



Review

Aging with multimorbidity: A systematic review of the literature

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ARTICLE INFO

Article history:

Received 30 January 2011

Received in revised form 3 March 2011

Accepted 7 March 2011

Available online 12 March 2011

Keywords:

Aging
Chronic diseases
Multimorbidity
Prevalence
Incidence
Risk factors
Consequences
Quality of care

ABSTRACT

A literature search was carried out to summarize the existing scientific evidence concerning occurrence, causes, and consequences of multimorbidity (the coexistence of multiple chronic diseases) in the elderly as well as models and quality of care of persons with multimorbidity. According to pre-established inclusion criteria, and using different search strategies, 41 articles were included (four of these were methodological papers only). Prevalence of multimorbidity in older persons ranges from 55 to 98%. In cross-sectional studies, older age, female gender, and low socioeconomic status are factors associated with multimorbidity, confirmed by longitudinal studies as well. Major consequences of multimorbidity are disability and functional decline, poor quality of life, and high health care costs. Controversial results were found on multimorbidity and mortality risk. Methodological issues in evaluating multimorbidity are discussed as well as future research needs, especially concerning etiological factors, combinations and clustering of chronic diseases, and care models for persons affected by multiple disorders. New insights in this field can lead to the identification of preventive strategies and better treatment of multimorbid patients.

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1. Introduction

Thousands of persons turn 65 years of age every day (Cohen, 2003; Kinsella and Velkoff, 2005). Life expectancy has already exceeded age 75 in 57 countries (World Health Organization, WHO, 2010), and it is expected to continue to rise (Oeppen and Vaupel, 2002). In the world, the proportion of 60+ year-old people has gradually increased from 8.1% in 1960 to 10% in 2000. Despite the worldwide aging phenomenon, data regarding health and time trends in the health of the elderly are still inadequate. What is certain is that over the last century, chronic health problems have replaced infectious diseases as the dominant health care burden, and almost all chronic conditions are strongly related to aging. Only in the last few years many health care planners and governments have becoming aware of this phenomenon and population-based studies regarding age-related chronic diseases have been implemented.

The majority of the available studies have focused on specific illnesses or on the coexistence of a relatively small number of diseases, such as cardiovascular diseases, diabetes, and cancer, rather than on the whole range of chronic morbidity affecting older persons. Few studies have investigated how diseases distribute or co-occur in the same individual, and most of them have used different approaches to address this issue (Gijzen et al., 2001). Two terms “comorbidity” and “multimorbidity” have been mostly used (Yancik et al., 2007). The term comorbidity was introduced 1970 and refers to the combination of additional diseases beyond an index disorder (Feinstein, 1970). This definition implies that the main interest is on an index condition and the possible effects of other disorders on the prognosis of this disease. In contrast, multimorbidity is defined as any co-occurrence of diseases in the same person indicating a shift of interest from a given index condition to individuals who suffer from multiple diseases (Batstra et al., 2002).

Different operational definitions of chronic multimorbidity are detectable in the literature. Indeed, multimorbidity has been addressed from three major perspectives which have led to three major operational definitions:

1. *Number (commonly two or three) of concurrent diseases in the same individual.* This definition, which has been used mostly in epi-

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demiological studies, includes both individuals who may live relatively unaffected by multimorbidity with the help of medications and those who face severe functional loss.

2. *Cumulative indices evaluating both number and severity of the concurrent diseases.* This definition is very suitable in clinical studies where the major aim is to identify persons at risk for negative health outcomes and might benefit from specific interventions. Most used indices are: the Charlson Comorbidity Index (Charlson et al., 1987), the Index of Co-Existent Diseases (ICED) (Greenfield et al., 1993), and the Cumulative Illness Rating Scale (CIRS) (Linn et al., 1968).
3. The simultaneous presence of diseases/symptoms, cognitive and physical functional limitations. In order to estimate trends of prevalence rates of elderly people with complex health problems that imply care needs involving several providers of both medical care and social services, studies address multimorbidity taking into account not only the cumulative effect of concurrent diseases, but also relevant factors such as symptoms, cognitive and physical dysfunctions, and psychosocial problems.

