

Accepted Manuscript

Title: Evidence on multimorbidity from definition to intervention: an overview of systematic reviews

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PII: S1568-1637(17)30012-0

DOI: <http://dx.doi.org/doi:10.1016/j.arr.2017.05.003>

Reference: ARR 764

To appear in: *Ageing Research Reviews*

Received date: 24-1-2017

Revised date: 9-5-2017

Accepted date: 9-5-2017



Please cite this article as: Xu, Xiaolin, Mishra, Gita D., Jones, Mark, Evidence on multimorbidity from definition to intervention: an overview of systematic reviews. *Ageing Research Reviews* <http://dx.doi.org/10.1016/j.arr.2017.05.003>

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Highlights

- This overview identified 53 systematic reviews on various aspects of multi-morbidity including definition, measurement, prevalence, risk factors, health outcomes, clinical practice and medication (polypharmacy), and intervention and management.
- Heterogeneity of topics, methods, and reporting has resulted in inconsistent findings among the included reviews.
- However there is general agreement that further prospective research is needed, especially longitudinal cohort studies and randomized control trials, in order to provide more definitive evidence on multimorbidity.

Evidence on multimorbidity from definition to intervention: an overview of systematic reviews

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ABSTRACT

The increasing challenge of multiple chronic diseases (multimorbidity) requires more evidence-based knowledge and effective practice. In order to better understand the existing evidence on multimorbidity, we performed a systematic review of systematic reviews on multimorbidity with pre-established search strategies and exclusion criteria by searching multiple databases and grey literature. Of 8006 articles found, 53 systematic reviews (including meta-analysis and qualitative research synthesis performed in some reviews) that stated multimorbidity as the main focus were included, with 79% published during 2013 to 2016. Existing evidence on definition, measurement, prevalence, risk factors, health outcomes, clinical practice and medication (polypharmacy), and intervention and management were identified and synthesised. There were three major definitions from three perspectives. Seven studies on prevalence reported a range from 3.5% to 100%. As six studies showed, depression, hypertension, diabetes, arthritis, asthma, and osteoarthritis were prone to be comorbid with other conditions. Four groups of risk factors and eight multimorbidity associated outcomes were explored by five and six studies, respectively. 27 studies evaluated interventions, which could be categorized into either organizational or patient-oriented, the effects of these interventions were varied. We were unable to draw solid conclusions from this overview due to the heterogeneity in methodology and inconsistent findings among included reviews. As suggested by all included studies, there is a need for prospective research, especially longitudinal cohort studies and randomized control trials, to provide more definitive evidence on multimorbidity.

Keywords: multimorbidity; systematic review; definition; prevalence; risk factors; outcomes; polypharmacy; intervention

1. Introduction

Age-associated multiple chronic diseases (multimorbidity) is a growing issue and poses a major challenge to health care systems around the world (Tarry-Adkins and Ozanne; World Health Organization., 2015). Dealing with multimorbidity is complex for both health care providers and researchers (Atun, 2015). Although research interest in multimorbidity is growing, for example, our previous research found an exponential growth of research outputs on multimorbidity in the past decade; a number of knowledge gaps in multimorbidity research need to be addressed (US Department of Health and Human Services., 2010). These knowledge gaps may include all aspects of multimorbidity. Healthy aging is a World Health Organization (WHO) global health and research priority for 2016 to 2020 (Executive Board 134 A69/17., 2016; World Health Organization., 2015)

Systematic reviews are recognized as the cornerstone of evidence-based health care (Pieper et al., 2014). It is important to assess the gaps in existing evidence by synthesising these systematic reviews, so that valuable knowledge and effective interventions on multimorbidity may be identified and put into practice. We did a systematic review of systematic reviews to assess the present evidence on multimorbidity to answer: What do we know about the current evidence on multimorbidity research and practice, and where do we go in the future based on the implications of current evidence?

2. Methods

2.1 Review eligibility criteria and search strategy

Inclusion criteria were: (1) review of primary studies by a systematic literature search; (2) the main focus of the article was on multimorbidity; (3) the subtopics can be broad, such as definition, epidemiology, outcomes, intervention, and intervention; (4) written in English; and (5) studies referring to humans. Studies whose contents primarily addressed refer to an index disease and its related comorbidity, such as diabetes and its comorbidities, were excluded. If studies included partial content about multimorbidity, we included them if we were able to extract relevant data.

We performed a systematic literature search to identify all published systematic reviews on multimorbidity. PubMed, Embase, and Cochrane Database of Systematic Review were searched from inception to August 2016. Details on search strategies are included in Appendices 1-4. We also used a Google search to identify grey literature, and manually searched the *Journal of Comorbidity* for potential reviews.

2.2 Data extraction and evidence synthesis

Two author (XX, MJ) conducted the searches, eligibility assessment, data extraction, evidence synthesis, and quality assessment. Regular study group meetings were held to review the process, and to resolve any discrepancies and questions (XX, GDM and MJ). For each systematic review, characteristics were extracted on the duration of included studies, author's country, review types, topics, and number of included studies. Specific data extraction forms were developed for prevalence, outcomes and interventions.

We did not perform meta-analysis because the heterogeneity and overlap of primary studies among some systematic reviews. Instead, we performed qualitative evidence synthesis in tables or narrative text based on the volume of evidence.

2.3 Quality assessment

We assessed methodologic quality of each included systematic review with the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007). The AMSTAR tool is a reliable and valid tool to assess both systematic reviews of randomized and non-randomized control studies (Pieper et al., 2014).

2.4 Ethical issues

The research used published data from secondary sources and did not involve any interactions with human subjects. Hence it is exempt from institutional review board (IRB) approval process.

3. Results

3.1 Overview of search results and quality assessment

A total of 8006 systematic reviews were identified, of which 107 articles were included for full text screening, with 54 excluded for various reasons. The study selection process is presented in Figure 1, and the excluded articles are listed in Appendix 5. The first review was published in 2004, and 79% (n=42) were published between 2013 and 2016. All of the reviews were in English, 51 were from Europe and North American, two were from China and India. All of the reviews were systematic reviews, five performed meta-analysis, and seven performed qualitative research synthesis, see Appendix 6.

