	1.40	1.40	1.40
Psoriasis	696.1	1.58	1.58	1.60	1.60	2.20	2.20
Prematurity	764	0.93	0.93	1.36	1.36	1.36	1.36
Intrauterine growth retardation	765	0.99	0.99	1.68	1.68	1.68	1.68

NA Not applicable.

[a] Relative risk estimates taken from Corrao et al. (1999); most major cost studies derived AAFs for acute and chronic pancreatitis directly (e.g. Australia, for 577.0: 0.24; for 577.1: 0.84 [English et al. 1995]).

[b] Heart failure AAF determined indirectly from other circulatory diseases.

[c] Relative risks not applicable because AAFs were usually obtained directly (e.g. Switzerland, for 530.7: 0.47).

Sources: unless otherwise indicated Gutjahr et al. (2001); Ridolfo and Stevenson (2001).

overview on beneficial effects of alcohol). The Australian meta-analysis by English et al. (1995) concluded that there was some evidence that alcohol may protect against the onset of type II diabetes. Since then, the findings from a cohort of more than 40 000 male health professionals showed that moderate alcohol consumption may reduce the risk of type II diabetes, perhaps through the effects of alcohol on insulin sensitivity (Rimm et al. 1995). In addition, findings from the British Regional Heart Study indicated a protective effect (Perry et al. 1995). Further, a follow-up of men enrolled in the United States Physicians Study revealed a marked negative association of incident type II diabetes with alcohol consumption (Ajani et al. 1999). In a recent prospective study, a U-shaped association was found between alcohol and type II diabetes (Wei et al. 2000).

On the other hand, Kao et al. (1998) found evidence (based on small numbers) of an inverse relationship between alcohol consumption and the risk of type II diabetes for women. This relationship was not found in men; indeed, men consuming more than 21 units of alcohol per week were at increased risk of type II diabetes. A protective effect of moderate alcohol consumption against type II diabetes may be mediated through the effects of alcohol on glucose tolerance and insulin resistance. Moderate alcohol drinking has been shown to increase insulin sensitivity (Facchini et al. 1994; Kiechl et al. 1996) and lower insulin resistance (Lazarus et al. 1997), even in young adult drinkers (Flanagan et al. 2000). Finally, there is some evidence that inflammatory processes may mediate alcohol-induced diabetes (Imhof et al. 2001; Pradhan et al. 2001). In summary, there is growing evidence from cohort studies that moderate alcohol consumption reduces the risk of diabetes and a plausible underlying biological mechanism has been identified. This was the reason for including this effect as a beneficial effect in subregions with beneficial drinking patterns (established market economies with best mortality pattern: AMR-A, EUR-A, WPR-A). For all other subregions, no effect was modelled for these drinking categories. However, evidence for the relationship between alcohol consumption and diabetes is far from conclusive at present.

There is evidence that alcohol consumption may offer some protection against gallstones (English et al. 1995; Holman et al. 1996). These findings have been substantiated by recent large-scale cohort and case–control studies, which reported an inverse relationship (Attili et al. 1998; Caroli-Bosc et al. 1998; Chen et al. 1999; Leitzmann et al. 1998). Table 12.11 gives an overview of diseases for which alcohol potentially has beneficial effects.

Table 12.11 Relative risks for chronic beneficial alcohol-related health effects for different drinking categories (compared to abstainers)

		Relative risk					
		Drinking category I		*Drinking category II*		*Drinking category III*	
Disease or condition	*ICD-9 code*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
Type II diabetes	250	0.99	0.92	0.57	0.87	0.73	1.13
Ischaemic stroke	433–435	0.94	0.52	1.33	0.64	1.65	1.06
Cholelithiasis	574	0.82	0.82	0.68	0.68	0.50	0.50

Source: Gutjahr et al. 2001; Ridolfo and Stevenson 2001.

3.8 IHD as a chronic condition for which alcohol has harmful and beneficial consequences

Epidemiology—average volume of consumption

IHD[23] is one of the leading causes of death in the world (Murray and Lopez 1996a). The most important health benefits of alcohol in terms of IHD have been found at low to moderate levels of average volume of consumption (Beaglehole and Jackson 1992; Doll 1998; Edwards et al. 1994; Fuchs et al. 1995; Goldberg et al. 1995; Hillbom 1998; Holman et al. 1996; Jackson 1994; Rehm et al. 1997; Single et al. 1999a; Svärdsudd 1998). Only a few individual-level studies have failed to substantiate this association in men (Hart et al. 1999) or women (Fillmore et al. 1998; Maskarinec et al. 1998).

While some studies have suggested that alcohol may offer protection against IHD across the entire continuum of consumption (Camargo et al. 1997; Doll et al. 1994; Keil et al. 1997; Rehm et al. 1997 [males only]; Kitamura et al. 1998; Thun et al. 1997), they nevertheless show that most of the protective effect is gained at low levels of consumption, such as one drink every other day.

Overall, average volume of drinking and IHD show a J-shape relationship in the usual medical epidemiological cohort studies in established market economies (Corrao et al. 2000). Compared to abstinence, low to moderate average consumption of alcohol has been found to confer a lower risk of IHD incidence and mortality. For higher levels of average volume of consumption, the risk relationship is reversed (e.g. Corrao et al. 2000; Friedman and Kimball 1986; Rehm et al. 1997), with heavy average consumption being associated with a risk larger than that for abstainers. In the most recent meta-analysis Corrao et al. (2000) demonstrated the described J-shape, and also demonstrated several other characteristics from the literature on average volume of consumption and IHD.

- There was a pronounced sex effect, showing that women were less protected for a given level of consumption, with an earlier upturn of the curve.
- The beneficial effect of alcohol was less pronounced for fatal outcomes.
- The study results were inconsistent, especially with respect to relative risk for higher intake, indicating additional influencing factors not controlled for.
- The better quality studies placed the maximum beneficial effect at lower levels of average alcohol intake. The maximum protective effect was measured at 20 g pure alcohol per day; the relative risk = 1 line, equivalent to abstainers' risk, was crossed at 72 g per day; and there was a significant detrimental effect over 89 g per day.
- More specifically, cohort studies, wholly adjusted studies, studies that compared drinkers with lifetime abstainers and those that excluded sick subjects at baseline showed less beneficial effects than case–control studies, unadjusted or partially adjusted studies, studies that compared drinkers with current abstainers and those that included sick subjects.
- Mediterranean countries showed more protective effects for the same levels of average consumption.

The epidemiological evidence that light to moderate average alcohol consumption protects against IHD is strengthened by substantial evidence concerning the biological mechanisms by which a protective effect could be mediated (Rankin 1994; Renaud et al. 1993; Single et al. 1999b; Svärdsudd 1998). First, moderate alcohol intake has been linked to favourable lipid profiles, especially an increase in high-density lipoproteins (HDL) (Baraona and Lieber 1998). It has been estimated that as much as 40–50% of the protective effect may be attributable to this mechanism (Criqui et al. 1987; Criqui and Ringel 1994; Suh et al. 1992). Second, moderate alcohol intake favourably affects coagulation profiles, particularly through its effects on platelet aggregation (McKenzie and Eisenberg 1996; Rubin 1999) and fibrinolysis (Reeder et al. 1996). Third, low to moderate consumption of alcohol has been shown to favourably affect insulin resistance (Kiechl et al. 1996; Lazarus et al. 1997; Rankin 1994). Fourth, it has been postulated that alcohol could protect against IHD through its effect on hormonal profiles, particularly its estrogen effects (Svärdsudd 1998). Fifth, the alcohol metabolite acetate has been postulated to protect against IHD by promoting vasodilation (U.S. Department of Health and Human Services 1997). Sixth, alcohol affects inflammation and, through this pathway, can influence IHD (Imhof et al. 2001; Jacques et al. 2001; Morrow and Ridker 2000; Ridker 2001). Finally, it is possible that some of the effect is mediated through the anti-

oxidative constituents of alcohol beverages, especially wine (Reinke and McCay 1996). Nevertheless, most of the protective effect appears to be linked to ethanol *per se*.

The protective effect of light to moderate consumption has been questioned on several grounds. The role of the comparison group has been questioned (Shaper 1990a, 1990b; Shaper et al. 1988), it being suggested that the abstainer group includes people who have stopped drinking because of health reasons and these are responsible for the elevated disease risk compared to light and moderate drinkers. Many subsequent studies controlled for this effect by taking lifetime abstainers as the comparison group (Rehm and Sempos 1995). Nevertheless, in most established market economies, where most of the research on alcohol and IHD has taken place, abstainers constitute only a minority of the general population and the possibility that they have other behavioural characteristics responsible for the elevated IHD risk cannot be excluded. No alternative explanation has ever been empirically demonstrated, however. For instance, social isolation has been theoretically claimed to confound the alcohol–mortality relationship (Skog 1996), but empirical research has not been able to substantiate this effect (Murray et al. 1999).

In conclusion, the relationship between average volume of drinking and IHD seems to be J-shaped. Light to moderate drinking is associated with a lower IHD risk than abstinence or heavy drinking. However, the results are inconsistent, indicating that factors other than those included in the study may also determine the relationship. One of the main factors may be pattern of drinking (i.e. the way in which the same average amount of alcohol is consumed). In this respect two patterns deserve mentioning: irregular heavy drinking and drinking with meals.

Epidemiology—patterns of drinking

Heavy drinking occasions

Heavy drinking occasions have been linked to adverse cardiovascular events for some time (Poikolainen 1983). However, many studies had used wider endpoints than IHD (Kauhanen et al. 1997b) or samples of problem drinkers or persons with alcohol-use disorders (Dyer et al. 1977; Rosengren et al. 1987; Rossow and Amundsen 1997), where heavy drinking patterns are confounded with volume.

Some of the more recent studies have controlled for (average) volume of drinking. A case–control study in Australia (McElduff and Dobson 1997) compared 11 511 cases of acute myocardial infarction or coronary death with 6077 randomly selected controls. If people drank in binges (usually five or more drinks on an occasion for women, nine or more drinks on an occasion for men), there were no protective effects for coronary events and relative risks were mainly larger than 1 compared to abstainers (indicating higher risks for major coronary events). This

elevated risk was present even in groups with low overall volume of drinking. As expected, the authors also found a protective effect of daily drinking, which was most pronounced for regular light to moderate drinkers.

Similarly, Murray et al. (2002) evaluated the cardiovascular consequences of binge drinking (eight or more drinks at a sitting) and usual (non-binge) drinking of alcohol in a longitudinal, population-based study. Interview data from 1154 men and women aged 18 to 65 years in Winnipeg, Canada were linked to health care utilization and mortality records in an eight-year follow-up period. Cox proportional hazards regressions were estimated separately for men and women. The outcomes included first event for physician visits, and hospitalizations and deaths due to IHD, hypertension, or other cardiovascular disease. Binge drinking increased the risk of IHD in men (hazard ratio [HR] of 2.3, 95% CI 1.2–4.2) and women (HR of 1.1, 95% CI 1.02–1.2) and increased the risk of hypertension in men (HR of 1.6, 95% CI 1.04–2.4) but not women. Binge drinking had no effect on the risk of other cardiovascular disease. All of these results were controlled for average volume of drinking. Again, the expected cardioprotective effects were confirmed in both men and women. The harmful effects of heavy drinking occasions on IHD morbidity and mortality could thus be disaggregated from the effect of average volume of drinking. Finally, Trevisan et al. (2001a) found in a case–control design that, after adjustment for average volume of consumption, weekend drinking by men was significantly related to risk of myocardial infarction compared to men drinking less than once a week (logistic regression: OR 1.9, 95% CI 1.2–3.2).

In addition to the effect on IHD, there appears to be a relationship between irregular heavy drinking occasions and other forms of cardiovascular death, especially sudden cardiac death (Kauhanen et al. 1997b; Wannamethee and Shaper 1992; Wood et al. 1998). This is consistent with the physiological mechanisms of increased clotting and reducing the threshold for ventricular fibrillation after heavy drinking occasions, which have been reviewed by McKee and Britton (1998). Specifically, heavy drinking occasions have been shown to increase the blood level of low-density lipoproteins (LDL), which in turn have been linked to negative cardiovascular outcomes. Contrary to low or moderate steady drinking, heavy irregular drinking occasions are not associated with an increase in levels of HDL, which have been linked to favourable cardiovascular outcomes. In addition, irregular drinking is associated with increased risk of thrombosis after cessation of drinking (Renaud and Ruf 1996). Finally, irregular heavy drinking seems to predispose to histological changes in the myocardium and conducting systems, as well as to a reduction in the threshold for ventricular fibrillation. In conclusion, irregular heavy drinking occasions are mainly associated with physiological mechanisms that increase the risk of sudden cardiac death and other cardiovascular outcomes, in contrast to the physiological

mechanisms triggered by regular low to moderate consumption that are linked to favourable cardiac outcomes. Nevertheless, individual-level studies are still scarce and some studies show no effects (Murray et al. 1998).

Drinking with meals

Trevisan et al. (2001b) reported on drinking with meals and IHD mortality based on the Risk Factor and Life Expectancy Study, a pooled series of epidemiological studies conducted in Italy with 8647 males and 6521 females aged 30–59 years at baseline and free of cardiovascular disease. Subjects were followed up for an average of seven years. Alcohol consumption showed a protective effect on IHD, and drinking wine with meals was linked to more positive outcomes than drinking wine outside meals. Compared to drinking with meals, drinking wine outside meals had a relative risk of 1.8, 95% CI 0.97–3.5 for IHD in males, adjusted for average volume of drinking and other potential confounders. There were not enough IHD cases to conduct a similar analysis for females, but the effects for all-cause mortality for females showed a five-fold risk for wine outside meals compared to wine with meals (relative risk of 5.0, 95% CI 1.5–10.9).

Another study (Trevisan et al. 2001a), using a case–control design, examined 443 male myocardial infarction survivors and 922 healthy controls aged 35–69 years. Compared to non-drinkers the age, education and smoking-adjusted odds ratios for former drinkers and current drinkers were 0.67, 95% CI 0.32–1.38 and 0.47, 95% CI 0.24–0.95, respectively, confirming the overall cardioprotective effect of alcohol consumption (see above). Men who reported drinking without food at least 75% of the time had an odds ratio of 1.5, 95% CI 0.96–2.3 compared to those who drank mainly with meals and snacks, after adjustment for age, education and volume of alcohol consumed.

The potential mechanisms linking consumption of alcoholic beverages with meals to a lower IHD risk, compared to consumption between meals, remain to be fully clarified. However a few mechanisms have been hypothesized. A study by Trevisan et al. (1987) in a large sample of Italian men and women found a significant association between drinking between meals and higher prevalence of hypertension, compared to drinking with meals, even after adjustment for differences in alcohol consumption between these drinking pattern categories. These findings were recently confirmed in another study using a population-based sample in the United States (Wu and Trevisan 2001). Finally, Foppa et al. (1999) found in a controlled randomized trial that moderate consumption of wine with a meal reduced postprandial blood pressure. Drinking with meals has also been shown to positively affect fibrinolysis (Hendriks et al. 1994) and lipid levels (Veenstra et al. 1990).

Other potential physiological links between drinking with meals and these IHD risk factors include a reduced absorption of alcohol owing to

the presence of food in the gastrointestinal tract (Gentry 2000). Another physiological link may be that food increases the alcohol elimination rate (Ramchandani et al. 2001).

Aggregate-level studies on patterns and average consumption

Given the described relative scarcity of individual-level studies, it is not surprising that much of the argumentation is based on aggregate-level studies, especially on Russian experience with the natural experiment of the Gorbachev anti-alcohol campaign. The Russian Federation is generally considered to be one of the countries with the highest rates of irregular heavy drinking (Bobak et al. 1999; Malyutina et al. 2001). Thus, if a heavy drinking style has an adverse impact on cardiovascular disease in general and on IHD in particular, such effects should have become evident at the population level in the experience of the anti-alcohol campaign during the last years of the Soviet Union. In the period 1984–1987, when estimated total alcohol consumption in the Russian Federation fell by about 25% (Shkolnikov and Nemtsov 1997), age-adjusted male deaths from circulatory disease fell by 9% (Leon et al. 1997). After the end of the campaign, the death rate rose again quite dramatically. The role of alcohol in the recent drastic increases in mortality in the Russian Federation, however, remains controversial, as many other changes occurred in the late 1980s and early 1990s (Bobak and Marmot 1999; Britton and McKee 2000; Leon et al. 1997; McKee et al. 2001; Notzon et al. 1998; Shkolnikow et al. 2001). There seems to be general agreement, however, that alcohol has played an important role in increasing mortality rates, although the level of impact is unclear.

There is another indirect line of research on the effect of heavy drinking on IHD. Countries with a tradition of heavier or binge drinking on weekends show proportionately high IHD or cardiovascular disease mortality on or immediately after the weekend (Germany, IHD: Willich et al. 1994; Moscow, cardiovascular disease events: Chenet et al. 1998; Lithuania, IHD events: Chenet et al. 2001; Scotland, IHD events: cf. Evans et al. 2000). Other aggregate-level research on per capita alcohol consumption and IHD have failed to find effects, even for countries with the best drinking pattern (i.e. drinking pattern = 1) in a time series analysis with differenced data, controlling for tobacco (Hemström 2001). Finally, Skog (1983) also found no significant effects in a time series analysis on differenced data for Norway.

Summary of the epidemiological evidence

In conclusion, the relationship between drinking and IHD is complex, and the epidemiological literature on it is evolving. There seems to be a clear beneficial effect, supported by biochemical evidence, of regular light to moderate drinking, but it is unclear how many people actually drink in a manner that will provide them with these benefits. Also, there are

indications that irregular bouts of heavy drinking are linked to physiological mechanisms, which are in turn linked to negative IHD outcomes, as well as to other negative cardiovascular disease outcomes. Better surveys are needed, including the measurement of biomarkers indicative of the relationships specified above. In these surveys, the relevant variables such as irregular heavy drinking or drinking with meals should also be included.

Many of the individual-level cohort studies on the relationship between average volume of drinking and IHD have been carried out on special populations such as nurses, doctors or other health professionals, mostly in established market economies, who have relatively regular and potentially beneficial drinking patterns. As a result, the effect of average volume of alcohol consumption may be overstated in the usual meta-analysis. Thus, the results of these analyses cannot be applied worldwide, since more detrimental patterns of drinking prevail in the majority of countries. Moreover, the impact of pattern of drinking has to be included, in addition to the effects of average volume of drinking.

Unfortunately, as described above, patterns of drinking cannot be modelled by meta-analysis owing to the scarcity of data on the relationship between exposure and outcome. Thus, we used the multilevel modelling approach described earlier to incorporate patterns of drinking into the estimates.

Measuring the effect of average volume of consumption and drinking pattern on IHD mortality

The details of determining the impact of average volume and pattern of drinking on IHD are described earlier. The characteristics of the data set are given in Table 12.12.

Table 12.13 gives an overview of the most important results with respect to the differential impact of alcohol consumption on IHD mortality. As predicted, in countries with consumption pattern 1, alcohol had beneficial effects on the incidence of IHD. For countries with pattern 2, the impact on IHD varied around zero (i.e. no marked impact of alcohol). In countries with pattern 3, alcohol showed a detrimental impact on IHD for males only. For countries with pattern 4, the detrimental impact of alcohol was pronounced for both males and females. Assuming interval scales between the categories of the pattern variable, the models were estimated as in Table 12.14.

Again, in countries with pattern 1, beneficial effects appeared for both males (–0.0214) and females (–0.0376). These consumption models indicate that the overall effect of IHD at an average pattern level (2.51 in the sample used) is detrimental for males and not significantly different from zero for females. In other words, the results from individual-level studies could be replicated in this aggregate-level study. This means that for countries such as France and Italy we expect a beneficial effect of alcohol on IHD mortality; for countries such as Slovenia and the United

Table 12.12 Characteristics of the data set for calculating the relationship between per capita consumption, patterns of drinking and IHD mortality (per 1000 population per year)

Country	*IHD mortality males*	*IHD mortality females*	*Average per capita alcohol consumption*	*Pattern of drinking*	*Per capita GNP*	*Year of first data*	*Year of latest data*	*Number of years*
Albania	0.99	0.40	2.20	3	585.71	1992	1998	7
Argentina	1.37	0.70	27.48	2	3 472.00	1966	1996	25
Armenia	3.34	2.30	2.53	2	507.14	1992	1998	7
Australia	2.75	1.36	11.19	2	10 341.76	1964	1997	34
Austria	1.92	1.00	14.16	1	11 136.05	1962	1999	38
Azerbaijan	4.10	2.40	2.10	3	746.67	1990	1999	9
Bahamas	0.95	0.46	14.33	2	7 067.69	1969	1995	13
Bahrain	2.04	1.72	5.33	2	7 423.33	1985	1988	3
Barbados	0.93	0.56	7.88	2	3 357.42	1964	1995	31
Belarus	4.03	2.20	9.68	4	2 651.11	1989	1998	9
Belgium	1.44	0.63	12.35	1	9 487.10	1964	1994	31
Belize	0.53	0.38	6.01	4	1 127.86	1964	1995	28
Bulgaria	2.14	1.28	11.97	2	1 898.24	1982	1998	17
Canada	2.45	1.22	9.74	2	11 367.65	1964	1997	34
Chile	1.16	0.74	11.58	3	1 562.26	1964	1994	31
Colombia	1.09	0.70	5.49	3	993.68	1967	1994	19
Costa Rica	1.30	0.84	4.48	4	1 268.13	1964	1995	32

continued

Table 12.12 Characteristics of the data set for calculating the relationship between per capita consumption, patterns of drinking and IHD mortality (per 1000 population per year) (*continued*)

Country	*IHD mortality males*	*IHD mortality females*	*Average per capita alcohol consumption*	*Pattern of drinking*	*Per capita GNP*	*Year of first data*	*Year of latest data*	*Number of years*
Croatia	1.78	1.03	13.24	3	3 638.33	1993	1998	6
Czech Republic	2.76	1.43	15.42	2	3 915.71	1986	1999	14
Denmark	2.59	1.32	10.91	2	13 139.70	1964	1996	33
Dominican Republic	0.46	0.31	2.91	2	729.52	1965	1985	21
Ecuador	0.37	0.24	2.30	3	882.90	1964	1995	31
El Salvador	0.38	0.25	1.95	4	564.74	1964	1993	19
Estonia	4.16	2.18	13.43	3	3 107.50	1992	1999	8
Finland	3.25	1.37	7.42	3	10 642.42	1964	1996	33
France	0.82	0.35	23.15	1	11 120.29	1964	1997	34
Germany	1.59	0.80	13.63	1	26 661.67	1993	1998	6
Greece	0.94	0.44	9.69	2	5 027.14	1964	1998	35
Guatemala	0.26	0.21	2.42	4	644.71	1964	1984	17
Guyana	1.17	0.69	8.42	3	540.00	1977	1994	5
Honduras	0.20	0.13	2.27	4	418.67	1966	1981	15
Hungary	2.54	1.30	15.85	3	2 837.83	1977	1999	23
Iceland	2.30	1.06	5.42	3	12 691.82	1964	1996	33
Ireland	2.80	1.39	10.86	3	5 865.76	1964	1996	33
Israel	1.89	1.19	3.04	2	8 236.36	1975	1996	22

Italy	1.35	0.74	18.48	1	8418.18	1964	1996	33
Jamaica	0.64	0.48	3.12	2	927.14	1964	1985	7
Japan	0.53	0.32	5.78	1	13654.41	1964	1997	34
Kazakhstan	3.79	2.10	7.24	4	1691.00	1989	1998	10
Kyrgyzstan	2.98	1.76	1.88	3	488.00	1995	1999	5
Latvia	4.27	2.06	8.53	3	3149.00	1989	1998	10
Lithuania	3.73	2.24	5.76	3	2380.00	1989	1998	5
Luxembourg	1.54	0.65	17.37	1	19366.77	1967	1997	31
Malta	2.05	1.23	5.27	1	4004.85	1965	1998	33
Mauritius	2.10	1.01	3.30	3	1473.71	1964	1998	35
Mexico	0.60	0.38	3.94	4	1877.94	1962	1995	34
Netherlands	1.86	0.83	9.39	1	10900.29	1964	1997	34
New Zealand	2.80	1.33	11.36	2	7426.29	1964	1998	35
Nicaragua	0.41	0.29	3.29	4	448.24	1964	1994	17
Norway	2.27	0.98	5.11	3	14216.06	1964	1996	33
Peru	0.42	0.32	6.10	3	828.89	1966	1989	18
Philippines	0.74	0.44	2.73	3	454.76	1964	1996	21
Portugal	1.06	0.59	18.85	1	3844.86	1964	1998	35
Republic of Korea	0.18	0.09	8.90	3	6664.62	1985	1997	13
Romania	2.16	1.37	10.78	3	1432.00	1989	1998	10
Russian Federation	3.87	1.92	8.88	4	2683.75	1991	1998	8

continued

Table 12.12 Characteristics of the data set for calculating the relationship between per capita consumption, patterns of drinking and IHD mortality (per 1000 population per year) (*continued*)

Country	*IHD mortality males*	*IHD mortality females*	*Average per capita alcohol consumption*	*Pattern of drinking*	*Per capita GNP*	*Year of first data*	*Year of latest data*	*Number of years*
Singapore	1.44	0.79	2.30	2	9 106.86	1964	1998	35
Slovakia	2.85	1.57	12.54	3	2 437.50	1992	1995	4
Slovenia	1.27	0.66	14.80	2	8 912.00	1994	1998	5
South Africa	1.01	0.46	10.30	3	3 606.67	1993	1995	3
Spain	0.83	0.40	17.20	1	5 554.17	1962	1997	36
Sri Lanka	0.45	0.22	.27	3	268.46	1964	1986	13
Suriname	0.92	0.54	6.43	3	1 749.05	1964	1992	21
Sweden	2.54	1.27	7.57	3	13 042.42	1964	1996	33
Switzerland	1.43	0.68	14.99	1	15 815.16	1964	1994	31
Thailand	0.02	0.01	3.58	3	541.20	1964	1994	25
The former Yugoslav Republic of Macedonia	1.22	0.58	5.76	3	1 350.00	1994	1997	4
Trinidad and Tobago	2.05	1.28	4.76	2	3 254.33	1962	1994	30
Ukraine	4.19	2.48	4.64	3	1 276.00	1990	1999	10
United Kingdom	2.67	1.23	9.49	2	9 210.00	1964	1998	35
United States	2.68	1.39	9.46	2	14 028.53	1964	1997	34
Uruguay	1.77	0.96	8.08	3	1 680.00	1966	1990	24
Uzbekistan	3.72	2.67	1.07	3	733.33	1996	1998	3
Venezuela	1.38	0.94	8.31	3	2 992.50	1969	1994	24

Table 12.13 Average effect of consumption of 1 litre of pure alcohol per capita[a] for different drinking patterns

Pattern of drinking	*Males*	*Females*
1	–0.016227	–0.038174
2	0.004050	–0.014323
3	0.053951	0.001908
4	0.084529	0.035584

[a] This corresponds to coefficient β_3 in the model shown in the footnote.

Level-1 model

$$\text{Mortality rate} = \beta_0 + \beta_1^a (\text{YEAR}) + \beta_2^a (\text{GNP\_PC}) + \beta_3^a(\text{PC\_ALCOHOL}) + \varepsilon$$

Level-2 model

$$\beta_0 = \gamma_{00} + \mu_0$$

$$\beta_1 = \gamma_{10} + \mu_1$$

$$\beta_2 = \gamma_{20}$$

$$\beta_3 = \gamma_{30} + \gamma_{31}^a (\text{PATB}) + \gamma_{32}^a (\text{PATC}) + \gamma_{33}^a (\text{PATD}) + \mu_3$$

where

mortality = age-standardized IHD mortality

YEAR = year of observation

GNP_PC = GNP per capita

PC_ALCOHOL = per capita adult (≥15 years) alcohol consumption

PATB = dummy variable for pattern 2

PATC = dummy variable for pattern 3

PATD = dummy variable for pattern 4.

Table 12.14 Effect of per capita consumption and drinking patterns on standardized IHD rates, assuming equal intervals between pattern values

	Coefficient	*SE*	*t-value*	*df*	*P*
Males					
Effect of per capita consumption at average pattern[a]	0.033503	0.013417	2.497	72	0.013
Deviations from average patterns	0.036353	0.011622	3.128	72	0.002
Females					
Effect of per capita consumption at average pattern[a]	–0.004433	0.008263	–0.537	72	0.591
Deviations from average patterns	0.021969	0.006806	3.228	72	0.002

[a] Patterns of drinking were entered grand-mean-centred into the equation. Thus, the effect of per capita consumption displayed here is the effect at the grand mean of pattern, which is 2.51 in this sample.

States there will be no overall effect; for countries such as the Republic of Korea and Ukraine we expect an overall detrimental effect of alcohol for males; and for countries such as the Russian Federation we expect a detrimental effect for both males and females. The results from this model are consistent with the finding that the anti-alcohol campaign in the Gorbachev era had such an impact on IHD mortality in the Russian Federation.

The model has limitations, however. Most notably, each country has been assigned one pattern value that is assumed to be stable over time. Whereas patterns have been found to be stable in the past (Room 1992; Simpura 2001), clearly this assumption is an oversimplification. Moreover, it is clear that in most countries there are people with different drinking patterns. Thus, future research should be based on distributions of patterns by sex and age, rather than on one pattern value per country.

The results of this model are not consistent with a recent ecological analysis by Hemström (2001), using a time series approach with differenced data. Hemström (2001) found a random distribution of insignificant negative (beneficial) and positive (detrimental) alcohol effect estimates. He used only per capita data without any control for drinking pattern. However, based on individual-level studies and the results of the present analysis, beneficial effects would have been expected for countries with a consumption pattern of 1, such as France, Italy, Portugal and Spain. We can only speculate on the difference in results between the two analyses. Hemström's time series were relatively short (45 years per country), not allowing some of the tests for correct model specification (Rehm and Gmel 2001a). There also may have been some overdifferencing problems with co-integration or the joint use of differencing and taking the logarithm, which may have obscured the effect (Greene 2000; Hatanaka 1996; Yaffee 2000).

On the other hand, the present analysis draws on relatively limited time series in a wide range of drinking cultures, which increases the ability to generalize but which also has limitations. Our findings for the pattern-1 subgroup have the strong advantage of convergent data from individual-level studies, supported by biological plausibility. We have therefore used our finding of a protective effect at the population level for the countries with beneficial patterns (pattern 1) as a current best estimate of effects (for comparison with results using coefficients from meta-analysis).

Given the limits of ecological analysis, individual-level data should always be given priority in judgements of causality, although not necessarily in terms of estimates of the overall effect of changes in a risk factor at the population level (Skog 1996). This applies to our analysis as well.

Determining AAFs for IHD, including patterns of drinking

To arrive at the AAFs, the results of the dummy regression were taken and only effects larger than ±0.015 were modelled. However, since the

multilevel analysis could only control for per capita GNP as a confounder, and since there are general limits in controlling for confounding in such analyses (Morgenstern 1998), the effects of alcohol indicators were halved in order to be conservative and to adjust for any other confounding. This approach, though arbitrary in the choice of halving, is consistent with that taken in risk analysis for other risk factors (e.g. tobacco) to avoid residual confounding.

Taking into consideration the distribution of patterns in all countries within the 14 subregions, and standardized mortality rates after 1994, the AAFs can be derived (Table 12.15).

Table 12.15 shows the effects of alcohol-attributable IHD mortality based on aggregate-level analysis, halving the effects to adjust for potential confounding. This can easily be done by using the respective values in the formulas above.

Alternatively, one may use the relative risks from the individual-level studies as a basis and apply them to the subregions AMR-A, EUR-A and WPR-A, as almost all of the studies come from these subregions. Such an approach leads to higher cardioprotective effects (see Table 12.16) and may well contain overestimates based on the usual cohort composition, where people with more regular drinking styles are overrepresented. However, individual-level studies are usually preferred to ecological studies both for establishing causality and for making estimates of impact (e.g. Morgenstern 1998). Further, with respect to overall disease burden attributable to alcohol, this provides a more conservative approach to estimating.

The resulting AAFs, using individual-level estimates of relative risk for AMR-A, EUR-A and WPR-A, would be –0.11, –0.15 and –0.15, respectively. The cardioprotective effect estimated in this way is larger than that given above (see Table 12.15). We used these estimates for the final calculations. The numbers for EUR-B are given only for sensitivity analysis. Overall, the average patterns for this subregion (2.9) are much closer to the average pattern for EUR-C (3.6) than that for EUR-A (1.3). Thus, we did not feel justified in using the estimates based on studies almost exclusively from countries with beneficial patterns (A subregions).

3.9 Depression

Background and epidemiology

Alcohol is implicated in a variety of mental disorders that are not alcohol-specific. However, no major overview on alcohol-attributable burden of disease has yet included these disorders (English et al. 1995; Gutjahr et al. 2001; Rehm et al. 2001a, 2001b; Ridolfo and Stevenson 2001; Single et al. 1999). While the causality of the relation is hard to define, sufficient evidence now exists for us to include an estimate of the causal role of alcohol in depression, a major mental disorder.

Table 12.15 AAFs predicted by the multilevel analysis

	Age group (years)					
Subregion	*All*	*15–29*	*30–44*	*45–59*	*60–69*	*≥70*
Males						
AFR-D	0.02	0.03	0.03	0.03	0.03	0.02
AFR-E	0.07	0.07	0.08	0.08	0.07	0.07
AMR-A[a]	0.00	0.00	0.00	0.00	0.00	0.00
AMR-B	0.16	0.15	0.15	0.16	0.17	0.15
AMR-D	0.08	0.09	0.10	0.11	0.10	0.08
EMR-B	0.00	0.00	0.00	0.00	0.00	0.00
EMR-D	0.01	0.01	0.01	0.02	0.01	0.00
EUR-A[a]	–0.04	–0.04	–0.04	–0.04	–0.04	–0.04
EUR-B	0.11	0.12	0.12	0.12	0.12	0.11
EUR-C	0.15	0.14	0.15	0.14	0.14	0.15
SEAR-B	0.01	0.02	0.03	0.04	0.02	0.00
SEAR-D	0.04	0.06	0.12	0.14	0.04	0.00
WPR-A[a]	–0.07	–0.07	–0.07	–0.08	–0.07	–0.07
WPR-B	0.01	0.01	0.01	0.01	0.01	0.01
Females						
AFR-D	0.00	0.00	0.00	0.00	0.00	0.00
AFR-E	0.00	0.00	0.00	0.00	0.00	0.00
AMR-A[a]	0.00	0.00	0.00	0.00	0.00	0.00
AMR-B	0.02	0.02	0.02	0.02	0.02	0.02
AMR-D	0.03	0.03	0.03	0.04	0.03	0.03
EMR-B	0.00	0.00	0.00	0.00	0.00	0.00
EMR-D	0.00	0.00	0.00	0.00	0.00	0.00
EUR-A[a]	–0.10	–0.10	–0.10	–0.10	–0.10	–0.10
EUR-B	0.00	0.00	0.00	0.00	0.00	0.00
EUR-C	0.03	0.03	0.03	0.03	0.03	0.03
SEAR-B	0.00	0.00	0.00	0.00	0.00	0.00
SEAR-D	0.00	0.00	0.00	0.00	0.00	0.00
WPR-A[a]	–0.10	–0.10	–0.11	–0.11	–0.10	–0.10
WPR-B	0.00	0.00	0.00	0.00	0.00	0.00

[a] The estimates for AMR-A, EUR-A and WPR-A serve only as sensitivity analysis as the AAFs for these subregions will be based on individual-level studies (see Table 12.16 below).

In the general population, alcohol dependence and major depression co-occur over-proportionally, on both a 12-month and a lifetime basis (Kessler et al. 1996, 1997; Lynskey 1998). Among alcohol consumers in the general population, higher volume of consumption is associated with more symptoms of depression (Graham and Schmid 1999; Mehrabian 2001; Rodgers et al. 2000). Compared to moderate drinkers, both higher

Table 12.16 Ischaemic heart disease AAFs for selected subregions, applying relative risk estimates[a]

	Age group (years)														
	15–29		*30–44*		*45–59*		*60–69*		*70–79*		*≥80*		*Total*		
Subregion	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*All*
AMR-A	–0.14	–0.12	–0.15	–0.13	–0.14	–0.11	–0.12	–0.08	–0.11	–0.07	–0.11	–0.07	–0.13	–0.08	–0.11
EUR-A	–0.18	–0.16	–0.17	–0.17	–0.17	–0.16	–0.17	–0.14	–0.16	–0.13	–0.16	–0.13	–0.16	–0.13	–0.15
EUR-B[b]	–0.15	–0.11	–0.13	–0.10	–0.14	–0.09	–0.13	–0.07	–0.12	–0.07	–0.12	–0.07	–0.13	–0.08	–0.11
WPR-A	–0.18	–0.17	–0.19	–0.17	–0.18	–0.16	–0.17	–0.14	–0.15	–0.12	–0.15	–0.12	–0.17	–0.13	–0.15

[a] Relative risks are 0.82, 0.83 and 1.12 for drinking categories I, II and III for men and 0.82, 0.83 and 1.00 for women.

[b] EUR-B estimates are only given for reasons of sensitivity analysis (see section 3.6).

(Bjork et al. 1999) and lower (Rodgers et al. 2000) levels of depressive symptoms have been found among abstainers. Among patients under treatment for alcohol abuse and dependence, the prevalence of major depression is higher than in the general population (Lynskey 1998; Schuckit et al. 1997a). Similarly the prevalence of alcohol abuse and dependence is higher for patients under treatment for depression (Alpert et al. 1999; Blixen et al. 1997).

This suggests that alcohol abuse is linked to depressive symptoms, and that alcohol dependence and depressive disorders co-occur to a larger degree than expected by chance. However, it is not clear in the individual case whether depression caused alcohol problems, whether alcohol consumption or alcohol problems caused depression, or whether both could be attributed to a third cause (Vaillant 1993). The pathway from depression to problematic alcohol use and alcohol dependence has long been discussed under the heading of self-medication (i.e. the use of alcohol to alleviate depressive symptoms). In addition, a shared third cause could be certain neurobiological mechanisms (see Markou et al. 1998) or genetic predisposition. Moreover, all three pathways of causation may co-exist at the same time, with different proportions of the co-occurring morbidities being attributable to each, and of course some co-occurrence being simply due to chance.

Establishing the causal link between alcohol and depression

Causal relations in epidemiology are usually based on several criteria (Hill 1965; Rothman and Greenland 1998a). Using these criteria, we will review the evidence that part of the burden of depression is caused by alcohol. As indicated above, this does not preclude the possibility that part of the burden of alcohol dependence is also caused by depression, or that part of the co-occurrence is causally related to some third factor. Following the majority of the literature, we base our argumentation mainly on alcohol dependence rather than alcohol consumption *per se*. This is done mostly for reasons of data availability: depression and alcohol dependence are usually part of the same mental health surveys, and almost all estimates of co-occurrence stem from this kind of survey. It is not usual to include questions on alcohol consumption *per se* in this type of survey, nor is it usual to include a diagnosis of depression in alcohol surveys.

Prevalences of alcohol dependence or alcohol use disorders (i.e. alcohol dependence and harmful use of alcohol) were thus used as indicator of alcohol consumption drinking categories, assuming a constant relationship between the two variables. This indicator relationship was also made possible by the fact that alcohol use disorders by definition have an AAF of 1.0—that is, under the counterfactual scenario (Murray and Lopez 1999) of no alcohol available at all, there would be no burden due to alcohol dependence. Moreover, in different regions of the world,

average volume of drinking and prevalence of alcohol dependence are correlated to a high degree ($r = 0.86$) (Rehm and Eschmann 2002).

Temporal order

Causal factors must precede consequences. Logically, therefore, only that fraction of depression in which the onset of alcohol problems preceded the onset of depression can be caused by alcohol problems. The fraction in which alcohol problems came first is an upper bound for the proportion of depressive disorders caused by alcohol dependence. This upper bound is summarized in Table 12.17 for different forms of depression in several countries, based on the International Consortium in Psychiatric Epidemiology (ICPE) (Merikangas et al. 1998).

Clearly, in all areas (i.e. countries, provinces and cities) mentioned in Table 12.17, the proportion of depressive disorders preceded by alcohol dependence is higher for males than for females. This corresponds to the higher prevalence of alcohol dependence in these areas. In fact, the proportion of rates of depressive disorders and alcohol problems correlate to 0.80 (major depression) and 0.82 (other depressions) for these areas (Pearson correlations; alcohol dependence rates from *World health report 2001* and Rehm and Eschmann 2002). This means that at least 64% of the variation in the proportion of depressive disorders in the various subregions can be statistically "explained" by the variation in alcohol dependence. Of course, the remarks made above on possible forms of causal pathway still apply. This relationship provides a basis for predicting such rates for other subregions where data are lacking (see below).

Another indicator of the role of alcohol dependence in causing some depressive disorders is the comparison between onsets for different mental disorders co-occurring with alcohol disorders. In the US National Comorbidity Survey (Kessler et al. 1996) the proportion of disorders preceded by alcohol dependence was higher for depression than for any other disorder.

Consistency

Epidemiological studies are very consistent, both in the general population and in clinical samples, in showing that alcohol dependence and depressive disorders co-occur to a higher degree than might be expected by chance. This has been observed in several countries and regions (e.g. Merikangas et al. 1998; Swendson et al. 1998). In fact, we do not know of any study where alcohol dependence and depressive disorders did not co-vary to a larger degree than that expected by chance.

The co-variation between the proportion of people with depressive disorders with a preceding alcohol dependence and the prevalence of alcohol dependence is also consistent across countries (see above).