Given the complexity and heterogeneity of the health status of the elderly and the age-related pathologies, no single operational criteria will serve all research and clinical purposes effectively (Valderas et al., 2009; Fratiglioni et al., 2010). However, the common denominator of all the definitions is given by concurrence of several chronic diseases whose severity can be graded or not with different methods. For that reason, in this review, we will focus only on chronic multimorbidity based on clinical diagnoses and defined as the co-occurrence of multiple diseases in the same individual. Specific aims of this study are to summarise the scientific evidence cumulated in the last 20 years concerning occurrence, causes and consequences of multimorbidity in older persons and to compare the most relevant studies concerning models and quality of care for persons with multimorbidity.

2. Methods

We used MEDLINE/Pubmed database from January the 1st 1990 through November the 1st 2010 to identify the relevant studies. Criteria for inclusion were: original articles, English language, human subjects, and the availability of an abstract in Pubmed. We used two search strategies. First, the keywords 'multimorbidity', 'multi-morbidity', 'multimorbidity AND comorbidity', 'multi-morbidity AND comorbidity', 'multimorbidity AND co-morbidity' were included as search criterion in all fields. Second, the terms 'multiple AND diseases' and 'multiple AND conditions' were used but sought in the title only.

Of the 302 articles identified with the first search strategy, 145 overlapped (i.e., the same articles were identified using different search terms). The abstracts of the remaining 157 articles were screened by two co-authors (A.M., S.A.) and 113 reports were excluded due to the following reasons: age < 65 years for the complete study population; evaluation of specific comorbidities, instead of overall multimorbidity; selection of specific subgroups, such as drug users or patients with psychiatric conditions, or specific index diseases such as diabetic persons; evaluation of very low sample size (<50 persons); evaluation of comorbidity indices; studies including only institutionalized or hospitalized persons; reports of meetings or conferences. The interagreement between the two co-authors was 98%. At the end of this process, 44 articles remained and were fully read. Additional 11 articles were excluded for similar reasons, leaving 33 articles described in the present review. Of these, 4 articles addressed only methodological issues in studying multimorbidity (van den Akker et al.,

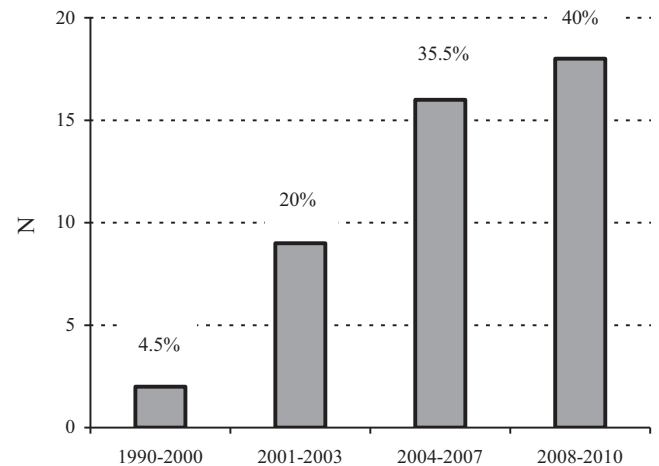


Fig. 1. Total number (N) and proportion (per 100) of articles on multimorbidity published from 1990 to 2010.

2001a; Batstra et al., 2002; Valderas et al., 2009; Marengoni et al., 2009a).

Using the second search strategy, 291 reports were identified; of these, 34 articles were fully read. Most papers were excluded as they focused on other topics (i.e., 'multiple' sclerosis or 'multiple' myeloma). Additional 26 articles were excluded for the same reasons detected only when reading the whole article. The remaining 8 studies are included in this review.

3. Results

The final number of articles included in the present review was 41, two published between 1990 and 2000 and 39 between 2001 and 2010 (Fig. 1).