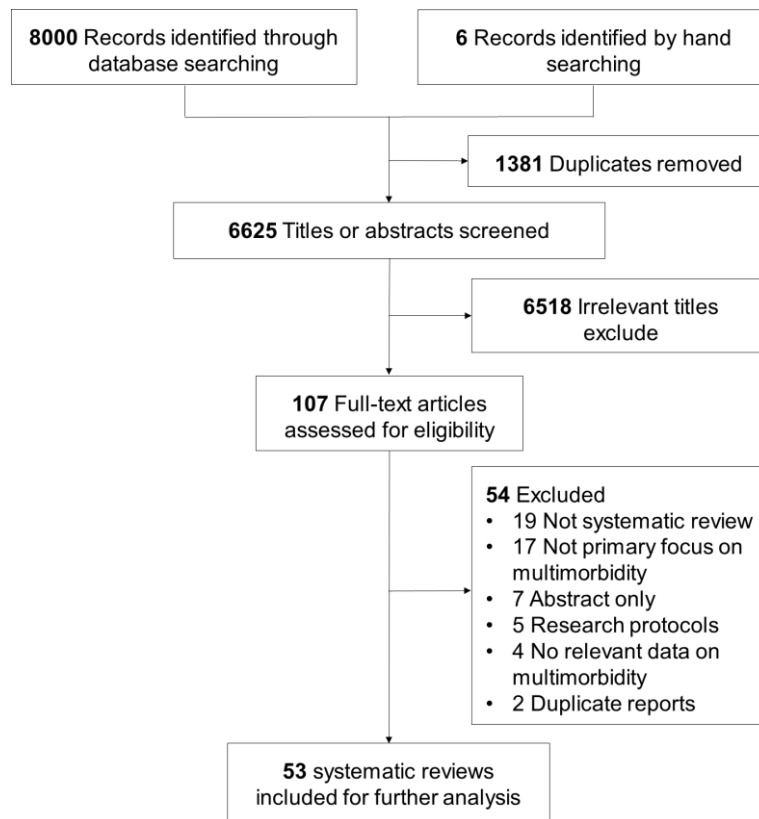


Figure 1. PRISMA flow chart for overview of systematic review of multimorbidity.

Of the included 53 systematic reviews, six reviewed definition and measurement, seven reviewed prevalence, nine reviewed disease clusters and patterns, five reviewed risk factors, nine reviewed outcomes, three reviewed clinical decision making, three reviewed clinical practice guidelines, eight reviewed medication, 11 reviewed intervention and management, and two reviewed inclusion multimorbidity in clinical and intervention trials and multimorbidity at the end of life (see Figure 2 and Appendix 6).

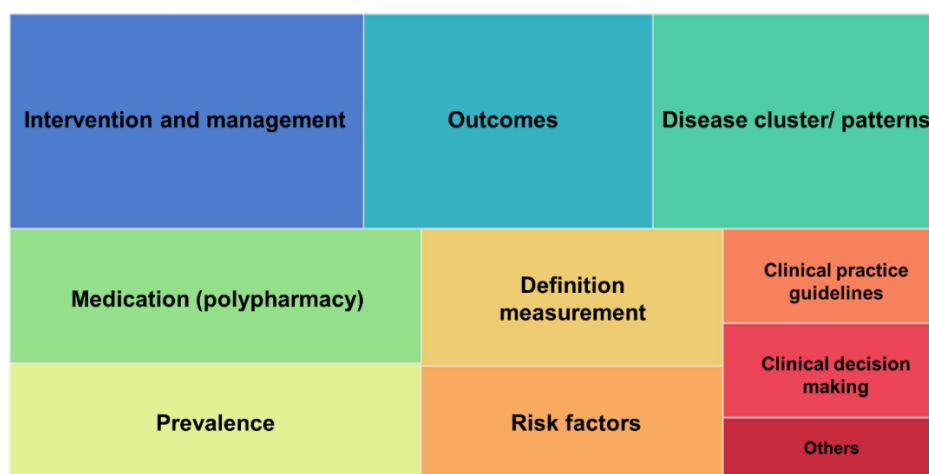


Figure 2. Summary of research topics on multimorbidity. The size of each rectangle for each topic in this tree map is proportional to the number of studies from all included systematic reviews.

The overall AMSTAR ratings was similar between the two independent reviews (intra-class correlation 0.91). Ratings ranged between 1 and 11 for each of the observers with a comparison between the two observers showing 87% ratings within 1 of each other and the remaining 13% within 2 of each other. Ratings by XX are presented in Appendix 7. As the AMSTAR tool was designed specifically for RCTs, the quality of reviews that performed meta-analysis with RCTs was high (average score was 8). However, the quality of reviews that performed qualitative research synthesis was generally low (average score was 4.4), because some items (e.g. the appropriate use of methods to combine findings of studies and assessment of the likelihood of publication bias) are not available for non-RCTs and qualitative research. The main methodological weaknesses were lack of 'a priori' design (protocol, ethics approval, or pre-determined/a priori published research objectives) and lack of a list of excluded studies.

3.2 Definition and measurement

Heterogeneity in definition and measurement of multimorbidity is the key issue in most included systematic reviews, which led to difficulties in results comparison and precluded meta-analysis. We detected two systematic reviews focused on definition (Le Reste et al., 2013; Willadsen et al., 2016), and five focused on measurement related topics (Diederichs et al., 2011; Holzer et al., 2014; Huntley et al., 2012; Willadsen et al., 2016; Zullig et al., 2016).

Three major definitions were detected from three major perspectives: epidemiology and public health, long term care and family medicine in primary care, and clinicians and patients in daily clinical practice (Table 1). Each of the definitions has strengths and limitations. The WHO definition is simple and easy to implement and was commonly used by most included studies. The other two definitions are comprehensive, yet more relevant to clinical practice for GPs and patients.

Most studies included chronic conditions in the definition, some studies included acute conditions (Le Reste et al., 2013), but inclusion of these conditions is undesirable as they inflate multimorbidity rates unnecessarily (Salive, 2013). However, other fundamental determinates: biopsychosocial factors and somatic risk factors, coping strategies of the patient, burden of disease, health care consumption, disability, quality of life, social network, and health outcome were suggested to be considered in long term care and family medicine (Le Reste et al., 2013).

Table 1
Definition of multimorbidity from different perspectives.

Sources	Perspective	Definition or main suggestion	Strengths	Limitations
(World Health Organization, 2015)	Epidemiology and public health	The co-occurrence of two or more chronic medical conditions in one person	Easy to use in research for epidemiological and disease burden	Is not sufficiently clear for a particular purpose, and could lead to

(Willadsen et al., 2016)	Clinicians and patients in daily clinical practice	The role of diseases, risk factors, symptoms, and severity need to be included in the definition	More relevant for daily clinical work, and has a better capacity for capturing the patient's perspective (symptoms)	numerous interpretations Very complicated, especially for the situation of compression among studies
(Le Reste et al., 2013)	Long term care and family medicine in primary care	Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk. Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the health consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity). Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty	Brings into focus the possible outcomes of multimorbidity (health outcomes, disability, quality of life, frailty) to keep physicians alert to those patients' needs	Including acute conditions makes the use of this definition more complicated, because acute conditions inflate multimorbidity rates unnecessarily

Studies on measurement of multimorbidity focused on the role of cut-points in the definition (Holzer et al., 2014; Willadsen et al., 2016), instruments to assess the level and outcome of multimorbidity (Diederichs et al., 2011; Huntley et al., 2012), and the role of complexity in the definition (Zullig et al., 2016).

The prevalence of multimorbidity primarily depends on how many conditions to include. 37% of studies used a cut-point of two or more conditions to a range of 4-147 different conditions in the definition (Willadsen et al., 2016). The cut-points of two or three chronic conditions provides essentially the same information on prevalence (Holzer et al., 2014). A list of at least 12 chronic diseases, is required in estimating stable prevalence rates (Fortin et al., 2012).

Multimorbidity indices are usually used to predict the disease severity and health outcome at the individual level. The most commonly used instruments were Charlson index, Chronic Disease Score, ACG System, and Cumulative Index Illness Rating Scale (Diederichs et al., 2011; Huntley et al., 2012). When choosing instruments we need to consider the type of data available and specific outcomes (Huntley et al., 2012).

