Multimorbidity and quality of life

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Review

Multimorbidity and quality of life: Systematic literature review and meta-analysis

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ABSTRACT

Multimorbidity is typically defined as the co-existence of two or more chronic diseases within an individual. Its prevalence is highest among the elderly, with poor quality of life (QoL) being one of the major consequences. This study aims to: (1) understand the relationship between multimorbidity and QoL or health-related quality of life (HRQoL) through systematic literature review; (2) explore the strength of this association by conducting the first meta-analysis on the subject.

Following PRISMA, Medline/PubMed, Embase, CINAHL and PsycINFO were searched for studies published through September 1st, 2018. Original studies with clear operationalization of multimorbidity and validated QoL (or HRQoL) measurement were retained. For random-effect meta-analysis, a minimum of three studies with the same multimorbidity tool (e.g. number of diseases or equal comorbidity index) and the same QoL tool were required. Number of diseases was most common and the only measure on which meta-analysis was carried out. The outcome of interest was the linear regression slope between increasing number of diseases and QoL. Heterogeneity was explored with meta-regression. Out of 25,890 studies initially identified, 74 studies were retained for systematic review (total of 2,500,772 participants), of which 39 were included in the meta-analysis. The mean decrease in HRQoL per each added disease, depending on the scale, ranged from: −1.55% (95%CI: −2.97%, −0.13%) for the mental component summary score of pooled SF-36, -12 and -8 scales to −4.37% (95%CI: −7.13%, −1.61%) for WHOQoL-BREF physical health domain. Additional studies considering severity, duration and patterns of diseases are required to further clarify this association.

1. Introduction

Owing to economic and social development, better health care, scientific advancements and health education and promotion practices, global life expectancy at birth has been increasing for decades (Kyu et al., 2018).

In Europe, the continent that reckons the highest number of senior citizens (UN, 2015), the percentage of the population 65 and over will rise to 27% by 2050, accounting for more than a quarter of the total population (WHO, 2012). At the global level this number is expected to reach 16% by the same year (WHO, 2011) as other continents are not lagging far behind, with particularly less developed countries displaying a more rapid growth in numbers of elderly (UN, 2015; WHO, 2011). This reduces the life expectancy gap between countries and marks an ageing society as a global phenomenon.

While greater longevity is undoubtedly one of the utmost achievements of humanity (WHO, 2002), it carries challenges along. Accumulation of chronic diseases appears to be one of them (Arbelle et al., 2014; Barnett et al., 2012b; Kingston et al., 2018; Lenzi et al., 2016; Salive, 2013).

Multimorbidity is most commonly defined as the co-occurrence of two or more chronic conditions within an individual (van den Akker

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et al., 1996; WHO, 2016) and, particularly in the context of an ageing society, has become a growing public health concern (McPhail, 2016; Pefoyo et al., 2015; Violan et al., 2014). The prevalence of multimorbidity for the general population over 60 years of age varies between 55% and 98% (Marengoni et al., 2011), even though in absolute numbers there are more people living with multimorbidity among those younger than 65 years, as they represent the largest segment of the population (Barnett et al., 2012b).

Poor quality of life (QoL) along with disability, functional decline and high health care costs are major consequences of multimorbidity (Marengoni et al., 2011). Moreover, patient QoL is a meaningful measure in the evaluation of health care services and patient-reported outcomes (WHOQOL Instruments). It provides a supplementary and valuable insight in patient satisfaction with regard to accessibility, organization and quality of care. It is useful in medical decision making for ensuring improvement of the life domains a patient deems most important, thus facilitating patient-focused care (Berghout et al., 2015; Rathert et al., 2013).

There have been several systematic reviews published on the relationship between multimorbidity and QoL in the past 15 years (Fortin et al., 2004; Hodek et al., 2010; Kanesarajah et al., 2018; Marengoni et al., 2011). The reviews addressed either primary care patients (Fortin et al., 2004) or particular age groups (Kanesarajah et al., 2018; Marengoni et al., 2011), and consistently showed a negative correlation between multiple conditions and QoL. No meta-analysis has yet been attempted.

We aimed, through an extensive literature review, to summarize findings on the association between multimorbidity and various measures of QoL, looking into study design, setting, population or disease types considered. Specifically, we quantified the strength of this association by performing the first meta-analysis on the subject, shedding light in parallel on the role of age, sex and number of diseases using meta-regression.

2. Materials and methods

2.1. Systematic literature review

The systematic review was performed following the PRISMA protocol and is registered at PROSPERO (identification number: CRD42017072983).

2.1.1. Description of the search strategy

Key words used for the systematic literature search were multimorbidity, comorbidity and quality of life, for exploring four databases: Medline/PubMed, Embase, CINAHL and PsycINFO. Multimorbidity and comorbidity are terms which are very often used interchangeably, even though their concepts and definitions differ (Nicholson et al., 2018). To ensure that no relevant publications were omitted due to imprecise terminology, both terms were included in the search strategy. We included all conceivable synonyms and spelling variations of the three key words, as well as their singular and plural forms; plus incorporated all entry MeSH term variations. Their MeSH related expressions were also cross-checked.

Table 1 shows the search strategy applied in Medline/PubMed, PsycINFO ("Academic journals" only) and CINAHL ("Academic journals" only), while the strategy was slightly different for Embase due to different functional specifications of the database (Table 2).

The literature search encompassed studies published through September 1st, 2018. No starting date restriction was applied in any of the databases.

2.1.2. Study selection

Only peer reviewed original studies associating multiple conditions with validated QoL tools were considered. Studies using an index disease, particular patterns of disease or multimorbidity as a binary variable were excluded. Details on exclusion criteria are listed in Table 3.

No language limitation was applied, owing to a multilingual research team. English, German, French and Spanish articles were identified during the search.

All references were screened (title/abstract and full text) by two independent reviewers (TM and MvdA) and compared for agreement. TM is MD, MPH trained, performing this study as part of her doctoral thesis; MvdA is a University Professor and an expert in multimorbidity. The two reviewers disagreed on less than 1% of studies and all disagreements were resolved without the need for a third party.

Two additional exclusion criteria were applied for selecting papers for meta-analysis (Table 4). Detailed reasons for exclusion per study can be found in Online resources 1.

Table 1
Search strategy for Medline/PubMed, CINAHL and PsycINFO.

Searched as key words and in all fields:
multimorbidity OR "multi-morbidity" OR "multi morbidity" OR multimorbidities OR "multi-morbidities" OR "multi morbidities" OR multimorbid OR "multi-morbid" OR "multi morbid" OR comorbidity OR "co-morbidity" OR "co morbidity" OR comorbidities OR "co-morbidities" OR "co morbidities" OR comorbid OR "co-morbid" OR "co morbid" OR "multiple chronic conditions" OR "multiple chronic illnesses" OR "multiple chronic diseases" OR "multiple conditions" OR "multiple illnesses" OR "multiple diseases" OR "multiple diagnoses" OR "morbidity pattern" OR "morbidity patterns" OR polymorbidity OR "poly-morbidity" OR "poly morbidity" OR polymorbidities OR "poly-morbidities" OR "poly morbidities" OR polypathology OR "poly-pathology" OR "poly pathology" OR polypathologies OR "poly-pathologies" OR "poly pathologies" OR pluripathology OR "pluri-pathology" OR "pluri pathology" OR multipathology OR "multi-pathology" OR "multi pathology" OR multipathologies OR "multi-pathologies" OR "multi pathologies" OR "multiple pathologies" OR "disease cluster" OR "disease clusters"
AND
"quality of life" OR "qualities of life" OR "life quality" OR "life qualities" OR "value of life" OR "values of life" OR "life value" OR "life values" OR "health related quality of life" OR "quality of well-being" OR "quality of well being" OR "QoL" OR "HRQoL" OR "HRQL" OR "QWB"

Table 2
Search strategy for Embase.

1. *comorbidity/	focus term
2. multimorbidity.mp	key word
3. *"quality of life"/	focus term
4. 1 or 2	
5. 3 and 4	

Table 3
Exclusion criteria for the systematic review and number of excluded studies.

Criteria for exclusion from systematic review	# Excluded
1 = Research question not about association multimorbidity – QoL[a]	99
2 = Index disease	29
3 = QoL not the outcome	8
4 = Review/Editorial	17
5 = Toll for assessing QoL not accordant with our research question or unclear	8
6 = Patterns or groups of diseases studied	8
7 = Unclear or inadequate operationalization of MM (e.g. polypharmacy used as proxy for MM)	2
8 = Particular population group (e.g. in mental health centre)	5
9 = Conference abstracts	16
10 = Population overlap[b]	6
11 = Qualitative study	5

[a] Studies with multimorbidity as a binary variable also excluded.
[b] If several reports considered the same or largely the same population, only one report was used; usually the most recent or the one with the largest population.

Table 4
Exclusion criteria for the meta-analysis and number of excluded studies.

Criteria for exclusion from meta-analysis	# Excluded
12 = Insufficient number of studies with the same multimorbidity and QoL measurement	28
13 = Insufficient data reported (e.g. reported correlation only, etc.)	7

2.1.3. Data extraction

Data extraction incorporated study details including author, year of publication, journal, country, design, setting and sample size; population demographics such as mean age, proportion female, proportion with a university degree, proportion of high-medium-low economic status as reported in the study (income was stated most frequently), rural/urban ratio, marital status, proportion living alone, race/ethnicity (proportion black, white, Hispanic, other); details on the concept of multimorbidity including definition, method of evaluation, number and type of diseases considered, mean number of diseases, disease severity; as well as information on the form of QoL assessment.

For the study setting we differentiated between hospital and non-hospital, where the non-hospital setting included community setting, primary care, outpatient clinics, nursing homes, home care patients or similar. Division between hospital and non-hospital settings was chosen to separate out studies with hospitalized individuals, a population with more disabling health problems, from those living in a community (including participants selected through primary care, outpatient clinics, nursing homes, etc.). The diversity of the non-hospital setting was deemed appropriate moreover considering that primary care settings play a major role in the management of multimorbid patients (Boult et al., 2013; Rijken et al., 2018), as the proportion visiting primary health care at least once a year is very high especially among older people.

The outcome of interest for the meta-analysis was the study specific slope of the linear regression investigating the relationship between the level of multimorbidity and QoL, and the associated standard error. We extracted mean slope and associated variance, adjusted for confounders where possible, unadjusted slopes otherwise. Where no linear regression was reported, we extracted mean QoL and associated variance as well as number of patients per multimorbidity group, in order to estimate the linear regression slope ourselves.