3.1. Cross-sectional studies on multimorbidity: prevalence and associated factors

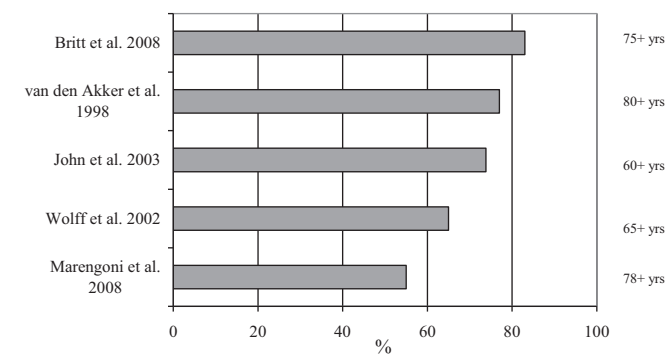
Twelve studies were identified on prevalence of multimorbidity (Table 1): four included only persons aged 60 years or older (Wolff et al., 2002; John et al., 2003; Sharkey, 2003; Marengoni et al., 2008) and eight evaluated people of different ages (van den Akker et al., 1998; Fortin et al., 2005; Walker, 2007; Schram et al., 2008; Uijen and van de Lisdonk, 2008; Britt et al., 2008; Schneider et al., 2009; Loza et al., 2009). Data were available only for a few countries: The Netherlands (van den Akker et al., 1998; Schram et al., 2008; Uijen and van de Lisdonk, 2008), Sweden (Marengoni et al., 2008), Australia (Walker, 2007; Britt et al., 2008), Canada (Fortin et al., 2005), Spain (Loza et al., 2009), and US (Wolff et al., 2002; John et al., 2003; Sharkey, 2003; Schneider et al., 2009). The ascertainment of diseases varied: four studies were based on self-reports (John et al., 2003; Sharkey, 2003; Walker, 2007; Loza et al., 2009); five on medical records only (van den Akker et al., 1998; Wolff et al., 2002; Fortin et al., 2005; Uijen and van de Lisdonk, 2008; Schneider et al., 2009); one on self-reports and medical records (Britt et al., 2008), and two on different sources of information including clinical examination (Schram et al., 2008; Marengoni et al., 2008).

Prevalence of multimorbidity (defined as 2+ concurrent diseases) widely varied across studies, around 20–30% when the whole population was considered but from 55 to 98% when only older persons were included. Fig. 2 shows the variability in prevalence of multimorbidity in the elderly population across different studies. In spite of the variability, all studies pointed out that the prevalence of multimorbidity in the elderly population is much higher than

Table 1

Description of the selected cross-sectional studies concerning multimorbidity: prevalence and associated factors.

Reference	Setting Participants	Ascertainment and definition of multimorbidity	Results Prevalence and associated factors
van den Akker et al. (1998)	Dutch general population N = 60,857 (all ages)	General practitioners records Multimorbidity defined as 2+ co-existing chronic diseases	74% in men and 80% in women aged 80+ years Female gender, older age, lower education, public health insurance and living in a home for elderly
Wolff et al. (2002)	US Medicare fee-for-service N = 1,217,103 (65+ years)	Administrative database Multimorbidity defined as 2+ co-existing chronic diseases	65%
John et al. (2003)	American Indian rural community residents N = 1039 (60+ years)	Self-report Multimorbidity defined as 2+ co-existing chronic diseases	73.8%
Sharkey (2003)	US homebound women N = 279 (60+ years)	Self-report Multimorbidity defined as number of chronic diseases	Food insufficiency was associated with having 3+ diseases
Fortin et al. (2005)	Canada residential N = 980 (18+ years)	General practitioner records Multimorbidity defined as 2+ co-existing chronic diseases	98% in 65+ years
Walker (2007)	Australian general population N = 17,450 (20+ years)	Self-report Multimorbidity defined as 3+ co-existing diseases	85% in 70+ years Older age, obesity, female gender, low socioeconomic status and living alone
Schram et al. (2008)	Dutch general population, institutionalized and hospitalized people N = 2693/599/2895/5610/1.058.234 (55+ years)	Self-report, clinical examination, general practitioner records Multimorbidity defined as 2+ co-existing chronic diseases	82% in nursing homes, 56–72% in the general population and GP registers, and 22% in hospital setting
Marengoni et al. (2008)	Swedish living in community and institutions N = 1099 (78+ years)	Medical examination, blood samples, inpatient register Multimorbidity defined as 2+ co-existing chronic diseases	55% Older age, female gender, lower education
Uijen and van de Lisdonk (2008)	Dutch general population N = 13584 (all ages)	General practitioners records Multimorbidity defined as increasing number of diseases; prevalence refers to people with 4+ co-occurring conditions	30% in 65–74; 55% in 75+ years Older age, female gender, low socio-economic class
Britt et al. (2008)	Australian general practitioner patients N = 9156 (all ages)	General practitioners records and self-report Multimorbidity defined as 2+ co-existing chronic diseases	83% in 75+
Schneider et al. (2009)	US Medicare recipients (institutional and not) N = 2,232,528 (all ages)	Chronic condition data warehouse Multimorbidity defined as 2+ co-existing chronic diseases	20.3%
Loza et al. (2009)	Spanish living in community N = 2192 (20+ years)	Self-report Chronic diseases Multimorbidity defined as 2+ co-existing chronic diseases	30%

