

**AHA PRESIDENTIAL ADVISORY**

# Dietary Fats and Cardiovascular Disease

## A Presidential Advisory From the American Heart Association

**ABSTRACT:** Cardiovascular disease (CVD) is the leading global cause of death, accounting for 17.3 million deaths per year. Preventive treatment that reduces CVD by even a small percentage can substantially reduce, nationally and globally, the number of people who develop CVD and the costs of caring for them. This American Heart Association presidential advisory on dietary fats and CVD reviews and discusses the scientific evidence, including the most recent studies, on the effects of dietary saturated fat intake and its replacement by other types of fats and carbohydrates on CVD. In summary, randomized controlled trials that lowered intake of dietary saturated fat and replaced it with polyunsaturated vegetable oil reduced CVD by  $\approx 30\%$ , similar to the reduction achieved by statin treatment. Prospective observational studies in many populations showed that lower intake of saturated fat coupled with higher intake of polyunsaturated and monounsaturated fat is associated with lower rates of CVD and of other major causes of death and all-cause mortality. In contrast, replacement of saturated fat with mostly refined carbohydrates and sugars is not associated with lower rates of CVD and did not reduce CVD in clinical trials. Replacement of saturated with unsaturated fats lowers low-density lipoprotein cholesterol, a cause of atherosclerosis, linking biological evidence with incidence of CVD in populations and in clinical trials. Taking into consideration the totality of the scientific evidence, satisfying rigorous criteria for causality, we conclude strongly that lowering intake of saturated fat and replacing it with unsaturated fats, especially polyunsaturated fats, will lower the incidence of CVD. This recommended shift from saturated to unsaturated fats should occur simultaneously in an overall healthful dietary pattern such as DASH (Dietary Approaches to Stop Hypertension) or the Mediterranean diet as emphasized by the 2013 American Heart Association/American College of Cardiology lifestyle guidelines and the 2015 to 2020 Dietary Guidelines for Americans.

**Frank M. Sacks, MD,**  
FAHA, Chair  
**Alice H. Lichtenstein, DSc,**  
FAHA  
**Jason H.Y. Wu, PhD, MSc**  
**Lawrence J. Appel, MD,**  
MPH, FAHA  
**Mark A. Creager, MD,**  
FAHA  
**Penny M. Kris-Etherton,**  
PhD, RD, FAHA  
**Michael Miller, MD, FAHA**  
**Eric B. Rimm, ScD, FAHA**  
**Lawrence L. Rudel, PhD,**  
FAHA  
**Jennifer G. Robinson, MD,**  
MPH, FAHA, Vice Chair  
**Neil J. Stone, MD, FAHA**  
**Linda V. Van Horn, PhD,**  
RD, FAHA, Vice Chair  
On behalf of the American Heart Association

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**C**ardiovascular disease (CVD) is the leading global cause of death, accounting for 17.3 million deaths per year, comprising 31.5% of total global deaths in 2013. Nearly 808 000 people in the United States died of heart disease, stroke, and other CVDs in 2014, translating to about 1 of every 3 deaths. The annual direct and indirect costs of these deaths total more than \$316.1 billion, including health expenditures and lost productivity.<sup>1</sup> Preventive treatment that reduces CVD by even a small percentage can substantially reduce, nationally and globally, the number of people who develop CVD and the costs of caring for them.

Since 1961, the American Heart Association (AHA) has recommended reduction in dietary saturated fat to reduce the risk of CVD.<sup>2,3</sup> The purpose of this AHA presidential advisory on dietary fats and CVD is to review and discuss the scientific evidence, including the most recent studies, on the effects on CVD of dietary saturated fat and its replacement by other types of fats and carbohydrates. A presidential advisory is initiated by the AHA president to address a topic of special current importance. This report discusses the major classes of dietary fatty acids, except for the very-long-chain n-3 fatty acids in fish, which are covered by other AHA reports.

The scientific rationale for decreasing saturated fat in the diet has been and remains based on well-established effects of saturated fat to raise low-density lipoprotein (LDL) cholesterol, a leading cause of atherosclerosis<sup>4</sup>; to cause atherosclerosis in several animal species, especially nonhuman primates<sup>5</sup>; to clear the atherosclerosis in animals<sup>6</sup> when it is reduced in the diet; and likewise to reverse atherosclerosis in humans.<sup>7,8</sup> In addition, reducing saturated fat and replacing it with polyunsaturated fat in randomized controlled trials has reduced the incidence of CVD.<sup>9,10</sup> Populations with very low saturated fat intake such as in East Asian and Mediterranean countries have very low rates of CVD,<sup>11</sup> and members of many single populations who have low saturated and high unsaturated fat intake have lower future incidence of CVD compared with those with high saturated and low unsaturated fat intake.<sup>12</sup> The current AHA/American College of Cardiology guideline is to decrease intake of saturated fat to 5% to 6% of total daily energy (calorie) intake for individuals with elevated LDL cholesterol concentration.<sup>3</sup> The 2015 to 2020 Dietary Guidelines for Americans recommend consuming <10% of calories from saturated fat for the general population and replacing saturated fat with unsaturated fat.<sup>13</sup> The average intake of saturated fat in adults in the United States is 11% of total daily energy intake<sup>13,14</sup>; only about 5% of adults consume <7%, and 30% to 40% consume <10%.<sup>14</sup> Thus, most adults need to reduce saturated fat to reduce their risk of CVD. The implementation strategy recommended to achieve this reduction is to shift food choices from those high in

saturated to those high in polyunsaturated and mono-unsaturated fats.<sup>3,13</sup>

In the past few years, meta-analyses of observational studies and randomized clinical trials have come to discordant conclusions about the relationship between dietary saturated fat and risk of CVD.<sup>9,10,12,15–17</sup> This has created confusion among patients, their physicians, and the public. In this article, we analyze and discuss the methodology and interpretation of results reported by these researchers and the reasons for the divergent findings.

## SUMMARY OF CONCLUSIONS

Dietary saturated fat, like any macronutrient, supplies energy (calories) to the diet. In randomized clinical trials on saturated fat, the group that is assigned a diet lower in saturated fat is taught how to replace it with foods higher in  $\geq 1$  other macronutrients, typically carbohydrates or unsaturated fats, to maintain the same total energy intake. Other trials, often called controlled feeding trials, actually provide to the research participants their assigned diet high or low in saturated fat balanced with a similar amount of energy from another macronutrient. Essential to the interpretation of the results from these trials (and the reason for the divergent results in meta-analyses noted above) is the macronutrient composition of the comparator diet. Clinical trials that used polyunsaturated fat to replace saturated fat reduced the incidence of CVD.<sup>9,10</sup> In contrast, trials that used mainly carbohydrates to replace saturated fat did not reduce CVD. However, the types of carbohydrate-containing foods were often unspecified and typically included sugar and other refined carbohydrates to maintain energy balance. Evidence from prospective observational studies indicates that carbohydrates from whole grains reduce CVD when they replace saturated fat.<sup>18</sup>

Prospective observational studies, also called cohort studies, are conducted in large populations in which dietary intake is assessed at the beginning of the study and in some studies reassessed repeatedly during the follow-up periods, and CVD is assessed at various points during follow-up. In prospective observational studies, the participants eat whatever diet they themselves choose, and the researchers request that participants report their recent or past dietary history. Research participants in observational studies who eat a large amount of saturated fat eat less of various other macronutrients, usually carbohydrates, unsaturated fat, or both, to maintain energy intake. Participants who eat a comparatively small amount of saturated fat eat more carbohydrates or unsaturated fats. Because carbohydrates and unsaturated fats differ in their metabolic effects, it is necessary to evaluate the effects of low and high saturated fat intakes in the context of the replacement

macronutrient. This is easier in a clinical trial because the trial controls the dietary intake but more complicated in observational studies in which the participants control their own diets.

Meta-analyses of prospective observational studies aiming to determine the effects on CVD of saturated fat that did not take into consideration the replacement macronutrient have mistakenly concluded that there was no significant effect of saturated fat intake on CVD risk.<sup>15,16</sup> In contrast, meta-analyses that specifically evaluated the effect of replacing saturated fat with polyunsaturated fat found significant benefit, whereas replacing saturated fat with carbohydrates, especially refined carbohydrates, yielded no significant benefit to CVD risk.<sup>12,17,18</sup> Thus, again, differences in the effects of the replacement or comparator nutrients, specifically carbohydrates and unsaturated fats, are at the root of the apparent discrepancies among studies and meta-analyses on whether lowering saturated fat reduces the risk of developing CVD. In fact, the evidence to recommend reduction of saturated fat and its replacement by polyunsaturated and monounsaturated fat has strengthened as better methodology is more widely adopted for the analysis of dietary intake in observational studies.

We judge the evidence to favor recommending n-6 polyunsaturated fat, that is, linoleic acid, stronger than monounsaturated fat to replace saturated fat because of the positive results of randomized clinical trials that used polyunsaturated fat compared with the paucity of trials that used monounsaturated fat<sup>10</sup>; the greater relative risk reduction for polyunsaturated fats in observational studies<sup>12,17,18</sup>; the greater reduction in LDL cholesterol with polyunsaturated fat<sup>4</sup>; and the regression of atherosclerosis in nonhuman primates by polyunsaturated but not monounsaturated fat.<sup>5</sup> However, progress in reducing CVD would be enhanced by replacing saturated fat by either type of unsaturated fat.

## FATTY ACID COMPOSITION OF FATS AND OILS

The fatty acid composition of major fats and oils in the diet is shown in the Table.<sup>19</sup> The main sources of saturated fat to be decreased are dairy fat (butter), lard (pork), beef tallow, palm oil, palm kernel oil, and coconut oil. Polyunsaturated fats are contained in canola oil, corn oil, soybean oil, peanut oil, safflower oil, sunflower oil, and walnuts. However, original high-linoleic varieties of safflower and sunflower oils are uncommon. High-oleic varieties of safflower and sunflower oil, olive oil, avocados, and tree nuts such as almonds, cashews, hazelnuts, pistachios, and pecans have mainly monounsaturated fats and are low in saturated fat.

## CVD OUTCOMES: RANDOMIZED CLINICAL TRIALS THAT LOWERED DIETARY SATURATED FAT

The randomized clinical trial, when designed appropriately to answer the research question and executed with high quality, is the cornerstone for health and medical guidelines and policy. However, a randomized trial of a food or nutrient must achieve a biologically meaningful difference in intake between treatment and control groups and sustain it for a long enough time to deliver a valid result. Participants may find it difficult to maintain intake of a diet to which they are not accustomed and may revert to their original more familiar diet. In some trials, the difference in dietary saturated fat was maintained for many years,<sup>20–22</sup> but in others, the difference fell well short of planned.<sup>23–25</sup> In addition, the comparator nutrient that replaced saturated fat, polyunsaturated fat or carbohydrates, differed among trials. Reviewers who evaluate these trials must take into account the specific nutritional experiment that was conducted and the level of its adherence throughout the follow-up period.