Table 12.17 Percentages of the population in which the onset of alcohol problems[a] occurred prior to diagnosis of depression, by country, age and sex

		Major depression[b]					*Other depressions*[c]				
	Age group	*Males*		*Females*		*Total*	*Males*		*Females*		*Total*
Country/Area	*(years)*	*n*	*%*	*n*	*%*	*%*	*n*	*%*	*n*	*%*	*%*
USA (NCS)	15–29	119	31.1	241	15.6	20.7	39	28.6	67	11.6	17.8
	30–44	168	47.0	286	21.1	30.6	68	51.7	121	22.4	33.0
	45–59	59	30.8	117	10.5	17.3	35	32.8	65	13.9	20.6
	60–69	—	—	—	—	—	—	—	—	—	—
	≥70	—	—	—	—	—	—	—	—	—	—
	Total	345	38.7	644	17.1	24.7	142	40.7	253	17.4	25.8
USA	15–29	46	20.8	78	13.7	16.3	25	34.8	32	17.0	24.8
CA	30–44	37	20.9	63	7.5	12.5	40	32.8	23	12.5	25.3
Fresno	45–59	11	1.8	24	21.4	15.1	9	14.3	10	0.0	6.7
	60–69	—	—	—	—	—	—	—	—	—	—
	≥70	—	—	—	—	—	—	—	—	—	—
	Total	94	18.5	165	12.5	14.7	74	31.3	65	12.9	22.7
Mexico	15–29	23	8.2	36	2.9	5.0	14	18.6	7	0.0	12.1
Mexico	30–44	12	30.1	50	2.0	7.3	4	40.4	11	0.0	11.7
City	45–59	6	31.8	14	0.0	9.8	4	20.4	8	0.0	6.3
	60–69	—	—	—	—	—	—	—	—	—	—
	≥70	—	—	—	—	—	—	—	—	—	—
	Total	41	17.9	99	2.0	6.7	22	23.4	26	0.0	10.6
Canada	15–29	56	20.6	123	20.3	20.4	43	26.8	54	19.7	22.8
Ontario	30–44	98	47.0	177	6.1	20.7	47	46.7	62	11.9	26.9
	45–59	29	33.6	85	3.0	10.8	9	22.4	36	2.8	6.7
	60–69	—	—	—	—	—	—	—	—	—	—
	≥70	—	—	—	—	—	—	—	—	—	—
	Total	183	36.8	386	10.0	18.6	98	35.8	152	12.5	21.7
Netherlands	15–29	70	26.9	177	10.1	14.9	46	17.4	76	6.4	10.6
	30–44	180	35.9	317	13.6	21.7	72	15.8	146	7.8	10.5
	45–59	129	31.9	180	7.2	17.5	58	32.2	118	3.7	13.2
	60–69	18	33.7	33	4.0	14.4	11	0.0	26	0.0	0.0
	≥70	—	—	—	—	—	—	—	—	—	—
	Total	397	32.9	707	10.7	18.7	187	20.4	366	5.7	10.6
Brazil	15–29	10	61.0	23	2.5	20.2	4	0.0	6	37.8	23.4
	30–44	21	10.0	53	17.0	15.1	7	28.6	22	22.2	23.8
	45–59	14	17.6	36	6.5	9.5	15	21.1	15	4.0	12.8
	60–69	2	66.7	10	0.0	12.8	2	100.0	6	22.2	38.5
	≥70	2	50.0	5	0.0	12.7	1	0.0	5	0.0	0.0
	Total	48	26.7	126	9.4	14.2	29	23.9	54	16.9	19.4
Germany	15–29	126	14.6	213	4.8	8.4	39	17.7	84	2.4	7.3
	30–44	—	—	—	—	—	—	—	—	—	—
	45–59	—	—	—	—	—	—	—	—	—	—
	60–69	—	—	—	—	—	—	—	—	—	—
	≥70	—	—	—	—	—	—	—	—	—	—
	Total	126	14.6	213	4.8	8.4	39	17.7	84	2.4	7.3

Table 12.17 Percentages of the population in which the onset of alcohol problems[a] occurred prior to diagnosis of depression, by country, age and sex (*continued*)

		Major depression[b]					*Other depressions*[c]				
	Age group	*Males*		*Females*		*Total*	*Males*		*Females*		*Total*
Country/Area	*(years)*	*n*	%	*n*	%	%	*n*	%	*n*	%	%
Japan	15–29	2	100.0	7	0.0	20.1	0	NA	5	0.0	0.0
	30–44	5	23.7	3	0.0	15.1	4	32.2	2	0.0	21.0
	45–59	4	0.0	5	0.0	0.0	2	0.0	6	0.0	0.0
	60–69	3	0.0	2	0.0	0.0	1	0.0	3	0.0	0.0
	≥70	1	100.0	1	0.0	49.8	1	100.0	1	0.0	49.8
	Total	14	24.9	17	0.0	11.4	7	27.4	16	0.0	8.3
Chile	15–29	37	28.6	67	11.3	17.4	11	0.0	47	11.4	9.3
	30–44	30	27.2	53	2.0	11.1	11	2.2	70	5.7	5.2
	45–59	13	44.0	42	6.7	15.4	18	39.3	50	1.7	11.6
	60–69	8	21.6	6	0.0	12.0	8	69.1	11	1.0	29.3
	≥70	2	7.2	6	0.0	1.9	1	20.4	5	0.0	2.8
	Total	89	29.2	173	6.6	14.3	48	26.5	182	5.6	10.0

NCS National Comorbidity Survey.

— No data.

[a] For NCS, Brazil, Chile and the Netherlands, defined as having an alcohol problem, alcohol dependence or alcohol abuse. In all other countries/areas, defined as either having alcohol dependence or alcohol abuse.

[b] In all countries, major depression is defined with exclusion and without hierarchy.

[c] In all countries, other depression is defined as having dysthymia or bipolar disorder with exclusions and without hierarchy.

Source: Table numbers were calculated using the International Consortium for Psychiatric Epidemiology data (see also Merikangas et al. 1998).

Strength of association

It has been consistently found that alcohol-dependent individuals demonstrate a two- to three-fold increase in risk of depressive disorders (e.g. Hilarski and Wodarki 2001; Schuckit 1996; Swendson et al. 1998). This is an effect comparable in size with many other causal effects (Gutjahr et al. 2001) (Table 12.19).

Reversibility (remission during abstinence)

Key evidence for a causal effect of alcohol dependence on depressive disorders comes from studies that analyse what happens to rates of depressive disorders when patients with clinical symptoms abstain from drinking. Most of these studies come to the conclusion that many depressive syndromes markedly improve within days or weeks of abstinence (Brown and Schuckit 1988; Dackis et al. 1986; Davidson 1995; Gibson and Becker 1973, Penick et al. 1988; Pettinati et al. 1982; Willenbring 1986). Of course, other things change within therapy, so not all of the

effect is necessarily due to the pharmacological effect of drinking. In addition, experimental studies have found that more symptoms of depression are reported during heavy drinking episodes (Isbell et al. 1955; Schuckit et al. 1997b; Tamarin et al. 1970; Weiner et al. 1971). In conclusion, there is sufficient evidence that abstinence substantially removes symptoms of depression in alcohol-dependent persons within a short time.

Family patterns

Several studies have tried to separate alcohol-dependent persons with primary (sometimes called "independent") depressive disorders from those with secondary (sometimes called "induced") depressive disorders by examining different family patterns of both alcohol dependence and depressive disorders. For instance, Hesselbrock et al. (1983) and Schuckit et al. (1997b) found higher rates of depressive disorders, rather than alcoholism, in close relatives of alcohol-dependent patients with primary depression than in patients with secondary depression. Other studies, both in clinical samples and in the general population, did not find different rates of alcohol dependence or affective disorders based on the primary–secondary distinction (Grant and Pickering 1997; Hasegawa et al. 1991). Thus, the studies on genetic vulnerability suggest differences between primary and secondary transmission, but are not conclusive.

Biological mechanisms

There are several plausible mechanisms by which alcohol dependence may cause depressive disorders (Markou et al. 1998), but research is not yet conclusive. It should be noted that there is a biological link via intoxication or heavy use rather than via dependence alone.

Dose–response relationship

Merikangas et al. (1998) found that there is a continuum in the magnitude of co-morbidity as a function of position on the spectrum of substance use (use, problems, dependence). While there are relationships at the level of symptoms in the general population, the relationships are strongest between alcohol dependence and depressive disorders (see above).

Potential alternative explanations

There may be other explanations for the co-occurrence of alcohol dependence and depressive disorders, either from genetic disposition or the environment. For example, Grant and Pickering (1997) suggested that alcoholism and major depression might be alternative manifestations of the same underlying disorder. Nevertheless, there is no explanation for the finding that depressive symptoms increase markedly during bouts of heavy drinking and disappear during periods of abstinence, even if no antidepressant medication is given. This is the strongest indication of a causal effect.

Summary of evidence on causality

Overall, we find sufficient evidence of causality for the influence of alcohol dependence on depressive disorders. The evidence indicates that a clear and consistent association exists between alcohol dependence and depressive disorders and that chance, confounding variables and other bias can be ruled out with reasonable confidence as factors in this association. Consistent with the assessments for other disease and injury categories, most weight was placed on consistency across several studies, strength of the association, reversibility, temporal order and the fact that the effect was at least physiologically plausible.

Estimating AAFs of depressive disorders

Quantitative estimates of the proportion of depressive disorders attributable to alcohol can be derived from the high correlation between alcohol dependence and the proportion of depressive disorders with preceding alcohol-use disorders (see above), using alcohol dependence rates in different subregions of the world (Table 12.18, columns 3 and 4).

The empirical data on proportion of depressive disorders with preceding alcohol-use disorders were regressed on survey results of alcohol dependence for the same subregions without a constant. The omission of the constant was due to the fact that in a situation without any alcohol dependence, the proportion of alcohol-attributable depressive disorders should also be zero. Thus, the regression line must pass through the origin. Since the relationship is quite close, the respective regression coefficients became highly significant even with few data points.

Clearly, the proportions in columns 3 and 4 of Table 12.18 are the upper limit of depressive disorders attributable to alcohol. In order to derive a realistic proportion of alcohol-attributable depressive disorders, we need to subtract the proportion of co-occurrences due to chance. In a situation of chance, the occurrence of alcohol-use disorders in depressed persons should be exactly equal to the occurrence of alcohol-use disorders in non-depressed persons (i.e. the general population). Thus, the prevalence of alcohol-use disorders was first subtracted from the upper limit to derive AAFs. The prevalence of alcohol dependence was taken from *The world health report 2001*, which itself was based on a pooled analysis of survey results. The relationship between alcohol dependence and alcohol abuse (i.e. harmful use in ICD-10) was derived from the US National Comorbidity Survey (Kessler 1998) and was assumed to be constant across subregions. This assumption was necessary as there were fewer data on alcohol abuse than on alcohol dependence, and as the diagnostic systems used vary considerably for this diagnosis.

To control for possible confounding, the effects were halved as has been done elsewhere (e.g. IHD analysis above) as well as for other risk factors (Peto et al. 1992 for smoking; see also chapter 11). The resulting estimates for AAFs of depressive disorders can be found in Table 12.18, columns 5 and 6.

Table 12.18 Prevalence of alcohol dependence by subregion and sex, and AAFs (percentage of depressive disorders) in people aged ≥15 years

Subregion	*Prevalence of alcohol dependence (%)*[a]	*Upper limit for AAF, major depression*	*Upper limit for AAF, other depression*	*AAF, major depression*	*AAF, other depression*
Males					
AFR-D	1.37	5.17	5.31	1.68	1.76
AFR-E	2.89	10.93	11.24	3.56	3.71
AMR-A	8.04	30.37	31.22	9.89	10.31
AMR-B	5.72	21.60	22.20	7.04	7.34
AMR-D	5.13	19.39	19.93	6.32	6.59
EMR-B	0.07	0.25	0.26	0.09	0.09
EMR-D	0.07	0.26	0.26	0.09	0.09
EUR-A	5.61	21.21	21.80	6.91	7.20
EUR-B	1.16	4.39	4.52	1.43	1.49
EUR-C	8.22	31.05	31.91	10.11	10.54
SEAR-B	0.77	2.91	2.99	0.95	0.99
SEAR-D	1.58	5.96	6.13	1.94	2.03
WPR-A	3.12	11.77	12.10	3.84	4.00
WPR-B	1.78	6.73	6.91	2.19	2.29
Females					
AFR-D	0.10	0.37	0.38	0.12	0.12
AFR-E	0.31	1.17	1.20	0.37	0.38
AMR-A	2.14	8.10	8.33	2.52	2.63
AMR-B	1.18	4.46	4.59	1.39	1.45
AMR-D	1.19	4.50	4.63	1.40	1.46
EMR-B	0.00	0.02	0.02	0.01	0.01
EMR-D	0.01	0.02	0.02	0.01	0.01
EUR-A	1.18	4.46	4.58	1.39	1.45
EUR-B	0.23	0.88	0.91	0.28	0.29
EUR-C	1.39	5.24	5.39	1.63	1.70
SEAR-B	0.07	0.26	0.26	0.08	0.09
SEAR-D	0.05	0.20	0.21	0.07	0.07
WPR-A	1.12	4.22	4.34	1.31	1.37
WPR-B	0.05	0.19	0.19	0.06	0.06

[a] From *World health report 2001*, based on survey results (Rehm and Eschmann 2002) and then estimated consistently with DisMod,[24] taking into account case fatality, duration and/or incidence.

These results show that AAFs of depressive disorders vary substantially in different subregions of the world. They reflect differences in rates of heavy alcohol consumption and alcohol dependence. Thus, AAFs are considerably larger for males than for females. They are highest in the

Russian Federation and its surrounding countries (EUR-C) and in North America (AMR-A), and almost nonexistent in Muslim-dominated areas (EMR-B and EMR-D).

Conclusions on alcohol and depression

Based on standard criteria of causality, we conclude that there is sufficient evidence for a causal relation between alcohol-use disorders and depressive disorders. We suspect that careful examination would also reveal a relationship between heavy drinking and depressive disorders, although heavy drinking unfortunately is not usually measured as an endpoint in epidemiological cohort studies.

The status of alcohol abuse as a causal agent in depression is not as clear. There are co-occurrences between alcohol abuse and depressive disorders that are larger than chance (Kessler et al. 1996, 1997), but the relationship is weaker compared to the relationship with alcohol dependence. This may have to do with the less clear conceptual status of alcohol abuse, which is defined in the current version of the *Diagnostic and statistical manual of mental disorders* (DSM) (American Psychiatric Association 1994) nosology to include social and legal responses to the patient's drinking, and which is not a category of disorder in ICD. On the other hand, many studies found only one factor when analysing criteria of alcohol dependence and alcohol abuse, or a division of factors that did not correspond to the division between the diagnoses in DSM. Thus, the relationship between alcohol abuse and depressive disorders should be clarified in future research. It may have relevance, beyond burden of disease research, in helping to clarify the status of alcohol abuse in general.

3.10 Summary of relative risk for chronic diseases, using CRA disease categories

Relative risk estimates are summarized in Table 12.19.

3.11 Acute adverse health consequences

Alcohol use has been associated with increased risk of injury in a wide variety of settings, including road traffic accidents (involving vehicles, bicycles and pedestrians), falls, fires, injuries related to sports and recreational activities, self-inflicted injuries and injuries resulting from interpersonal violence (Cherpitel 1992; Freedland et al. 1993; Hingson and Howland 1987, 1993; Hurst et al. 1994; Martin 1992; Martin and Bachman 1997; U.S. Department of Health and Human Services 1997, 2000). There is also some evidence that the presence of alcohol in the body at the time of injury may be associated with a greater severity of injury and a less positive outcome (Fuller 1995; Li et al. 1997).

Table 12.19 Relative risk for major chronic disease categories by sex and average drinking category

			Males			*Females*		
Disease	*ICD-9 (4-digit)*	*ICD-10 (4-digit)*	*Drinking category I*	*Drinking category II*	*Drinking category III*	*Drinking category I*	*Drinking category II*	*Drinking category III*
Conditions arising during the perinatal period	760–779 except 771.3	P00–P96						
Low birth weight	764–765	P05–P07	1.00	1.40	1.40	1.00	1.40	1.40
Malignant neoplasms	140–208	C00–C97						
Mouth and oropharynx cancers	140–149	C00–C14	1.45	1.85	5.39	1.45	1.85	5.39
Oesophagus cancer	150	C15	1.80	2.38	4.36	1.80	2.38	4.36
Liver cancer	155	C22	1.45	3.03	3.60	1.45	3.03	3.60
Female breast cancer*	174	C50	NA	NA	NA	1.14	1.41	1.59
>45 years of age*			NA	NA	NA	1.15	1.41	1.46
≥45 years of age*			NA	NA	NA	1.14	1.38	1.62
Other neoplasms	210–239	D00–D48	1.10	1.30	1.70	1.10	1.30	1.70
Type II diabetes	250	E10–E14	1.00	0.57	0.73	0.92	0.87	1.13

Neuro-psychiatric conditions	290–319, 324–359	F01–F99, G06–G98						
Unipolar major depression	300.4	F32–F33	AAFs were estimated indirectly based on prevalence of alcohol dependence					
Epilepsy	345	G40–G41	1.23	7.52	6.83	1.34	7.22	7.52
Alcohol-use disorders	291, 303, 305.0	F10	AAF 100%	AAF 100%	AAF 100%	AAF 100%	AAF 100%	AAF 100%
Cardiovascular diseases	390–459	I00–I99						
Hypertensive disease	401–405	I10–I13	1.40 0.82	2.00 0.83	4.10 1.00	1.40 0.82	2.00 0.83	2.00 1.12
Ischaemic heart disease	410–414	I20–I25	AAFs were modelled including patterns of drinking (see text above for details)					
Cerebrovascular disease	430–438	I60–I69						
Ischaemic stroke*	433–435		0.94	1.33	1.65	0.52	0.64	1.06
Haemorrhagic stroke*	430–432		1.27	2.19	2.38	0.59	0.65	7.98
Digestive diseases	530–579	K20–K92						
Cirrhosis of the liver	571	K70, K74	1.30	9.50	13.00	1.30	9.50	13.00

NA Not applicable.

Sources: Gutjahr et al. 2001; Ridolfo and Stevenson 2001; if indicated by * the category III estimates for IHD were based on Corrao et al. 2000.

Unintentional injuries

Alcohol consumption produces effects that are often perceived as positive, as evidenced by the widespread popularity of drinking. But it also leads to actions that result in unintentional injury and death. This section highlights research findings on causality of alcohol involvement and findings relevant to establishing dose–response relationships and drinking patterns. It focuses on traffic injuries, as most of the research has been conducted in this area, and traffic accidents are the most important component of unintentional injuries (Rehm et al. 2003b).

Studies relating average volume of drinking to risk of injury have found the risk of injury to be positively related to increasing average intake levels of alcohol, with the risk increasing at relatively low volumes of intake (Cherpitel et al. 1995). Two studies of injury among older adults reported a U-shaped relationship between alcohol use and occupational injury (Zwerling et al. 1996) and traumatic deaths (Ross et al. 1990). However, abstinence could be related to existing health problems or cognitive deficits that are, in turn, related to accident risk (Zwerling et al. 1996). Hence the higher risk among abstainers is likely to be purely spurious.

Several patterns of drinking have been related to risk of injury. Frequent heavy drinking and frequent subjective drunkenness are both associated with injury, particularly injury resulting from violence (Cherpitel 1996a). Frequency of heavy drinking has also been associated with a greater likelihood of death due to injury, relative to other causes (Li et al. 1994). One important line of research in this area has empirically defined a parameter of usual drinking pattern that is most closely associated with the risk of injury and drunk driving behaviour, after adjusting for other drinking pattern variables and characteristics of the drinker (Gruenewald and Nephew 1994; Gruenewald et al. 1996a, 1996b; Treno and Holder 1997; Treno et al. 1997). The greatest risk was found in individuals who consume relatively large amounts on some occasions, and whose highest amounts are markedly greater than their average amount per occasion.

Several retrospective studies have compared BAC in individuals who have experienced a collision or trauma, compared with selected individuals not involved in trauma, using a case–control design (Cherpitel 1992; Freedland et al. 1993; Fuller 1995; Hurst et al. 1994; Stoduto et al. 1993; U.S. Department of Health and Human Services 1997). One of the most influential case–control series was the Grand Rapids Study of 5985 collisions (Borkenstein et al. 1964; Hurst et al. 1994). Statistically adequate re-analysis of the Grand Rapids Study indicates that all levels of BAC are associated with an increased risk of crashes, relative to a BAC of zero, with an accelerating slope in which the risk of injury increases markedly with high BACs (Hurst et al. 1994).

There are clear reasons why alcohol is related to injury. Moderate doses of alcohol have been demonstrated in controlled experimental studies to have cognitive and psychomotor effects that are relevant to the risk of injury, such as reaction time, cognitive processing, coordination and vigilance (Eckardt et al. 1998; Kruger et al. 1993; Moskowitz and Robinson 1988; U.S. Department of Health and Human Services 1997). The comprehensive recent review by Eckardt et al. (1998) concluded that the threshold dose for negative effects on psychomotor tasks is generally found at around 40–50 mg% (equivalent to 0.04–0.05%). The authors also stated, "injury can occur as a result of alcohol's disruption of psychomotor function in individuals at BACs of approximately 10 mM", which is equal to a BAC of little less than 50 mg%.

Dose–response curves observed in experimental data are not always monotonic. For example, a recent experimental study (Lloyd and Rogers 1997) assessed the effects of low doses of alcohol given with a meal, and found that 8 g of absolute alcohol (about 0.25 litre of beer) resulted in improved performance of complex cognitive tasks relative to no alcohol, but that 24 g of absolute alcohol produced impaired performance. Such J-shaped or U-shaped effects of low ethanol doses on task-specific performance are explicable pharmacologically (Eckardt et al. 1998). The Grand Rapids Study also found that dose–response curves varied somewhat between novices and frequent, experienced drinkers.

In summary, the evidence indicates that the amount consumed per occasion, and more specifically the blood alcohol content, is the critical feature in determining risk of injury. Blood alcohol concentrations as low as 40–50 mg% may cause psychomotor impairment, leading to increased risk of injury in circumstances such as driving or operating machinery.

Thus, despite methodological problems, there is evidence of causality for the most researched injury category (traffic accidents). Table 12.20 gives the AAFs for different kinds of injuries in four recent reviews. The reviews based their estimates on meta-analyses or other summaries of the relations found in published studies. It should be recognized that, while there are many such studies, they are mostly from a relatively small range of countries. Most of the AAFs were directly derived, for example from police statistics, although there are case–control studies as well (McLeod et al. 1999).

Causality, at least for traffic accidents, can be established since:

- alcohol is clearly associated with the outcome;
- there is a dose–response relationship: the higher the BAC, the higher the chance of injury;
- there is a biochemical explanation for the relationship; and
- with suitable interventions to reduce alcohol consumption, the outcome is reduced as well. Thus, in a meta-analysis, Shults et al.

Table 12.20 AAFs of acute alcohol-related health effects in the adult general population

		Review							
		Stinson et al. 1993; USA		*English et al. 1995; Australia*		*Single et al. 1996; Canada*		*Ridolfo and Stevenson 2001; Australia*	
Injury	*ICD-9 code*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
Motor vehicle traffic accidents	E810–E819	0.42	0.42	0.37	0.18	0.43	0.43	0.33 (d);[a] 024 (h);[a] pedestrians 0.40 (d); 0.37 (h)	0.11 (d) and (h); pedestrians 0.17 (d); 0.06 (h)
Motor vehicle nontraffic accidents	E820–E825	0.42	0.42	0.37	0.18	0.43	0.43		
Bicycle accident injuries	E826	0.20	0.20	0.37	0.18	0.20	0.20		
Other road vehicle accident injuries	E829	0.20	0.20	0.37	0.18	0.20	0.2		
Water transport accident injuries	E830–E839	0.20	0.20	—	—	0.20	0.20	—	—
Air-space transport accident injuries	E840–E845	0.16	0.16	—	—	0.16	0.16	—	—
Accidental ethanol and methanol poisoning	E860.0–E860.2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Accidental fall injuries	E880–E888	0.35	0.35	0.34	0.34	0.20–0.34[b]	0.13–0.34[b]	0.22 for age <65; 0.12 for age ≥65	0.14 for age <65; 0.04 for age ≥65

Arson injuries	E890–E899	0.45	0.45	0.44	0.44	0.38	0.38	0.44	0.44
Accidental excessive cold	E901	0.25	0.25	—	—	0.25	0.25	—	—
Accidental drowning	E910	0.38	0.38	0.34	0.34	0.31–0.50[b]	0.31–0.50[b]	0.34	0.34
Accidental aspiration	E911	0.25	0.25	1.00	1.0	0.25	0.25	1.00	1.00
Striking against/struck by objects	E917	0.25	0.25	—	—	0.07	0.07	—	—
Caught in/between objects	E918	0.25	0.25	—	—	0.07	0.07	—	—
Occupational and machine injuries	E919–E920	0.25	0.25	0.07	0.07	0.07	0.07	0.07	0.07
Accidental firearm missile injuries	E922	0.25	0.25	—	—	0.25	0.25	—	—
Suicide, self-inflicted injuries	E950–E959	0.28	0.28	0.12	0.08	0.23–0.31[b]	0.11–0.19[b]	0.32	0.29
Victim fight, brawl, rape	E960	0.46	0.46	0.47	0.47	0.27	0.27	0.47	0.47
Victim assault, firearms	E965	0.46	0.46	0.47	0.47	0.27	0.27	0.47	0.47
Victim assault, cutting instrument	E966	0.46	0.46	0.47	0.47	0.27	0.27	0.47	0.47
Victim child battering	E967	0.46	0.46	0.16	0.16	0.16	0.16	0.16	0.16
Victim assault, other	E968	0.46	0.46	0.47	0.47	0.27	0.27	0.47	0.47
Late effects of injuries by another	E969	0.46	0.46	0.47	0.47	0.27	0.27	0.47	0.47

— No data.

[a] (d), deaths; (h), hospitalizations.

[b] Ranges refer to age-specific AAFs; minimum (>0) and maximum estimates are shown.

(2001) found random breath-testing programmes or selective breath-testing checkpoints to be effective in reducing mortality from traffic accidents by 18% and 20%, respectively.

Intentional injuries

Alcohol is strongly associated with violent crime (Graham and West 2001), although this association varies considerably across settings (Murdoch et al 1990; Room and Rossow 2001). Studies on violence have repeatedly shown that alcohol consumption precedes violent events, and that the amount of drinking is related to the severity of the subsequent violence. In addition, the experimental literature suggests that alcohol plays a causally contributing role[25] in aggression. Meta-analyses of experimental studies suggest a small to moderate effect size of about 0.22 (Bushman 1997) in the overall relationship between alcohol consumption and aggression. Some effort has been made to separate pharmacological effects from expectations,[26] but the general conclusion is that expectations form part of the "psycho-pharmacological" effects of alcohol (Bushman 1997; Graham et al. 1998), and neither can nor should be separated in attempting to understand the effects of alcohol. Alcohol bathes the brain in chemicals and it is likely that a number of different effects of alcohol contribute to the increased likelihood of aggressive behaviour. First, alcohol seems to have an effect on the serotonin (5HT) and GABA brain receptors, similar to that produced by some benzodiazepines (Pihl et al. 1993). The subjective experience of this effect may be a reduced level of fear and anxiety about social, physical or legal consequences of one's actions. This reduced fear or anxiety may result in increased risk-taking by some drinkers. This particular causal pathway has received support from animal research linking alcohol, GABA receptors and aggression (Miczek et al. 1993) and from experimental and observational research showing higher risk taking associated with alcohol intoxication (Graham et al. 2000; Pihl and Peterson 1993). Alcohol also affects cognitive functioning (Peterson et al. 1990), leading to impaired problem solving in conflict situations (Sayette et al. 1993) and overly emotional responses or emotional lability (Pihl et al. 1993). Other behavioural and attitudinal effects of alcohol related to aggression have been identified, although at this point not necessarily linked to particular pharmacological effects on the brain. These include a narrow and tenacious focus on the present (Graham et al. 2000; Washburne 1956), also described as "alcohol myopia" (Steele and Josephs 1990) and increased concerns with demonstrating personal power, at least for men (Graham et al. 2000; McClelland et al. 1972; Tomsen 1997).

Alcohol-related violence involves more complex issues of social interaction than would be relevant to drink–driving and other alcohol-related accidental injuries. In particular, the effects of alcohol are moderated by both the environment and the characteristics of the drinker (Chermack and Giancola 1997; Lipsey et al. 1997; Rossow et al. 2001; U.S. Depart-

ment of Health and Human Services 2000). For example, meta-analysis of experimental research on alcohol and aggression found that the effects of environmental manipulation to increase aggression were stronger for intoxicated than for sober participants. In another meta-analysis, Ito et al. (1996) found that the effects of alcohol were greater in situations characterized by greater anxiety, inhibition conflict and frustration, while differences between sober and intoxicated persons were smaller in situations involving high provocation or self-focused attention. Further, given sufficient disincentives for aggression the effects of alcohol on aggression can be reduced or even eliminated altogether (Hoaken et al. 1998; Jeavons and Taylor 1985).

As with alcohol-related accidents, some proportion of violence that occurs after people have been drinking might have occurred anyway, without the involvement of alcohol. Alcohol-related violence involves an interaction of the effects of alcohol on one or more people, the environment and the personality of the drinker (Graham et al. 1998). However, the environment for alcohol-related aggression is not independent of drinking.[27] For example, in environments devoted to drinking (e.g. bars, pubs), it does not make sense to try to determine the proportion of violence that would have occurred even if the person had not been drinking, because this particular environment does not exist without drinking. Although a few incidents that occur in bars involve interpersonal conflict between friends or couples that might have occurred in another setting, almost all incidents of aggression that occur in bars are unplanned, emerge from the social interaction in the bar (Graham and Wells 2001) and often involve strangers. Therefore, it seems reasonable to assume that close to 100% of incidents of violence occurring in bars and other environments where drinking is the main activity should be considered attributable to alcohol, either directly through the pharmacological effects of alcohol or indirectly through the social norms related to drinking.

Estimating the proportion of violence in other settings that should be attributed to alcohol is more problematic. There are pharmacological effects of alcohol, as described above, that make aggressive interactions more likely. This is more likely to be the case if all those involved have been drinking, owing to the interaction of the effects of alcohol on each person (Leonard 1984). In addition, alcohol is known to increase the likelihood of the escalation of conflict (Martin and Bachman 1997; Sharps et al. 2001). On the other hand, marital violence, for example, often occurs when neither party has been drinking. Therefore, the assessment of the exact proportion of alcohol-related violent injuries and death that should be attributable to alcohol is often difficult, and needs to be assessed from different sources, such as time series analyses, natural experiments, case–control studies, emergency-room studies, general population surveys and experimental designs (Pernanen 2001).

Deriving the AAFs for different subregions for injuries (both intentional and unintentional)

Injuries are also influenced by average volume of alcohol consumption and by patterns of drinking, especially by acute levels of BAC or intoxication. To model this relationship, a multilevel analysis identical to the one on IHD was used (for statistical derivation and specification of the model see section 3.2; for formulas see notes below Table 12.13). Table 12.21 gives an overview of the underlying data. Table 12.22 gives the main results of the analysis.

The effect of alcohol on injury at pattern 1 is 0.013 for males and 0.010 for females. The effect for pattern 2 populations is the same, as the coefficients did not significantly differ. For pattern 3, the effect is 0.056 for males and 0.014 for females. For pattern 4, the respective effects are 0.196 for males and 0.027 for females.

The results can be summarized as follows.

- Average volume of drinking has a significant detrimental effect on risk of injury even at consumption pattern 1, independent of sex. The impact is larger in males.
- The impact of per capita consumption on injury is different between different countries, as shown by the significant variance component.
- No significant difference in the effect of drinking on injury risk was found between patterns 1 and 2.
- Pattern 3 has a significantly higher injury risk for both sexes, but the impact is much stronger in males (about 10 times).
- Pattern 4 has the highest injury risk for both sexes, and again the impact is much stronger for males.

To estimate AAFs for injuries we used the Australian AAFs, since these reflected the most up-to-date information (Ridolfo and Stevenson 2001). These were converted into odds ratios,[28] which were applied to estimated exposure prevalence for all subregions, as with other diseases, multiplicatively adjusted by pattern weights from Table 12.22 and average volume of alcohol consumption. This procedure must be regarded as a crude approximation, yet the best attainable at present. Given the potential variation in the role of alcohol in casualties across settings, there is an urgent need for empirical studies of the relationship in different world regions, using a variety of methods. The WHO Collaborative Study on Alcohol and Injuries (www.who.int/substance_abuse/topic_alcohol_injuries.htm) constitutes a step forward on this.

Appendix B gives an overview of the derived AAFs for mortality for major categories of accidental and intentional injuries, as defined for the CRA project.

Table 12.21 Characteristics of data set to calculate the relationship between per capita consumption, patterns of drinking and injury mortality

Country	*Injury mortality, males per 1000*	*Injury mortality, females per 1000*	*Average per capita alcohol consumption*	*Pattern of drinking*	*Year of first data*	*Year of last data*	*Number of years*
Albania	0.74	0.21	2.20	3	1992	1998	7
Argentina	0.87	0.28	27.48	2	1966	1996	25
Armenia	0.37	0.10	2.53	2	1992	1998	7
Australia	0.78	0.31	11.19	2	1964	1997	34
Austria	1.07	0.39	14.16	1	1962	1999	38
Azerbaijan	0.68	0.14	2.10	3	1990	1999	9
Bahamas	0.97	0.30	14.30	2	1969	1995	13
Bahrain	0.33	0.09	5.33	2	1985	1988	3
Barbados	0.63	0.17	7.88	2	1964	1995	31
Belarus	1.55	0.35	9.68	4	1989	1998	9
Belgium	0.87	0.41	12.35	1	1964	1994	31
Belize	0.59	0.17	6.01	4	1964	1995	28
Bulgaria	0.89	0.26	11.97	2	1982	1998	17
Canada	0.81	0.31	9.74	2	1964	1997	34
Chile	1.44	0.33	11.58	3	1964	1994	31
Colombia	1.72	0.32	5.49	3	1967	1994	19
Costa Rica	0.94	0.25	4.48	4	1964	1995	32
Croatia	0.93	0.31	13.24	3	1993	1998	6
Czech Republic	0.92	0.40	15.42	2	1986	1999	14
Denmark	0.77	0.40	10.91	2	1964	1996	33
Dominican Republic	0.63	0.20	2.91	2	1965	1985	21
Ecuador	1.23	0.33	2.30	3	1964	1995	31
El Salvador	1.99	0.36	1.95	4	1964	1993	19
Estonia	2.50	0.58	13.43	3	1992	1999	8
Fiji	0.50	0.26	2.98	3	1978	1978	1
Finland	1.21	0.35	7.42	3	1964	1996	33
France	1.02	0.43	23.15	1	1964	1997	34
Germany	0.54	0.21	13.63	1	1993	1998	6
Greece	0.58	0.23	9.69	2	1964	1998	35
Guatemala	1.49	0.26	2.33	4	1964	1984	14
Guyana	0.90	0.24	9.50	3	1979	1994	4
Honduras	0.62	0.10	2.62	4	1976	1979	4
Hungary	1.39	0.54	15.85	3	1977	1999	23
Iceland	0.85	0.29	5.42	3	1964	1996	33
Ireland	0.60	0.24	10.86	3	1964	1996	33
Israel	0.56	0.29	3.04	2	1975	1996	22
Italy	0.64	0.24	18.48	1	1964	1996	33
Jamaica	0.41	0.10	3.12	2	1964	1985	7
Japan	0.68	0.27	5.78	1	1964	1997	34

continued

Table 12.21 Characteristics of data set to calculate the relationship between per capita consumption, patterns of drinking and injury mortality (*continued*)

Country	*Injury mortality, males per 1000*	*Injury mortality, females per 1000*	*Average per capita alcohol consumption*	*Pattern of drinking*	*Year of first data*	*Year of last data*	*Number of years*
Kazakhstan	1.65	0.44	7.24	4	1989	1998	10
Kyrgyzstan	0.91	0.25	1.88	3	1995	1999	5
Latvia	2.09	0.52	8.53	3	1989	1998	10
Lithuania	2.26	0.51	5.76	3	1989	1998	5
Luxembourg	0.97	0.37	17.37	1	1967	1997	31
Malta	0.35	0.14	5.27	1	1965	1998	33
Mauritius	0.80	0.26	3.30	3	1964	1998	35
Mexico	1.60	0.33	3.94	4	1962	1995	34
Netherlands	0.51	0.27	9.39	1	1964	1997	34
New Zealand	0.81	0.35	11.36	2	1964	1998	35
Nicaragua	1.25	0.28	3.29	4	1964	1994	17
Norway	0.69	0.27	5.11	3	1964	1996	33
Peru	0.67	0.21	6.13	3	1966	1989	16
Philippines	0.67	0.16	2.59	3	1964	1993	18
Portugal	0.98	0.28	18.85	1	1964	1998	35
Qatar	0.47	0.17	.84	2	1995	1995	1
Republic of Korea	1.09	0.38	8.90	3	1985	1997	13
Romania	1.11	0.33	10.78	3	1989	1998	10
Russian Federation	2.05	0.50	8.88	4	1991	1998	8
Singapore	0.64	0.23	2.30	2	1964	1998	35
Slovakia	1.04	0.31	12.54	3	1992	1995	4
Slovenia	1.15	0.38	14.80	2	1994	1998	5
Spain	0.60	0.19	17.20	1	1962	1997	36
Sri Lanka	1.01	0.40	.27	3	1964	1986	13
Suriname	1.05	0.37	6.43	3	1964	1992	21
Sweden	0.72	0.30	7.57	3	1964	1996	33
Switzerland	0.93	0.38	14.99	1	1964	1994	31
Tajikistan	0.58	0.16	2.52	3	1992	1992	1
Thailand	0.92	0.26	3.58	3	1964	1994	25
The former Yugoslav Republic of Macedonia	0.47	0.15	5.76	3	1994	1997	4
Trinidad and Tobago	0.95	0.27	4.79	2	1962	1994	29
Turkmenistan	0.43	0.18	2.13	3	1995	1995	1
Ukraine	1.41	0.32	4.64	3	1990	1999	10
United Kingdom	0.47	0.23	9.49	2	1964	1998	35
United States	0.92	0.32	9.46	2	1964	1997	34
Uruguay	0.84	0.28	8.08	3	1966	1990	24
Uzbekistan	0.46	0.15	1.07	3	1996	1998	3
Venezuela	1.29	0.33	8.31	3	1969	1994	24

Table 12.22 Effects of per capita consumption and patterns of drinking on risk of injury mortality

	Coefficient	*SE*	*t-value*	*df*	*P*	*Variance component*	*df*	χ^2	*P*
Males									
Average volume = per capita consumption									
Not adjusted	0.045	0.013	3.46	79	0.001	0.0106	72	584.1	0.000
Adjusted by GNP, year	0.047	0.012	3.90	79	0.000	0.0097	72	620.6	0.000
After inclusion of pattern dummy variables on second level	0.013	0.006	2.05	76	0.040	0.0080	69	532.1	0.000
Patterns of drinking[a]									
Pattern 2	–0.009	0.011	<1	76	0.391				
Pattern 3	0.043	0.014	3.13	76	0.002				
Pattern 4	0.173	0.062	2.77	76	0.006				
Females									
Average volume = per capita consumption									
Not adjusted	0.0097	0.0023	4.19	79	0.000	0.00028	72	398.7	0.000
Adjusted by GNP, year	0.0121	0.0021	5.91	79	0.000	0.00021	72	496.2	0.000
After inclusion of pattern dummy variables on second level	0.0096	0.0021	4.46	76	0.000	0.00020	69	412.8	0.000
Patterns of drinking[a]									
Pattern 2	–0.0024	0.0031	<1	76	0.440				
Pattern 3	0.0041	0.0030	1.40	76	0.163				
Pattern 4	0.0171	0.0077	2.24	76	0.025				

[a] Patterns 2, 3 and 4 are compared to pattern 1.

Another point concerns the relation of alcohol with type of outcome—morbidity vs mortality. In general, more severe outcomes are more related to alcohol than less severe outcomes (Rehm et al. 2003b; Single et al. 1999b). Consequently, the AAFs for mortality should be higher than the AAFs for morbidity. Unfortunately, most research to determine AAFs for injury did not explicitly separate mortality and morbidity (see, e.g. Table 12.20). Ridolfo and Stevenson (2001) explicitly separated the AAFs for motor vehicle accidents, and for males found 0.328 for deaths and 0.247 for hospitalizations; they lacked sufficient data for females. Based on their work and that of Cherpitel (1994, 1996b), we determined the ratio of AAF for morbidity as two thirds of the AAF for mortality. The ratio for other kinds of injury is lower (Cherpitel 1994, 1996b). To

be conservative, these ratios were set at 0.44 (or two thirds of the ratio for motor vehicle accidents) (Cherpitel 1994, 1996b).

3.12 Quantitative and qualitative sources of uncertainty

Since most of the chronic disease relationships with alcohol depend on biochemical processes linked to average volume of consumption over time, their hazards have been fairly stable across countries (Corrao et al. 2000). On the other hand, injuries are context-dependent to a much larger degree. A good example is the difference between liver cancer and traffic accidents. Based on biochemical evidence, there are reasons to believe that the relationship between average volume of alcohol consumption and liver cancer is relatively stable across different countries and societies, even though epidemiological work tends to be concentrated in established market economies. The most notable exception for chronic disease has been IHD, where patterns of drinking play a decisive role in determining the impact of average volume of drinking. On the other hand, the number of accidents (and alcohol-related traffic accidents in particular) depends on many background variables, as illustrated above. Thus, the risk relations between injuries and alcohol are much less stable and their transferability is more questionable. Where it has to be done, it should carry wider CIs.

Based on the above considerations, the following pertain.

- For chronic diseases, estimates of relative risk are usually based on meta-analyses of more than 20 studies with relatively small CIs. The uncertainty introduced by cross-population transfer of data is not that large, as the relationships depend on biochemical mechanisms. It is therefore suggested that ± 15% of the point estimate be used as the standard in an uncertainty analysis. This applies to all chronic disease categories where AAFs are directly derived from prevalence and relative risk.
- In all cases where AAFs are derived in other ways (e.g. injury), these fractions are more influenced by contextual differences from one region to another and should thus be modelled with more uncertainty. We suggest ± 30% of the point estimate to account for additional assumptions.
- IHD is the notable exception. In this case, estimates differ considerably (see the heterogeneity in the meta-analysis of Corrao et al. 2000), with respect not only to the magnitude but also to the direction of the relation. To account for this uncertainty and the difference of estimates in different models, we suggest the values set out in Table 12.23.

Table 12.23 is based on the following assumptions.