Complexity is another factor that poses challenges for definition of multimorbidity in research (Grembowski et al., 2014). To improve care, current models for multimorbidity patient's needs to include social and medical components to address the spectrum of factors driving complexity (Zullig et al., 2016). Zullig and colleagues identified a Cycle of Complexity model, which strengthened the weakness of former complexity models in five aspects: contextual factors, dynamics of complexity, patients' preference, acute health shocks, and resilience.

3.3 Epidemiology

3.3.1 Prevalence

There were seven systematic reviews (Fortin et al., 2012; Hu et al., 2015; Marengoni et al., 2011; Pati et al., 2015; Salive, 2013; Van Den Brink et al., 2013; Violan et al., 2014) focused on the prevalence of multimorbidity. Detailed information extracted from the systematic reviews is summarized in Table 2.

Of the seven included systematic reviews, four were from Europe and North American countries, one from China, and one from India and Bangladesh. Studies methods included cross-sectional studies and various national and local medical databases. The number of conditions varied from two to many, with prevalence from 3.5% (at age 75) to 100% (at mean age 85). The prevalence increased with the increase of age, an S-shape curve for prevalence by age was detected in the general population (Fortin et al., 2012), and the prevalence in older persons is nearly 100% (Fortin et al., 2012; Marengoni et al., 2011; Van Den Brink et al., 2013). However, the results vary widely among studies, and no meta-analysis was performed as the heterogeneity was large in terms of definition, sample, and methods among primary studies (Fortin et al., 2012; Pati et al., 2015).

Table 2

Characteristics of systematic review concerning prevalence of multimorbidity.

Study	Design & Samples	Duration	Countries	Settings	Age	Number of conditions	Results	Quality of included studies
(Marengoni et al., 2011)	12 cross-sectional	1998-2009	Dutch, US, Canada, Australia, Sweden, Spain	General population, community, hospital and institution based people	All	$\geq 2-4$	20.3%-98 % (20-30% when the whole population was considered, 55-98% when older persons were included)	NA
(Fortin et al., 2012)	21 NA study types	1989-2010	Netherlands, UK, Canada, Australia, Greece, US, Israel, Finland, Italy, Ireland, Spain	General population and primary care	All	From 2 to many	An S-shape curve for prevalence by age, with lower estimates before 40 years (< 20%) and then a steep increase in prevalence followed by a plateau at about 70 years (around 75%), the prevalence at age 75 in primary care is 3.5%-98.5% and the general population is 13.1-71.8% 13% at age of 10 to 83% at age ≥ 75	All were good quality (Strengthening the Reporting of Observational Studies in Epidemiology, STROBE)
(Salive, 2013)	17 self-reported medical database, recruited cohort	1989-2012	US, Israel, Finland, Netherlands, Italy, Canada, Ireland, Australia, Germany, Sweden, Spain	National sample survey, medical claim data, cohort study, clinical assessment	All	From 2 to 6-many		NA
(Van Den Brink et al., 2013)	1 cross-sectional	2009	Norway	Long-term care facilities	85	6-33	Nearly 100%	Poor quality
(Pati et al., 2015)	13 cross-sectional	2002-2015	India, Bangladesh	Community based (urban and rural)	≥ 18	From 2 to 7-16 (1 study did not list)	4.5%-83%	Good quality (STROBE)
(Hu et al., 2015)	9 cross-sectional	2002-2011	China	Community based	≥ 60	From 2 to 7-14	6.4%-76.5%	2 low risk, 2 high risk, 5

(Violan et al., 2014)	39 21 cross-sectional, 18 cohort	1984-2013	Italy, UK, Australia, Spain, Canada, Ireland, Germany, US, Sweden, Netherlands, Greece, Switzerland, Spain	Health records, interview, claims	All	From 2 to 5-335	12.9%-95.1%	unclear (STROBE) High in most studies (STROBE)
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3.3.2 Disease clusters and patterns

Knowledge about the patterns, specific diseases combinations, and common diseases of multimorbidity will provide essential information for guideline development, clinical management, and public intervention. Three disease patterns (cardiovascular and metabolic disease, mental health related problems, and musculoskeletal disorders) were identified among 97 patterns composed of two or more diseases and 63 patterns were composed of three or more diseases (Prados-Torres et al., 2014). Four statistics methodologies were detected to determine patterns: cluster analysis techniques, factor analysis, the observed-to-expected ratio, and multiple correspondence analyses (Prados-Torres et al., 2014).

Sinnige and colleagues identified 165 combinations of two diseases from 63 diseases in Europe and North America. Of the combinations, depression was most commonly clustered, followed by hypertension, diabetes, and coronary artery disease (Sinnige et al., 2013). An Australian elderly population based systematic review found that over 50% of the elderly patients with arthritis also had hypertension, followed by CVD, dyslipidemia, diabetes, and mental health problems; whereas 60% of elderly patients with asthma reported arthritis followed by CVD and diabetes (Caughey et al., 2008). Certain disease combinations may have greater risk for certain types of health outcomes (France et al., 2012), such as chronic respiratory disease, congestive heart failure, and diabetes may result in higher physical decline than other combinations.

Six systematic reviews reported common diseases in the included studies (Caughey et al., 2008; Diederichs et al., 2011; Hu et al., 2015; Pati et al., 2015; Sinnige et al., 2013; Willadsen et al., 2016). The detailed information extracted from systematic reviews are summarized in Table 3 and Appendix 8.

Table 3

Summary of disease patterns, disease combinations, and common diseases in multimorbidity.

Disease patterns	Disease combinations	Common diseases
<ul style="list-style-type: none"> Cardiovascular and metabolic diseases Mental health related problems Musculoskeletal disorders 	<ul style="list-style-type: none"> Depression comorbid with other 8 conditions (e.g. hypertension, arthritis, diabetes) Hypertension comorbid with other 6 conditions (e.g. osteoarthritis, diabetes, cancer) Diabetes comorbid with other 6 conditions (e.g. hypertension, coronary artery disease) Arthritis comorbid with hypertension, CVD, dyslipidemia, diabetes, and mental health problems 	<ul style="list-style-type: none"> Diabetes Heart disease Cancer Hypertension Depression COPD Stroke Arthritis/ osteoarthritis Osteoporosis Asthma Gastrointestinal problems Heart failure Dementia Hearing problems

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- | | |
|---|---|
| <ul style="list-style-type: none"> • Asthma comorbid with arthritis, CVD, and diabetes • Osteoarthritis comorbid with CVD and/or metabolic conditions | <ul style="list-style-type: none"> • Vision problems • Unitary problems • Thyroid diseases |
|---|---|
-

3.2.3 Risk factors

Five systematic reviews (Boutayeb et al., 2013; France et al., 2012; Marengoni et al., 2011; Pati et al., 2015; Violan et al., 2014) summarized risk factors for multimorbidity (Table 4). Identified risk factors for multimorbidity may be categorized into four groups: biomedical and individual factors, health behaviours, socioeconomic characteristics, and social and environment factors. Although most studies suggested low economic status and lower education were risk factors for multimorbidity, some studies reported opposite findings, such as high income as a risk factor in LMICs (Pati et al., 2015).

Table 4

Summary of risk factors for multimorbidity.

