



RESEARCH

Open Access



Multimorbidity and functional decline in community-dwelling adults: a systematic review

Aine Ryan^{1,3*}, Emma Wallace¹, Paul O'Hara² and Susan M. Smith¹

Abstract

Background: Multimorbidity affects up to one quarter of primary care populations. It is associated with reduced quality of life, an increased risk of mental health difficulties and increased healthcare utilisation. Functional decline is defined as developing difficulties with activities of daily living and is independently associated with poorer health outcomes. The aim of this systematic review was to examine the association between multimorbidity and functional decline and to what extent multimorbidity predicts future functional decline.

Methods: A systematic literature search (1990-2014) and narrative analysis was conducted. Inclusion criteria: Population; Community-dwelling adults (≥ 18 years), Risk; Multimorbidity defined as the presence of ≥ 2 chronic medical conditions in an individual, Primary outcome; Physical functional decline measured using a validated instrument, Study design; cross-sectional or cohort studies. The following databases were included: PubMed, EMBASE, CINAHL, the Cochrane Library and the International Research Community on Multimorbidity (IRCMo) publication list. Methodological quality assessment of included studies was conducted with a suitable risk of bias tool.

Results: A total of 37 studies were eligible for inclusion (28 cross-sectional studies and 9 cohort studies). The majority of cross-sectional studies ($n = 24/28$) demonstrated a consistent association between multimorbidity and functional decline. Twelve of these studies reported that increasing numbers of chronic condition counts were associated with worsening functional decline. Nine cohort studies included 14,133 study participants with follow-up periods ranging from one to six years. The majority ($n = 5$) found that multimorbidity predicted functional decline. Of the five studies that reported the impact of increasing numbers of conditions, all reported greater functional decline with increasing numbers of conditions. One study examined disease severity and found that this also predicted greater functional decline. Overall, cohort studies were of good methodological quality but were mixed in terms of participants, multimorbidity definitions, follow-up duration, and outcome measures.

Conclusions: The available evidence indicates that multimorbidity predicts future functional decline, with greater decline in patients with higher numbers of conditions and greater disease severity. This review highlights the importance of considering physical functioning when designing interventions and systems of care for patients with multimorbidity, particularly for patients with higher numbers of conditions and greater disease severity.

* Correspondence: aineryan@rcsi.ie

¹HRB Centre for Primary Care Research, Department of General Practice, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland

³Department of Population Health Sciences, Royal College of Surgeons in Ireland, Beaux Lane House, Lower Mercer Street, Dublin 2, Ireland
Full list of author information is available at the end of the article

Background

Multimorbidity is commonly defined as the co-occurrence of two or more chronic medical conditions within an individual [1]. Average life expectancy is rising and so too are the numbers of patients living with multiple chronic medical conditions [2, 3]. One of the main challenges facing both healthcare providers and governments globally is to provide healthcare for the growing numbers of patients living with multiple co-existing diseases [4]. The prevalence of multimorbidity depends on the definition used and the population studied and has been reported from 17–98 % [1, 10–12]. While linked to both deprivation and ageing, this phenomenon is not exclusive to the elderly. In an Australian study 15 % of the 40–59 age group suffered with multiple co-existing medical conditions. A Scottish primary care study demonstrated that the prevalence of multimorbidity increased substantially with age and was present in most of the cohort aged 65 years and older (65–84 years: 64.9 % with multimorbidity). The study also reported that 30.4 % of 45–64 year olds presented with multimorbidity and given the higher numbers of people in this age range, in absolute terms there are more middle aged people with multimorbidity despite the perception that is predominantly an issue for older patients [13]. Multimorbidity is the norm in clinical practice and has been shown to be associated with increased healthcare utilisation, increased emergency hospital admissions and decreased quality of life [14, 15]. It has also been associated with an increased decline in function [16].

Functional decline is defined as a deterioration in self-care skills, where functional autonomy is diminished and disability is increased [5, 6]. A systematic review of 14 cohort studies examining outcomes in older patients admitted to hospital found that functional status predicts length of hospital stay, readmission rates, patient discharge destination and also mortality [7]. In a Japanese longitudinal study of patients over 65 years patients with low Activities of Daily Living (ADL) scores, mortality rate was twice as high over a 5 year follow up compared to patients with higher scores [8]. Functional decline can also lead to increased rates of depression and decreased life satisfaction [6, 9]. Conversely engaging in physical activity is inversely associated with health care utilisation and is associated with increased life satisfaction [6, 9, 17, 18].

It is important for healthcare providers to have a greater understanding of the association between multimorbidity and functional decline considering its impact on patient outcomes. A Cochrane review of interventions to improve outcomes in patients with multimorbidity in primary care suggested that interventions focusing on functional difficulties experienced by patients with multimorbidity may improve outcomes [19]. A previous systematic review completed in 2004 examined the relationship between multimorbidity and

quality of life in primary care and reported that multimorbidity is associated with reduced quality of life [20]. However, to date there has been no systematic review of the literature examining the relationship between physical functioning and multimorbidity in community dwelling adults.

The aim of this systematic review was to examine the association between multimorbidity and functional difficulties and whether and to what extent multimorbidity predicts future functional decline.

Methods

The PRISMA-P Guidelines for reporting systematic reviews were utilised in the conduct of this study [21]. The protocol for this study was published on an international prospective register for systematic reviews (PROSPERO): http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012003502.

Data sources

A systematic literature search was carried out using the following search engines: PubMed, EBSCO, EMBASE, CINAHL and the Cochrane library. References from retrieved articles were also searched by hand for relevant articles. The search was carried out from January 1990 to November 2014 and was limited to publications in the English language. Similar systematic reviews have used 1990 as a cut-off date for searches as multimorbidity was a relatively new concept up to that date and does not appear in the literature before this time [16, 19]. Primary healthcare, family practice and family physicians were included as Medical Subject Heading (MeSH) terms. As multimorbidity does not have a MeSH term it was searched for as a keyword and comorbidity was used as a MeSH term.

Two researchers performed the initial screening of titles and abstracts (POH, EW) and irrelevant studies were eliminated. Studies considered eligible for inclusion were read fully in duplicate and their suitability for inclusion to the study was independently determined by two researchers (AR, EW). Any ambiguous findings were discussed with a third researcher (SS) and a consensus reached. Additional information around eligibility was sourced from authors where necessary.

Inclusion criteria

We included retrospective and prospective cohort studies and cross-sectional study designs. Participants included adults (>18 years) with multimorbidity defined as the presence of two or more chronic medical conditions in an individual [1]. The study setting was primary care or the community. Primary care was defined as: integrated, easy to access health care services by clinicians who are

accountable for addressing a large majority of personal health care needs, developing a sustained and continuous relationship with patients, and practicing in the context of family and community [22]. The primary outcome was functional status measured using a validated measure of function e.g. SF-36. Studies carried out in long term care/residential settings and in-patient settings were excluded. Studies that examined physical function in an index condition and related co-morbidities were also excluded. The current concept of multimorbidity is that no condition is privileged over any other. Studies which investigate index conditions and their co-morbidities also have a different management focus targeting a single disease. This is discussed in a Cochrane review which investigates interventions for patients with multimorbidity [19].

