

Accepted Manuscript

Title: Multimorbidity and quality of life at mid-life: A systematic review of general population studies

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PII: S0378-5122(17)30998-2
DOI: <https://doi.org/10.1016/j.maturitas.2017.12.004>
Reference: MAT 6926

To appear in: *Maturitas*

Received date: 27-10-2017
Revised date: 24-11-2017
Accepted date: 5-12-2017

Please cite this article as: Kanesarajah Jeeva, Waller Michael, Whitty Jennifer A, Mishra Gita D. Multimorbidity and quality of life at mid-life: A systematic review of general population studies. *Maturitas* <https://doi.org/10.1016/j.maturitas.2017.12.004>

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Multimorbidity and quality of life at mid-life: A systematic review of general population studies**Short title:** HrQoL and multimorbidity at midlife*Jeeva Kanesarajah^{a*}, Michael Waller^a, Jennifer A Whitty^{b,c}, Gita D Mishra^a*^a School of Public Health, The University of Queensland^b School of Pharmacy, The University of Queensland^c Norwich Medical School, University of East Anglia, Norwich, UK

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Highlights

- There is substantial multimorbidity at mid-life but little is known about the strength of evidence on multimorbidity and health-related quality of life (HrQoL) at mid-life in the general population. Eight articles, from four databases, were identified for review.
- Multimorbidity is consistently associated with poorer HrQoL at mid-life.
- Two cross-sectional studies found that adults with multimorbidity at early mid-life reported poorer HrQoL than adults with multimorbidity at late mid-life, while another found the reverse.
- Two distinct disease clusters were identified: mental health conditions, and cardiovascular disease (CVD). Those in the mental health cluster reported poorer HrQoL than those in the CVD cluster at mid-life.
- Limitations of the selected studies include lack of longitudinal evidence, use of self-reported conditions and no assessment of disease severity or trajectory. Future research using a weighted disease severity index and multimorbidity trajectories based on longitudinal data is needed.

Abstract

There is substantial multimorbidity at mid-life but little is known about the strength of evidence on multimorbidity and health-related quality of life (HrQoL) at mid-life. This review addresses this gap, focusing on studies of the general population. PubMed, Web of Science, Embase and APA PsycNET databases were screened on 6 March 2017 for original research on multimorbidity and HrQoL in adults aged 40-65 years from the general population. Studies focused on index conditions, using single-item HrQoL measures, unlikely to represent the general population (e.g. primary care), and papers that were not in the English language were excluded. A narrative synthesis was presented due to heterogeneity in the measurement of multimorbidity. Of the 2557 articles, 83 underwent full text screening and 8 were included in the review. Included studies were of moderate to high quality and no exclusions were made on the basis of quality or bias. Multimorbidity was associated with poorer HrQoL at mid-life. Two cross-sectional studies found that adults with multimorbidity at early mid-life reported poorer HrQoL than adults with multimorbidity at late mid-life, while another found the reverse. Two distinct disease clusters were identified: mental health conditions and cardiovascular disease (CVD). Those in the mental health cluster reported poorer HrQoL than those in the CVD cluster, women more so than men. Limitations of the selected studies include lack of longitudinal evidence, use of self-reported conditions and no assessment of disease severity. Multimorbidity is associated with poor HrQoL at mid-life at the population level, with some evidence of differences in association with age and disease cluster and sparse evidence on sex differences. Longitudinal research using a weighted disease severity index and multimorbidity trajectories is needed to strengthen the evidence base.

Keywords: Health-related quality of life; multimorbidity; middle age; general population

1. Introduction

Multimorbidity, the co-occurrence of at least two health conditions in an individual [1-6], is an increasing health problem. It is brought about by population aging, unhealthy lifestyle habits, emerging chronic conditions, reduced mortality from improved medical care and technologies, and earlier detection and treatment of conditions [7]. Globally, multimorbidity prevalence is estimated to be between 3.5% and 100% [8]. The large variation in estimates observed is driven by differences in definition and measurement of multimorbidity, population setting, participant age range, and country income levels [9]. Despite this, there is consensus that multimorbidity represents significant and growing burden to society [7]. Increased multimorbidity burden can lead to greater complexity in patient health management, reduced health related quality of life (HrQoL), and increased health care use and costs [10-12].

While multimorbidity is common in older adults, studies have shown that those under 65 years old also experience a substantial multimorbidity burden [1, 13, 14, 15]. A recent systematic review highlighted a 'S' shape curve of multimorbidity prevalence with age [2], where prevalence increased steeply at mid-life, and plateaued in those age 75 years and above. The onset of conditions at mid-life may affect HrQoL. Previous systematic reviews on multimorbidity and HrQoL have focused on primary care populations [12, 16] or older adults (age 65+) [17] and have shown that multimorbidity is negatively associated with HrQoL in these populations. However little is known on the strength of evidence on multimorbidity and HrQoL at mid-life or at the general population level. Given the substantially higher prevalence and disease burden of multimorbidity in primary care compared to the general populations [18], there is a need for synthesis of evidence at a population level to assist in health service planning.

It is unclear whether multimorbidity rates differ between males and females. The prevalence of multimorbidity is slightly higher in females compared to males, however findings are inconsistent [7, 14, 19]. Some patterns of multimorbidity differ between males and females [19]. For example, depressive symptoms are more common in females while psychiatric and substance abuse is more common in young males [19]. These sex differences in prevalence and patterns of multimorbidity coupled with the onset of conditions at midlife may modify the association between multimorbidity and HrQoL.

This review aims to quantify the relationship between multimorbidity and HrQoL at mid-life, at the population level. It will clarify whether the relationship is consistent between sexes, for different methods to measure multimorbidity, and between preference weighted and non-preference weighted HrQoL instruments.