**Fig. 2.** Variability in prevalence of multimorbidity (defined as 2+ co-existing chronic diseases) in the population across different studies (only 60+ year-old population are included).

the prevalence of the most common diseases of the elderly such as heart failure and dementia (Marengoni et al., 2008). Consistently across studies, older persons, women, and persons from low social classes were more likely to be affected by multimorbidity.

3.2. Studies on incidence and risk factors for multimorbidity

Four articles examined incidence and risk factors for multimorbidity (Table 2); three of them were embedded in the same population-based study from The Netherlands (van den Akker et al., 1998, 2000, 2001b) and one was carried out in Germany (Nagel et al., 2008). Disease ascertainment in these studies was based on general practitioners' records. Only one study reported 1-year incidence of multimorbidity (defined as 2 or more new diseases) which was 1.3% in the whole population (van den Akker et al., 1998). Identified risk factors for multimorbidity were: increasing age, higher number of previous diseases, and lower education, whereas a large social network seemed to play a protective role. No studies evaluating genetic background, biological causes, life styles, or environmental factors as risk factors for multimorbidity were found.

3.3. Studies on consequences of multimorbidity

The majority of the identified articles ($n=22$) addressed the consequences of multimorbidity (some of them evaluated more than one outcome simultaneously) (Tables 3a–3d). In particular, five articles examined disability or functional performance

Table 2

Characteristics of the selected studies concerning incidence and risk factors of multimorbidity.

Author, year of publication	Setting Participants	Study design/ascertainment of diseases	Results Incidence and risk factors
van den Akker et al. (1998)	South Netherlands Community residents N = 60,857 (all ages)	Longitudinal General practitioners records	1-year incidence: 5.6% in men and 6.1% in women in 80+ years Risk factors: older age, public health insurance and previous multimorbidity
van den Akker et al. (2000)	South Netherlands Community residents N = 3745 (20+ years)	Nested case–control study General practitioners records	Risk factors: increasing age, higher no. of previous diseases, and low socioeconomic status
van den Akker et al. (2001)	South Netherlands Community residents N = 3551 (all ages)	Longitudinal General practitioners records	Protective factors: a high internal locus of control belief, living with someone and large social network
Nagel et al. (2008)	Heidelberg, Germany Community residents N = 13,781 (50–75 years)	Longitudinal Self-report	Risk factors: low education (BMI was an intermediate factors in the association)

Table 3a

Description of the selected studies on consequences of multimorbidity: disability and functional decline.

Author, year of publication	Setting Participants	Study design/ascertainment of diseases	Results
Bayliss et al. (2004)	US N = 1574 (57.6, SD = 15.4)	Longitudinal Medical records	Having 4+ chronic diseases was associated with 4-year decline in the physical component summary score SF-36
Kadam et al. (2007)	Community dwellers in UK N = 9439 (50+ years)	Cross-sectional General practice consultations	Compared to those with one disease, having 2–3, 4–5, or 6+ diseases was associated with poorer physical function measured with the SF-12
Hudon et al. (2008)	Residential households in Quebec, Canada N = 16782 (18–69 years)	Cross-sectional Interview and self-report	Multimorbidity was not associated with physical activity levels
Marengoni et al. (2009)	Swedish living in community and institutions N = 1099 (78+ years)	Longitudinal Diagnoses from clinical examination, lab data, drugs and medical records.	Increasing number of chronic conditions increased the risk of 3-year functional decline
Loza et al. (2009)	Spanish living in community N = 2192 (20+ years)	Cross-sectional Questionnaires	Multimorbidity was associated with impaired functioning

Table 3b

Description of the selected studies on consequences of multimorbidity: mortality.