Data were extracted and compared by two independent reviewers (TM as one reviewer; the role of a second was shared between MvdA, SS, CD, AGM).

2.2. Study quality assessment

All studies included in the systematic review were assessed for quality.

Studies were evaluated by using the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NIH). The tool suggests slightly different approaches for cohort and cross-sectional studies. The vast majority of the studies we assessed were cross-sectional. A few studies were longitudinal, however for our research only the information from the baseline time point was used. Therefore, these studies were also evaluated as cross-sectional. Not all NIH quality criteria were applicable to our research, hence we only applied 8 out of 14 (Table 5).

Each positive response carried 1 point, and no point was given for negative or unclear responses. The maximum number of possible points was 8. Criteria which were not applicable were excluded from the evaluation.

2.3. Summary method for studies not included in meta-analysis

All quantitative studies which associated multimorbidity, measured either by way of a disease count or one of the recognized multimorbidity/comorbidity indices with a validated QoL tool, and which did not meet any of the 11 exclusion criteria (Table 3), were included in the systematic review. We briefly described some of their findings relevant to our research question.

2.4. Meta-analysis

We fitted several meta-analysis models to determine the overall effect of the relationship between level of multimorbidity and QoL (or HRQoL). We employed a random effects model due to the high level of heterogeneity observed in the dataset. All calculations were conducted in R (The R Project for Statistical Computing). Meta-analysis models were fitted using the metafor package (Viechtbauer, 2010).

Studies were split into hospital vs. non-hospital setting, and separate models were fitted for different measures of multimorbidity as well as different measures of QoL. Meta-analysis was only performed for groups of a minimum of three studies with the same multimorbidity and the same QoL tool. While meta-analysis is technically possible with two studies (Valentine et al., 2010), a random effects model requires a minimum of 3 studies in order to extract information on between trial variance.

Where no linear regression was reported, we calculated a slope by means of weighted linear regression using the number of patients per group as weights where possible and the inverse variance otherwise. Where data was provided for groups of multimorbidity (e.g. 0–2 diseases, 3–5 diseases, etc.), we used the midpoint. To adjust for the small degrees of freedom in the weighted regression, we retrieved the standard error of the slope parameter using the within group variation.

When not presented in the study but where it seemed the information of interest might be available, authors were asked to provide the additional data of interest, which was primarily the information on the regression slope. The authors of 17 studies were contacted, 5 provided supplementary information, 3 of which we were able to use.

We explored the impact of potential confounders using meta-regression (also metafor package in R). In meta-regression, we adjusted for mean age, proportion female, mean number of diseases per patient, total number of diseases considered in a study, study quality and whether the analysis within each study was adjusted. Where the mean number of diseases per patient was not reported, we calculated it based on the number of subjects per multimorbidity group where possible. For studies defining the highest multimorbidity group as “X or more diseases” we used X, so in those situations our calculation may have been an underestimate of the true population mean.

Furthermore, in order to strengthen our findings, we performed two scenario analyses. The first scenario only included studies of the highest quality (those which scored 7 or 8 points). The second scenario only included studies which clearly reported both the number of diseases and details on which diseases were considered; these are two key elements in clearly defining multimorbidity.

3. Results

3.1. Literature search

The search identified a total of 25,890 references. After 6474 duplicates were removed, 19,416 remained for title/abstract screening. Subsequently 19,139 references were eliminated leaving 277 for full text reading; 203 were excluded for reasons specified in Table 3 and Online resources 1, leaving 74 papers in the systematic review. After applying 2 additional exclusion criteria (Table 4), 39 of the 74 studies were included in the meta-analysis (Fig. 1).

While many excluded papers failed multiple criteria, only one major reason was assigned per study (Online resources 1). The most prevalent reason for exclusion from the systematic review was that the research question did not address the association between the level of

Table 5
NIH quality assessment tool for observational cohort and cross-sectional studies.

NIH criteria	Number of yes/no/other study responses per question		
	Yes	No	Other (CD, NR, NA)[a]
1. Was the research question or objective in this paper clearly stated?	74		
2. Was the study population clearly specified and defined?	74		
3. Was the participation rate of eligible persons at least 50%?	34	12	CD(11) NR(17)
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	73		CD(1)
5. Was a sample size justification, power description, or variance and effect estimates provided?	17	57	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	71	2	NR(1)
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	74		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	53	17	CD (3) NR (1)

[a] CD = cannot determine; NR = not reported; NA = not applicable.

multimorbidity and QoL. These studies either described both outcomes separately, or multimorbidity was treated as a binary variable.

The search also highlighted an increasing interest in the topic over time, as shown in Fig. 2 plotting the number of publications against the year of publication.

3.2. Description of studies included in the systematic review

Seventy-four quantitative studies included in the systematic review analyzed the data of a total of 2,500,772 study participants (Abdala et al., 2015; Agborsangaya et al., 2014; Agborsangaya et al., 2013;

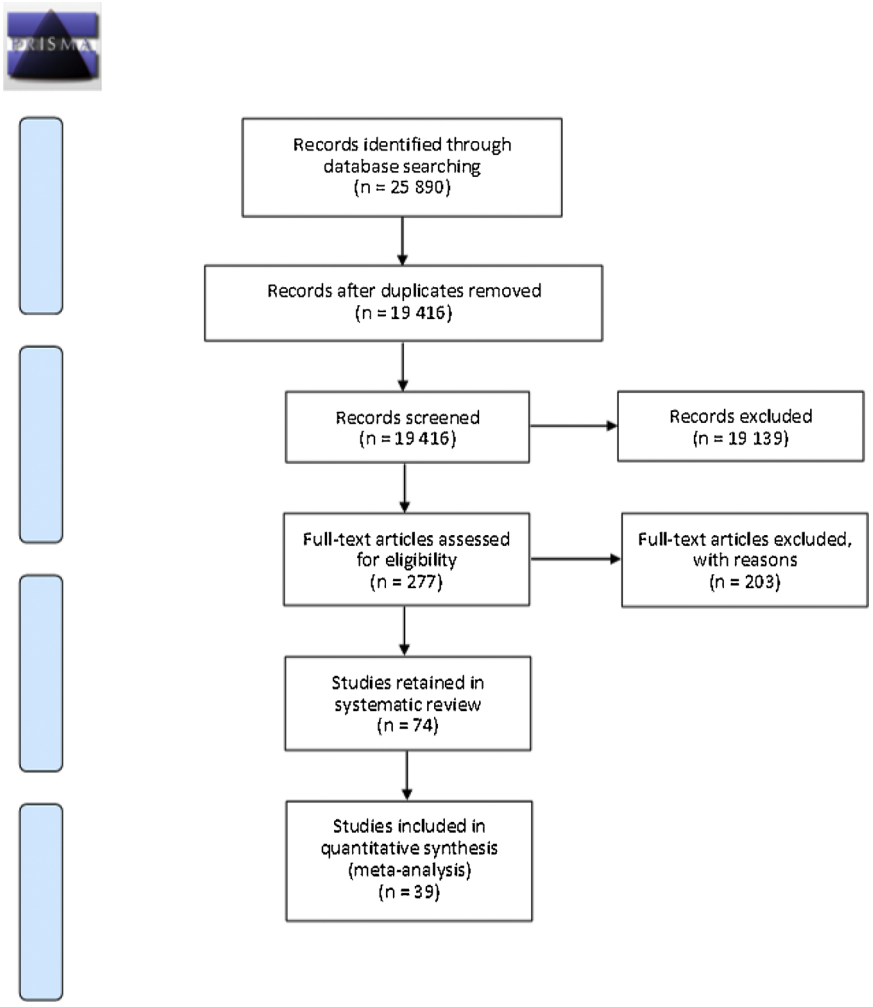

Fig. 1. PRISMA flow diagram.

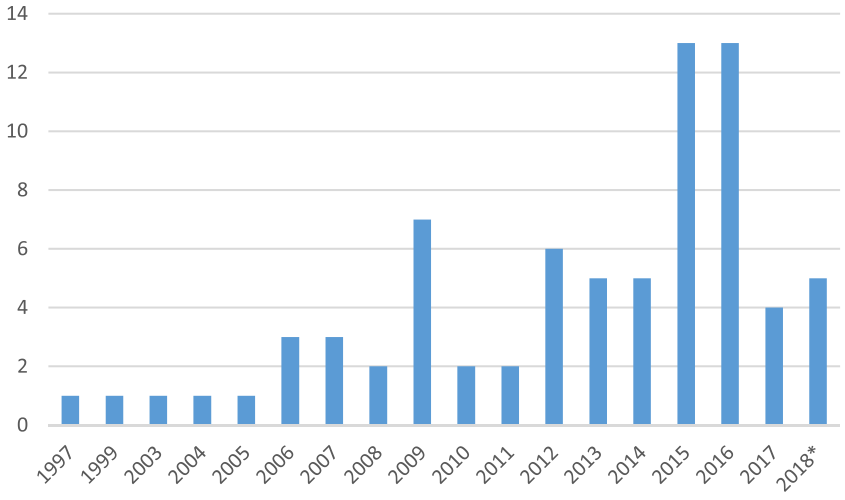

Fig. 2. Number of publications per year.
* includes articles published through 1st September 2018.

Ahmad et al., 2015; Alonso-Moran et al., 2015; Arokiasamy et al., 2015; Barile et al., 2012; Barra et al., 2015; Bornet et al., 2017; Brettschneider et al., 2013; Byles et al., 2005; Chen et al., 2011; Cheng et al., 2003; Chin et al., 2016; Cuijpers et al., 1999; De Nobrega et al., 2009; Der-Martirosian et al., 2013; Drageset et al., 2009; Ferrer et al., 2010; Fortin et al., 2006; Gambin et al., 2015; Gariballa and Alessa, 2017; Garin et al., 2014; Garrido-Abejar et al., 2012; Gerber et al., 2016; Grimby and Svanborg, 1997; Groessl et al., 2007; Hanmer et al., 2010; Heyworth et al., 2009; Hodek et al., 2009; Hu, 2007; Keles et al., 2007; Kim et al., 2012; Kosilov et al., 2018; Lang et al., 2015; Lawson et al., 2013; Li et al., 2016; Lim et al., 2012; Lima et al., 2009; Loza et al., 2009; Luo et al., 2015; Mirhaghjou et al., 2016; Mondor et al., 2016; Mujica-Mota et al., 2015; N'Goran et al., 2017; Naveiro-Rilo et al., 2014; Panagioti et al., 2018; Parlevliet et al., 2014; Peters et al., 2018; Prazeres and Santiago, 2016; Punniyakotti et al., 2016; Quah et al., 2016; Rabadi and Vincent, 2013; Renne and Gobbens, 2018; Rillamas-Sun et al., 2016; Rose et al., 2018; Sakthong et al., 2015; Sanchez-Arenas et al., 2014; Selim et al., 2004; Seoane et al., 2009; Sullivan et al., 2012; Taype-Rondan et al., 2017; Tooth et al., 2008; Torisson et al., 2016; Tuzun et al., 2015; Tyack et al., 2016; Vogel et al., 2012; Weeks et al., 2006; Wikman et al., 2011; Williams and Egede, 2016; Winkler et al., 2006; Witham et al., 2008; Xie et al., 2016; Yamada et al., 2015). Their features are briefly summarized here; details are provided in Online resources 3.