### Low Saturated, High Polyunsaturated Fat Diets

In the mid-1950s, 4 research groups reported that replacing saturated fat from animal products with polyunsaturated fat from vegetable oils substantially reduced serum cholesterol levels.<sup>26–29</sup> Soon, controlled trials followed to test whether the reduction in serum cholesterol caused by substituting polyunsaturated for saturated fat prevented CVD. We examined several recent systematic reviews and meta-analyses<sup>9,10,16</sup> from which we identified and here discuss 4 trials<sup>20–22,30</sup> that make up the core evidence on this important question on the basis of quality of study design, execution, and adherence. These trials compared high saturated with high polyunsaturated fat intake; did not include *trans* unsaturated fat as a major component; controlled the dietary intake of the intervention and control groups; had at least 2 years of sustained intake of the assigned diets; proved adherence by objective biomarkers such as serum cholesterol or blood or tissue levels of polyunsaturated fatty acids; and collected and validated information on cardiovascular or coronary disease events. The reason for the 2-year minimum duration is that changes in polyunsaturated fatty acids very slowly equilibrate with tissue fatty acid levels; it takes ≈2 years to achieve 60% to 70% of the full effect.<sup>20,30</sup> Trials of serum cholesterol-lowering agents show that a reduction in coronary heart disease (CHD) incidence occurs with a lag of 1 to 2 years.<sup>31</sup> These systematic reviews<sup>9,10,16</sup> together found and analyzed 6 additional trials<sup>7,23,32–35</sup> that replaced saturated with polyunsaturated

**Table. Fatty Acid Composition of Fats and Oils**

	Saturated, g/100 g			Monounsaturated, g/100 g		Polyunsaturated, g/100 g		
	Total	Lauric (12:0), Myristic (14:0), Palmitic (16:0)	Stearic (18:0)	Total	Oleic (18:1)	Total	Linoleic (18:n-6)	$\alpha$ -Linolenic (18:3n-3)
Canola oil	7	4	2	63	62	28	19	9
Coconut oil	82	67	3	6	6	2	2	0
Corn oil	13	11	2	28	27	55	53	1
Dairy fat (butter)	63	39	12	26	21	4	3	0
Lard (pork)	39	25	14	45	41	11	10	1
Olive oil	14	11	2	73	71	10	10	1
Palm oil	49	45	4	37	37	9	9	0
Palm kernel oil	82	72	3	11	11	2	2	0
Peanut oil	17	10	2	46	45	32	32	0
Safflower oil (high linoleic)	6	4	2	14	14	75	75	0
Safflower oil (high oleic)*	8	5	2	75	75	13	13	1
Soybean oil	16	10	4	23	23	58	50	7
Sunflower oil (high linoleic)	10	6	4	20	20	66	66	0
Sunflower oil (high oleic)*	10	5	4	84	83	4	4	0
Tallow (beef)	50	30	19	42	36	4	3	1

A zero value equals <0.5 g/100 g.

\*Primary safflower and sunflower oils of commerce.

Data from US Department of Agriculture food composition tables.<sup>19</sup>

fat but did not have  $\geq 1$  of these characteristics crucial to testing the hypothesis. We also discuss these “noncore” trials and evaluate their potential impact on the overall result on dietary saturated and polyunsaturated fat and risk of CVD.

### **Core Trials on Replacing Saturated With Polyunsaturated Fat**

The Wadsworth Hospital and Veterans Administration Center in Los Angeles (Dayton et al<sup>20</sup>) conducted a high-quality, double-blind, well-controlled trial. There were 846 men with a mean age of 65 years, and 30% had CVD. The experimental diet used corn, soybean, safflower, and cottonseed oils, all high in polyunsaturated linoleic acid, to replace saturated fat in the control diet. The participants were served their meals at the center, with each diet group in a separate dining room. Adherence was confirmed by objective measures demonstrating enrichment with linoleic acid in blood, adipose tissue, and atherosclerosis specimens in the coronary arteries and aorta. Moreover, the investigators established double-blind conditions. The average duration was 8 years. The experimental diet reduced serum cholesterol by 13%. There were 20% fewer primary events, myocardial infarction or sudden death, in the diet group than in the control group, not a statistically significant difference. The diet significantly reduced the CVD end point, definite myocardial infarction, sudden death, or ischemic stroke, by 34% ( $P=0.04$ ) and total CVD events by 31% ( $P=0.01$ ). There were 41% fewer

men who had an ischemic stroke in the diet group than in the control group ( $P=0.055$ ).

By contemporary standards, the trial needed more participants to reach a definitive conclusion. However, the strict dietary control and 8-year-long intervention period ensured both a large difference in the dietary fatty acid intakes and enough CVD events to reach a statistically significant treatment effect for the secondary CVD outcomes, which were more highly powered because of their larger numbers of events.

The Oslo Diet-Heart Study<sup>21</sup> assigned at random 412 men who had had a myocardial infarction to either a control group who continued their usual high-saturated fat diet or an experimental group who changed to a low saturated, high polyunsaturated fat diet. The men in the experimental group and their wives were taught in their homes how to select and prepare foods that were low in saturated fat and high in polyunsaturated vegetable oils. The polyunsaturated fat diet lowered serum cholesterol by 14% (41 mg/dL), thereby confirming adherence, and this effect was sustained throughout the 5-year trial. The polyunsaturated fat diet significantly reduced the primary outcome, recurrent myocardial infarction and new cases of angina pectoris or sudden death, significantly by 29% ( $P=0.011$ ). Among the components of the primary outcome, myocardial infarction and angina pectoris were significantly reduced by 37% and 66%, respectively, whereas incidence of sudden death was the same in both groups. The end point, myocardial

infarction or sudden death, was reduced by 25% ( $P=0.05$ ). There were fewer cardiovascular deaths in the experimental group by 27% ( $P=0.09$ ). The low saturated, high polyunsaturated fat group continued to experience reduced cardiovascular mortality compared with the high saturated fat control group for an additional 6 years after the trial ended.

The British Medical Research Council compared a diet containing soybean oil, 86 g/d, with a diet with saturated fat from animal products in 393 men after myocardial infarction.<sup>22</sup> They were instructed to drink half the soybean oil allotment with fruit juice and use half in cooking, and they were counseled on how to reduce the saturated fat in their diet so that the total fat contents of the intervention and control groups were similar. Replacing animal fat with soybean oil lowered serum cholesterol by 16%. The primary outcome was first relapse (myocardial infarction, angina, sudden death). After 4 years, 62 of 199 in the soybean oil group had had a recurrent coronary event compared with 74 of 194 in the high saturated fat group; the difference,  $-18\%$  (95% CI,  $-38$  to  $7$ ), was not statistically significant.

The Finnish Mental Hospital Study compared a diet high in polyunsaturated fat, mainly from soybean oil, with a diet high in saturated fat in 1222 patients at 2 psychiatric hospitals.<sup>30,36,37</sup> In 1 hospital, the high polyunsaturated fat diet was given first, followed by the saturated fat diet; in the other hospital, the diets were given in the reverse order. Each diet period lasted 6 years. There were 2 cohorts. One comprised the entire patient populations of the 2 hospitals; 25% had evidence of CHD on an ECG, and 57% were women. The other cohort included only patients who had no evidence of CHD, that is, a primary prevention cohort. Women made up 44%. Serum cholesterol was 38 mg/dL (14%) lower on the high polyunsaturated fat diet than on the high saturated fat diet. Adherence was also demonstrated by 3-fold enrichment of linoleic acid in adipose tissue. In the mixed primary and secondary prevention cohort, CHD death, the primary outcome, was significantly lower by 41% (95% CI,  $-26$  to  $-53$ ) during the polyunsaturated than the saturated fat diet (Figure 1). In the primary prevention cohort, CHD death or myocardial infarction was the primary outcome, and the incidence was significantly lower also by 41% (95% CI,  $-17$  to  $-58$ ) during the polyunsaturated than during the saturated fat periods. In each hospital, CHD events were lower during the times when the polyunsaturated fat diet was given. Results were similar in men and women.

We performed a fixed-effects meta-analysis of these 4 core trials using the primary outcome chosen by each trial (Figure 2). This approach ensures that the results of the meta-analysis are based on prospectively defined primary outcomes, thereby having more validity than

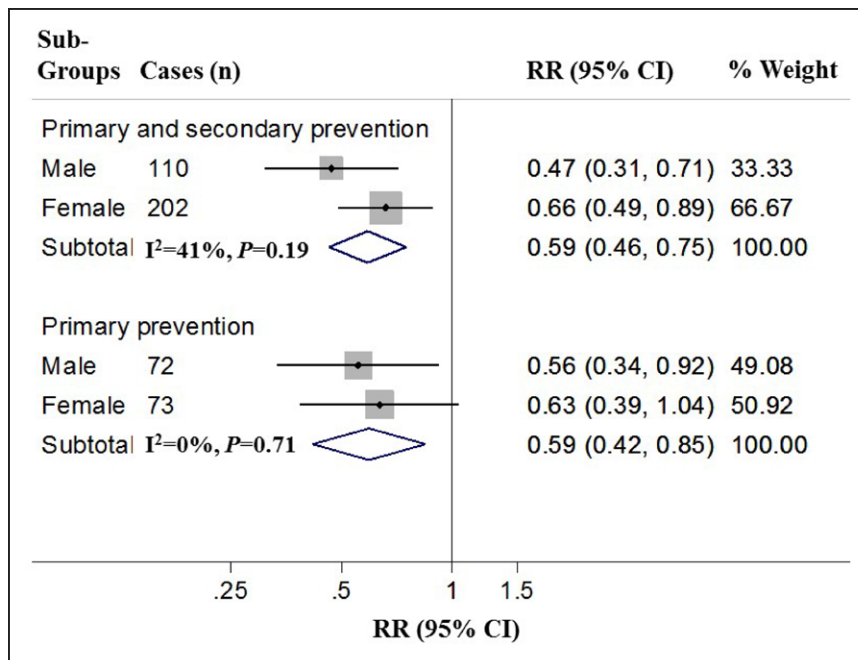
an alternative approach that redefines a new common outcome for all the component trials. This alternative approach would have a serious weakness, the selection of a new outcome that is post hoc and potentially influenced by researchers' bias. We included the entire Finnish trial population, primary and secondary prevention, women and men combined.

The results showed that lowering saturated fat and replacing it with vegetable oil rich in polyunsaturated fat, primarily soybean oil, lowered CHD by 29%. This effect on CHD is consistent with the effect of the experimental diet on serum cholesterol.<sup>31</sup> Each trial achieved a crucial element in clinical trial execution, producing and maintaining the required difference in diets as objectively documented by blood and tissue fatty acid biomarkers and serum cholesterol, that was needed to test the study aim. However, these trials were conducted in the 1960s, before widespread use of statins, when serum cholesterol levels were higher than now, as was the saturated fat content of the diet.