- For AMR-A, EUR-A and WPR-A, the results from the individual-level meta-analysis (Corrao et al. 2000) were taken as best estimates. For

Table 12.23 AAF estimates and uncertainty intervals for IHD by subregion

	Best estimates	
Subregion	*Males*	*Females*
AFR-D	0.02 (–0.05, 0.05)	0.00 (–0.03, 0.03)
AFR-E	0.07 (0.00, 0.09)	0.00 (–0.03, 0.03)
AMR-A[a]	–0.13 (–0.17, 0.00)	–0.08 (–0.12, 0.00)
AMR-B	0.16 (0.00, 0.21)	0.02 (–0.05, 0.05)
AMR-D	0.08 (0.00, 0.12)	0.03 (–0.05, 0.05)
EMR-B	0.00 (–0.03, 0.03)	0.00 (–0.03, 0.03)
EMR-D	0.01 (–0.03, 0.03)	0.00 (0.03, 0.03)
EUR-A[a]	–0.16 (–0.21, 0.10)	–0.13 (–0.17, 0.04)
EUR-B	0.11 (–0.13, 0.15)	0.00 (–0.08, 0.05)
EUR-C	0.15 (0.10, 0.20)	0.03 (0.02, 0.04)
SEAR-B	0.01 (–0.03, 0.03)	0.00 (–0.03, 0.03)
SEAR-D	0.04 (–0.03, 0.03)	0.00 (–0.03, 0.03)
WPR-A[a]	–0.17 (–0.23, –0.10)	–0.13 (–0.17, –0.07)
WPR-B	0.01 (–0.05, 0.05)	0.00 (–0.03, –0.03)

[a] Best estimates derived from relative risk and not from multilevel estimates.

these subregions the results from the aggregate multilevel analysis were taken as upper limits, and 30% lower than the best estimate as lower limits.

- For EUR-B, the aggregate multilevel results were taken as best estimates, and the results from the individual-level analysis was taken as lower limit, and 30% higher than the best estimate as upper limit.
- For all other subregions, the aggregate multilevel analysis results were taken as best estimates and, based on pattern and volume of the subregion, uncertainty intervals were chosen as follows:
  - ±0.03 in the case of low-volume drinking (average <3 g/day) and average pattern values lower than 3.5;
  - ±0.05 in the case of females for volumes >3 g/day and average pattern values lower than 3.5 (this restriction for females was intended to account for the higher uncertainty of pattern values for females); and
  - for all other estimates zero was taken as the lower bound, and the best estimate plus 30% as the upper bound (except for EUR-C, the only subregion with an average pattern value greater than 3.5).

A number of points need to be emphasized when interpreting these results. The underlying research for chronic disease is quite heterogeneous with respect to quality. In particular, measurement of alcohol provides limited information on patterns of drinking and for characteristics of abstainers. Most studies have just one time measurement of exposure. Often cohorts were selected with respect to minimizing loss to follow-up, and thus samples with more regular, low-to-moderate drinking styles were used. This constitutes a problem for estimating the effects of patterns of drinking, as well as for estimating the effects of continuous heavy drinking.

There is also a problem of measuring exposure with respect to acute consequences, although slightly different because often the BAC is given as the only indicator. Such a measure does not allow one to differentiate between the effects of pattern of drinking and average volume of alcohol consumption, as a heavy drinking occasion may be the exception or the norm. But for the population level, we need both types of information, as numbers of injuries will depend on both (see above). In addition, the BAC alone does not allow one to determine if alcohol was a contributing causal factor or not, only in combination with other information on control conditions, i.e. series of BACs in accident and non-accident conditions (Borkenstein et al. 1964). Unfortunately, such control conditions are lacking in most research (Gmel and Rehm 2003). Thus, with the exception of traffic accidents, the overall quality of the underlying research for most alcohol-related acute outcomes is of poor quality and derived AAFs may be subject to considerable error. This is reflected in the wide uncertainty margins suggested above.

3.13 Estimates of risk reversibility

Part of the risk from alcohol is immediately reversible: all acute risks can be completely reversed if alcohol is removed. Chronic diseases often depend on lifetime exposure, and thus risk is often reduced but not completely eliminated by removal of alcohol.

On the other hand, there are indications that a reduction of alcohol consumption in populations is associated with a fairly rapid decrease in chronic diseases such as liver cirrhosis. For example, time series analyses showed that decreases in per capita consumption were associated with considerable concurrent reductions in liver cirrhosis (e.g. Ramstedt 2001; Skog 1980; and especially Cook and Tauchen 1982).

Another example of a chronic condition with rapid, sometimes almost immediate remission is depression. In fact, most studies come to the conclusion that many depressive syndromes markedly improve within days to weeks of abstinence (Brown and Schuckit 1988; Dackis et al. 1986; Davidson 1995; Gibson and Becker 1973, Penick et al. 1988; Pettinati et al. 1982; Willenbring 1986).

It is not clear what effect alcohol removal would have on alcohol use disorders. Clearly, some criteria of both alcohol dependence and harmful

use of alcohol would no longer apply (e.g. continued use despite harmful consequences).

4. Discussion of estimates of alcohol-attributable burden

4.1 Mortality

Alcohol-related burden of disease is considerable: 3.2% of global mortality and 4.0% of global burden of disease as measured in DALYs. In terms of alcohol-related mortality, almost half of the global burden (46%) is related in acute causes, i.e. unintentional and intentional injuries (see Table 12.24; details in Appendix C). Within this mortality burden, for acute causes, unintentional injuries are by far the most important. The next important category is malignant neoplasms with 20% of the overall alcohol-related mortality burden, followed by cardiovascular diseases (15% of all alcohol-attributable deaths) and other noncommunicable diseases, a category almost entirely made up of liver cirrhosis (13%). Cardiovascular deaths are a special case in that different patterns of drinking lead to beneficial and detrimental outcomes. Thus, the net result of 15% does not give a clear picture of the underlying structure. Going beyond the net result, alcohol was estimated to cause a total of almost 600 000 cardiovascular deaths in the year 2000, exceeding even the alcohol-related burden of unintentional injuries. This figure was partly "offset" by the beneficial effects of alcohol on IHD and stroke. More males than females die of the effects of alcohol, with a ratio of about 10:1.

Table 12.24 Global deaths (000s) attributable to alcohol by major disease and injury categories, 2000

Disease or injury	*Males*	*Females*	*Total*	*Percentage of all alcohol-attributable deaths*
Conditions arising during the perinatal period	2	1	3	0
Malignant neoplasms	269	86	355	20
Neuro-psychiatric conditions	91	19	111	6
Cardiovascular diseases	392	−124	268	15
Other noncommunicable diseases (type II diabetes, liver cirrhosis)	193	49	242	13
Unintentional injuries	484	92	577	32
Intentional injuries	206	42	248	14
Alcohol-related mortality (all causes)	1638	166	1804	100
All deaths	29232	26629	55861	In comparison, estimated
Percentage of all deaths that can be attributable to alcohol	5.6	0.6	3.2	total for 1990: 1.5

The overall relationship between average volume of alcohol consumption and all-cause mortality is thus J-shaped in established market economies for age groups under 45 years, where benefits of light to moderate consumption on IHD apply (Holman et al. 1996; Rehm et al. 2001c). In countries with a predominant pattern of irregular heavy drinking, no J-shape can be expected and the shape between alcohol and all-cause mortality is expected to increase monotonically.

The estimated percentage of alcohol-attributable mortality (3.2%) is more than double that estimated in the 1990 GBD study (3.2% vs 1.5%). There are several reasons for this increase. First, alcohol consumption has increased overall, especially in the very populous SEAR-B, SEAR-D and WPR-B subregions, including China and India. In addition, in these subregions we do not expect benefits of drinking, unless the current patterns of drinking change to the positive. Second, the relative impact of injuries and chronic disease on overall mortality, both of which are related to alcohol, has increased over the past 10 years. Third, the methodologies are not comparable between the two estimates. The 2000 estimate differs in the following three major respects.

- It is much more disaggregated, with respect both to burden categories and to regional data. Thus, the present work has included adult per capita data for almost all countries, and much more survey-related data than available for the 1990 estimates.
- The present exercise explicitly includes quantifiable patterns of drinking for both IHD and injuries, whereas the 1990 estimates were almost entirely based on volume of consumption. This difference is most striking with regard to IHD, where the 1990 study considered only beneficial effects. The current exercise estimates both beneficial and detrimental effects, depending on patterns of drinking.
- The meta-analyses on average volume of consumption and different disease outcomes have become much more refined in terms of methodology (compare, e.g. Corrao et al. 1999, 2000 with the methodology of English et al. 1995).

Finally, the estimates in this work are restricted to GBD disease categories. Several diseases related to alcohol could not be accounted for, most notably cardiac arrhythmias and heart failure. In the GBD disease categories, cardiac arrhythmias and heart failure would be part of "other cardiac conditions". We had neither epidemiological studies on the hazards for various diseases in this broad category nor any data on the relative proportion of cardiac arrhythmias and heart failure among other cardiac conditions by subregion and sex, in order to separate these diseases. In addition, oesophageal varices, acute and chronic pancreatitis and several conditions occurring during the perinatal period could not be included for similar reasons. However, their alcohol-attributable mor-

tality burden would be likely to be minor compared to the "other cardiac conditions" mentioned above.

4.2 DALYs

Alcohol-attributable DALYs are summarized in Table 12.25. See Appendix D for details by subregion.

The biggest shift in the relative impact of disease categories compared to the pattern for alcohol-caused mortality is seen for neuropsychiatric diseases. Neuropsychiatric diseases are often disabling, but rarely fatal, and this is reflected in the markedly higher proportion of overall disease burden due to alcohol (38%) in this category compared to alcohol-attributable mortality (6%). Males have far more (>5-fold) alcohol-related disease burden than females. The mortality and burden of disease figures presented here are net figures, where the alcohol-related beneficial effects on disease have been subtracted from its harmful effects. Therefore, the detrimental effects of alcohol on mortality, and disease burden in general, far outweigh the beneficial effects.

What are the most striking differences between subregions? Clearly alcohol-related burden is most detrimental in the developed world. Here 9.2% of the entire disease burden is attributable to alcohol, only exceeded by the burden attributable to tobacco and blood pressure (see Table 12.26 and WHO 2002). Here also, the ratio of males to females is lowest. However, as Table 12.26 indicates, alcohol also places a toll on health in the developed world, with relatively low mortality

Table 12.25 Global burden of disease in 2000 attributable to alcohol according to major disease categories (DALYs in 000s)

Disease or injury	*Males*	*Females*	*Total*	*Percentage of all alcohol-attributable DALYs*
Conditions arising during the perinatal period	68	55	123	0
Malignant neoplasm	3180	1021	4201	7
Neuro-psychiatric conditions	18090	3814	21904	38
Cardiovascular diseases	4411	–428	3983	7
Other non-communicable diseases (type II diabetes, liver cirrhosis)	3695	860	4555	8
Unintentional injuries	14008	2487	16495	28
Intentional injuries	5945	1117	7062	12
Alcohol-related disease burden all causes (DALYs)	49397	8926	58323	100
All DALYs	761562	693911	1455473	In comparison, estimated total for 1990: 3.5
Percentage of all DALYs that can be attributable to alcohol	6.5	1.3	4.0	

Table 12.26 Burden of disease in 2000 attributable to tobacco, alcohol and drugs, by development status and sex

	High-mortality developing subregions (AFR-D, AFR-E, AMR-D, EMR-D, SEAR-D)			*Low-mortality developing subregions (AMR-B, EMR-B, SEAR-B, WPR-B)*			*Developed subregions (AMR-A, EUR-A, EUR-B, EUR-C, WPR-A)*		
	Males	*Females*	*Total*	*Males*	*Females*	*Total*	*Males*	*Females*	*Total*
Total DALYs (000s)	420711	412052	832763	223181	185316	408497	117670	96543	214213
Smoking and oral tobacco	3.4%	0.6%	2.0%	6.2%	1.3%	4.0%	17.1%	6.2%	12.2%
Alcohol	2.6%	0.5%	1.6%	9.8%	2.0%	6.2%	14.0%	3.3%	9.2%
Illicit drugs	0.8%	0.2%	0.5%	1.2%	0.4%	0.8%	2.4%	1.2%	1.8%

patterns. Here the disease burden attributable to alcohol is the highest of all 26 risk factors examined in the CRA of the GBD study in 2000 (Ezzati et al. 2002). In high-mortality developing subregions, in Africa and parts of south-east Asia, alcohol is not yet one of the major risk factors. Here, the most important risk factors are underweight, unsafe sex, unsafe water, sanitation and hygiene, and other environmental factors. However, if past developments can help predict the future, we can expect that the alcohol-attributable burden will increase in these subregions along with economic development (see also section 5).

4.3 Conclusions

Alcohol causes a considerable burden of disease, in terms both of mortality and disability. While the total elimination of alcohol is not realistic, there are evidence-based policy measures that could substantially reduce the burden of alcohol. The recent review by Ludbrook et al. (2001) on measures to reduce alcohol misuse assessed the quality of evidence for four types of intervention aimed at reducing alcohol use and its consequences. Their findings coincide with a number of earlier reviews (e.g. Bruun et al. 1975; Edwards et al. 1994) and with the overview of Babor et al. (2003). In sum, the following measures were found quite effective:

- policy and legislative interventions, including taxation on alcohol sales, drink-driving laws, restricted licensing of outlets and advertising controls;
- law enforcement, for example random breath-testing of drivers;
- community interventions; and
- brief interventions.

On the other hand, mass media and awareness campaigns were not found to be very effective, although they seemed to be somewhat more popular with politicians and policy-makers.

Since these interventions exist and have been empirically shown to reduce the burden of both chronic and acute disease caused by alcohol, and also alcohol-attributable social harm, there is no justification for alcohol-related disease to remain at such a high level in many parts of the world.

5. Projections of the future

Quantitative projections regarding future exposure to alcohol are feasible only for average volume of drinking, since it is extremely difficult if not impossible to judge how drinking patterns will alter over time (see Figures 12.3–12.5).

Adult per capita consumption in EUR-A and EUR-B seems to be driven by long-term trends (Mäkelä et al. 1981; Simpura 1998). There

Figure 12.3 Adult per capita consumption in litres of absolute alcohol for the AFR, EMR and EUR subregions

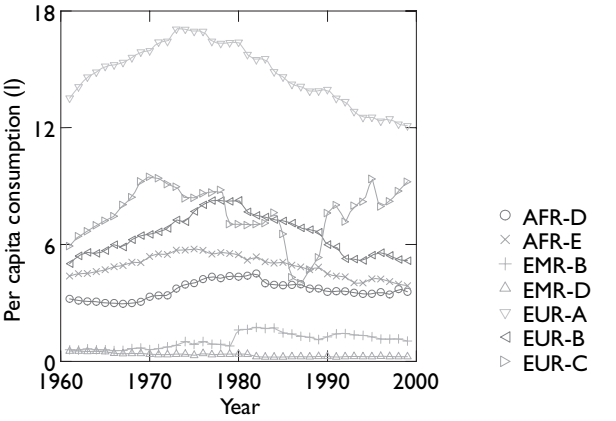
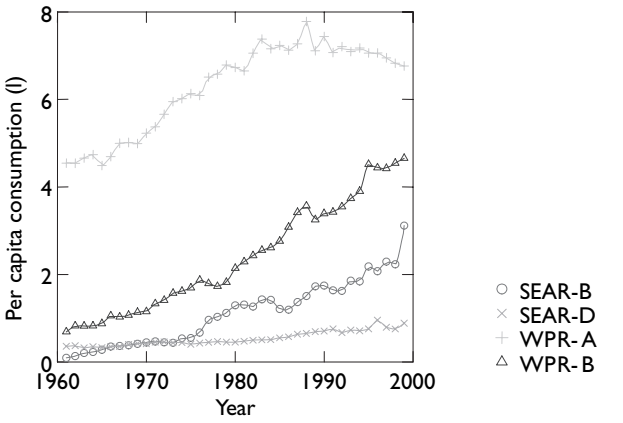
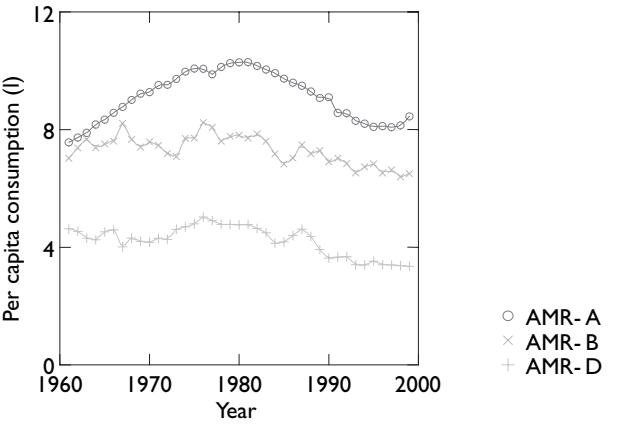


Figure 12.4 Adult per capita consumption in litres of absolute alcohol for the SEAR and WPR subregions



are indications that the current downward trend is levelling off. However, it is very hard to determine the period of long-term waves with short-term time series since 1960 or so. Thus, we predict a stable exposure for EUR-A and EUR-B at about the average level of consumption of the past 10 years. For EUR-C, the curve shows the most change. The dip at the end of the 1980s is due to the anti-alcohol campaign of the Gorbachev period in the former Soviet Union (White 1996). At the end

Figure 12.5 Adult per capita consumption in litres of absolute alcohol for the AMR subregions



of the campaign, alcohol consumption rose again to former levels. Again, since there is no clear trend after the campaign, we predict about the same level of consumption as the average of the years after the end of the Gorbachev campaign. No trends are apparent for EMR-B, EMR-D and AFR-D. Therefore, the most reasonable projection of future alcohol consumption would be the level of current consumption. To obtain more stable estimates, the average of the 1990s has been used.

For the South-East Asia and Western Pacific subregions, the following predictions appear justified based on the trend data shown in Figure 12.4. For WPR-A, there was an upward trend that seems to have stopped at the end of the 1980s; thus, the average volume of the 1990s was used as the best projection. For WPR-B and SEAR-B, consumption clearly increased and we modelled future consumption by a linear upward trend. The upward trend in SEAR-D was less pronounced, but nonetheless present, and we therefore again used the linear upward trend.

In the Americas, there has been a long wave of increasing and then decreasing consumption for North America (AMR-A), almost parallel to the European consumption. For AMR-B and AMR-D there are slight downward trends. Since the long-term wave seems to turn upwards again, and since the downward trends did not reach significance, it seems prudent to model the future for all three subregions at about the same as the average of the 1990s, as a stable estimate of the status quo.

Trends in drinking patterns have been studied in very special subsets of populations, such as youth in Europe (Hibell et al. 2000). But at the global level, for pattern of drinking, there is not even enough reliable data concerning the current situation, and thus quantitative predictions

are not possible. Therefore we assumed constant drinking patterns under a "business-as-usual" scenario. Projections of future adult per capita alcohol consumption are given in Table 12.27.

In three subregions (SEAR-B, SEAR-D and WPR-B) unrecorded consumption has to be added in order to predict burden, and these data need to be converted into drinking categories as above, based on surveys. Since we have neither survey data on the future nor any predictions for survey or unrecorded consumption, we suggest modelling future consumption as follows.

- For all subregions except SEAR-B, SEAR-D and WPR-B, predictions are based on 2000 data on proportions of drinking categories.
- Proportions of drinking categories II and III are increased by 2.1% over those for 2000 for SEAR-B and WPR-B, and by 0.7% for SEAR-D (Table 12.28). Of course, there are limits of linear increase, and we considered the current levels of consumption in the A subregions as upper limits.

In summary, the best estimates predict global increases in average consumption of alcohol, triggered by increases in developing and emerging economies in the South-East Asia and Western Pacific regions.

Table 12.27 Projections of adult per capita consumption by subregion, in litres of pure alcohol, excluding SEAR-B, SEAR-D and WPR-B

	Subregion					
	AFR-D	*AFR-E*	*AMR-A*	*AMR-B*	*AMR-D*	
Mean	3.543	4.127	8.276	6.669	3.462	
95% CI upper	3.608	4.258	8.428	6.826	3.558	
95% CI lower	3.478	3.996	8.125	6.512	3.366	
SD	0.085	0.171	0.197	0.204	0.125	
Trend	No trend	No trend	Long waves	No trend	No trend	
	EMR-B	*EMR-D*	*EUR-A*	*EUR-B*	*EUR-C*	*WPR-A*
Mean	1.248	0.238	12.632	5.372	8.316	7.012
95% CI upper	1.355	0.245	13.008	5.552	8.845	7.127
95% CI lower	1.142	0.231	12.255	5.192	7.787	6.897
SD	0.139	0.009	0.490	0.234	0.688	0.149
Trend	No trend	No trend	Long waves	No trend	No trend	Long waves

Table 12.28 Projections of adult per capita consumption by subregion, in litres of pure alcohol, for SEAR-B, SEAR-D and WPR-B

	Subregion		
	SEAR-B	*SEAR-D*	*WPR-B*
Increase per year in litres of pure alcohol after 2000	0.063	0.014	0.108
95% CI upper	0.068	0.016	0.115
95% CI lower	0.057	0.012	0.102
Increase in adult per capita consumption 2000 (%)	2.1	0.7	2.1
Trend	Linear upward	Linear upward	Linear upward
Shared variation: year and 1960–1999[a] consumption	88.0%	93.2%	96.8%

[a] The shared variation or "explained variance" denotes a measure of strength of the relationship, i.e. how much of the variation of adult per capita consumption is explained by the linear trend.

Acknowledgements

Parts of an earlier version of the contributions were made available on the WHO listserve for discussion, and we should like to thank all who responded. In addition, the authors would like to thank the following participants in the WHO expert meetings on alcohol as a risk factor for the burden of disease, held in Geneva on 29–30 January and 7–8 May 2001, for their valuable comments when revising prior versions: Mary Jane Ashley, Mary Assunta, Vivek Benegal, Susan Bondy, Ruth Bonita, Maximilian de Courten, Majid Ezzati, Oye Gureje, Wei Hao, Jennifer Hillebrand, Claudio Jeronimo da Silva, Håkan Leifman, Alan Lopez, Maria-Elena Medina-Mora, Zofia Mielecka-Kubien, Alexander Nemtsov, Ian B. Puddey, Margret Rihs-Middel, Leanne Riley, Kari J. Rummukainen, Shekhar Saxena, Raquel Shaw Moxam, Jussi Simpura, Bedirhan Üstün and Justin Willis.

Many people, too numerous to be listed here, contributed with data, and we wish to thank all of them for their help. Special thanks go to Ed Adlaf, Tom Greenfield, Wei Hao, Håkan Leifman, Maria-Elena Medina-Mora and Tim Stockwell for conducting data analyses or data searches specifically for this exercise. Special thanks also go to Ron Kessler and his team, who provided specific estimates for the point on alcohol and depression, without which it would have been impossible to estimate alcohol-attributable burden on depression.

WHO, the Swiss Federal Office of Public Health (contract no. 00.001588), the Swiss National Science Foundation, the Addiction Research Institute in Zurich, Switzerland, the Swiss Institute for the Prevention of Alcohol and Other Drug Problems in Lausanne, and the

Centre for Addiction and Mental Health in Toronto, provided financial and/or technical support for this study.

Parts of the assessment of relations between alcohol and disease were undertaken for the report *The social costs of alcohol consumption in Switzerland* and received financial support from the Swiss Federal Office of Public Health (grant no. 98-000794/8120).

Several anonymous reviewers, as well as the members of the editorial committee (Majid Ezzati, Alan Lopez, Anthony Rodgers), deserve special thanks for their help in finalizing the text, as does Steve Vander Hoorn for the repeated burden calculations.

Finally, the authors would like to thank the staff at the Swiss Institute for the Prevention of Alcohol and Other Drug Problems in Lausanne and the Addiction Research Institute in Zurich, especially Irene Bosshard and Elisabeth Grisel, for technical assistance.

Notes

1 See preface for an explanation of this term.

2 Social outcomes of alcohol consumption are defined as changes that affect the social behaviour of individuals, or their interaction with partners and other family members, or their circumstances (Rehm 2001). Social outcomes would include family problems, public disorder, or workplace problems (for overviews see Gmel and Rehm 2003; Klingeman and Gmel 2001). Social outcomes or consequences are not addressed in this chapter unless they are included in ICD-10. The majority of these problems are not covered by ICD-10, even though health is broadly defined by WHO to include well-being.

3 Intoxication and dependence are of course also influenced by biochemistry. However, since these two intermediate outcomes are central in shaping the effect of alcohol on many health and social outcomes, they are discussed separately. The other effects (e.g. on promotion of blood clot dissolution) are often specific for one disease or a limited group of diseases. Both intoxication and dependence are defined as health outcomes in ICD-10.

4 This is not to imply that there is no drinking to intoxication or occasions of heavy drinking in countries with established market economies; it is simply to say that this pattern of drinking is more common in countries with developing or emerging economies.

5 There are other ways of estimating unrecorded consumption, such as those based on available raw materials (see the estimates for the Russian Federation by Nemtsov 1998, 2000, 2002).

6 Surveys do not necessarily underestimate the recorded per capita consumption, even though the literature sometimes appears to imply it. For some countries, e.g. Mexico, adding up the figures from the survey may lead to higher estimates than the recorded per capita consumption.

7 This questionnaire can be obtained from the first author on request. It was finalized at a WHO expert meeting in Geneva, May 2001.

8 For comparison, a 75-cl bottle of wine contains about 70 g of pure alcohol.

9 As part of the process of developing these ratings, an earlier list of derived and assigned pattern values as shown in Table 12.3 was made available on a WHO listserve to a large number of key informants for critical assessment. This process resulted in the identification of local surveys, which helped improve the estimates.

10 This reasoning was also behind the list of those invited to a WHO workshop on unrecorded consumption in May 2001, where experts from Brazil, China, India, Nigeria and the Russian Federation met with other experts on the methodology of estimating unrecorded consumption to discuss current estimates and develop a methodology to improve data gathering.

11 Ledermann had been the first to claim that the distribution of alcohol consumption among drinkers is log-normal. Subsequent research found the exact shape to be different but still approximately log-normally distributed (e.g. Duffy 1986 and rejoinders).

12 These analyses are sometimes also called hierarchical linear analyses (Bryk and Raudenbush 1992). Since the term "hierarchical" is ambivalent (in sociology it has also been used to describe stepwise regression), we exclusively use the term "multilevel" in this chapter.

13 In the statistical literature units are called sections, hence the method used is called cross-sectional time series analysis. In our case, countries are sections.

14 Europe was taken as a pilot as data are most available there. The current analysis included data from 81 countries for injuries and 74 countries for IHD, most of them outside Europe.

15 Year is only controlling for the linear part of the time structure. However, sensitivity analyses were carried out to estimate the performance of the method used.

16 "Random" does not mean that the underlying relationships are completely random. Effects may be partly deterministic owing, for example, to different policies. The term "random" here means that effects across sections or countries cannot be estimated without error, and the errors are assumed to have a random distribution.

17 If the patterns were estimated as deviations from mean patterns, then the value of γ_{10} would reflect the average impact of adult per capita consumption.

18 Even for biologically based relationships, the relationship could be moderated by other factors such as diet (e.g. alcohol may be related to breast cancer through hormonal effects, but diet also affects hormonal levels and this may have an influence on the alcohol–breast cancer relationship). However, except for IHD, meta-analyses on alcohol and chronic disease have yielded fairly similar effects for different populations, so the assumption of applying the same effect for average volume of drinking is probably justified.

19 Such "categorical" attribution is quite different from the statistical estimation used in other epidemiological studies. For the usual derivation of alcohol-attributable fractions see Rothman and Greenland (1998b).

20 Type of beverage has been excluded so far from our consideration of patterns of drinking. While the evidence is not conclusive on the effect of beverage on all-cause mortality or on cardiovascular disease (e.g. Gruenewald et al. 2000; Kerr et al. 2000; Rimm et al. 1996), there are some indications that cancers of the gastrointestinal tract are differentially influenced by alcohol in higher concentration.

21 Part of this lack of an influence on patterns of cancer risk may be due to methodological reasons. Most epidemiological studies measure only volume of consumption and model only monotonically increasing trends, and thus could not detect any influence of patterns of drinking even if they were present.

22 In the Inter-American Investigation of Mortality, which studied 4000 deaths in each of 12 cities in 1962–1964, the final assignment of all deaths from cirrhosis "with mention of alcoholism" was 80.4% of all cirrhosis deaths. About half of these had been "without mention" on the death certificate. Only in Santiago and Mexico City was the final assignment for "with mention" less than twice the initial number. The study used searches of medical records and interviews with decedents' families and attending physicians to reassign deaths from the initial classification (Room 1972, based on Puffer and Griffith 1967).

23 IHD is used here for denoting all diseases with ICD-9 rubrics 410–414 (ICD-10: I20–I25). The same categories have also been labelled coronary heart disease (CHD).

24 DisMod is a software tool that may be used to check the internal consistency of epidemiological estimates of incidence, prevalence, duration and case fatality for diseases. The latest version (DisMod II) is distributed by WHO:

http://www3.who.int/whosis/burden/burden_dismod/burden_dismod_dismod2.cfm?path=whosis,burden,burden_dismod,burden_dismod_dismod2&language=english.

25 The notion of a causal contributing role is at the heart of the epidemiological concept of causality (Rothman and Greenland 1998). According to such standards, as explained in the text, the causal role of alcohol in intentional injuries is established. According to criteria used in criminology, this may not be the case.

26 Part of the effect of alcohol on aggression or on other more social outcomes is due to psychological variables. The term "expectations" denotes the individual predictions and expectancies of what will happen after consumption of alcohol. Experimental research has demonstrated that such psychological variables play a role in determining outcome.

27 Often traffic accidents are described as if the environment's effects are totally independent of the person's behaviour. However, tired drunk-drivers on the road at 03:00 might well not have been there if they had not been drinking. Intentionality (and alcohol's effects on it) forms part of what are called "accidents".

28 Odds = $p/(1 - p)$.

References

Abel EL (1997) Maternal alcohol consumption and spontaneous abortion. *Alcohol and Alcoholism*, **32**:211–219.

Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M (2000) *Age standardization of rates: a new WHO world standard*. (GPE Discussion Paper No. 31. EIP/GPE/EBD). World Health Organization, Geneva.

Ajani UA, Cook N, Hebert P et al. (1998) Alcohol consumption and incidence of malignant neoplasms: the physicians' health study. *American Journal of Epidemiology*, **147**:S45.

Ajani UA, Hennekens C, Spelsberg A, Manson J (1999) Alcohol consumption and risk of type two diabetes mellitus. *American Journal of Epidemiology*, **149**:S3.

Alpert JE, Fava M, Uebelacker LA et al. (1999) Patterns of axis I comorbidity in early-onset versus late-onset major depressive disorder. *Biological Psychiatry*, **46**:202–211.

Alvear J, Andreani S, Cortés F (1998) Fetal alcohol syndrome and fetal alcohol effects: importance of early diagnosis and nutritional treatment. *Revista Medica de Chile*, **126**:407–412.

American Psychiatric Association (1994) *DSM-IV Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association, Washington, DC.

Ammann RW, Heitz PU, Klöppel G (1996) Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. *Gastroenterology*, **111**:224–231.

Apte MV, Wilson JS, Korsten MA (1997) Alcohol-related pancreatic damage: mechanisms and treatment. *Alcohol Health and Research World*, **21**:13–20.

Ashley MJ, Rehm J, Bondy S, Single E, Rankin J (2000) Beyond ischemic heart disease: are there other health benefits form drinking alcohol? *Contemporary Drug Problems*, **27**:735–777.

Attili AF, Scafato E, Marchioli R, Marfisi RM, Festi D (1998) Diet and gallstones in Italy: the cross-sectional MICOL results. *Hepatology*, **27**:1492–1598.

Babor T, Caetano R, Casswell S et al. (2003) *Alcohol: no ordinary commodity. Research and public policy.* Oxford University Press, Oxford.

Bagnardi V, Blangiardo M, La Vecchia C, Corrao G (2001) Alcohol consumption and the risk of cancer. *Alcohol Research and Health*, **25**:236–270.

Bandera EV, Freudenheim JL, Vena JE (2001) Alcohol and lung cancer: a review of the epidemiologic evidence. *Cancer Epidemiology, Biomarkers and Prevention*, **10**:813–821.

Baraona E, Lieber CS (1998) Alcohol and lipids. In: *The Consequences of Alcoholism*. Galanter M, ed. Plenum Press, New York.

Beaglehole R, Jackson R (1992) Alcohol, cardiovascular diseases and all causes of death: a review of the epidemiological evidence. *Drug and Alcohol Review*, **11**:175–290.

Beilin LJ, Puddey IB, Burke V (1996) Alcohol and hypertension—kill or cure? *Journal of Human Hypertension*, **10**:S1–5.

Berger K, Ajani UA, Kase CS et al. (1999) Light-to-moderate alcohol consumption and the risk of stroke among U.S. male physicians. *New England Journal of Medicine*, **341**:1557–1564.

Bijleveld CCJH, van der Kamp LJT (1998) *Longitudinal data analysis: designs, models and methods*. Sage Publications Ltd., London.

Biork JM, Dougherty DM, Moeller FG (1999) Symptomatology of depression and anxiety in female "social drinkers". *American Journal of Drug and Alcohol Abuse*, **25**:173–182.

Bland JM, Altman DG (1994) Statistics notes: correlation, regression, and repeated data. *British Medical Journal*, **308**:896.

Blixen CE, McDougall GJ, Suen LJ (1997) Dual diagnosis in elders discharged from a psychiatric hospital. *International Journal of Geriatric Psychiatry*, **12**:307–313.

Bobak M, McKee M, Rose R et al. (1999) Alcohol consumption in a national sample of the Russian population. *Addiction*, **94**:857–866.

Bobak M, Marmot M (1999) Alcohol and mortality in Russia: is it different than elsewhere? *Annals of Epidemiology*, **9**:335–338.

Bobak M, Skodova Z, Marmot M (2000) Effect of beer drinking on risk of myocardial infarction: population based case-control study. *British Medical Journal*, **320**:1378–1379.

Bode C, Bode JC (1997) Alcohol's role in gastrointestinal tract disorders. *Alcohol Health and Research World*, **21**:76–83.

Bondy SJ (1996) Drinking patterns and their consequences: report from an international meeting—overview of studies on drinking patterns and consequences. *Addiction*, **91**:1663–1674.

Bondy S, Rehm J (1998) The interplay of drinking patterns and other determinants of health. *Drug and Alcohol Review*, **17**:399–411.

Borkenstein RF, Crowther RF, Shumate RP (1964) *The role of the drinking driver in traffic accidents*. Department of Police Administration, Bloomington, IN.

Boutron MC, Faivre J, Dop MC, Quipourt V, Senesse P (1995) Tobacco, alcohol, and colorectal tumors, a multistep process. *American Journal of Epidemiology*, **141**:1038–1046.

Bowlin SJ, Leske MC, Varma A, Nasca P, Weinstein A, Caplan L (1997) Breast cancer risk and alcohol consumption: results from a large case-control study. *International Journal of Epidemiology*, **26**:915–923.

Bradley KA, Badrinath S, Bush K, Boyd-Wickizier J, Anawalt B (1998) Medical risks for women who drink alcohol. *Journal of General Internal Medicine*, **13**:627–639.

Breslow RA, Weed DL (1998) Review of epidemiologic studies of alcohol and prostate cancer: 1971–1996. *Nutrition and Cancer*, **30**:1–13.

Brewers Association of Canada (1997) *Alcoholic beverage taxation and control policies*. 9th edn. Brewers Association of Canada, Ottawa.

Britton A, McKee M (2000) The relation between alcohol and cardiovascular disease in Eastern Europe: explaining the paradox. *Journal of Epidemiology and Community Health*, **54**:328–332.

Brown SA, Schuckit MA (1988) Changes in depression among abstinent alcoholics. *Journal of Studies on Alcohol*, **49**:412–417.

Bruemmer B, White E, Vaughan TL, Cheney CL (1997) Fluid intake and the incidence of bladder cancer among middle-aged men and women in a three-county area of western Washington. *Nutrition and Cancer*, **29**:163–168.

Bruun K, Edwards G, Lumio M et al. (1975) *Alcohol control policies in public health perspective*. Finnish Foundation for Alcohol Studies, Helsinki.

Bryk AS, Raudenbush SW (1992) *Hierarchical linear models: applications and data analysis methods*. Advanced Quantitative Techniques in the Social Sciences. Sage Publications, Newbury Park, CA.

Bryk AS, Raudenbush SW, Congdon R (1996) *HLM: Hierarchical linear and nonlinear modeling with the HLM/2L and HLM/3L programs*. Scientific Software International, Inc., Chicago, IL.

Bushman BJ (1997) Effects of alcohol on human aggression: validity of proposed mechanisms. In: *Recent developments in alcoholism. Alcohol and violence*. Galanter M, ed. Plenum, New York.

Camargo CA, Hennekens C, Gaziano JM, Glynn RJ, Manson J, Stampfer MJ (1997) Prospective study of moderate alcohol consumption and mortality in US male physicians. *Archives of Internal Medicine*, **157**:79–85.

Caroli-Bosc FX, Deveau C, Peten EP et al. (1998) Cholelithiasis and dietary risk factors: an epidemiologic investigation in Vidauban, southeast France. General practitioner's group of Vidauban. *Digestive Diseases and Sciences*, **43**:2131–2137.

Catalano P, Chikritzhs T, Stockwell T, Webb M, Rohlin C-J, Dietze P (2001) *Trends in per capita alcohol consumption in Australia 1990/91–1998/99*. No. 4. National Drug Research Institute, Perth.

Chadwick DJ, Goode JA (1998) *Alcohol and cardiovascular diseases*. John Wiley & Sons, Chichester.

Chen CY, Lu CL, Lee PC, Wang SS, Chang FY, Lee SD (1999) The risk factors for gallstone disease among senior citizens: an Oriental study. *Hepatogastroenterology*, **46**:1607–1612.

Chenet L, McKee M, Leon D, Shkolnikov V, Vassin S (1998) Alcohol and cardiovascular mortality in Moscow; new evidence of a causal association. *Journal of Epidemiology and Community Health*, **52**:772–774.

Chermack ST, Giancola HM (1997) The relation between alcohol and aggression: An integrated biopsychosocial conceptualization. *Clinical Psychology Review*, **17**:621–649.

Cherpitel CJ (1992) The epidemiology of alcohol-related trauma. *Alcohol Health and Research World*, **16**:191–196.

Cherpitel CJ (1994) Alcohol and casualties: a comparison of emergency room and coroner data. *Alcohol and Alcoholism*, **29**:211–218.

Cherpitel CJ (1996a) Drinking patterns and problems and drinking in the event: an analysis of injury by cause among casualty patients. *Alcoholism, Clinical and Experimental Research*, **20**:1130–1137.

Cherpitel CJ (1996b) Alcohol in fatal and nonfatal injuries: a comparison of coroner and emergency room data from the same county. *Alcoholism, Clinical and Experimental Research*, **20**:338–342.

Cherpitel CJ, Tam T, Midanik L, Caetano R, Greenfield T (1995) Alcohol and non-fatal injury in the U.S. general population: A risk function analysis. *Accident Analysis Prevention*, **27**:651–661.

Church MW, Eldis F, Blakley BW, Bawle EV (1997) Hearing, language, speech, vestibular, and dentofacial disorders in fetal alcohol syndrome. *Alcoholism, Clinical and Experimental Research*, **21**:227–237.

Clarke R, Shipley M, Lewington S et al. (1999) Underestimation of risk associations due to regression dilution in long term follow-up of prospective studies. *American Journal of Epidemiology*, **150**:341–353.

Collins D, Lapsley H (1991) *Estimating the economic costs of drug abuse in Australia*. Vol. No. 15. Commonwealth of Australia, Canberra.

Connor PD, Streissguth AP (1996) Effects of prenatal exosure to alcohol across the life span. *Alcohol Health and Research World*, **20**:170–174.

Cook PJ, Tauchen G (1982) The effect of liquor taxes on heavy drinking. *Addiction*, **13**:379–390.

Corrao G, Arico S, Zambon A, Torchio P, Di Orio F (1997) Female sex and the risk of liver cirrhosis. Collaborative groups for the study of liver diseases in Italy. *Scandinavian Journal of Gastroenterology*, **32**:1174–1180.

Corrao G, Bagnardi V, Zambon A, Arico S (1999) Exploring the dose–response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction*, **94**:1551–1573.

Corrao G, Bagnardi V, Zambon A, Torchio P (1998) Meta-analysis of alcohol intake in relation to risk of liver cirrhosis. *Alcohol and Alcoholism*, **33**:381–392.

Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K (2000) Alcohol and coronary heart disease: a meta-analysis. *Addiction*, **95**:1505–1523.

Corrao G, Zambon A, Torchio P et al. (1998) Attributable risk for symptomatic liver cirrhosis in Italy. *Journal of Hepatology*, **28**:608–614.

Criqui MH, Cowan LD, Tyroler JA et al. (1987) Lipoprotein mediators for the effects of alcohol consumption and cigarette smoking on cardiovascular mortality. Results from the lipid research clinics follow-up study. *American Journal of Epidemiology*, **126**:629–637.

Criqui MH, Ringek BL (1994) Does diet or alcohol explain the French paradox? *The Lancet*, **344**:1719–1723.

Curtis AB, Sherman JA, Strogatz DS, Raghunathan TE, Siobàn H (1997) Alcohol consumption and changes in blood pressure among African Americans—The Pitt county study. *American Journal of Epidemiology*, **146**:727–733.

Dackis CA, Gold MS, Pottash ALC, Sweeney DR (1986) Evaluating depression in alcoholics. *Psychiatry Research*, **17**:105–109.

Davidson KM (1995) Diagnosis of depession in alcohol dependence: changes in prevalence with drinking status. *British Journal of Psychiatry*, **166**:199–204.

De Stefani E, Boffetta P, Carzoglio J, Mendilaharsu S, Deneo-Pellegrini H (1998) Tobacco smoking and alcohol drinking as risk factors for stomach cancer: a case-control study in Uruguay. *Cancer Causes Control*, **9**:321–329.

de Vries JHM, Lemmens P, Pietinen P, Kok FP (1999) Assessment of alcohol consumption. In: *Health issues related to alcohol consumption*. 2nd edn. Macdonald I, ed. Blackwell Science Ltd., London.