2. Methods

2.1 Protocol and registration

The corresponding review protocol is registered at PROSPERO ([CRD42017056911](#)).

2.2 Study Selection

This review focused on original quantitative epidemiological research that evaluated the association between multimorbidity and HrQoL in mid-age adults (aged 40 to 65 years) in the general population. We also included cohort or cross-sectional studies on adults where separate estimates of multimorbidity and HrQoL were available for adults aged 40-65 years. For the purpose of this review, multimorbidity is defined as “multiple acute or chronic medical and/or psychiatric conditions which may or may not be related” [1-4]. Studies using validated measures of HrQoL which encapsulate multiple dimensions (e.g. physical function and psychological health) with multimorbidity definitions consistent with this review were considered eligible for inclusion.

2.3 Search strategy

Primary searches were conducted using PubMed, Web of Science, Embase and APA PsycNET databases, illustrated in Figure 1. Relevant studies available on 6 March 2017 were extracted from each database. Initial searches for each topic (multimorbidity, quality of life, adult, middle age, general population) were conducted separately, using a combination of keywords and subject headings (MeSH/Emtree/Thesaurus) terms (Supplementary data, Table A). Existing literature were used to identify common and popular keywords [1, 20]. Variants of terms including mis-spellings were also used as search terms (Supplementary Table A). As some studies use comorbidity to mean multimorbidity, keywords on “Co-morbidity” were also included in the search to capture all relevant literature. Parallel strategies were used to identify studies on quality of life, adults, at mid-life and from community settings. Search results were then combined using Boolean terms (Supplementary data, Supplement 1).

2.4 Selection Criteria

One reviewer performed the 'Title-Abstract' screening process (JK), where literature was refined based on inclusion and exclusion criteria. Only peer reviewed articles published or were in-press were considered. No language or document type distinction was applied during the search. However, only original articles written completely in English were considered for full text screening, to ensure uniform level of comprehension of the articles. Full text were screened based on the inclusion and exclusion criteria to further refine the literature.

Inclusion criteria:

- 1) Original peer reviewed published or in-press research written in English
- 2) Studies conducted in the general population that estimated the association between multimorbidity and HrQoL in mid-age adults (aged 40 to 65 years).
- 3) Studies consistent with the definition of HrQoL and multimorbidity described

Exclusion criteria:

- 1) Studies on single health conditions or focused on an index condition
- 2) Studies unlikely to represent the general population (e.g. primary care, clinical setting, or specific patient or user populations)
- 3) Studies which used single item self-rated health instrument to measure HrQoL

2.5 Critical appraisal

The critical appraisal of original papers was conducted independently by two reviewers (JK and MW) based on evaluation criteria adapted from Fortin et al. [12], used to assess for methodological quality (Supplementary data, Supplement 2). Each article was scored out of 30, based on criteria on originality, population studied, definition and measurement of multimorbidity and HrQoL, and limitations of the study. Risk of bias was assessed using an adapted version of the Newcastle-Ottawa Scale(NOS) [21] (Supplementary data, Supplement 3) suitable for observational studies, with good reliability and face validity [22]. Studies with scores of at least 15 out of 30 using the Fortin checklist, and 4 out of 9 stars using the NOS were eligible for data extraction and synthesis. There were no disagreements between the two reviewers eligibility of the included studies.

2.6 Data extraction

Data eligible for synthesis were extracted using a pre-defined questionnaire (see Supplementary Data, Supplementary Methods). The prevalence of multimorbidity defined as the presence of two or

more conditions (MM2+) or three or more conditions (MM3+) were reported. Multimorbidity prevalence is associated with aging [8]. Hence to ensure fair comparisons between studies when reporting prevalence of multimorbidity and its association with HrQoL, studies were grouped based on whether they were from adult populations spanning young to late adult life (Adult studies, age 16+, n=5) [23-27] or studies focused at mid-life (Mid-life studies, age 40+, n=3) [28-30]. Prevalence specific to mid-life (age 40-65 years), and gender were reported where possible. However, as few studies report prevalence of multimorbidity specific to mid-life, overall prevalence in the study was presented to give an indication of the heterogeneity of multimorbidity across studies. Estimates on the association between multimorbidity and HrQoL (mean or mean difference), overall, and by life-stage and gender were extracted where available. Due to substantial heterogeneity in the measurement of multimorbidity and in association with HrQoL, and 'mid-life' age groups across studies, meta-analysis was not performed, instead a narrative synthesis is presented. Additional details on data extracted for synthesis are available at Supplementary data, Supplement Methods.

3. Results

3.1 Study Selection: Overall description of screening/assessment process

A total of 3698 articles were identified from the four databases, and 2557 were screened based on title and abstract (Figure 1). After full text screening and quality and risk of bias assessment, 8 articles were included in the review, of which one article was identified from the reference list of an included article. All articles included in synthesis were moderate to high quality based on the Fortin and NOS assessments (Table 1). No articles were excluded on the basis of quality or risk of bias. During quality assessment, the main limitations with most studies were lack of results stratified by gender, insufficient or lack of information on non-responders or drop outs, and insufficient discussion of the limitations of the research. Common biases include lack of information on non-responders, exposure information obtained from self-report, and the outcome of interest was present at the start of the study.