Biomedical and individual factors	Socioeconomic characteristics	Social and environment factors	Health behaviours
<ul style="list-style-type: none"> • Aging • Women • High number of previous disease • Negative life events • External health locus of control • Mental disorders 	<ul style="list-style-type: none"> • Lower social economic status • High income Group (LMICs) • Lower education • Less social networks • Fully dependent • Unemployed/retired 	<ul style="list-style-type: none"> • Living in urban (LMICs) 	<ul style="list-style-type: none"> • Tobacco • Overweight and obese • high risk waist hip ration • Inactive physical actives

3.2.4 Multimorbidity associated outcomes

Six systematic reviews addressed seven types of multimorbidity associated outcomes (one studies summarized more than one outcomes) (Table 5). Of the six reviews, one assessed the risk of mortality (Marengoni et al., 2011), two assessed disability and functional decline (Marengoni et al., 2011; Ryan et al., 2015), two evaluated the quality of life (Fortin et al., 2004; Marengoni et al., 2011), three focused on healthcare use and cost (France et al., 2012; Lehnert et al., 2011; Marengoni et al., 2011), one evaluated the “Do Not Resuscitate” orders (DNR) decision making process (de Decker et al., 2014), and one focused on patients safety (Panagioti et al., 2015).

The evidence from these systematic reviews demonstrates the significant association between multimorbidity and various adverse outcomes with few controversial results. Some reviews evaluated the relationship between number of diseases, disease combinations and outcomes (Fortin et al., 2004; France et al., 2012; Marengoni et al., 2011). One review demonstrated multimorbidity could predict future functional decline, with greater decline in patients with higher numbers of conditions and

greater disease severity (Ryan et al., 2015). Certain combinations of chronic conditions are related to certain outcomes, for example, chronic respiratory disease, congestive heart failure, and diabetes presented a greater risk for physical decline than others (France et al., 2012).

The role of multimorbidity in the risk stratification tools to predict negative outcomes is important but infrequently used and assessed. Alonso-Morán and colleagues conducted a qualitative synthesis from 36 studies and found that most risk stratification tools were developed to predict hospital admission or readmission, with some tools (e.g. the Charlson Comorbidity Index) dealing with multimorbidity (Alonso-Morán et al., 2015).

Table 5

Summary of included systematic reviews on multimorbidity with different outcomes.

Study	Countries Study & duration	Samples	Population	Outcomes	Outcome scales	Results	Quality of included studies
(Marengoni et al., 2011)	Finland, Italy, Netherlands, Australia, Sweden 2001-2010	5 4 self-report with others, 1 clinical and medical record	Community and veterans and war widows Age ≥ 65	Mortality	Number of years mortality	Significant results were found on the effect of multimorbidity on mortality, as an increasing number of coexisting diseases was significantly related to an increasing risk of mortality in some studies	NA
(Marengoni et al., 2011)	Canada, US, Spain, UK, Sweden, 2004-2009	5 3 cross-sectional 2 longitudinal	Community dwellers, Residential households and institutional Age ≥ 18	Disability and functional decline	Physical component summary score SF-36, physical function measured with the SF-12, physical activity levels, 3-year functional decline, impaired functioning	An increasing number of diseases were consistently associated with increasing odds or risk for disability	NA
(Ryan et al., 2015)	Canada, US, Germany, Italy, Spain, UK, Australia, India, turkey, Sweden, Netherlands, 1999-2014	37 28 cross-sectional, 9 cohort	Community-dwellings, Age ≥ 18	Functional decline	EQ-5D, SF-36, AIMS2, SPPB, four minute walking speed score, ALDs and IALDs, CDC HRQOL-4, hand grip test, multi-dimensional functional assessment questionnaire (OARS), standardised rapid disability rating scale-2, Barthel index, Friend's criteria, Groningen activity restriction scale, FDI	Multimorbidity predicts future functional decline, with greater decline in patients with higher numbers of conditions and greater disease severity	Overall good quality (Cochrane Tool for the Assessment of Bias)
(Fortin et al., 2004)	US, Netherlands, Sweden 1993-2003	7 cross-sectional and longitudinal	Ambulatory, family medicine Age ≥ 18	Quality of life	SF-36, European organization for research of cancer quality of life questionnaire (EORTCQOL), SF-20, modified	An inverse relationship between the number of medical conditions and QOL or HRQOL, multimorbidity mostly affects physical dimensions of	Met the criteria (self-devised evaluation)

					Nottingham health profile(NHP), quality of well-being scale(QWB)	QOL or HRQOL, social and psychological dimensions may be affected in patients with 4 or more diagnoses	criteria scale)
(Marengoni et al., 2011)	Australia, Canada, Hong Kong(China), Spain 2005-2009	6 5 cross-sectional, 1 longitudinal	General population, veterans and war widows Age ≥ 20	Quality of life	SF-36, Indice de Détresse Psychologique de l'Enquête Santé Québec, SF-12	Multimorbidity was associated with depression, distress and generally with pool quality of life	NA
(Lehnert et al., 2011)	US, Sweden, Germany, Canada, Italy, Spain, South Korea, China(Hong Kong) 1992-2009	35 30 cross-sectional, 3 cohort, 2 cross-control	Hospital and community Age ≥ 55	Health care utilization, health care cost	Physician use, hospital use, pharmaceuticals, total health care costs, out-of-pocket payment	A positive association between multimorbidity and health care utilization and cost, use/costs significantly increased with each additional condition	NA
(Marengoni et al., 2011)	US, Australia, Germany, Sweden 2002-2009	8 5 cross-sectional, 1 longitudinal	Residents from primary healthcare and hospitals All age	Health care utilization	Hospitalization, complications, care needs, expenditures, learning self-managing diseases and medication	The number of diseases was significantly associated with the number of prescriptions, referrals, hospital admissions and expenditures	NA
(France et al., 2012)	US, Netherlands 1994-2004	3 cohort	Primary health care	Health care utilization, health care cost	Number/rate of consultations and episodes of disease, patient visits and charges, severity of disease	Patients with multimorbidity had higher healthcare utilisation than those with only a single condition. Increasing multimorbidity predicted higher healthcare charges in an outpatient setting and an increased likelihood of inpatient admission	Good quality (STROBE)
(de Decker et al., 2014)	NA 1986-2010	22 18 cross-sectional 4 cohort	Inpatients in dialysis centre, intensive	“Do Not Resuscitate ” orders (DNR)	Advance medical directives to withhold cardiopulmonary resuscitation during cardiac arrest	DNR orders were positively associated with multimorbidity, and confirmed by further meta-analysis (OR=1.25), especially with three	Met the criteria (STROBE, CONSORT)

			care unit, emergency or burn department			morbidities, this association depends on the types of morbidity, cognitive impairment, cancer and stroke was significantly associated with the decision of DNR	
			Age from 60-86.5 years				
(Panagioti et al., 2015)	US, Australia, Germany, Spain, Canada, Netherlands, Italy, Ireland, UK, Norway, Algeria, Bahrain, Brazil, Sweden, Japan, China 2004-2015	75 31 cross- sectional, 32 retrospective cohort, 8 prospective cohort, 3 case control and 1 trial	General population, primary care, outpatients Age from 38 to 80	Patient safety incidents	Active patient incidents (adverse drug events, medical complications), precursors of safety incidence (prescription errors, medication non- adherence, poor quality of care and diagnostic errors)	The association between multimorbidity and patient safety is complex, and varies by type of multimorbidity and type of safety incident. Meta-analysis demonstrated that physical-mental multimorbidity was associated with an increased risk for 'active patient safety incidents' and 'precursors of safety incidents'. Physical multimorbidity was associated with an increased risk for active safety incidents but was not associated with precursors of safety incidents	Generally low (The Effective Public Health Practice Project instrument)