Devlin NJ, Scuffham PA, Bung LJ (1997) The social costs of alcohol abuse in New Zealand. *Addiction*, **92**:1491–1505.

Doll R (1998) The benefit of alcohol in moderation. *Drug and Alcohol Review*, **17**:353–363.

Doll R, Peto R, Hall E, Whealey K, Gray R (1994) Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *British Medical Journal*, **309**:911–918.

Donato F, Boffetta P, Fazioli R, Aulenti V, Gelatti U, Porru S (1997) Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia, northern Italy. *European Journal of Epidemiology*, **13**:795–800.

Drummond DC (1990) The relationship between alcohol dependence and alcohol-related problems in a clinical population. *British Journal of Addiction*, **85**:357–366.

Duffy J-C (1986) Distribution of alcohol consumption: 30 years on. *British Journal of Addiction*, **81**:735–741.

Dyer AR, Stamler J, Paul O et al. (1977) Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. *Circulation*, **56**:1067–1074.

Eckardt MJ, File SE, Gessa GL et al. (1998) Effects of moderate alcohol consumption in the central nervous system. *Alcoholism, Clinical and Experimental Research*, **22**:998–1040.

Edwards G, Anderson P, Babor TF et al. (1994) *Alcohol policy and the public good*. Oxford University Press, Oxford.

Ellison LF, Stokes J, Gibbons L et al. (1998) Monographs series on aging-related diseases: X. Prostate cancer. *Chronic Diseases in Canada*, **19**:1–18.

Emanuele N, Emanuele MA (1997) The endocrine system: alcohol alters critical hormonal balance. *Alcohol Health and Research World*, **21**:53–64.

English DR, Holman CDJ, Milne E et al. (1995) *The quantification of drug caused morbidity and mortality in Australia 1995*. Commonwealth Department of Human Services and Health, Canberra.

European Addiction Research (2001) Special issue on alcohol addiction treatment. *European Addiction Research*, **7**: 95–157.

Evans C, Chalmers J, Capewell S et al. (2000) "I don't like Mondays" day of the week of coronary heart disease deaths in Scotland: study of routinely collected data. *British Medical Journal*, **320**:218–219.

Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJL, the Comparative Risk Assessment Collaborating Group (2002) Selected major risk factors and global and regional burden of disease. *The Lancet*, **360**:1347–1360.

Facchini F, Chen YD, Reaven GM (1994) Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. *Diabetes Care*, **17**:115–119.

Faden VB, Graubard BI, Dufour M (1997) The relationship of drinking and birth outcome in a US national sample of expectant mothers. *Paediatric and Perinatal Epidemiology*, **11**:167–180.

Fahrenkrug H, Rehm J (1994) Trinkkontexte und Freizeitaktivitäten in der Vorphase alkoholbezogener Strassenverkehrsunfälle junger Fahrerinnen und Fahrer in der Schweiz. *Sucht*, **41**:169–180.

Fillmore KM (1988) *Alcohol use across the life course: a critical review of 70 years of international longitudinal research*. Addiction Research Foundation, Toronto.

Fillmore KM, Golding JM, Graves KL et al. (1998) Alcohol consumption and mortality. III. Studies of female populations. *Addiction*, **93**:219–229.

Flanagan DEH, Moore VM, Godsland IF, Cockington RA, Robins JS, Phillips DI (2000) Alcohol consumption and insulin resitance in young adults. *European Journal of Clinical Investigation*, **30**:297–301.

Foppa M, Fuchs FD, Preissler L, Andrighetto A, Rosito GA, Duncan BB (1999) Wine with the noon meal lowers post meal blood pressure: randomized trial in centrally obese hypertensive patients. *Hypertension*, **33**:119.

Freedland E, McMicken D, D'Onofrio G (1993) Alcohol and trauma. *Emergency Medicine Clinics of North America*, **11**:225–239.

Friedman HS (1998) Cardiovascular effects of alcohol. In: *The Consequences of Alcoholism*. Galanter M, ed. Plenum Press, New York.

Friedman L-A, Kimball A-W (1986) Coronary heart disease mortality and alcohol consumption in Framingham. *American Journal of Epidemiology*, **124**:481–489.

Fuchs CS, Stampfer MJ, Colditz GA et al. (1995) Alcohol consumption and mortality among women. *New England Journal of Medicine*, **332**:1245–1250.

Fuller M (1995) Alcohol use and injury severity in trauma patients. *Journal of Affective Disorders*, **14**:47–53.

Galduróz JCF, Noto AR, Nappo SA, Carlini EA (2000) *I levantomento domicilar nacional sobre o uso de drogas psicotrópicas. Parte A: Estudo envolvendo as 24 majores cidades do estado de São Paulo 1999*. CEBRID, São Paulo.

Gapstur SM, Potter JD, Folsom AR (1994) Alcohol consumption and colon and rectal cancer in postmenopausal women. *International Journal of Epidemiology*, **23**:50–57.

Gentry RT (2000) Effect of food on the pharmocokinetics of alcohol consumption. *Alcoholism, Clinical and Experimental Research*, **24**:403–404.

Gibson S, Becker J (1973) Changes in alcoholics' self-reported depression. *Quarterly Journal of Studies on Alcohol*, **34**:829–836.

Giesbrecht N, Greenfield TK, Lemmens P, Österberg E (2000) Estimating alcohol consumption: measurement and policy issues related to legal and illegal sources of alcohol. *Contemporary Drug Problems*, **27**:221–233.

Gmel G, Gutjahr E (2001) Alcohol consumption and social harm: quantitative research methodology. In: *Mapping the social consequences of alcohol consumption*. Klingeman H, Gmel G, eds. Kluwer Academic Publishers, Dordrecht.

Gmel G, Rehm J (2003) Harmful alcohol use. *Alcohol Research and Health*, **27**:52–62.

Gmel G, Rehm J, Frick U (2001) Methodological approaches to conducting pooled cross-sectional time series analysis: the example of the EU states. *European Addiction Research*, **7**:128–137.

Gmel G, Rehm J, Room R, Greenfield TK (2000) Dimensions of alcohol-related social harm in survey research. *Journal of Substance Abuse*, **12**:113–138.

Goldberg DM, Hahn SE, Parkes JG (1995) Beyond alcohol: beverage consumption and cardiovascular mortality. *Clinica Chimica Acta*, **237**:155–187.

Graham K, Leonard KE, Room R et al. (1998) Current directions in research on understanding and preventing intoxicated aggression. *Addiction*, **93**:659–676.

Graham K, Schmidt G (1999) Alcohol use and psychosocial well-being among older adults. *Journal of Studies on Alcohol*, **60**:345–351.

Graham K, Wells S (2001) Aggression among young adults in the social context of the bar. *Addiction Research*, **9**:193–219.

Graham K, West P (2001) Alcohol and crime. In: *International handbook of alcohol dependence and problems*. Heather N, Peters TJ, Stockwell T, eds. John Wiley & Sons, London.

Graham K, West P, Wells S (2000) Evaluating theories of alcohol-related aggression using observations of young adults in bars. *Addiction*, **95**:847–863.

Grant BF, Harford TC (1995) Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. *Drug and Alcohol Dependence*, **39**:197–206.

Grant BF, Pickering RP (1997) Familial aggregation of DSM-IV alcohol disorders: examination of the primary-secondary distinction in a general population sample. *Journal of Nervous and Mental Disease*, **185**:335–343.

Greene WH (2000) *Econometric analysis*. Prentice Hall, Upper Saddle River, NJ.

Greenfield TK (2001) Individual risk of alcohol-related disease and problems. In: *International handbook of alcohol dependence and problems*. Heather N, Peters TJ, Stockwell T, eds. Wiley & Sons, Chichester.

Grobbee DE, Rimm EB, Keil U, Renaud SC (1999) Alcohol and the cardiovascular system. In: *Health issues related to alcohol consumption.* Macdonald I, ed. Blackwell & ILSI, Oxford.

Groves RM (1989) *Survey errors and survey costs.* John Wiley & Sons, New York.

Gruenewald PJ, Hermos JA, Rehm J et al. (2000) Commentaries on Kerr et al.'s "Beverage-specific alcohol consumption and cirrhosis mortality in a group of English-speaking beer-drinking countries". *Addiction*, **95**:347–358.

Gruenewald PJ, Mitchell PR, Treno AJ (1996) Drinking and driving: drinking patterns and drinking problems. *Addiction*, **91**:1649.

Gruenewald PJ, Nephew T (1994) Drinking in California: theoretical and empirical analysis of alcohol consumption patterns. *Addiction*, **89**:707–723.

Gruenewald PJ, Ponicki WR (1995) Relationship of alcohol sales to cirrhosis mortality. *Journal of Studies on Alcohol*, **56**:635–641.

Gruenewald PJ, Treno AJ, Mitchell PR (1996) Drinking patterns and drinking behaviours: theoretical models of risky acts. *Contemporary Drug Problems*, **23**:407–440.

Gurr M (1996) *Alcohol: health issues related to alcohol consumption.* 2nd edn. ILSI Europe, Brussels.

Gutjahr E, Gmel G (2001) *Die sozialen Kosten des Alkoholkonsums in der Schweiz: Epidemiologische Grundlagen 1995–1995*. Forschungsbericht Nr. 36. Schweizerische Fachstelle für Alkohol- und andere Drogenprobleme (SFA), Lausanne.

Gutjahr E, Gmel G, Rehm J (2001) Relation between average alcohol consumption and disease: an overview. *European Addiction Research*, **7**:117–127.

Habbick BF, Snyder RE (1997) Mortality in foetal alcohol syndrome. *Canadian Journal of Public Health*, **88**:181–183.

Haberman PW, Weinbaum DF (1990) Liver cirrhosis with and without mention of alcohol as cause of death. *British Journal of Addiction*, **85**:217–222.

Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH (1997) Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the lowa women's health study. *Cancer Epidemiology, Biomarkers and Prevention*, **6**:1081–1086.

Hart CL, Smith GD, Hole DJ, Hawthorne VM (1999) Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort study of Scottish men with 21 years of follow up. *British Medical Journal*, **318**:1725–1729.

Harwood H, Fountain D, Livermore G, The Lewin Group (1998) *The economic costs of alcohol and drug abuse in the United States, 1992*. Vol. No. 98-4327. U.S. Department of Health and Human Services, National Institue on Drug Abuse (NIDA), Rockville, MD.

Hasegawa K, Mukasa H, Nakazawa Y, Kodama H, Nakamura K (1991) Primary and secondary depression in alcoholism: Clinical features and family history. *Drug and Alcohol Dependence*, **27**:275–281.

Hatanaka M (1996) *Time-series-based econometrics. Unit root and co-intergration.* Oxford University Press, New York.

Hayes RB, Brown LM, Schoenberg JB et al. (1996) Alcohol use and prostate cancer risk in US blacks and whites. *American Journal of Epidemiology*, **143**:692–697.

Hemström Ö (2001) Per capita alcohol consumption and ischaemic heart disease mortality. *Addiction*, **96**:S93–112.

Hendriks HF, Veenstra J, Velthuis-te Wierik EJ, Schaafsma G, Kluft C (1994) Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *British Medical Journal*, **308**:1003–1006.

Hesselbrock V, Tennen H, Stabenau J, Hesselbrock M (1983) Affective disorder in alcoholism. *International Journal of the Addictions*, **18**:435–444.

Hiatt RA, Armstrong MA, Klatsky AL, Sidney S (1994) Alcohol consumption, smoking, and other risk factors and prostate cancer in a large health plan cohort in California (United States). *Cancer Causes Control*, **5**:66–72.

Hibell B, Andersson B, Ahlström S et al. (2000) *The 1999 ESPAD Report. Alcohol and other drug use among students in 30 European countries*. Pompidou Group; Council of Europe, Stockholm.

Hilarski C; Wodarki JS (2001) Comorbid substance abuse and mental illness: Diagnosis and treatment. *Journal of Social Work Practice in the Addictions*, **1**:105–119.

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, **58**:295–300.

Hillbom M (1998) Alcohol consumption and stroke: benefits and risks. *Alcoholism, Clinical and Experimental Research*, **22**:S352–358.

Hillbom M, Juvela S, Karttunen V (1998) Mechanisms of alcohol-related strokes. In: *Alcohol and Cardiovascular Diseases.* Chadwick DJ, Goode JA, eds. John Wiley & Sons, Inc., New York.

Hingson R, Howland J (1987) Alcohol as a risk factor for injury or death resulting from accidental falls: a review of the literature. *Journal of Studies on Alcohol*, **48**:212–219.

Hingson R, Howland J (1993) Alcohol and non-traffic unintended injuries. *Addiction*, **88**:877–883.

Hoaken PNS, Assaad JM, Phil RO (1998) Cognitive functioning and the inhibition of alcohol-induced aggression. *Journal of Studies on Alcohol*, **59**:599–607.

Holman CD, English DR, Milne E, Winter MJ (1996) Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations. *Medical Journal of Australia*, **164**:141–145.

Horn-Ross PL, Ljung BM, Morrow M (1997) Environmental factors and the risk of salivary gland cancer. *Epidemiology*, **8**:414–419.

Hox JJ (1995) *Applied multilevel analysis.* 2nd edn. TT-Publikaties, Amsterdam.

Hurst PM, Harte WJ, Firth WJ (1994) The Grand Rapids dip revisited. *Accident, Analysis and Prevention*, **26**:647–654.

Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W (2001) Effect of alcohol consumption on systemic markers of inflammation. *The Lancet*, **357**:763–767.

Isbell H, Fraser HF, Wikler A, Belleville RE, Eisenman AJ (1955) Experimental study of the etiology of "rum fits" and delirium tremens. *Quarterly Journal of Studies on Alcohol*, **16**:1–33.

Ito TA, Miller N, Pollock VE (1996) Alcohol and aggression: a meta-analysis on the moderating effects of inhibitory cues, triggering events, and self-focused attention. *Psychological Bulletin*, **120**:60–82.

Jackson R (1994) Cardiovascular disease and alcohol consumption: evidence of benefit of epidemiological studies. *Contemporary Drug Problems*, **21**:5–24.

Jacques PF, Bostom AG, Wilson PW, Rich S, Rosenberg IH, Selhub J (2001) Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. *American Journal of Clinical Nutrition*, **73**:613–621.

Jallon P, Smadja D, Cabre P et al. (1998) Crises épileptiques, épilepsies et facteurs de risque: expérience d'une enquête en Martinique. *Revue Neurologique*, **154**:408–411.

Jeavons CM, Taylor SP (1985) The control of alcohol-related aggression: redirecting the inebriate's attention to socially appropriate conduct. *Aggressive Behavior*, **11**:93–101.

Ji BT, Chow WH, Yang G et al. (1996) Influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer*, **77**:2449–2457.

Jutkovitz JM, Hongsook E (1994) Drug prevalence in Latin America and Caribbean countries: a cross-national analysis. *Drugs: Education, Prevention and Policy*, **1**:199–251.

Kao WHL, Brancati FL, Boland LL, Watson RL, Puddey IB (1998) Gender differences in the association of alcohol consumption and the risk of type 2 diabetes mellitus: the Atherosclerosis Risk in Communities (ARIC) study. *American Journal of Epidemiology*, **147**:S60.

Kauhanen J, Kaplan GA, Goldberg DE et al. (1997b) Frequent hangovers and cardiovascular mortality in middle-aged men. *Epidemiology*, **8**:310–314.

Kauhanen J, Kaplan GA, Goldberg DE, Salonen JT (1997a) Beer drinking and mortality: results from the Kuopio ischemic heart disease risk factors study, a prospective population based study. *British Medical Journal*, **315**:846–851.

Keil U, Chambless LE, Döring A, Filipiak B, Stieber J (1997) The relation of alcohol intake to coronary heart disease and all-cause mortality in a beer-drinking population. *Epidemiology*, **8**:150–156.

Kerr WC, Fillmore KM, Marvy P (2000) Beverage-specific alcohol consumption and cirrhosis mortality in a group of English-speaking beer-drinking countries. *Addiction*, **95**:339–346.

Kessler RC (1998) Sex differences in DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Journal of the American Medical Women's Association*, **53**:148–158.

Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC (1997) Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Archives of General Psychiatry*, **54**:313–321.

Kessler RC, Nelson CB, McGonagle KA, Edlund MJ, Frank RG, Leaf PJ (1996) Epidemiology of co-occuring addictive and mental disorders: Implications for prevention and service utilization. *American Journal of Orthopsychiatry*, **66**:17–31.

Kiechl S, Willeit J, Poewe W et al. (1996) Insulin sensitivity and regular alcohol consumption: large, prospective, cross-sectional population study (Bruneck study). *British Medical Journal*, **313**:1040–1044.

Kitamura A, Iso H, Sankai T et al. (1998) Alcohol intake and premature coronary heart disease in urban Japanese men. *American Journal of Epidemiology*, **147**:59–65.

Klatsky AL (1995) Cardiovascular effects of alcohol. *Scientific American. Science and Medicine*, **2**:28–37.

Klatsky AL (1996) Alcohol, coronary heart disease, and hypertension. *Annual Review of Medicine*, **47**:149–160.

Klingeman H, Gmel G (2001) *Mapping the social consequences of alcohol consumption*. Kluwer Academic Publishers, Dordrecht.

Knuiman MW, Vu HT (1996) Risk factors for stroke mortality in men and women: the Busselton Study. *Journal of Cardiovascular Risk*, **3**:447–452.

Kohlmeier L, Mendez M (1997) Controversies surrounding diet and breast cancer. *Proceedings of the Nutrition Society*, **56**:369–382.

Koskinen P, Kupari M, Leinonen H, Luomanmaki K (1987) Alcohol and new onset atrial fibrillation: a case-control study of a current series. *British Heart Journal*, **57**:468–473.

Kozarevic D, Demirovic JTG et al. (1982) Drinking habits and coronary heart disease. The Yugoslavia cardiovascular disease study. *American Journal of Epidemiology*, **116**:748–758.

Kreft IGG, de Leeuw J (1998) *Introducing multilevel modelling*. ISM Introducing Statistical Methods. 2nd edn. Sage Publications, London.

Krüger HP, Utzelmann H-D, Berghaus G, Kroj G (1993) Effects of low alcohol dosage: a review of the literature. In: *Alcohol, drugs and trafic safety—T'92*. Krüger HP, Utzelmann H-D, Berghaus G, Kroj G, eds. Verlag TÜV Rheinland, Cologne.

Kühlhorn E, Hibell B, Larsson S, Ramstedt M, Zetterberg HL (1999) *Alkoholkonsumtionen i Sverige under 1990-talet. [Alchol consumption in Sweden in the 1990s.]* OAS, Socialdepartmentet [Ministry of Health and Social Affairs], Stockholm.

Larkby C, Day N (1997) Effects of prenatal alcohol exposure. *Alcohol Health and Research World*, **21**:192–198.

Larroque B, Kaminski M (1996) Alcohol consumption during pregnancy. *Annals of Epidemiology*, **6**:169.

Lazarus R, Sparrow D, Weiss ST (1997) Alcohol intake and insulin levels. The Normative Aging Study. *American Journal of Epidemiology*, **145**:909–916.

Lehtonen R, Pahkinen EJ (1994) *Practical methods for design and analysis of complex surveys*. John Wiley & Sons Ltd., Chichester.

Leifman H (2001) Estimations of unrecorded alcohol consumption levels and trends in 14 European countries. *Nordic Studies on Alcohol and Drugs*, **18**: S54–70.

Leitzmann MF, Willett WC, Giovannucci EL et al. (1998) Alcohol intake and the risk of symptomatic gallstones in men. *American Journal of Epidemiology*, **147**:S54.

Lelbach WK (1975) Cirrhosis in the alcoholic and its relation to volume of alcohol abuse. *Annals of the New York Academy of Sciences*, **252**:85–105.

Lelbach WK (1976) Epidemiology of liver disease. In: *Progress in liver diseases*. Popper H, Schaffner F, eds. Grune & Stratton, New York.

Leon DA, Chenet L, Shkolnikov V et al. (1997) Huge variation in Russian mortality rates 1984–94: artefact, alcohol, or what? *The Lancet*, **350**:383–388.

Leonard KE (1984) Alcohol consumption and escalatory aggression in intoxicated and sober dyads. *Journal of Studies on Alcohol*, **45**:75–80.

Leone M, Bottacchi E, Beghi E et al. (1997) Alcohol use is a risk factor for a first generalized tonic clonic seizure. *Neurology*, **48**:614–620.

Li G, Keyl PM, Smith GS, Baker SP (1997) Alcohol and injury severity: reappraisal of the continuing controversy. *Journal of Trauma*, **42**:562–569.

Li G, Smith GS, Baker SP (1994) Drinking behaviour in relation to cause of death among U.S. adults. *American Journal of Public Health*, **84**:1402–1406.

Liang KY, Zeger SL (1986) Longitudinal data analysis using generalized linear models. *Biometrika*, **73**:13–22.

Lipsey MW, Wilson DB, Cohen MA, Derzon JH (1997) Is there a causal relationship between alcohol use and violence? In: *Recent developments in alcoholism, Vol. 13, Alcohol and violence*. Galanter M, ed. Plenum, New York.

Lloyd HM, Rogers PJ (1997) Mood and cognitive performance improved by a small amount of alcohol given with a lunchtime meal. *Behavioural Pharmacology*, **8**:88–195.

Longnecker MP (1999) Invited commentary: the Framingham results on alcohol and breast cancer. *American Journal of Epidemiology*, **149**:102.

Longnecker MP, Enger SM (1996) Epidemiological data on alcohol beverage consumption and risk of cancer. *Clinica Chimica Acta*, **246**:121–141.

Longnecker MP, Wolz M, Parker DA (1981) Ethnicity, distilled spirits consumption and mortality in Pennsylvania. *Journal of Studies on Alcohol*, **42**:791–796.

Ludbrook A, Godfrey C, Wyness L et al. (2002) *Effective and cost-effective measures to reduce alcohol misuse in Scotland: a literature review.* Health Economics Research Unit, Aberdeen.

Lundberg JC, Passik SD (1997) Alcohol and cancer: a review for psycho-oncologists. *Psychooncology*, **6**:253–266.

Lynskey MT (1998) The comorbidity of alcohol dependence and affective disorders: treatment implications. *Drug and Alcohol Dependence*, **52**:201–209.

MacAndrew C, Edgerton RB (1969) *Drunken comportment. A social explanation.* Aldine, Chicago, IL.

Malyutina S, Bobak M, Kurilovitch S, Ryizova E, Nikitin Y, Marmot M (2001) Alcohol consumption and binge drinking in Novosibirsk, Russia, 1985–1995. *Addiction*, **96**:987–995.

Markou A, Kosten TR, Koob GF (1998) Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. *Neuropsychopharmacology*, **18**:135–174.

Martin SE (1992) Epidemiology of alcohol-related interpersonal violence. *Alcohol Health and Research World*, **16**:230–237.

Martin SE, Bachman R (1997) The relationship or alcohol to injury in assault cases. In: *Recent developments in alcoholism, Vol. 13, Alcohol and violence.* Galanter M, ed. Plenum, New York.

Martín R, Díaz C, Nuévalos C, Matías-Guiu J (1995) Etiological and prognostic factors in the late onset epilepsy. *Revista de Neurologica*, **23**:285–289.

Maskarinec G, Meng L, Kolonel LN (1998) Alcohol intake, body weight, and mortality in a multiethnic prospective cohort. *Epidemiology*, **9**:654–661.

Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL (1997) Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. *Journal of Pediatrics*, **131**:718–721.

Mäkelä K, Room R, Single E, Sulkunen P, Walsh B, with 13 others (1981) *Alcohol, society, and the state: 1. A comparative history of alcohol control.* Addiction Research Foundation, Toronto.

McClelland DC, Davis WN, Kalin R, Wanner E (1972) *The drinking man. Alcohol and human motivation.* Collier-Macmillan, Toronto.

McElduff P, Dobson AJ (1997) How much alcohol and how often? Population based case-control study of alcohol consumption and risk of a major coronary event. *British Medical Journal*, **314**:1159

McKee M, Britton A (1998) The positive relationship between alcohol and heart disease in eastern Europe: potential physiological mechanisms. *Journal of the Royal Society of Medicine*, **91**:402–407.

McKee M, Shkolnikov V, Leon DA (2001) Alcohol is implicated in the fluctuations in cardiovascular disease in Russia since the 1980s. *Annals of Epidemiology*, **11**:1–6.

McKenzie CR, Eisenberg PR (1996) Alcohol, coagulation, and arterial thrombosis. In: *Alcohol and the cardiovasular system.* Zakhari S, Wassef M, eds. National Institues of Health, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

McLeod R, Stockwell T, Stevens M, Philips M (1999) Relationship between alcohol consumption patterns and injury. *Addiction*, **94**:1719–1734.

Mehrabian A (2001) General relations among drug use, alcohol use, and major indexes of psychopathology. *Journal of Psychology*, **135**:71–86.

Merikangas KR, Mehta RL, Molnar BE et al. (1998) Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addictive Behaviors: An International Journal*, **23**:893–907.

Miczek KA, Weerts EM, DeBold JF (1993) Alcohol, benzodiazepine-GABA receptor complex and aggression: ethiological analysis of individual differences in rodents and primates. *Journal of Studies on Alcohol*, **11**:S170–179.

Midanik LT (1988) Validity of self-reported alcohol use: a literature review and assessment. *British Journal of Addiction*, **83**:1019–1029.

Midanik LT, Harford TC (1994) Overview of alcohol consumption measurement papers. *Addiction*, **89**:393–394.

Morgenstern H (1998) Ecologic studies. In: *Modern epidemiology.* Rothman KJ, Greenland S, eds. Lippincott-Raven Publishers, Philadelphia, PA.

Morrow DA, Ridker PM (2000) C-reactive protein, inflammation, and coronary risk. *Medical Clinics of North America*, **84**:149–161.

Moskowitz H, Robinson C (1988) *Effects of low doses of alcohol on driving-related skills: a review of the evidence*. National Highway Traffic Safety Administration, Washington, DC.

Mukamal KJ, Rimm EB (2001) Alcohol's effects on the risk for coronary heart disease. *Alcohol Research and Health*, **25**:255–261.

Murdoch DD, Pihl RO, Ross D (1990) Alcohol and crimes of violence: present issues. *International Journal of the Addictions*, **25**:1065–1081.

Murray CJL, Lopez A, eds (1996a) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol. I. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJL, Lopez A (1996b) Quantifying the burden of disease and injury attributable to ten major risk factors. In: *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol. I. Murray CJL, Lopez A, eds. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJL, Lopez A (1999) On the comparable quantification of health risk: lessons from the Global Burden of Disease Study. *Epidemiology*, **10**:594–605.

Murray RP, Connett JE, Tyas SL et al. (2002) Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? *American Journal of Epidemiology*, **155**:242–248.

Murray RP, Istvan JA, Daniels K, Beaudoin CM (1998) Alcohol and morbidity in the Lung Health Study. *Journal of Studies on Alcohol*, **59**:250–257.

Murray RP, Rehm J, Shaten J, Connett JE (1999) Does social integration confound the relation between alcohol consumption and mortality in the

Multiple Risk Factor Intervention Trial (MRFIT)? *Journal of Studies on Alcohol*, **60**:740–745.

Muscat JE, Wynder EL (1998) A case-control study of risk factors for major salivary gland cancer. *Otolaryngology and Head and Neck Surgery*, **118**: 195–198.

Mustonen H, Beukes L, Du Preez V (2001) Alcohol drinking in Namibia. In: *Surveys of drinking patterns and problems in seven developing countries*. World Health Organization, Geneva.

Nasca PC, Liu S, Baptiste MS, Kwon CS, Jacobson H, Metzger BS (1994) Alcohol consumption and breast cancer: estrogen receptor status and histology. *American Journal of Epidemiology*, **140**:980–987.

Nemtsov AV (1998) Alcohol-related harm and alcohol consumption in Moscow before, during and after a major anti-alcohol campaign. *Addiction*, **93**:1501–1510.

Nemtsov AV (2000) Estimates of total alcohol consumption in Russia, 1980–1994. *Drug and Alcohol Dependence*, **58**:133–142.

Nemtsov AV (2002) Alcohol-related human losses in Russia in the 1980s and 1990s. *Addiction*, **97**:1413–1425.

Newcomb PA, Trentham-Dietz A, Storer BE (1997) Alcohol consumption in relation to endometrial cancer risk. *Cancer Epidemiology, Biomarkers and Prevention*, **6**:775–778.

Norström T (2001) Per capita alcohol consumption and all-cause mortality in 14 European countries. *Addiction*, **96**:S113–128.

Notzon FC, Komarov YM, Ermakov SP, Sempos CT, Marks JS, Sempos EV (1998) Causes of declining life expectancy in Russia. *Journal of the American Medical Association*, **279**:793–800.

Parazzini F, La Vecchia C, D'Avanzo B, Moroni S, Chatenoud L, Ricci E (1995) Alcohol and endometrial cancer risk: findings from an Italian case-control study. *Nutrition and Cancer*, **23**:55–62.

Passaro K-AT, Little RE (1997) Childbearing and alcohol use. In: *Gender and alcohol: individual and social perspectives*. Wilsnack RW, Wilsnack SC, eds. Rutgers Center of Alcohol Studies, New Brunswick, NJ.

Passaro KT, Little RE, Savitz DA, Noss J (1996) The effect of maternal drinking before conception and in early pregnancy on infant birthweight. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Epidemiology*, **7**:377–383.

Penick EC, Powell BJ, Liskow BI, Jackson JO, Nickel EJ (1988) The stability of coexisting psychiatric syndromes in alcoholic men after one year. *Journal of Studies on Alcohol*, **49**:395–405.

Pernanen K (2001) What is meant by "alcohol-related" consequences? In: *Mapping the social consequences of alcohol consumption*. Klingeman H, Gmel G, eds. Kluwer Academic Publishers, Dordrecht.

Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG (1995) Prospective study of risk factors for development of non-insulin

dependent diabetes in middle aged British men. *British Medical Journal*, **310**:560–564.

Peterson JB, Rothfleisch J, Zelazo P, Pihl RO (1990) Acute alcohol intoxication and neuropsychological functioning. *Journal of Studies on Alcohol*, **51**:114–122.

Peto R, Lopez AD, Boreham J, Thun M, Heath CW Jr. (1992) Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *The Lancet*, **339**:1268–1278.

Pettinati H, Sugerman A, Maurer HS (1982) Four-year MMPI changes in abstinent and drinking alcoholics. *Alcoholism, Clinical and Experimental Research*, **6**:487–494.

Piette JD, Barnett PG, Moos RH (1998) First-time admissions with alcohol-related medical problems: a 10-year follow-up of a national sample of alcoholic patients. *Journal of Studies on Alcohol*, 89–96.

Pihl RO, Peterson J (1993) Alcohol/drugs use and aggressive behavior. In: *Mental disorder and crime*. Hodgkins S, ed. Sage, London.

Pihl RO, Peterson J, Lau M (1993) A biosocial model of the alcohol-aggression relationship. *Journal of Studies on Alcohol*, **11**:S128–139.

Poikolainen K (1983) Inebriation and mortality. *International Journal of Epidemiology*, **12**:151–155.

Polygenis D, Wharton S, Malmberg C et al. (1998) Moderate alcohol consumption during pregnancy and the incidence of fetal malformations: a meta-analysis. *Neurotoxicology and Teratology*, **20**:61–67.

Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM (2001) C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *Journal of the American Medical Association*, **286**:327–234.

Productschap voor Gedistilleerde Dranken (1999) *World drink trends, 1999. International beverage consumption and production trends*. NTC, Schiedam, the Netherlands.

Productschap voor Gedistilleerde Dranken (2000) *World drink trends, 2000. International beverage consumption and production trends*. NTC, Schiedam, the Netherlands.

Puddey IB, Rakic V, Dimmitt SB, Beilin LJ (1999) Influence of drinking on cardiovascular disease and cardiovascular risk factors: a review. *Addiction*, **94**:649–663.

Puffer R, Griffith GW (1967) *Patterns of urban mortality.* No. 151. Pan American Health Organization, Washington, DC.

Putnam SC, Cerhan JR, Parker AS, Wallace RB, Cantor KP, Lynch CF (1998) Alcohol consumption and prostate cancer in a cohort of Iowa males. *American Journal of Epidemiology*, **147**:42.

Ramchandani VA, Kwo PY, Li TK (2001) Effect of food and food composition on alcohol elimination rates in healthy men and women. *Journal of Clinical Pharmacology*, **41**:1345–1350.

Ramstedt M (1996a) Per capita alcohol consumption and liver cirrhosis mortality in 14 European countries. *Addiction*, **96**:19–34.

Ramstedt M (1996b) Alcohol and suicide in 14 European countries. *Addiction*, **96**:59–75.

Rankin J (1994) Biological mechanisms at moderate levels of alcohol consumption that may affect coronary heart disease. *Contemporary Drug Problems*, **21**:45–57.

Reeder VC, Aikens ML, Li X-N, Booyse FM (1996) Alcohol and the fibrinolytic system. In: *Alcohol and the cardiovascular system*. Zakhari S, Wassef M, eds. National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Rehm J (1998a) Measuring quantity, frequency and volume of drinking. *Alcoholism, Clinical and Experimental Research*, **22**:S4–14.

Rehm J (1998b) Measuring alcohol consumption: how about adopting usual epidemiological standards. *Addiction*, **93**:970–972.

Rehm J (2000) Re: "Alcohol intake assessment: the sober facts". *American Journal of Epidemiology*, **151**:436–438.

Rehm J (2001) Concepts, dimensions and measures of alcohol-related social consequences. A basic framework for alcohol-related benefits and harm. In: *Mapping social consequences of alcohol consumption*. Klingeman H, Gmel G, eds. Kluwer, Dordrecht.

Rehm J, Ashley MJ, Room R et al. (1996) Drinking patterns and their consequences: report from an international meeting. *Addiction*, **91**:1615–1621.

Rehm J, Bondy S, Sempos CT, Vuong CV (1997) Alcohol consumption and coronary heart disease morbidity and mortality. *American Journal of Epidemiology*, **146**:495–501.

Rehm J, Eschmann S (2002) Global monitoring of average volume of alcohol consumption. *Zeitschrift für Sozial- und Präventivmedizin*, **47**:48–58.

Rehm J, Gmel G (2000a) Aggregating dimensions of alcohol consumption to predict medical and social consequences. *Journal of Substance Abuse*, **12**: 155–168.

Rehm J, Gmel G (2000b) Gaps and needs in international alcohol epidemiology. *Journal of Substance Use*, **5**:6–13.

Rehm J, Gmel G (2001a) Aggregate time-series regression in the field of alcohol. *Addiction,* **96**:945–954.

Rehm J, Gmel G (2001b) Applying principles of comparative risk analysis to substance-abuse related burden. *European Addiction Research*, **7**:95–97.

Rehm J, Gmel G, Room R et al. (2001a) *Alcohol as a risk factor for burden of disease*. World Health Organization, Geneva.

Rehm J, Gmel G, Sempos CT, Trevisan M (2003b) Alcohol-related mortality and morbidity. *Alcohol Research and Health*, *27*:39–51.

Rehm J, Greenfield TK, Rogers JD (2001d) Average volume of alcohol consumption, patterns of drinking and all-cause mortality. Results from the U.S. National Alcohol Survey. *American Journal of Epidemiology*, **153**:64–71.

Rehm J, Gutjahr E, Gmel G (2001c) Alcohol and all-cause mortality: a pooled analysis. *Contemporary Drug Problems*, **28**:337–361.

Rehm J, Monteiro M, Room R et al. (2001b) Steps towards constructing a global comparative risk analysis for alcohol consumption: determining indicators and empirical weights for patterns of drinking, deciding about theoretical minimum, and dealing with different consequences. *European Addiction Research*, **7**:138–147.

Rehm J, Sempos CT (1995) Alcohol consumption and mortality—questions about causality, confounding and methodology. *Addiction*, **90**:493–498.

Rehm J, Sempos CT, Trevisan M (2003a) Alcohol and cardiovascular disease—more than one paradox to consider. Average volume of alcohol consumption, patterns of drinking and risk of coronary heart disease: a review. *Journal of Cardiovascular Risk*, **10**:15–20.

Reinke LA, McCay PB (1996) Interaction between alcohol and antioxidants. In: *Alcohol and the Cardiovascular System*. Zakhari S, Wassef M, eds. National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Renaud SC, Criqui MH, Farchi G, Veenstra J (1993) Alcohol drinking and coronary heart disease. In: *Health issues related to alcohol consumption*. Verschuren PM, ed. International Life Sciences Institute, Washington, DC.

Renaud SC, Ruf JC (1996) Effects of alcohol on platelet function. *Clinica Chimica Acta*, **246**:77–89.

Rhodés J, Salaspuro M, Sorenson TIA (1993) Alcohol and liver diseases. In: *Health issues related to alcohol consumption*. Verschuren PM, ed. International Life Sciences Institute, Washington, DC.

Rice DP, Kelman S, Miller LS (1991) The economic cost of alcohol abuse. *Alcohol Health and Research World*, **15**:307–316.

Ridker PM (2001) Role of inflammatory biomarkers in prediction of coronary heart disease. *The Lancet*, **358**:946–948.

Ridolfo B, Stevenson C (2001) *The quantification of drug-caused mortality and morbidity in Australia 1998*. Australian Institute of Health and Welfare, Canberra.

Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC (1995) Prospective study for cigarette smoking, alcohol use, and the risk of diabetes in men. *British Medical Journal*, **310**:555–559.

Rimm EB, Klatsky A, Grobbe D, Stampfer M (1996) Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine or spirits. *British Medical Journal*, **312**:731–735.

Rimm EB, Willett WC, Hu FB et al. (1998) Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *Journal of the American Medical Association*, **279**:359–364.

Rimm EB, Williams P, Fosher K, Criqui MH, Stampfer MJ (1999) Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *British Medical Journal*, **319**: 1523–1528.

Robles-Diaz G, Gorelick FS (1997) Alcohol and acute pancreatitis. *Yale Journal of Biology and Medicine*, **70**:77–87.

Rodgers B, Korten AE, Jorm AF, Jacomb PA, Christensen H, Henderson AS (2000) Non-linear relationships in associations of depression and anxiety with alcohol use. *Psychological Medicine*, **30**:421–432.

Roebuck TM, Mattson SN, Riley EP (1998) A review of the neuroanatomical findings in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcoholism, Clinical and Experimental Research*, **22**:339–344.

Room R (1972) Alcohol-related urban mortality: a cross-national study. *Drinking and Drug Practices Surveyor*, **5**:11–13.

Room R (1992) The impossible dream? Routes to reducing alcohol problems in a temperance culture. *Journal of Substance Abuse*, **4**:91–106.

Room R, Jernigan D, Carlini-Marlatt B et al. (2002) *Alcohol in developing societies: a public health approach*. Finnish Foundation for Alcohol Studies in collaboration with the World Health Organization, Helsinki.

Room R, Mäkelä K (2000) Typologies of the cultural position of drinking. *Journal of Studies on Alcohol*, **61**:475–483.

Room R, Rossow I (2001) The share of violence attributable to drinking. *Journal of Substance Use*, **6**:218–228.

Rosenberg L, Metzger LS, Palmer JR (1993) Alcohol consumption and risk of breast cancer: a review of the epidemiologic evidence. *Epidemiologic Reviews*, **15**:133–144.

Rosengren A, Wilhelmsen L, Pennert K, Berglund G, Elmfeldt D (1987) Alcoholic intemperance, coronary heart disease and mortality in middle-aged Swedish men. *Acta Medica Scandinavica*, **222**:201–213.

Rosenqvist M (1998) Alcohol and cardiac arrhythmias. *Alcoholism, Clinical and Experimental Research*, **22**:S318–322.

Ross R, Bernstein L, Trent L, Henderson B, Paganini-Hill A (1990) A prospective study of risk factors for traumatic deaths in a retirement community. *Alcoholism, Clinical and Experimental Research*, **20**:1130–1137.

Rossow I, Amundsen A (1997) Alcohol abuse and mortality: a 40-year prospective study of Nowegian conscripts. *Social Science and Medicine*, **44**:261–267.

Rossow I, Pernanen K, Rehm J (2001) Alcohol, suicide and violence. In: *Mapping the Social Consequences of Alcohol Consumption*. Klingeman H, Gmel G, eds. Kluwer Academic Publishers, Dordrecht.

Rothman KJ, Greenland S (1998b) *Modern epidemiology*. 2nd edn. Lippincott-Raven Publishers, Philadelphia, PA.

Rothman KJ, Greenland S (1998a) Causation and causal inference. In: *Modern epidemiology. 2nd edn*. Rothman KJ, Greenland S, eds. Lippincott-Raven Publishers, Philadelphia, PA.

Royo-Bordonada MA, Martin-Moreno JM, Guallar E et al. (1997) Alcohol intake and risk of breast cancer: the Euramic Study. *Neoplasma*, **44**:150–156.

Rubin R (1999) Effect of ethanol on platelet function. *Alcoholism, Clinical and Experimental Research*, **23**:1114–1118.

Sacco RL, Elkind M, Boden-Albala B et al. (1999) The protective effect of moderate alcohol consumption in ischemic stroke. *Journal of the American Medical Association*, **281**:53–60.

Sarles H, Bernard JP, Johnson CD (1996) Alcohol and the pancreas. In: *Alcohol misuse: a european perspective*. Peters TJ, ed. Harwood Academic Publishers, Amsterdam.

Sayette MA, Wilson T, Elias MJ (1993) Alcohol and aggression: a social information processing analysis. *Journal of Studies on Alcohol*, **54**:399–407.

Sayrs LW (1989) *Pooled time series analysis*. Sage Publications, Newbury Park, CA.

Schatzkin A, Longnecker MP (1994) Alcohol and breast cancer: where are we now and where do we go from here? *Cancer*, **74**:1101–1110.

Schmidt DN (1991) Apparent risk factors for chronic and acute pancreatitis in Stockholm county: spirits but not wine and beer. *International Journal of Pancreatology*, **8**:45–50.

Schuckit MA (1996) Alcohol, anxiety, and depressive disorders. *Alcohol Health and Research World*, **20**:81–85.

Schuckit MA, Tipp JE, Bergman M, Reich W, Hesselbrock VM, Smith TL (1997b) Comparison of induced and independent major depressive disorders in 2,945 alcoholics. *American Journal of Psychiatry*, **154**:948–957.