In addition to replacing dietary saturated fat with polyunsaturated fat, these clinical trials lowered dietary cholesterol. The cholesterol content of the diets was listed in 3 of the core trials.<sup>20,22,30</sup> We used the Keys<sup>38</sup> equation to estimate that the decreased cholesterol intake lowered serum cholesterol by  $\approx 5$  to 8 mg/dL, making up 15% to 20% of the total reduction in serum cholesterol. For example, in the Dayton et al<sup>20</sup> study, cholesterol intake decreased from 653 to 365 mg/d, and serum cholesterol decreased from 233 to 203 mg/dL, a 30-mg/dL difference, of which 6 mg/dL was accounted for by reduced dietary cholesterol. Because many foods that are high in saturated fat also contain cholesterol, the benefits to serum cholesterol lowering by reducing saturated fat will be augmented by consequent reduction in dietary cholesterol.

### **Noncore Trials on Replacing Saturated With Polyunsaturated Fat**

In addition to the 4 core trials, several other trials aimed to test the hypothesis that replacing saturated with polyunsaturated fats reduces CHD.<sup>7,23,32–35</sup> We did not include these trials in our core group because they had a mixed dietary intervention in which polyunsaturated and carbohydrate replaced saturated fat and had insufficient duration, low adherence, few events, and/or serious flaws in study design. STARS (Saint Thomas Atherosclerosis Regression Study) was a 3.3-year trial that achieved its primary aim of reducing the severity of stenoses (blockages) in the coronary arteries.<sup>7</sup> The dietary treatment lowered saturated fat intake and replaced it with carbohydrates and polyunsaturated fat. The diet lowered serum cholesterol by 11%. CVD events (fatal CHD or nonfatal myocardial infarction) occurred in 2 of 27 participants in the diet group versus 5 of 28 in the control group.



**Figure 1. Finnish Mental Hospital Study.**<sup>30,36,37</sup>

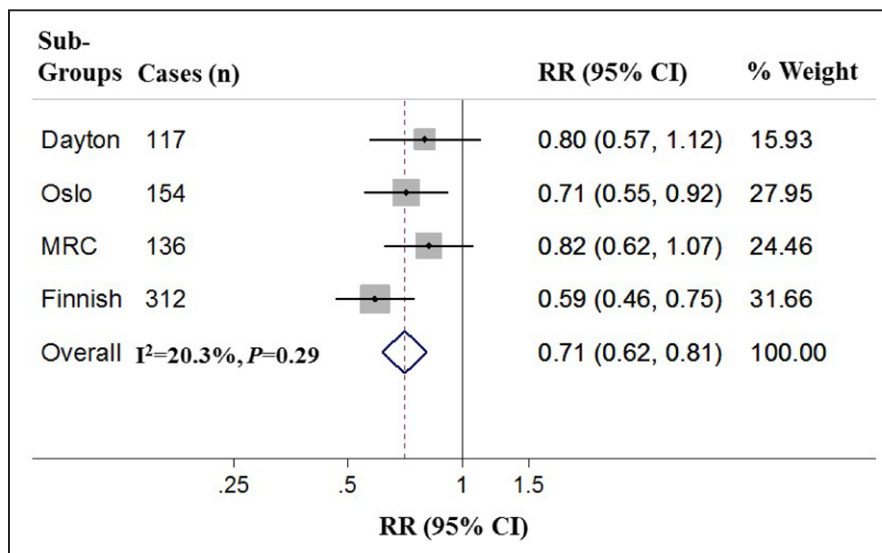
Significant reduction in coronary heart disease (CHD) by replacing saturated with polyunsaturated fat. Results are shown separately for participants in the primary and secondary CHD prevention cohorts of the trial and participants who were in the primary CHD prevention cohort. Relative risks (RRs) of the primary CHD outcome, CHD death, were calculated on the basis of age-adjusted deaths rates, and results were pooled across sex by inverse-variance fixed-effects meta-analyses. CI indicates confidence interval. Meta-analysis by Drs Yanping Li and Jason H.Y. Wu.

The Welsh DART study (Diet and Reinfarction Trial)<sup>23</sup> compared the effect of fat advice with no fat advice on CVD during 2 years. The fat advice group reduced saturated fat from 15% to 11% of total calories, increased polyunsaturated fat from 7% to 9%, and increased carbohydrate intake from 44% to 46%. These changes fell well short of intended and produced only a 3.5% reduction in serum cholesterol. There were 8% fewer men with CHD death or nonfatal myocardial infarction in the fat advice group compared with the no-fat advice group, not statistically significant but similar to what is predicted from the small decrease in serum cholesterol.<sup>31</sup>

Houtsmuller et al<sup>32</sup> conducted a 6-year trial in patients with newly diagnosed diabetes mellitus that re-

duced saturated fat and replaced it with mainly polyunsaturated fat. Serum cholesterol decreased significantly by 7%. The high polyunsaturated, low saturated fat diet reduced the progression of diabetic microvascular disease, which was the primary outcome. CVD events were determined by electrocardiography; however, those reading the ECGs were not blinded to treatment assignment. For this reason, this trial was not included in the core group. The high polyunsaturated, low saturated fat group experienced significantly fewer CVD events, 8 of 51 versus 24 of 51, a 67% reduction, much greater than the 12% predicted by the modest lowering of serum cholesterol.

Rose et al<sup>33</sup> conducted a trial in male patients with CVD that replaced saturated fat with polyunsaturated



**Figure 2. Meta-analysis of core trials on replacing saturated with polyunsaturated fat.**

Significant reduction in coronary heart disease (CHD). Relative risk (RR) of the primary CHD outcome of each trial. Findings across studies were pooled by inverse-variance fixed-effects meta-analyses. Risk reduction is the same with random-effects meta-analysis: RR, 0.71 (95% confidence interval [CI], 0.61–0.83). Data are from Dayton et al,<sup>20</sup> Oslo Diet-Heart Study,<sup>21</sup> Medical Research Council,<sup>22</sup> and Finnish studies.<sup>30,36,37</sup> Result from the Finnish trial used the total cohort (ie, patients who participated in the primary or secondary prevention cohorts). Meta-analysis by Drs Yanping Li and Jason H.Y. Wu.

corn oil. There were 26 patients in the control group and 28 in the corn oil group. The mean duration for receiving corn oil was 1.5 years. There were 12 cardiovascular events in the corn oil group versus 6 in the control group, not a statistically significant difference. The small number of participants and short duration of the trial excluded it from the core group.

The Minnesota Coronary Survey<sup>34</sup> compared high polyunsaturated with high saturated fat diets in patients hospitalized for mental illness. The participants were given the assigned diets only when they were patients in the hospital. Because hospitalization for mental illness became less common and less prolonged after the study started, as a national trend, the patients received the assigned diets intermittently, contrary to the intent of the researchers, and for a much shorter time than planned. The researchers originally enrolled 9570 participants in the trial and intended to study them for at least 3.6 years to be able to adequately test the effect of the diets. However, the trend toward outpatient treatment of mental illness resulted in  $\approx 75\%$  of the participants being discharged from inpatient care during the first year of the study. Only about half the remaining patients stayed in the study for at least 3 years. The average duration was only 384 days. The incidence of CHD events was similar in the 2 groups, 25.7 and 27.2 per 1000 person-years in the control and polyunsaturated fat groups, respectively. A recent reanalysis of this trial restricted to the participants who remained in the trial for at least 1 year also found no significant differences in CHD events or CHD deaths.<sup>39</sup> We excluded this trial from the core group because of the short duration, large percentage of withdrawals from the study, and intermittent treatment, which is not relevant to clinical practice. Another concern is the use of lightly hydrogenated corn oil margarine in the polyunsaturated fat diet. This type of margarine contains *trans* linoleic acid, the type of *trans* fatty acid most strongly associated with CHD.<sup>40</sup>

The Sydney Heart Study<sup>35</sup> was unique among the diet trials on CVD because a margarine high in *trans* unsaturated fat was a major component of the diet for participants assigned to the high polyunsaturated diet. When this trial was conducted, there was little recognition of the harms of *trans* unsaturated fat in partially hydrogenated vegetable oils, so the researchers inadvertently tested substitution of saturated with an even more atherogenic *trans* fat. As predicted from current knowledge about *trans* unsaturated fat, CVD events were higher in the experimental group. If anything, this trial confirmed the results of observational studies that also report higher CVD risk from results from regression models in which *trans* unsaturated fat replaced saturated fat.<sup>41,42</sup> We did not include this trial in our evaluation of the effects of lowering dietary saturated fat because *trans* fats are not recommended<sup>3,13</sup> and are being eliminated from the food supply.<sup>43</sup>

Two meta-analyses<sup>9,16</sup> analyzed the 4 core trials plus Minnesota,<sup>34</sup> STARS,<sup>7</sup> and DART.<sup>23</sup> Both meta-analyses showed a significant reduction in CVD of 19% by replacing saturated with polyunsaturated fat. Another systematic review and meta-analysis<sup>10</sup> included the Dayton et al study,<sup>20</sup> the Oslo Diet-Heart Study,<sup>21</sup> the Medical Research Council study,<sup>22</sup> the study by Houtsmuller et al,<sup>32</sup> the Rose et al study,<sup>33</sup> and the Sydney Diet Heart Study<sup>35</sup> and excluded the Finnish trial.<sup>30,36,37</sup> The Finnish trial was not included because it had 2 hospitals rather than at least 6 in the cluster randomization scheme, as required by the researchers conducting this meta-analysis.<sup>10</sup> In this group of trials, reduced saturated fat and increased polyunsaturated fat significantly lowered CVD events by 27% (see Table 9 in Reference 10). The extent of reduction in dietary saturated fat was significantly associated with the extent of decrease in CVD events among the trials. Reduction in serum cholesterol, as a consequence of reduced saturated fat and increased polyunsaturated fat, explained virtually all the variation among the trials in CVD event reduction.

The core trials reviewed in this section were started in the late 1950s and early 1960s. Readers may wonder why at least 1 definitive clinical trial has not been completed since then. Reasons include the high cost of a trial having upward of 20 000 to 30 000 participants needed to achieve satisfactory statistical power, the feasibility of delivering the dietary intervention to such a large study population, technical difficulties in establishing food distribution centers necessary to maintain high adherence for at least 5 years, and declining CVD incidence rates caused by improved lifestyle and better medical treatment. These linked issues, which must be managed to obtain a definitive result, remain the central considerations for dietary trials on CVD and indeed are the overarching reason why few of these trials have ever been done. Finally, by the 1980s, with rising rates of breast and colon cancer, the US government committed to conducting the WHI (Women's Health Initiative),<sup>24</sup> a trial that studied a diet aimed at decreasing total fat in the diet to 20% with the expectation that saturated fat would likewise be substantially decreased. Consequently, carbohydrates were increased in the diet. Details are discussed subsequently.