The majority of studies were conducted in the United States of America (n = 17), followed by the United Kingdom (n = 9) and Spain (n = 7). Other countries were represented in four or less than four studies.

Sixty-six studies were of a cross-sectional design; eight were longitudinal. Seven studies were performed in a hospital setting, 67 in a non-hospital setting. Non-hospital setting comprised 29 studies done in primary care and clinical settings, 29 were conducted among general population, 2 among veteran population, 3 in nursing homes, 2 among home care clients and 1 each in residential homes for elderly and penal institution. The sample size ranged from 37 participants to 831,537 participants.

3.2.1. Study population characteristics

Mean age varied between 39.4 and 94.3 years; however, most of the studies (73%) considered an elderly population with a mean age over 60. Twelve studies did not report mean age. The proportion of female participants ranged from 0% to 100%. While most studies (81%) reported a majority of female participants, the overall population included 44% of females. The percentage of women was not reported in only one study.

Due to variability in reporting as well as missing data, information on education, economic status, marital status, living arrangements and ethnicity could not be summarized.

3.2.2. Multimorbidity assessment

Our literature search found high variability between the studies, beginning with the definition of multimorbidity, the number and profile of diseases considered, as well as how information was collected about the patient diseases.

We considered that a clear definition of multimorbidity was applied when it was stated in the objectives or the methodology of the study, or if it was clearly referred to in the discussion. Fifteen publications described multimorbidity as having two and more diseases, while two publications used a cut-off point of three diseases. In the vast majority of studies (n = 57), the authors either did not specify a definition, or they used alternative terminology such as "multiple chronic diseases or conditions" or terms referring to the concept of comorbidity (e.g. "co-morbidity", "multiple comorbid conditions" or "multiple co-morbidities"), where in our view the term multimorbidity could have been more appropriate. On occasion it would appear that the terms multimorbidity and comorbidity were even used interchangeably in the same study.

The total number of diseases considered per study was the number specified by the authors or clearly referred to in the tables in the study. It varied between 4 and 147, with an approximate overall mean of 20 diseases per study; 9 studies did not specify. In the majority of studies (n = 44), diseases were identified by an already predetermined list of diseases suggested by the authors, or conditioned by the tool used, such as Charlson Comorbidity Index (CCI), Seattle Index of Comorbidity (SIC), Cumulative Illness Rating Scale (CIRS) or Functional Comorbidity Index (FCI). Eleven studies used a predetermined list with the allowance to add any other potentially existing condition. If the number of additional diseases was not reported, we increased the total number of diseases in the list by one, to distinguish from the studies that did not offer this option. Four studies used an open-ended questionnaire with no predetermined list; eight studies identified conditions through medical records, while seven studies did not specify the method.

The mean number of diseases per patient ranged from estimated 0.3 to 7.7. The mean number of diseases was not reported or could not be estimated in 21 studies.

Types of diseases were identified in 63 studies either through a provided list of diseases or by referencing the comorbidity/multimorbidity indexes applied in the studies. Overall, the most frequently

considered were cardiovascular diseases (61 studies), diabetes (60 studies), joint and musculoskeletal disorders (59 studies), respiratory diseases (59 studies), cancer (42 studies) and mental health disorders (38 studies). Various types of gastrointestinal and genitourinary disorders were also found, as well as hearing and visual impairment, pain, falls, fractures and hyperlipidaemia among others. The vast majority of studies ($n = 63$) did not specify which disease classification system was used. Four studies applied ICD-9, of which two applied ICD-9-CM. Five studies used ICD-10 classification, one study used both ICD-9 and ICD-10, while one study considered the ICPC-2 coding system.

Although most researchers considered long lasting conditions, those which may reoccur or may produce consequences, it is important to note that on occasion it was difficult to ascertain the author's assumption of the chronic nature of the diseases. This was due to the fact that most studies did not provide a definition of chronic disease used.

Details on diseases considered in each study are provided in Online resources 4.

In the majority of cases, the *mean of reporting multimorbidity* was self-report as the only tool used ($n = 33$). In 19 studies medical records were assessed to obtain this information. Other studies used a combination of these and/or a few other methods, such as requesting evidence of prescribed medications, or directly assessing blood pressure levels or visual acuity. Six studies did not specify the method.

In most of the studies ($n = 53$) *multimorbidity was measured* as a disease count only. Two studies used a severity-weighted number of diseases, and one used a Diseases Burden Impact Scale (DBIS) in addition to a simple count. Eight studies applied the Charlson Comorbidity Index (CCI), and two applied the Cumulative Illness Rating Scale (CIRS). Two studies used a combination of these with a disease count. Comorbidity indices developed by the authors were found in four studies, either as the sole instrument or in combination with disease count, while the Functional Comorbidity Index (FCI) and Seattle Index of Comorbidity (SIC) were used in one study each.

The *severity of diagnoses* was assessed in only 18 out of 74 studies through the severity-weighted number of diseases or some of the author defined indices, while CCI, CIRS, SIC, DBIS consider disease severity as an integral part of multimorbidity assessment.

3.2.3. Quality of life assessment

Variability was also found within the instruments used to assess QoL. Table 6 lists encountered QoL (or HRQoL) scales.

Only two studies used a condition-specific scale, while other studies applied generic instruments. We found both psychophysical and preference based outcomes in the studies. One can distinguish between psychophysical measures (non-preference based) and preference-based measures of QoL. The former describes an individual's health status using a numerical summary, while the latter takes into account the value a population places on individual health states. While most studies used one QoL instrument, some studies applied more than one.

The most commonly used instrument was the non-preference based Short Form Health Survey (SF) questionnaire reported in 27 studies. The SF questionnaire "is a set of generic, coherent and easily admitted quality of life measures" (RAND Health) which comes in several versions. The original version SF-36 consisting of 36 questions was used in 14 studies. Abbreviated versions (SF-20, SF-12 or SF-8) were utilized in 12 articles. One study applied the veteran SF-36, a variation of the SF-36. Health-related quality of life measured by the SF non-preference based questionnaires was typically reported with two main summary scores: the physical component score (PCS) and the mental component score (MCS). Few studies reported subdomain scores or rarely a total score.

Brazier and colleagues have developed a preference based outcome measure based on the responses to the SF-36 questionnaire, the Six Dimensions Short Form (SF-6D) (Brazier et al., 2002; Brazier and Roberts, 2004). Four studies reported the SF-6D as their HRQoL measure.

The EuroQoL (EQ-5D) questionnaire was the second most commonly reported QoL instrument and was applied in 24 studies. The EQ-5D is a preference based HRQoL scale considering five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/

Table 6
Quality of life scales identified in the systematic review.

Short Form Health Survey scales	SF-36, SF-12, SF-8, MOS-SF-20, Veterans SF-36	Study (Abdala et al., 2015; Ahmad et al., 2015; Byles et al., 2005; Cheng et al., 2003; Chin et al., 2016; Cuijpers et al., 1999; Der-Martirosian et al., 2013; Drageset et al., 2009; Fortin et al., 2006; Gariballa and Alessa, 2017; Garrido-Abejar et al., 2012; Hodek et al., 2009; Hu, 2007; Keles et al., 2007; Lim et al., 2012; Lima et al., 2009; Loza et al., 2009; Luo et al., 2015; Naveiro-Rilo et al., 2014; Prazeres and Santiago, 2016; Rillamas-Sun et al., 2016; Selim et al., 2004; Tooth et al., 2008; Tyack et al., 2016; Weeks et al., 2006; Williams and Egede, 2016; Xie et al., 2016)
Six Dimensions Short Form scale	SF-6D	Study (Barra et al., 2015; Hanmer et al., 2010; Kosilov et al., 2018; Lawson et al., 2013)
Euro Quality of Life scales	EQ-5D-3L, EQ-5D-5L, EQ-6D	Study (Agborsangaya et al., 2014; Agborsangaya et al., 2013; Alonso-Moran et al., 2015; Barra et al., 2015; Brettschneider et al., 2013; Ferrer et al., 2010; Gerber et al., 2016; Heyworth et al., 2009; Hodek et al., 2009; Kim et al., 2012; Lang et al., 2015; Li et al., 2016; Mujica-Mota et al., 2015; N'Goran et al., 2017; Parlevliet et al., 2014; Peters et al., 2018; Punniyakotti et al., 2016; Quah et al., 2016; Rabadi and Vincent, 2013; Sakthong et al., 2015; Sanchez-Arenas et al., 2014; Seoane et al., 2009; Sullivan et al., 2012; Taype-Rondan et al., 2017; Vogel et al., 2012)
World Health Organization questionnaires	WHOQoL-100, WHOQoL-BREF, WHOQoL-OLD, WHOQoL-AGE	Study (Arokiasamy et al., 2015; Bornet et al., 2017; De Nobrega et al., 2009; Gambin et al., 2015; Garin et al., 2014; Panagioti et al., 2018; Punniyakotti et al., 2016; Renne and Gobbens, 2018; Tuzun et al., 2015; Winkler et al., 2006; Yamada et al., 2015)
Centre for Diseases Control and Prevention Health Related Quality of Life scale	CDCHRQoL	Study (Barile et al., 2012; Chen et al., 2011)
Nottingham Health Profile	NHP I&II	Study (Grimby and Svanborg, 1997)
Quality of Well Being Self-Administered scale	QWB-SA	Study (Groessl et al., 2007)
Menopausal Quality of Life scale	MENQOL	Study (Mirhaghjou et al., 2016)
Minimum Data Set Health Status Index	MDS-HSI	Study (Mondor et al., 2016)
Quality of Life in Alzheimer's Disease scale	QoL-AD	Study (Torisson et al., 2016)
Control, Autonomy, Self-realization and Pleasure scale	CASP-19	Study (Wikman et al., 2011)
Patient Generated Index	PGI	Study (Witham et al., 2008)
The Patient-Reported Outcomes Measurement Information System 29-item profile	PROMIS-29 v2.0	Study (Rose et al., 2018)

depression) with three levels (no problems, some problems, and extreme problems). A newer version of the EQ-5D has been recently developed with five levels (EQ-5D-5L) (EuroQol Group). An individual's health state is defined by their response, which can be transformed into an index scale based on population preference values. The EQ-5D further includes the visual analogue scale as a quantitative measure of how an individual judges his/her personal health, however this outcome was not included in our study. EQ-6D is a rarely applied scale and it is constructed by adding cognition to the EQ-5D (Hoeymans et al., 2005). Only one study used this scale; in meta-analysis we considered 5 out of the 6 EQ dimensions.