Author, year of publication	Setting Participants	Ascertainment of diseases	Results
Menotti et al. (2001)	Men rural community in Finland, Italy, and the Netherlands N = 2285 (65–84 years)	Clinical examination and self-report	Having 2 or 3+ diseases significantly increased the 10-year mortality risk in all cohorts
Deeg et al. (2002)	Community-dwelling in the Netherlands N = 2141 (65–85 years)	Self-report	Having a multimorbidity profile was associated with 3-year mortality
Byles et al. (2005)	Australian veterans and war widows N = 1541 (70+ years)	Self-administered questionnaire	Having 7+ diseases increased the risk of 2-year mortality
Marengoni et al. (2009)	Swedish living in community and institutions N = 1099 (78+ years)	Diagnoses from clinical examination, lab data, drugs and medical records	3-year risk of death was the same for people with one disease as well as 4+ diseases
Landi et al. (2010)	Italians living in community N = 364 (80+ years)	Self report and medical records	Multimorbidity affected 4-year mortality, only if associated with disability

(Bayliss et al., 2004; Kadam et al., 2007; Hudon et al., 2008; Marengoni et al., 2009b; Loza et al., 2009; Table 3a); five studies examined the risk of death (Menotti et al., 2001; Deeg et al., 2002; Byles et al., 2005; Marengoni et al., 2009b; Landi et al., 2010; Table 3b); seven focused on quality of life or well-being (Byles et al., 2005; Fortin et al., 2006a,b; Walker, 2007; Min et al., 2007; Wong et al., 2008; Loza et al., 2009; Table 3c); and eight examined health care utilization and costs (Wolff et al., 2002; Noël et al., 2005, 2007; Byles et al., 2005; Friedman et al., 2006; Laux et al., 2008; Condelius et al., 2008; Schneider et al., 2009; Table 3d). With few exceptions, all studies found a significant effect of multimorbidity on disability, poor quality of life and high health care utilization and costs, even after adjustment for multiple confounders.

3.3.1. Studies on functional status

Among articles evaluating the association of multimorbidity with disability or functional performances (Table 3a), two were longitudinal with a follow-up time of 3–4 years (Bayliss et al., 2004; Marengoni et al., 2009b) and three used a cross-sectional study design (Kadam et al., 2007; Hudon et al., 2008; Loza et al., 2009). The ascertainment of diseases was made by medical records in two studies (Bayliss et al., 2004; Kadam et al., 2007), by self-report in two studies (Hudon et al., 2008; Loza et al., 2009), and by multiple information including clinical examination in one study (Marengoni et al., 2009b). An increasing number of diseases were consistently associated with increasing odds or risk for disability. Only one study (Hudon et al., 2008) showed no association between multimorbidity and physical functioning.

Table 3c

Description of the selected studies on consequences of multimorbidity: quality of life.

Author, year of publication	Setting Participants	Study design and ascertainment of diseases	Results
Byles et al. (2005)	Australian veterans and war widows N = 1541 (70+ years)	Longitudinal Self-administered questionnaire	An increasing number of diseases decreased quality of life, assessed by the 36-item Medical Outcomes Study Short Form (SF-36) QoL measure (both in the physical and the mental components)
Fortin et al. (2006a)	Residential in Canada N = 238 (56.5, SD = 17.4)	Cross-sectional General practitioners records	Multimorbidity measured by a count of conditions was related to the physical component of the SF-36 but not the mental one
Fortin et al. (2006b)	Residential in Canada N = 238 (56.5, SD = 17.4)	Cross-sectional General practitioners records	Multimorbidity measured with a count of diseases was not related to psychological distress, assessed with the 14-item questionnaire Indice de Détresse Psychologique de l'Enquête Santé Québec
Walker (2007)	Australian general population N = 17,450 (20+ years)	Cross-sectional Self-report	Persons with 3+ conditions were more likely to feel distressed or pessimistic about their lives
Wong et al. (2008)	Residential volunteers in Hong Kong N = 3394 (65+ years)	Cross-sectional Standardized questionnaires	Depression prevalence was associated with the number of chronic conditions
Loza et al. (2009)	Spanish living in community N = 2192 (20+ years)	Cross-sectional Questionnaires	Multimorbidity was associated with lower quality of life, assessed by the 12-item short form (SF-12) health status

Table 3d

Description of the selected studies on consequences of multimorbidity: health care utilization.