In summary, randomized controlled trials that lowered intake of saturated fat and replaced it with polyunsaturated vegetable oil reduced CVD events by  $\approx 30\%$ , similar to the reduction achieved by statin treatment.<sup>31</sup> Adding trials weakened by a short duration, low adherence, or use of *trans* unsaturated fat partially diluted the effect of the higher-quality core trials, but the results of meta-analyses that included both core and noncore trials still showed significant and substantial reduction in CVD when saturated fat is replaced with polyunsaturated fat.<sup>9,10,16</sup>

## Low-Fat, High-Carbohydrate Diets

Few trials have studied the effect of reducing saturated fat and replacing it mainly with carbohydrates, without including with the diet other treatments such as antihypertensive or lipid-lowering medication. The British Medical Research Council<sup>25</sup> studied 252 men after myocardial infarction aiming to reduce total fat from 41% to 22% and maintaining it at 41% in the control group. The type of fat was similar in the high- and low-fat groups, mainly saturated fat from dairy products and meat. The low-fat, high-carbohydrate diet lowered serum cholesterol by 5%, less than expected from the planned reduction in saturated fat. The researchers remarked that the low-fat diet was unpleasant and difficult to tolerate. There were 48 CHD events in the control group compared with 46 in the low-fat group. The specific carbohydrate-containing foods in the low-fat diet group were not described except that sugar intake and skim milk were increased and biscuits and cakes were decreased.

DART, described previously,<sup>23</sup> lowered total fat from 35% to 31% by reducing saturated fat, replacing it partly with carbohydrates and partly with polyunsaturated fat. The reduction in CHD events, 8%, was not significant.

Originally designed as a diet study to prevent breast and colon cancer, the WHI tested the hypothesis that reducing all types of fats and replacing them with high-carbohydrate foods, particularly fruits and vegetables, decreases CVD.<sup>24</sup> Enrolled between 1993 and 1998 and conducted in postmenopausal women 50 to 79 years of age, this trial assigned 30 000 women at random to maintain their usual high-fat diet (37% of total energy intake) and 20 000 to a low-fat diet (20% of energy intake). They were followed up for 8 years. This trial was not a test of reduction purely in saturated fat because monounsaturated and polyunsaturated fats were also reduced to meet the primary dietary objective of decreasing total fat. The emphasis on reduction of all types of fat came from its primary aim to test the hypothesis that decreasing dietary fat of any kind reduces breast and colon cancer. The effect of this type of diet on CVD was a secondary aim. After 5 years, the low-fat diet group lowered LDL cholesterol by 4 mg/dL, an ≈3% reduction, similar to the British Medical Research Council trial<sup>25</sup> and DART.<sup>23</sup> Similar to those studies, the participants in the low-fat group did not achieve the goal for reducing dietary fat (24% after the first year and 29% after the eighth year compared with 35% and 37%, respectively, in the control group). Also like the earlier studies, the low-fat diet in the WHI had no significant effect on coronary events or stroke.

A systematic review and meta-analysis<sup>10</sup> identified 6 trials that reduced saturated fat, replacing it mainly with carbohydrates. In contrast to the favor-

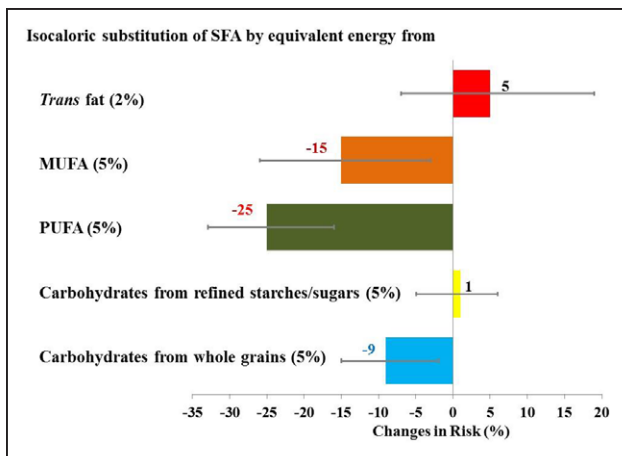
able results of trials using polyunsaturated fat as the replacement macronutrient reported in the same article,<sup>10</sup> the low-fat, high-carbohydrate approach did not significantly reduce CVD events (relative risk, -7%; 95% CI, -21 to 8).

In summary, a dietary strategy of reducing intake of total dietary fat, including saturated fat, and replacing the fats mainly with unspecified carbohydrates does not prevent CHD. In contrast to trials of polyunsaturated fat, adherence to the low-fat regimen fell short of the intention, impairing the ability of the trials to test a biologically based or efficacy hypothesis. The authors of these and other dietary trials<sup>20,23,25</sup> remarked on the difficulty experienced by participants in adhering to and maintaining goals to reduce dietary total fat. Finally, we note that a trial has never been conducted to test the effect on CHD outcomes of a low-fat diet that increases intake of healthful nutrient-dense carbohydrates and fiber-rich foods such as whole grains, vegetables, fruits, and legumes that are now recommended in dietary guidelines.

## CVD OUTCOMES: PROSPECTIVE OBSERVATIONAL STUDIES

Prospective observational studies of diet and disease refer to research in which large populations provide information on their diet, lifestyle, health, and other characteristics and behaviors at the beginning and then are followed up for many years for the occurrence of disease.<sup>44</sup> This research technique has several key advantages over randomized controlled trials but also important weaknesses. Compared with clinical trials, prospective observational studies include larger and potentially more representative populations and have longer durations. Most important, participants choose their own intake of foods and beverages and do not have to adapt their diet to randomized diet assignment; therefore, the problem of sustaining adherence has no relevance. Furthermore, prospective observational studies can update dietary information periodically during the follow-up period. Observational studies are much less expensive than randomized controlled trials (expressed as cost per participant or cost per hypothesis tested). However, the observational approach likewise has weaknesses. Participants who have a high intake of saturated fat may have dietary and nondietary characteristics that differ from those with low intake of saturated fat, and these differences could affect CVD, creating a confounding situation. Incomplete or inaccurate ascertainment of dietary components can affect associations with disease. Meticulous collection of diet and health information and the statistical methods used can reduce or even eliminate the influence of confounding to isolate the effect of the nutrient itself. In summary, randomized controlled trials and prospective





**Figure 3. Replacement of saturated fat with other types of fat or carbohydrates.**

Association with risk of cardiovascular disease in the Nurses' Health Study and Health Professionals Follow-Up Study. Multivariable adjustment. MUFA indicates monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; and SFA, saturated fatty acids. Modified from Li et al<sup>18</sup> with permission from The American College of Cardiology Foundation. Copyright © 2015, The American College of Cardiology Foundation.

observational studies are complementary research approaches. When the results are similar, the assumption of causality is strengthened between consumption of a dietary component and disease.

Fundamentally, methodology in observational analyses of diet and disease differs from that in analyses of biomarkers and genetic markers in relation to disease risk and is less familiar to scientists who work in other fields of epidemiology or in clinical trials. Observational studies in nutrition have special complexities, especially when studying foods or macronutrients such as fat and carbohydrates that make up a substantial portion of daily energy intake. For example, a low saturated fat intake occurs in the context of different dietary patterns, including low-fat, high-carbohydrate diets or Mediterranean diets high in unsaturated fat.

In North America and many European countries, the diets of people who eat a low-saturated fat diet typically are high in refined carbohydrates and low in unsaturated fats. For this reason, comparing CVD incidence in those with high and those with low saturated fat intakes primarily compares saturated fat with carbohydrates, most coming from refined grains, fruit juice, sweet desserts and snacks, sugar-sweetened beverages, and other foods. Well-publicized results of a meta-analysis reporting that saturated fat is not associated with CVD implicitly compare a high saturated fat diet with commonly eaten diets low in saturated fat and high in carbohydrate-containing foods made with refined carbohydrates and added sugars that themselves are associated with CVD.<sup>15,16</sup>

Further adding complexity, high-carbohydrate foods are very heterogeneous and may have beneficial or harmful associations with disease. For example, high-carbohydrate diets that include whole grains and cereal fiber are associated with lower rates of CVD, whereas refined grains and added sugars are associated with higher rates (Figure 3).<sup>18</sup>

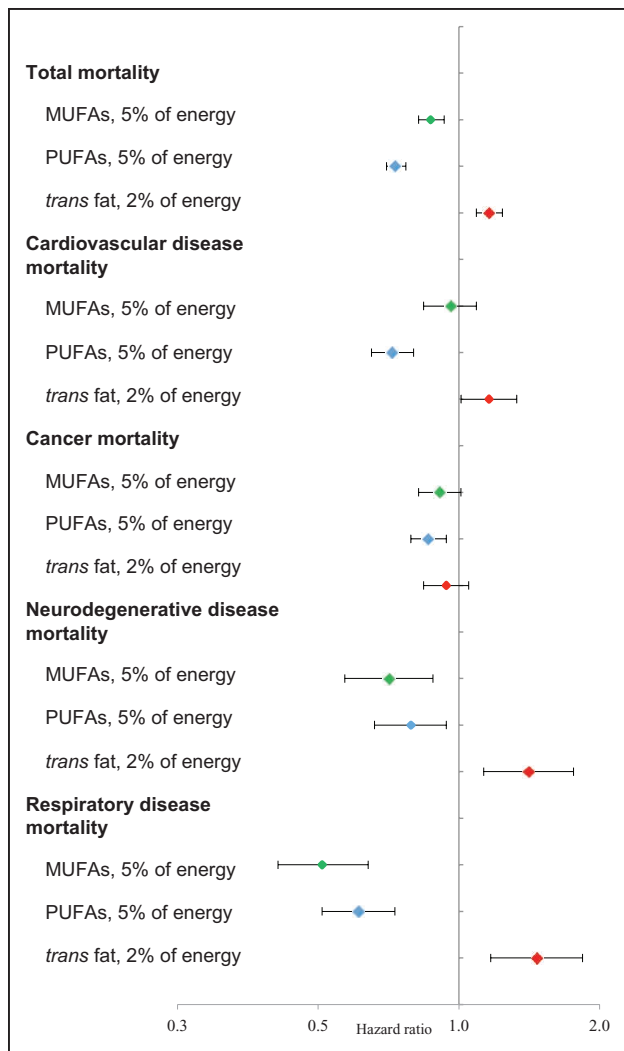
Therefore, it is critical to the interpretation of findings in nutritional epidemiological studies that the contrast in dietary patterns between high and low saturated fat intake be well characterized. Simply comparing disease rates between people in a population who have low compared with high intake of saturated fat is fraught with potential for misinterpretation and misunderstanding.