SF-36: Short-Form-36 Health Survey; SF-20: Short-Form-20 Health Survey; SF-12: Short-Form-12 Health Survey; QOL: Quality Of Life; HRQOL: Health Related Quality Of Life; EQ-5D; AIMS2: arthritis impact measurement scale 2; FDI: functional dependency index; SPPB: short physical performance battery; CONSORT: Consolidated Standards of Reporting Trials; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

3.4 Clinical practice and medication

3.4.1 Clinical decision making with multimorbidity

Clinical decision making with multimorbidity requires complex communications and collaborations among generalists, specialists, pharmacists, nurses, and patients. Better understanding of roles in the process of decision making, especially those of patients', may be useful for clinical decisions and interventions development (Sinnott et al., 2013).

Fraccaro and colleagues evaluated the current state of clinical decision systems (CDS) for multimorbidity and found that generalist doctors were the main decision makers, yet there were no studies referring to patients in the decision-making process or to patient self-management. There were no rigorous evaluations of usability or effectiveness of the CDS systems reported (Fraccaro et al., 2015). Sinnott and colleagues reviewed 275 general practitioners' perspectives on the management of patients with multimorbidity, and identified four difficulties: disorganization and fragmentation of healthcare, the inadequacy of guidelines and evidence-based medicine, challenges in delivering patient-centred care and barriers to shared decision-making (Sinnott et al., 2013). Mangin and colleagues examined current tools to assess patient treatment priorities and preferences with multimorbidity, only two studies use questionnaires (control preference scale and priority) to ask patients priorities on which outcome was more important to them, and their preferences on decision-making (Mangin et al., 2016).

3.4.2 Clinical practice guideline

Evidence-based clinical practice guidelines are important tools for medical care and disease management. However, the traditional guidelines focused on single diseases with limited recommendations for multimorbidity (Lugtenberg et al., 2011; Wyatt et al., 2014). Lugtenberg and colleagues assessed the extent that guidelines addressed comorbidity by systematic analysis of guidelines focusing on four highly prevalent chronic conditions: chronic obstructive pulmonary disease, depressive disorder, diabetes mellitus type 2, and osteoarthritis (Lugtenberg et al., 2011). Of 20 included guidelines published between 2005 and 2009 from North America, Europe, Singapore, Australia and New Zealand, 17 (85%) addressed the issue of comorbidity and 14 (70%) provided specific recommendations on comorbidity. However, of the 59 comorbidity related recommendations provided, only 8 (14%) addressed the discordant comorbidities (i.e. they are not directly related in their pathogenesis or management and do not share an underlying predisposing factor), and 73% of the recommendations were not adequately translated into the guidelines.

Most guidelines did not take into account patients with multimorbidity. Wyatt and colleagues systematically examined the current clinical practice guidelines for patients with type 2 diabetes mellitus, and of the 28 eligible guidelines, only 8 (29%) incorporated the impact of multimorbidity

(Wyatt et al., 2014). This study suggested clinical practice guidelines for one chronic disease should consider the context of patients with multimorbidity. Young and colleagues systematically reviewed the clinical practice guidelines of Australia from 2006 to 2014, and only identified 13 patient-preference recommendations and consumer-engagement processes (Young et al., 2015). Of these, 12 included at least one core patient-preference recommendation, 10 used consumer-engagement processes including participation in development groups (7 guidelines) and reviewing drafts (10 guidelines), but more practical details are required.

3.4.3 Medication (polypharmacy)

Multimorbidity usually involves multi-drug therapy (polypharmacy). Seven reviews were identified on medication use (with some of them focused on more than one topic simultaneously). Four studies focused on definition (Doos et al., 2014; Fulton and Allen, 2005; Jekanovic et al., 2015; Patterson Susan et al., 2014), two summarized prevalence of polypharmacy (Fulton and Allen, 2005; Jekanovic et al., 2015), one examined the polypharmacy patterns (Doos et al., 2014), two assessed risk factors (Fulton and Allen, 2005; Jekanovic et al., 2015), one examined the relationship between polypharmacy and outcomes (Fried et al., 2014), and three assessed intervention to improve appropriate use and adherence to medicine (George et al., 2008; Patterson Susan et al., 2014; Williams et al., 2008). The detailed evidence is summarized in Table 6.

Very few studies have investigated associations between specific patterns of multimorbidity and related multi-drug therapy in family practice. For instance, a systematic review focused on six common chronic conditions- diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, osteoarthritis, and depression- identified few studies on the relationship between multimorbidity and prescribed multiple drug therapy (Koch et al., 2015). This study highlighted the combination of chronic conditions and depression is associated with suboptimal drug treatment in multiple drug therapy.

Table 6

Summary of the evidence on medication (polypharmacy) for multimorbidity.

Evidence	Notes
Definition	
<p>Polypharmacy was often defined by two categories: number of medications and whether clinically indicated</p> <ul style="list-style-type: none"> • the concomitant ingestion of 4 or more medications • 5 or more medications in long term care facilities (LTCF) • the specific use of two or more drugs for two or more conditions in an individual (multi-drug therapy) • the use of medications that are not clinically indicated in clinical practice 	<p>European studies defined polypharmacy according to the number of medications taken, whereas the studies conducted in the United States defined polypharmacy according to whether a medication was clinically indicated</p>
Prevalence	

Prevalence varied among different definitions, sample size, and settings

- up to 91%, 74%, and 65% of residents were taking more than 5, 9, and 10 medications, respectively in LTCF
- ranged from 5% to 78% in patient populations

Patterns

The combination of chronic conditions and depression is associated with suboptimal drug treatment in polypharmacy

Very few studies have investigated association between multimorbidity and polypharmacy

Risk factors

- older age and women
- diseases
 - comorbidity including circulatory diseases, endocrine and metabolic disorders and neurological motor dysfunctioning
 - cognitive impairment
- medications
 - number of medications
 - medication without a clear indication
- access to health services
 - number of visits to a primary care physician per year
 - recent hospital discharge
 - length of stay in the LTCF
- disability in activities of daily living

Health outcomes

The evidence was mixed, with some studies demonstrating an association between polypharmacy and falls, falls risk factors, and fall-related injury; adverse drug events, hospitalization, mortality, and a variety of measures of symptoms and physical and cognitive function

The results from this review provide sufficient preliminary evidence to support RCTs in this research area

Interventions

The following interventions were used for improving adherence and appropriate use

- pharmacist- led medication review
- group and individual education
- individualized medication cards
- behavioural strategies
- simplified medication regimens
- information and communication technology (ICT): email or telephone assessment and education
- computer decision support (CDS)

Psychosocial interventions engaging people in medication self-management offer potential for improved patient outcomes in complex diseases

3.5 Intervention and management

A total of nine systematic reviews were identified on intervention for multimorbidity. Considering most of the included interventions involved multiple model types and were named arbitrarily (de Bruin et al., 2012; Hopman et al., 2016; Smith Susan et al., 2016), we have used the Cochrane Effective Practice and Organisation of Care (EPOC) categorization of these interventions (Smith

Susan et al., 2016). Of the 14 included interventions, seven were categorized into organizational (Bleich et al., 2015; Crowe et al., 2016; Lupari et al., 2011; Rydwik et al., 2004; Smith Susan et al., 2016), five were primarily patient-oriented (Bleich et al., 2015; Dennis et al., 2013; Quiñones et al., 2014; Smith Susan et al., 2016), and two focused on both (de Bruin et al., 2012; Hopman et al., 2016). Although the overall results from included interventions were mixed, some improvement in clinical, satisfaction, and health services use and cost outcomes were detected from both organisational and patient-oriented interventions.