Assessment of risk of bias

Included studies were assessed for methodological quality using the Cochrane Tool for the Assessment of Bias in Cohort Studies [23] (Additional file 1: Appendix A). This checklist was modified for assessment of the included cross-sectional studies (Additional file 2: Appendix B).

Statistical analysis

Due to heterogeneity meta-analysis was not possible and a narrative synthesis was conducted. Each article was assessed under the following headings; publication year and country, population and setting, definition and prevalence of multimorbidity, functional decline outcome measure, findings and follow up period (cohort studies).

Results

Of 5532 articles screened, 89 were assessed in full text and evaluated according to the study's inclusion and exclusion criteria. A total of 37 studies were eligible for inclusion: 28 cross-sectional studies [24–52] and 9 cohort studies [53–60]. Figure 1 illustrates the search strategy. Reasons for exclusion of studies are presented in the flow diagram and references provided as an appendix (Additional file 3: Appendix C). Tables 1 and 2 describe the study designs, definitions and outcomes reported in the 37 included studies.

Cross sectional studies

The 28 cross-sectional studies included 1,357,498 participants in total. Overall, 22 of the 28 studies included participants aged over 50 years with 11 of these including participants aged 60 years or older. Sample sizes varied from 186 [33] to 830,537 [47]. The studies were carried out in twelve different countries, the majority in Europe ($n = 13$) and North America ($n = 11$). A total of 22 studies measured multimorbidity using the definition of two or more conditions with three studies using three or more conditions. Two studies used weighted indices such as the

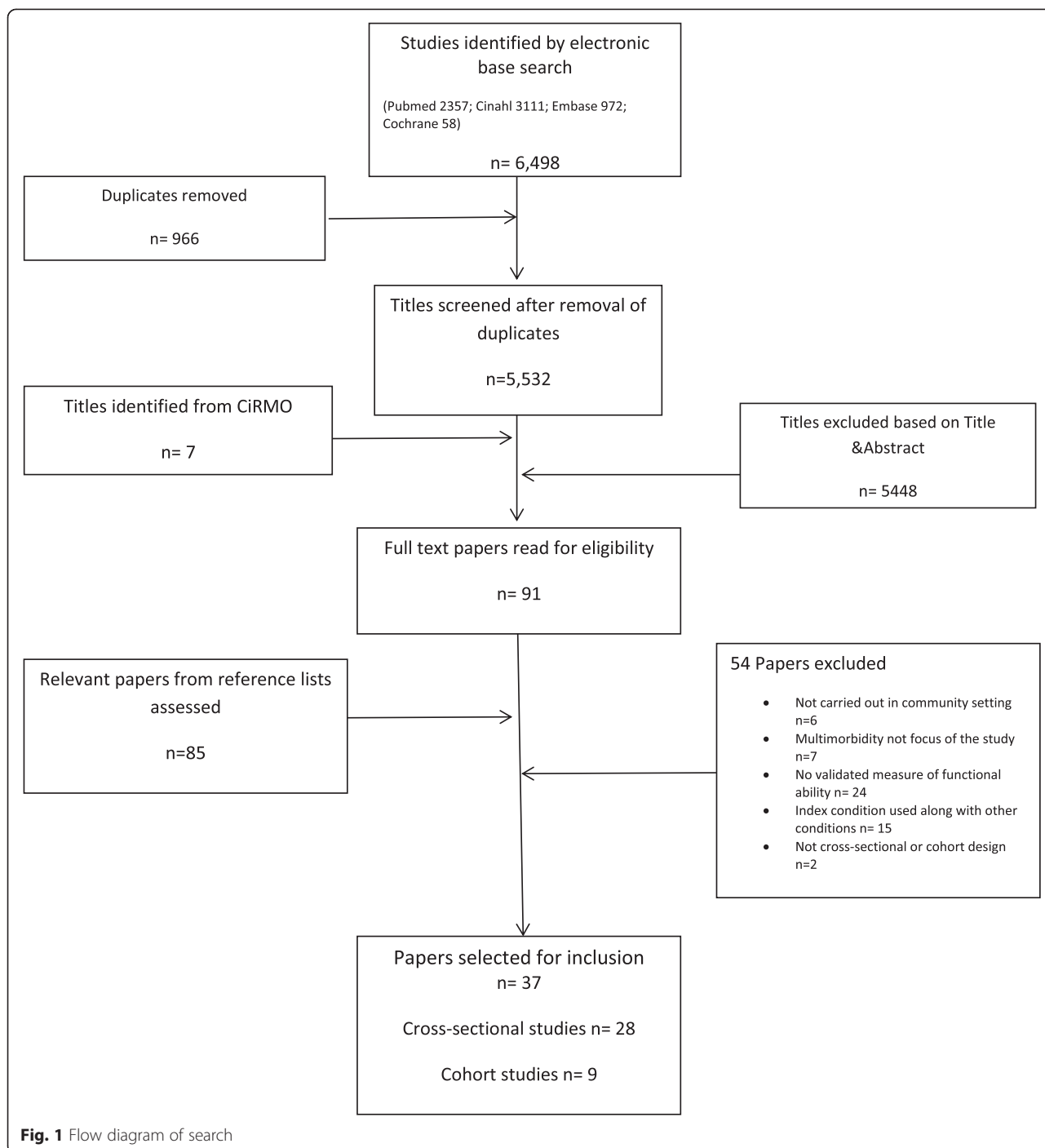
Charlson Co-morbidity Index to measure the degree of multimorbidity. Ascertainment of conditions varied between self-report, physician report, chart review and use of software, with the majority ($n = 17$) using self-report to identify conditions. To note, five of the 28 studies did not include mental health conditions [36–39, 50]. There was significant variation in the prevalence of multimorbidity in included studies ranging from 13 % [50] to 90 % [31].

Ten different validated outcome measures were used to measure functional decline in the included 28 studies. Approximately half (46.4 %) used the SF-36 /SF-12, followed by 25 % administering the EQ-5D. The majority of cross-sectional studies demonstrated a consistent association between multimorbidity and functional decline ($n = 24/28$). Twelve of these studies reported that higher condition counts were associated with increased functional decline. In contrast two studies concluded that there was no significant association between the number of conditions and physical functioning [25, 49]. Two studies reported that higher morbidity severity was associated with poorer physical health [34, 42].

Cohort studies

A total of nine cohort studies included 14,133 study participants with follow-up periods ranging from one to six years [52–60]. Six of these nine studies included participants 65 years or older with sample sizes varying between 492 [60] and 4672 [59]. Four studies were conducted in Europe, four in North America and one study in Australia. The majority defined multimorbidity as ≥ 2 chronic conditions but most restricted condition inclusion using pre-defined lists ranging from five to 96 conditions. Similar to the cross-sectional studies, self-report was the most prevalent method of ascertaining conditions ($n = 5$), followed by identification through medical record review ($n = 4$). There was similar variation in prevalence rates of multimorbidity in the cohort populations, ranging from 25.3 to 93.1 %. Five different validated outcome measures were used with just over half of the cohort studies ($n = 5$) using the SF-36 or SF-12 as their measure of functional decline.