3.2 Overall descriptions of studies

Of the eight articles included in the review, three were from United States [26, 28]. Other studies were from Australia [27], New Zealand [30], France [29], Canada [25], Denmark [23] and Scotland [24] (Table 1). All studies were cross-sectional design (n=8). Data collection years ranged from 2001 to 2013 while study sample sizes ranged from 1710 people to 47178. The majority of studies

included both genders (n=6, % female: 50.4-59.5), one studies was exclusively undertaken in female populations [28], while another reported it was a representative sample from the Scottish population but did not report gender balance [24]. Percentages of mid-age adults in these studies ranged from 31% to 100%. There was some heterogeneity in age ranges for 'mid-life' age groups across studies, however within age range of 40-65. All eight studies used a validated, multi-domain instruments to measure HrQoL, four used preference based HrQoL measures (AQoL-4D, SF-6D, EQ-5D-3L).

3.3 Multimorbidity measurement

Multimorbidity was generally consistently defined as "the presence of two or more co-existing medical conditions" across four of the five studies which reported a definition for multimorbidity [25-27, 29] (Table 1). Lawson et al defined multimorbidity as the presence of two or more longstanding conditions from different systems of the body [24]. All studies used one data source (self-report surveys) to describe multimorbidity. Number of conditions used to define multimorbidity varied widely, from 6 to 118 conditions. Seven studies reported including only chronic conditions [24-30]. Two studies did not report a list of conditions used to define multimorbidity [26, 30]. The remaining six studies included both physical and mental health conditions [23-25, 27-29]. While one study used the Disease Burden Morbidity Assessment instrument to measure multimorbidity [25], most studies used a predefined list (n=7) to measure multimorbidity, using either self-reported conditions checklists or in combination with validated screening instruments.

All studies used a count of conditions method to measure multimorbidity (Table 1). There was heterogeneity in how counts were grouped: 2+ vs < 2 conditions; 3+ vs < 3 conditions; 0, 1, 2, 3+ conditions; 0, 1, ..., 9, 10+ conditions. Two studies also examined clusters of conditions [27, 29], with one calculating a disease association score which represent the number and strength of association between conditions within each cluster [29]. There were no studies that weighted for disease severity or described multimorbidity trajectories.

Common chronic conditions included in nearly every multimorbidity list were cancer, stroke, diabetes, asthma, cardiovascular conditions (including hypertension), chronic obstructive pulmonary disease (COPD), mental health conditions (including depression and anxiety), arthritis conditions, osteoporosis, migraine/headaches, hearing impairment, allergies/hay fever and back pain (data not shown). One study included overweight or obesity ($BMI \geq 25 \text{ kg/m}^2$) as a condition [25] which was highly prevalent (58.5%). Of the four studies which reported prevalence of individual conditions, the prevalence of arthritis (n=2; %: 19 to 41), vision impairment (n=2; %: 8 to 40), osteoporosis (n=2; %:

9 to 31), asthma (n=2; %: 10 to 20) were heterogeneous across studies. There was less variation in the prevalence of hypertension (n=3; %: 24 to 28), and depression (n=3; %: 7 to 13).

3.4 The prevalence of multimorbidity measured using count of conditions indices and the association between HrQoL and multimorbidity

When multimorbidity was measured using count of conditions, mid-life studies generally reported higher prevalence of multimorbidity compared to adult studies (Table 2). Within each study, the prevalence of MM3+ was markedly lower compared to MM2+ in both study types, and across number of conditions groups [25, 27-29]. Differences in prevalence based on sex were observed, but direction was inconsistent in both population types [25, 27, 29]. Comparisons of multimorbidity prevalence in mid-life age range (40-65), in both population types, show that multimorbidity prevalence increases with age in mid-life [25, 27, 29].

3.4.1 Association between HrQoL and multimorbidity at mid-life

Seven of the eight studies examined the association between multimorbidity, measured using count of conditions and HrQoL [23-28, 30]. Multimorbidity was consistently associated with poorer HrQoL in the mid-life period, in adult and mid-life studies (Table 3). Findings were consistent amongst studies that reported preference weighted and non-preference weighted measures of HrQoL. Two cross-sectional studies found that adults with multimorbidity in early mid-life years reported poorer HrQoL than those at late mid-life years (Wang et al, mean AQoL-4D age 46-55 vs 56-65: MM 2+ 0.68 vs 0.73; MM3+ 0.57 vs 0.66) [23, 27]. However, another cross-sectional study found that adults with multimorbidity in late mid-life report significantly poorer HrQoL than those in early mid-life [26]. None examined sex differences in the association between multimorbidity and HrQoL at mid-life.

3.5 The prevalence of multimorbidity measured using multimorbidity cluster indices, and the association between HrQoL and multimorbidity

Wang et al. examined clusters of conditions at a general population level and found a *Cardiovascular disease (CVD)/Arthritis* cluster (prevalence 9.1%) and a *Major depressive disorder (MDD)/Anxiety* cluster (prevalence 4.3%) [27]. On average, those in the *MDD/Anxiety* cluster were younger than those the *CVD/Arthritis* cluster (mean age 63.8 vs 41.7 years). The prevalence of each cluster was similar between males and females. At mid-life, those with the *MDD/Anxiety* cluster of conditions reported markedly poorer HrQoL compared to those with the *CVD/Arthritis* cluster of conditions. At mid-life, those age 46-55 with *CVD/Arthritis* experienced poorer HrQoL, compared to those age 56-65 (mean AQoL-4D age 46-55 vs 56-65: 0.68 vs 0.72), while for those with *MDD/Anxiety*, this

relationship was reversed with those at early mid-life experiencing poorer HrQoL (mean AqoL-4D age 46-55 vs 56-65: 0.49 vs 0.44). Sex differences were not examined in this research.