Eleven studies applied a variation of QoL tools developed by the World Health Organization (WHO) including the initially developed generic instrument WHOQoL-100 and its abbreviated version WHOQoL-BREF, as well as variations for elderly populations WHOQoL-OLD and WHOQoL-AGE (WHOQOL: Measuring Quality of Life).

The WHOQoL-OLD questionnaire is a supplementary component to the WHOQoL-BREF, while the WHO-AGE is a newer shorter version which can be administrated alone (Caballero et al., 2013). These appeared in less than three studies which measured multimorbidity with a disease count, and were therefore not included in the meta-analysis.

Only studies that used the WHOQoL-BREF met the minimum requirement for quantitative synthesis. For comparability with SF HRQoL domains, we used two out of four WHOQoL-BREF dimensions (physical and mental).

3.2.4. Study quality

The quality of studies was evaluated using eight criteria of the NIH tool as described previously. Results are displayed in Table 5 and Fig. 3. Details on quality evaluation per study are provided in Online resources 2.

Thirty-three studies were of an excellent quality achieving 7 or 8 out of 8 points. The minimum number of points was 4 (3 studies), 10 studies scored 5 points, while the remaining studies scored 6 points (n = 28). The main reasons for scoring lower were not providing information on the sample size justification, missing to adjusting for potential confounders, and/or not meeting a participation rate of at least 50% (Table 5).

3.3. Summary of findings for studies not included in meta-analysis

Thirty-five records were excluded from meta-analysis due to an insufficient number of studies with the same multimorbidity and QoL measurement or missing a slope parameter (Table 4). However, we found it relevant to briefly mention their individual findings related to the research question. The vast majority of studies indicated a negative association between level of multimorbidity and QoL across all QoL dimensions or have displayed a stronger association on some of the scale domains (e.g. physical). Very few studies (1%) showed no significant correlation between level of multimorbidity and QoL. These findings did not show discord with our meta-analysis output.

3.4. Results of meta-analysis

3.4.1. Description of studies selected for meta-analysis

Out of 74 papers included in the systematic review, 39 qualified for inclusion in the meta-analysis (Agborsangaya et al., 2014; Agborsangaya et al., 2013; Alonso-Moran et al., 2015; Barra et al., 2015; Cheng et al., 2003; Chin et al., 2016; Ferrer et al., 2010; Fortin et al., 2006; Gambin et al., 2015; Garrido-Abejar et al., 2012; Gerber et al., 2016; Hanmer et al., 2010; Heyworth et al., 2009; Hodek et al., 2009; Hu, 2007; Kim et al., 2012; Lang et al., 2015; Lawson et al., 2013; Li et al., 2016; Lim et al., 2012; Loza et al., 2009; Luo et al., 2015; Mujica-Mota et al., 2015; N'Goran et al., 2017; Naveiro-Rilo et al., 2014; Panagioti et al., 2018; Peters et al., 2018; Prazeres and Santiago, 2016; Quah et al., 2016; Rabadi and Vincent, 2013; Rillamas-Sun et al., 2016; Sakthong et al., 2015; Sullivan et al., 2012; Tuzun et al., 2015; Tyack et al., 2016; Vogel et al., 2012; Williams and Egede, 2016; Winkler et al., 2006; Xie et al., 2016). Data extracted from these studies are reported in Table 7.

The sole measure of multimorbidity for meta-analysis was disease count; while four measures of QoL were: EQ-5D (including both, EQ-5D-3L and EQ-5D-5L), SF (including SF-36, SF-12 and SF-8), SF-6D and WHOQoL-BREF (physical and mental domains only).

All included studies were performed in a non-hospital setting. Features of included studies corresponded to those described in the larger set of studies. Variation in study size, sex distribution, mean age, considered disease profiles and mean number of diseases remained high. Conditions were mainly selected from a predetermined list via self-reporting. Three of the studies were longitudinal, however, only baseline information was used in the meta-analysis.

The slope relating QoL with an increasing number of diseases was adjusted for confounding factors in the majority of cases (n = 29), however the included confounders varied. The most frequently considered were age and sex, but also education, income, employment, marital status, ethnicity, occasionally smoking, BMI, urbanicity and social support, among others. Fifteen studies reported the outcome of interest as the result of a linear regression model, while we calculated the slope using weighted regression based on group level data in 22 studies. In two studies outcomes were either given or calculated,

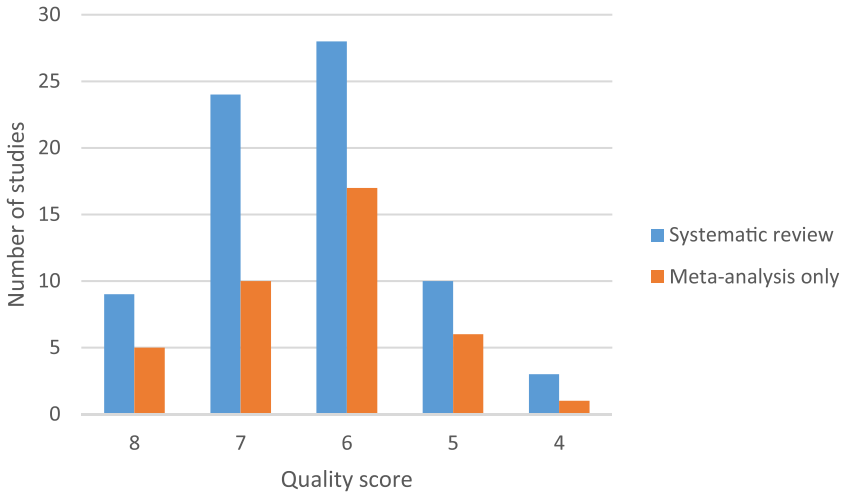

Fig. 3. Study quality distribution (systematic review and meta-analysis only studies).

Table 7
Details on studies included in the meta-analysis.

1st Author	Year of publication	Country	Study quality	Population (*N*)	Female (%)	Age (mean)	Diseases considered in the study (*N*)	Number of diseases per patient (mean)	List of diseases provided	Disease classification	Multimorbidity definition
Barra M (Barra et al., 2015)	2015	United States of America	6	39,817	54.5	45.4	NS	3.3	NR	ICD-9-CM	Other
Hodek JM (Hodek et al., 2009)	2009	Germany	6	2120	53.7	76.3	4	1.8	Yes	NS	Other
Alonso-Moran E (Alonso-Moran et al., 2015)	2015	Spain	8	1125	82.1	NR	52	4.7	Yes[a]	NS	2+
Lang K (Lang et al., 2015)	2015	United States of America	6	3058	100	53.4	6	1.1***	Yes	NS	Other
Li J (Li et al., 2016)	2016	United Kingdom	5	27,806	56.3	NR	12+**	1.5	Yes	NS	2+
Mujica-Mota RE (Mujica-Mota et al., 2015)	2015	United Kingdom	6	831,537	51	NR	13	0.9	Yes	NS	2+
Quah JH (Quah et al., 2016)	2016	Singapore	8	498	49	73.9	14	3.6	Yes	NS	2+
Sullivan PW (Sullivan et al., 2012)	2012	United States of America	6	47,178	52	45	118	1.9	NR	ICD-9	Other
Vogel I (Vogel et al., 2012)	2012	Germany	6	103	53.4	70	20	4.2	Yes	NS	2+
Agborsangaya CB (Agborsangaya et al., 2013)	2013	Canada	6	4946	52.3	46.6	16	0.7	Yes	NS	2+
Ferrer A (Ferrer et al., 2010)	2010	Spain	7	37	68	94.3	NS	NS	NR	NS	Other
Rabadi MH (Rabadi and Vincent, 2013)	2013	United States of America	5	170	4	69.4	NS	4.8***	NR	NS	Other
N'Goran AA (N'Goran et al., 2017)	2017	Switzerland	5	888	51.8	72.9	75	5.1***	Yes	NS	3+
Heyworth IT (Heyworth et al., 2009)	2009	United Kingdom	6	4836	54.9	47.9	6	0.6	Yes	NS	Other
Kim KI (Kim et al., 2012)	2012	Korea	5	1419	60.7	72.4	20	3.9	Yes	NS	Other
Agborsangaya CB (Agborsangaya et al., 2014)	2014	Canada	6	4752	55.7	47.7	15	1.3	Yes	NS	2+
Sakthong P (Sakthong et al., 2015)	2015	Thailand	6	1156	52	50.4	14	2.3	Yes	NS	Other
Peters M (Peters et al., 2018)	2018	United Kingdom	6	827	50.9	67	28	6.5	Yes	NS	2+
Gerber AM (Gerber et al., 2016)	2016	South Africa	4	104	72.1	77	11	2.6	Yes	NS	Other
Lim L (Lim et al., 2012)	2012	Singapore	7	2645	62.1	40.4	16+**	0.4***	NR	NS	Other
Loza E (Loza et al., 2009)	2009	Spain	7	2192	53.7	46.1	9	2.8	Yes	NS	2+
Prazeres F (Prazeres and Santiago, 2016)	2016	Portugal	8	521	64.1	58.2	147	4.5	Yes	ICPC-2	2+
Chin WY (Chin et al., 2016)	2016	China/Hong Kong	7	9028	57.8	48*	7+**	1.0*	Yes	NS	Other
Garrido-Abejar M (Garrido-Abejar et al., 2012)	2012	Spain	6	281	55	82	7	1.8	Yes	NS	Other
Naveiro-Rilo JC (Naveiro-Rilo et al., 2014)	2014	Spain	6	369	55.1	79.9	NS	4.5	Yes[b]	NS	Other
Williams JS (Williams and Egede, 2016)	2016	United States of America	7	23,789	51.9	NR	9	1.2***	Yes	NS	Other
Cheng L (Cheng et al., 2003)	2003	United States of America	7	316	52.8	60.3	7	2.6	Yes	ICD-9	Other
Fortin M (Fortin et al., 2006)	2006	Canada	8	238	71	59	NS	5.3	NR	NS	Other
Hu J (Hu, 2007)	2007	United States of America	7	83	73.4	NR	5	NS	Yes	NS	2+
Luo J (Luo et al., 2015)	2015	United States of America	5	75,198	100	63.5	10	1.5***	Yes	NS	Other
Tyack Z (Tyack et al., 2016)	2016	Australia	8	351	58.4	58.8	25+**	7	Yes	NS	Other
Rillamas-Sun E (Rillamas-Sun et al., 2016)	2016	United States of America	6	33,386	100	NR	12	1.6***	Yes	NS	2+
Xie H (Xie et al., 2016)	2016	China	7	407	57	NR	7+**	0.5***	Yes	NS	Other
Hanmer J (Hanmer et al., 2010)	2010	United States of America	6	95,195	54.4	72.25[c]	15	NS	Yes	NS	Other
Lawson KD (Lawson et al., 2013)	2013	United Kingdom	7	7054	NR	72.7	40	0.7***	Yes	ICD-10	2+
Tuzun H (Tuzun et al., 2015)	2015	Turkey	5	2560	61.2	39.4	8	0.3***	Yes	ICD-10	Other
Panagioti M (Panagioti et al., 2018)	2018	United Kingdom	6	4377	52.6	74.5	21+**	2.2	NR	NS	2+
Winkler I (Winkler et al., 2006)	2006	Germany	6	377	49.7	72.6	CD	NS	NR	NS	Other
Gambin G (Gambin et al., 2015)	2015	Brazil	7	197	49.2	69.7	8+**	NS	Yes	NS	Other