Seven of the nine cohort studies reported that baseline multimorbidity predicted future functional decline [53–56, 58–60]. Five studies out of nine established that any degree of multimorbidity was predictive of functional decline [53, 55, 56, 59, 60]. Two of these studies stipulated that specific numbers of chronic conditions at baseline were predictive of future decline [54, 58]. The remaining two studies reported that higher numbers of conditions were needed to predict future decline with Nikolova et al. [58] reporting significant functional decline only for those with four or more conditions and Bayliss et al. [17] reporting it for those with six or more conditions. Two studies found no significant



relationship between functional disability and multimorbidity over time [52, 57]. Abizanda et al [52] stated that disability and frailty were not associated with multimorbidity over two years [52]. Kiely et al [57] reported that additional conditions were associated with increased impairment at baseline but that functional decline over time did not differ between subjects with no conditions and those with multimorbidity [57].

Five studies examined condition type, disease severity and the impact of cognitive impairment on functional decline. Bayliss et al. examined condition type and reported that those with congestive heart failure, diabetes and/or chronic respiratory disease were at greater risk of functional decline over time compared to other conditions [54]. Prior et al. also examined condition types and reported that those with cardiovascular disease were

Table 1 Included Cross-Sectional Studies

Author Publication Year Country	Population and setting	Definition and prevalence of multimorbidity (MM)	Functional decline outcome measure	Results
Agborsangaya 2012 Canada	Population based survey 4946 adults ≥ 18 years	Self-report chronic conditions from list of 1619 % with ≥ 2 conditions	EQ-5D	MM associated with a significant reduction in EQ5D index score -0.12
Baker 2000 USA	Primary care clinic 194 adults, 48 % > 60 years	Self-report of > 1 diagnosis according to ICPC categories 51 % > 1 condition	SF-36	SF36 PCS scores decline with increasing numbers conditions (p < 0.05 on one way MANOVA analysis)
Baker 2006 USA	Community dwelling 247 African American adults, mean age 69	Self-report of doctor-diagnosed conditions used to create condition count Mean 2.9 conditions	AIMS2 (Arthritis Impact Measurement Scale)	No significant association between number of conditions and physical functioning on multivariate analysis
Bayliss M2012 USA	Population based survey 3877 adults 63 % ≥ 45 years 36 % ≥ 60 years	Self-report of conditions from 26 condition checklist Mean 2.4 conditions Grouped into physical condition MM, mental health MM or both	SF-36	Reduction in PCS score v healthy group: Physical MM : - 6.4 Mental health MM: - 11 Combined physical and mental health MM: -15
Bayliss EA2012 USA	Primary care, members of HMO 961 aged ≥ 65 years	Self-report of 3 or more conditions from a list of 10 conditions Mean 7.9 conditions	SF-36	Higher condition counts associated with significantly lower PCS scores on multivariate analysis
Brettschneider 2013 Germany	Primary Care – GP databases 3189 patients 65–85 years	Co-existence of 3 or more chronic conditions from a list of 29 Measured by a weighted counts score Mean 7 conditions	EQ-5D	Increased condition count and severity associated with significant reductions in EQ5D-VAS on multivariate analysis
Cesari 2006 Italy	Population – cohort study in mountain community 364 adults ≥ 80 years	Physician report of ≥ 3 conditions based on self- report and chart review 136 patients with ≥ 3 conditions (37.4 %)	Short Physical Performance Battery (SPPB) Four minute walking speed score MDS-HC: ADLs and IADLs	MM significantly associated with lower SPPB score, lower walking speed scores and lower IADLs, but no difference in ADLs
Chen 2011 USA	Population based survey (Behavioural Risk Factor Surveillance System) 430,912 adults ≥ 18 years	Self-report from list of 8 conditions >90 % participants had ≥ 2 conditions	CDC HRQOL - 4 domains: general health, mental distress, physical distress and activity limitations	Participants with ≥ 3 conditions had highest risk of reporting fair or poor health (AOR 8.7, 95 % CI 8.0 to 9.4)
Cheng 2003 USA	Primary care clinics 316 consecutive clinic attenders 55 –64 years	80 % of patients in the study had ≥ 2 conditions confirmed on chart review	SF-36	Number of conditions significantly associated with decreases in PCS scores in multivariate analysis
Formiga 2005 Spain	Community based 186 adults aged ≥ 90 years	Charlson Comorbidity index, mean score 1.43		Higher comorbidity score significantly associated with worse functional and cognitive capacity on multivariate analysis

Table 1 Included Cross-Sectional Studies (Continued)

			Barthel Index (ADLs) Lawton and Brody Scale (IADLS)	
Fortin 2007 Canada	Primary care 238 adults attending primary care clinic (randomly collected from a larger study cohort) Mean age 59.0 years	Chart confirmed \geq two conditions Severity assessed using CIRS score Mean 5.3 (+/-2.8) diagnoses	SF-36	MM measured by simple count was associated with significantly reduced PCS scores on multivariate analysis Increases in MM severity (CIRS scores) associated with greater decreases in PCS scores than simple counts alone
Goins 2010 USA	Community based sample 505 adults \geq 55 years	Comorbidity scale – self-report from list of 32 conditions Combined with severity assessment using score 0–3 Mean score 5.8	Short Physical Performance Battery (SPPB) Hand grip test	Higher comorbidity scores significantly associated with poor SPPB and hand grip scores in multivariate analysis
Griffith 2010 Canada	Population based sample 8858 adults \geq 65 years	Self-report of \geq 2 from list of 12 conditions 72.0 % with \geq 2 conditions	Multi-dimensional functional assessment questionnaire (OARS)	Combination of foot problems, arthritis and heart problems had most impact on functional disabilities on multivariate analysis A significant association between 11 conditions and functional disability.
Heyworth 2009 UK	Primary care registered patients 4836 adults Mean age 47.9	Self-report from a list of 6 conditions, confirmed by chart review 24 % had \geq 2 conditions	EQ-5D	Increasing numbers conditions significantly associated with lower EQ5D scores on multivariate analysis
Hunger 2011 Germany	Population based 4412 adults \geq 65 years	Self-report of \geq 2 conditions from a list of 6 conditions Prevalence of MM within sample not reported	EQ-5D	Combinations of conditions significantly associated with reduced EQ5D index scores on multivariate analysis (examined in pairs and compared to single condition alone)
Jayasinghe 2009 Australia	Primary care 96 General practices 7606 adults \geq 18 years Mean age 59.1	Software selected patients with at least one of three chronic conditions. MM: two or more chronic conditions. $n = 1497$ (19.7 %)	SF-12	Number of chronic conditions negatively associated with PCS-12 scores (physical component summary).
Joshi 2003 India	Population based survey 200 adults \geq 60 years	Self-report of conditions (ICD-10 codes) confirmed by chart review 83 % had \geq 4 conditions	Standardised Rapid Disability Rating Scale-2	Number of conditions significantly associated with increased mean disability scores
Kadam 2007 UK	Primary care registered patients 9439 aged \geq 50 years	1. Simple condition counts using chart review for \geq 2 coded conditions 81 % had \geq 2 conditions 2. Combinations of 185 selected conditions classified by severity on 4 point scale by GPs	SF-12 dichotomised into poor and good function	Increasing number of conditions significantly associated with poor physical function. AOR 1.6 for 2 or 3 conditions AOR 5 for \geq 6 conditions Increasing strength of association between MM severity and poor function
Kadam 2009 UK			SF-12	