Schuckit MA, Tipp JE, Bucholz KK et al. (1997a) The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls. *Addiction*, **92**:1289–1304.

Segi M (1960) *Cancer mortality for selected sites in 24 countries (1950–57)*. Department of Health, Tohoku University of Medicine, Sendai, Japan.

Seitz HK, Poschl G, Simanowski UA (1998a) Alcohol and cancer. *Recent Developments in Alcoholism*, **14**:67–95.

Seitz HK, Simanowski UA, Homann N, Waldherr R (1998b) Cell proliferation and its evaluation in the colorectal mucosa: effect of ethanol. *Zeitschrift für Gastroenterologie*, **36**:645–655.

Shaper AG (1990a) Alcohol and mortality: a review of prospective studies. *British Journal of Addiction*, **85**:837–847.

Shaper AG (1990b) A response to commentaries: the effects of self-selection. *British Journal of Addiction*, **85**:859–861.

Shaper AG, Wannamethee SG, Walker M (1988) Alcohol and mortality in British men: explaining the U-shaped curve. *The Lancet*, **2**:1267–1273.

Sharps PW, Campbell D, Gary F, Webster D (2001) The role of alcohol use in intimate partner femicide. *American Journal on Addictions*, **10**:122–135.

Shkolnikov V, McKee M, Leon DA (2001) Changes in live expectancy in Russia in the mid-1990s. *The Lancet*, **357**:917–921.

Shkolnikov VM, McKee M, Chervyakov VV, Kyrianov NA (2002) Is the link between alcohol and cardiovascular death among young Russian men due to misclassification of acute alcohol intoxication? Evidence from the city of Izhevsk. *Journal of Epidemiology and Community Health*, **56**:171–174.

Shkolnikov VM, Nemtsov A (1997) The anti-alcohol campaign and variations in Russian mortality. In: *Premature Death in the New Independent States*. Bobadilla JL, Costello CA, Mitchell F, eds. National Academy Press, Washington DC.

Shu I, Shaten BJ, Cutler JA, Kuller LH (1992) Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. The Multiple Risk Factor Intervention Trial Research Group. *Annals of Internal Medicine*, **116**:881–887.

Shu XO, Hatch MC, Mills J, Clemens J, Susser M (1995) Maternal smoking, alcohol drinking, caffeine consumption, and fetal growth from a prospective study. *Epidemiology*, **6**:115–120.

Shults RA, Elder RW, Sleet DA, et al. (2001) Reviews of evidence regarding interventions to reduce alcohol-impaired driving. *American Journal of Preventive Medicine*, **21**:S66–88.

Simpura J (1998) Mediterranean mysteries: mechanisms of declining alcohol consumption. *Addiction*, **93**:1301–1304.

Simpura J (2001) Trends in alcohol consumption and drinking patterns: sociological and economic explanations and alcohol policies. *Nordic Studies on Alcohol and Drugs*, **18**:S3–13.

Single E, Ashley MJ, Bondy S, Rankin J, Rehm J (1999) *Evidence regarding the level of alcohol consumption considered to be low-risk for men and women. Final report submitted to the Australian Commonwealth Department of Health and Aged Care*.

Single E, Robson L, Rehm J, Xie X (1999) Morbidity and mortality attributable to alcohol, tobacco, and illicit drug use in Canada. *American Journal of Public Health*, **89**:385–390.

Single E, Robson L, Xie X, Rehm J (1996) *The cost of substance abuse in Canada*. Canadian Centre on Substance Abuse, Ottawa, Ontario.

Singletary KW, Gapstur SM (2001) Alcohol and breast cancer: Review of epidemiologic and experimental evidence and potential mechanisms. *JAMA: Journal of the American Medical Association*, **86**:2143–2151.

Skinaze F, Lévy P, Bernades P (1995) Les pancréatities aguiës alcooliques rélèventelles toujours une pancréatite chronique? *Gastroentérologie Clinique et Biologique*, **19**:266–269.

Skinner CJ, Holt D, Smith TMF (1989) *Analysis of complex surveys*. John Wiley & Sons Ltd., Chichester.

Skog O-J (1980) Liver cirrhosis epidemiology: some methodological problems. *British Journal of Addiction*, **75**:227–243.

Skog O-J (1983) Methodological problems in the analysis of temporal covariation between alcohol consumption and ischaemic heart disease. *British Journal of Addiction*, **78**:157–172.

Skog O-J (1996) Public health consequences of the J-curve hypothesis of alcohol problems. *Addiction*, **91**:325–337.

Smith-Warner SA, Spiegelman D, Yaun S-S et al. (1998) Alcohol and breast cancer in women: a pooled analysis of cohort studies. *Journal of the American Medical Association*, **279**:535–540.

Soler M, Chatenoud L, La Vecchia C et al. (1998) Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. *European Review of Cancer Prevention*, **7**:455–460.

StataCorp (1999) *Stata reference manual, release 6—volume 4 Su-Z*. Stata Press, College Station, Texas.

Steele CM, Josephs RA (1990) Alcohol myopia: its prized and dangerous effects. *American Psychologist*, **45**:921–933.

Stinson FS, Dufour MC, Steffens RA et al. (1993) Alcohol-related mortality in the United States, 1979–1989. *Alcohol Health and Research World*, **17**:251–260.

Stoduto G, Vingilis E, Kapur B et al. (1993) Alcohol and drug use among motor vehicle collision victims admitted to a regional trauma unit: demographic, in-jury and crash characteristics. *Accident, Analysis and Prevention*, **25**:411–420.

Svärdsudd K (1998) Moderate alcohol consumption and cardiovascular disease: is there evidence for a preventive effect? *Alcoholism, Clinical and Experimental Research*, **22**:S307–314.

Swanson CA, Coates FJ, Malone KE et al. (1997) Alcohol consumption and breast cancer risk among women under age 45 years. *Epidemiology*, **8**:231–237.

Swendsen JD, Merikangas KR, Canino GJ et al. (1998) Comorbidity of alcoholism with anxiety and depressive disorders in four geographic communities. *Comprehensive Psychiatry*, **39**:176–184.

Tamerin JS, Weiner S, Mendelson JH (1970) Alcoholics' expectancies and recall of experiences during intoxication. *American Journal of Psychiatry*, **126**:1697–1704.

Tavani A, Negri E, Franceschi S et al. (1994) Alcohol consumption and risk of prostate cancer. *Nutrition and Cancer*, **21**:25–31.

Thakker KD (1998) An overview of health risks and benefits of alcohol consumption. *Alcoholism, Clinical and Experimental Research*, **22**:S285–298.

Thun JM, Peto R, Lopez AD et al. (1997) Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *New England Journal of Medicine*, **337**:1705–1714.

Tomsen SA (1997) A top night out—social protest, masculinity and the culture of drinking violence. *British Journal of Criminology*, **37**:990–1002.

Treno AJ, Gruenewald PJ, Ponicki WR (1997) The contribution of drinking patterns to the relative risk of injury in six communities: A self-report based probability approach. *Journal of Studies on Alcohol*, **58**:372–381.

Treno AJ, Holder HD (1997) Measurement of alcohol-involved injury in community prevention: the search for a surrogate III. *Alcoholism, Clinical and Experimental Research*, **21**:1695–1703.

Trevisan M, Krogh V, Farinaro E et al. (1987) Alcohol consumption, drinking pattern and blood pressure: analysis of data from the Italian National Research Council Study. *International Journal of Epidemiology*, **16**:520–527.

Trevisan M, Ram M, Hovey K et al. (2001b) Alcohol drinking patterns and myocardial infaction. *American Journal of Epidemiology*, **153**:S97.

Trevisan MT, Schisterman E, Mennotti A et al. (2001a) Drinking pattern and mortality: The Italian Risk Factor and Life Expectancy Pooling Project. *Annals of Epidemiology*, **11**:312–319.

Trotter RT, Rehm J, Chatterji S et al. (2001) Cross-Cultural Applicability Research (CAR) Methods. In: *Disability and culture: universalism and diversity.* Üstün TB, Chatterji S, Bickenbaach JE, et al., eds. Hogrefe & Huber Publishers, Göttingen.

U.S. Department of Health and Human Services (1997) *Ninth special report to the US Congress on alcohol and health* (Vol. No. 97-4017). U.S. Department of Health and Human Services, National Institute on Alcohol Abuse and Alcoholism (NIAAA), Rockville, MD.

U.S. Department of Health and Human Services (2000) *10th special report to the US Congress on alcohol and health: highlights from current research,* Vol. No. 97-4017. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health (NIH), National Institute on Alcohol Abuse and Alcoholism (NIAAA), Rockville, MD.

Vaillant GE (1993) Is alcoholism more often the cause or the result of depression? *Harvard Review of Psychiatry*, **1**:94–99.

Vaillant GE, Hiller-Sturmhofel S (1996) Natural history of alcoholism. *Alcohol Health and Research World*, **20**:152–161.

Van den Brandt PA, Goldbohm RA, Van't Veer P (1995) Alcohol and breast cancer: results from the Netherland Cohort Study. *American Journal of Epidemiology*, **141**:907–915.

Veenstra J, Ockhuizen T, van de Pol et al. (1990) Effects of moderate dose of alcohol on blood lipids and lipoproteins postprandially and in the fasting state. *Alcohol,* **25**:371–377.

Vikhert A, Tsiplenkova VG, Cherpachenko N (1986) Alcoholic cardiomyopathy and sudden cardiac death. *Journal of the American College of Cardiology*, **8**:A3–11.

Walsh G, Rehm J (1996) Daily drinking and harm. *Contemporary Drug Problems*, **23**:465–478.

Wannamethee SG, Shaper AG (1991) Alcohol intake and variations in blood pressure by day of examination. *Journal of Human Hypertension*, **5**:59–67.

Wannamethee SG, Shaper AG (1992) Alcohol and sudden cardiac death. *British Heart Journal*, **68**:443–448.

Wannamethee SG, Shaper AG (1996) Patterns of alcohol intake and risk of stroke in middle-aged British men. *Stroke*, **27**:1033–1039.

Washburne C (1956) Alcohol, self and the group. *Quarterly Journal of Studies on Alcohol*, **12**:108–123.

Washburne C (1961) *Primitive drinking. A study of the use and functions of alcohol in preliterate societies*. College and University Press, New York, NY.

Wei H, Derson Y, Shuiyuan X et al. (1999) Alcohol consumption and alcohol-related problems: Chinese experience from six area samples. *Addiction*, **94**:1467–1476.

Wei M, Gibbons LW, Mitchell TL et al. (2000) Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care*, **23**:18–22.

Weiner S, Tamerin JS, Steinglass P (1971) Familial patterns in chronic alcoholism:a study of a father and son during experimental intoxication. *American Journal of Psychiatry*, **127**:82–87.

Whistler D, White KJ, Wong SD et al. (2001) *Shazam: the econometric computer program, version 9. User's reference manual*. Northwest Econometrics, Ltd., Vancouver, BC.

White S (1996) *Russia goes dry: alcohol, state and society*. Cambridge University Press, Cambridge, MA.

WHO (1999) *Global status report on alcohol*. World Health Organization, Substance Abuse Department, Geneva.

WHO (2000) *International guide for monitoring alcohol consumption and related harm*. World Health Organization, Department of Mental Health and Substance Dependence. Copenhagen.

WHO (2001) *Surveys of drinking patterns and problems in seven developing countries*. World Health Organization, Department of Mental Health and Substance Dependence. Geneva.

WHO (2002) *World Health Report 2002: reducing risks, promoting healthy life*. World Health Organization, Geneva.

Willenbring ML (1986) Measurement of depression in alcoholics. *Journal of Studies on Alcohol*, **49**:412–417.

Willich SN, Lowel H, Lewis M et al. (1994) Weekly variation of acute myocardial infarction. Increased Monday risk in the working population. *Circulation*, **90**:87–93.

Windham GC, Fenster L, Hopkins B et al. (1995) The association of moderate maternal and paternal alcohol consumption with birthweight and gestational age. *Epidemiology*, **6**:591–597.

Windham GC, Von Behren J, Fenster L et al. (1997) Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology*, **8**:509–514.

Wingo PA, Calle EE, Thun JM et al. (1997) Alcohol consumption and the risk of fatal breast cancer in a prospective cohort of United States women. *American Journal of Epidemiology*, **145**:S28.

Wood D, de Backer G, Faegeman O et al. (1998) Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies in Coronary Prevention. *Atherosclerosis*, **140**:199–270.

Wu T, Trevisan M (2001) Drinking pattern and hypertension in a population-based sample. *American Journal of Epidemiology*, **153**:S59.

Yaffee R (2000) *Introduction to time-series analysis and forecasting*. Academic Press Inc., San Diego, CA.

Yang M, Rasbash J, Goldstein H et al. (1999) *MLwiN macros for advanced multilevel modelling*. Version 2.0. Multilevel Models Project, Institute of Education, London.

You R, McNeil J, O'Malley H et al. (1997) Risk factors for stroke due to cerebral infarction in young adults. *Stroke*, **28**:1913–1918.

Yu Y, Hu J, Wang PP et al. (1997) Risk factors for bladder cancer: a case-control study in northeast China. *European Review of Cancer Prevention*, **6**:363–369.

Yuan J-M, Ross RK, Gao Y-T et al. (1997) Follow-up study of moderate alcohol intake and mortality among middle-aged men in Shanghai, China. *British Medical Journal*, **314**:18–23.

Zakhari S (1997) Alcohol and the cardiovascular system: molecular mechanisms for beneficial and harmful action. *Alcohol Health and Research World*, **21**:21–29.

Zhang Y, Kreger BE, Dorgan JF et al. (1999) Alcohol consumption and risk of breast cancer: the Framingham study revisited. *American Journal of Epidemiology*, **149**:93–101.

Zwerling C, Sprince N, Wallace R et al. (1996) Alcohol and occupational injuries among older workers. *Accident, Analysis and Prevention*, **28**:371–376.

Appendix A: "Pattern of drinking" variables and their relative weights

Heavy drinking occasions

(Maximum of 11 points for this component)

Daily drinking
Less than 20% daily drinking for males: 1 point
Less than 10% daily drinking for females: 1 point

Frequency of getting drunk
Most male drinkers usually get drunk when they are drinking: 2 points
Most males drinkers often get drunk: 1 point
Most female drinkers usually or often get drunk: 1 point

Usual quantity per drinking session
Males: more than 60% typically consume four or more drinks per session: 2 points
Males: between 40% and 60% consume four or more drinks per session: 1 point
Females: more than 50% consume four or more drinks per session: 2 points
Females: between 35% and 50% consume four or more drinks per session: 1 point

Fiesta binge drinking
Males: fiesta drinking commonly occurs: 1 point
Females: fiesta drinking commonly occurs: 1 point

Drinking with meals

(Maximum of 4 points for this component)

Males: rarely or never with meals: 2 points
Males: sometimes with meals: 1 point

Females: rarely or never with meals: 2 points
Females: sometimes with meals: 1 point

Drinking in public places

(Maximum of 2 points for this component)
Males: common and everyday: 1 point
Females: common and everyday: 1 point

Scoring (possible range: 0–17 points)

Scoring by summation of individual questions: range 0–17
10–17 points: assign a pattern value of 4
7–9 points: assign a pattern value of 3
4–6 points: assign a pattern value of 2
0–3 points: assign a pattern value of 1

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries

Note: AAFs for morbidity from injuries were derived by multiplying the mortality AAFs by two thirds for motor vehicle accidents and by four ninths for all other types of injury.

AFR-D			*Age group (years)*											
U148	*III.*	*Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.10	0.07	0.25	0.08	0.28	0.12	0.12	0.09	0.10	0.07	0.10	0.07
U151		Poisonings	0.00	0.00	0.19	0.15	0.10	0.09	0.10	0.09	0.10	0.09	0.05	0.04
U152		Falls	0.00	0.00	0.14	0.09	0.14	0.09	0.14	0.09	0.11	0.05	0.07	0.02
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.17	0.16	0.21	0.20	0.21	0.20	0.16	0.16	0.16	0.16
U155		Other unintentional injuries	0.10	0.03	0.19	0.15	0.19	0.15	0.16	0.12	0.16	0.12	0.16	0.12
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.09	0.06	0.09	0.06	0.07	0.05	0.07	0.05	0.03	0.03
U158		Homicide	0.08	0.08	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.06	0.06

continued

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries (*continued*)

AFR-E		*Age group (years)*											
U148	*III. Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
		Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A. Unintentional injuries												
U150	Motor vehicle accidents	0.15	0.10	0.50	0.12	0.54	0.17	0.31	0.13	0.26	0.10	0.26	0.10
U151	Poisonings	0.00	0.00	0.42	0.21	0.25	0.14	0.25	0.14	0.25	0.14	0.13	0.06
U152	Falls	0.00	0.00	0.34	0.13	0.34	0.13	0.34	0.13	0.27	0.08	0.20	0.04
U153	Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154	Drownings	0.00	0.00	0.39	0.23	0.45	0.28	0.45	0.28	0.37	0.22	0.37	0.22
U155	Other unintentional injuries	0.15	0.04	0.42	0.21	0.42	0.21	0.36	0.17	0.36	0.17	0.36	0.17
U156	B. Intentional injuries												
U157	Self-inflicted injuries	0.00	0.00	0.24	0.09	0.24	0.09	0.18	0.07	0.18	0.07	0.09	0.04
U158	Homicide	0.12	0.12	0.40	0.25	0.40	0.25	0.40	0.25	0.40	0.25	0.40	0.25
U159	War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160	Other intentional injuries	0.00	0.00	0.31	0.18	0.31	0.18	0.31	0.18	0.31	0.18	0.17	0.09

AMR-A			Age group (years)											
U148	III.	Injuries	0–15		15–29		30–44		45–59		60–69		≥70	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.18	0.12	0.38	0.14	0.42	0.20	0.21	0.16	0.17	0.12	0.17	0.12
U151		Poisonings	0.00	0.00	0.31	0.25	0.17	0.16	0.17	0.16	0.17	0.16	0.09	0.08
U152		Falls	0.00	0.00	0.24	0.15	0.24	0.15	0.24	0.15	0.18	0.10	0.13	0.04
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.28	0.27	0.33	0.32	0.33	0.32	0.27	0.26	0.27	0.26
U155		Other unintentional injuries	0.18	0.05	0.31	0.25	0.31	0.25	0.26	0.20	0.26	0.20	0.26	0.20
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.16	0.11	0.16	0.11	0.12	0.09	0.12	0.09	0.05	0.05
U158		Homicide	0.15	0.15	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.11	0.11

continued

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries (*continued*)

AMR-B			*Age group (years)*											
U148	*III.*	*Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.18	0.12	0.56	0.14	0.60	0.20	0.36	0.16	0.30	0.12	0.30	0.12
U151		Poisonings	0.00	0.00	0.48	0.25	0.30	0.16	0.30	0.16	0.30	0.16	0.16	0.08
U152		Falls	0.00	0.00	0.39	0.15	0.39	0.15	0.39	0.15	0.32	0.10	0.24	0.04
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.44	0.27	0.50	0.32	0.50	0.32	0.43	0.26	0.43	0.26
U155		Other unintentional injuries	0.18	0.06	0.48	0.25	0.48	0.25	0.42	0.21	0.42	0.21	0.42	0.21
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.28	0.11	0.28	0.11	0.22	0.09	0.22	0.09	0.11	0.06
U158		Homicide	0.15	0.15	0.45	0.29	0.45	0.29	0.45	0.29	0.45	0.29	0.45	0.29
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.36	0.22	0.36	0.22	0.36	0.22	0.36	0.22	0.20	0.11

AMR-D			Age group (years)											
U148	III.	Injuries	0–15		15–29		30–44		45–59		60–69		≥70	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.11	0.07	0.42	0.09	0.46	0.13	0.24	0.10	0.20	0.07	0.20	0.07
U151		Poisonings	0.00	0.00	0.34	0.16	0.20	0.10	0.20	0.10	0.20	0.10	0.10	0.05
U152		Falls	0.00	0.00	0.27	0.09	0.27	0.09	0.27	0.09	0.21	0.06	0.15	0.03
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.31	0.18	0.37	0.21	0.37	0.21	0.30	0.17	0.30	0.17
U155		Other unintentional injuries	0.11	0.03	0.34	0.16	0.34	0.16	0.29	0.13	0.29	0.13	0.29	0.13
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.18	0.07	0.18	0.07	0.14	0.05	0.14	0.05	0.06	0.03
U158		Homicide	0.09	0.09	0.32	0.19	0.32	0.19	0.32	0.19	0.32	0.19	0.32	0.19
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.24	0.14	0.24	0.14	0.24	0.14	0.24	0.14	0.12	0.07

continued

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries (*continued*)

EMR-B			*Age group (years)*											
U148	*III.*	*Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.03	0.02	0.08	0.02	0.09	0.03	0.03	0.02	0.03	0.02	0.03	0.02
U151		Poisonings	0.00	0.00	0.06	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.01	0.01
U152		Falls	0.00	0.00	0.04	0.02	0.04	0.02	0.04	0.02	0.03	0.01	0.02	0.01
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.05	0.05	0.06	0.06	0.06	0.06	0.05	0.04	0.05	0.04
U155		Other unintentional injuries	0.03	0.01	0.06	0.04	0.06	0.04	0.04	0.03	0.04	0.03	0.04	0.03
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.03	0.02	0.03	0.02	0.02	0.01	0.02	0.01	0.01	0.01
U158		Homicide	0.02	0.02	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.02	0.02

EMR-D		Age group (years)											
U148	III. Injuries	0–15		15–29		30–44		45–59		60–69		≥70	
		Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A. Unintentional injuries												
U150	Motor vehicle accidents	0.01	0.01	0.04	0.01	0.04	0.01	0.02	0.01	0.01	0.01	0.01	0.01
U151	Poisonings	0.00	0.00	0.03	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00
U152	Falls	0.00	0.00	0.02	0.01	0.02	0.01	0.02	0.01	0.01	0.01	0.01	0.00
U153	Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154	Drownings	0.00	0.00	0.02	0.02	0.03	0.03	0.03	0.03	0.02	0.02	0.02	0.02
U155	Other unintentional injuries	0.01	0.00	0.03	0.02	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02
U156	B. Intentional injuries												
U157	Self-inflicted injuries	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.00
U158	Homicide	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
U159	War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160	Other intentional injuries	0.00	0.00	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.01

continued

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries (*continued*)

EUR-A			*Age group (years)*											
U148	*III.*	*Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.23	0.15	0.46	0.18	0.50	0.25	0.27	0.21	0.22	0.15	0.22	0.15
U151		Poisonings	0.00	0.00	0.38	0.31	0.22	0.21	0.22	0.21	0.22	0.21	0.12	0.10
U152		Falls	0.00	0.00	0.30	0.20	0.30	0.20	0.30	0.20	0.24	0.13	0.17	0.06
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.35	0.33	0.40	0.39	0.40	0.39	0.33	0.32	0.33	0.32
U155		Other unintentional injuries	0.23	0.07	0.38	0.31	0.38	0.31	0.32	0.26	0.32	0.26	0.32	0.26
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.21	0.14	0.21	0.14	0.16	0.12	0.16	0.12	0.07	0.07
U158		Homicide	0.19	0.19	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.14	0.14

EUR-B		Age group (years)											
U148	III. Injuries	0–15		15–29		30–44		45–59		60–69		≥70	
		Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A. Unintentional injuries												
U150	Motor vehicle accidents	0.17	0.11	0.54	0.13	0.58	0.19	0.34	0.15	0.29	0.11	0.29	0.11
U151	Poisonings	0.00	0.00	0.46	0.24	0.28	0.15	0.28	0.15	0.28	0.15	0.15	0.07
U152	Falls	0.00	0.00	0.37	0.14	0.37	0.14	0.37	0.14	0.30	0.09	0.22	0.04
U153	Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154	Drownings	0.00	0.00	0.42	0.26	0.48	0.31	0.48	0.31	0.41	0.25	0.41	0.25
U155	Other unintentional injuries	0.17	0.05	0.46	0.24	0.46	0.24	0.40	0.20	0.40	0.20	0.40	0.20
U156	B. Intentional injuries												
U157	Self-inflicted injuries	0.00	0.00	0.27	0.10	0.27	0.10	0.20	0.08	0.20	0.08	0.10	0.05
U158	Homicide	0.14	0.14	0.44	0.28	0.44	0.28	0.44	0.28	0.44	0.28	0.44	0.28
U159	War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160	Other intentional injuries	0.00	0.00	0.34	0.21	0.34	0.21	0.34	0.21	0.34	0.21	0.19	0.10

continued

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries (*continued*)

EUR-C			*Age group (years)*											
U148	*III.*	*Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.32	0.23	0.71	0.27	0.74	0.36	0.52	0.29	0.46	0.23	0.46	0.23
U151		Poisonings	0.00	0.00	0.64	0.42	0.45	0.30	0.45	0.30	0.45	0.30	0.27	0.16
U152		Falls	0.00	0.00	0.55	0.28	0.55	0.28	0.55	0.28	0.47	0.19	0.37	0.09
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.61	0.45	0.66	0.51	0.66	0.51	0.59	0.44	0.59	0.44
U155		Other unintentional injuries	0.32	0.11	0.64	0.42	0.64	0.42	0.58	0.36	0.58	0.36	0.58	0.36
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.43	0.21	0.43	0.21	0.35	0.18	0.35	0.18	0.19	0.11
U158		Homicide	0.28	0.28	0.62	0.47	0.62	0.47	0.62	0.47	0.62	0.47	0.62	0.47
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.52	0.38	0.52	0.38	0.52	0.38	0.52	0.38	0.33	0.21

SEAR-B		*Age group (years)*											
U148	*III. Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
		Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A. Unintentional injuries												
U150	Motor vehicle accidents	0.07	0.04	0.30	0.05	0.34	0.08	0.16	0.06	0.13	0.04	0.13	0.04
U151	Poisonings	0.00	0.00	0.24	0.10	0.13	0.06	0.13	0.06	0.13	0.06	0.06	0.03
U152	Falls	0.00	0.00	0.18	0.06	0.18	0.06	0.18	0.06	0.14	0.04	0.09	0.02
U153	Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154	Drownings	0.00	0.00	0.21	0.11	0.26	0.14	0.26	0.14	0.20	0.11	0.20	0.11
U155	Other unintentional injuries	0.07	0.02	0.24	0.10	0.24	0.10	0.19	0.08	0.19	0.08	0.19	0.08
U156	B. Intentional injuries												
U157	Self-inflicted injuries	0.00	0.00	0.12	0.04	0.12	0.04	0.09	0.03	0.09	0.03	0.04	0.02
U158	Homicide	0.06	0.06	0.22	0.12	0.22	0.12	0.22	0.12	0.22	0.12	0.22	0.12
U159	War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160	Other intentional injuries	0.00	0.00	0.16	0.09	0.16	0.09	0.16	0.09	0.16	0.09	0.08	0.04

continued

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries (*continued*)

SEAR-D			*Age group (years)*											
U148	*III.*	*Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.05	0.03	0.22	0.04	0.25	0.05	0.11	0.04	0.09	0.03	0.09	0.03
U151		Poisonings	0.00	0.00	0.17	0.07	0.09	0.04	0.09	0.04	0.09	0.04	0.04	0.02
U152		Falls	0.00	0.00	0.12	0.04	0.12	0.04	0.12	0.04	0.09	0.02	0.06	0.01
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.15	0.08	0.19	0.10	0.19	0.10	0.14	0.07	0.14	0.07
U155		Other unintentional injuries	0.05	0.01	0.17	0.07	0.17	0.07	0.14	0.06	0.14	0.06	0.14	0.06
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.08	0.03	0.08	0.03	0.06	0.02	0.06	0.02	0.03	0.01
U158		Homicide	0.04	0.04	0.16	0.08	0.16	0.08	0.16	0.08	0.16	0.08	0.16	0.08
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.11	0.06	0.11	0.06	0.11	0.06	0.11	0.06	0.05	0.03

WPR-A			Age group (years)											
U148	III.	Injuries	0–15		15–29		30–44		45–59		60–69		≥70	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.33	0.11	0.36	0.13	0.40	0.18	0.20	0.15	0.16	0.11	0.16	0.11
U151		Poisonings	0.00	0.00	0.29	0.23	0.16	0.15	0.16	0.15	0.16	0.15	0.08	0.07
U152		Falls	0.00	0.00	0.22	0.14	0.22	0.14	0.22	0.14	0.17	0.09	0.12	0.04
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.26	0.25	0.31	0.30	0.31	0.30	0.25	0.24	0.25	0.24
U155		Other unintentional injuries	0.16	0.05	0.29	0.23	0.29	0.23	0.24	0.19	0.24	0.19	0.24	0.19
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.15	0.10	0.15	0.10	0.11	0.08	0.11	0.08	0.05	0.05
U158		Homicide	0.14	0.14	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.10	0.10

continued

Appendix B: Alcohol-attributable fractions (AAFs) for mortality from injuries (*continued*)

WPR-B			*Age group (years)*											
U148	*III.*	*Injuries*	*0–15*		*15–29*		*30–44*		*45–59*		*60–69*		*≥70*	
			Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
U149	A.	Unintentional injuries												
U150		Motor vehicle accidents	0.10	0.07	0.25	0.08	0.28	0.12	0.13	0.09	0.10	0.07	0.10	0.07
U151		Poisonings	0.00	0.00	0.19	0.15	0.10	0.09	0.10	0.09	0.10	0.09	0.05	0.04
U152		Falls	0.00	0.00	0.14	0.09	0.14	0.09	0.14	0.09	0.11	0.06	0.07	0.02
U153		Fires	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U154		Drownings	0.00	0.00	0.17	0.16	0.21	0.20	0.21	0.20	0.16	0.16	0.16	0.16
U155		Other unintentional injuries	0.10	0.03	0.19	0.15	0.19	0.15	0.16	0.12	0.16	0.12	0.16	0.12
U156	B.	Intentional injuries												
U157		Self-inflicted injuries	0.00	0.00	0.09	0.06	0.09	0.06	0.07	0.05	0.07	0.05	0.03	0.03
U158		Homicide	0.08	0.08	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
U159		War	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U160		Other intentional injuries	0.00	0.00	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.06	0.06

APPENDIX C: ALCOHOL-ATTRIBUTABLE DEATHS (000S) IN 2000 BY DISEASE CATEGORY, SEX AND SUBREGION

		Subregions														*World*	
Disease category	*Sex*	*AFR-D*	*AFR-E*	*AMR-A*	*AMR-B*	*AMR-D*	*EMR-B*	*EMR-D*	*EUR-A*	*EUR-B*	*EUR-C*	*SEAR-B*	*SEAR-D*	*WPR-A*	*WPR-B*	*World*	*Total*
Maternal and perinatal conditions	Males	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3
	Females	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
Cancer	Males	7	18	10	10	1	0	1	30	6	15	4	7	13	147	269	355
	Females	3	6	7	7	1	0	0	21	4	9	1	1	5	23	86	
Neuro-psychiatric diseases	Males	5	12	7	14	2	1	1	13	4	8	4	9	1	13	91	111
	Females	1	3	2	2	0	0	0	4	1	3	0	1	0	2	19	
Cardiovascular diseases	Males	8	16	–27	48	4	1	3	–38	49	120	6	51	–6	157	392	268
	Females	3	5	–40	16	2	0	0	–129	11	37	1	0	–37	8	–124	
Other noncommunicable diseases	Males	9	14	10	24	3	0	1	27	12	26	4	6	4	54	193	242
	Females	3	4	2	5	1	0	0	9	6	12	1	2	1	3	49	
Unintentional injury	Males	17	45	19	56	9	3	2	26	22	112	31	60	7	75	484	577
	Females	4	7	6	5	1	0	1	8	3	18	5	12	3	20	92	
Intentional injury	Males	6	21	8	55	3	0	0	7	7	58	4	14	3	19	206	248
	Females	2	5	2	3	0	0	0	2	1	10	1	4	1	10	42	
All alcohol-attributable deaths	Males	53	125	27	207	22	6	8	65	100	338	51	148	23	465	1 638	1 804
	Females	15	30	–22	39	6	1	1	–85	25	88	9	21	–28	66	166	
All deaths	Males	2 206	3 154	1 342	1 459	290	409	1 750	2 020	1 034	1 878	6 358	616	5 483	55 862	26 629	55 861
	Females	6	3 001	1 392	1 120	237	287	1 602	2 054	916	1 721	1 022	5 764	519	4 944	29 232	
Deaths attributable to alcohol as a percentage of all deaths	Males	2.4	4.0	2.0	14.2	7.6	1.5	0.4	3.2	9.6	18.0	0.8	24.1	0.4	0.8	6.2	3.2
	Females	0.8	1.0	–1.6	3.5	2.3	0.3	0.1	–4.1	2.8	5.1	0.9	0.4	–5.3	1.3	0.6	

Appendix D: Alcohol-related disease burden in DALYs (000s) in 2000 by disease category, sex and subregion

		Subregion													World	
Disease category	*Sex*	*AFR-D*	*AFR-E*	*AMR-A*	*AMR-B*	*AMR-D*	*EMR-B*	*EMR-D*	*EUR-A*	*EUR-B*	*EUR-C*	*SEAR-B*	*SEAR-D*	*WPR-A*	*WPR-B*	*World*	*Total*
Maternal and perinatal conditions	Males	9	17	1	15	1	0	1	2	4	2	1	15	0	0	68	123
	Females	7	13	1	12	1	0	0	2	3	2	1	13	0	0	55	
Cancer	Males	107	260	99	116	12	6	11	282	72	175	58	125	117	1740	3180	4201
	Females	38	72	79	81	13	1	1	202	45	103	14	17	49	305	1021	
Neuro-psychiatric diseases	Males	305	828	2113	2979	305	20	170	1867	575	1509	524	1500	361	5033	18090	21904
	Females	31	141	682	792	82	3	9	514	109	398	74	101	160	717	3814	
Cardiovascular diseases	Males	98	207	–174	480	38	14	42	–233	449	1161	86	851	–39	1432	4411	3983
	Females	30	53	–256	162	16	1	1	–627	87	234	9	5	–219	76	–428	
Other noncommunicable diseases	Males	149	252	165	531	55	8	12	380	232	486	94	220	67	1045	3695	4555
	Females	44	74	25	101	20	2	2	147	96	196	17	69	3	66	860	
Unintentional injury	Males	576	1425	498	1815	268	100	80	643	675	2771	912	1837	141	2268	14008	16495
	Females	162	280	119	177	29	11	17	136	81	402	133	359	34	545	2487	
Intentional injury	Males	198	632	222	1919	110	14	12	162	176	1439	118	379	62	502	5945	7062
	Females	81	153	53	118	9	3	5	42	25	234	35	110	17	231	1117	
All alcohol-attributable DALYs	Males	1441	3621	2925	7854	789	162	328	3103	2183	7543	1793	4927	708	12020	49397	58323
	Females	393	785	702	1443	170	22	36	416	446	1570	284	675	43	1941	8926	
DALYs attributable to alcohol as a percentage of all DALYs	Males	2.0	3.5	11.9	17.3	8.6	1.3	0.6	11.1	10.2	21.5	5.3	2.8	8.1	29.1	6.5	4.0
	Females	0.6	0.8	3.2	4.1	2.2	0.2	0.1	1.6	2.5	6.5	1.0	0.4	0.6	1.8	1.3	

Chapter 13

Illicit drug use

Louisa Degenhardt, Wayne Hall,
Matthew Warner-Smith and Michael Lynskey

Summary

Estimating mortality directly attributable to illicit drug use such as overdose death—the most tangible adverse heath effect of illicit drug use—is difficult because of variations in the quality and quantity of mortality data. As a result, it is necessary to make indirect estimates, involving estimates of the prevalence of illicit drug use. However, it is difficult to make even indirect estimates because the use of these drugs is illegal, stigmatized and hidden. Nonetheless, efforts must be made to estimate the contribution that illicit drug use makes to the global burden of disease, because it is a pattern of behaviour that has a substantial adverse effect on the health of those who engage in it. In cohort studies of treated drug users the problematic use of illicit drugs has been associated with an increased overall rate of mortality, and with an elevated rate of a number of individual causes of death, four of which were estimated here: AIDS, overdose, suicide and trauma.

Definitions of the variable of interest are difficult because of deficiencies in the data collected by countries on illicit drug use, and by disagreements over what constitutes "problematic" illicit drug use. The definition used here was long-term regular injecting use of opioids, amphetamines or cocaine. Data on the prevalence of problematic illicit drug use were derived from a range of sources that used variable methods of deriving estimates.

A literature search was conducted of all studies that estimated the prevalence of problematic drug use. Available data on prevalence in countries with data were used to estimate the prevalence of problematic illicit drug use for subregions.[1] A search was also completed for cohort studies of drug users that had estimated mortality due to the four individual causes of death, and to all causes of death. Data on the number of years of follow-up were extracted from each study and a weighted average annual mortality rate was calculated for each of the four causes

of death, and for their sum. A standardized mortality ratio (SMR) was also derived from previous estimates of the excess mortality from all causes attributable to illicit drugs. Estimates were made for some causes by applying an attributable fraction obtained from sources such as the Joint United Nations Programme on HIV/AIDS (UNAIDS) (for HIV-related deaths) to estimates of total deaths for some causes. The median estimate of a range of estimates was used as the estimate for each subregion. Estimates were limited to persons aged 15–54 years.

In 2000, the median number of global deaths attributed to illicit drugs estimated by summing the four causes of death was 194 058. There were an additional 10 000 deaths from overdose above and beyond those coded as drug use disorders (added to unintentional injuries) or when coded drug use disorder deaths were higher than estimated overdose deaths. The median 2000 estimate derived using the all-cause method was 197 383. Both estimates had wide uncertainty intervals around them (113 494 to 276 584 for sum of four causes; and 101 751 to 322 456 for all-cause estimates). When morbidity attributable to illicit drug use is added to the estimated mortality, this risk factor accounts for 0.8% of global disability-adjusted life years (DALYs). The distribution of numbers of deaths between subregions varied between the two methods. These variations in the estimates reflect the considerable uncertainty about prevalence of drug use in different subregions and uncertainty about the applicability of mortality data derived in developed countries to mortality among illicit drug users in developing countries.

The current estimates suggest that illicit drug use is a significant cause of premature mortality among young adults. This is an underestimate of total disease burden because: (i) there are deficits in data on mortality attributable to the use of some illicit drug (most notably cannabis and the newer synthetic drugs like MDMA[2]); (ii) there are differences across subregions in the quality of data available on the causes of mortality that *were* included in the current estimates; (iii) there is an absence of data that would permit estimates of some other causes of mortality and morbidity attributable to illicit drug use, such as hepatitis B and hepatitis C and violence. There is a need for better data on: the prevalence of illicit drug use in developed and developing countries, and on the mortality and morbidity attributable to problematic drug use.

1. Introduction

The use of legally proscribed psychotropic substances for non-medical purposes appears to be increasing in many parts of the world (Frischer et al. 1994; UNDCP 2000; UNODCCP 2000) but it is difficult to quantify the rate of increase. It is difficult to estimate the prevalence of this behaviour and its adverse health consequences in individual societies because this behaviour is illicit and therefore often hidden. Even estimating mortality related to illicit drug use, the most tangible adverse

heath effect, is difficult for reasons that are discussed below (Thorley et al. 1977). Nonetheless, efforts must be made to estimate the contribution that illicit drug use makes to the global burden of disease because it is a pattern of behaviour that has a substantial adverse effect on the health and well-being of those who engage in it, producing substantial loss of life and disability (Hulse et al. 1999).

The global burden of death and disability attributable to illicit drugs was first estimated by Donoghoe (1996), as part of the Global Burden of Disease (GBD) project (Murray and Lopez 1996). Donoghoe estimated that illicit drug use was responsible for 100 000 deaths globally in 1990, the majority of which (62%) occurred in developing countries. Murray and Lopez (1996) pointed out that this estimate may be too low because of difficulties in reliably estimating the prevalence of illicit drug use and its adverse health effects. Donoghoe's estimate was based on the attributable fractions of various causes of mortality and morbidity attributed to illicit drug use by English et al. (1995), who reviewed all studies published up to 1993. The great majority of these studies, which were principally cohort studies, were conducted in the United States of America and Europe.

Since these estimates were made, there has been an apparent increase in illicit drug consumption in developed societies (Australian Bureau of Criminal Intelligence 2000; EMCDDA 2000; Frischer et al. 1994; UNODCCP 2000), and increased incidence of HIV contracted as a result of sharing of injecting equipment by illicit drug users in developing societies (Stimson 1993). This suggests that Donoghoe's 1990 estimates are likely to substantially underestimate the contribution that illicit drug use makes to the global burden of disease in 2000.

In this chapter, we have attempted to estimate the burden of disease due to illicit drug use by combining a range of sources of data on the prevalence of use and indicators of outcome. We also outline the definitions of the "exposure" variable used in making estimates, and outline the causes of burden considered in this chapter. As will become clear, estimates made of this cause of burden are difficult to make given: (i) paucity of data on the prevalence of illicit drug use around the world; (ii) the fact that data on causes of death related to illicit drug use are not well-recorded, so it is necessary to rely on indirect estimates derived from inaccurate prevalence estimates; and (iii) an absence of evidence on the risk of mortality and morbidity due to some causes among illicit drug users.

1.1 Exposure variable

Substances included

Illicit drug use includes the non-medical use of a variety of drugs that are prohibited by international law. These drugs include: amphetamine-type stimulants,[3] cannabis,[4] cocaine,[5] heroin[6] and other opioids,[7] and MDMA (ecstasy). In order to estimate mortality and morbidity attrib-

utable to illicit drug use, we need to clearly define what is and is not included in this risk factor.

This chapter will focus on the burden attributable to amphetamines, cocaine and opioids. Other substances that are illegal in most countries, such as ecstasy, solvents and cannabis, have not been included in the present analysis as there is currently insufficient research information to quantify the health risks associated with these drugs. Thus, their exclusion should not be interpreted as meaning that the use of these drugs is safe. Rather, it reflects a paucity of research on the harm caused by their use.