1st Author	Diseases measurement form	Diseases identification	Means of reporting diseases	Disease severity	QoL scale	SLOPE	SE	Adjusted (yes/no)
Barra M (Barra et al., 2015)	Simple and weighted DC	NS	MR	With severity weighted count	1) EQ-5D-3L 2) SF-6D	1) −0.0271 2) −0.0224	1) 0.0004 2) 0.0003	Yes
Hodek JM (Hodek et al., 2009)	DC	PD	MR	NR	1) EQ-5D-3L 2) SF-8	1) −0.0120 2) −0.0088 (physical); ***2) −0.0026 (mental)***	1) 0.0005 2) 0.0022 (physical); ***2) CD (mental)***	1) yes 2) yes (physical)/no (mental)
Alonso-Moran E (Alonso-Moran et al., 2015)	DC	MR	MR	NR	EQ-5D-3L	−0.0257	0.0028	Yes

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Table 7 (*continued*)

1st Author	Diseases measurement form	Diseases identification	Means of reporting diseases	Disease severity	QoL scale	SLOPE	SE	Adjusted (yes/no)
Lang K (Lang et al., 2015)	DC	PD	SR and AS	NR	EQ-5D-3L	***−0.096***	***CD***	No
Li J (Li et al., 2016)	DC	PD + OE	SR	NR	EQ-5D-3L	***−0.1095***	***0.001***	No
Mujica-Mota RE (Mujica-Mota et al., 2015)	DC	PD	SR	NR	EQ-5D-3L	***−0.1185***	***CD***	Yes
Quah JH (Quah et al., 2016)	DC	PD	SR	NR	EQ-5D-3L	***−0.0185***	***0.0011***	Yes
Sullivan PW (Sullivan et al., 2012)	DC	OE	SR	NR	EQ-5D-3L	***−0.0364***	***CD***	Yes
Vogel I (Vogel et al., 2012)	DC	PD	SR	NR	EQ-5D-3L	−0.05	0.0102	Yes
Agborsangaya CB (Agborsangaya et al., 2013)	DC	PD + OE	SR	NR	EQ-5D-3L	***−0.0428***	***0.0023***	Yes
Ferrer A (Ferrer et al., 2010)	DC and CCI	PD (based on CCI)	NS	Based on CCI	EQ-5D-3L	0.013	0.0243	Yes
Rabadi MH (Rabadi and Vincent, 2013)	DC	OE	SR, MR and AS	NR	EQ-5D-3L	***−0.0132***	***0.0017***	No
N'Goran AA (N'Goran et al., 2017)	DC	PD	NS	NR	EQ-5D-3L	***−0.0215***	***0.0043***	No
Heyworth IT (Heyworth et al., 2009)	DC	PD	MR	NR	EQ-5D-3L	−0.079	0.0051	Yes
Kim KI (Kim et al., 2012)	DC	PD	SR and AS	NR	EQ-5D-3L	***−0.0281***[*****]	***CD***	No
Agborsangaya CB (Agborsangaya et al., 2014)	DC	PD	SR	NR	EQ-5D-5L	***−0.0438***	***0.0016***	Yes
Sakthong P (Sakthong et al., 2015)	DC	NS	SR	NR	EQ-5D-5L	***−0.02***	***CD***	No
Peters M (Peters et al., 2018)	DC and DBIS	PD + OE	SR	With DBIS	EQ-5D-5L	***−0.0433***	***0.0031***	Yes
Gerber AM (Gerber et al., 2016)	DC	NS	NS	NR	EQ-6D (EQ-5D part used)	***−0.023***	***0.0067***	No
Lim L (Lim et al., 2012)	DC	PD + OE	SR and AS	NR	SF-12	−0.0206 (physical); −0.0114 (mental)	0.0014 (physical); 0.002 (mental)	Yes
Loza E (Loza et al., 2009)	DC	OE	SR, MR and PR	NR	SF-12	***−0.0202 (physical); −0.0163 (mental)***	***0.0016 (physical); 0.002 (mental)***	Yes
Prazeres F (Prazeres and Santiago, 2016)	DC	PD	SR and MR	NR	SF-12	−0.0241 (physical); ***−0.0086 (mental)***	0.0031 (physical); ***0.0027 (mental)***	Yes (physical)/no (mental)
Chin WY (Chin et al., 2016)	DC	PD + OE	SR	NR	SF-12v2 (physical only)	−0.0266	0.0011	Yes
Garrido-Abejar M (Garrido-Abejar et al., 2012)	DC	PD	MR	NR	SF-12v2	−0.0152 (physical); −0.0013 (mental)	0.0041 (physical); 0.0067 (mental)	Yes
Naveiro-Rilo JC (Naveiro-Rilo et al., 2014)	DC	NS	SR and MR	NR	SF-12v2	***−0.0451 (physical); −0.027 (mental)***	***CD***	No
Williams JS (Williams and Egede, 2016)	DC	PD	SR	NR	SF-12v2	***−0.0222 (physical); −0.0061 (mental)***	***0.0004 (physical); 0.0007 (mental)***	Yes
Cheng L (Cheng et al., 2003)	DC	MR	MR	NR	SF-36	***−0.0335 (physical); −0.0283 (mental)***	***0.006 (physical); 0.0074 (mental)***	Yes
Fortin M (Fortin et al., 2006)	DC and CIRS	MR	MR	Based on CIRS	SF-36	−0.0136 (physical); 0.0005 (mental)	0.0038 (physical); 0.0033 (mental)	Yes
Hu J (Hu, 2007)	DC	PD	SR	NR	SF-36	−0.1174 (physical); −0.0393 (mental)	0.0258 (physical); 0.0265 (mental)	Yes
Luo J (Luo et al., 2015)	DC	PD	SR, AS and PR	NR	SF-36	***−0.0794 (physical); −0.0443 (mental)***	***0.0007 (physical); 0.0005 (mental)***	No
Tyack Z (Tyack et al., 2016)	DC	PD + OE	SR	NR	SF-36	0.002 (physical); −0.0016 (mental)	0.0018 (physical); 0.0016 (mental)	Yes
Rillamas-Sun E (Rillamas-Sun et al., 2016)	DC	PD	SR, MR and PR	NR	SF-36 (physical only)	***−0.0543***	***0.0012***	Yes
Xie H (Xie et al., 2016)	DC	MR	MR	NR	SF-36	−0.0563 (physical); −0.0283 (mental)	0.0087 (physical); 0.0083 (mental)	Yes
Hanmer J (Hanmer et al., 2010)	DC	PD	SR	NR	SF-6D	***−0.0247***[****]	***CD***	Yes
Lawson KD (Lawson et al., 2013)	DC	PD	SR	NR	SF-6D	***−0.0736***	***CD***	Yes
Tuzun H (Tuzun et al., 2015)	DC	OE	SR	NR	WHOQoL-BREF	***−0.0912 (physical); −0.0385 (mental)***	***0.0051 (physical); 0.0045 (mental)***	No

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Table 7 (*continued*)

1st Author	Diseases measurement form	Diseases identification	Means of reporting diseases	Disease severity	QoL scale	SLOPE	SE	Adjusted (yes/no)
Panagioti M (Panagioti et al., 2018)	DC	PD + OE	SR	NR	WHOQoL-BREF	−0.045 (physical); −0.0105 (mental)	0.0016 (physical); 0.0012 (mental)	Yes
Winkler I (Winkler et al., 2006)	DC	NS	SR	NR	WHOQoL-BREF	−0.0181 (physical); −0.0072 (mental)	0.0055 (physical); NA (mental)	Yes
Gambin G (Gambin et al., 2015)	DC	PD + OE	SR	NR	WHOQoL-BREF	−0.0184 (physical); −0.0078 (mental)	0.0094 (physical); 0.0034 (mental)	Yes

Disease classification
ICD-9 = International Classification of Diseases, 9th Revision; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10 = International Classification of Diseases, 10th Revision;
ICPC-2 = International Classification of Primary Care, 2nd Edition

Diseases measurement form
DC = Disease count
CCI = Charlson Comorbidity Index
CIRS = Cumulative Illness Rating Scale
DBIS = Disease Burden Impact Scale

Diseases identification
PD = predetermined list of diseases
PD + OE = PD + open end for additional illnesses
OE = open end questionnaire for types of diseases
NS = not specified
MR = information taken out from medical records

Means of reporting diseases
SR = self-reported
MR = taken out from medical records
AS = assessed (e.g. blood pressure measurement, visual acuity)
PR = proved (e.g. by providing evidence of prescribed medication or the exact name of medication)

* Median.
** Used one number higher in meta-analysis.
*** Calculated estimate; often an underestimation as when exact upper number was not indicated, e.g. 3+ we used 3.
**** Group regression assumed equal weight for nod = 0 and nod = 1 as no variance was reported for nod = 0.
***** Ruler used to estimate the mean value of the association between QoL and disease groups from the graph.
NR = not reported.
NS = not specified.
EQ – 5D – 3L; – 5L = Euro Quality of Life-3 level; -5 level scale.
SF – 36; – 20; – 12; – 8 = Medical Outcomes Study Short Form.
SF – 6D = Six Dimensions Short Form.
WHOQoL – BREF = shorter variation of World Health Organization Quality of Life scale.
In bold italics – calculated slope using weighted regression based on group level data.
[a] With prevalence > 1%.
[b] Yes, but unclear whether the list was exhaustive.
[c] Weighted mean.

depending on the health domain.