Walker et al, using data from a mid-age population, found two clusters: cluster 1, predominately anxiety/depression, sleep troubles and body impairments (*Anxiety/depression* cluster), and cluster 2, predominantly CVD/metabolic diseases [29]. The researchers computed a multimorbidity score based on strength of association between conditions within cluster. The higher the multimorbidity score, the greater the number and associations of morbidities [29]. In both males and females, multimorbidity scores increased with age for each cluster. Women reported higher scores for *Anxiety/depression* cluster than men, while men reported higher scores for the *CVD/metabolic diseases* cluster. At mid-life, those with *Anxiety/depression* clusters reported poorer physical and mental HrQoL, compared to those with *CVD/metabolic disease* clusters, females more so than males. In both males and females, differences were observed on impact of each cluster on physical and mental HrQoL between early and late mid-life. However, within each sex, the direction of association were inconsistent between different HrQoL measures used (Duke and SF-36).

4. Discussion

This review highlights that recent data on multimorbidity and HrQoL at mid-life, using studies based on the general population is sparse, limited to cross-sectional research, and with substantial heterogeneity in the measurement and reporting of multimorbidity [4]. There were consistent findings across adult and mid-life studies that multimorbidity was associated with poorer HrQoL at mid-life. While there has been no review of the literature on multimorbidity and HrQoL focused at mid-life to date, this finding has been seen more broadly in primary care studies and in studies focused on adults age 65 and above [8, 12, 17].

4.1 Age and sex differences

Two cross-sectional studies suggest that adults with multimorbidity at early mid-life have poorer HrQoL compared to those at later mid-life [23, 27]. This may be due to initial adjustment periods associated with health transitions at mid-life, coupled adjustments to potential onset of new conditions or symptoms which together may result in poorer HrQoL early mid-life compared to late mid-life. Another cross-sectional study using age as a continuous variable found the reverse [26].

It is still unclear whether there are any sex differences in estimates of prevalence of multimorbidity at mid-life and its association with HrQoL. A previous primary care based review found that females report higher prevalence of multimorbidity compared to males, however evidence is mixed with some studies suggesting no significant difference [19]. Current evidence suggest that males generally report significantly higher HrQoL compared to females, a gap in HrQoL which widens at mid-life [31, 32]. The number, type and onset of health changes at mid-life and its severity may differ between the sexes [33]. For females, timing of the onset of health symptoms and conditions due to menopause transitions during midlife is likely to affect HrQoL and result in higher prevalence of multimorbidity compared to age-matched males [34]. Alternatively males and females may adapt to health changes differently, which in turn may explain observed sex based difference in HrQoL during this period. Given the steep increase in multimorbidity prevalence at mid-life [2, 19], further research is needed using longitudinal cohort of mid-age males and females to clarify the role of sex and timing of multimorbidity onset in the association between multimorbidity and HrQoL.

4.2 Measurement of multimorbidity

When multimorbidity was measured using clusters of conditions, two distinct clusters emerge: one with mental health conditions, and the other with CVD; consistent with other research [35]. Across the two studies, those in clusters which include mental health conditions reported poorer HrQoL

than those in CVD clusters [27, 29]. This highlights the importance of mental health in the context of HrQoL and the need for multimorbidity studies to include mental health conditions as part of the pre-defined list of conditions [12]. There were inconsistencies in findings relating to age differences for these two studies. While such inconsistencies have been seen in other research [12], inconsistencies observed may be partly driven by differences in study populations (general adult populations vs Mid-life population), differences in analysis (analysis on overall sample vs analysis stratified by age and sex), and the heterogeneity in the measurement of multimorbidity.

Almost all studies used count of conditions index to quantify multimorbidity when examining its association between HrQoL. While this method simple and can be used broadly across studies, it does not account for disease severity or duration of disease, both which can influence HrQoL [12]. No studies in this review used a weighted multimorbidity index or examined multimorbidity trajectories in association with HrQoL. As severity of conditions and multimorbidity patterns of an individual may influence HrQoL, measuring multimorbidity with these methods may increase the validity and usefulness of findings than using a simple count of conditions [4]. Nevertheless, due to the heterogeneity of the measurement of multimorbidity, presenting results for count of conditions, in addition to another multimorbidity index is useful to assist with basic comparability across studies. Only two studies in this review examined clusters of conditions and its association with HrQoL [27, 29]. Despite this, the demonstrated differential impact of clusters of conditions on health outcomes highlight the importance of multimorbidity studies which identify groups of conditions that co-occur. Further analysis examining age, life-stage and gender differences may assist in the targeted and early intervention of those at risk.

4.3 Measurement of HrQoL

All studies in this review used validated multi-domain instruments to measure HrQoL. Five studies assessed the impact of multimorbidity on physical and mental HrQoL domains separately while the remaining four used preference weighted measures of HrQoL which allowed assessment of multimorbidity on overall HrQoL [24]. Study findings were consistent between preference weighted and non-preference weighted HrQoL measures. Co-existing physical and mental health conditions in a multimorbid individual may impact multiple domains of quality of life. Hence, preference based measure of HrQoL may be more useful to quantify the impact of multimorbidity on overall HrQoL. Such measures summarises an individual's HrQoL in a single score, by weighting multiple health domains based in its perceived importance as part of HrQoL [24]. Using preference based HrQoL measures are beneficial in health policy and planning as such data can help inform economic evaluations of health interventions targeted at those with multimorbidity [32].

4.4 Strengths and limitations

To our best knowledge, this is the first review to assess available evidence on multimorbidity and HrQoL at mid-life. We summarised results from four bibliography databases and used a comprehensive list of keywords and topic headings, and targeted search strategies to ensure maximum coverage of articles. There may be relevant articles missed during the screening process due to language barriers (only articles in English were included), publication bias or available only as grey literature. We limited studies to those from general population to ensure estimates are generalizable at a general population level. Studies included were primarily from Western, high income countries, with predominantly Caucasian populations. Thus the findings of this review may only be generalizable to similar populations.