Willett<sup>44</sup> developed a statistical framework for multivariable regression analysis that isolates effects of specific macronutrient exchanges. The method compares high saturated fat intake separately with high polyunsaturated fat, monounsaturated fat, *trans* unsaturated fat, and carbohydrates. The multivariable analysis equalizes other prognostic factors. In this way, the method simulates a randomized trial that compares 5 diets differing in type and amount of fat and carbohydrates. To determine the relationship of saturated fat with CVD outcomes in prospective observational studies, we used systematic reviews and meta-analyses published from 2009 to 2015,<sup>12,17</sup> the 2015 US Dietary Guidelines Advisory Committee Report,<sup>13</sup> and studies published after the report was released.<sup>18,45</sup> We considered studies that used multivariable regression analysis that isolates effects of specific nutrient exchanges.

The results showed that replacing 5% of energy intake from saturated fats with equivalent energy intake from polyunsaturated fats, monounsaturated fats, or carbohydrates from whole grains was associated highly significantly with a 25%, 15%, and 9% lower risk of CHD, respectively (Figure 3).<sup>18</sup> Replacing saturated fats with carbohydrates from refined starches/added sugars was not significantly associated with CHD risk (1% higher incidence). This pattern of results on dietary fats and CHD continued in analyses of total and cause-specific deaths; replacement of saturated fat by polyunsaturated fat (mainly linoleic acid) or monounsaturated fat was associated with lower rates of not only CVD death but also all deaths, deaths resulting from CVD, cancer, neurodegenerative disease, and lung disease (Figure 4).<sup>45</sup>

### Key Points: Randomized Clinical Trials and Prospective Observational Studies on Replacement of Dietary Saturated Fat With Polyunsaturated or Monounsaturated Fat or Carbohydrates

- Four core randomized trials replacing saturated fat with polyunsaturated fat had at least 2 years'



**Figure 4. Replacement of saturated fat with other dietary fats.**

Total and cause-specific mortality. Hazard ratio (95% confidence interval) for substituting energy from saturated fat by the same energy from specific types of fat. Nurses' Health Study and Health Professionals Follow-up Study. MUFA indicates monounsaturated fatty acids; and PUFA, polyunsaturated fatty acids. Modified with permission from Wang et al.<sup>45</sup> Copyright © 2016, American Medical Association. All rights reserved.

duration, good adherence proven by blood or tissue levels of cholesterol and/or polyunsaturated fat, and standard outcome ascertainment. Meta-analysis showed a 29% reduction in CHD events.

- Six additional trials were not considered core trials because of short duration, low adherence, or nonstandard outcome ascertainment. However, meta-analyses that included several of these trials along with some or all of the core trials also found a significant reduction in CHD events on the polyunsaturated fat diet.

- The Sydney Diet Heart Study showed that using a margarine rich in *trans* unsaturated fat to replace saturated fat increased CHD events, confirming similar adverse results in epidemiological studies.
- Several trials that replaced saturated fat with carbohydrates did not show reduced CHD. Adherence was much less than expected in these trials.
- Prospective observational studies consistently found the following:
  - Lower risk of CHD when saturated fat was replaced with polyunsaturated or monounsaturated fat, more so for polyunsaturated than monounsaturated.
  - No decrease in risk of CHD when saturated fat was replaced with carbohydrates, especially carbohydrates from refined grains and added sugars. However, replacement with whole grains was associated with reduced CHD.
  - Lower risk of death resulting from CVD and all causes with replacement of saturated with polyunsaturated or monounsaturated fat.

## DIETARY PATHOGENESIS OF ATHEROSCLEROSIS IN NONHUMAN PRIMATES

Because of their evolutionary similarities to human beings, nonhuman primate species were studied to determine the effects of diet on atherosclerosis. In these experiments,<sup>5,46</sup> to induce hypercholesterolemia and atherosclerotic lesion formation, one group of monkeys typically was fed lard or palm oil at 35% of their daily energy intake and dietary cholesterol to raise serum cholesterol levels into the 300- to 400-mg/dL range to model hypercholesterolemia in human beings at high risk for CHD. A second group of monkeys was fed a monounsaturated fat, high-oleic safflower oil, and a third group was fed a polyunsaturated fat linoleic acid-rich diet using safflower oil. Saturated fatty acids promoted higher LDL cholesterol concentrations and more coronary artery atherosclerosis. Linoleic acid lowered LDL cholesterol concentrations and decreased the amount of coronary artery atherosclerosis. In the oleic acid group, LDL cholesterol concentrations were lowered to an extent similar to that in the linoleic acid group, but paradoxically, the amount of coronary artery atherosclerosis was more like that in the saturated fat group.<sup>5,47</sup> In the oleic acid-rich diet group, the LDL particles of the monkeys were enriched in cholesteryl oleate and bound to arterial proteoglycans more avidly compared with the polyunsaturated fat diet group, an action that may be viewed as promoting atherosclerosis.<sup>47,48</sup> In humans as well, intake of high-oleic canola oil enriches LDL with cholesteryl oleate, but opposite to the findings in monkeys, this LDL has reduced bind-

ing to vascular proteoglycan, a potentially beneficial mechanism.<sup>49</sup> Atherosclerosis extent has consistently been positively correlated with high LDL proteoglycan binding affinity.<sup>48,50</sup>

Finally, a diet typical of the 1980s in the United States, high in saturated fat, fed to rhesus monkeys for 2 years increased serum cholesterol to 383 mg/dL and caused atherosclerosis that had complex pathological features similar to atherosclerosis in young human adults who died of trauma.<sup>51</sup> In contrast, a “prudent” diet recommended by the AHA to prevent CHD, low in saturated and high in polyunsaturated fat, produced lower serum cholesterol levels, 199 mg/dL, and less atherosclerosis.

In summary, in rhesus monkeys, African green monkeys, and cynomolgus monkeys, dietary saturated fat promoted coronary atherosclerosis during 1 to 5 years, whereas polyunsaturated fat reduced LDL cholesterol and coronary atherosclerosis.<sup>5,6,46–51</sup> The results strongly support the strong atherogenicity of saturated fatty acids through effects to raise LDL cholesterol concentrations compared with the effects of n-6 polyunsaturated fatty acids. Although monounsaturated fatty acids promoted atherosclerosis despite lowering LDL cholesterol, mechanisms related to LDL binding to proteoglycan may differ in humans. Generalization from these studies is limited by the high serum cholesterol levels produced by the atherogenic diets. Clearly, in >50 years of studies in nonhuman primates, saturated fat has proven to be atherogenic compared with polyunsaturated fat.

### LDL CHOLESTEROL-MEDIATING DIETARY EFFECTS ON CVD

Dietary saturated and polyunsaturated fats are notable for their established opposing connections to LDL cholesterol levels. Reducing LDL cholesterol is a primary focus for preventive therapy. Replacing dietary saturated fat with unsaturated fat decreases LDL cholesterol levels, n-6 polyunsaturated fat more than monounsaturated fat.<sup>4</sup>

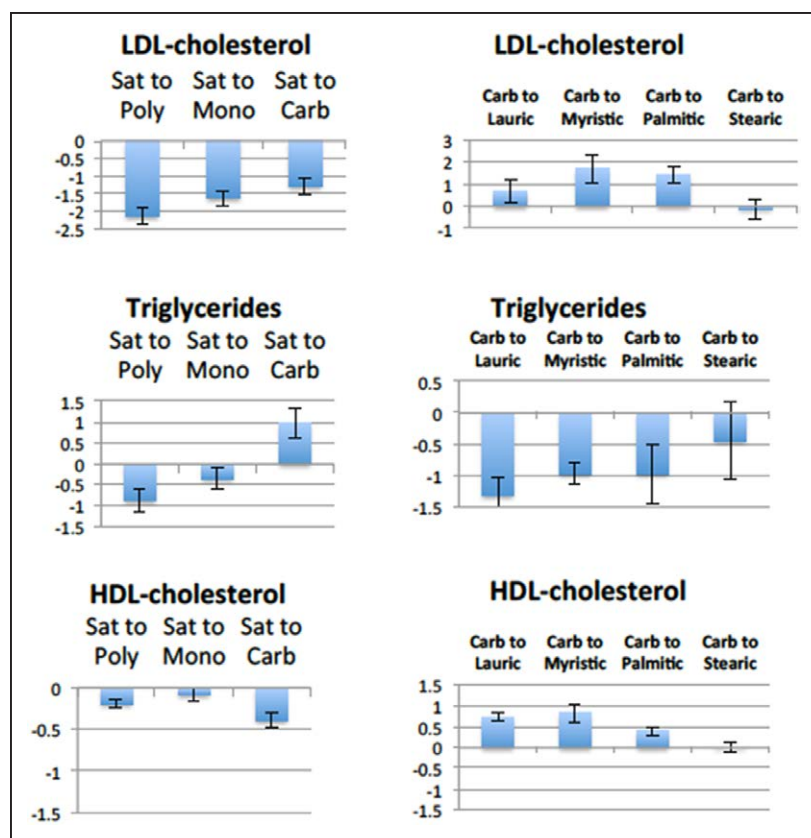
The LDL theory of atherosclerosis and CVD has support from the widest range of research studies<sup>52</sup>: studies that compare populations that vary in LDL cholesterol<sup>52</sup>; studies in single populations<sup>52</sup>; genetic studies of high LDL cholesterol caused by mutations impairing the action of LDL receptors to remove LDL from the blood circulation and lower LDL cholesterol levels<sup>52</sup>; studies of mutations in numerous other genes that affect LDL cholesterol by other mechanisms<sup>53,54</sup>; pharmacological studies that lower LDL cholesterol by decreasing cholesterol synthesis and increasing synthesis of LDL receptors by statins,<sup>31</sup> decreasing cholesterol absorption,<sup>55</sup> or inhibiting proprotein con-

vertase subtilisin/kexin type 9 to increase LDL receptors<sup>56</sup>; studies of mutations in genes that interfere with assembly of LDL and its precursor very-low-density lipoprotein (VLDL) in the liver that decrease the amounts that are secreted into the circulation; correlations between LDL cholesterol and CVD reduction in meta-analyses of randomized clinical trials of statin and other LDL cholesterol-lowering treatments<sup>31,55</sup>; animal models that increase LDL cholesterol by diet or by genetic manipulation<sup>6,57</sup>; and studies of the processes by which atherosclerosis starts, progresses, and regresses in arterial vessels and cells.<sup>57–59</sup> Taking into consideration the totality of evidence, LDL cholesterol links saturated fat and its replacement macronutrients to CVD by very strong scientific evidence that satisfies rigorous criteria for causality.<sup>60</sup> Three independent guidelines committees rated this evidence as Level A, Strong.<sup>3,13,61</sup>