Table 1 Included Cross-Sectional Studies (Continued)

	Primary care 8791 English aged ≥ 50 years 7753 from Netherlands aged ≥ 18 years	Classified based on 78 conditions which were classified on a 4 point severity index by GPs		Higher morbidity severity was significantly associated with poorer physical health on multivariate analysis
Keles 2007 Turkey	Community based survey 4605 parents /grandparents Mean age 53.2 (male) 51.6 (female)	Self-report of conditions from a list of 11 conditions 46 % of participants >1 chronic condition (n ~ 2118)	SF-12	As number of chronic conditions increased physical functioning declined Number of comorbidities an independent predictor of physical functioning
Kim 2012 Korea	Population based survey 1419 adults ≥ 65 years	Self-report of ≥ 2 conditions from list of 20 conditions Mean 3.88 conditions	EQ-5D	MM significantly associated with lowerEQ-5D index score in multivariate analysis
Lawson 2013UK	Population based survey 7054 aged ≥ 20 years	Self-report of ≥ 2 conditions from list of 40 conditions 18 % ≥ 2 conditions	SF-12 (no breakdown into physical component scores)	Number of conditions all significantly associated with reductions in SF12 scores in multivariate analysis
Michelson 2001 Sweden	Population based survey 3069 adults, Mean age 51	Self-report from list of 13 conditions Categorised into groups - no problems (0 conditions); few problems (1-2 conditions); some problems (3-4 conditions) and a lot (5-13 conditions) 28 % had some or a lot of problems	EORTC QLQ-C30 (HRQOL, specific to Cancer)	Multiple chronic health problems significantly associated with reduced HRQOL adjusted for age
Mujica-Mota 2014 UK	Population based survey 831,537 aged ≥ 18 years	Self-report of ≥ 2 conditions from list of 12 conditions 23 % ≥ 2 conditions	EQ-5D	Number of conditions significantly associated with decrease in EQ-5D scores in multivariate analysis
Noel 2007 USA	Primary care enrolled patients 422 adults Mean age 57 years	≥ 2 ICD-9 coded conditions from a list of 45 conditions 54 % ≥ 2 conditions	SF-12	Multimorbidity group had significantly lower PCS score (34.8) compared to single morbidity group (39.5)
Parker 2014 UK	Population based survey 5849 adults ≥ 65 years	Self-report of ≥ 2 conditions from list of 15 conditions, verified by chart review HADS score for depression 26 % ≥ 2 conditions	EQ-5D	Total number of conditions not associated with decreased EQ-5D scores on multivariate analysis
Rijken 2005 Netherlands	Primary care sample 1673 chronic disease patients	Coded conditions identified by chart review from list of six conditions 13 % ≥ 2 conditions	SF-36	Multimorbidity associated with significantly lower PCS scores
Wensing 2001 Netherlands	Primary care attenders 4040 adults (28 % ≥ 60 years)	Self-report of ≥ 2 conditions from a list of 25 conditions 16 % ≥ 2 conditions	SF-36	Increasing number conditions associated with lower PCS scores but effect disappeared when controlled for age

Table 2 Included Cohort Studies

Author Publication Year Country	Population and setting	Definition and prevalence of multimorbidity (MM)	Functional decline outcome measure/s	Follow-up period Losses to follow-up (%)	Results
Abizanda 2014 Spain	General population (FRADEA Study) 842 adults aged >70 yrs	MM ≥ 2 chronic diseases in a specific period of time. 14 pre-specified conditions selected for prevalence and impact on disability/mortality Chronic diseases identified from medical records and coded via ICD-10 580 ≥ 2 conditions (69.0 %)	Barthel index (disability) Fried's criteria (frailty)	2 years 7.5 % loss to follow-up	Disability and frailty was not associated with MM over two years.
Aarts 2012 Netherlands	Primary care (Maastricht Aging Study) 1184 adults aged 21–84 years	MM ≥ 2 chronic diseases co-occurring within one person Morbidities sourced from GP database including all current and past health problems by clinician 96 included conditions based on medical literature and clinical experience 35.5 % ≥ 2 chronic diseases	SF-36	3 and 6 years 16.4 % loss to follow-up	MM significantly associated with poorer physical functioning at all 3 follow-up points ($p < 0.001$) Significant steep decline in physical function between 3 and 6 year follow up in those with MM ($p < 0.001$) Participants whose morbidity status changed from baseline to 3 year follow up (either to single or MM) associated with significantly lower physical function ($p < 0.001$)
Bayliss 2004 USA	Primary care (Medical Outcomes Study) 2708 adults, mean age 57.6 years	No definition of MM reported Self-report of 7 pre-specified chronic conditions. Condition presence also sourced from records Conditions chosen as of high prevalence in practice and in literature 686 ≥ 2 chronic diseases (25.3 %)	SF-36 (PCS scores)	4 years 41.9 % loss to follow up	≥ 4 chronic diseases associated with significant decline in physical function ($p < 0.05$) Reduction in PCS by 6.5 used as criteria for clinically significant <4 chronic diseases no association with physical decline Congestive Heart Failure, diabetes and/or respiratory disease predictive of clinically significant decline in PCS ($p < 0.05$)
Byles 2005 Australia	Primary care (Veteran's Affairs Preventative Care Trial) 1417 adults ≥ 70 years	Co-existence of multiple diseases in the same individual Self-reported MM questionnaire consisting of 25 conditions Severity measure incorporated and included mild cognitive decline 1107 > 3 conditions (78.1 %)	SF-36	2 years 7.2 % lost to follow up	Quality of Life (QoL) decreases as number of conditions increases The presence of each condition associated with significantly lower SF-36 scores (except heart bypass, stroke and diabetes) Data not shown
Drewes 2011 Netherlands	General population (Leiden 85-plus study) 594 adults aged 85 years	MM ≥ 2 chronic diseases at age 85 years Chart confirmed presence of 9 common conditions pre-specified 234 ≥ 2 chronic diseases (39.4 %)	Groningen Activity Restriction Scale	5 years 53.9 % loss to follow up	Participants with MM had an accelerated progression of ADL (activities of daily living) disability over time compared to those without MM (95 % CI 0.21 -0.63, $p < 0.001$) MM demonstrated accelerated increase in ADL disability in older people with optimal cognitive function (95 % CI 0.39-0.95, $p < 0.001$) This was not observed in participants with lower MMSE scores.
Kiely 1997 USA	Community based (Sample first drawn 1982: Massachusetts state-supported home care programme) 1060 adults aged ≥ 65 years	No definition of MM reported Self-report of 5 pre-specified medical conditions MM numbers not reported	Functional Dependency Index (FDI)	3 years 22.5 % loss to follow up	Each additional medical condition resulted in a significant increase in the FDI score ($p < 0.001$) Rate of decline did not differ by total number of medical conditions ($p = 0.67$)