The heterogeneity in the measurement and reporting of multimorbidity across these studies limits comparability across studies, thus a narrative synthesis of results was presented. There was variation in the number and types of conditions, grouping of conditions (individually e.g. depression vs in groups e.g. Depression/Anxiety) used to define multimorbidity which may have influenced the prevalence reported and its associations with health outcomes [2]. While most studies used count of conditions to describe multimorbidity, there were differences in the multimorbidity thresholds used, and choice reference level for multimorbidity variable in association with HrQoL. All studies used self-reported conditions to define multimorbidity, which may result in under-reporting of conditions. Some studies did not report conditions used to describe multimorbidity [26, 30], while one study included overweight and obesity as a condition which likely have inflated its multimorbidity estimates [25]. All studies reported using only chronic conditions. However, including acute conditions and health symptoms specific to life-stage should be explored as it may influence HrQoL[12]. The definition of “Mid-life” varied across studies due to the variation age group interval lengths and cut points. To ensure some consistency across studies we included age groups generally captured the “mid-life” stage usually between ages 40 to 65years. Despite these limitations, the consistent findings on multimorbidity and HrQoL at mid-life provides some evidence of robustness of results.

4.5 Implications public health, health policy and research

This review highlights the need for longitudinal evidence on the association between multimorbidity and HrQoL at mid-life. The prevalence and combinations of conditions associated with multimorbidity differs based on life-stage [14]. However, there is a substantial multimorbidity burden at mid-life as seen in this review and in other research [15]. Given mid-life is a period of health transition and represents a critical period for health optimization [33], longitudinal evidence

on how the onset of new conditions and different multimorbidity trajectories influence HrQoL at mid-life is needed. To strengthen the evidence base, future research should also focus on investigating associated differences between early and late midlife using a cohort of men and women with repeated data over the midlife period (between ages 40-65 years). This may assist with patient care, target early interventions tailored to specific stages of mid-life, future health service planning and inform clinical guidelines on the management of people with multimorbidity at mid-life. Our finding on the differential impact of CVD vs mental health clusters on HrQoL suggest that health care strategies for the management of people with multimorbidity may need to be tailored based on individuals' combination of conditions as a whole (rather than based on single condition), considering both burden of treatment and disease, and patients' health priorities and circumstances [36]. Adults with multimorbidity, with a mental health conditions may need a holistic, integrative approach to patient care incorporating both biomedical and psychosocial models of care [37].

Multimorbidity indices that incorporate severity and duration of diseases are needed to better understand the combined effect of presence of disease, its severity and duration, and its influences on HrQoL. Using multiple indices to measure multimorbidity is recommended as different indices provide complementary information useful for different sectors of health. For example, from an epidemiological and health planning perspective, using count of condition to describe multimorbidity is useful to establish the prevalence of multimorbidity in a population which can inform service planning. However, for clinical practice and health policy, evidence on patterns and clusters of condition that tend to co-occur, and its impact HrQoL is more useful. Nevertheless, it is recommended that the prevalence of multimorbidity, defined using count of conditions, and its association with HrQoL is described in future research to facilitate comparisons across studies. Reporting of results overall, and with age and gender estimates, and including count of conditions in addition to other multimorbidity index will be useful to assist with basic comparisons across studies.

Conclusion

This review identified eight relevant studies and found consistently, multimorbidity was associated with poorer HrQoL at mid-life. There was some cross-sectional evidence of a difference in this association between early and late mid-life, and disease cluster, however more research is needed for conclusive findings. Given that the onset of morbidity at mid-life can affect HrQoL, research from longitudinal studies which measure multimorbidity using indices that incorporate severity of disease and disease trajectories is needed to strengthen the evidence base to assist with future health service delivery.

Contributors

Jeeva Kanesarajah performed the literature review, designed the search strategy, screened titles and abstracts and full text, determined quality of the articles and performed the data extraction, and drafted the manuscript.

Michael Waller determined quality of the articles

All authors contributed to study conception and designed the review, participated in data synthesis/analysis and data interpretation. All authors contributed to the critical revision of the manuscript, and saw and approved the final version.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Jeeva Kanesarajah is funded by the Australian Government Research Training Program. Gita D. Mishra is supported by NHMRC Principal Research Fellowship.

Provenance and peer review

This article has undergone peer review.

Acknowledgements

Thanks to Scott McIntyre, Xiaolin Xu and Louise Wilson for their valuable advice during the systematic review process.