As Table 7 shows, various measurement indicators were used to evaluate the effectiveness of interventions. Of 27 included studies, all of the process measures were disease-specific, with some non-disease-specific measures (functional outcomes, healthcare utilisation and patient- rated measures) also identified (Pillay et al., 2014).

Table 7

Summary of evidence examining interventions on multimorbidity.

Review	Countries & Study duration	Samples	Participant and settings	Intervention *	Components of intervention	Results	Quality of included studies
(Bleich et al., 2015)	US 2008-2014	3 2 RCTs, 1 case study	Hospital or medical centre based	Chronic disease self-management (patient-oriented)	Provide information to patients and engage them in actively managing their chronic conditions	Improvement in clinical outcomes (mortality, functional status, and pain)	NA
(Smith Susan et al., 2016)	US, UK, Canada 1999-2015	6 RCTs	Primary care and community settings	Patient-oriented Self-management (patient-oriented)	Diet and physical activity intervention with self-management support, OPTIMAL support course, multicomponent home intervention (the ABLE programme), “Making the most of your healthcare”, chronic diseases self-management programme, LIFE intervention	Mixed results, that do not suggest patient-oriented interventions are generally effective; one study reported functional capacity and activity participation may be effective; another reported a reduction in mortality at longer-term follow up	Overall quality was good (Cochrane)
(Bleich et al., 2015)	US 2008-2014	7 6 RCTs, 1 quasi-experimental	Hospital or medical centre based	Disease management (patient-oriented)	Provide patients with information about their chronic conditions in writing or telephone	Improvement in patient satisfaction, clinical, and health care use and cost outcomes	NA
(Bleich et al., 2015)	US 2008-2014	14 3RCTs, 9 quasi-experimental, 1 case-control, 1 cohort	Home, community, and hospital based All age	Care and case management (organisational)	Nurse or social workers help patients and their families to assess problems	Improvement in patient satisfaction, clinical outcomes and successful health care use and costs	NA
(Smith Susan et al., 2016)	US, UK, Canada 2000-2015	12 RCTs	Primary care and community settings	Case management and coordination of care or the enhancement of skill mix in	UPBEAT intervention, integrated care, Guide Care programme, COINCIDE collaborative care model, APTCare intervention, TEAMcare intervention, WISE intervention,	Little or no difference in clinical outcomes, mental health outcomes improved and modest reductions in mean depression scores for the	Overall quality was good (Cochrane)

				multidisciplinary (organisational)	pharmaceutical care plan, cognitive behavioural therapy programme, TrueBlue collaborative care model, senior care connections intervention, home telehealth	comorbidity studies that targeted participants with depression, a small improvement in patient- reported outcomes, little or no difference to health service use, may slightly improve medication adherence, slightly improves patient related health behaviours, and probably improves provider behaviour in terms of prescribing behaviour and quality of care, cost data were limited	
(Lupari et al., 2011)	US, UK 1996-2008	8 7 quantitative design and /or mixed approach, 1 qualitative study	Home based, Older patients	Nurse-led, home based management (organisational)	Hospital resources used (hospital readmission rates and lengths of stay), patients (health- related quality of life, satisfaction and mortality), caregiver (satisfaction, carer strain or burden), cost-effectiveness metrics (from the perspective of the NHS payer)	Access to car management services had a positive impact on the patient (health-care related quality of life, satisfaction and mortality), the carer (satisfaction, carer strain or burden) and the healthcare staff (workload)	NA
(Bleich et al., 2015)	US 2008-2014	1 case control	Long-term care Age ≥ 65	Nursing home (organisational)	Primary care provided by an advanced-practice nurse or physician assistant	Significant improvement in clinical, health care use and cost outcomes	NA
(Bleich et al., 2015)	US 2008-2014	1 quasi- experimental	Academic medical centre	Transitional care (organisational)	Facilitate smoother, safer, and more efficient transitions from hospital to the next site of care	No significant improvement in clinical, health care use and cost outcomes	NA
(Crowe et al., 2016)	US, UK, Australia 1999-2013	12 5 RCTs, 4 open-label studies, 1 concurrent	Home based Age from 65 to 78.5	Transdiagnostic health management (organisational)	CDSM, home-based interventions (care co-ordination via distance monitoring, multicomponent intervention), community-based intervention (fitness programme with	Structured transdiagnostic health management interventions may be clinically effective for older people with multimorbidity. Ten studies	2 with a low risk of bias, 4 with unclear risk bias, 6 with

		controlled cohort study, 1 case control study, 1 quasi-experimental study			nutritional counselling and weight management, Health Habits Program, generic self-management programme “Moving On”), service level interventions(inter-disciplinary collaborative practice intervention, intervention practice with an intensive self-management education package)	reported statistically significant improvements in health outcomes, three studies identified some statistically significant reductions in health services utilization	high risk bias (Cochrane)
(Quiñone s et al., 2014)	US, Spain, China, Netherlands 1999-2007	4 RCTs	Community based Age from 57 to 68	Educational groups visits (patient-oriented)	Educational group visits led by non-prescribing facilitators for patients, teach patients self-management skills, such as goal-setting and contracting, and build skills to reinterpret symptoms	Overall, the peer-led, community-based program was associated with medium-term improvements in self-efficacy, health status, and utilization; and these effects may persist long-term	2 fairs, 1 poor, 1 NA (GRADE)
(Rydwik et al., 2004)	NA 1989-2000	16 RCTs	Institutional elderly patients Age ≥70	Physical training (organisational)	Physical performance: muscle strength, mobility, gait, ADL, balance, endurance, rang of motion	A positive effect of physical training on muscle strength and mobility; moderate evidence for an effect on range of motion; and contradictory evidence regarding gait, activities of daily living, balance and endurance	An average of 54 points out of a maximum of 100 (Cochrane)
(Dennis et al., 2013)	US 2008	1	About 30% of demonstration enrolees were aged 65 or younger, and ~9% were age 85 or over	Telephone health coaching (patient-oriented)	Specific DM services include educating patients about their medical conditions, helping patients adhere to physicians’ treatment plans, and improving patients’ self-care skills	Some improvement in quality of care measures, medication adherence, satisfaction, health services use and cost, but not statistically significant	NA
(de Bruin et al.,	US, Canada, Australia,	28 14 RCTs, 8	Hospital, community	Comprehensive care program	Enhanced care initiatives, Integrated services for frail elders,	Moderate evidence for comprehensive care on	6 with score of 0, 6