Fifteen studies had excellent quality, scoring 7 or 8 points (Fig. 3). Seven studies scored 4 or 5 points; the main reasons were as in the systematic review description, not complying with or not providing information on quality criteria 5, 3 and 14 (Table 5).

All HRQoL outcomes were rescaled to a range from 0 (worst possible QoL) to 1 (best possible QoL) to allow for comparison. Separate meta-analysis models were fitted for the four QoL instruments included; EQ-5D and SF-6D were measured as a single index score, while we analyzed two summary scores relating to the physical and mental aspects of life separately for the SF and the WHOQoL-BREF. In total, we conducted six base case meta-analysis models. Studies reporting the outcome of interest on more than one scale were included in multiple models.

Results are summarized as forest plots (Figs. 4–9); numerical summaries are displayed in Table 8.

3.4.1.1. EQ-5D health-related quality of life scale. Nineteen studies (Agborsangaya et al., 2014; Agborsangaya et al., 2013; Alonso-Moran et al., 2015; Barra et al., 2015; Ferrer et al., 2010; Gerber et al., 2016; Heyworth et al., 2009; Hodek et al., 2009; Kim et al., 2012; Lang et al., 2015; Li et al., 2016; Mujica-Mota et al., 2015; N'Goran et al., 2017; Peters et al., 2018; Quah et al., 2016; Rabadi and Vincent, 2013; Sakthong et al., 2015; Sullivan et al., 2012; Vogel et al., 2012) with an EQ-5D index score were included in this meta-analysis. Our model estimated an overall decline in HRQoL of −3.88% (95%CI: −5.37%, −2.39%) with each added disease. Heterogeneity was very high as expected (I^2 = 99.79%) (Fig. 4).

3.4.1.2. SF-6D health-related quality of life scale. The analysis of SF-6D included three studies (Barra et al., 2015; Hanmer et al., 2010; Lawson et al., 2013) indicating that HRQoL decreased −4.02% (95%CI: −7.30%, −0.75%) with each added condition. Heterogeneity was again very high I^2 = 99.99% (Fig. 5).

3.4.1.3. SF health-related quality of life scales. Fifteen studies (Cheng et al., 2003; Chin et al., 2016; Fortin et al., 2006; Garrido-Abejar et al., 2012; Hodek et al., 2009; Hu, 2007; Lim et al., 2012; Loza et al., 2009; Luo et al., 2015; Naveiro-Rilo et al., 2014; Prazeres and Santiago, 2016; Rillamas-Sun et al., 2016; Tyack et al., 2016; Williams and Egede, 2016; Xie et al., 2016) were included in the analysis of the physical component of the SF instrument, while 13 studies (Cheng et al., 2003; Fortin et al., 2006; Garrido-Abejar et al., 2012; Hodek et al., 2009; Hu, 2007; Lim et al., 2012; Loza et al., 2009; Luo et al., 2015; Naveiro-Rilo et al., 2014; Prazeres and Santiago, 2016; Tyack et al., 2016; Williams and Egede, 2016; Xie et al., 2016) were included in the mental component score analysis. Results showed that physical health deteriorates −3.27% (95%CI: −4.79%, −1.74%) with each added condition, while the mental health decline was less steep, −1.55% (95%CI: −2.97%, −0.13%). Heterogeneity was I^2 = 99.78% for the physical component and I^2 = 99.53% for the mental component (Figs. 6 and 7).

3.4.1.4. WHOQoL-BREF quality of life scale (physical and mental domain). This analysis included four studies (Gambin et al., 2015; Panagioti et al., 2018; Tuzun et al., 2015; Winkler et al., 2006). Overall decline in QoL per additional disease was estimated as −4.37% (95%CI: −7.13%, −1.61%) for the physical domain, and a smaller effect was observed for the mental domain, −1.57% (95%CI: −2.70%, −0.44%). Heterogeneity was I^2 = 97.34% for the physical domain and I^2 = 92.31% for the mental domain (Figs. 8 and 9).

3.4.2. Meta-regression

Meta-regression was possible only for studies with EQ-5D and SF non-preference based questionnaires due to the small number of studies for the remaining QoL instruments. Confounders considered were mean age, proportion female, mean number of diseases per patient, total number of diseases considered in a study, study quality and whether the analysis within each study was adjusted. Different confounders appeared significant for different HRQoL outcomes, however the direction of the effect was the same across the outcomes for all confounders.

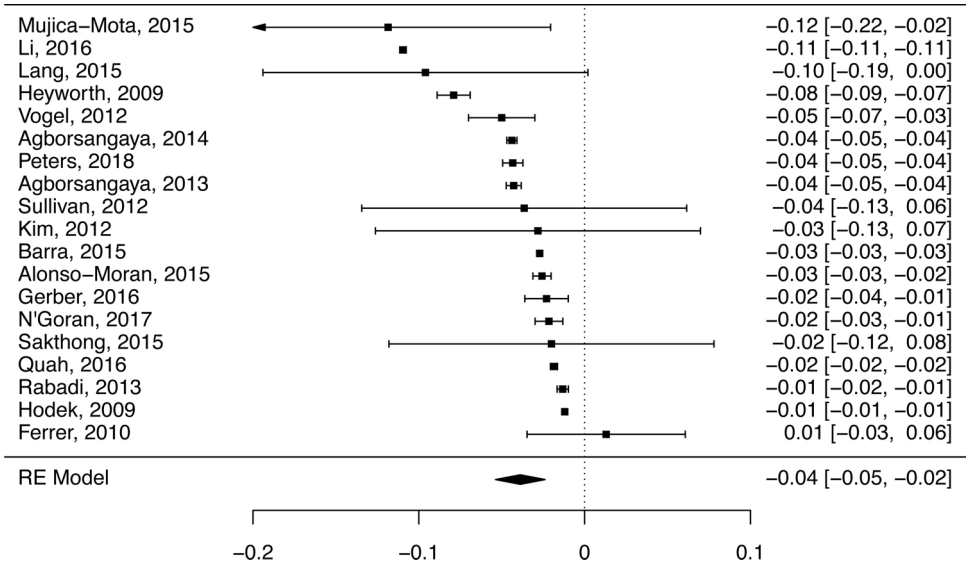

Fig. 4. Meta-analysis on studies with EQ-5D health-related quality of life scale.

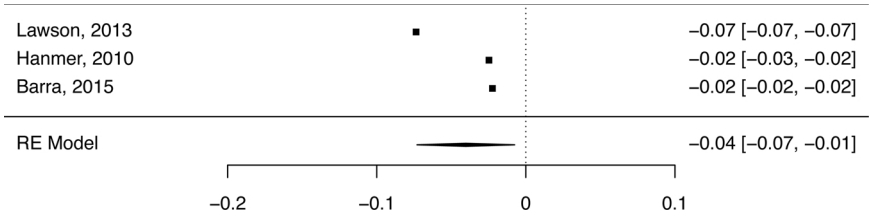

Fig. 5. Meta-analysis on studies with SF-6D health-related quality of life scale.

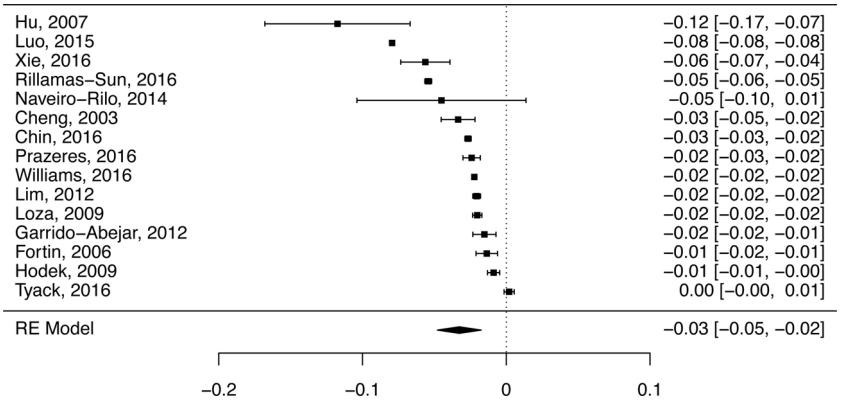

Fig. 6. Meta-analysis on studies with SF physical component score.

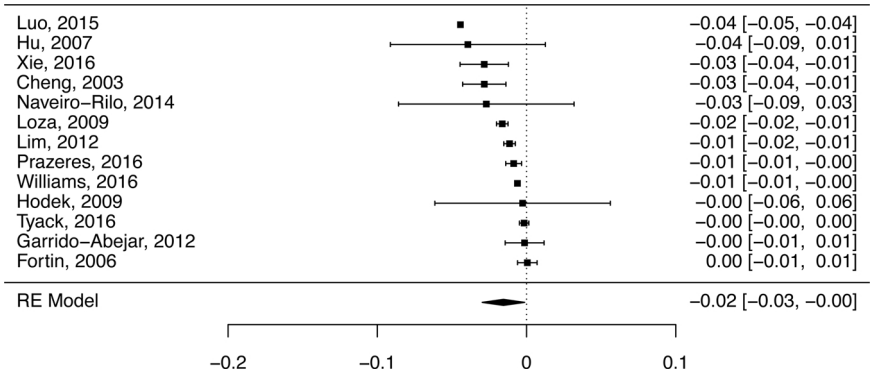

Fig. 7. Meta-analysis on studies with SF mental component score.