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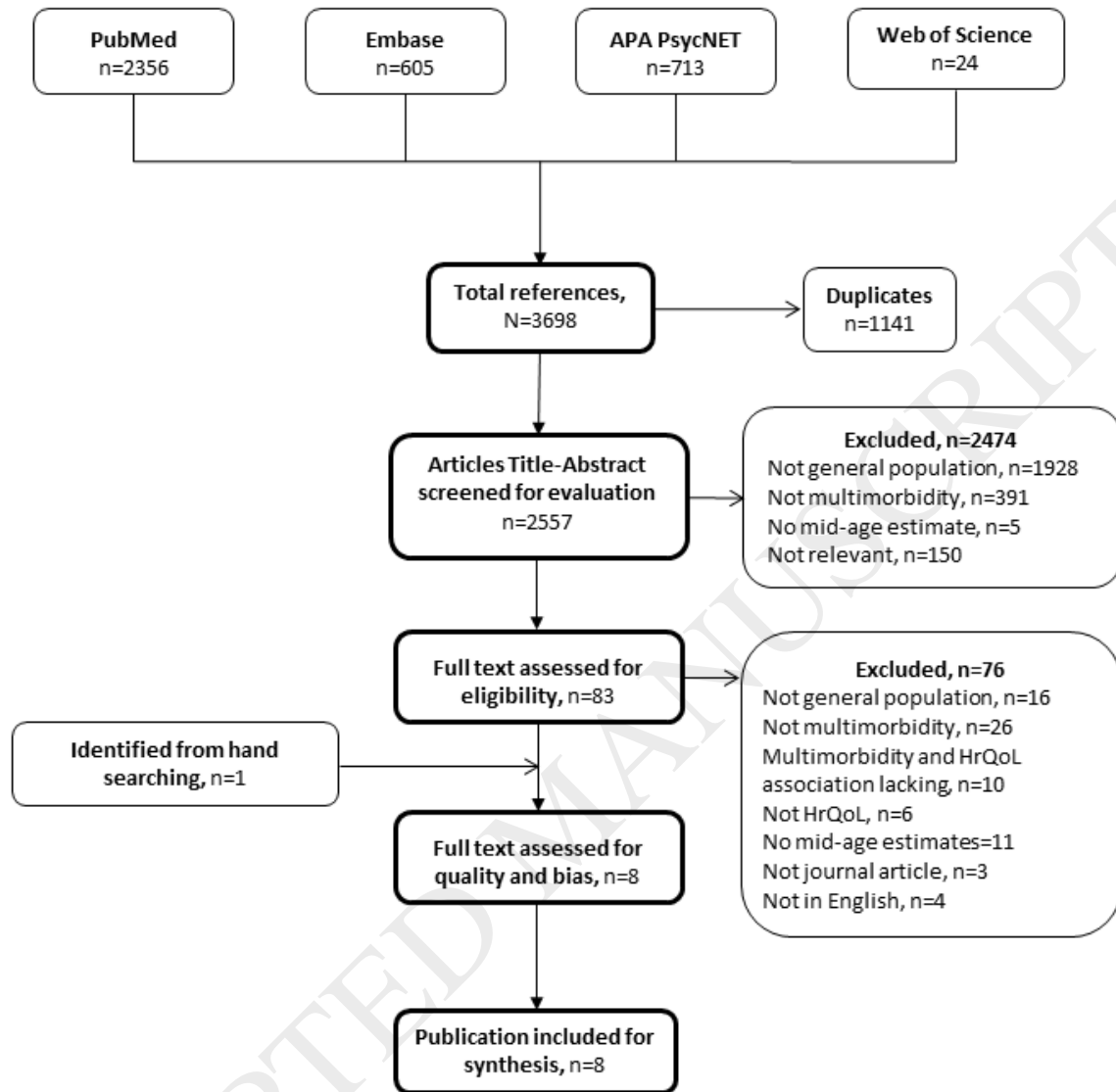
Figure 1 PRISMA flowchart of the selection procedure for articles used in the systematic review

Table and Figures

Table 1 Characteristics of studies included in the systematic review

Author (country)	Quality score	Study design	Year data collected	Population (age range, % female, % mid-age, Sample size)	Mid-life age group ^a	Multimorbidity	HrQoL scale	Study Limitations
Adult studies (age 16+, n = 5)								
Wang et al. (2017) [27] <i>Australia</i>	Fortin ^b : 29 NOS ^c : 8	Cross-sectional, private dwelling	2007	Aged 16-85 years, mean age=44, 50.4% female, 31.7% mid age. N=8841	46-55, 56-65	9 chronic conditions, obtained from self-report. MM measured using count of conditions (2+, 3+) and cluster of conditions	Assessment of Quality of Life (AQoL-4D), 4 domains, interview administered. Preference weighted-HrQoL	Cross-sectional data. Did not incorporate diseases severity or duration in multimorbidity measure. Conditions self-reported, collected from face to face interview, but mental health conditions derived from diagnostic interview.
Ramond-Roquin et al. (2016) [25] <i>Canada</i>	Fortin ^b : 28 NOS ^c : 6	Cross-sectional, part of cohort study	2010	Community dwelling, aged 25-75 year, no major cognitive impairment, reside in 4 local healthcare networks in Quebec. Mean age 51.3 (SD 12.5). 59.5% women. N=1710	46-64	Two chronic conditions lists (21 conditions; 6 condition list), self-report. MM measured using count of conditions (2+, 3+)	Short Form 12 (SF-12v2) PCS, self-administered	Cross-sectional data, under representative of young and deprived individuals. Did not incorporate diseases severity or duration in multimorbidity measure. Conditions list adapted from validated Disease Burden Morbidity Assessment but still self-reported. Included overweight and obesity (BMI ≥ 25) as condition. Physical HrQoL estimated only. No HrQoL estimates for those without multimorbidity, only population norms.
Juul et al. (2014) [23] <i>Denmark</i>	Fortin ^b : 25 NOS ^c : 6	Cross-sectional	2013	20-90 years, 959 (52%) Females, 873 (47.7%) males. Overall mean age 58.3 (SD 18.7). N=1832	50-49, 50-59	20 condition list, self-reported. MM measured using count of conditions (0,1, 2+)	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-C30 Global health status scale. Self-administered	Cross-sectional data. Did not incorporate diseases severity or duration in multimorbidity measure. Conditions self-reported. HrQoL instrument was developed for use in cancer patients, but adequate as a generic HrQoL measure.