Table 2 Included Cohort Studies (Continued)

Nikolova 2011 Canada	Community based (Research Program on Integrated Services for the Elderly) 1164 disabled adults ≥65 years Disability status estimated using the Functional Autonomy Measurement System (SMAF) Score ≥10 excluded	Comorbidity : number of chronic diseases Self-report of comorbidities using 16 item questionnaire Diseases not specified but grouped into four categories: 0-1 disease2-3 diseases4-5 diseases ≥6 diseases 1084 ≥ 2 diseases (93.1 %)	Functional status measured using 7 item IADL subscale of the OAR and Katz ADL index	3 yearsHigh rate of attrition discussed but loss to follow up number NR	Comorbidity burden is a strong predictor in developing IADL and ADL disability 6 diseases vs 0-1 diseaseOR (95 % CI)IADL 6.42 (1.52; 27.18) ADL 16.73 (3.08; 91.06) 4 -5 diseases vs 0-1 diseaseOR(95 % CI)IADL 1.20 (0.52; 2.80) ADL 0.89 (0.26; 2.98) 2-3 diseases vs 0 -1 diseaseOR(95 % CI) IADL 1.00 (0.46; 2.20) ADL 1.44 (0.49; 4.15) ≥6 morbidities-6 times more likely to develop ADL disability and 17 times more likely to develop IADL disability
Prior 2011UK	Primary care 4672 adults aged ≥50 years	Comorbidity -number of chronic diseases Record confirmed condition counts over previous 2 yearsIn addition to number of GP consultations for morbidity in 2 year period Specific cardiovascular and musculoskeletal conditions (n = 15) chosen as most prevalent in developed countries Stage of disease as proxy for severity 561 ≥ 1 CVD & MSK condition MM in overall group not reported	SF-12 (PCS)	3 years46 % loss to follow up	Cardiovascular cohort: higher comorbidity and increasing severity in disease associated with greater deterioration in PCS. Significant deterioration shown for HTN (p < 0.001) with PCS score deteriorating by -0.86 over three years Musculoskeletal cohort: no association
Rigler 2002 USA	Community based (Veteran's Affairs Medical Centre) 492 adults aged ≥65 years	Comorbidity scores: based on sum of the domains affected, and the sum of the domains which patients reported affected function. Self-report of 18 prevalent conditions from 8 organ domains via self-report335 ≥ 2 diagnoses (68.1 %)	MOS-36Physical Function IndexSelf-report ADL and IADL	1 year7.2 % loss to follow up	Increasing comorbidity significantly associated with increased risk of future functional decline (p < 0.001) OR 1.09: 2 conditions OR 2.41: ≥ 3 conditions Presence of ADL and IADL problems at baseline demonstrated to have a significant impact on new ADL problems developing at one year (p < 0.001) OR 4.77: 1 IADL problem at baseline OR 15.6: 1 ADL problem at baseline

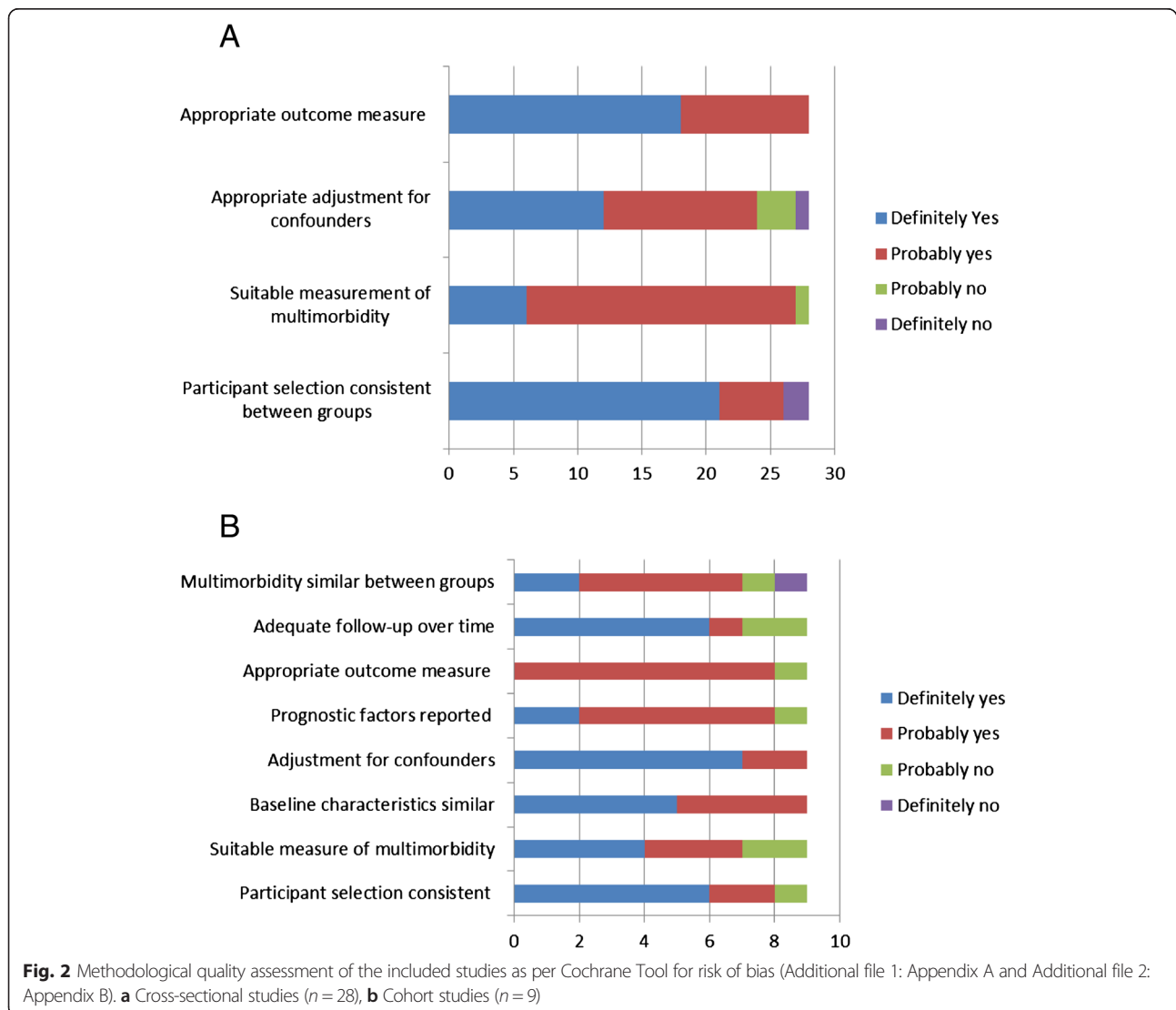
more likely to have deterioration in physical health compared to those with musculoskeletal conditions [59]. Disease severity was also examined in this study and was found to predict greater functional decline [59]. Two cross-sectional studies examined six different conditions and their combinations [38, 50]. Hunger et al. reported that stroke and bronchitis in combination had the greatest negative impact on function. Rijken et al. stated that combinations of diabetes, cardiovascular disease and chronic respiratory disease lead to a higher risk of physical disability. Drewes et al. examined the role of cognitive impairment in predicting disability in patients with multimorbidity [56]. They found that multimorbidity predicted an accelerated increase in ADL disability in participants with optimal cognitive function at baseline, but not in participants with lower MMSE scores at baseline. This may be explained by the fact that those with poor cognitive function at baseline already had