### QUANTITATIVE EFFECTS OF DIETARY FATS AND CARBOHYDRATES ON LDL CHOLESTEROL

A systematic review and meta-regression analysis published last year identified and evaluated 84 randomized controlled trials including 2353 participants that studied the effect of dietary fats on LDL cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol.<sup>4</sup> The results were expressed as the amount of change in these lipids caused by a decrease in saturated fats of 1% of total daily calories and a 1% increase in polyunsaturated fat, monounsaturated fat, or carbohydrates. Polyunsaturated fat lowered LDL cholesterol by 2.1 mg/dL, monounsaturated fat by 1.6 mg/dL, and carbohydrates by 1.3 mg/dL (Figure 5, left). Replacing saturated with polyunsaturated fat is the most effective of these exchanges because the change from saturated to polyunsaturated fat combines a reduction in a LDL cholesterol-raising fat, saturated fat, with an increase in a LDL cholesterol-lowering fat, polyunsaturated fat. The independent effect of polyunsaturated fat is demonstrated by comparing it with carbohydrates: Replacing carbohydrates with polyunsaturated fat, 1% of daily energy, lowers LDL cholesterol by 0.9 mg/dL. The reductions in total or LDL cholesterol after diet change correlate well with the extent of reductions in CVD.<sup>10</sup>

The lifestyle report of the AHA and American College of Cardiology summarized studies that assessed the effect of dietary patterns on LDL cholesterol.<sup>3</sup> The report, taking an efficacy-based biological approach, reviewed “feeding trials” that composed complete diets and gave them to the study participants. These trials were DASH (Dietary Approaches to Stop Hypertension),<sup>62</sup> DASH-Sodium,<sup>63</sup> and DELTA (Dietary Effects on Lipoproteins



**Figure 5.** Effects of dietary fat and carbohydrates on blood low-density lipoprotein (LDL) cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol (mg/dL) in meta-regression analysis.

**Left,** Replacing saturated fat (Sat) with polyunsaturated fat (Poly) (n-6), mono-unsaturated fat (Mono), or carbohydrates (Carb). **Right,** Replacing carbohydrates with individual saturated fatty acids, lauric, myristic, palmitic, or stearic acid. Error bars show 95% confidence intervals. Data from Mensink.<sup>4</sup>

and Thrombogenic Activity).<sup>64</sup> Taken together, the trials found that a reduction in saturated fat in the context of dietary patterns intended to benefit lipid and other CVD risk factors lowered LDL cholesterol by amounts similar to those predicted by the meta-analysis.<sup>4</sup>

## LDL Sizes

Some observational studies found that the concentration or proportion of large LDL predicts higher rates of CVD,<sup>65–67</sup> whereas other studies reported that small LDL predicts CVD<sup>68,69</sup> or both large and small LDLs predict CVD.<sup>70,71</sup> Still other studies found that LDL size, per se, does not predict CVD in a multivariable analysis that includes triglycerides or LDL concentration.<sup>65,72–76</sup> Dietary fat, in an equal combination of saturated and polyunsaturated replacing carbohydrates, increased the concentration of larger LDL and decreased smaller LDL sizes.<sup>77</sup> In another study, monounsaturated fat, replacing carbohydrates, reduced medium and small LDL, also shifting the distribution to the larger size.<sup>78</sup> Therefore, the effects of replacing carbohydrates with various kinds of fats qualitatively at least may be similar by increasing larger and decreasing smaller LDL sizes. Replacing saturated with monounsaturated fat lowered the concentrations of large, medium, and small LDL.<sup>79</sup> Replacing monounsaturated fat from olive oil with polyunsaturated fat from corn oil significantly lowered the concentrations of the total LDL cholesterol concen-

tration, intermediate-density lipoprotein cholesterol, large LDL cholesterol, and nonsignificantly small LDL cholesterol.<sup>80</sup> Replacing *trans* unsaturated soybean oil with n-6 polyunsaturated corn oil lowered the concentration of small LDL.<sup>81</sup> In conclusion, this sparse set of findings suggests that replacement of saturated with monounsaturated or polyunsaturated fat reduces the concentration all sizes of LDL.

## HDL CHOLESTEROL AND TRIGLYCERIDES: ADDITIONAL LIPID MEDIATORS

### HDL Cholesterol

The aforementioned meta-analysis<sup>4</sup> also computed the effects of dietary fats and carbohydrates on 2 other blood lipid biomarkers of CVD risk, HDL cholesterol and triglycerides. A low HDL cholesterol level is associated with a high incidence of CVD in the context of a wide variety of concomitant conditions such as diabetes mellitus and obesity.<sup>82</sup> HDL can stimulate the removal of cholesterol from cells, including those involved in atherosclerosis, and can deliver the cholesterol to the liver where some of it may be secreted in bile and excreted, a process called reverse cholesterol transport.<sup>83</sup> However, unlike LDL cholesterol, genetic variation that affects HDL cholesterol is not associated with expected differences in

CVD unless LDL cholesterol or triglyceride is also affected by the genetic variants<sup>84</sup> or reverse cholesterol transport is impaired.<sup>85</sup> Still, these genetic studies, often called mendelian randomization, may not be capturing important loci for the protective effect of HDL that may be reflective in HDL cholesterol raising by dietary fats compared with carbohydrates. Although increases in HDL cholesterol by some pharmacological treatments have not decreased CVD,<sup>86,87</sup> this does not directly pertain to the effects of dietary fat because the underlying mechanisms of effects of drugs such as a cholesteryl ester transfer protein inhibitor and nicotinic acid are probably not the same as those affected by dietary fats and carbohydrates. The HDL field is working toward a functional approach to CVD risk prediction and treatment. For example, a small experimental study showed that consumption of saturated fat reduces the anti-inflammatory potential of HDL and impairs arterial endothelial function. In contrast, the anti-inflammatory activity of HDL improves after consumption of polyunsaturated fat.<sup>88</sup>

Replacing saturated fat with polyunsaturated or monounsaturated fat (1% daily energy exchanged) lowers HDL cholesterol slightly by 0.2 and 0.1 mg/dL (Figure 5, left).<sup>4</sup> Using carbohydrates as a replacement lowers HDL cholesterol more by 0.4 mg/dL. Carbohydrates also lower HDL cholesterol when replacing monounsaturated or polyunsaturated fats. Both low- and high-glycemic-index carbohydrates lower HDL cholesterol.<sup>89,90</sup>

### Triglycerides

The plasma level of triglyceride is a well-established independent biomarker of CVD risk,<sup>91</sup> and triglyceride-rich lipoproteins have atherogenic properties. Triglyceride predicts CVD in a wide range of circumstances. Its association with CVD risk is partly attenuated by adjustment for HDL cholesterol, with which it is moderately correlated.<sup>92</sup> Genetic variation associated with lifelong low triglyceride levels is associated with a lower incidence of CVD.<sup>90</sup> Triglyceride is carried primarily within large lipoproteins, chylomicrons, and VLDL, which are also rich in cholesterol and like LDL can enter the arterial wall and stimulate atherosclerosis. These triglyceride-rich lipoproteins carry various atherogenic proteins such as apolipoprotein C-III, itself associated with atherosclerosis and CVD.<sup>93</sup>

Replacing 1% of daily energy intake from saturated fat with polyunsaturated or monounsaturated fat lowers triglyceride by 0.9 or 0.4 mg/dL, respectively (Figure 5, left),<sup>4</sup> perhaps more in those with hypertriglyceridemia.<sup>91</sup> Replacing the 1% saturated fat with 1% carbohydrates raises serum triglycerides by  $\approx$ 1 mg/dL. Dietary carbohydrates raise plasma triglyceride levels by increasing the production by the liver of triglycerides and subsequent incorporation into VLDL.<sup>91</sup> The magni-

tude that dietary carbohydrates increase plasma triglyceride is similar whether the carbohydrate has a high or low glycemic index.<sup>89</sup>

### INDIVIDUAL SATURATED FATTY ACIDS

The Mensink<sup>4</sup> meta-regression analysis determined the effects on blood lipids of replacing carbohydrates with the individual saturated fatty acids that are in common foods, including lauric, myristic, palmitic, and stearic acids. Lauric, myristic, and palmitic acids all had similar effects in increasing LDL cholesterol and HDL cholesterol and decreasing triglycerides when replacing carbohydrates (Figure 5, right).

Stearic acid makes up  $\approx$ 20% of the fat in beef, 30% of the fat in pure cocoa (chocolate), and 10% to 15% in lard (pork fat) and lamb fat (Table). In contrast to the other saturated fatty acids, stearic acid does not increase LDL cholesterol or HDL cholesterol or decrease triglycerides when replacing carbohydrates (Figure 5, right). However, replacing stearic acid with unsaturated fat lowers LDL cholesterol.<sup>4</sup>

In summary, the common individual saturated fats raise LDL cholesterol. Their replacement with monounsaturated or polyunsaturated fats lowers LDL cholesterol. Differences in the effects of the individual fatty acids are small and should not affect dietary recommendations to lower saturated fat intake.

### COCONUT OIL

A recent survey reported that 72% of the American public rated coconut oil as a "healthy food" compared with 37% of nutritionists.<sup>94</sup> This disconnect between lay and expert opinion can be attributed to the marketing of coconut oil in the popular press. The fatty acid profile of coconut oil is 82% saturated, about half lauric acid, and the rest myristic, palmitic, stearic, and short-chain fatty acids (Table). Lauric acid replacing carbohydrates increases LDL cholesterol but by about half as much as myristic and palmitic acids (Figure 5, right). Lauric acid increases HDL cholesterol about as much as myristic but more than palmitic acid. The net effect of increasing lauric acid and decreasing carbohydrates is a slight reduction in the ratio of LDL cholesterol to HDL cholesterol. However, as discussed earlier in this report, changes in HDL cholesterol caused by diet or drug treatments can no longer be directly linked to changes in CVD, and therefore, the LDL cholesterol-raising effect should be considered on its own. Furthermore, with respect to CVD, the informative comparison is between coconut oil and vegetable oils high in monounsaturated and polyunsaturated fats. A carefully controlled experiment compared the effects of coconut oil, butter, and safflower oil supplying polyunsaturated linoleic acid.<sup>95</sup>

Both butter and coconut oil raised LDL cholesterol compared with safflower oil, butter more than coconut oil, as predicted by the meta-regression analysis of individual dietary saturated fatty acids (Figure 5, right). Another carefully controlled experiment found that coconut oil significantly increased LDL cholesterol compared with olive oil.<sup>96</sup> A recent systematic review found 7 controlled trials, including the 2 just mentioned, that compared coconut oil with monounsaturated or polyunsaturated oils.<sup>97</sup> Coconut oil raised LDL cholesterol in all 7 of these trials, significantly in 6 of them. The authors also noted that the 7 trials did not find a difference in raising LDL cholesterol between coconut oil and other oils high in saturated fat such as butter, beef fat, or palm oil. Clinical trials that compared direct effects on CVD of coconut oil and other dietary oils have not been reported. However, because coconut oil increases LDL cholesterol, a cause of CVD, and has no known offsetting favorable effects, we advise against the use of coconut oil.