Author (country)	Quality score	Study design	Year data collected	Population (age range, % female, % mid-age, Sample size)	Mid-life age group ^a	Multimorbidity	HrQoL scale	Study Limitations
Lawson et al. (2013) [24] <i>Scotland</i>	Fortin ^b : 27 NOS ^c : 6	Cross-sectional, household survey	2003	Aged 18+, rep of gen pop across Scotland. 37% mid-age N=7054	45-64	40 chronic condition list reduced to 15 body systems. Conditions self-reported. MM defined as the presence of two or more longstanding conditions from different systems of the body. MM measured using dichotomous categories (MM2+, Not MM 2+)	Short Form-6 Dimension (SF-6D). Self-administered, Preference weighted HrQoL	Cross-sectional data. Conditions self-reported. Did not incorporate diseases severity or duration in multimorbidity measure. Data under representative of those in lowest SES.
Sullivan et al. (2012) [26] <i>United States</i>	Fortin ^b : 24 NOS ^c : 6	Cross-sectional, pooled household survey	2001, 2003	Adults 18+, 52% female, 26% mid-age. N=47178	45-58	118 chronic conditions (lasting >1 year) self-reported, but conditions list not provided. Multimorbidity measured as count of conditions (0,1, 2,...,9,10+)	EuroQoL-5 dimension 3 level (EQ-5D 3L), self-administered, Preference weighted HrQoL	Pooled cross-sectional data. Conditions self-reported, but list of conditions not reported. Only chronic conditions were included (lasting 1 year or more). Used 11-level number of conditions variable, rather than having 2+ or 3+ thresholds. Did not incorporate diseases severity or duration in multimorbidity measure. EQ-5D scores using United States scoring algorithm exhibit strong ceiling effects hence may not be sensitive to discriminate within mild disease states.
Mid-life population studies (age 18+, n = 3)								
Yeung and Breheny (2016) [30] <i>New Zealand</i>	Fortin ^b : 21 NOS ^c : 6	Cross-sectional, part of longitudinal cohort study	2012	Aged 50-87, mean age (SD) =66.1 (7.8), 56% female, 46% mid-age. N=2793	50-64	14 chronic condition, self-report but conditions list not provided. Multimorbidity measured as count of conditions (0, 1, 2, 3+)	Short Form -12 (SF-12) PCS and MCS, self-administered.	Cross-sectional data. All conditions were self-reported. Number of conditions reported but list of conditions used were not reported. Did not incorporate disease severity or duration in measurement.

Author (country)	Quality score	Study design	Year data collected	Population (age range, % female, % mid-age, Sample size)	Mid-life age group ^a	Multimorbidity	HrQoL scale	Study Limitations
Walker et al. (2016) [29] <i>France</i>	Fortin ^b : 26 NOS ^c : 5	Cross-sectional design in cohort follow-up	2007-2009	age 55+ at enrolment, mean age 63.2(SD 4.9), 51.5% female, 86% mid-age, N=5647	55-59, 60-64	19 chronic condition, self-reported. Multimorbidity measured as count of conditions (MM 2+) and disease association score.	Medical Outcomes Study (SF-36 PCS and MCS), Duke Health Profile (Duke Physical and Mental Health). Self-administered	Cross-sectional data. Examined associates stratified by age and gender, so no overall estimates of HrQoL in the sample. Self-reported conditions, but conditions used were selected based on relevance of overall health by a geriatrician. Did not incorporate disease severity or duration in multimorbidity measure. Instead measured multimorbidity using a disease association score.
Lang et al. (2015) [28] <i>United States</i>	Fortin ^b : 23 NOS ^c : 7	Cross-sectional	2012	Female, aged 40-64 at data collection, English or Spanish speakers, N=3058	40-64	6 chronic conditions, self-reported using diagnostic scales. Multimorbidity measured using count of conditions (0, 1, 2, 3+)	EuroQoL-5 dimension 3 Level (EQ-5D 3L), self-administered interviewed, Preference weighted HrQoL	Cross-sectional data limited to women at mid-life stage and specific conditions. Too few conditions considered, and self-reported conditions (using diagnostic tools) relevant to women at midlife only (Depression, Chronic pain, Urinary incontinence, Osteoporosis, Vasomotor symptoms, vulvar/vaginal atrophy). Did not incorporate diseases severity or duration in multimorbidity measure. EQ-5D scores using United States scoring algorithm exhibit strong ceiling effects hence may not be sensitive to discriminate within mild disease states.

Note: NOS, Newcastle-Ottawa Scale; HrQoL, Health related quality of life, MM, multimorbidity, MM2+, multimorbidity defined as two or more conditions; MM 3+, multimorbidity defined as three or more conditions, NA not available
^a Relevant Mid-life age-group (ages 40-65) reported in each study

^b Fortin M. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes*. 2004;2:51.

^c Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses: The Ottawa Hospital Research Institute; [cited 2017 24/10/2017]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Table 2 Prevalence of multimorbidity in general population and mid-life studies by number of conditions

Studies	Adult studies (age 18+, n=5)					Mid-Life studies (age 40+, n=3)			
	< 8	8-14	15+			< 8	15+		
	RR ¹	Wang ²	RR ¹	Juul ³	Lawson ⁴	Sullivan ⁵	Lang ⁶	Yeung ⁷	Walker ⁸
All age groups									
MM2+									
Overall, %	13.8	26.0	63.8	36.0	18.0	44.0			63.0
Male	16.0	23.8	65.6	36.4					60.0
Female	14.4	27.9	62.5	35.7			31.0		67.3
MM3+									
Overall, %	3.8	10.1	48.9			29.0		50.0	40.5
Male	4.8	8.7	50.8						36.6
Female	3.2	11.4	47.6				13.0		44.1
Mid-Life age group									
MM2+									
Age groups ^a	46-55	56-65		45-64		40-64		55-59	60-64
Overall, %	26.6	42.2		19.0				55.8	61.6
Male								44.5	56.7
Female						31.0		61.6	66.7
MM3+									
Age groups ^a	46-55	56-65				40-64		55-59	60-64
Overall, %	9.5	18.7						32.8	36.5
Male								22.5	31.8
Female						13.0		38.0	41.4