Author, year of publication	Setting Participants	Study design/ascertainment of diseases	Outcome	Results
Wolff et al. (2002)	US Medicare fee-for-service N = 1,217,103 (65+ years)	Cross-sectional Administrative database	Hospitalizations, complications, and expenditures	Increasing no. of diseases increases hospitalizations, preventable complications, and expenditures
Noël et al. (2005)	Ambulatory primary care in US N = 60 (30–80 years)	Cross-sectional Medical records	Care needs	Identified problems included: poor functioning, negative psychological reactions, inference with work and leisure, polypharmacy. Overall satisfaction with primary care. Participants willing to use technology
Byles et al. (2005)	Australian veterans and war widows N = 1541 (70+ years)	Longitudinal Self-administered questionnaire	Hospital admission	An increasing number of diseases were not associated with hospital admissions
Friedman et al. (2006)	US hospitalized persons	Cross-sectional Hospital medical records	Hospital costs	The number of chronic conditions influences independently hospital costs
Noël et al. (2007)	Ambulatory primary care in US N = 720 (50, median)	Cross-sectional Medical records	Learning self-managing of diseases	A higher % of multimorbidity patients compared to single morbidity were willing to learn self-management skills and to see non-physician providers
Laux et al. (2008)	Residential in Germany N = 39,699 (all ages)	General practice consultations during 1 year	Medical prescriptions and referrals	The number of chronic diseases had a significant impact on the number of prescriptions and referrals
Condelius et al. (2008)	Southern Swedish residential N = 4907 (65–104 years)	Prospective Medical records	Hospital admissions	The number of diagnosis groups was associated with number of hospital admissions
Schneider et al. (2009)	US Medicare recipients (institutional and not) N = 2,232,528 (all ages)	Cross-sectional Chronic condition data warehouse	Expenditures	As the number of chronic diseases increases, the average per beneficiary payment amount increases

3.3.2. Studies on mortality

Among articles evaluating risk of death, none examined cause-specific mortality (Table 3b). The follow-up time varied from 1 to 10 years. The ascertainment of diseases were based on self-reported in two studies ([Deeg et al., 2002](#); [Byles et al., 2005](#)), by self-report and medical examination in one study ([Landi et al., 2010](#)) and multiple information including clinical examination

in two studies ([Menotti et al., 2001](#); [Marengoni et al., 2009b](#)). Controversial 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 ([Menotti et al., 2001](#); [Byles et al., 2005](#); [Deeg et al., 2002](#)) but not in others ([Marengoni et al., 2009b](#); [Landi et al., 2010](#)).

3.3.3. Studies on quality of life

Six studies explored the association between multimorbidity and quality of life or well-being (Table 3c). Of these, only one was longitudinal (Byles et al., 2005). The ascertainment of diseases was based on self-report in four studies (Byles et al., 2005; Walker, 2007; Wong et al., 2008; Loza et al., 2009) and on medical records in two studies (Fortin et al., 2006a,b). Multimorbidity was associated with depression, distress and generally with poor quality of life. Only one study showed no association between multimorbidity, as a simple count of diseases, and psychological distress (Fortin et al., 2006b); however, in the same study, the authors found that psychological distress increased in people with multimorbidity when disease severity was taken into account (Fortin et al., 2006b).

3.3.4. Studies on health care utilization

Eight studies examined the effect of multimorbidity on health care (Table 3d); three were longitudinal (Byles et al., 2005; Laux et al., 2008; Condelius et al., 2008) and five cross-sectional (Wolff et al., 2002; Noël et al., 2005, 2007; Friedman et al., 2006; Schneider et al., 2009). Different outcomes were used: care needs (Noël et al., 2005), learning self-management of diseases (Noël et al., 2007), hospital admission and related costs (Wolff et al., 2002; Byles et al., 2005; Friedman et al., 2006; Condelius et al., 2008), number of prescription and satisfaction in primary care (Laux et al., 2008), and medical expenditures (Schneider et al., 2009). The number of diseases was significantly associated with the number of prescriptions, referrals, hospital admissions and expenditures.