## DAIRY PRODUCTS

Dairy fat is composed of 27% palmitic acid, 12% stearic acid, 9% myristic acid, and 3% lauric acid, for a total of 51% saturated fatty acids that raise LDL cholesterol compared with the unsaturated fatty acids (Table). Short-chain saturated fatty acids total 11%; monounsaturated, 26%; and polyunsaturated, 4%. Dairy fat also contains a very small amount of odd-chain fatty acids, 15:0 and 17:0, ≈0.5% to 1% of total fatty acids, and *trans* unsaturated fat, 4%, both made by bacteria in the ruminant gut. As we discuss subsequently, *trans* unsaturated fat made by ruminants has adverse effects on lipid risk factors similar to those of *trans* made industrially by partial hydrogenation.

Recent epidemiological studies measured blood levels of odd-chain fatty acids; one study found that they are associated with lower risk of CHD,<sup>98</sup> whereas another did not find such a relation.<sup>99</sup> It is not clear whether blood levels of odd-chain fatty acids represent intake of dairy fat or an effect of fat absorption and metabolism because the correlations between dairy fat intake and blood levels of odd-chain fatty acids (15:0, 17:0) are low (0.3).<sup>99</sup> Because of increasing consumption of low- and reduced-fat milk and other dairy products and decreasing consumption of full-fat dairy, especially whole milk, in the US population, the amount of dairy fat from low-fat compared with full-fat dairy is likely to have substantially increased. Therefore, dairy fat biomarkers may reflect both high- and low-fat dairy consumption patterns in the population. To the best of our knowledge, there are no biological mechanisms that link odd-chain fatty acids to protection against atherosclerosis and CVD.

For many years, there has been sporadic speculation that cheese is a unique food category, protective against CVD because it is manufactured by fermenta-

tion. To the best of our knowledge, no information from controlled studies supports the hypothesis that fermentation adds beneficial nutrients to cheese that counteract the harmful effects of its saturated fat. Recently, a clinical trial compared 3 diets, one with a high content of cheese, another with a high content of beef, and a third that was low in all types of fat, saturated, monounsaturated, and polyunsaturated.<sup>100</sup> The cheese and beef diets had higher amounts of saturated, monounsaturated, and polyunsaturated fatty acids. Neither the beef nor the cheese diet increased LDL cholesterol compared with the low-fat diet, as expected because of the counteracting effects of saturated and unsaturated fats on LDL cholesterol. Both the cheese and meat diets increased HDL cholesterol, consistent with the known effects of dietary fat to raise HDL cholesterol.<sup>4</sup> Therefore, the findings from this study do not support the hypothesis that cheese has special protective effects compared with beef on lipid risk factors for CVD.

Many controlled trials showed that dairy fat, often the major source of saturated fat in a study, increased LDL cholesterol compared with monounsaturated and polyunsaturated vegetable oils, reflecting the preponderance of saturated fatty acids, as reviewed previously in this report. Prospective observational studies found that the substitution of polyunsaturated fat for dairy fat, 5% of total daily calories, was associated with a 24% to 25% lower risk of CHD and stroke.<sup>101</sup> In contrast, substituting refined carbohydrates for dairy fat was not associated with reduced risk of CVD, whereas substituting carbohydrates from whole grains for dairy fat was associated with a 34% lower incidence of CHD and a 16% lower incidence of stroke. This analysis demonstrates again that it is essential to analyze the effects of unsaturated fats, refined carbohydrates, and whole grains separately to reach an informed and useful result for dietary advice.

In Finland, a successful nationwide health project to lower the very high rate of CHD mortality, started in 1972, had as a major goal the reduction in the high intake of saturated fat.<sup>102</sup> The project reduced intake of high-fat milk and butter, which lowered serum cholesterol by 13% in men and 18% in women. By 1992, CHD death rates decreased by 55% in men and 68% in women. Reduction in serum cholesterol accounted for ≈50% of the total reduction in CHD mortality.<sup>103</sup> Other dietary changes that may have contributed to the lower CHD mortality included increased fruits and vegetables, increased fish, decreased sugar, a shift from fatty to lean meats, and reduced sodium.

## TRANS UNSATURATED FATS AND CVD

*Trans* unsaturated fatty acids are monounsaturated or polyunsaturated fatty acids containing at least 1 double bond in the *trans* configuration. There are 2 major types of *trans* fatty acids: naturally occurring found in meat and

milk of ruminant animals (eg, cattle and sheep), called ruminant *trans* fatty acids, and produced by chemical and enzymatic action for use in partially hydrogenated vegetable oils, called industrial *trans* fatty acids.<sup>40,41</sup> Both sources of *trans* fatty acids contain a range of fatty acid isomers, and there is considerable overlap. Food manufacturers have taken advantage of the low cost, long shelf-life, and the ability of *trans* fatty acids to withstand repeated heating and use partially hydrogenated vegetable oil in a variety of processed foods, including margarines, baked foods, and commercial deep-fried foods.

Clinical trials have consistently documented the adverse effects of *trans* fatty acids on the lipid risk factors for CVD. Replacement of calories from other types of fats with *trans* fatty acids raises LDL cholesterol, apolipoprotein B, triglycerides, and lipoprotein(a), as well as lowering HDL cholesterol and apolipoprotein A1.<sup>104</sup> Such effects are particularly large when *trans* fatty acids replace monounsaturated or polyunsaturated fatty acids but also occur when substituted for saturated fatty acids. The effects of *trans* fatty acids on blood lipids are potentially mediated through mechanisms including a reduction in the catabolism of LDL apolipoprotein B-100 and an increase in the catabolism of HDL apolipoprotein A-I, as well as enhancement of cholesteryl ester transfer protein activity.<sup>105–107</sup> Although most human trials were conducted with partially hydrogenated vegetable oil, emerging evidence suggest the ruminant *trans* fatty acids have similar adverse effects on blood lipids.<sup>108–110</sup>

Prospective observational studies have consistently concluded that higher total *trans* fatty acid intake is associated with elevated risk of CHD. A recent systematic review and meta-analysis of observational studies reported that higher intake of total *trans* fatty acid intake was associated with a 21% higher risk in total CHD (95% CI, 10–33; n=6 studies) and a 28% higher risk in CHD mortality (95% CI, 9–50; n=5 studies).<sup>111</sup> Although industrial *trans* fatty acids were consistently associated with total CHD and CHD death in observational studies, ruminant *trans* fatty acids were generally not.<sup>112</sup> The exact reason for these discrepant relationships remains unknown but may relate to the very low levels of ruminant *trans* fatty acids in these studied populations (mean intake, ≈0.7% of total energy),<sup>112</sup> differences in *trans* fatty acid isomers between ruminant and industrial *trans* fatty acids that have diverse biological effects, or confounding by the high amount of saturated fat in the major source of ruminant *trans* fatty acids.

In summary, the concordance between the adverse effects of *trans* fatty acids on lipid risk factors for CVD and the robust association of higher *trans* fatty acid intake with elevated CHD risk in observational studies provides the impetus for current policy actions of many local and national jurisdictions to reduce industrial *trans* fatty acids in the food supply.<sup>113</sup> Recognizing the need to act, in addition to requiring the *trans* fatty acid con-

tent of packaged foods to be listed on the Nutrition Facts label, the US Food and Drug Administration has recently revoked the generally recognized as safe status of partially hydrogenated vegetable oil, which should ensure further reductions in the population-level industrial *trans* fatty acid intake.<sup>43</sup>

### N-3 (OMEGA-3) FATTY ACIDS

Polyunsaturated fatty acids exist in the n-3 or n-6 isomeric configuration. Both isomers are essential nutrients and have different biological effects. N-3 and n-6 fatty acids are not interconverted. Dietary n-6 polyunsaturated fatty acids, primarily linoleic acid, are much more prevalent than n-3 polyunsaturated fatty acids in vegetable oils and the total diet.  $\alpha$ -Linolenic acid, a dietary n-3 polyunsaturated fatty acid, is present in soybean and rapeseed (canola) oil, walnuts, some green vegetables in very small amounts, chickens fed high- $\alpha$ -linolenic acid feed and their eggs, and grass-fed beef. Fish oil contains the very-long-chain n-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid.

#### $\alpha$ -Linolenic Acid (Vegetable Omega-3)

A systematic review identified 4 randomized controlled trials that tested  $\alpha$ -linolenic acid 2 to 6 g/d.<sup>16</sup> The Alpha-Omega trial tested the effect of  $\alpha$ -linolenic acid 2 g/d compared with the same amount of oleic acid (both from 20 g margarine) in an older Dutch population with CHD.<sup>114</sup> There were ≈2400 participants in the  $\alpha$ -linolenic acid and the oleic acid groups. After an average of 3.4 years of follow-up, the incidence of major cardiovascular events was 13.2% compared with 14.5% in the  $\alpha$ -linolenic acid and control group, a 9% difference, not statistically significant. Two trials were conducted in Norway, one in 200 men who had CHD<sup>115</sup> and another in 13400 men who were healthy and without CHD.<sup>116</sup>  $\alpha$ -Linolenic acid 5 g/d supplied by flaxseed or linseed oil was tested and compared with sunflower oil, which has mainly n-6 linoleic acid.  $\alpha$ -Linolenic acid did not significantly reduce CHD in either trial.

A meta-analysis of 7 prospective observational studies on dietary  $\alpha$ -linolenic acid found an overall relative risk of 1.02 for CHD (nonsignificant).<sup>16</sup> However, there is consistent evidence that higher  $\alpha$ -linolenic acid intake and higher blood levels of  $\alpha$ -linolenic acid are associated with lower risk of fatal CHD.<sup>117,118</sup>  $\alpha$ -Linolenic acid does not lower LDL cholesterol, but it has been shown to have antiarrhythmic properties in experimental studies.<sup>119,120</sup>

It has been proposed that  $\alpha$ -linolenic acid affects CVD mainly in the low part of its range in the diet or when the background diet of the population under

study is almost completely devoid of eicosapentaenoic acid and docosahexaenoic acid.<sup>121,122</sup> This interesting hypothesis requires evidence from clinical trials.

In summary, randomized controlled trials and observational studies do not provide clear evidence that  $\alpha$ -linolenic acid reduces the overall incidence of CVD, although higher intake of  $\alpha$ -linolenic acid may reduce fatal CHD.

### Eicosapentaenoic Acid, Docosapentaenoic Acid, and Docosahexaenoic Acid

The n-3 marine fatty acids eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid are present in fish and dietary supplements having a >10-fold range of n-3 fatty acid contents. High-dose prescription forms are also available to treat hypertriglyceridemia. The n-3 fatty acids contribute little energy to the daily diet and do not pertain closely to the topic covered by the present advisory. We refer readers who have interest in this complex topic to the AHA's library of guidelines, statements, and advisories.