Relationship to dose, frequency and route of administration

The risk of premature mortality and morbidity from illicit drug use is dependent on dose, frequency and route of administration. Consequently it is necessary to define what is meant by "use" when defining the exposure variable "illicit drug use". The mortality risks of illicit drug consumption increase with increasing frequency and quantity of consumption (Fischer et al. 1997). Simple prevalence estimates of the proportion of the population that have *ever* used an illicit drug are likely to be associated with a low average risk since a single occasion of use and infrequent use, the most common patterns of use reported in population surveys, are associated with a small increase in mortality. More accurate estimates of the burden of disease attributable to illicit drugs require estimates of the prevalence of the most hazardous patterns of illicit drug use. These are found in highest prevalence among dependent drug users who typically inject drugs daily or near daily over periods of years. This pattern of use exposes users to the highest chance of fatal overdose (Warner-Smith et al. 2001) and of contracting bloodborne viral diseases (Ross et al. 1992).

The World Health Organization (WHO), following the International Classification of Diseases, defines problem drug use as "harmful drug use" and "drug dependence". Harmful drug use is defined by clear evidence that the substance use is responsible for physical (e.g. organ damage) and psychological harm (e.g. drug-induced psychosis). Drug dependence, as defined in the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), requires the presence of three or more indicators of drug dependence (WHO 1993). These include: a strong desire to take the substance; impaired control over the use; a withdrawal syndrome on ceasing or reducing use; tolerance to the effects of the drug; requiring larger doses to achieve the desired psychological effect; a disproportionate amount of the user's time is spent obtaining, using and recovering from drug use; and the user continuing to take other drugs despite associated problems. The problems should have been experienced for at least one month at some time during the previous year. The United Nations Drug Control Programme

(UNDCP) identifies "problem drugs" based on "the extent to which use of a certain drug leads to treatment demand, emergency room visits (often due to overdose), drug-related morbidity (including HIV/AIDS, hepatitis etc.), mortality and other drug-related social ills" (UNDCP 2000).

Most prevalence estimates vary with the assumptions made and the methodology employed. Data provided by the UNDCP do not have the same reliability as large-scale household surveys of the type generally conducted in developed countries. Unfortunately the expense of conducting such surveys makes their use in developing countries unfeasible. Even if such surveys were feasible in all countries, it is generally accepted that surveys underestimate harmful illicit drug use (Hall et al. 2000b).

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has invested considerable resources in developing methods for the collection of data on the prevalence of harmful illicit drug use that are both valid and comparable (EMCDDA 1997). While these standards have been developed for use within the European Union the global adoption of such standards may greatly improve estimates of drug-related harm. The EMCDDA defines "problem drug use" as injecting drug use (IDU) or long duration or regular use of opioids, cocaine or amphetamines (EMCDDA 1999). The EMCDDA definition is the one that we have adopted in estimating mortality attributable to illicit drugs.

Illicit drugs not included in current estimates of mortality

Cannabis

Cannabis has a high prevalence of use in many developed societies (Hall et al. 1999b) but there is a lack of well-controlled studies showing that its use increases mortality (Hall and Solowij 1998; WHO 1997). For example, we identified two cohort studies that have examined the effects of regular, prolonged cannabis use on risks of cancer. One of these reported no increase in overall cancer rates among cannabis users (although there were slightly increased rates of prostate and cervical cancer) (Sidney et al. 1997b). A case–control study found a doubling of the odds of aerodigestive cancers among heavy users of cannabis (Zhang et al. 1999) but it was difficult to disentangle the effects of cannabis smoking from those of tobacco smoking because many cannabis users also smoked tobacco (Andreasson and Allebeck 1990).

There are two prospective epidemiological studies of mortality among cannabis users. A Swedish study over 15 years of mortality among male military conscripts found an increased risk of premature death among men who had smoked cannabis 50 or more times by age 18 years (Andreasson and Allebeck 1990). Violent and accidental deaths were the major contributor to this excess. However, the association between mortality and cannabis use disappeared after multivariate statistical adjustment for alcohol and other drug use. Sidney et al. (1997a) re-

ported a 10-year study of mortality in cannabis users among 65 171 members of the Kaiser Permanente Medical Care Program aged between 15 and 49 years. The sample comprised 38% who had never used cannabis, 20% who had used less than six times, 20% who were former users, and 22% who were current cannabis users. Regular cannabis use had a small association with premature mortality (relative risk of 1.3) that was wholly explained by increased AIDS deaths in men, probably because cannabis use was a marker for male homosexual behaviour in this cohort. It is too early to conclude that cannabis use does not increase mortality because the average age at follow-up was only 43 years, and cigarette smoking and alcohol use were only modestly associated with premature mortality. For these reasons, we have not included any estimate of cannabis' effects on overall premature mortality.

Cannabis produces dose-related impairments in cognitive and behavioural functions that may potentially impair driving an automobile or operating machinery (Chait 1992). These impairments are larger and more persistent in difficult tasks involving sustained attention (Chait 1992). The most serious possible consequence of acute cannabis use is a motor vehicle accident if a user drives while intoxicated (Hall et al. 1994).

The effects of recreational doses of cannabis on driving performance in laboratory simulators and standardized driving courses have been reported as similar to blood alcohol concentrations between 0.07% and 0.10% (Hall et al. 1994). However, studies of the effects of cannabis on driving under more realistic conditions on roads have found much more modest impairments (Bates and Blakely 1999; Robbe 1994; Smiley 1999). This is probably because cannabis users are more aware of their impairment and less inclined to take risks than alcohol users (Smiley 1999).

Epidemiological studies of motor vehicle accidents have produced equivocal results because most drivers who have cannabinoids in their blood also have high blood alcohol levels (Hall et al. 1994, 2001). Studies with reasonable numbers of persons who have *only* used cannabis have not found clear evidence of increased culpability in these drivers (Bates and Blakely 1999; Chesher 1995). For these reasons we have not included any estimate of the contribution that cannabis makes to motor vehicle fatalities.

Other illicit drugs

Estimating the contribution that MDMA (ecstasy), hallucinogenic substances and inhalants make to premature mortality presents similar problems to cannabis (Boot et al. 2000). While there are case reports of deaths associated with MDMA intoxication (Dowling et al. 1987; Henry et al. 1992; Parr et al. 1997) these appear to be rare by comparison with overdose deaths due to opioids and cocaine in developed societies with good mortality data, such as Australia (Ridolfo and Stevenson

2001). The illicit use of pharmaceuticals and anabolic steroids have also been excluded from further analysis because difficulties in measuring (i) the prevalence of their harmful use and (ii) mortality attributable to their use mean that it is not possible to calculate relative risks. Similarly, the failure to include solvents stems largely from a lack of good evidence on the prevalence and extent or harm attributable to their use.

The exposure variable for illicit drug use in this analysis is, therefore, injection or long duration of use of amphetamines, cocaine or opioids. The failure to include cannabis, MDMA, hallucinogens and inhalants in our estimates of burden of disease attributable to illicit drugs reflects our ignorance of their health risks; it does not imply that the use of these drugs is without risk to users.

Counterfactual exposure distribution

The *theoretical* minimum counterfactual exposure distribution is zero illicit drug use. There may be countries in the world that can truly claim to have zero illicit drug use but there must be few of these now. Even countries that have the policy goal of achieving a drug-free society, such as Sweden, do not have zero illicit drug use. Arguably, once illicit drug use and dependence have appeared in a society, it is unrealistic to expect to be able to return to a zero level of illicit drug use. It may be reasonable to aim to reduce the prevalence of the most harmful types of illicit drug use and to minimize the harm that their use causes.

One approach to defining a *plausible* counterfactual exposure would be to use developed countries with the lowest prevalence of illicit drug use as the basis for the estimate. Countries like Finland and Sweden may be suggested as examples. The weakness with this strategy is that illicit drug use trends are dynamic and countries that currently have low rates may show increases in rates of use (as has recently happened in Sweden) as availability of illicit drugs increases and more favourable social attitudes develop towards illicit drug use among young adults.

It is also not clear what are feasible minimum counterfactuals. It is not clear whether prevention programmes, such as school-based and other intervention programmes, can prevent problem drug use (National Research Council 2001). These programmes have been most widely implemented and evaluated in the United States. After reviewing this evidence, the United States National Research Council recently concluded that the

> effectiveness of most of these approaches for reducing substance use is unknown . . . Some prevention approaches are effective at delaying the initiation or reducing the frequency of tobacco, alcohol and marijuana use [but] . . . the magnitude of these effects are generally small . . . [and it] is not clear that preventing or reducing the use of gateway substances translates into a reduced use of cocaine or other illegal drugs (pp. 233–234).

These conclusions have been supported by a recent study of the likely impact of the most effective school-based prevention programmes, which concluded that they would have, at best, very modest effects in preventing cocaine use (Caulkins et al. 1999).

There is better evidence that some treatment programmes (e.g. opioid agonist maintenance treatment) can substantially reduce illicit opioid use and premature mortality from drug overdose[8] among opioid-dependent persons (Warner-Smith et al. 2001). In the case of opioid-dependent persons, one could examine the effects that enrolling 10%, 20%, 30%, etc. of persons who were dependent on illicit opioids in opioid maintenance treatment would have on illicit opioid use, overdose deaths and disability produced by illicit opioid dependence. Similar estimates could be made of the expected reduction in HIV/AIDS among injecting drug users from the introduction of needle and syringe exchange and distribution programmes.

1.2 Data sources

To provide data on the prevalence and risks of illicit drug use, a series of extensive computer searches using databases listed below was conducted. The specific parameters of these searches are also listed.

Databases searched

We carried out a citation search of Medline, Psychinfo and Web of Science, a search of reference lists of identified papers, including a literature search provided by English et al. (1995), which covered the literature published prior to 1993.

Search terms

1. *Illicit drug*, or *substance use*, or *substance abuse*, or *drug use*, or *drug abuse*, or *heroin*, or *opiates*, or *cocaine*, or *amphetamine*—limited to human studies published in the English language.
2. *Prevalence*
3. *Cohort*, or *case–control*
4. *Mortality*
5. *Morbidity*
6. *Suicide*, or *accidents*, or *HIV*, or *assault*

Strategy: combine 1 and 2; 1 and 3 and 4; 1 and 3 and 5; 1 and 3 and 6.

2. Risk factor exposure

2.1 Prevalence studies

Given the lack of reliable direct estimates of the health consequences of illicit drug use, it was necessary to make indirect estimates of burden. Hence, the first challenge in quantifying the burden of disease attributable to illicit drugs was to determine the prevalence of exposure to this risk factor. Illicit drug use differs from other risk factors in the GBD project in that one of its defining features, its illegality, makes it difficult to quantify. This presents two problems. First, illicit drug-using individuals are "hidden" and are thus difficult to identify. Second, even if all drug users can be located and interviewed, they may attempt to conceal their use of these drugs.

There are no well-tested and widely accepted "gold standard" methods for producing credible estimates of the number of people who make up the "hidden population" of such drug users (Hartnoll 1997). The preferred strategy is to look for convergence in estimates produced by a variety of different methods of estimation (EMCDDA 1997, 1999). These methods are of two broad types, *direct* and *indirect*. Direct estimation methods attempt to estimate the number of illicit drug users in representative samples of the population. Indirect estimation methods attempt to use information from known populations of illicit drug users (such as those who have died of opioid overdoses, and those who are in treatment or the criminal justice system) to estimate the size of the hidden population of illicit drug users.

A large number of studies purporting to be prevalence studies do not present credible prevalence data. Prevalence data reported in peer-reviewed literature are scarce and often unrepresentative. In addition, the range of methodologies used makes comparisons between studies difficult. For this reason, other sources of data were sought to complement prevalence estimates reported in the peer-reviewed literature.

2.2 Prevalence of problematic illicit drug use

For the purposes of estimating global mortality, data collated by the UNDCP (2000) provides a convenient and comprehensive tabulation of the most recent international prevalence data. The aggregated prevalence data for subregions are displayed in Table 13.1. The principal advantage of using UNDCP data is that it provides a readily accessible set of estimates for the majority of countries in the world. The quality of the data collected and reported by the UNDCP varies across countries and regions from high quality national survey data to key informant and indicator data of uncertain validity.

In some cases, prevalence data provided by the UNDCP were supplemented by data from other agencies, such as the EMCDDA, and the Asian Harm Reduction Network (AHRN). In regions where these addi-

tional data were available, they were used in indirect estimation methods as an additional source of prevalence estimates, thus meaning that these regions had additional estimates of causes of mortality.

UNDCP 2000 DATA ON THE PREVALENCE OF 12-MONTH USE AMONG PERSONS AGED >15 YEARS

Table 13.1 shows the population estimates of each of the 14 subregions, as well as the UNDCP-derived prevalence estimates of problematic use of the three substances considered in current estimates. It can be seen that problematic cocaine use is largely restricted to the Americas, the European Union and the developed countries of Oceania. Conversely, opioid abuse appears to be restricted to Asia and eastern and central Europe, as well as the developed countries of Oceania, the European Union and North America. Patterns of use in developing countries appear to reflect proximity to production areas and trafficking routes that supply the drug markets of developed "consumer" countries.

A challenge when estimating the prevalence of illicit drug consumption is to avoid double counting individuals who use more than one substance. There is strong evidence (principally from developed countries) that few drug users use one drug exclusively (Darke and Hall

Table 13.1 Prevalence (%) of problematic illicit drug use in the past 12 months among persons aged >15 years, by subregion (UNDCP-derived estimates of prevalence)[a]

Subregion	*Population >15 years (000s)*	*Opioids*	*Cocaine*	*Amphetamine*
AFR-D	159577	0.09	0.26	0.31
AFR-E	190152	0.01	0.05	0.12
AMR-A	255420	0.13	0.78	0.20
AMR-B	297625	0.03	0.24	0.20
AMR-D	44658	0.07	0.43	0.11
EMR B	86853	0.55	—	0.02
EMR-D	204039	0.41	—	0.14
EUR-A	339446	0.11	0.18	0.24
EUR-B	161213	0.09	0.01	0.10
EUR-C	152432	0.19	0.01	0.04
SEAR-B	206870	0.04	—	0.10
SEAR-D	818521	0.15	—	—
WPR-A	129888	0.04	0.28	0.22
WPR-B	1131503	0.02	—	0.34

— No data available, assumed to be negligible.

[a] Some estimates for subregions are based on data from a small number of countries in the subregion.

1995; Topp et al. 1999). Rather, most users nominate a drug of choice but regularly use a wide range of substances (Darke and Hall 1995; Klee et al. 1990). Thus combining estimates of the size of each population will overestimate the size of the drug-using population. Given that many opioid and stimulant users are polydrug users, and that these drugs are the most harmful illicit drugs, the simplest approach to this problem may be to use the prevalence of regular users of opioids and/or stimulants in each country as the prevalence estimate for problem illicit drug use.

In order to address this issue, a range of three prevalence estimates was derived from the above UNDCP data:

- a low estimate, which assumed that 50% of each of the prevalence estimates was unique and therefore additive;
- a medium estimate which assumed that 75% of each of the prevalence estimates was unique and therefore additive; and
- a high estimate, which assumed that the prevalence estimates were completely additive (i.e. that those who used opioids were a separate group from those who used cocaine and amphetamines).

In order to estimate the proportion of persons who had used these drugs *problematically* in the past year, data from the 1997 Australian National Survey of Mental Health and Well-Being were used. This survey was a structured diagnostic interview of a representative sample of Australian adults aged ≥18 years (Hall et al. 1999d; Henderson et al. 2000). It assessed persons who had used opioids and stimulant drugs for symptoms of DSM-IV[9] defined abuse and dependence. Of those who had reported using these drugs within the past year, 28% met criteria for DSM-IV abuse or dependence.

In the current calculations, therefore, it was assumed that 28% of those who had used these drugs within the past year were problematic users of these drugs.

It must be noted that prevalence estimates were not available for all countries in all subregions. In making estimates from UNDCP data, where countries had no reported prevalence estimates, subregional estimates of prevalence were used by deriving a weighted average prevalence rate from the data that were available from countries in the subregion. This weighted average rate was used in making subregional estimates. Some subregions therefore had estimates based upon only some countries within the subregion, which may make these estimates less representative:

- AFR-D: prevalence estimates based upon estimates provided for Cameroon, Chad, Ghana, Mauritius, Nigeria, Senegal and Sierra Leone;

- AFR-E: prevalence estimates based upon estimates provided for Ethiopia, Kenya, Namibia, Rwanda, South Africa, Uganda, the United Republic of Tanzania and Zimbabwe;
- AMR-D: prevalence estimates based upon estimates for Bolivia, Ecuador and Peru;
- EMR-D: prevalence estimates based upon estimates provided for Egypt, Morocco and Pakistan; and
- WPR-B: prevalence estimates based upon estimates provided for China, the Lao People's Democratic Republic, Malaysia, the Philippines, the Republic of Korea and Viet Nam.

EMCDDA estimates of "problem drug users"

These estimates were used to derive alternative estimates of prevalence in countries from EUR-A: Austria, Belgium, Croatia, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Norway, Spain, Sweden and the United Kingdom.

A weighted prevalence rate was derived from these estimates for the whole of EUR-A. The EMCDDA produced low and high estimates of "problem drug users" for countries in the European Union using a variety of estimation methods including capture-recapture and back-projection methods. Both these estimates were used to make lower and upper estimates of prevalence using these data. A median estimate was also calculated when making median estimates for each of the four major causes of mortality, and for all-cause mortality.

AHRN estimates of IDU in the Asian region

Numbers from the AHRN were used to make estimates of the prevalence of IDU in these countries (IDU in this case was taken to represent the prevalence of "problem drug use" used in the other two estimates). Weighted prevalence estimates of IDU prevalence were only made in the subregion they were classified under if two or more countries reported (see www.ahrn.net). The countries were as follows:

- SEAR-B: Indonesia (no estimate made);
- SEAR-D: Myanmar (no estimate made);
- WPR-A: Japan, Singapore;
- WPR-B: Cambodia, China, Malaysia, Mongolia, the Philippines, the Republic of Korea and Viet Nam.

Table 13.2 shows the prevalence estimates produced from the EMCDDA and AHRN sources. Comparison with estimates in Table 13.1 reveals that the estimates are fairly similar.

In the current chapter, we have used *all* available estimates of prevalence to make a range of estimates of each cause of mortality. Hence, for

Table 13.2 Alternative estimates of prevalence of problematic drug use in three subregions

Subregion	*EMCDDA low estimate (%)*	*EMCDDA high estimate (%)*	*AHRN (%)*
EUR-A	0.2	0.4	NA
WPR-A	NA	NA	0.3
WPR-B	NA	NA	0.01

NA Not applicable.

example, EUR-A has two sources of prevalence estimates: EMCDDA estimates (low and high) and UNDCP estimates (low, median and high). This approach was taken so as to make estimates based on as much of the available data as possible.

3. Health outcomes

3.1 Premature mortality

The major causes of premature death among illicit drug users are relatively directly related to their patterns of drug use. Evidence for these causes comes from studies of premature mortality among cohorts of illicit drug users who have been treated in Europe and North America. (It must be remembered that there is a range of issues surrounding the use of such cohort studies in deriving global estimates of mortality rates, which are discussed in section 6.2.)

Notwithstanding these issues, illicit drug users have elevated rates of four main causes of premature death by comparison with age peers who do not use illicit drugs, namely, drug overdose, HIV/AIDS, suicide and trauma.

Overdose

"Overdose" refers to two ICD-10 classifications of cause of death: (i) accidental or intentional fatal poisoning caused by specific drugs, and (ii) poisoning deaths occurring among dependent drug users that are attributed to drug dependence. Despite the conceptual simplicity of drug overdose deaths it has been difficult to quantify the number of such deaths with any precision, even in developed countries, for reasons that are discussed below.

HIV/AIDS

The connection between illicit drug use and HIV/AIDS largely arises from injection as the route of drug administration via drug users sharing

contaminated injecting equipment. This means that it is necessary to establish the prevalence of injecting drug use, rather than harmful drug use *per se*, in order to calculate the proportion of incident HIV cases that can be attributed to harmful drug use. This can be accomplished by extrapolating from data on the prevalence of injecting drug use among persons who are illicit drug users as indicated in studies in the peer-reviewed literature. It can also be estimated by the proportion of HIV/AIDS cases that are attributed to IDU in each country. One issue that exists concerns a lack of data from some countries on the prevalence of AIDS cases that are attributable to IDU. In the current study, we have only used UNAIDS estimates of mortality attributable to injecting drug use.

Suicide

Suicide is a cause of death in the ICD-10 but, as with overdose deaths, the reliability with which this cause of death is diagnosed may vary between countries depending on a number of variables. Cultural variations in attitudes towards suicide may influence coroners' and mortality registrars' willingness to classify a death as intentional (Domino and Lenaars 1989; Domino and Takahashi 1991).

Trauma

Trauma includes homicide, motor vehicle accidents and other forms of accidental death. It is likely that this will be underestimated since few cohort studies report mortality rates from all forms of trauma and it is difficult to calculate attributable fractions for these causes because many trauma deaths in drug users may not be recognized as being drug-related.

All-cause mortality

Several studies have calculated standardized mortality ratios (SMRs) for problem drug users. These studies indicated that problem drug users have substantially increased mortality rates, with typical estimates suggesting that they are approximately 13 times more likely to die than their peers (English et al. 1995; Hulse et al. 1999).

3.2 Likely sources of morbidity attributable to illicit drug use

Premature *death* is the most serious adverse health outcome experienced by problem drug users; it is also the best-studied health outcome in this population. Nevertheless, the contribution that illicit drug use makes to the burden of disease is not exhausted by premature death.

First, each of the major causes of premature mortality probably causes substantial morbidity. Second, drug dependence, which is highly prevalent among problem drug users, is also a cause of disability. Third, evidence suggests that the prevalence of hepatitis B and hepatitis C viruses (HBV and HCV) is high among injecting drug users (Alter et al. 1990;

Anderson et al. 1994; Levine et al. 1994; MacDonald et al. 1996, 2000). Both of these viruses are associated with substantial morbidity and premature death due to the sequelae of chronic infection (Alter et al. 1990; MacDonald et al. 1996, 2000).

However, there is little good evidence that allows quantification of the morbidity related to the use of illicit drugs, and it is not possible to make estimates of the burden of disease caused by morbidity resulting from illicit drug use. This means that current estimates of the burden of disease attributable to illicit drug use significantly underestimate the total burden of illicit drug use. An American analysis of the economic costs of drug use (National Institute on Drug Abuse 1992) revealed that problematic illicit drug use cost the United States an estimated US$98 billion in 1992; of this, the figure for the impact of premature deaths was US$14.6 billion. Health care expenditure cost an estimated US$9.9 billion, and impaired productivity resulting from drug-related morbidity cost an additional US$14.2 billion—clearly, costs from mortality attributable to drug use in the United States were a fraction of those attributable to morbidity. This means that our estimates are likely to underestimate the global burden of disease attributable to illicit drugs. Future estimates of the global burden of disease would be substantially improved by research into the total morbidity that is attributable to illicit drug use.

Outlined below are some of the major outcomes of illicit drug use that may be significant sources of morbidity. Future research is required to better document the nature and extent of morbidity attributable to the use of illicit drugs. In the absence of such data, we assumed that for each of the four causes included, the population attributable fractions for mortality could also be used to estimate the proportion of morbidity explained by that cause. Equivalently, we assumed that if illicit drug use causes a certain proportion of AIDS mortality, it does so by increasing its incidence, also increasing AIDS-related morbidity by a similar proportion. While uncertain, this assumption is closer to underlying mechanisms than assuming that illicit drug use contributed to none of AIDS-related morbidity. This approach cannot be used to estimate morbidity due to conditions that do not cause deaths, such as, neuropsychological impairment.

Non-fatal overdose

The prevalence of non-fatal overdose is not well studied in problem drug users apart from among opioid users in some developed societies, where non-fatal overdose is a common event (Darke et al. 1996; Gossop et al. 1996; Warner-Smith et al. 2001). An unknown proportion of these cases requires acute medical treatment and hospitalization and some of these may develop persistent medical sequelae as a result of non-fatal overdoses, such as cognitive impairment (Darke et al. 2000) and other medical problems (Warner-Smith et al. 2001). There are no good esti-

mates of the prevalence of these outcomes that would permit an estimate to be made of their contribution to the burden of disease. It should be a research priority to obtain better estimates of the prevalence of these forms of morbidity in future studies of illicit drug users so that the contribution that illicit drug use makes to the burden of disease can be better understood.

AIDS

In developed societies, the widespread availability of anti-retroviral drugs has extended the life expectancy of persons living with HIV/AIDS (Donoghoe and Wodak 1998), with the result that HIV/AIDS may become a chronic condition. However, in these countries we rarely have data on the proportion of treated cases who acquired their infections as a result of IDU. We have assumed that the proportion of *treated* HIV/AIDS cases that are attributable to IDU is the same as the proportion of AIDS-related deaths that are attributed to IDU.

Hepatitis B and C

Many injecting drug users in developed countries are infected with HCV. In Australian needle and syringe attendees, for example, the prevalence of HCV infection is estimated at between 50% and 60% (National Centre in HIV Epidemiology and Clinical Research 1998). Chronic infection has been estimated to occur in 75% of infections, and 3–11% of chronic HCV carriers will develop liver cirrhosis within 20 years. Given the large number of injecting drug users infected with HCV, and the more protracted complications arising from this infection, the net health and economic cost of HCV transmitted by injecting drug use may be as high as, or considerably higher than, those of HIV. Data on the prevalence of this infection among injecting drug users in developed countries is limited; it is non-existent in many developing countries.

Similarly, the prevalence of HBV has been documented as quite high among injecting drug users in developed countries. There is, however, a lack of good evidence on (i) the prevalence of HBV among illicit drug users; (ii) the risk of premature mortality caused by this disease; and (iii) the extent of morbidity that it causes. HBV has therefore not been included in current estimates for these reasons. It would be desirable in future to include estimates of morbidity and disability that HBV and HCV cause among illicit drug users.

Attempted suicide

Recent studies in Norway (Rossow and Lauritzen 1999) and Australia (Darke and Ross 2000) have found high rates of self-reported suicide attempts among problematic opioid users (Darke and Ross 2000; Rossow and Lauritzen 1999). Survivors of such suicide attempts may require psychiatric and medical treatment and some suffer from medical sequelae. As with non-fatal overdose, there are no data that permit the

morbidity attributable to this cause among problem drug users, but estimates could be obtained by applying the same attributable fraction for suicide deaths to morbidity caused by attempted suicides.

Trauma

In developed societies there are approximately 20 cases of severe injury for every death caused by a motor vehicle accident (MVA) (English et al. 1995). We could assume the same is true for problem drug users if we had a credible estimate of the proportion of motor vehicle fatalities that were attributable to problem drug use. In the absence of this data we estimated the proportion of MVA morbidity attributable to illicit drugs by applying the same attributable fraction for MVA deaths to morbidity caused by motor vehicle accidents.

Psychiatric disorder

Studies of treated populations of opioid-dependent persons have found a high prevalence of major depression and anxiety disorders (Darke and Ross 1997). It is difficult to sort out cause and effect from these cross-sectional data so it is unclear in what proportion of these cases psychiatric disorders preceded and contributed to the development of problem drug use or vice versa. Nor is it clear to what extent pre-existing psychiatric disorders have been exacerbated by problem illicit drug use or vice versa. It is accordingly difficult to estimate what proportion of these disorders are attributable to problem illicit drug use. For these reasons such estimates have not been included in this chapter. Better understanding of the causal relationships between the two is a priority for future research.

3.3 Causality

The main evidence for believing that illicit drug use is a cause of premature death, morbidity and disability comes from cohort studies and cross-sectional studies of illicit drug users.

Mortality

The cohort studies have identified a number of causes of mortality that are more prevalent among problem illicit drug users than their peers, indicating an association between harmful illicit drug use and these causes of mortality. They have rarely been well controlled for potential confounders, such as social disadvantage, which is common among illicit drug users. English et al. (1995) have argued that the mortality excess among illicit drug users is too large to be wholly accounted for by social disadvantage. Moreover, there are good reasons for believing that the relationship is causal in the case of deaths caused by overdose and blood-borne virus infection. The major illicit drugs are known to have adverse effects in overdose that can be fatal. Opioids, for example, produce respiratory depression that can cause death, and this is especially likely to

occur if opioids are used in combination with other central nervous system depressant drugs such as alcohol and benzodiazepines (Darke and Zador 1996; Warner-Smith et al. 2001). Stimulant drugs, such as cocaine and amphetamines, can cause fatal cardiac arrhythmias and strokes (Goldfrank and Hoffman 1993; Platt 1997), which are very rare causes of death in young adults who do not use these drugs. Similarly, the viruses that cause HIV/AIDS, HBV and HCV infections are efficiently spread by contaminated blood in shared injection equipment (Donoghoe and Wodak 1998; MacDonald et al. 1996).

The case for illicit drug use being a contributory cause of suicide is less direct. Depression is a risk factor for suicide and it occurs at higher rates among illicit drug users. Intoxicating drugs like alcohol and opioids, and dependence on these drugs, have been shown in case–control and prospective studies to be risk factors for suicide (Beautrais et al. 1998, 1999). Opioid-dependent persons in treatment report very high rates of attempted suicide (Darke and Ross 2000).

The case for a causal connection between illicit drug use and trauma deaths is less direct still. Driving while intoxicated by alcohol is a well-known risk factor for fatal motor vehicle crashes (English et al. 1995) and the heavy use of alcohol is common among illicit drug users (Darke and Hall 1995; Darke and Ross 1997; Gossop et al. 1998). Opioids are also intoxicating substances that adversely affect driving, although they are much less commonly found in persons killed in fatal car crashes.

Morbidity

The case for a causal connection between illicit drug use and morbidity caused by drug overdose, HIV/AIDS and HCV, suicide and trauma are the same as for mortality. To these must be added psychiatric disorders and drug dependence. By definition, drug dependence is caused by regular illicit drug use and most regular illicit drug users are dependent on one or more of the drugs that they regularly use.

The causal relationship between psychiatric disorder and illicit drug use is less clear. The two are associated in the general population and this is not attributable to confounding by social and demographic variables (Degenhardt et al. 2001). The direction of the causal relationship is less certain. Conduct disorders, depression and anxiety disorders that develop in early adolescence may predispose young adults to become dependent on illicit drugs. These disorders may also arise as a result of the adverse effects that illicit drug dependence has on the lives of those affected by it, or the rigours of regular illicit drug use may prolong pre-existing depressive and anxiety disorders that may have resolved in its absence.

4. Risk factor–disease relationship

4.1 Outcome studies

Inclusion criteria

The following inclusion criteria were used:

- cohort studies on the use of opioids, cocaine or amphetamines and mortality;
- studies in which SMRs were reported. SMRs are the ratio of observed numbers of deaths in the cohort to the expected number of deaths in people of the same age and sex distribution in the general population; and
- studies in which crude mortality rates (CMRs) could be derived from the available data in the article.

Exclusion criteria

The following exclusion criteria were used:

- multiple reports of same data set;
- subsets of a cohort; and
- reviews, commentaries, letters and abstracts.

Table 13.3 shows those studies that were not included in the present analyses. CMRs were derived from data on the number of deaths, period of follow-up and number of participants. Where person-years were not calculated by the authors, persons lost to follow-up were assumed to be alive at the end of study period and included in our calculation of person-years observation (to maintain consistency with studies that did not report numbers lost to follow-up). Following previous research (Hulse et al. 1999) it was assumed that persons dying during the period of

Table 13.3 Outcome studies that were not included

Reference	*Reason for exclusion*
Vaillant (1966)	Data are a subset of Vaillant (1973)
Watterson et al. (1975)	Series of cross-sections, not longitudinal
Thorley et al. (1977)	Data are a subset of Wille (1981)
Wiepert et al. (1978)	Poorly defined cohort
Ghodse et al. (1985)	Study of death register, not a predefined cohort
Selwyn et al. (1989)	No cohort defined
Frischer et al. (1993)	Retrospective
Fischer et al. (1999)	No mortality reported

follow-up died in the middle of the period (when estimating the person-years at risk). CMRs are unadjusted, expressed as per cent mortality per annum.

4.2 Quantification of risk

In determining the risks associated with harmful illicit drug use, it is necessary to rely on the results of cohort studies that have conducted long-term follow-up of individuals identified as using illicit drugs. English et al. (1995) identified a total of 13 such studies investigating mortality associated with illicit opioid use up to 1993 (Barr et al. 1984; Bewley et al. 1968; Cherubin et al. 1972; Engstrom et al. 1991; Frischer et al. 1993; Ghodse et al. 1985; Haastrup and Jepson 1984; Hser et al. 1993; Joe et al. 1982; Perucci et al. 1991; Thorsen and Haarstrup 1975; Vaillant 1973). Through extensive literature searches we identified a further 16 studies that have been published since 1993, excluding studies which used previously published data (Capelhorn et al. 1996; Eskild et al. 1993; Friedman et al. 1996; Fugelstad et al. 1995, 1997; Galli and Musicco 1994; Goedert et al. 1995; Goldstein and Herrera 1995; Keenan et al. 1993; McAnulty et al. 1995; Oppenheimer et al. 1994; Orti et al. 1996; Robertson et al. 1994; van Haastrecht et al. 1996; Wahren et al. 1997; Zaccarelli et al. 1994). The studies summarized in Tables 13.4–13.8 were all studies identified that followed up cohorts of problem or injecting drug users.

The general limitations of cohort studies have been discussed elsewhere (Dart 1995; Feldman 1993; Freeman 1996). The particular limitations of the cohort studies that are most relevant to this project are, first, that these studies were conducted exclusively in developed countries (principally the United States with 11 studies, western Europe with 22 studies and the Western Pacific with two studies). Second, with one exception (McAnulty et al. 1995) these studies drew their samples from people receiving treatment for drug-related problems. Third, the majority of the studies have been done on opioid users, usually injectors. There is much less data on mortality among problem stimulant users. Finally, the majority of cohort studies were conducted in the pre-AIDS era. These limitations will be discussed in more detail later in this chapter.

In studies of all-cause mortality (Table 13.8), a total of 152 432 subjects were included, which involved a total of 1 035 574 person-years of observation, during which time 11 633 deaths were recorded. The weighted average all-cause mortality rate was 1.12% per annum. Pooled crude death rates from the specific causes of death identified by English et al. (1995) were calculated from data reported in these studies (see Tables 13.4–13.7).

Table 13.4 Included outcome studies that examined rates of mortality due to AIDS among problematic drug users

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug used*	*Crude mortality rate per 1000*
Australia, Sydney	Capelhorn et al. (1996)	296	Methadone	13	39	3 484	Heroin	0
Italy	Goedert et al. (1995)	4962	Treatment	3.88	—	21 130	…	0.71
Italy, Milan	Galli and Musicco (1994)	2432	Treatment	6.7	—	16 415	Methadone (94%)	0.88
Italy, Rome	Davoli et al. (1997)	3955	Treatment	4	198	15 820	IDU	1.06
Italy, Rome	Perucci et al. (1991)	4200	Methadone treatment	8	Nil	33 600	Opioids	0.05
Italy, Rome	Zaccarelli et al. (1994)	2431	Treatment	3.2	—	7872	IDU	1.13
Netherlands, Amsterdam	Mientjes et al. (1992)	390	Methadone treatment	2.2	—	810	Opioids	0.37
Netherlands, Amsterdam	van Haastrecht et al. (1996)	632	HIV– methadone and STD clinic patients	4.4	18	2781	…	0.43
New Zealand, Wellington	Dukes et al. (1992)	997	Treatment	9.1	—	9073	Injecting opioid users	Nil
Norway, Oslo	Eskild et al. (1993)	1009	HIV test centre clients	3.67	—	3706	IDU	0.11
Spain, Catalonia	Orti et al. (1996)	15711	Hospital emergency departments and treatment	2.8	—	43 717	Opioids	1.08
Spain, Catalonia	Sanchez-Carbonell and Seus (2000)	135	Treatment	10.5	—	1418	Heroin	1.48
Sweden	Gronbladh et al. (1990)	368	Methadone and untreated	5–11	—	3283	Heroin	0
Sweden, Gothenburg	Benson and Holmberg (1984)	618	Drug using conscripts, rehab. & psych. patients, drug using welfare recipients	10	—	5789	Cannabis, solvents, LSD, stimulants (opioids rare)	0
Sweden, Lund	Tunving (1988)	524	Persons in treatment for opioid, amphetamine, and both opioid and amphetamine use	10	0	5240	Opioids, amphetamines	0

continued

Table 13.4 Included outcome studies that examined rates of mortality due to AIDS among problematic drug users (*continued*)

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug used*	*Crude mortality rate per 1000*
Sweden, Stockholm	Fugelstad et al. (1995)	472	HIV+	3.8	—	1 793	…	0.39
Sweden, Stockholm	Fugelstad et al. (1997)	1 640	Drug-related hospitalization	8	Nil	13 120	14% heroin; 35% amphetamine; 23% polydrug	0.14
United Kingdom, England, London	Oppenheimer et al. (1994)	128	Treatment	22	7	2 816	Heroin	Nil
United Kingdom, Scotland, Edinburgh	Bucknall and Robertson (1986)	184	Heroin users attending a general practice	4	4	720	Heroin	0
United Kingdom, Scotland, Edinburgh	Robertson et al. (1994)	203	GP	10	17	2 030	IDU	0.79
USA, CA	Hser et al. (1993)	581	Males in compulsory treatment	24	35	13 064	"Narcotics"	0
USA, CT, New Haven	Musto and Ramos (1981)	91	Under treatment for drug abuse when recruited	52	—	4 732	Morphine	0
USA, New York	Friedman et al. (1996)	858	Drug and alcohol dependants on welfare	8	—	6 864	Drugs and alcohol	1.23
USA, OR, Portland	McAnulty et al. (1995)	1 769	Not in treatment	1.78	—	3 149	IDU	0
USA, PA, Philadelphia	Zanis and Woody (1998)	507	Methadone	1	5	507	Heroin	0
Netherlands, Amsterdam; USA, MD, Baltimore	van Ameijden et al. (1999)	2 809	Treatment shelters and community agencies	6–9	—	15 107	IDU	0

— No data.

4.3 Overview of methods of estimating the mortality burden of illicit drugs

Methods for estimating mortality attributable to harmful illicit drug use can be "direct" or "indirect". Direct methods count the number of deaths attributed to illicit drug use by applying attributable fractions to ICD-classified causes of death in national mortality registers. Indirect methods involve estimating mortality by multiplying measures of mortality risk (e.g. relative risk) by the prevalence of the risk factor in the population.

Direct methods

The first method, which requires the greatest amount of data, uses the attributable fraction of mortality attributed to harmful illicit drug use calculated for a population for which direct measures of specific cause mortality data are available. This attributable fraction is then used to extrapolate the mortality attributable to harmful illicit drug use in another population.

This method has the advantage of excluding deaths in those exposed that are *not* due to the risk factor. The source of mortality data to use with this method is the All-Cause Mortality Database compiled by WHO. Attributable fractions for illicit drug use (which have been calculated in countries where direct estimates have been made) can be applied to these data.

In some countries direct measures of mortality are available from mortality registers. This is straightforward, in principle, for deaths caused by overdose, which has an attributable fraction of 1. Aside from individual country mortality registers, other sources of directly measured mortality data include HIV/AIDS surveillance data available from agencies such as UNAIDS and the United States Census Bureau.

The difficulties involved in applying this method are exemplified by the case of "overdose" deaths. This is the only cause of death that is wholly attributable to harmful illicit drug use so all mortality due to this cause must be the result of the risk factor. It is the cause of death that should be the most easily quantified. However, the great many difficulties inherent in assigning any particular case to this cause of death have been well documented (Advisory Council on the Misuse of Drugs 2000; Danish National Board of Health 1997; WHO 1998).

In most United Nations Member States, cause of death is classified according to ICD-10 codes, which specify whether the cause of death was intentional poisoning (suicide), unintentional poisoning or dependence. Despite the existence of ICD-10 criteria for classification of cause of death, countries differ in the way that deaths are registered and causes of death are classified (Danish National Board of Health 1997; WHO 1998). For example there is one European country in which: "... it is well known that about 90% of drug-related deaths are coded

with the code for unknown cause of death" (p. 51) (Sanchez-Carbonell and Seus 2000).

A recent report by the Home Office has been critical of the system for recording drug-related deaths in the United Kingdom (Advisory Council on the Misuse of Drugs 2000). It noted that deaths may not be classified as drug-related if they are not referred to the coroner (as may happen when a certifying doctor is unaware that the deceased was a drug user) or the death is due to an indirect effect of harmful drug use, such as a viral infection. There also appears to be a great deal of variation between individual coroners in their preparedness to record deaths as drug related. The report notes that: "there are coroners working in areas of known high drug prevalence who never certify a death as related to drug misuse" (p. 80).

Other sources of variation identified in the British report were that neither post-mortem nor toxicological analysis are formally required for suspected drug-related deaths; that the verdicts available to the coroner are not mutually exclusive; that coroners do not have the necessary skills to distinguish between the verdicts available to them, most notably "dependence on drugs" and "non-dependent abuse of drugs"; and that there is no requirement of the coroner to identify the drugs involved (Advisory Council on the Misuse of Drugs 2000).

There are also variations between countries in how much information is gathered about the circumstances or cause of death (Danish National Board of Health 1997; WHO 1998). In Australia, for example, autopsy is routinely conducted on all suspected overdose deaths, making forensic and toxicological data the basis for the classification of cause of death. This, however, is a far from universal practice. In the United States, only 20% of drug-related deaths are subject to autopsy (WHO 1998). Similarly, the immediate cause of death is recorded in death registers but contributing factors may or may not (Danish National Board of Health 1997; WHO 1998). This can cause large differences in rates of drug-related deaths based on death register data.

For causes other than overdose, where the attributable fraction is less than 1, the difficulties involved in attributing a death to illicit drug use are compounded. In addition to the caveats discussed above, the simple fact that there is a complete absence of such data in the majority of countries in the world necessitates the use of indirect methods to estimate mortality attributable to harmful drug use.

Indirect methods

Indirect methods of estimating mortality can be used when directly recorded data are unavailable or unreliable. The estimates provided by these methods can be validated against direct methods in countries where reliable mortality data are available. For the vast majority of countries in the world, indirect methods provide the only indicator of the extent

of the health consequences of harmful illicit drug use, because of the absence of epidemiological data on drug-related mortality. Three indirect methods can be used to estimate the burden of mortality attributable to illicit drugs.

The simplest method is to multiply mortality rates in cohort studies by the estimated prevalence of problem illicit drug use in the country. This provides an estimate of deaths caused by illicit drugs for each of the causes of death that we have considered.