The impact on HRQoL seemed stronger for females; however, a significant effect of sex was only observed for the two SF scales. Older age was associated with a less steep reduction in HRQoL with increasing number of diseases, but only when measured using the EQ-5D. Adjusted analyses were also associated with a less steep reduction, showing a significant association for both SF scales. A reduced impact on HRQoL was observed for studies of higher quality, but only for the physical summary component of the SF questionnaires. The average number of diseases per patient, as well as the number of diseases considered per study did not appear significant in any analysis. Details are presented in Table 9.

3.4.3. Scenario analyses

The first scenario only included studies of the highest quality, scoring 7 or 8 points. The minimum number of studies for this analysis was met for the EQ-5D (Alonso-Moran et al., 2015; Ferrer et al., 2010; Quah et al., 2016) and SF physical (Cheng et al., 2003; Chin et al., 2016; Fortin et al., 2006; Hu, 2007; Lim et al., 2012; Loza et al., 2009;

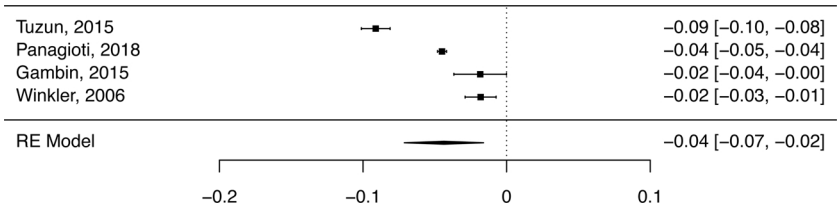

Fig. 8. Meta-analysis on studies with WHOQoL-BREF physical domain.

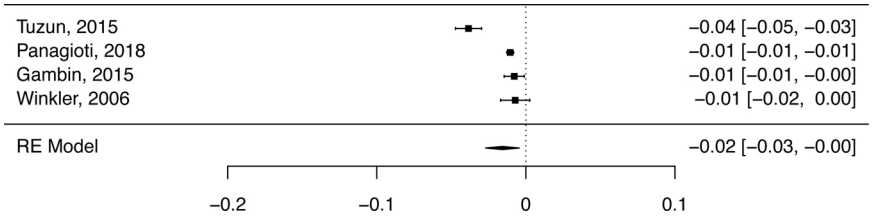

Fig. 9. Meta-analysis on studies with WHOQoL-BREF mental domain.

Table 8
Summary meta-analysis table.

	EQ – 5D	SF physical component score	SF mental component score	SF – 6D	WHOQoL – BREF physical domain	WHOQoL – BREF mental domain
Slope	−0.0388	−0.0327	−0.0155	−0.0402	−0.0437	−0.0157
95%CI	−0.0537, −0.0239	−0.0479, −0.0174	−0.0297, −0.0013	−0.0730, −0.0075	−0.0713, −0.0161	−0.0270, −0.0044
I^2	99.79%	99.78%	99.53%	99.99%	97.34%	92.31%

Table 9
Summary meta-regression table; slope (95%CI).

	EQ-5D	SF physical component score	SF mental component score
MR1: Sex	−0.0003 (−0.0011, 0.0006)	***−0.0010 (−0.0014, −0.0006)***	***−0.0006 (−0.0010, −0.0003)***
MR2: Age	***0.0010 (0.0005, 0.0014)***	0.00 (−0.0018, 0.0016)	0.00 (−0.0015, 0.0016)
MR3: Average number of diseases per patient	0.0079 (−0.0020, 0.0177)	0.0062 (−0.0038, 0.0163)	0.0033 (−0.0054, 0.0119)
MR4: Total number of diseases considered	0.0003 (−0.0007, 0.0013)	0.0001 (−0.0003, 0.0006)	0.0001 (−0.0003, 0.0005)
MR5: Adjusted analyses	0.0066 (−0.0171, 0.0303)	***0.0490 (0.0231, 0.0748)***	***0.0345 (0.0234, 0.0456)***
MR6: Study quality	0.0472 (−0.0613, 0.1557)	***0.1089 (0.0074, 0.2097)***	0.0860 (−0.0004, 0.1724)

In bold italics – significant effect.

Prazeres and Santiago, 2016; Tyack et al., 2016; Williams and Egede, 2016; Xie et al., 2016) and mental summaries (Cheng et al., 2003; Fortin et al., 2006; Hu, 2007; Lim et al., 2012; Loza et al., 2009; Prazeres and Santiago, 2016; Tyack et al., 2016; Williams and Egede, 2016; Xie et al., 2016). Estimates of the overall decline in HRQoL per additional disease were smaller compared to the base case analysis. The EQ-5D analysis showed a decline of −2.09% (95%CI: −2.82%, −1.35%) now, nevertheless the number of included studies was significantly smaller. SF physical and mental scores showed a decline of −2.25% (95%CI: −2.80%, −1.70%) and −0.99% (95%CI: −1.43%, 0.55%), respectively.

The second scenario analysis only included studies where both the number and list of diseases were clearly provided (Agborsangaya et al., 2013, 2014; Alonso-Moran et al., 2015; Gerber et al., 2016; Heyworth et al., 2009; Hodek et al., 2009; Kim et al., 2012; Lang et al., 2015; Li et al., 2016; Mujica-Mota et al., 2015; N'Goran et al., 2017; Peters et al., 2018; Quah et al., 2016; Sakthong et al., 2015; Vogel et al., 2012) for EQ-5D, (Cheng et al., 2003; Chin et al., 2016; Garrido-Abejar et al., 2012; Hodek et al., 2009; Hu, 2007; Li et al., 2016; Loza et al., 2009; Luo et al., 2015; Prazeres and Santiago, 2016; Rillamas-Sun et al., 2016; Tyack et al., 2016; Williams and Egede, 2016; Xie et al., 2016) for the SF physical component score, and (Cheng et al., 2003; Garrido-Abejar et al., 2012; Hodek et al., 2009; Hu, 2007; Loza et al., 2009; Luo et al., 2015; Prazeres and Santiago, 2016; Tyack et al., 2016; Williams and Egede, 2016; Xie et al., 2016) for the SF mental component score. This analysis showed a slight increase of the mean estimate (more obvious for EQ-5D). Heterogeneity in the scenario analyses remains high. Details are summarized in Table 10.

Table 10
Scenario analyses.

	EQ-5D	SF physical component score	SF mental component score
SA1: high quality only	−0.0209 95%CI:(−0.0282, −0.0135) I^2 = 73.47%	−0.0225 95%CI:(−0.0280, −0.0170) I^2 = 96.12%	−0.0099 95%CI:(−0.0143, 0.0055) I^2 = 87.10%
SA2: proper definition only	−0.0458 95%CI:(−0.0699, −0.0217) I^2 = 99.83%	−0.0350 95%CI:(−0.0526, −0.0175) I^2 = 99.83%	−0.0173 95%CI:(−0.0338, −0.0008) I^2 = 99.63%

4. Discussion

4.1. Summary of findings

This systematic review identified a substantial number of studies evaluating the association between multimorbidity and QoL (or HRQoL). The vast majority of studies were cross-sectional. They were mainly performed in high-income countries, in non-hospital settings and in the elderly population with mean age between 70 and 80 years (n = 26 studies). Representation of both sexes was good.

While most of the studies did not specify the definition of multimorbidity used, some defined multimorbidity as the co-occurrence of two or more or rarely three or more diseases. Multimorbidity measurements varied, but a simple disease count was most frequent. The total number of conditions considered per study as well as the mean number of diseases per patient differed significantly. Most authors used a predetermined list of diseases and collected participant information using self-reporting. Cardiovascular diseases were most represented, followed by diabetes, musculoskeletal system disorders, respiratory system disorders, cancer and mental health disorders. The majority of studies adjusted for confounders, however the set of confounders varied across studies. The severity of diagnoses was very often not assessed.

The systematic search comprised of studies using both QoL and HRQoL scales. Nevertheless, we can specify that our meta-analysis addressed health aspects of QoL due to the health-related scales or health domains used. The most common scales appearing in the search were the SF and EQ-5D.

In line with other systematic reviews (Fortin et al., 2004; Kanesarajah et al., 2018; Marengoni et al., 2011), our results corroborate previous evidence on association of multimorbidity with poor QoL. Moreover, our meta-analysis showed a coherence between preference-based scales on one side, and physical and mental domains of non-preference based QoL scales on the other side. Both preference based scales (EQ-5D and SF-6D) presented approximately the same mean deterioration of HRQoL with each added condition. However, uncertainty in the outcome of the SF-6D scale was much higher as expected, due to the smaller number of studies included and the discrepancy in their findings. The decline displayed by the non-preference based scales (SF and WHOQoL-BREF) was stronger for physical health compared to mental. Further, the physical health decline appeared steeper when measured by the WHOQoL scale. The deterioration of mental health was milder on both scales. Mental health problems were in general quite well represented in our systematic review (38 studies). Therefore, we believe that underrepresentation of mental conditions is not likely the reason for this finding. It could be that patients under-reported their psychological problems having feared their social acceptance, as described by Fortin et al., 2006 (Fortin et al., 2006). Psychological adaptation of a patient to a health change (Walker et al., 2004), or potentially limitations of measurement tools to capture the change on psychological domain for multimorbid patients may also be a factor. A stronger inverse relationship between multimorbidity and physical QoL domains was previously noted (Fortin et al., 2004; Hodek et al., 2010).

Heterogeneity in the dataset was very high, as illustrated by the high I^2 statistics in all analyses. High statistical heterogeneity was caused by methodological and clinical heterogeneity between the studies, such as the differences in baseline demographics as well as the evaluation of multimorbidity and QoL.

Meta-regression was performed to elucidate possible explanations, keeping in mind that meta-regression can identify potential reasons for heterogeneity but does not allow firm conclusions to be drawn (Thompson and Higgins, 2002). We were not able to test all the variables of interest as we were limited to what was reported across the studies and how. We found general agreement across HRQoL measures as the direction of effect was the same across all measures for each explored covariate; nevertheless, none of the confounders was found to be significant across all outcomes. The decline in HRQoL with increasing multimorbidity burden was stronger in younger populations (significant for EQ-5D). Potential reasons may be an adaptation of patients to their conditions over time with enhanced resilience, or lower expectations as age increases (N'Goran et al., 2017). While previous systematic reviews did not find firm evidence for sex differences of multimorbidity impact on HRQoL (Fortin et al., 2004; Kanesarajah et al., 2018), our meta-analysis indicated the association to be stronger for females (significant for SF physical and mental score).