Note: RR, Ramond-Roquin et al.; MM, multimorbidity; MM2+, multimorbidity defined as two or more conditions; MM 3+, multimorbidity defined as three or more conditions, missing prevalence indicates prevalence was not reported

1 Ramond-Roquin, A., Haggerty, J., Lambert, M., Almirall, J., Fortin, M., 2016. Different Multimorbidity Measures Result in Varying Estimated Levels of Physical Quality of Life in Individuals with Multimorbidity: A Cross-Sectional Study in the General Population. *BioMed research international* 2016, 7845438.

2 Wang, L., Palmer, A.J., Cocker, F., Sanderson, K., 2017. Multimorbidity and health-related quality of life (HRQoL) in a nationally representative population sample: implications of count versus cluster method for defining multimorbidity on HrQoL. *Health Qual Life Outcomes* 15, 7.

3 Juul, T., Petersen, M.A., Holzner, B., Laurberg, S., Christensen, P., Grønvold, M., 2014. Danish population-based reference data for the EORTC QLQ-C30: Associations with gender, age and morbidity. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care & Rehabilitation* 23, 2183-2193.

4 Lawson, K.D., Mercer, S.W., Wyke, S., Grieve, E., Guthrie, B., Watt, G.C., Fenwick, E.A., 2013. Double trouble: the impact of multimorbidity and deprivation on preference-weighted health related quality of life a cross sectional analysis of the Scottish Health Survey. *International journal for equity in health* 12, 67.

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6 Lang, K., Alexander, I.M., Simon, J., Sussman, M., Lin, I., Menzin, J., Friedman, M., Dutwin, D., Bushmakina, A.G., Thrift-Perry, M., Altomare, C., Hsu, M.-A., 2015. The impact of multimorbidity on quality of life among midlife women: Findings from a U.S. nationally representative survey. *J. Womens Health* 24, 374-383.

7 Yeung, P., Breheny, M., 2016. Using the capability approach to understand the determinants of subjective well-being among community-dwelling older people in New Zealand. *Age Ageing* 45, 292-298.

8 Walker, V., Perret-Guillaume, C., Kesse-Guyot, E., Agrinier, N., Hercberg, S., Galan, P., Assmann, K.E., Briançon, S., Rotonda, C., 2016. Effect of multimorbidity on health-related quality of life in adults aged 55 years or older: Results from the SU.VI.MAX 2 Cohort. *PLoS One* 11.

a Relevant Mid-life age-group (ages 40-65) reported in each study.

Table 3 Synthesis of the association between multimorbidity (measured with count of conditions) and HrQoL at mid-life (age 40-65)

Author	MM exposure group	Mid-life age range	Overall results	Early vs late mid-life HrQoL comparisons for those multimorbid
Adult Studies (age 18+, n=5)				
Wang et al. (2017) [27] <i>Australia</i>	MM2+ mean HrQoL scores compared to population norm ^a	46-55, 56-65	↓ AqoL compared to population norm ^a	Late ↑ AqoL vs Early
	MM3+ mean HrQoL scores compared to population norm ^a	46-55, 56-65	↓ AqoL compared to population norm ^a	Late ↑ AqoL vs Early
	MM2+ vs MM3+	46-55, 56-65	MM 3+ ↓ AqoL vs MM2+	
Ramond-Roquin et al. (2016) [25] <i>Canada</i>	MM2+ mean HrQoL scores compared to population norm ^b	46-64	↓ SF-12 PCS compared to population norm ^b	NA
	MM3+* MM mean scores compared to population norms ^b	46-64	↓ SF-12 PCS compared to population norm ^b	NA
	MM2+ vs MM3+	46-64	MM3+ ↓ SF-12 PCS vs MM2+	NA
Lawson et al. (2013) [24] <i>Scotland</i>	<2 (reference) vs 2+	45-64	↓ SF-6D	NA
Juul et al. (2014) [23] <i>Denmark</i>	0, 1, 2+	40-49, 50-59	↓ EORTC QLQ-C30 Global quality of life with increasing number of conditions	Late ↑ EORTC QLQ-C30 Global quality of life with vs Early
Sullivan et al. (2012) [26] <i>United States</i>	0,1,2,3,...,9, 10+	45-58	↓ EQ-5D with increasing number of conditions	Late ↓ EQ-5D vs Early
Mid-life studies (ages 40+, n=2)				
Yeung and Breheny (2016) [30] <i>New Zealand</i>	0, 1, 2, 3+	50-64	↓ SF-12 PCS, ↓ MCS with increasing number of conditions	NA
Lang et al. (2015) [28] <i>United States</i>	0, 1, 2, 3+	40-64	↓ EQ-5D with increasing number of conditions	NA

Note: HrQoL, Health related quality of life, ↑ significantly higher mean scores with HrQoL, ↓ significantly lower mean scores with HrQoL, ↔ no significant difference in mean HrQoL. MM, multimorbidity, MM2+, multimorbidity defined as two or more conditions; MM 3+, multimorbidity defined as three or more conditions, NA not available

a AqoL-4D Australian population norms based on Hawthorne and Richardson [38]

b SF-12v2 PCS population norms based on Saris-Baglana et al. [39]