### MEDITERRANEAN DIETS, LYON HEART STUDY, AND PREDIMED

The Seven Countries Study kindled interest in Mediterranean diets.<sup>11</sup> Total fat intake was highest in Crete, Greece, at 43%, mainly from olive oil, where prevalence of CVD was lowest worldwide. Traditionally, Mediterranean diets had an abundance of plant foods, including vegetables, legumes, nuts, fruits, and grains, and fish.<sup>123</sup> As dietary patterns trended away from a traditional Mediterranean diet in Greece, individuals who maintained traditional diets experienced lower rates of death resulting from CVD, cancer, and all causes.<sup>124</sup>

The Lyon Heart Study<sup>125</sup> was a randomized controlled trial that provided  $\alpha$ -linolenic acid 2 g/d as part of a Mediterranean diet intervention in 605 men with acute myocardial infarction. The Mediterranean diet replaced animal fat with polyunsaturated vegetable oil rich in  $\alpha$ -linolenic acid; meat, butter, and cream were reduced, and fish, legumes, bread, fruits and vegetables were increased. A control group was assigned a low-fat diet. Mean follow-up was 27 months. Cardiovascular death or nonfatal myocardial infarction totaled 8 in the Mediterranean group and 33 in the control group, a significant difference. Although the researchers emphasized the  $\alpha$ -linolenic acid component of the diet as contributing to the benefit, many other dietary changes occurred as part of the Mediterranean diet, making it impossible to determine to what extent  $\alpha$ -linolenic acid contributed to the reduction in recurrent CHD.

The PREDIMED trial (Prevencion con Dieta Mediterranea) was a parallel-group, multicenter randomized

trial in Spain conducted among 7447 men (age, 55–80 years) and women (age, 60–80 years) free of CVD at baseline and having either type 2 diabetes mellitus or 3 other risk factors for CVD.<sup>126</sup> They were assigned at random to a Mediterranean diet supplemented with 50 g extra virgin olive oil, a Mediterranean diet supplemented with 30 g nuts (half walnuts, one fourth almonds, and one fourth hazelnuts), or a reduced-fat control diet. Follow-up was 4 to 5 years. The primary end point, a composite of myocardial infarction, stroke, and death resulting from CVD, was lower significantly by 30% in the olive oil group and 29% in the nut group. The olive oil group increased intake of olive oil, partly replacing their usual kind of olive oil low in polyphenols with extravirgin olive oil high in polyphenols. The nuts group increased intake of  $\alpha$ -linolenic acid and linoleic acid. Saturated fat intake was low, 9% of daily energy in all 3 groups during the trial. Monounsaturated fat intake was 21% to 22% in the Mediterranean groups compared with 19% in the reduced-fat group. Total fat was 41% in the Mediterranean and 37% in the reduced fat group. As intended by the researchers, the dietary changes reflected the aim to test a Mediterranean dietary pattern, not a specific alteration in dietary fat intake. Intake of fruits, vegetables, legumes, nuts, wine, and fish increased in the Mediterranean diet groups compared with the control diet group.

In summary, observational studies and 2 randomized clinical trials together suggest that a Mediterranean dietary pattern in which unsaturated fats predominate lowers the incidence of CVD.

### CHILDREN

In 2012, the National Heart, Lung, and Blood Institute published the "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents."<sup>127</sup> An expert panel reviewed the evidence building from the 2010 US Dietary Guidelines Advisory Committee Report.<sup>128</sup> Although evidence for dietary fat and cardiovascular risk in children was limited, key epidemiological studies provided the strongest data available. The Bogalusa Heart Study found that in children intake of animal fat, the major source of dietary saturated fat, was associated with higher body weight.<sup>129</sup>

The Cardiovascular Risk in Young Finns study (Young Finns) was a multicenter longitudinal cohort study of 3956 individuals 3 to 18 years of age in 1980 who had ongoing follow-up assessment of diet and blood lipids over 21 years.<sup>130</sup> Two major dietary patterns emerged, a "traditional" pattern including rye, potatoes, butter, sausages, milk, and coffee and a "health-conscious" pattern including vegetables, legumes and nuts, rye, cheese and other dairy products, and alcoholic beverages. In both men and women, at the end of follow-up, those following the traditional diet had higher levels of



total serum cholesterol and LDL cholesterol. Higher levels of LDL cholesterol in childhood predicted increased common carotid artery intima-media thickness, an indicator of atherosclerosis.<sup>131</sup>

The National Heart, Lung, and Blood Institute National Growth and Health Study recruited 2379 black and white 9-year-old girls in 3 different US cities and followed up their diets, growth, and development for a decade.<sup>132</sup> Girls who consumed a dietary pattern higher in fruits and vegetables, dairy products, and fiber-rich grains and lower in sugar, fried foods, burgers, pizza, and total fat for >10 years had lower body mass index, percentage of body fat, and waist circumference; these differences were significant for white girls.<sup>132</sup> Body mass index and central adiposity were correlated with LDL cholesterol.<sup>133</sup>

The STRIP trial (Special Turku Coronary Risk Factor Intervention Project for Babies) with >20 years of follow-up is the only randomized study that examined and reported improved long-term health effects from a multifactorial program that included a reduction in saturated fat starting in infancy compared with usual dietary intake and lifestyle among normal children from infancy through adolescence.<sup>134,135</sup> LDL cholesterol levels were lower in the intervention compared with the control group through 14 years of age, significant in boys but not girls.<sup>135</sup>

Likewise, the Diet Intervention Study in Children<sup>136,137</sup> was a randomized controlled trial designed to assess the safety and efficacy of a reduced-fat dietary intervention among prepubertal children with elevated LDL cholesterol levels (between the 80th and 98th percentiles) at baseline. A behavior-based, nutritionist-tailored intervention advocated adherence to a diet with 28% of energy from fat, <8% from saturated fat, and <9% from polyunsaturated fat. Saturated fat intake decreased in the intervention group compared with the control group throughout 7 years of follow-up.<sup>136,137</sup> LDL cholesterol was lower in the intervention compared with the control group, significant at 1 and 3 years but not at 5 and 7 years.

The PDAY study (Pathobiological Determinants of Atherosclerosis in Youth) provided crucial evidence that risk factors for developing CHD in adults were associated with atherosclerosis in men and women 15 to 34 years of age who died of accidents, homicide, or suicide.<sup>138,139</sup> Atherosclerosis was measured directly in the right coronary artery and abdominal aorta. The concentration of VLDL and LDL cholesterol was significantly directly associated and HDL cholesterol was inversely associated with early and intermediate lesions in both arteries. These results suggest that dietary factors that raise VLDL and LDL cholesterol produce atherosclerosis in teenagers and young adults.

Overall, these results suggest that reduced saturated fat intake within a healthful dietary pattern is feasible and effective for sustaining lower LDL cholesterol, a preventive effort against CVD in growing children.

## CONCLUSIONS AND RECOMMENDATIONS

The key evidence to reduce saturated fat and replace it with polyunsaturated and monounsaturated fat is summarized below:

- Randomized clinical trials showed that polyunsaturated fat from vegetable oils replacing saturated fats from dairy and meat lowers CVD.
- A dietary strategy of reducing intake of total dietary fat, including saturated fat, and replacing the fats mainly with unspecified carbohydrates does not prevent CHD.
- Prospective observational studies in many populations showed that lower intake of saturated fat coupled with higher intake of polyunsaturated and monounsaturated fat is associated with lower rates of CVD and all-cause mortality.
- Saturated fat increases LDL cholesterol, a major cause of atherosclerosis and CVD, and replacing it with polyunsaturated or monounsaturated fat decreases LDL cholesterol
- Replacing saturated with polyunsaturated or monounsaturated fat lowers blood triglyceride levels, an independent biomarker of risk for CVD.
- Replacing saturated with polyunsaturated fat prevents and regresses atherosclerosis in nonhuman primates.
- Overall, evidence supports the conclusion that polyunsaturated fat from vegetable oils (mainly n-6, linoleic acid) reduces CVD somewhat more than monounsaturated fat (mainly oleic acid) when replacing saturated fat.

Evidence has accumulated during the past several years that strengthens long-standing AHA recommendations to replace saturated fat with polyunsaturated and monounsaturated fat to lower the incidence of CVD. Reduction in total dietary fat or a goal for total fat intake is not recommended. This shift from saturated to unsaturated fats should occur simultaneously in an overall healthful dietary pattern such as the DASH or Mediterranean diet as emphasized by the 2013 AHA/American College of Cardiology lifestyle guidelines and the 2015 to 2020 Dietary Guidelines for Americans.

## FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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## DISCLOSURES

### Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Frank M. Sacks	Harvard School of Public Health Nutrition	None	None	None	None	None	None	None
Jennifer G. Robinson	University of Iowa Epidemiology	Amarin, Amgen, AstraZeneca, Eli Lilly, Esai, Glaxo-Smith Kline, Merck, Pfizer, Regeneron/Sanofi, Takeda†	None	None	None	None	Amgen, Eli Lilly Pfizer, Regeneron/Sanofi; Akcea/Ionis*; Merck*; Dr Reddy*	None
Linda V. Van Horn	Northwestern University Preventive Medicine	None	None	None	None	None	None	None
Lawrence J. Appel	Johns Hopkins University Medicine	None	None	None	None	None	None	None
Mark A. Creager	Dartmouth-Hitchcock Medical Center Heart and Vascular Center	None	None	None	None	None	None	None
Penny M. Kris-Etherton	Pennsylvania State University, Department of Nutritional Sciences	California Walnut Commission†; Ag Canada and Canola Oil Council†; National Cattlemen's Beef Association†	None	None	None	None	Seafood Nutrition Partnership*; California Walnut Commission*; TerraVia*; Avocado Nutrition Science Advisors*	None
Alice H. Lichtenstein	Tufts University Cardiovascular Nutrition	None	None	None	None	None	None	None
Michael Miller	University of Maryland	None	None	None	None	None	None	None
Eric B. Rimm	Harvard T.H. Chan School of Public Health	None	None	None	None	None	None	None
Lawrence L. Rudel	Wake Forest University School of Medicine Pathology	None	None	None	None	None	None	None
Neil J. Stone	Northwestern University Cardiology	None	None	None	None	None	None	None
Jason H.Y. Wu	The George Institute for Global Health, the University of New South Wales	None	Unilever†	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10,000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

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Sergio Fazio	Oregon Health and Science University	None	None	None	None	None	None	None
Edward A. Fisher	New York University School of Medicine	None	None	None	None	None	None	None
Theodore Mazzone	North Shore University Health System	None	None	None	None	None	None	None

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