2012)	UK, Italy, Norway. 1995-2011	pretest-post-test studies, 5 controlled clinical trials, 3 cluster RCTs, 2 post-test only studies, 1 case control study	and home care, and specialized clinics, managed care organizations	(organisational and patient-oriented)	guided care, transitional care service model, outpatients geriatric evaluation and management clinic, rural home care project, older hospitalized patients' discharge planning and in-home follow-up protocol, integrated multidisciplinary advocacy program, integrated care for older people, home telehealth care, geriatric assessment service, nurse care management system, after discharge care management of low-income frail elderly, nurse physician collaborative partnership, geriatric resources for assessment and care of elders. Multi-disease care management program, frail elderly community-based care management project, chronic disease self-management program, health enhancement project, telecom care, transitional care intervention, geriatric evaluation management unit, geriatric evaluation and management, geriatric home hospitalization service, disease state management program	inpatient healthcare utilization and healthcare costs, health behaviour of patients, perceived quality of care, and satisfaction of patients and caregivers. Insufficient evidence was found for a beneficial effect of comprehensive care on health-related quality of life in terms of mental functioning, medication use, and outpatient healthcare utilization and healthcare costs	with score of 1, 10 with score of 2, 3 with score of 3, 7 with score of 4, 1 with score of 5, 1 with score of 6 (sum-score of 6)
(Hopman et al., 2016)	US, Canada, 2011-2013	3 2 RCTs, 1 cluster RCTs	Hospital and primary health care setting	Comprehensive care program (organisational and patient-oriented)	Community resources, self-management program, delivery system design, clinical information system, decision support	Can reduce length of hospital stay, decrease unplanned charges and total charges, Improve the health-related quality of life, and decrease costs	2 good quality

CDSM: Chronic disease self-management programs; ADL: activities of daily living

Patient-oriented self-management is being increasingly recognized as a key intervention for patients with multimorbidity. Four systematic reviews synthesised qualitative evidence on the identification of patients' living experience with multimorbidity (Coventry et al., 2015); patients' perceptions on facilitators and barriers associated with multimorbidity management (Koch et al., 2015; Liddy et al., 2014); and facilitators, and barriers in priority setting and decision-making (Bratzke et al., 2015). We summarized the evidence as shown in Figure 3, depicting the self-management process, the facilitators and barriers in the managing process, and external and internal factors influencing the priority setting and decision making process.

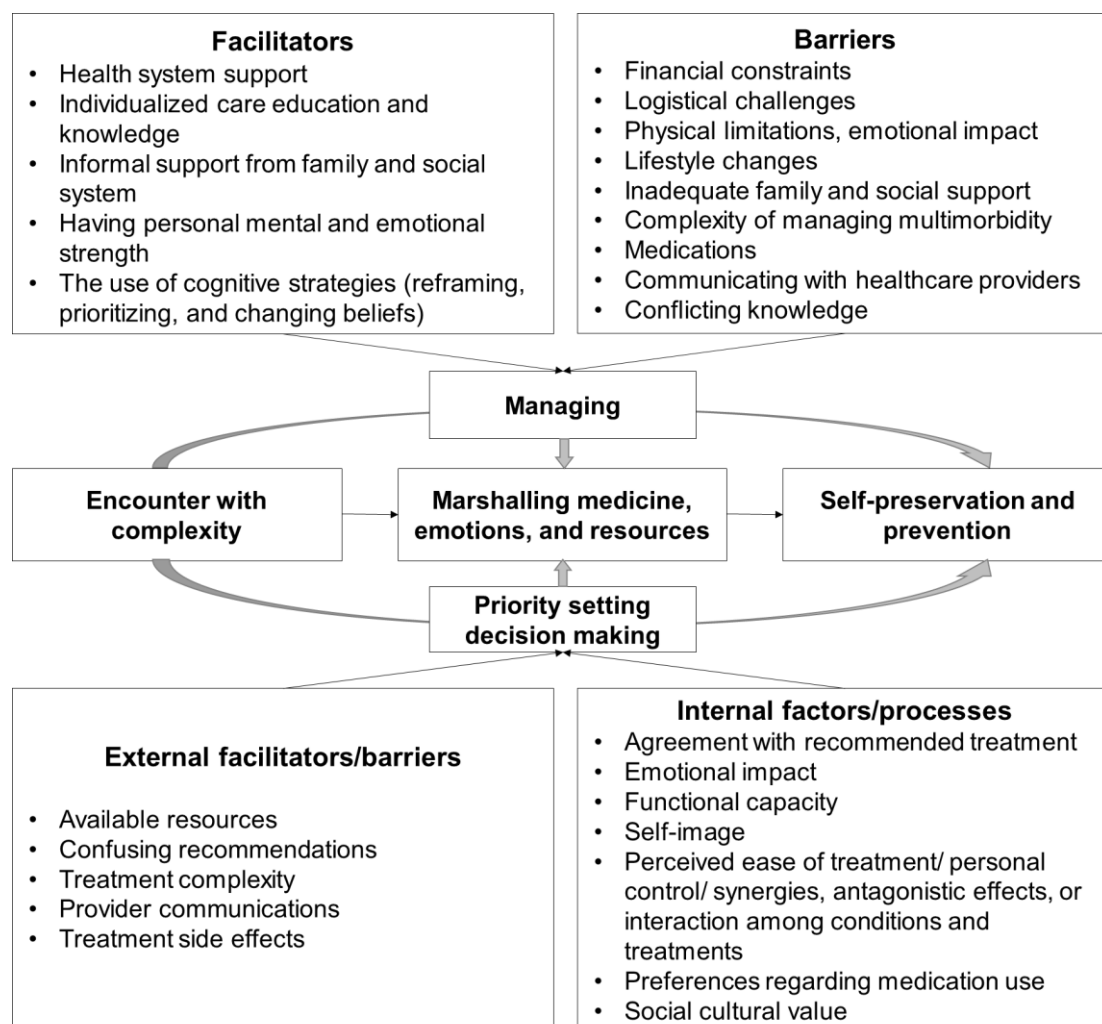


Figure 3. Summary of the qualitative evidence on self-management process, priority setting and decision making in multimorbidity.

3.6 Others

3.6.1 Including multimorbidity in clinical and interventional trials

Patients with multimorbidity are routinely excluded from many trials and guidelines, however, the trial reporting and presentation may impact on the external validity of trials. Kenning and colleagues

evaluated 164 unique trials on self-management and found that 60% of trials excluded patients with forms of multimorbidity, with reasons poorly described or identified (Kenning et al., 2014). In the trials that considered multimorbidity, only 35% reported multimorbidity in their patient sample, and few trials explored the impact of multimorbidity. Trials need to be more inclusive of patients with multimorbidity and analyse the effects of multimorbidity on outcome, in order to improve the external validity of results for clinical populations.