higher levels of disability so had less change in function over time.

One study analyzed the accrual of additional conditions over time and the impact that this had on function decline [53]. The authors reported that participants whose morbidity status changed from baseline to three year follow up (either to single or multimorbidity) had significantly lower physical function at follow up.

Risk of bias in included studies

Overall, the methodological quality of the included studies was good. The risk of bias assessment is presented in Figs. 2a and b. The majority of cross-sectional studies used valid and reliable outcome measures ($n = 18$) and most studies accounted for possible confounders ($n = 24$). We can also be reasonably confident that multimorbidity was measured appropriately. All papers used valid outcome



measures however, blinding and details of assessors was not reported in all. The majority of the cohort studies reported adequate follow up over time ($n = 6$) along with appropriate adjustment for confounding ($n = 7$). Overall, the outcome measures used were suitable and participant groups were well matched.

Discussion

Overall findings

This systematic review retrieved 37 relevant studies (nine cohort studies and 28 cross-sectional). Overall the majority of studies demonstrated an association between multimorbidity and functional decline. In addition, 77.8 % (seven out of nine) of the included cohort studies reported that multimorbidity predicts future functional decline. This was more marked with increasing numbers of conditions and was also linked to condition severity. Two cohort studies reported no significant association between functional disability and multimorbidity over time [52, 57]. The conditions included in these studies did not vary considerably from those seven studies which did demonstrate significance (Additional file 4: Appendix D). However, both studies included participants aged 70 years or older [52] and 65 years or older [57]. Abizanda et al. reported that functional ability was impaired at baseline in their participants [52]. It could be argued that the detection of further functional decline was limited due to the age group of participants.

This review adds to the growing evidence base examining the negative impact of multimorbidity on patient outcomes. It highlights a potential cumulative effect in that both multimorbidity and functional decline independently predict poorer outcomes. This review examines one direction of effect, i.e. that baseline multimorbidity predicts future functional decline but it is also possible that poor physical functioning will lead to worsening of multimorbidity, a relationship that our study group plan to examine in an ongoing prospective cohort study in Ireland [61]. For instance, patients with poorer physical function may be less able to engage in physical activity, which may then worsen health through weight gain or other effects on well-being. There is also considerable overlap with the concept of frailty which is also receiving increasing attention in the literature [62].

The findings of this review are consistent with existing evidence linking multimorbidity and poorer health related quality of life [16]. It is also consistent with the qualitative literature exploring the perspectives of patients with multimorbidity, which highlights problems with daily functioning [63]. Some of the impact of multimorbidity on functional decline may relate to the emerging concept of treatment burden [64] as those with multiple conditions are more likely to be attending

multiple healthcare providers and undergoing complex treatments.

Strengths and limitations of this review

We can be reasonably confident in the findings of this review as overall, there was minimal risk of bias in the included studies. However, variation in participants, multimorbidity definitions, follow-up duration, and outcome measures resulted in meta-analysis not being possible. The included studies also varied widely in the number and age of participants. This will have introduced some selection bias for participants. For example, one study reported that 20 % of non-responders and 10 % of responders were less than 40 years [39]. There was also disparity in the prevalence of multimorbidity in the included studies and not all studies examined the impact of numbers of conditions condition type and possible combinations or condition severity. The study settings varied which adds to generalizability though all were conducted in high income countries so results may not apply outside these settings. A further potential limitation was only studies published in English were included.

Implications of findings

This review highlights the need to carefully consider functional decline in patients with multimorbidity. The Cochrane review of community-based interventions to improve outcomes for people with multimorbidity suggested that such an approach could have a role to play in improving outcomes [19]. Two studies included in the updated Cochrane review had a strong focus on physical functioning and investigated occupational therapist and physiotherapist led interventions [65, 66]. Both studies reported significant improvements in patient outcomes including functional capacity with one demonstrating a reduction in mortality over time [66]. Future research should focus on the development and testing of interventions that incorporate a multidisciplinary approach that prioritizes physical function for this patient group. This is particularly important for patients with higher numbers of conditions and greater disease severity. Such an approach was also advocated in a recent clinical management review of multimorbidity, which also suggested that, depending on patient priorities, general practitioners should consider referral to allied health professionals who can intervene to prevent physical decline [67].

Given the complexities highlighted in this review around participant selection and definitions of multimorbidity, future research should be mindful that such variability in terminology exists and carefully consider

these issues when developing and reporting interventions [68].

Conclusion

Multimorbidity is recognised internationally as having a serious impact on health outcomes. This systematic review suggests that multimorbidity predicts future functional decline, which in turn will worsen health outcomes. Interventions are needed that effectively protect physical function in patients with multimorbidity to prevent this inevitable cascade towards poorer health outcomes.

Additional files

Additional file 1: Appendix A. Tool to Assess Risk of Bias in Cohort Studies (Cochrane). (DOC 43 kb)

Additional file 2: Appendix B. Tool to Assess Risk of Bias in Cross-sectional studies. (DOC 39 kb)

Additional file 3: Appendix C. Excluded Papers. (DOCX 20 kb)

Additional file 4: Appendix D: Included Conditions. (DOC 84 kb)

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

AR completed acquisition of the data, conducted analysis and interpretation of the data, drafted and revised the manuscript. EW conceived the idea and study design, conducted analysis and interpretation of the data along with drafting and revising the manuscript. POH conceived the idea and study design with EW, completed acquisition of the data and revised the manuscript. SS oversaw all aspects of the review and specifically advised on analysis and write-up. All authors were involved in article selection, writing and read and approved the final manuscript.

Acknowledgements

AR is funded by the Health Research Board (HRB) of Ireland as partSS oversaw all aspects of the review and of the HRB Structured PhD in Population Health and Health Services Research (SPHeRE) programme (SPHeRE/2013/01). SS and EW are based in the HRB funded Centre for Primary Care Research.