Key informant data

A final source of data is that which researchers in the drug and alcohol field can provide. The WHO Management of Dependence Project surveyed drug researchers in Member States and asked them to provide estimates of the prevalence of harmful drug use and resultant mortality in their country, using the best available data. The sources range in quality from large-scale population surveys to educated guesses based on clinical experience, but such consultations provide an independent source of estimates against which to check the sources outlined above.

Only 15 responses were returned and in most cases responses either reported on published data or data whose validity was difficult to evaluate. This source has not been included formally in current estimates. Future attempts to estimate the contribution that illicit drug use makes to global burden of disease may include such data.

Key informants may also be of use to judge the accuracy and validity of estimates of mortality attributable to the different causes of death. Such key informants are extremely invaluable and note has been made in the text of instances in which key informants reported that our estimates were likely to be underestimates.

4.4 Methods used for each cause of mortality

AIDS

UNAIDS estimates of death related to IDU were used. No upper and lower estimates were obtained.

Drug overdose

It should be noted that rates derived from research on opioid overdoses were included in these calculations and separate estimates of the number of persons dying from stimulant-related overdoses have not been made. There is a lack of good data on rates and/or risk of dying from stimulant-related overdoses. However, it is likely that in countries which have a higher prevalence of cocaine use, cocaine-related overdoses may account for a considerable proportion of all fatal drug overdoses. In the United States, for example, the Drug Abuse Warning Network indicated that in 1999, 28% of single-drug overdoses were due to co-

caine (National Institute on Drug Abuse, personal communication, 2002).

Our approach has been to assume that overdose rates derived from research on opioid overdose may be applicable to stimulant drugs. In estimates made of overdose deaths, rates of drug use (which include opioids, amphetamines and cocaine) were multiplied by the rate of opioid overdoses derived from cohort studies. Hence, it has been assumed that the same rate of overdose deaths applies to these other drugs as it does to opioid drug use. In the estimates derived from "all-cause" rates in cohort studies, overdoses due to amphetamines and cocaine use will be included in this rate. Direct estimates made from the WHO Mortality Database included only deaths due to opioids so may be an underestimate.

In this chapter, data used to derive a number of estimates of the number of persons dying from overdoses were derived from the following sources.

Direct estimates: attributable fractions combined with data from WHO all-cause mortality database

An attributable fraction was derived from EUR-A countries. This involved obtaining estimates of the total number of deaths coded in ICD as attributed to mental disorders and accidental poisoning due to opioids. The median attributable fraction of these countries was 0.1164. This attributable fraction was applied to all other subregions to enable a direct estimate to be made.

Data were taken from the WHO all-cause mortality database on deaths attributed to mental disorders and accidental poisoning. Not all countries reported such data. In making estimates for subregions when some data were missing from countries in the subregion, an average overdose rate was calculated using the available data, and this rate was used to estimate the total number of trauma deaths in the subregion. It must be noted that many countries in some subregions did not report data in the WHO database, and some subregions had no countries that reported such data; the following subregions had estimates made from only few countries in the subregion, or had no estimates made:

- AFR-D: Mauritius;
- AFR-E: no estimate;
- AMR-B: Argentina, Belize, Brazil, Costa Rica and El Salvador;
- AMR-D: no estimate;
- EMR-B: Kuwait;
- EMR-D: no estimate;
- EUR-C: Armenia, Azerbaijan, Bulgaria, Kyrgyzstan, Poland, Romania and Slovakia;

- SEAR-B: Thailand;
- SEAR-D: the Democratic People's Republic of Korea;
- WPR-B: no estimate.

Indirect estimates: cohort-derived mortality rate

A weighted average mortality rate was calculated from cohort studies (see Table 13.5 for included studies). The average was 0.43% per annum (to 2 decimal places). The upper and lower 95% confidence intervals of this rate were 0.25% per annum and 0.64% per annum.

Suicide

Suicide was considered as a cause of mortality among illicit opioid users only. Hence, when making indirect estimates of deaths, only rates of opioid use were considered in analyses. Median estimates are reported. Where only one source of data was available in estimating a cause of mortality, then the median of this was used, and the lowest and highest estimate used for the range. If more than one source of estimates was available for a subregion, then the lowest and highest *median* estimates were used as the range.

Direct estimates: attributable fractions combined with data from WHO all-cause mortality database

An attributable fraction of 0.09 was used to calculate the proportion of all suicides that were among opioid users. This attributable fraction was derived from an Australian study reported by English et al. (1995). Data were taken from the WHO all-cause mortality database on the number of deaths due to suicide by country, for persons aged >15 years. The year for which data were available varied. For those countries that had more than one year of data, the most recent year's data were used.

Not all countries reported such data. In making estimates for subregions in which some data were missing from countries in the subregion, an average suicide rate was calculated using the available data. This rate was used to estimate the total number of suicide deaths in the subregion. It must be noted that many countries in some subregions did not report data in the WHO database, and in some subregions there were no countries that reported such data. The subregions in which estimates were made from only few countries, or which provided no estimates are as follows:

- AFR-D: Mauritius;
- AFR-E: no estimate;
- AMR-B: Argentina, Belize, Brazil and Costa Rica;
- AMR-D: no estimate;

Table 13.5 Included outcome studies that examined rates of mortality due to overdose among problematic drug users

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Crude mortality rate per 1000*
Australia, Sydney	Capelhorn et al. (1996)	296	Methadone	13	39	3 484	Heroin	0.66
Denmark, Copenhagen	Haastrup and Jepson (1984)	300	Treatment	7	19	1 967	Morphine	1.37
Italy	Goedert et al. (1995)	4962	Treatment	3.88	—	21 130	…	0.30
Italy, Milan	Galli and Musicco (1994)	2432	Treatment	6.7	—	16 415	Methadone (94%)	0.92
Italy, Rome	Davoli et al. (1997)	3955	Treatment	4	198	15 820	IDU	0.58
Italy, Rome	Perucci et al. (1991)	4200	Methadone	8	Nil	33 600	Opioids	0.24
Italy, Rome	Zaccarelli et al. (1994)	2431	Treatment	3.2	—	7 872	IDU	0.55
Netherlands, Amsterdam	van Haastrecht et al. (1996)	632	HIV– methadone and STD clinic patients	4.4	18	2 781	…	0.56
New Zealand, Wellington	Dukes et al. (1992)	997	Treatment	9.1	—	9 073	Injecting opioid users	0.25
Norway, Oslo	Eskild et al. (1993)	1009	HIV test centre clients	3.67	—	3 706	IDU	1.56
Spain, Catalonia	Orti et al. (1996)	15711	Hospital ER and treatment	2.8	—	43 717	Opioids	1.09
Sweden	Gronbladh et al. (1990)	368	Methadone and untreated	5–11	—	3 283	Heroin	1.74
Sweden, Gothenburg	Benson and Holmberg (1984)	618	Drug-using conscripts, rehab. & psych. patients, drug-using welfare recipients	10	—	5 789	Cannabis, solvents, LSD, stimulants (opioids rare)	0.05 (poisoning)
Sweden, Lund	Tunving (1988)	524	Treatment: opioid, amphetamine, and both opioid and amphetamine	10	0	5 240	Opioids, amphetamines	0.67

Sweden, Stockholm	Engstrom et al. (1991)	1630	Drug-related hospitalization	12	—	19560	41% cocaine/ amphetamine; 12% heroin; 16% polydrug; 31% other	0.16
Sweden, Stockholm	Fugelstad et al. (1995)	472	HIV+	3.8	—	1793	…	2.29
Sweden, Stockholm	Fugelstad et al. (1997)	1640	Drug-related hospitalization	8	Nil	13120	14% heroin; 35% amphetamine; 23% polydrug	0.82
Sweden, Stockholm	Wahren et al. (1997)	1494	Hospitalized for drug dependence	22	—	32868	57% stimulants; 39% opioids	0.09
United Kingdom	Ghodse et al. (1998)	92802	"Drug addicts" notified to Home Office	27	—	687673	65% opioids	0.38
United Kingdom, England, London	Oppenheimer et al. (1994)	128	Treatment	22	7	2816	Heroin	0.64
United Kingdom, England, London	Wille (1981)	128	Treatment (Rx heroin)	10	—	1280	Heroin	0.86
United Kingdom, Scotland, Edinburgh	Bucknall and Robertson (1986)	184	Heroin users attending a general practice	4	4	720	Heroin	0.55
United Kingdom, Scotland, Edinburgh	Robertson et al. (1994)	203	GP	10	17	2030	IDU	0.74
USA, CA	Hser et al. (1993)	581	Males in compulsory treatment	24	35	13064	"Narcotics"	0.40
USA, CT, New Haven	Musto and Ramos (1981)	91	Treatment	52	—	4732	Morphine	0

continued

Table 13.5 Included outcome studies that examined rates of mortality due to overdose among problematic drug users (*continued*)

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Crude mortality rate per 1000*
USA, NM, Albuquerque	Goldstein and Herrera (1995)	1013	Methadone	22	243	22 286 (16 940 excl. lost)	…	0.53 (0.70)
USA, New York	Concool et al. (1979)	1156	Treatment (84% methadone)	7	102	8092	Heroin	0.07
USA, New York	Friedman et al. (1996)	858	Drug and alcohol dependents on welfare	8	—	6864	Drugs and alcohol	0.12
USA, New York	Vaillant (1973)	100	Treatment, male	20	17	1660	Narcotics	0.35
USA, OR, Portland	McAnulty et al. (1995)	1769	Not in treatment	1.78	—	3149	IDU	0.41
USA, PA, Philadelphia	Zanis and Woody (1998)	507	Methadone	1	5	507	Heroin	1.18
USA, 18 treatment agencies	Joe and Simpson (1987)	697	Treatment	6	142	3330	Opioids	0.75
USA, 34 treatment agencies	Joe et al. (1982)	3324	Treatment	4	—	11 710	Opioids	0.59
Netherlands, Amsterdam; USA, MD, Baltimore	van Ameijden et al. (1999)	2809	Treatment shelters and community agencies	6–9	—	15 107	IDU	0.50

— No data.

- EMR-B: Kuwait;
- EMR-D: no estimate;
- SEAR-B: Thailand;
- SEAR-D: the Democratic People's Republic of Korea;
- WPR-B: no estimate.

Indirect estimates: cohort-derived crude mortality rates

The crude mortality rate due to suicide from cohort studies was also estimated (see Table 13.6 for included studies). The weighted average rate of death per annum due to suicide was 0.24% (shown here to 2 decimal places). In order to make a range of estimates around this average rate, the standard error of the rate was calculated and 95% confidence intervals constructed around the rate. These were used as the lower and upper ranges of the mortality rates due to suicide: these were 0.15% per annum and 0.33% per annum, respectively.

Trauma

It must be noted that there are significant problems with estimates of rates/attributable fractions due to trauma, since cohort studies reported different sorts of trauma, and different numbers of causes. In the attributable fraction method of calculation, only road traffic accidents were used to calculate the number attributable to illicit drug use as it is unclear the extent to which homicides or other trauma deaths are due to illicit drug use.

Median estimates are reported. Where only one source of data was available in estimating a cause of mortality, then the median of this estimate was used, and the lowest and highest estimates were used for the range. If more than one source of estimates was available for a subregion, then the lowest and highest *median* estimates were used as the range.

Direct estimates: attributable fraction combined with data from WHO all-cause mortality database

Data were taken from the WHO all-cause mortality database on the number of deaths due to motor vehicle or other road traffic accidents (ICD-9 codes E470–E474 and E479) by country. Not all countries reported such data. In making estimates for subregions when data were missing from some countries, an average trauma rate was calculated using the available data. This rate was used for estimating the total number of trauma deaths in the subregion. It must be noted that many countries in some subregions did not report data in the WHO database, and some subregions had no countries that reported such data. In the following subregions estimates were made from only few countries, or no estimates were made:

Table 13.6 Included outcome studies that examined rates of mortality due to suicide among problematic drug users

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Crude mortality rate (per 1000)*
Australia, Sydney	Capelhorn et al. (1996)	296	Methadone	13	39	3484	Heroin	0.14
Denmark, Copenhagen	Haastrup and Jepson (1984)	300	Treatment	7	19	1967	Morphine	0.61
Italy, Milan	Galli and Musicco (1994)	2432	Treatment	6.7	—	16415	Methadone (94%)	0.06
Italy, Rome	Perucci et al. (1991)	4200	Methadone	8	Nil	33600	Opioids	0.03
Italy, Rome	Zaccarelli et al. (1994)	2431	Treatment	3.2	—	7872	IDU	0.04
Netherlands, Amsterdam	van Haastrecht et al. (1996)	632	HIV– methadone and STD clinic patients	4.4	18	2781	…	0.36
New Zealand, Wellington	Dukes et al. (1992)	997	Treatment	9.1	—	9073	Injecting opioid	0.09
Norway, Oslo	Eskild et al. (1993)	1009	HIV test centre clients	3.67	—	3706	IDU	0.24
Sweden	Gronbladh et al. (1990)	368	Methadone and untreated	5–11	—	3283	Heroin	0.09
Sweden, Gothenburg	Benson and Holmberg (1984)	618	Drug-using conscripts, rehab. & psych. patients, drug-using welfare recipients	10	—	5789	Cannabis, solvents, LSD, stimulants (opioids rare)	0.29
Sweden, Lund	Tunving (1988)	524	Treatment: opioid, amphetamine, and both opioid and amphetamine	10	0	5240	Opioids, amphetamines	0.33
Sweden, Stockholm	Engstrom et al. (1991)	1630	Drug-related hospitalization	12	—	19560	41% cocaine/ amphetamine; 12% heroin; 16% polydrug; 31% other	0.79

Sweden, Stockholm	Fugelstad et al. (1995)	472	HIV+	3.8	—	1793	…	0.50
Sweden, Stockholm	Fugelstad et al. (1997)	1640	Drug-related hospitalization	8	Nil	13120	14% heroin; 35% amphetamine; 23% polydrug	0.22
Sweden, Stockholm	Wahren et al. (1997)	1494	Hospitalized for drug dependence	22	—	32868	57% stimulants; 39% opioids	0.30
United Kingdom, England, London	Oppenheimer et al. (1994)	128	Treatment	22	7	2816	Heroin	0.07
United Kingdom, England, London	Wille (1981)	128	Treatment (Rx heroin)	10	—	1280	Heroin	0.08
United Kingdom, Scotland, Edinburgh	Bucknall and Robertson (1986)	184	Heroin users attending a general practice	4	4	720	Heroin	0.14
USA, CT, New Haven	Musto and Ramos (1981)	91	Treatment	52	—	4732	Morphine	0.02
USA, NM, Albuquerque	Goldstein and Herrera (1995)	1013	Methadone	22	243	22286 (16940 excl. lost)	…	0.05 (0.07)
USA, New York	Vaillant (1973)	100	Treatment, male	20	17	1660	Narcotics	0.20
USA, PA, Philadelphia	Zanis and Woody (1998)	507	Methadone	1	5	507	Heroin	0
Netherlands, Amsterdam; USA, MD, Baltimore	van Ameijden et al. (1999)	2809	Treatment shelters and community agencies	6–9	—	15107	IDU	0.59

— No data.

- AFR-D: no estimate;
- AFR-E: no estimate;
- AMR-B: Argentina, Belize, Brazil, Costa Rica, El Salvador and Paraguay;
- AMR-D: no estimate;
- EMR-B: Kuwait;
- EMR-D: no estimate;
- SEAR-B: Thailand;
- SEAR-D: no estimate;
- WPR-B: the Philippines and the Republic of Korea.

The attributable fraction derived by Ridolfo and Stevenson (2001) of 0.015 was used to calculate direct estimates of trauma due to illicit drugs.

Indirect estimates: cohort-derived crude mortality rates

Indirect estimates of the number of road traffic accident deaths due to illicit drug use were also made using pooled estimates of the rates of death due to trauma from cohort studies (Table 13.7). Rates of traumatic injury were also high in this group: the weighted average rate of death per annum due to trauma was 0.35%. In order to make a range of estimates around this average rate, the standard error of the rate was calculated and 95% confidence intervals constructed around the rate. These were used as the lower and upper ranges of the mortality rates due to trauma: these were 0.23% per annum and 0.46% per annum, respectively (shown here only to 2 decimal places).

All-cause mortality

Median estimates are reported. Where only one source of data was available in estimating a cause of mortality, then the median of this was used, and the lowest and highest estimate used for the range. If more than one source of estimates was available for a subregion, then the lowest and highest *median* estimates were used as the range.

Direct estimates: attributable fractions combined with data from WHO all-cause mortality database

Data were taken from the WHO all-cause mortality database on the total number of deaths by country, for persons aged between 15 and 54 years. The year for which data were available varied so the data from the most recent year were used in those countries that had more than one year of data.

This age group (15–54 years) was chosen as the age group within which excess mortality rates would occur among problem illicit drug

Table 13.7 Included outcome studies that examined rates of mortality due to trauma among problematic drug users

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Crude mortality rate (per 1000)*
Australia, Sydney	Capelhorn et al. (1996)	296	Methadone	13	39	3484	Heroin	0.23
Italy	Goedert et al. (1995)	4962	Treatment	3.88	—	21130	…	1.8
Italy, Milan	Galli and Musicco (1994)	2432	Treatment	6.7	—	16415	Methadone (94%)	0.15
Italy, Rome	Davoli et al. (1997)	3955	Treatment	4	198	15820	IDU	0.25
Italy, Rome	Perucci et al. (1991)	4200	Methadone	8	Nil	33600	Opioids	0.15
Italy, Rome	Zaccarelli et al. (1994)	2431	Treatment	3.2	—	7872	IDU	0.20
Netherlands, Amsterdam	van Haastrecht et al. (1996)	632	HIV– methadone and STD clinic patients	4.4	18	2781	…	0.18
New Zealand, Wellington	Dukes et al. (1992)	997	Treatment	9.1	—	9073	Injecting opioid users	0.12
Norway, Oslo	Eskild et al. (1993)	1009	HIV test centre clients	3.67	—	3706	IDU	0.22
Spain, Catalonia	Orti et al. (1996)	15711	Hospital ER and treatment	2.8	—	43717	Opioids	0.37
Sweden	Gronbladh et al. (1990)	368	Methadone and untreated	05–11	—	3283	Heroin	0.06
Sweden, Gothenburg	Benson and Holmberg (1984)	618	Drug-using conscripts, rehab. & psych. patients, drug-using welfare recipients	10	—	5789	Cannabis, solvents, LSD, stimulants (opioids rare)	0.07
Sweden, Lund	Tunving (1988)	524	Treatment: opioid, amphetamine, and both opioid and amphetamine	10	0	5240	Opioids, amphetamines	0.15

continued

Table 13.7 Included outcome studies that examined rates of mortality due to trauma among problematic drug users (*continued*)

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Crude mortality rate (per 1000)*
Sweden, Stockholm	Engstrom et al. (1991)	1630	Drug-related hospitalization	12	—	19560	41% cocaine/ amphetamine; 12% heroin; 16% polydrug; 31% other	0.35
Sweden, Stockholm	Fugelstad et al. (1995)	472	HIV+	3.8	—	1793	…	0.11
Sweden, Stockholm	Fugelstad et al. (1997)	1640	Drug-related hospitalization	8	Nil	13120	14% heroin; 35% amphetamine; 23% polydrug	0.21
Sweden, Stockholm	Wahren et al. (1997)	1494	Hospitalized for drug dependence	22	—	32868	57% stimulants; 39% opioids	0.22
United Kingdom, England, London	Oppenheimer et al. (1994)	128	Treatment	22	7	2816	Heroin	0.14
United Kingdom, England, London	Wille (1981)	128	Treatment (Rx heroin)	10	—	1280	Heroin	0.16

United Kingdom, Scotland, Edinburgh	Bucknall and Robertson (1986)	184	Heroin users attending a general practice	4	4	720	Heroin	0.14
USA, CA	Hser et al. (1993)	581	Males in compulsory treatment	24	35	13064	"Narcotics"	0.35 (incl. suicide)
USA, CT, New Haven	Musto and Ramos (1981)	91	Treatment	52	—	4732	Morphine	0.08
USA, NM, Albuquerque	Goldstein and Herrera (1995)	1013	Methadone	22	243	22286 (16940 excl. lost)	…	0.27 (0.35)
USA, New York	Vaillant (1973)	100	Treatment, male	20	17	1660	Narcotics	0.1
USA, New York	Concool et al. (1979)	1156	Treatment (84% methadone)	7	102	8092	Heroin	0.26
USA, OR, Portland	McAnulty et al. (1995)	1769	Not in treatment	1.78	—	3149	IDU	0.16
USA, PA, Philadelphia	Zanis and Woody (1998)	507	Methadone	1	5	507	Heroin	0
USA, 18 treatment agencies	Joe and Simpson (1987)	697	Treatment	6	142	3330	Opioids	0.45
USA, 34 treatment agencies	Joe et al. (1982)	3324	Treatment	4	—	11710	Opioids	0.38
Netherlands, Amsterdam; USA, MD, Baltimore	van Ameijden et al. (1999)	2809	Treatment shelters and community agencies	6–9	—	15107	IDU	0.25

— No data.

users compared to non-users. After calculating mortality rates among this age group, an SMR of 13 was used to calculate the rate of all-cause mortality death among problematic illicit drug users. This was taken from previous studies estimating the excess rates of mortality in this group (English et al. 1995; Hulse et al. 1999). It was assumed for these calculations that the resulting rate of death applied to all illicit drug users. This will underestimate the mortality rate among the minority of illicit drug users who are older than 54 years.

Some countries did not have any death data included in the WHO database. For these countries no individual estimates were made. However, in making calculations for subregions, a weighted average of the all-cause mortality rates was calculated using the data from countries that were included. It was assumed that the countries for which no data were available had the average rate of the other countries in the subregion from which they came. Some subregions, however, had no countries which had appropriate estimates. Those subregions in which there were few or no countries for which estimates could be made were as follows:

- AFR-D: Mauritius;
- AFR-E: South Africa;
- AMR-B: Argentina, Belize, Brazil, Costa Rica, El Salvador and Paraguay;
- AMR-D: no estimate;
- EMR-B: Kuwait;
- EMR-D: no estimate;
- SEAR-B: Thailand;
- SEAR-D: no estimate;
- WPR-B: the Philippines and the Republic of Korea.

Indirect estimates: cohort-derived crude mortality rate

Crude all-cause mortality rates were also derived from cohort studies included in this project (see Table 13.8). A weighted average all-cause mortality rate was calculated (1.12% per annum), with a 95% CI of the average rate estimated as between 0.78% per annum and 1.46% per annum.

Table 13.8 Included outcome studies that examined rates of all-cause mortality among problematic drug users

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Standardized mortality ratio*	*No. of deaths*	*Crude mortality rate (per 1000)*
Australia, Sydney	Capelhorn et al. (1996)	296	Methadone	13	39	3 484	Heroin	...	42	1.21
Denmark, Copenhagen	Haastrup and Jepson (1984)	300	Treatment	7	19	1 967	Morphine	20	47	2.40
Denmark, Copenhagen	Haastrup and Jepson (1988)	300	First time entrants to treatment	11	30	2 970	Opioids	...	78	2.63
Denmark, Copenhagen	Segest et al. (1990)	169	Methadone	8	—	1 352	Opioids	...	39	2.88
Ireland	Keenan et al. (1993)	45	Pregnant on methadone	6	—	270	Opioids	...	7	2.59
Italy	Goedert et al. (1995)	4962	Treatment	3.88	—	21 130	...	18	332	1.57
Italy, Milan	Galli and Musicco (1994)	2432	Treatment	6.7	—	16 415	Methadone (94%)	13.5	413	2.52
Italy, Rome	Davoli et al. (1997)	3955	Treatment	4	198	15 820	IDU	21.2 (Males) 38.5 (Females)	387	2.45
Italy, Rome	Perucci et al. (1991)	4200	Methadone	8	Nil	33 600	Opioids	10.1	239	0.71
Italy, Rome	Zaccarelli et al. (1994)	2431	Treatment	3.2	—	7 872	IDU	(Males) 30.3 HIV+ 11.1 HIV– (Females) 19.4 HIV+ 4.9 HIV–	181	2.30

continued

Table 13.8 Included outcome studies that examined rates of all-cause mortality among problematic drug users (*continued*)

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Standardized mortality ratio*	*No. of deaths*	*Crude mortality rate (per 1000)*
Netherlands, Amsterdam	Mientjes et al. (1992)	390	Methadone	2.2	—	810	Opioids	…	29	3.58
Netherlands, Amsterdam	van Haastrecht et al. (1996)	632	HIV– methadone and STD clinic patients	4.4	18	2781	…	…	72	2.59
New Zealand, Wellington	Dukes et al. (1992)	997	Treatment	9.1	—	9073	Injecting opioid users	2.44	67	0.74
Norway, Oslo	Eskild et al. (1993)	1009	HIV test centre clients	3.67	—	3706	IDU	…	87	2.35
Spain, Catalonia	Orti et al. (1996)	15711	Hospital ER and treatment	2.8	—	43717	Opioids	…	1315	3.01
Spain, Catalonia	Sanchez-Carbonell and Seus (2000)	135	Treatment	10.5	—	1418	Heroin	28.5	41	3.4
Sweden	Gronbladh et al. (1990)	368	Methadone and untreated	5–11	—	3283	Heroin	63 street 4 methadone	96 26	2.92 0.45
Sweden, Gothenburg	Benson and Holmberg (1984)	618	Drug-using conscripts, rehab. & psych. patients, drug-using welfare recipients	10	—	5789	Cannabis, solvents, LSD, stimulants (opioids rare)	…		
Sweden, Lund	Tunving (1988)	524	Treatment: opioid, amphetamine, and both opioid and amphetamine	10	0	5240	Opioids, amphetamines	5.4 (opioids) 2.5 (amphetamines)	62	1.18
Sweden, Stockholm	Engstrom et al. (1991)	1630	Drug-related hospitalization	12	—	19560	41% cocaine/ amphetamine; 12% heroin; 16% polydrug; 31% other	5.3 (18.3 for opioid users; 9.0 for cocaine/ amphetamine)	446	2.3

Sweden, Stockholm	Fugelstad et al. (1995)	472	HIV+	3.8	—	1 793	…	…	69	3.85
Sweden, Stockholm	Fugelstad et al. (1997)	1 640	Drug-related hospitalization	8	Nil	13 120	14% heroin; 35% amphetamine; 23% polydrug	…	214	1.63
Sweden, Stockholm	Wahren et al. (1997)	1 494	Hospitalized for drug dependence	22	—	32 868	57% stimulants; 39% opioids	6.9	521	1.59
United Kingdom	Bewley et al. (1968)	1 272	Heroin addicts known to Home Office	1.8	—	2 291	Heroin	28	85	2.7
United Kingdom	Ghodse et al. (1998)	92 802	"Drug addicts" notified to Home Office	27	—	687 673	65% opioids	7.0	5310	0.77
United Kingdom, England, London	Bewley and Ben-Arie (1968)	100	Hospitalized male heroin addicts	2.25	—	225	Heroin	…	13	5.7
United Kingdom, England, London	Oppenheimer et al. (1994)	128	Treatment	22	7	2 816	Heroin	11.9	41	1.53
United Kingdom, England, London	Wille (1981)	128	Treatment (Rx heroin)	10	—	1 280	Heroin	…	19	1.48
United Kingdom, Scotland, Edinburgh	Bucknall and Robertson (1986)	184	Heroin users attending a general practice	4	4	720	Heroin	11.6	7	0.972
United Kingdom, Scotland, Edinburgh	Robertson et al. (1994)	203	GP	10	17	2 030	IDU	…	40	1.97
USA, CA	Hser et al. (1993)	581	Males in compulsory treatment	24	35	13 064	"Narcotics"	…	161	1.23
USA, CT, New Haven	Musto and Ramos (1981)	91	Treatment	52	—	4 732	Morphine		40	0.84

continued

Table 13.8 Included outcome studies that examined rates of all-cause mortality among problematic drug users (*continued*)

Site	*Reference*	*n*	*Population studied*	*Follow-up (years)*	*Lost*	*Person-years*	*Drug*	*Standardized mortality ratio*	*No. of deaths*	*Crude mortality rate (per 1000)*
USA, NM. Albuquerque	Goldstein and Herrera (1995)	1013	Methadone	22	243	22286 (16940 excl. lost)	…	4.0 (Males) 6.8 (Females)	348	1.56 (2.05)
USA, New York	Concool et al. (1979)	1156	Treatment (84% methadone)	7	102	8092	Heroin	1.5	45	0.56
USA, New York	Friedman et al. (1996)	858	Drug and alcohol dependents on welfare	8	—	6864	Drugs and alcohol	…	183	2.67
USA, New York	Vaillant (1973)	100	Treatment, male	20	17	1660	Narcotics	…	23	1.15
USA, OR, Portland	McAnulty et al. (1995)	1769	Not in treatment	1.78	—	3149	IDU	8.3		1.05
USA, PA, Philadelphia	Zanis and Woody (1998)	507	Methadone	1	5	507	Heroin	…	13	2.56
USA, 18 treatment agencies	Joe and Simpson (1987)	697	Treatment	6	142	3330	Opioids	6.9	52	1.56
USA, 34 treatment agencies	Joe et al. (1982)	3324	Treatment	4	—	11710	Opioids	14 (<21 years) 10 (21–30 years) 4 (>30 years)	179	1.52
Netherlands, Amsterdam; USA, MD, Baltimore	van Ameijden et al. (1999)	2809	Treatment shelters and community agencies	6–9	—	15107	IDU	…	264	1.75

— No data.

5. Estimated mortality attributable to illicit drug use, 2000

5.1 Burden of mortality attributable to specific causes

Table 13.9 shows the median indirect estimates of the number of deaths attributed to illicit drug use in 2000 for each of the 14 subregions (Table 13.10 also shows low and high range estimates around these medians).

AIDS

The second largest individual cause of death was AIDS, with a global median estimate of 59 000 deaths. The largest proportion of these deaths was estimated to have occurred in WPR-B (17 000). The other two subregions in which the greatest number of deaths from AIDS related to illicit drug use were EMR-D (11 000) and SEAR-B (11 000).

There is some indication that the estimates for some subregions may be too low. The United States Centers for Disease Control and Prevention reported that in 1999, 5932 AIDS-related deaths occurred in the United States that were attributed to IDU (see http://www.cdc.gov/hiv/stats/hasr1202.htm). Similarly, reports from UNAIDS experts indicate that estimates for EUR-C may also be too low, with reports that in the Ukraine alone, approximately 3440 deaths occurred due to AIDS in 1999 (UNAIDS, personal communication, 2001). While some reviewers commented that South-East Asian estimates were higher than they expected, recent work has indicated that the number of AIDS deaths in Thailand (one of the countries in this region) was higher than previously estimated (A. Lopez, personal communication, 2001). Recent work in the South-East Asia Region is consistent with the possibility that AIDS-related deaths have been underestimated in this region (Reid and Costigan 2002).

Overdose

Opioid overdose was the next largest cause of death among illicit drug users, with a median estimate of 69 152 deaths globally. The two subregions that accounted for the largest number of opioid overdose deaths were SEAR-D (22 989) and EMR-D (12 852), followed by EUR-C and AMR-A.

The estimates may be too low for some subregions. For example, WPR-A, which includes Australia, had a median estimate of 825 deaths, with a high and low estimate of 954 and 696, respectively. Data from the Australian Bureau of Statistics indicates that in 2000, a total of 737 deaths occurred among persons aged 15–44 years (National Drug and Alcohol Research Centre 2000).

Suicide

Suicide among opioid users was estimated to account for 32 216 deaths in 2000. SEAR-D accounted for the greatest proportion of these deaths

Table 13.9 Median indirect estimates of mortality attributed to illicit drug use, by subregion

Subregion	*AIDS*	*Opioid overdose*	*Suicide*	*Trauma*
AFR-D	0	1 891	1 191	2 768
AFR-E	0	407	64	922
AMR-A	4 000	6 397	2 034	4 057
AMR-B	5 000	1 845	922	2 342
AMR-D	0	498	78	716
EMR-B	0	3 881	673	813
EMR-D	11 000	12 852	2 015	2 954
EUR-A	0	5 527	2 355	3 387
EUR-B	1 000	1 281	1 465	651
EUR-C	3 000	6 895	4 156	830
SEAR-B	11 000	955	576	797
SEAR-D	7 000	22 989	14 982	3 128
WPR-A	0	825	1 251	1 028
WPR-B	17 000	2 909	456	9 295
Total (median)	59 000	69 152	32 216	33 689

Note: There were an additional 10 000 deaths from overdose above and beyond those coded as drug use disorders (added to unintentional injuries) or when coded drug use disorder deaths were higher than estimated overdose deaths.

(14 982), with EUR-C accounting for the next largest. A similar number of deaths were estimated to be due to trauma (34 184). WPR- B had the largest numbers of deaths due to this cause (9295), followed by AMR-A (4057).

5.2 All-cause mortality attributable to illicit drugs

Table 13.11 compares two methods of calculating the total mortality attributable to illicit drug use: (i) adding the above four causes; and (ii) using estimates of "all-cause" mortality derived from cohort studies and attributable fractions. There are some reassuring similarities between the two sources, and some noteworthy discrepancies.

Overall, the global estimates were remarkably similar ("all-cause" estimate 197 383 vs "sum" estimate 194 058). Of note was the fact that the subregions that had discrepant estimates were largely developing subregions, and not the subregions from which the majority of cohort studies and attributable fractions had been derived. One of the subregions that accounted for the slightly lower estimates using the all-cause mortality method was SEAR-D, whose all-cause estimate (around 11 000) was only 23% of its sum estimate. In general, however, for most other subregions, estimates were within close range of each other, or the all-cause estimates were higher. The overall rate of death per 1 000

Table 13.10 Mortality range attributable to illicit drug use, by subregion

Subregion	*AIDS*	*Opioid overdose*	*Suicide*	*Trauma*	*All-cause*
AFR-D	**0**[a]	**1 891**	**1 191**	**2 768**	**19 046**
Low	0	1 526	354	1 235	9 754
High	0	2 256	2 028	4 807	28 338
AFR-E	**0**	**407**	**64**	**922**	**8 286**
Low	0	246	40	412	3 251
High	0	609	87	1 602	13 321
AMR-A	**4 000**	**6 397**	**2 034**	**4 057**	**40 356**
Low	4 000	5 144	806	718	23 186
High	4 000	7 649	3 261	7 397	54 647
AMR-B	**5 000**	**1 845**	**922**	**2 342**	**18 425**
Low	5 000	1 530	240	985	13 034
High	5 000	2 159	1 604	3 699	23 817
AMR-D	**0**	**498**	**78**	**716**	**2 522**
Low	0	300	49	319	1 070
High	0	744	107	1 243	3 985
EUR-A	0	**5 527**	**2 355**	**3 387**	**16 453**
Low	0	2 791	866	712	11 026
High	0	9 108	4 481	4 690	19 533
EUR-B	**1 000**	**1 281**	**1 465**	**651**	**5 794**
Low	1 000	214	336	473	2 923
High	1 000	2 348	2 595	829	8 665
EUR-C	**3 000**	**6 895**	**4 156**	**830**	**10 709**
Low	3 000	4 507	707	674	3 474
High	3 000	9 284	7 605	986	17 944
EMR B	**0**	**3 881**	**673**	**813**	**5 012**
Low	0	431	196	317	4 612
High	0	7 332	1 149	1 309	5 412
EMR D	**11 000**	**12 852**	**2 015**	**2 954**	**10 411**
Low	11 000	7 757	1 271	1 319	4 416
High	11 000	19 212	2 759	5 131	16 454
SEAR-B	**11 000**	**955**	**576**	**797**	**5 688**
Low	11 000	581	208	745	2 625
High	11 000	1 330	943	849	8 751
SEAR-D	**7 000**	**22 989**	**14 982**	**3 128**	**11 024**
Low	7 000	1 824	2 059	1 396	4 676
High	7 000	44 154	27 105	5 434	17 423
WPR-A	**0**	**825**	**1 251**	**1 028**	**9 916**
Low	0	696	109	246	6 375
High	0	954	2 394	1 809	13 457
WPR-B	**17 000**	**2 909**	**456**	**9 295**	**33 741**
Low	17 000	1 756	288	8 111	11 329
High	17 000	3 439	624	10 479	90 709
Total median	**59 000**	**69 152**	**32 216**	**33 689**	**197 383**
Low	59 000	29 303	8 330	17 622	101 751
High	59 000	110 577	56 742	50 264	322 456

[a] Figures in bold: the median estimates from Table 13.9.

Table 13.11 Estimates of total mortality attributed to illicit drug use, by subregion

Subregion	*Population (000s) >15 years*	*Sum of four causes of mortality*[a]	*Population mortality rate (per 1000)*	*All-cause mortality*[b]	*Population mortality rate (per 1000)*
AFR-D	159577	5850	0.04	19046	0.12
AFR-E	190152	1393	0.01	8286	0.04
AMR-A	255420	16488	0.06	40356	0.16
AMR-B	297625	10109	0.03	18425	0.06
AMR-D	44658	1292	0.03	2522	0.06
EMR-B	86853	5367	0.06	5012	0.06
EMR-D	204039	28821	0.14	10411	0.05
EUR-A	339446	11269	0.03	16453	0.05
EUR-B	161213	4397	0.03	5794	0.04
EUR-C	152432	14881	0.10	10709	0.07
SEAR-B	206870	13328	0.06	5688	0.03
SEAR-D	818521	48099	0.06	11024	0.01
WPR-A	129888	3104	0.02	9916	0.08
WPR-B	1131503	29660	0.03	33741	0.03
World	4178197	194058	0.05	197383	0.05

[a] Sum of the median estimates of the following four causes: AIDS, opioid overdose, suicide via opioids and trauma.

[b] Median estimates of all-cause mortality derived from SMR analyses and pooled CMRs.

persons aged ≥15 years due to illicit drug use, on a global level, was estimated at 0.5 per annum. The highest all-cause *mortality rate* was estimated to have occurred in AMR-A (0.16 per 1000 persons aged ≥15 years), followed by AFR-D (0.12 per 1000 persons aged ≥15 years). The lowest rates using all-cause estimates occurred within SEAR-D (0.01 per 1000), WPR-B (0.03) and SEAR-B (0.03).

The discrepancies between the two sources of estimates for developed societies suggested that in general (with the exception of AMR-A), the consistency between the two was reasonable. If anything, the all-cause method produced a higher estimate, which is consistent with the fact that the "four cause" method does not include an exhaustive list of all possible causes of death.

In some developing subregions (such as SEAR-D) there was marked discrepancy between the two sources of estimates. This could be due to higher rates of AIDS-related deaths among injecting drug users in these subregions, which were not adequately assessed by using the all-cause method (in which some cohort studies were carried out before AIDS became an issue).

Table 13.12 Proportion of causes of death attributed to illicit drug use among males, by subregion

Subregion	*Proportion among males*
AFR-D	0.89
AFR-E	0.83
AMR-A	0.56
AMR-B	0.63
AMR-D	0.72
EMR-B	0.85
EMR-D	0.82
EUR-A	0.59
EUR-B	0.64
EUR-C	0.79
SEAR-B	0.96
SEAR-D	0.83
WPR-A	0.93
WPR-B	0.79

5.3 Age and sex breakdowns

Our ability to make reliable and valid estimates of the age and sex breakdowns of deaths attributable to illicit drug use is extremely limited. Not only are estimates of the prevalence of drug use according to these characteristics limited (or absent) in many countries, it is also the case that evidence on the characteristics of persons dying from the causes examined here are limited. The estimates made below have been made with reference to limited data on the age and sex breakdowns of persons dying from AIDS, overdose, trauma and suicide.

Sex

We made the following estimates of the sex breakdown. This was completed by using estimates of the proportion of tobacco users who were males in each of the 14 subregions. These had been calculated in each subregion from the smoking risk factor for the GBD project. Table 13.12 shows the estimates for proportion of deaths among males in each of the subregions. Table 13.13 shows the resulting numbers of deaths attributable to illicit drugs by subregion and sex. Table 13.14 provides estimates of the total DALYs attributable to illicit drugs by subregion and sex.

Age groups

Similarly to the sex breakdowns, the age breakdowns are based on limited data concerning the age distribution of persons dying from the

Table 13.13 Number of deaths attributed to illicit drug use, by subregion and sex

Subregion	*Sum of four causes of mortalty*[a]	*All-cause mortality*[b]
AFR-D		
Males	5207	16951
Females	643	2095
AFR-E		
Males	1156	6877
Females	237	1409
AMR-A		
Males	9233	22599
Females	7255	17757
AMR-B		
Males	6369	11608
Females	3740	6817
AMR-D		
Males	930	1816
Females	362	706
EMR-B		
Males	4562	4260
Females	805	752
EMR-D		
Males	23633	8537
Females	5188	1874
EUR-A		
Males	6649	9707
Females	4620	6746
EUR-B		
Males	2814	3708
Females	1583	2086
EUR-C		
Males	11756	8460
Females	31251	2249
SEAR-B		
Males	12795	5460
Females	533	228
SEAR-D		
Males	39922	9150
Females	8177	1874
WPR-A		
Males	2887	9222
Females	217	694
WPR-B		
Males	23431	26655
Females	6229	7086
World		
Males	149425	145012
Females	44633	52371

[a] Sum of the median estimates of the following four causes: AIDS, opioid overdose, suicide via opioids and trauma.

[b] Median estimates of all-cause mortality derived from SMR analyses and pooled CMRs.

Table 13.14 Burden of disease (000s of DALYs) attributed to illicit drug use in the subregions, by sex

Subregion	*Males*	*Females*
AFR-D	428	134
AFR-E	460	150
AMR-A	594	185
AMR-B	586	13
AMR-D	193	59
EMR-B	376	64
EMR-D	478	109
EUR-A	599	172
EUR-B	130	39
EUR-C	340	102
SEAR-B	95	22
SEAR-D	703	116
WPR-A	173	76
WPR-B	256	55
World	5402	1477

four main causes of death considered here. It was assumed that no persons aged <15 years and no persons aged >54 years were problematic users of illicit drugs; the 15–54-year age group has typically been found to contain the vast majority of problematic illicit drug users (Anthony and Helzer 1991).