3.6.2 Multimorbidity at the end of life

Most patients suffered from more than five severe comorbidities in the last 6 month of life (Van Nordennen et al., 2014), with polypharmacy a key issue. Van Nordennen and colleagues reviewed the decision making about medication use for comorbid diseases at the end of life. The findings suggest that to avoid inappropriate medication use in end-life-care patients, geriatric care providers need to consider goals of care, treatment targets, remaining life expectancy, time until benefit, number needed to treat to harm, and adverse drug reactions when making decisions. Meanwhile, medication that does not benefit the patients in any way should be avoided, such as statins, antihypertensive agents, antihyperglycaemic agents, anticoagulants and antibiotics. The aim of medication use at the end of life should be for symptom control.

4. Discussion

4.1 Summary of evidence

There is a challenge to synthesize a comprehensive body of evidence in a single overview, however, this work is valuable and timely during the transition from the era of “single chronic disease medicine” to the era of “multimorbidity medicine” (Fabbri et al., 2015; Tinetti et al., 2012). In this overview, we identified 53 systematic reviews that focused on multimorbidity and synthesised the evidence by research topics. The main findings of this overview can be summarized as below:

- Three major definitions were detected from three major perspectives: epidemiology and public health, long term care and family medicine in primary care, and clinicians and patients in daily clinical practice.
- The prevalence of multimorbidity may range from 3.5% to 100%, increasing with the increase in age, with an S-shaped curve by age detected in the general population.
- Cardiovascular and metabolic disease, mental health related problems, and musculoskeletal disorders were the main three disease patterns. Common disease combinations are: depression, hypertension, diabetes, arthritis, asthma, and osteoarthritis comorbid with other conditions; the most common diseases included in multimorbidity were: diabetes, heart disease, cancer, hypertension, depression, COPD, stroke, arthritis/osteoarthritis, osteoporosis, and asthma.

- Four groups of risk factors of multimorbidity were identified: biomedical and individual factors, health behaviours, socioeconomic characteristics, and social and environment factors.
- Multimorbidity associated outcomes, such as mortality, disability and functional decline, quality of life, health care use and cost, “Do Not Resuscitate” orders decision making process, and patients’ safety were assessed by various systematic reviews.
- Patients are often excluded in clinical decision making. Most guidelines did not take into account patients with multimorbidity.
- Patients with multimorbidity are usually associated with polypharmacy, with topics on definition, prevalence, patterns, risk factors, health outcomes, and interventions on polypharmacy reviewed.
- Interventions on multimorbidity were varied. Following Cochrane Effective Practice and Organisation of Care (EPOC) methodology, all interventions could be categorized into either organizational (care and case management, nursing home, transitional care, and physical training) or patient-oriented (self-management, disease management, educational groups visits, and telephone health coaching). Some improvement in clinical outcomes, satisfaction, health services use and cost outcomes were detected from both organisational and patient-oriented interventions. The process, facilitators and barriers in the managing and decision making on self-management were evaluated using qualitative research synthesis.

4.2 Strengths and limitations of the overview

To our knowledge this is the first overview of systematic reviews to assess current evidence on multimorbidity. There are some strengths and limitations associated with this overview. An overview of systematic reviews can provide a wide-perspective on the research topic. We used broader search strategies and inclusion criteria than most included systematic reviews. Qualitative research (Bratzke et al., 2015; Coventry et al., 2015; Koch et al., 2015; Liddy et al., 2014) and systematic reviews on guidelines (Lugtenberg et al., 2011; Wyatt et al., 2014; Young et al., 2015) were also included. Despite the broader approach, publication bias may be a limitation of our study. As we only considered systematic reviews for inclusion the most recently published primary studies may not have been captured. We only performed qualitative evidence synthesis because of large heterogeneity in the included studies and some primary studies may have been included in more than one systematic review.

4.3 Implications for practice and policy

Despite the explosion of research interest in multimorbidity, there remains limited progress in including multimorbidity in clinical trials and guidelines, appropriate clinical practice and decision making, and health policy making (Fraccaro et al., 2015; Lugtenberg et al., 2011; Sinnott et al., 2013; Wyatt et al., 2014).

As implicated from this overview, comprehensive policy and practice need multisectoral actions from all stakeholders, not only including health care systems, but also including public health, social, and environment support. This implication is consistent with WHO health aging action 2016-2020 (Executive Board 134 A69/17., 2016). However, the first key step is making patient values visible in the decision making in the context of patient-centred care and person focused care (Dierckx et al., 2013). Policy and programming should be better aligned with patients' perspectives, and this can be achieved by a patient-centred approach (Liddy et al., 2014). There is a need to develop tools to incorporate patient's priorities in clinical decision making and to test their effectiveness (Mangin et al., 2016). Meanwhile, better understanding of patients' living experience with multimorbidity is a crucial factor to design and deliver self-management interventions.

Few studies have been conducted in low-and-middle-income countries (Pati et al., 2015). With the increasing multimorbidity related disease burden, it is urgent that we accumulate evidence on all aspects of multimorbidity to inform health policy making in these countries.

4.4 Implications for research

As suggested by all included reviews, there is a need for prospective research, especially longitudinal cohort studies and randomized control trials, to provide more-definitive evidence on multimorbidity (de Bruin et al., 2012). Few longitudinal studies based in primary care have investigated multimorbidity. Further large, long-term prospective studies on prevalence, disease patterns, risk factors, various outcomes are required to provide evidence for trials on interventions and management (France et al., 2012).

How to define and measure multimorbidity is the first and key issue. Although there isn't a uniform methodology to define and measure multimorbidity, standardized methods for measuring multimorbidity in different perspectives are needed, such as public health surveillance, clinical practice and patients' perspectives (Le Reste et al., 2013; Willadsen et al., 2016). Regarding research in prevalence, some fundamental determinants such as setting, age, gender, geographic area have to be examined (Holzer et al., 2014). Much more work is needed to develop an understanding of causal pathways, disease patterns and trajectories of multimorbidity in longitudinal studies (Marengoni et al., 2011; Salive, 2013).

The evidence on the effectiveness of interventions for patients with multimorbidity was mixed. More research and consistent methods are needed to understand the most appropriate interventions and management (Bleich et al., 2015). More research is required to identify sub-groups who respond to these interventions (Crowe et al., 2016), and to determine which specific target groups at what moment will benefit from the given interventions (Hopman et al., 2016), to allow the development of more targeted interventions.

Research on new and novel health care interventions for disease treatment and management should be taken as priorities. Health informatics related technology is helpful in clinical decision processes (Fraccaro et al., 2015) and in patients management and intervention programmes (Quiñones et al., 2014), especially aligning treatment and medication information among different specialists and generalists because prescriptions from multiple health care providers may conflict with each other. However, more research is needed to understand how to embed these with existing services (Dennis et al., 2013).

5. Conclusions

Our overview of systematic reviews summarized current evidence on multimorbidity globally, and some preliminary evidence was identified and recommended for further research and practice. There is an explosion of interest in multimorbidity, yet the existing evidence is limited. There is a need for prospective research, especially longitudinal cohort studies and randomized control trials, to provide more-definitive evidence on multimorbidity to inform clinical practice and policy making.

Role of funding sources

There was no specific funding obtained to conduct this study. XX is funded by an International Postgraduate Research Scholarship from the Australian government and a UQ Centennial Scholarship from The University of Queensland. GM is funded by an Australian Research Council future fellowship (FT120100812).

Conflict of interest

The authors of this manuscript have no conflict of interest to declare.

Appendix A. Supplementary data

See supplementary data.docx.

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