3.4. Studies on models and quality of care

Six studies evaluated models or quality of care in patients with multimorbidity by using different outcomes (Table 4): applicability and experience of clinical guidelines in elderly with multimorbidity (Boyd et al., 2005), applicability of a new primary care practice model for caring for patients with multimorbidity (Soubhi et al., 2010), evaluation of new models of health care feasible to physicians, patients, and caregivers (Boyd et al., 2007), quality of care indicators in persons with multimorbidity (Min et al., 2007), and clinicians' experience of people affected by multiple diseases (Fried et al., 2011). One study addressed methodological issues in evaluating quality of care in persons with multimorbidity (Kirk et al., 2003).

4. Discussion

4.1. Methodological issues

Several methodological problems emerged during the evaluation of the selected articles. First, age structure of the study population and selection of different care settings can have a large impact on study results. Second, information on health status including disease ascertainment was collected in different ways across studies, which leads to great variability in measuring the outcome of interest. Current methods include interviews, self-reports, medical record reviews, administrative databases, and clinical examinations. Analyses of surveys containing both self-report and objective measurements of health status have documented systematic biases in self-reports according to age, sex and socioeconomic status (Sadana, 2000). It has been shown that older age is associated with less accurate self-reports of diseases, independently of cognitive status (Kriegsman et al., 1996), and that having multiple diseases decreased the agreement between self-reports and medical records in older women (Simpson et al., 2004). The Italian Longitudinal Study on Aging showed substantial under- and over-reporting for several chronic diseases by elderly persons (ILSA

working group, 1997). The use of different sources of medical diagnoses (i.e., clinical examination, medical records, blood samples or medical tests) may limit potential errors which often affect the accuracy of the assessment of multimorbidity in the elderly population. Technology might also be helpful; i.e., the use of electronic health records may result in standardization of the language and allow a feasible exchange of information from general practitioners or hospitals to research. Moreover, the development of research international networks may be a valuable approach to overcome the barrier of limited financial resources for the design of studies with large samples size and longitudinal follow-up.

Third, the evaluation of multimorbidity using number of chronic conditions affecting the elderly person has both advantages and disadvantages (Lash et al., 2007). A chief advantage of this procedure is parsimony, especially when a high number of diseases are evaluated. In addition, the resulting composite expresses multimorbidity in an additive form, and it conveniently differentiates people at each level of morbidity. Finally, using the count variable approach, the contribution of a given disease, expressed in the multimorbidity term, can be estimated, avoiding problems of insufficient statistical power, especially if rare diseases are evaluated (Ferraro and Wilmoth, 2000). On the contrary, one of the most reported disadvantages is that all diseases are scored equally, independently of their severity. Further, the prevalence of multimorbidity largely depends on the number of diseases studied in different studies and the diagnostic criteria used (Schram et al., 2008).

Finally, the distribution and combination of different diseases received very little attention. Diseases may co-occur due to several reasons. If disorders are completely independent of one another, they can be expected to co-occur at a rate which equals the product of the prevalence of the separate conditions (coincidental multimorbidity) (van den Akker et al., 1996). For some pairs of conditions, the rate of co-occurrence could be higher than expected. There are a number of possible explanations for the increase in observed versus expected co-prevalence for conditions not generally recognized as associated (Guralnik et al., 1989). Detection bias could influence the results, as persons affected by one condition may have more contacts with the medical care system and greater likelihood of being diagnosed with a second condition. An example of bias is the over-reporting of comorbidity associated with certain conditions like depression (Neeleman et al., 2001). When the prevalence of multimorbidity exceeds the expected (coincidental) level and biases can be excluded, the association could be causal (van den Akker et al., 1998; Batstra et al., 2002) or due to a common underlying biological basis. Genetic, environmental, and psychosocial factors may increase a general susceptibility to diseases, resulting in the co-occurrence of disorders in late life. Associative multimorbidity is defined when coexisting diseases share the same risk factors or when the risk factor for disease X is associated with the risk factor for disease Y (e.g., alcohol drinking and smoking). Different measures have been used to describe coexistence and patterns of multiple diseases (van den Akker et al., 2001a; Batstra et al., 2002; Marengoni et al., 2009a): prevalence figures, conditional count, odds and risk ratios, cluster analysis and cluster coefficients as well as specific statistical packages were taken into account and applied to population-based dataset (Valderas et al., 2009; van den Akker et al., 2001a; Batstra et al., 2002; Marengoni et al., 2009a).