The adjustment for confounders as well as high study quality appeared to be associated with a lesser decline in HRQoL (significant only using SF scales). We found no association with the mean number of diseases or number of diseases considered in the study. The high heterogeneity in the reporting and measurement of diseases across the studies may have interfered with the measurement of an effect.

Scenario analysis performed only on studies with the highest quality, showed a smaller decline of HRQoL for all outcomes. Use of proper operationalization of multimorbidity with a specified number and list of diseases did not impact the association to a large extent.

The assessment of a publication bias was limited to EQ-5D and SF analyses due to the small number of trials with the other outcomes. By using a funnel plot, publication bias was not proven for these two outcomes.

We are aware of the uncertainty of performing meta-analysis on observational studies (Egger et al., 1998), yet having prudently evaluated the possible reasons for heterogeneity, we believe that our meta-analysis produces valuable summary estimates for the average impact of an increasing number of diseases on HRQoL. We were able to produce the first solid pooled quantitative estimate of a HRQoL decline based on a vast amount of data. Further, the analysis strengthened previous indications that physical domains are affected more strongly, and highlighted that females and younger population groups may need more consideration when it comes to dealing with an increasing multimorbidity burden.

4.2. Strengths and limitations

This is the most comprehensive review on the association between multimorbidity and QoL performed to date, which provided the very first quantitative pooled estimate.

The study was not restricted to age, setting, language or date of publication, with the aim to encompass all relevant literature, thus

producing a solid overview of the current knowledge on the subject. The study identified a spectrum of multimorbidity and QoL measurements and the approaches most frequently used to explore their association. It indicated the preferred study design and settings. It displayed the most often applied methods to assess and report multimorbidity, and identified which diseases were considered most frequently. The study highlighted the increasing interest in the topic over the last two decades.

Nevertheless, a number of limitations need to be mentioned. Only studies evaluating multimorbidity as a disease count could be included in the meta-analysis. While the number of diseases can provide an estimate of the disease burden (Fortin et al., 2006), it does not take into consideration the severity of diagnosis. Meta-analysis of studies evaluating multimorbidity using tools which account for severity would allow the estimation of the impact of a number of diagnoses coupled with severity on HRQoL. As suggested earlier (Fortin et al., 2006) this association may be stronger, as the incorporation of severity could provide a more differentiated view on disease burden. Our meta-analysis also only included studies conducted in a non-hospital setting, precluding the comparison with multimorbid hospitalized patients as initially planned.

Another important restraint was the heterogeneity in the number of diseases considered per study. We reported as the total number of diseases, the number given by authors, but diseases were formulated differently. For instance, authors would on occasion list very specific conditions (e.g. diabetes, stroke, hypertension, etc.), while in other cases a group of diseases (e.g. heart diseases) was counted as one condition. The latter method may have led to underestimation of the total number of disease we considered in the study. Further, the mean number of diseases per patient varied extensively.

Also, we did not distinguish between the terms condition and disease in our study. This is a matter of a larger ongoing discussion in the field and was not the focus of this paper.

Predetermined lists of diseases and self-report were the most common ways of assessing multimorbidity. Predetermined lists may have limited the number and type of conditions and prevented reporting other diseases potentially existing in a patient. Some authors argue that medical records are the most reliable source for estimating disease burden (de Groot et al., 2003), but there is supportive evidence that self-report also provides a solid estimate (Bayliss et al., 2005). The level of reporting detail in medical records also depends on a country's coding system.

Time of living with a medical condition was not part of the evaluation. It was recognized earlier (Busija et al., 2017; Sparring et al., 2013) that a long duration of illness in chronic patients has a negative impact on QoL, but the association is not static. Data on this is particularly scarce in multimorbid patients. Longitudinal studies and focused questions assessing the time since diagnoses may assist in providing more information, as well as subgoup analyses accounting for age, sex and types of diseases.

Even though many studies adjusted for confounders, a significant number missed to adjust. In addition, the types of confounders considered differed. This contributed to the heterogeneity in our findings. Study quality was variable and our sensitivity analysis including only high quality studies highlighted the potential overestimation of the impact on HRQoL in studies of a lesser quality.

Lastly, we assumed a linear relationship between an increasing number of diseases and HRQoL. While there is evidence of multiplicative effects of multimorbidity on health (Di Angelantonio et al., 2015), Barra et al. (2015) concluded an equal performance of additive and multiplicative models for the relationship of multimorbidity and QoL. The most commonly proposed model in the studies was a linear model, which is why we chose a linear relationship for our analysis. Nevertheless, additional analyses investigating alternative models could provide an improved fit.

4.3. Recommendations for policy and practice

Care for patients with multimorbidity is complex and may account for up to two thirds of health care expenditures (Johns Hopkins Bloomberg School of Public Health, 2010; Ontario Ministry of Health and Long-Term Care). Some of this cost is avoidable and is due to uncoordinated care of this patient group, duplications of tests and unnecessary hospitalizations (Johns Hopkins Bloomberg School of Public Health, 2010). Health care systems are still largely single disease oriented and lack clinical guidelines for multimorbidity (Barnett et al., 2012a; Salisbury et al., 2011; Uhlig et al., 2014). Patients with multiple conditions are obliged to visit numerous health care providers and follow treatments with sometimes conflicting recommendations (Johns Hopkins Bloomberg School of Public Health, 2010). Treatment burden together with disease burden further impacts patient QoL (Sav et al., 2015). There is a recommendation that QoL should be evaluated, among others as a crucial quality of care indicator for multimorbid patients (Colombo et al., 2016). Future practice should aim to organize care for patients with multiple health care needs more efficiently, and to actively involve patients in planning their care. National Institute for Health and Care Excellence (NICE, 2016) provides a comprehensive guideline on how to clinically assess and manage care for multimorbid patients, paying particular attention to improving patent QoL.

Multimorbidity is rarely taught in medical education (Lewis et al., 2016), let alone QoL per se. Both should be part of the curriculum in order to prepare future health forces for growing challenges.

Also, it can be observed that the vast majority of studies are performed in high-income countries, specifically in North America and Western Europe. This perhaps is not a surprise, but it provides a map of current efforts and growing expertise. It might also serve as a call to middle- and low-income regions where life expectancy is increasing at a higher rate (WHO, 2011). These countries might soon catch up with better off nations in terms of additional health and societal challenges associated with an ageing society. This could further burden their health systems if not addressed in a timely manner.

4.4. Recommendations for further research

Our systematic review revealed a good deal of published evidence on the relationship between multimorbidity and QoL. Meta-analysis confirmed the negative effect of an increasing multimorbidity burden. However, more research into the role of heterogeneity is required.

Considering that HRQoL had a stronger decline in younger populations, and the already existing evidence that multimorbidity in absolute numbers imposes the highest burden among those younger than 65 years (Barnett et al., 2012b; Stewart et al., 2014), future research should give more attention to co-occurrence of conditions among younger groups to identify and manage their needs earlier. This could potentially prevent or at least postpone the onset of new diseases, and optimize care to respond better to their goals and preferences in order to enhance QoL.

Females were well represented in the studies, though very few focused on potential differences in QoL between sexes. Prevalence and patterns of multimorbidity differ between men and women (Abad-Diez et al., 2014), but little is known about how different their experiences are. This may be useful in helping tailoring care and prevention services to respond better to sex difference.

The spectrum of diseases across studies was large. It could be worthwhile to look into the occurring patterns of diseases and their particular relationship with QoL. This could possibly help to anticipate the onset of new conditions, and in parallel patient needs. Consequently, it may allow the organization of health care in a more efficient manner.

Very few longitudinal studies were identified in our review. With the aim to assess changes in the impact multiple conditions may have on patient QoL over time, additional longitudinal studies as well as

clinical trials are warranted.

Authors should ensure that variables which may mitigate the relationship between multimorbidity and QoL are properly accounted for, and that protocols for study quality are followed. This would enable better comparability between the studies and more precise estimation of the impact. Based on previous research, at a minimum analysis should be adjusted for age, sex, household income, education, self-perception of economic status and perceived social support (Fortin et al., 2006; Vogel et al., 2012). Employment could have more significance for younger population groups. Severity and duration of diseases are essential to consider as they provide a good estimate of individual disease burden.

Very few studies adjusted for behavioural habits like smoking and physical activity. There is some evidence on the association of lifestyle factors and multimorbidity (Fortin et al., 2014), and much more on lifestyle factors and QoL (Berra, 2003; Mosher et al., 2009). Thus considering behavioural factors as confounding may be beneficial. Furthermore, none of the studies considered treatment burden in their analysis. Although a relatively new concept in the literature, treatment burden is particularly abundant in patients with multiple conditions and can impact their QoL (Duncan et al., 2018). Therefore, for example multiple visits to health professionals and use of several medications should be considered when addressing this research question.

Including a definition of chronic diseases in their methodology and using one of the international coding systems when selecting diseases would additionally facilitate the comparability between studies.

Finally, few qualitative studies (Jeon et al., 2012; Lowe and McBride-Henry, 2012; Sefcik et al., 2016; Slightam et al., 2018; White et al., 2016) identified during the review process reflected on the challenges of multimorbid patients to manage daily activities, to comply with demanding treatments, particularly with changing health status where priorities may alternate between the conditions, or financial and social impact of multimorbidity. Studies have nevertheless also mirrored patients' determination and creativity in adapting. They showed how adjusting personal goals and having the means and support to do so, may help in sustaining satisfying QoL. Therefore, bearing in mind the subjectivity in assessing QoL and that scales cannot always capture what may be important to a patient, seizing individual experiences living with multiple conditions through qualitative studies is encouraged.

5. Conclusion

Quality of life decreases with an increasing number of diseases. Physical health seems to be impacted more than mental. Longitudinal studies and clinical trials using validated multimorbidity tools which account for severity and duration of disease may be useful for better clarifying the impact multimorbidity has on QoL. Focusing on patterns of diseases may provide valuable information for focused, patient group policy planning. As age and sex are relevant, additional attention should be given to assessing particular needs across different age and sex groups.

Consideration of patient QoL and creating personalized objectives should be a daily practice in the management, planning and evaluation of health care in the context of multimorbidity.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.arr.2019.04.005.

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