Author details

¹HRB Centre for Primary Care Research, Department of General Practice, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland. ²South East Training Programme for General Practice, General Practice Training Department, Waterford Regional Hospital, Dunmore Road, Waterford, Ireland. ³Department of Population Health Sciences, Royal College of Surgeons in Ireland, Beaux Lane House, Lower Mercer Street, Dublin 2, Ireland.

Received: 7 July 2015 Accepted: 18 September 2015

Published online: 15 October 2015

References

- Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med*. 2005;3(3):223–8.
- Van den Aker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence and determinants of co-occurring and recurrent disease. *J Clin Epidemiol*. 1998;51(5):365–75.
- Uijen AAA, Van de Lisdonk EH. Multimorbidity in Primary care: prevalence and trend over the past 20 years. *Eur J Gen Pract*. 2008;14(suppl):28–32.
- WHO. Global status report on noncommunicable diseases 2010: description of the global burden of NCDs, their risk factors and determinants. Geneva: World Health Organization; 2011. http://www.who.int/nmh/publications/ncd_report2010/en.
- Inouye SK, Wagner R, Acampora D, Horowitz RI, Cooney LM, Hurst LD, et al. A predictive index for functional decline in hospitalized elderly patients. *J Gen Intern Med*. 1993;8:645–52.
- Hebert R. Functional decline in old age. *Can Med Assoc J*. 1997;157:1037–45.
- Campbell SE, Seymour DG, Primrose WR, for the ACMEplus Project. A systematic literature review of factors affecting outcome in older medical patients admitted to hospital. *Age Aging*. 2004;33:110–5.
- Koyano W, Shibata H, Haga H, Suyama Y. Prevalence and outcome of low ADL and incontinence among the elderly: five years follow-up in a Japanese urban community. *Arch Gerontol Geriatr*. 1986;5(3):197–206.
- Ní Mhaoláin AM, Gallagher D, O'Connell H, Chin AV, Bruce I, Hamilton F, et al. Subjective well-being amongst community-dwelling elders: what determines satisfaction with life? Findings from the Dublin Healthy Aging Study. *Int Psychogeriatr*. 2012;24(2):316–23.
- Taylor AW, Price K, Gill TK, Adams R, Pilkington R, Carrangis N, et al. Multimorbidity - not just an older person's issue. *BMC Public Health*. 2010;10:718. doi:10.1186/1471-2458-10-718.
- Wolff J, Starfield B, Anderson G. Prevalence, expenditure and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;62:2269–76.
- Hoffman C, Rice D, Sung HY. Persons with chronic conditions. Their prevalence and costs. *JAMA*. 1996;276:1473–79.
- Barnett K, Mercer S, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of Multimorbidity and implications for health care, research, and medical education: a cross sectional study. *Lancet*. 2012;380(9836):37–43.
- Van Den Bussche H, Shon G, Kolonko T, Wegscheider K, Glaeske G, Koller D. Patterns of ambulatory medical care utilisation in elderly patients with special reference to chronic diseases and multimorbidity- results from a claims data based observational study in Germany. *BMC Geriatr*. 2011;11:54.
- Fortin M, Bravo G, Hudon C, Lapointe L, Almirall J, Dubois MF, et al. Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual Life Res*. 2006;15:83–91.
- Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10(4):430–9.
- Ambrose-Liu TYL, Ashe MC, Marra C and The Physical Activity and Chronic Conditions Research Team. Among older adults with multiple chronic conditions, physical activity is independently and inversely associated with health care utilization. *British Journal of Sports Medicine*. 2008; doi:10.1136/bjism.2008.046458.
- Kadam UT, Croft PR, North Staffordshire GP Consortium Group. Clinical multimorbidity and physical function in older adults: a record and health status linkage study in general practice. *Fam Pract*. 2007;24(5):412–9.
- Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev*. 2012;4:CD006560.
- Fortin M, Lapointe L, Hudon C, Vanasse A, Ntutu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes*. 2004;2:51.
- Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1.
- National Academy Press. Primary care: America's health in a new era. Washington, DC: National Academy Press; 1996.
- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Baker JG, Johnston MV. Prevalence and identification of problems in daily functioning in a primary medicine clinic. *Disabil Rehabil*. 2000;22(16):716–24.
- Baker TA, Whitfield KE. Physical functioning in older blacks: an exploratory study identifying psychosocial and clinical predictors. *J Natl Med Assoc*. 2006;98(7):1114–20.
- Bayliss M, Rendas-Baum R, White MK, Maruish M, Bjorner J, Tunis SL. Health-related quality of life (HRQL) for individuals with self-reported chronic physical and/or mental health conditions: panel survey of an adult sample in the United States. *Health Qual Life Outcomes*. 2012;10:154.