It was assumed that two-thirds of overdose deaths occurred among the 25–44-year age group, with on-sixth each occurring in the 15–24- and 45–54-year age groups, in line with previous research suggesting the bulk of deaths occur in such a pattern (Hall et al. 1999c, 2000c). Deaths related to illicit drug use that were due to trauma were assumed to be disproportionately distributed among younger age groups, with smaller proportions among those aged 35–54 years (see Table 13.15). With the knowledge that AIDS-related deaths usually occur years after contracting HIV, we assigned the deaths the same age distribution as the total HIV/AIDS deaths in each subregion.

6. Discussion

6.1 Methodological caveats

A number of potential sources of inaccuracy need be acknowledged in our estimates. First, there are a number of factors that determine the proportion of cases of any particular cause of mortality that are attribut-

Table 13.15 Estimated distribution of causes of death attributed to illicit drug use, by age

	Age (years)					
Cause of death	*<15*	*15–24*	*25–34*	*35–44*	*45–54*	*>54*
Overdose	0	1/6	1/3	1/3	1/6	0
Suicide	0	1/3	1/3	1/6	1/6	0
Trauma	0	1/3	1/3	1/6	1/6	0
Total[a]	0	0.13	0.34	0.29	0.24	0

[a] Weighted average of the three causes.

able to harmful illicit drug use. These include environmental, cultural or behavioural factors, which are also likely to interact. The risk of contracting HIV/AIDS through injecting drug use, for example, is greatly reduced by providing sterile injecting equipment, and the use of such equipment will be affected by attitudes towards needle sharing. In countries with needle and syringe programmes the attributable fraction of HIV due to injecting drug use is likely to be relatively small compared to similar countries that do not have needle and syringe programmes, even assuming a similar prevalence of other risk factors for HIV transmission in both countries (Hurley et al. 1997). An illustration of this was provided by Lurie and Drucker (1997) who assessed the impact of needle and syringe programmes on the development of the HIV epidemic in Australia and the United States. They estimated that between 10 000 and 25 000 HIV infections in the United States could have been prevented if needle exchange programmes were implemented as they had been in Australia.

Second, the availability of drug treatment programmes, medical care and a host of other factors that differ between otherwise similar countries may produce differences in the attributable fractions in those countries. For example, van Ameijden et al. (1999) compared mortality in cohorts of heroin users in Amsterdam and Baltimore. They found Amsterdam drug users had an overdose/suicide mortality rate approximately twice that of their counterparts in Baltimore. This was despite the fact that a greater proportion of users in Amsterdam were in methadone maintenance treatment, which has been shown to reduce the risk of overdose. This finding contrasts with a previous finding of the same research group, which attributed lower mortality rates from infectious disease in Amsterdam to drug users having better access to primary health care in Amsterdam than in New York (Mientjes et al. 1992). The variation in mortality rates that result from differences in the complex interactions

of determinants of mortality makes comparisons of cohort studies conducted in different countries problematic.

Third, attributable fractions can only be reliably calculated in countries that collect accurate mortality data. These data are most likely to be found in developed countries vs developing countries (Muller 1982). Caution is required in applying fractions estimated in developed countries to developing ones.

6.2 Limitations of cohort studies

As mentioned earlier, the cohort studies of problem illicit drug users have a number of major limitations when used for the purpose of estimating the contribution of problem illicit drug use to the global burden of disease.

Treatment populations

The vast majority of cohort studies of mortality among illicit drug users have included people seeking treatment for problem drug use. A small number of studies have compared mortality of drug users while in and out of treatment (Capelhorn et al. 1996; Fugelstad et al. 1995; Gronbladh et al. 1990; Sanchez-Carbonell and Seus 2000; Zanis and Woody 1998). These studies have found that the relative risk of death while in treatment varied from less than 0.2 to 0.8, with a mean of approximately 0.4. These studies can be used to produce more accurate estimates of mortality by applying different mortality rates for proportions of users who are and are not in treatment.

Illicit drugs used

Injecting opioid users are over-represented in the cohort studies by comparison with cocaine and other stimulant users. The few studies that report separate data on problem illicit opioid and stimulant use suggest that mortality is higher among opioid users (Engstrom et al. 1991), probably because of the greater risk of fatal overdose from opioids. Stimulant users, by contrast, may be at higher risk of contracting diseases from bloodborne viruses such as hepatitis B and C from sharing injection equipment because they inject at a high frequency when bingeing on their drug of choice (Bux et al. 1995; Chaisson et al. 1989). They may also be more likely to engage in sex for drugs (Chiasson et al. 1991; Darke et al. 1995; Edlin et al. 1994).

Extrapolation across subregions

Applying direct measures of mortality from cohort studies in developed countries to populations in developing countries is problematic. Developing countries generally have all-cause mortality rates that are significantly higher than the developed countries in which most cohort studies are conducted (WHO 2001). Thus it may be that there is less of a dif-

ferential in mortality rates between the general population and problem drug users in developing countries. Applying the relative risks from developed countries to developing ones may therefore overestimate the mortality attributable to illicit drug use in the latter.

HIV/AIDS

The majority of cohort studies identified for this project were conducted before the HIV/AIDS epidemic began to affect mortality among injecting drug users. Changes in the epidemiology of HIV and other drug-related conditions since these studies were conducted may reduce the validity of using prevalence or incidence data to predict mortality. In some developed nations, for example, the incidence of HIV and AIDS may be declining but the large number of prevalent cases may still produce a high burden of mortality (CDC 2001; UNAIDS 2001). Conversely, countries that are still in the early stages of the epidemic may have a high incidence of HIV/AIDS cases that have not yet begun to contribute to mortality. In either case mortality estimates based on the number of incident cases may be inaccurate, for very different reasons. However, in the absence of better data on this issue, UNAIDS data on the number of AIDS deaths in the year 2000 have been used to estimate mortality, since there are significant problems with making estimates from incident cases.

Despite the limitations of cohort studies, they present the most robust epidemiological evidence on the relationship between problem illicit drug use and mortality. When quantifying the burden of mortality attributed to illicit drugs, therefore, cohort studies provide the best basis on which to estimate risk and identify mortality outcomes.

In terms of estimating risk, as we have described above, the use of annual mortality rates derived from studies of illicit drug users in developed countries may underestimate mortality in developing countries. By contrast, applying SMRs from the cohort studies to developed societies may overestimate the mortality rate of drug users in developing countries (which already have higher mortality rates in general), since it is probable that the higher the general mortality rate in any given country, the lower will be the SMR for illicit drug users in that country (Muller 1982). We have used UNAIDS estimates in the current study.

Other data sources can be used to validate estimates of risk derived from cohort studies in some developed societies. In populations where reliable mortality data are collected the attributable fraction of mortality due to a range of conditions that may be related to problem illicit drug use can be calculated. These fractions can then be applied to estimates of mortality in other countries using the WHO all-cause mortality database. The main weaknesses of this method are: that it does not take into account variations in the prevalence of the risk factor; it assumes homogeneity between the population from which the attributable fraction was derived and the population to which it is being applied;

and that cohort studies are representative of the population at risk. It is nonetheless an independent method of calculating mortality that can be used to check estimates of mortality derived by multiplying measures of risk by prevalence estimates.

6.3 Summary and conclusions

In summary, in this work we have attempted to estimate the extent of global mortality and morbidity attributable to illicit drug use in 2000. This required estimates of both the global prevalence of problem illicit drug use and the mortality attributable to it. Ideally, such data would include estimation of the numbers of problem, or dependent users, as these are the individuals at greatest risk for drug-related harm. Currently, there are poor data on the prevalence of problem illicit use in many developing countries and there is no consensus on the definition and operationalization of "problem drug use". UNDCP data, supplemented by other sources, provide the best available data, although these have major limitations.

Similarly, there is a considerable amount of data from cohort studies of individuals identified as problem illicit drug users that can be used to estimate the relative risks of death among this group. Unfortunately, most of these studies have been conducted in developed countries on problem opioid users and many were conducted prior to the AIDS pandemic among injecting drug users. A priority for future research must be to assess mortality among illicit drug users in developing countries and, in particular, to examine the extent to which the findings of studies conducted in developed countries are applicable to developing countries.

Furthermore, much of this research has been based on samples of people entering treatment for drug-related problems. Further work is needed to quantify mortality among problem drug users who are *not* in treatment. Nonetheless, it is clear from the existing cohort studies that problem illicit drug users have a greatly elevated risk of premature death from drug overdose, HIV/AIDS, suicide and trauma.

By comparison with the extensive literature on the health effects of tobacco and alcohol use, very little is known about the adverse health effects of illicit drug use. This situation reflects at least three factors: the recent history of illicit drug use in many countries; the low prevalence of its use in the population compared to alcohol and tobacco; and the fact that its illicit nature encourages users to conceal or deny their drug use, hence inhibiting research on its effects on mortality and morbidity.

In 2000, the median of the two methods of estimating the number of global deaths attributed to illicit drugs was 195 721. Estimates produced by both methods had wide uncertainty intervals around them (113 494 for sum of four causes; and 101 751 to 322 456 for all-cause estimates). When morbidity attributable to illicit drug use is added to the estimated mortality this risk factor accounts for 0.8% of global DALYs. The distribution of DALYs between subregions varied, reflecting variations in

drug use and death rates, with considerable uncertainty about the applicability of mortality data derived in developed countries to mortality among illicit drug users in developing countries.

Nonetheless, the current estimates suggest that illicit drug use is a significant cause of premature mortality among young adults in the developed and developing world. Our estimate is certainly an underestimate of total disease burden because: (i) there are deficits in data on mortality attributable to the use of some illicit drugs (most notably cannabis and the newer synthetic drugs like MDMA); (ii) there are differences across subregions in the quality of data available on the causes of mortality that *were* included in the current estimates; and (iii) there is an absence of data that would permit estimates of some other causes of mortality and morbidity attributable to illicit drug use, such as hepatitis B and C and violence.

Given public concerns about the effects of illicit drug use, and indications of a worldwide increase in the production and use of illicit drugs, better research must be done on the adverse health effects of their use. With that in mind we include a list of research priorities.

6.4 Research priorities

- There is a need for more rigorously designed prospective studies of mortality and morbidity among problem illicit drug users in developing countries, especially ones which have high rates of HIV/AIDS infection among injecting drug users, and which have experienced substantial increases in rates of such problem drug use in recent years.
- There is also a need for cohort studies of injecting drug users who are *not* in treatment, since there is evidence that rates of mortality are higher among this group.
- There is a need for better studies of morbidity attributable to nonfatal overdoses, bloodborne viral diseases such as hepatitis B and C, suicide attempts, and trauma among problem illicit drug users in both developed and developing countries.
- There is a global need for better surveillance systems to collect data on key drug-related consequences.
- There is a need for better prevalence estimates of problem illicit drug use in developed and developing countries, especially where there are indications of increased illicit drug use because of proximity to source countries.
- Other specific data collection needs include the following:
  - — improving the comparability and quality of data on the prevalence of drug use across regions;

— improving methods for accurately estimating the prevalence of, and burden associated with, illicit drug use among non-institutionalized populations;

— improving estimates of the number of "problem drug users" *per se*, to take into account polydrug use using consistent definitions of "problem drug use";

— obtaining mortality and morbidity data from developing regions from which more accurate methods to estimate the burden of illicit drug use can be derived for those regions;

— improving data on drug use among psychiatric patients, and data on psychiatric morbidity among drug users;

— developing more comparable and accurate mortality data by improving the consistency of procedures used to identify and register drug-related deaths across subregions, for both developed and developing subregions;

— systematic monitoring of mortality by drug type to provide data on mortality associated with non-opioid drugs, especially in the context of developing countries and countries with high HIV prevalence; and

— measurement of the coverage and nature of services in place to reduce burden, especially those aimed at reducing the transmission of bloodborne viruses.

7. Projections of illicit drug-related harm

There are a number of indications that rates of illicit drug use and illicit drug-related harm have risen in the past decade. First, developed countries with reasonable mortality data have shown steady increases in drug-related deaths, especially drug overdose deaths, over the past decade, for example, in Australia (Hall et al. 1999a); Spain (de la Fuente et al. 1995); and the United Kingdom (Hall et al. 2000c). Estimates derived from back projections of both overdose deaths and treatment entry in Australia have shown an increase in estimated number of dependent opioid users (Hall et al. 2000a, 2000b). Second, illicit drug use and drug-related harm such as overdoses and HIV/AIDS have been reported in an increasing number of countries where it was previously rare, such as in eastern Europe, the former Soviet Union, Asia and Africa (UNAIDS 2001; UNDCP 2000; UNODCCP 2000).

Despite indications that drug-related harm is increasing, it is difficult to predict future patterns of illicit drug use and drug-related harm for the following reasons.

First, there is a lack of good time series data on the prevalence of illicit drug use and data on drug-related harm may not be comparable over

time, even in countries with good mortality data systems, because of changes in classification systems (such as successive iterations of the ICD classification system), and because of improvements (and deterioration) in the quality of data that are collected.

Second, although the general trend has been for drug-related deaths to *increase* during the 1990s, there have also been a number of countries in which drug-related deaths have fallen sharply, often after various policy initiatives have been introduced. In France (Lepere et al. 2001) and Switzerland, for example, drug-related deaths have fallen markedly in the later half of the 1990s, probably in response to a marked expansion of opioid substitution treatment in both countries. In the past two years, Australia has also seen a substantial drop in opioid overdose deaths, after a steep rise from the early 1990s until 1999 (Degenhardt 2002). In this case, some of the early decrease may have been attributable to expanded treatment and educational initiatives to reduce overdose among opioid users. Since the beginning of 2001, the major driver of reduced overdose deaths in Australia has been a substantial drop in the availability of heroin (Weatherburn et al. 2001).

Third, there have been changes in the scale of illicit drug production and in the choice of drugs for illicit manufacture. For example, restrictions on opioid production in Afghanistan in the late 1990s may have reduced heroin supply to Europe, while the supply of cocaine and amphetamine type stimulants (ATS) increased (UNODCCP 2000). The net effect of these changes on drug-related harm is difficult to predict because the effects of ATS on mortality are less well studied and understood than that of opioids (Darke et al. 2000a).

7.1 Options for projection

A conservative option may be to assume that: (i) the current global problem will remain at about the current level, but that (ii) the distribution of burden will shift between developed and developing countries with declines in drug-related deaths in developed countries (resulting from expanded opioid substitution treatment) being offset by increases in drug-related deaths in developing societies.

A less conservative option would be to assume that in developed countries, rates of opioid use and opioid-related deaths will continue to rise, but at a slower rate (e.g. 50%) than that observed during the 1990s, because of expanded treatment availability. In developing countries, the rate of increase could be projected to follow the same pattern and magnitude as that observed in developed countries like Australia, which have reasonable time series data on trends in opioid-related deaths over the period when illicit opioid use was first introduced and spread (Hall et al. 2000b).

Substantial uncertainty intervals would need to be placed around these estimates to indicate our ignorance of underlying trends and to empha-

size the need to undertake better epidemiological research to improve our estimates of the global burden of disease attributable to illicit drug use.

Notes

1 See preface for an explanation of this term.

2 MDMA: 3,4 methylenedioxymethamphetamine, a synthetic drug that is used as a stimulant.

3 Amphetamine-type stimulant (ATS): one of a class of sympathomimetic amines with powerful stimulant action on the central nervous system.

4 Cannabis: a generic term for psychoactive preparations (e.g. marijuana, hashish and hash oil) derived from the *cannabis sativa* plant.

5 Cocaine: an alkaloid central nervous system stimulant drug that is derived from the coca plant.

6 Heroin: an opioid drug derived from the opium poppy.

7 Opioids: generic term applied to derivatives from the opium poppy, their synthetic analogues, and compounds synthesized in the body, which act upon the opioid receptors in the brain. They have the capacity to relieve pain and produce a sense of euphoria, as well as cause stupor, coma and respiratory depression.

8 Drug overdose: the use of any drug in such an amount that acute adverse physical or mental effects are produced. Overdose in this chapter refers to cases in which death is the outcome.

9 DSM-IV: American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

References

Advisory Council on the Misuse of Drugs (2000) *Reducing drug related deaths*. The Stationery Office, London.

Alter M, Hadler SC, Margolis H et al. (1990) The changing epidemiology of hepatitis B in the United States. *Journal of the American Medical Association*, **263**:1218–1222.

Anderson B, Bodsworth N, Rohrsheim R, Donovan B (1994) Hepatitis B virus infection and vaccination status of high risk people in Sydney: 1982 and 1992. *Medical Journal of Australia*, **161**:368–371.

Andreasson S, Allebeck P (1990) Cannabis and mortality among young men: a longitudinal study of Swedish conscripts. *Scandinavian Journal of Social Medicine*, **18**:9–15.

Anthony JC, Helzer J (1991) Syndromes of drug abuse and dependence. In: *Psychiatric Disorders in America*. Robins LN, Regier DA, eds. The Free Press, New York.

Anthony JC, Warner L, Kessler R (1994) Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic find-

ings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology*, **2**:244–268.

Australian Bureau of Criminal Intelligence (2000) *Australian illicit drug report 1998–1999*. Australian Bureau of Criminal Intelligence Publications, Canberra.

Barr HL, Antes D, Ottenberg DJ, Rosen A (1984) Mortality of treated alcoholics and drug addicts: the benefits of abstinence. *Journal of Studies on Alcohol*, **45**:440–452.

Bates MN, Blakely TA (1999) Role of cannabis in motor vehicle crashes. *Epidemiologic Reviews*, **21**:222–232.

Beautrais AL, Joyce PR, Mulder RT (1998) Psychiatric illness in a New Zealand sample of young people making serious suicide attempts. *New Zealand Medical Journal*, **111**:44–48.

Beautrais AL, Joyce PR, Mulder RT (1999) Cannabis abuse and serious suicide attempts. *Addiction*, **94**:1155–1164.

Benson G, Holmberg MB (1984) Drug-related mortality in young people. *Acta Psychiatrica Scandinavica*, **70**:525–534.

Bewley T, Ben-Arie O (1968) Morbidity and mortality from heroin dependence. 2. Study of 100 consecutive patients. *British Medical Journal*, **1**:727–730.

Bewley T, Ben-Arie O, James IP (1968) Morbidity and mortality from heroin dependence. 1. Survey of heroin addicts known to Home Office. *British Medical Journal*, **1**:725–726.

Boot BP, McGregor LS, Hall W (2000) MDMA (Ecstasy) neurotoxicity: assessing and communicating the risks. *The Lancet*, **355**:1818–1821.

Bucknall ABV, Robertson JR (1986) Deaths of heroin users in a general practise population. *Journal of the Royal College of General Practitioner*s, **36**:120–122.

Bux D, Lamb R, Iguchi M (1995) Cocaine use and HIV risk behaviour in methadone maintenance patients. *Drug and Alcohol Dependence*, **37**:29–35.

Capelhorn JRM, Dalton MSYN, Halder F, Petrenas A-M, Nisbet JG (1996) Methadone maintenance and addicts risk of fatal heroin overdose. *Substance Use and Misuse*, **31**:177–196.

Caulkins J, Rydell C, Everingham S (1999) *An ounce of prevention, a pound of uncertainty. The cost effectiveness of school-based drug prevention programs*. Drug Policy Research Center, Santa Monica, CA.

CDC (2001) *Centre for Disease Control, National Centre for HIV, STD and TB Prevention. Surveillance reports*. Retrieved, 2001, from http://www.cdc.gov/hiv/stats/hasr1201.htm.

Chaisson RE, Osmond D, Brodie B, Sande MA, Moss AR (1989) Cocaine use and HIV infection in intravenous drug users in San Francisco. *Journal of the American Medical Association*, **261**:561–565.

Chait LD, Pierri J (1992) Effects of smoked marijuana on human performance: a critical review. In: *Marijuana/cannabinoids: neurobiology and neurophysiology*. Murphy L, Bartke A, eds. CRC Press, Boca Raton, FL.

Cherubin C, McCusker J, Baden M, Kavaler F, Amsel Z (1972) The epidemiology of death in narcotic addicts. *American Journal of Epidemiology*, **96**:11–22.

Chesher G (1995) Cannabis and road safety: an outline of research studies to examine the effects of cannabis on driving skills and actual driving performance. In: *The effects of drugs (other than alcohol) on road safety*. Parliament of Victoria Road Safety Committee, ed. Road Safety Committee, Parliament of Victoria, Melbourne.

Chiasson M, Stoneburner R, Hildebrandt D, Ewing W, Telzak E, Jaffe H (1991) Heterosexual transmission of HIV-1 associated with the use of smokable freebase cocaine (crack). *AIDS*, **5**:1121–1126.

Concool B, Smith H, Stimmel B (1979) Mortality rates of persons entering methadone maintenance: a seven-year study. *American Journal of Drug and Alcohol Abuse*, **6**:345–353.

Danish National Board of Health (1997) *Drug related death in Europe: quality and comparability of data on drug-related deaths*: Danish National Board of Health—EMCDDA Working Group, Copenhagen.

Darke S, Hall W (1995) Levels and correlates of polydrug use among heroin users and regular amphetamine users. *Drug and Alcohol Dependence*, **39**:231–235.

Darke S, Ross J (1997) Polydrug dependence and psychiatric comorbidity among heroin injectors. *Drug and Alcohol Dependence*, **48**:135–141.

Darke S, Ross J (2000) *The relationship between suicide and overdose among methadone maintenance patients*. (NDARC Technical Report No. 100.) National Drug and Alcohol Research Centre, University of New South Wales, Sydney.

Darke S, Ross J, Cohen J, Hando J, Hall W (1995) Injecting and sexual risk-taking behaviour among regular amphetamine users. *AIDS Care*, **7**:19–26.

Darke S, Ross J, Hall W (1996) Overdose among heroin users in Sydney, Australia. I. Prevalence and correlates of non-fatal overdose. *Addiction*, **91**:405–411.

Darke S, Ross J, Hando J, Hall W, Degenhardt L (2000a) *Illicit drug use in Australia: epidemiology, use patterns and associated harm*. Australian Government Publishing Service, Canberra.

Darke S, Sims J, McDonald S, Wicks W (2000b) Cognitive impairment among methadone maintenance patients. *Addiction*, **95**:687–695.

Darke S, Zador D (1996) Fatal heroin "overdose": a review. *Addiction*, **91**:1765–1772.

Dart JK (1995) The use of epidemiological techniques to assess risk: the epidemiology of microbial keratitis. *Eye*, **9**:679–683.

Davoli M, Perucci C, Rapiti E et al. (1997) A persistent rise in mortality among injecting drug users in Rome, 1980 through 1992. *American Journal of Public Health*, **87**:851–854.

de la Fuente L, Barrio G, Vicente J, Bravo M, Santacreu J (1995) The impact of drug related deaths on mortality among young adults in Madrid. *American Journal of Public Health*, **85**:102–105.

Degenhardt L (2002) Opioid overdose deaths in Australia, 2001 edition. Sydney: National Drug and Alcohol Research Centre, University of New South Wales. Available at http://ndarc.med.unsw.edu.au/ndarc.nsf/website/DrugInfo.factsheets.

Degenhardt L, Hall W, Lynskey M (2001) The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. *Social Psychiatry and Psychiatric Epidemiology*, **36**:219–227.

Domino G, Lenaars AA (1989) Attitudes toward suicide: a comparison of Canadian and U.S. college students. *Suicide and Life-Threatening Behaviour*, **19**:345–359.

Domino G, Takahashi Y (1991) Attitudes towards suicide in Japanese and American medical students. *Suicide and Life-Threatening Behaviour*, **21**:345–359.

Donoghoe M (1996) Illicit drugs. In: *Quantifying global health risks: the burden of disease attributable to selected risk factors*. Murray CJL, Lopez AD, eds. Harvard University Press, Cambridge, MA.

Donoghoe M, Wodak A (1998) Health and social consequences of injecting drug use. In: *Drug injecting and HIV infection: Global dimensions and local responses*. Stimson G et al., eds. UCL Press, London.

Dowling GP, McDonough E, Bost RO (1987) Eve and ecstasy. A report of five deaths associated with the use of MDEA and MDMA. *Journal of the American Medical Association*, **257**:1615–1617.

Dukes PD, Robinson GM, Robinson BJ (1992) Mortality of intravenous drug users: attenders of the Wellington Drug Clinic, 1972–89. *Drug and Alcohol Review*, **11**:197–201.

Edlin B, Irwin K, Faraque S, McCoy C, Word C (1994) Intersecting epidemics—crack cocaine use and HIV infection among inner city young adults. Multicenter Crack Cocaine and HIV Infection Study Team. *New England Journal of Medicine*, **331**:1422–1427.

EMCDDA (1997) *Estimating the prevalence of problem drug use in Europe* (Scientific Monograph No. 1). European Monitoring Centre for Drugs and Drug Addiction, Luxembourg.

EMCDDA (1999) *Study to obtain comparable national estimates of problem drug use prevalence for all EU member states*. European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

EMCDDA (2000) *Annual report on the state of the drugs problem in the European Union*. European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

English D, Holman C, Milne E et al. (1995) *The quantification of drug caused morbidity and mortality in Australia, 1995*. Commonwealth Department of Human Services and Health, Canberra.

Engstrom A, Adamson C, Allebeck P, Rydberg U (1991) Mortality in patients with substance abuse: a follow-up in Stockholm County, 1973–1984. *The International Journal of the Addictions*, **26**:91–106.

Eskild A, Magnus P, Samuelson SO, Sohlberg C, Kittelsen P (1993) Differences in mortality rates and causes of death between HIV positive and HIV negative intravenous drug users. *International Journal of Epidemiology*, **22**:315–319.

Feldman U (1993) Epidemiologic assessment of risks of adverse reactions associated with intermittent exposure. *Biometrics*, **49**:419–428.

Fischer B, Gliksman L, Rehm J, Daniel N, Medved W (1999) Comparing opiate users in methadone treatment with untreated opiate users: results of a follow-up study with a Toronto opiate user cohort. *Canadian Journal of Public Health*, **90**:299–305.

Fischer B, Kendall P, Rehm J, Room R (1997) Charting WHO-goals for licit and illicit drugs for the year 2000: are we "on track"? *Public Health*, **111**:271–275.

Freeman, J (1996) Quantitative epidemiology. *Infection control and hospital epidemiology*, **17**:249–255.

Friedman LN, Williams MT, Singh TP, Frieden TR (1996) Tuberculosis, AIDS, and death among substance abusers on welfare in New York city. *The New England Journal of Medicine*, **334**:828–833.

Frischer M, Bloor M, Goldberg D, Clark J, Green S, McKeganey N (1993) Mortality among injecting drug users: a critical reappraisal. *Journal of Epidemiology and Community Medicine*, **47**:59–63.

Frischer M, Green ST, Goldberg D (1994) *Substance abuse related mortality: a worldwide review*. United Nations International Drug Control Programme, Vienna.

Fugelstad A, Annell A, Rajs J, Agren G (1997) Mortality and causes and manner of death among drug addicts in Stockholm during the period 1981–1992. *Acta Psychiatrica Scandinavica*, **96**:169–175.

Fugelstad A, Rajs J, Bottiger M, de Verdier MG (1995) Mortality among HIV-infected inravenous drug addicts in relation to methadone treatment. *Addiction*, **90**:711–716.

Galli M, Musicco M (1994) Mortality of intravenous drug users living in Milan, Italy: role of HIV-1 infection. *AIDS*, **8**:1457–1463.

Ghodse AH, Oyefeso A, Kilpatrick B (1998) Mortality of drug addicts in the United Kingdom 1967–1993. *International Journal of Epidemiology*, **27**:473–478.

Ghodse AH, Sheehan M, Taylor C, Edwards G (1985) Deaths of drug addicts in the United Kingdom 1967–81. *British Medical Journal*, **290**:425–428.

Goedert JJ, Pizza G, Gritti FM et al. (1995) Mortality among drug users in the AIDS era. *International Journal of Epidemiology*, **24**:1204–1210.

Goldfrank L, Hoffman R (1993) The cardiovascular effects of cocaine—update. In: *Acute cocaine intoxication: current methods of treatment*. (Research

Monograph No. 123). Sorer H, ed. National Institute on Drug Abuse, Rockville, MD.

Goldstein A, Herrera J (1995) Heroin addicts and methadone treatment in Albuquerque: a 22 year follow-up. *Drug and Alcohol Dependence*, **40**:139–150.

Gossop M, Griffiths P, Powis B, Williamson S, Strang J (1996) Frequency of non-fatal heroin overdose: survey of heroin users recruited in non-clinical settings. *British Medical Journal*, **313**:402.

Gossop M, Marsden J, Stewart D (1998) *NTORS at one year*. Department of Health, London.

Gronbladh L, Ohund LS, Gunne LM (1990) Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatrica Scandinavica*, **82**:223–227.

Haastrup S, Jepson PW (1984) Seven year follow-up of 300 young drug abusers. *Acta Psychiatrica Scandinavica*, **70**:503–509.

Haastrup S, Jepson PW (1988) Eleven year follow-up of 300 young opioid addicts. *Acta Psychiatrica Scandinavica*, **77**:22–26.

Hall W, Degenhardt L, Lynskey M (1999a) Opioid overdose mortality in Australia, 1964–1997: birth cohort trends. *Medical Journal of Australia*, **171**:34–37.

Hall W, Degenhardt L, Lynskey M (2001) *The health and psychological consequences of cannabis use* (NCADA Monograph No. 44). Australian Publishing Service, Canberra.

Hall W, Johnston L, Donnelly N (1999b) Epidemiology of cannabis use and its consequences. In: *The health effects of cannabis*. Kalant H et al., eds. Centre for Addiction and Mental Health, Toronto.

Hall W, Lynskey M, Degenhardt L (1999c) *Heroin use in Australia: its impact upon public health and public order* (NDARC Monograph No. 42). National Drug and Alcohol Research Centre, University of New South Wales, Sydney.

Hall W, Lynskey M, Degenhardt L (2000c) Trends in opiate-related deaths in the United Kingdom and Australia, 1985–1995. *Drug and Alcohol Dependence*, **57**:247–254.

Hall W, Ross J, Lynskey M, Law M, Degenhardt L (2000a) How many dependent heroin users are there in Australia? *Medical Journal of Australia*, **173**:528–531.

Hall W, Ross J, Lynskey M, Law M, Degenhardt L (2000b) *How many dependent heroin users are there in Australia?* (NDARC Monograph No. 44). National Drug and Alcohol Research Centre, University of New South Wales, Sydney.

Hall W, Solowij N (1998) Adverse effects of cannabis. *The Lancet*, **352**: 1611–1616.

Hall W, Solowij N, Lemon J (1994) *The health and psychological consequences of cannabis use* (NDARC Monograph No. 25). Australian Publishing Service, Canberra.

Hall W, Teesson M, Lynskey M, Degenhardt L (1999d) The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian

adults: findings from the National Survey of Mental Health and Well-Being. *Addiction*, **94**:1541–1550.

Hartnoll R (1997) Cross-validating at local level. In: *Estimating the prevalence of problem drug use in Europe*. European Monitoring Centre for Drugs and Drug Addiction, ed. Office for Official Publications of the European Communities, Luxembourg.

Henderson S, Andrews G, Hall W (2000) Australia's mental health: an overview of the general population survey. *Australian and New Zealand Journal of Psychiatry*, **34**:197–205.

Henry JA, Jeffreys KJ, Dawling S (1992) Toxicity and deaths from 3,4 methylenedioxymethamphetamine ("ecstasy"). *The Lancet*, **340**:284–287.

Hser Y, Anglin D, Powers K (1993) A 24-year follow-up of Californian narcotics addicts. *Archives of General Psychiatry*, **50**:577–584.

Hulse G, English D, Milne E, Holman C (1999) The quantification of mortality resulting form the regular use of illicit opiates. *Addiction*, **94**:221–230.

Hurley S, Jolley D, Kaldor J (1997) Effectiveness of needle-exchange programmes for prevention of HIV infection. *The Lancet*, **349**:1797–1800.

Joe GW, Lehman W, Simpson DD (1982) Addicts death rates during a four-year post-treatment follow-up. *American Journal of Public Health*, **72**:703–709.

Joe GW, Simpson DD (1987) Mortality rates among opioid addicts in a longitudinal study. *American Journal of Public Health*, **77**:347–348.

Keenan E, Dorman A, O'Connor J (1993) Six year follow-up of forty five pregnant opiate addicts. *Irish Journal of Medical Science*, **162**:444–445.

Klee H, Faugier J, Hayes C, Boulton T, Morris J (1990) AIDS-related risk behaviour, polydrug use and temazepam. *British Journal of Addiction*, **85**:1125–1132.

Lepere B, Gourarier L, Sanchez M et al. (2001) Reduction in the number of lethal heroin overdoses in France since 1994. Focus on substitution treatments. *Annales de Medecine Interne*, **152**:S5–12.

Levine S, Vlahov D, Nelson K (1994) Epidemiology of hepatitis B virus: seroprevalence, risk factors and viral interactions. *Epidemiologic Reviews*, **16**:418–436.

Lurie P, Drucker E (1997) An opportunity lost: HIV infections associated with a lack of needle-exchange programmes in the USA. *The Lancet*, **349**:604–608.

MacDonald M, Crofts N, Kaldor J (1996) Transmission of hepatitis C virus: rates, routes, and cofactors. *Epidemiologic Reviews*, **18**:137–148.

MacDonald M, Wodak A, Dolan K, van Beek I, Cunningham P, Kaldor J (2000) Hepatitis C virus antibody prevalence among injecting drug users at selected needle and syringe programs in Australia, 1995–1997. *Medical Journal of Australia*, **172**:57–61.

Mathers C, Vos T, Stevenson C (1999) *The Burden of Disease and Injury in Australia*. Australian Institute of Health and Welfare, Canberra.

McAnulty JM, Tesselaar H, Fleming DW (1995) Mortality among injection drug users identified as "out of treatment". *American Journal of Public Health*, **85**:119–120.

Mientjes GH, van Ameijden EK, van den Hoek AJAR, Coutinho RA (1992) Increasing morbidity without rise in non-AIDS mortality among HIV-infected intravenous drug users in Amsterdam. *AIDS*, **6**:207–212.

Muller M (1982) *The Health of Nations: a North-South investigation*. Faber and Faber, London.

Murray CJL, Lopez AD, eds. (1996) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global burden of Disease and Injury, Vol. 1. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Musto DF, Ramos MR (1981) A follow-up study of the New Haven morphine maintenance clinic of 1920. *The New England Journal of Medicine*, **304**:1071–1077.

National Centre in HIV Epidemiology and Clinical Research (1998) *HIV/AIDS and related diseases in Australia: Annual Surveillance Report 1998*. National Centre in HIV Epidemiology and Clinical Research, Sydney.

National Drug and Alcohol Research Centre (2000) *1999 Australian Bureau of Statistics data on opioid overdose deaths*. National Drug and Alcohol Research Centre, University of New South Wales. Retrieved from http://www.med.unsw.edu.au/ndarc.

National Institute on Drug Abuse (1992) *The economic costs of alcohol and drug abuse in the United States—1992*. Available at http://165.112.78.61/EconomicCosts/Index.html.

National Research Council (2001) *Informing America's policy on illegal drugs: what we don't know keeps hurting us*. National Academy Press, Washington, DC.

Oppenheimer E, Tobutt C, Taylor C, Andrew T (1994) Death and survival in a cohort of heroin addicts from London clinics: a 22-year follow-up study. *Addiction*, **89**:1299–1308.

Orti RM, Domingo-Salvany A, Munoz A, MacFarlane D, Suelves JM, Anto JM (1996) Mortality trends in a cohort of opiate addicts, Catalonia, Spain. *International Journal of Epidemiology*, **25**:545–553.

Parr MJA, Heather ML, Botterill P (1997) Hyponatraemia and death after "ecstacy" ingestion. *Medical Journal of Australia*, **166**:136–141.

Perucci CA, Davoli M, Rapiti E, Abeni DD, Forastiere F (1991) Mortality of intravenous drug users in Rome: a cohort study. *American Journal of Public Health*, **81**:1307–1310.

Platt JJ (1997) *Cocaine addiction: theory, research, and treatment*. Harvard University Press, Cambridge, MA.

Reid G, Costigan G (2002) *Revisiting "The hidden epidemic": a situation assessment of drug use in Asia in the context of HIV/AIDS*. The MacFarlane Burnet Institute for Medical Research and Public Health, Melbourne.

Ridolfo B, Stevenson C (2001) *The quantification of drug-caused mortality and morbidity in Australia, 1998*. Australian Institute of Health and Welfare, Canberra.

Robbe HWJ (1994) *Influence of marijuana on driving*. Institute for Human Psychopharmacology, University of Limberg, Maastricht.

Robertson JR, Ronald PM, Raab GM, Ross AJ, Parpia T (1994) Deaths, HIV infection, abstinence and other outcomes in a cohort of injecting drug users followed up for 10 years. *British Medical Journal*, **309**:369–372.

Ross M, Wodak A, Loxley W, Stowe A, Drury M (1992) *Staying negative. Summary of the results of the Australian National AIDS and Injecting Drug Use Study*. ANAIDUS, Sydney.

Rossow I, Lauritzen G (1999) Balancing on the edge of death: suicide attempts and life-threatening overdoses among drug addicts. *Addiction*, **94**:209–219.

Sanchez-Carbonell X, Seus L (2000) Ten-year survival analysis of a cohort of heroin addicts in Catalonia: the EMETYST project. *Addiction*, **95**:941–948.

Segest E, Mygind O, Bay H (1990) The influence of prolonged stable methadone maintenance treatment on mortality and employment: an 8-year follow-up. *The International Journal of the Addictions*, **25**:53–63.

Selwyn PA, Hartel D, Wasserman W, Drucker E (1989) Impact of the AIDS epidemic on morbidity and mortality among intravenous drug users in a New York methadone maintenance program. *American Journal of Public Health*, **79**:1358–1362.

Sidney S, Beck JE, Tekawa IS, Quesenberry CP Jr., Friedman GD (1997a) Marijuana use and mortality. *American Journal of Public Health*, **87**: 585–590.

Sidney S, Quesenberry CP, Friedman GD, Tekawa IS (1997b) Marijuana use and cancer incidence (California, United States). *Cancer Causes and Control*, **8**:722–728.

Smiley A (1999) Marijuana: on road and driving simulator studies. In: *The health effects of cannabis*. Kalant H et al., eds. Addiction Research Foundation, Toronto.

Stimson G (1993) The global diffusion of injecting drug use: implications for human immunodeficiency virus infection. *Bulletin on Narcotics*, **45**:3–17.

Thorley A, Oppenheimer E, Stimson GV (1977) Clinic attendance and opiate prescription status of heroin addicts over a six-year period. *British Journal of Psychiatry*, **130**:565–569.

Thorsen K, Haarstrup S (1975) Follow-up of 97 young non-psychotic male opiate abusers: relationship between achieving abstinence, age and duration of abuse. *Acta Psychiatrica Scandinavica*, **51**:289–296.

Topp L, Hando J, Dillon P, Solowij N (1999) Ecstasy use in Australia: patterns of use and associated harm. *Drug and Alcohol Dependence*, **55**:105–115.

Tunving K (1988) Fatal outcome in drug addiction. *Acta Psychiatrica Scandinavica*, **77**:551–566.

UNAIDS (2001) *Joint United Nations Programme on HIV/AIDS*. Retrieved, 2001, from http://www.unaids.org.

UNDCP (2000) *Global illicit drug trends 2000*. United Nations International Drug Control Programme, Vienna.

UNODCCP (2000) *World drug report 2000*. United Nations Office for Drug Control and Crime Prevention. Oxford University Press, Oxford.

Vaillant GE (1966) Twelve-year follow-up of New York narcotic addicts. II. The natural history of a chronic disease. *The New England Journal of Medicine*, **275**:1282–1288.

Vaillant GE (1973) A 20-year follow-up of New York narcotic addicts. *Archives of General Psychiatry*, **29**:237–241.

van Ameijden EJC, Krol A, Vlahov D, Flynn C, van Haastrecht HJA, Coutinho RA (1999) Pre-AIDS mortality and morbidity among injection drug users in Amsterdam and Baltimore: an ecological comparison. *Substance Use and Misuse*, **34**:845–865.

van Haastrecht HJA, van Ameijden EJC, van den Hoek JAR, Mientjes GHC, Bax JS, Coutinho RA (1996) Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users. *American Journal of Epidemiology*, **143**:380–391.

Wahren CA, Brandt L, Allebeck P (1997) Has mortality in drug addicts increased? A comparison between two hospitalized cohorts in Stockholm. *International Journal of Epidemiology*, **26**:1219–1226.

Warner-Smith M, Darke S, Lynskey M, Hall W (2001) Heroin overdose: causes and consequences. *Addiction*, **96**:1113–1125.

Watterson O, Simpson DD, Sells SB (1975) Death rates and causes of death among opioid addicts in community drug treatment programs during 1970–1973. *American Journal of Drug and Alcohol Abuse*, **2**:99–111.

Weatherburn D, Jones C, Freeman K, Makkai T (2001) *The Australian heroin drought and its implications for drug policy.* (Crime and Justice Bulletin No. 59). New South Wales Bureau of Crime Statistics and Research, Sydney.

WHO (1993) *The ICD-10 Classification of mental and behavioural disorders—diagnostic criteria for research*. World Health Organization, Geneva.

WHO (1997) *Cannabis: a health perspective and research agenda.* World Health Organization, Geneva.

WHO (1998) *Opioid overdose. Trends, risk factors, interventions and priorities for action.* World Health Organization, Programme on Substance Abuse, Geneva.

WHO (2001) *World Health Organization All-Cause Mortality Database*. Retrieved, 2001, from http://www-nt.who.int/whosis/statistics/menu.cfm.

Wiepert GD, Bewley TH, d'Orban PT (1978) Outcomes for 575 British opiate addicts entering treatment between 1968 and 1975. *Bulletin on Narcotics*, **30**:21–32.

Wille R (1981) Ten-year follow-up of a representative sample of London heroin addicts: clinic attendance, abstinence and mortality. *British Journal of Addiction*, **76**:259–266.

Zaccarelli M, Gattari P, Rezza G et al. (1994) Impact of HIV infection on non-AIDS mortality among Italian injecting drug users. *AIDS*, **8**:345–350.

Zanis DA, Woody GE (1998) One-year mortality rates following methadone treatment discharge. *Drug and Alcohol Dependence*, **52**:257–260.

Zhang Z-F, Morgenstern H, Spitz M et al. (1999) Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiology, Biomarkers and Prevention*, **8**:1071–1078.