27. Bayliss Ellis JL, Shoup JA, Zeng C, McQuillan DB, Steiner JF. Association of patient-centered outcomes with patient-reported and ICD-9-based morbidity measures. *Ann Fam Med*. 2012;10(2):126–33.
28. Bretschneider C, Leicht H, Bickel H, Dahlhaus A, Fuchs A, Gensichen J, et al. Relative impact of multimorbid chronic conditions on health-related quality of life—results from the MultiCare Cohort Study. *PLoS One*. 2013;8(6), e6742.
29. Agborsangaya CB, Lau D, Lahtinen M, Cooke T, Johnson JA. Health-related quality of life and healthcare utilization in multimorbidity: results of a cross-sectional survey. *Qual Life Res*. 2013;22(4):791–9.
30. Cesari M, Onder G, Russo A, Zamboni V, Barillaro C, Ferrucci L, et al. Comorbidity and physical function: results from the aging and longevity study in the Sirente geographic area (iSIRENTE study). *Gerontology*. 2006;52(1):24–32.
31. Chen HY, Baumgardner DJ, Rice JP. Health-related quality of life among adults with multiple chronic conditions in the United States, Behavioral Risk Factor Surveillance System, 2007. *Prev Chronic Dis*. 2011;8(1):A09.
32. Cheng L, Cumber S, Dumas C, Winter R, Nguyen KM, Nieman LZ. Health related quality of life in pregeriatric patients with chronic diseases at urban, public supported clinics. *Health Qual Life Outcomes*. 2003;1:63.
33. Formiga F, Pujol R, Perez-Castejon JM, Ferrer A, Henriquez E. Low comorbidity and male sex in nonagenarian community-dwelling people are associated with better functional and cognitive abilities: the NonaSantfeliu study. *J Am Geriatr Soc*. 2005;53(10):1836–7.
34. Fortin M, Dubois MF, Hudon C, Soubhi H, Almirall J. Multimorbidity and quality of life: a closer look. *Health Qual Life Outcomes*. 2007;5:52.
35. Goins RT, Pilkerton CS. Comorbidity among older American Indians: the native elder care study. *J Cross Cult Gerontol*. 2010;25(4):343–54.
36. Griffith L, Raina P, Wu H, Zhu B, Stathokostas L. Population attributable risk for functional disability associated with chronic conditions in Canadian older adults. *Age Ageing*. 2010;39(6):738–45.
37. Heyworth IT, Hazell ML, Linehan MF, Frank TL. How do common chronic conditions affect health-related quality of life? *Br J Gen Pract*. 2009;59(568):e353–8.
38. Hunger M, Thoron B, Chunk M, During A, Men P, Peters A, et al. Multimorbidity and health-related quality of life in the older population: results from the German KORA-age study. *Health Qual Life Outcomes*. 2011;9:53.
39. Jayasinghe UW, Proudfoot J, Barton CA, Amoroso C, Holton C, Davies GP, et al. Quality of life of Australian chronically-ill adults: patient and practice characteristics matter. *Health Qual Life Outcomes*. 2009;7:50.
40. Joshi K, Kumar R, Avasthi A. Morbidity profile and its relationship with disability and psychological distress among elderly people in Northern India. *Int J Epidemiol*. 2003;32(6):978–87.
41. Kadam UT, Croft PR. Clinical multimorbidity and physical function in older adults: a record and health status linkage study in general practice. *Fam Pract*. 2007;24(5):412–9.
42. Kadam UT, Schellevis FG, Lewis M, van der Windt DA, de Vet HC, Bouter LM, et al. Does age modify the relationship between morbidity severity and physical health in English and Dutch family practice populations? *Qual Life Res*. 2009;18(2):209–20.
43. Keles H, Ekici A, Ekici M, Bulcun E, Altinkaya V. Effect of chronic diseases and associated psychological distress on health-related quality of life. *Intern Med J*. 2007;37(1):6–11.
44. Kim KI, Lee JH, Kim CH. Impaired health-related quality of life in elderly women is associated with multimorbidity: results from the Korean National Health and Nutrition Examination Survey. *Gend Med*. 2012;9(5):309–18.
45. Lawson KD, Mercer SW, Wyke S, Grieve E, Guthrie B, Watt GC, et al. 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. *Int J Equity Health*. 2013;12:67.
46. Michelson H, Bolund C, Brandberg Y. Multiple chronic health problems are negatively associated with health related quality of life (HRQoL) irrespective of age. *Qual Life Res*. 2000;9(10):1093–104.
47. Mujica-Mota RE, Roberts M, Abel G, Elliott M, Lyratzopoulos G, Roland M, et al. Common patterns of morbidity and multi-morbidity and their impact on health-related quality of life: evidence from a national survey. *Qual Life Res*. 2015;24(4):909–18.
48. Noel PH, Parchman ML, Williams Jr JW, Cornell JE, Shuko L, Zeber JE, et al. The challenges of multimorbidity from the patient perspective. *J Gen Intern Med*. 2007;22 Suppl 3:419–24.
49. Parker L, Moran GM, Roberts LM, Calvert M, McCahon D. The burden of common chronic disease on health-related quality of life in an elderly community-dwelling population in the UK. *Fam Pract*. 2014;31(5):557–63.
50. Rijken M, van Kerkhof M, Dekker J, Schellevis FG. Comorbidity of chronic diseases: effects of disease pairs on physical and mental functioning. *Qual Life Res*. 2005;14(1):45–55.
51. Wensing M, Vingerhoets E, Grol R. Functional status, health problems, age and comorbidity in primary care patients. *Qual Life Res*. 2001;10(2):141–8.
52. Abizanda P, Romero L, Sanchez-Jurado PM, Martinez-Reig M, Alfonso-Silguero SA, Rodriguez-Manas L. Age, frailty, disability, institutionalization, multimorbidity or comorbidity. Which are the main targets in older adults? *J Nutr Health Aging*. 2014;18(6):622–7.
53. Aarts S, den Akker M, Bosma H, Tan F, Verhey F, Metsemakers J, et al. The effect of multimorbidity on health related functioning: temporary or persistent? Results from a longitudinal cohort study. *J Psychosom Res*. 2012;73(3):211–7.
54. Bayliss EA, Bayliss MS, Ware Jr JE, Steiner JF. Predicting declines in physical function in persons with multiple chronic medical conditions: what we can learn from the medical problem list. *Health Qual Life Outcomes*. 2004;2:47.
55. Byles JE, D'Este C, Parkinson L, O'Connell R, Treloar C. Single index of multimorbidity did not predict multiple outcomes. *J Clin Epidemiol*. 2005;58(10):997–1005.
56. Drewes YM, den Elzen WP, Mooijaart SP, de Craen AJ, Assendelft WJ, Gussekloo J. The effect of cognitive impairment on the predictive value of multimorbidity for the increase in disability in the oldest old: the Leiden 85-plus Study. *Age Ageing*. 2011;40(3):352–7.
57. Kiely DK, Morris JN, Morris SA, Cupples LA, Ooi WL, Sherwood S. The effect of specific medical conditions on functional decline. *J Am Geriatr Soc*. 1997;45(12):1459–63.
58. Nikolova R, Demers L, Beland F, Giroux F. Transitions in the functional status of disabled community-living older adults over a 3-year follow-up period. *Arch Gerontol Geriatr*. 2011;52(1):12–7.
59. Prior JA, Jordan KP, Kadam UT. Influence of chronic diseases on long-term change in physical health: a consultation-survey linkage cohort study in general practice. *Qual Life Res*. 2012;21(4):581–91.
60. Rigler SK, Studenski S, Wallace D, Reker DM, Duncan PW. Co-morbidity adjustment for functional outcomes in community-dwelling older adults. *Clin Rehabil*. 2002;16(4):420–8.
61. Whelan BJ, Savva GM. Design and methodology of the Irish Longitudinal Study on Ageing. *J Am Geriatr Soc*. 2013;61 Suppl 2:S265–8.
62. Kahlon S, Pederson J, Majumdar SR, Belga S, Lau D, Fradette M, et al. Association between frailty and 30-day outcomes after discharge from hospital. *CMAJ*. 2015;187(11):799–804.
63. Noel PH, Frueh BC, Larme AC, Pugh JA. Collaborative care needs and preferences of primary care patients with multimorbidity. *Health Expect*. 2005;8(1):54–63.
64. Mair FS, May CR. Thinking about the burden of treatment. *BMJ (Clinical research ed)*. 2014;349:g6680.
65. Garvey J, Connolly D, Boland F, Smith SM. OPTIMAL, an occupational therapy led self-management support programme for people with multimorbidity in primary care: a randomized controlled trial. *BMC Fam Pract*. 2015;16:59.
66. Gitlin LN, Winter L, Dennis MP, Corcoran M, Schinfeld S, Hauck WW. A randomized trial of a multicomponent home intervention to reduce functional difficulties in older adults. *J Am Geriatr Soc*. 2006;54(5):809–16.
67. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. *BMJ (Clinical research ed)*. 2015;350:h176.
68. Smith SM, Bayliss EA, Mercer SW, Gunn J, Vestergaard M, Wyke S, et al. How to design and evaluate interventions to improve outcomes for patients with multimorbidity. *Journal of Comorbidity*. 2013;3:10–7.