4.2. Discussion of the current scientific evidence

Despite the increasing interest of the researchers on this field, there is still a remarkable gap between the harmful impact of multimorbidity at the individual and societal level and the amount of scientific and clinical research devoted to this topic.

Table 4

Models and quality of care for persons with multimorbidity: description of most relevant studies.

Author, year of publication	Aim	Methods	Results and conclusions
Kirk et al. (2003)	To investigate problems in assessing quality of care of multimorbidity	Quality indicators on 23 clinical conditions were used to assess quality of care in patients records	There are significant problems in relation to poor data quality, low prevalence of some conditions, and methodological complexities in calculating summary scores for care providers
Boyd et al. (2005)	To evaluate the applicability of disease-specific clinical guidelines in elderly with multimorbidity	Different aspects of clinical guidelines for the most common chronic diseases were evaluated	Adhering to disease-specific clinical guidelines in caring elderly with multimorbidity may have undesirable effects such as adverse interactions between drugs and diseases
Min et al. (2007)	To evaluate quality indicators satisfaction in elderly with or without multimorbidity	Cross-sectional Medical records	Mean proportion of quality indicators on health care processes satisfied (among 207 identified) increased from 47% for elderly with 0 conditions to 59% for those with 5–6 conditions
Boyd et al. (2007)	To test the feasibility of a new model of health care for older adults	To practice Guided Care, a nurse uses a customized electronic health report working with primary care physicians to meet health care needs of patients with multimorbidity in order to create two management plans; a care guide for professionals and an action plan for patient and caregiver	Guided Care is feasible and acceptable to physicians, patients, and caregivers. If successful in a controlled trial, Guided Care could improve the quality of life and efficiency of health care for older persons with multimorbidity
Soubhi et al. (2010)	To introduce a primary care model for caring patients with multimorbidity	A model of care with the emphasis on knowledge management, case-based learning, informal ties and shared motivation among community members	The study underlines the hypothesis that relationships and collective learning of practice can improve primary care for patients with multimorbidity
Fried et al. (2011)	To evaluate clinicians' experience with elderly with multimorbidity	Open-ended questions about treatment decision making in elderly with multimorbidity were given to 40 primary care physicians	Clinicians struggle with the uncertainties of applying disease-specific guidelines to older patients with multimorbidity

The main findings of this review can be summarized in the following points: (1) multimorbidity affects more than half of the elderly population; (2) the prevalence increases in very old persons, women and people from lower social classes; (3) very little is known about risk factors for multimorbidity: we did not find a single study evaluating genetic background, biological causes (such as cholesterol, blood pressure, obesity), life styles (smoking, drinking, nutrition, physical activity), or environmental factors (air pollution, social environment) in relation to the development of multimorbidity; (4) functional impairment, poor quality of life and high health care utilization and costs are major consequences of multimorbidity; and (5) data are insufficient to provide scientific basis for evidence-based care of patients affected by multimorbidity.

Prevalence figures varied across studies probably due to the different methods used. As discussed previously, prevalence differs according to the number of conditions evaluated, the age structure of the study population, the settings (community, institutions, and hospitals), case ascertainment ([Sadana, 2000](#)), and different cut-off number used to define multimorbidity (2, 3, 4 or more diseases or a continuous number). The increasing prevalence of multimorbidity in older persons can be explained by the longer exposure and increased vulnerability to risk factors for chronic health problems. Women are more likely to be affected by multimorbidity than men because they live longer than men, or because men who survive are healthier than women. Moreover, women are more affected than men by non-fatal diseases such as osteoarthritis ([Minas et al., 2010](#)). People from lower social classes are more likely to be affected by multimorbidity, whereas persons with large social networks may be protected. Persons with a low level of education may have little awareness of healthy behaviours, difficulties in accessing care, and being more likely to manage poorly their health, both in term of compliance with pharmacological and non-pharmacological treatments and use of preventive services. Moreover, a low educational level could be also an indicator of a low socioeconomic status in the family of origin. On the other hand, people living in a large social

network may be more careful regarding their health status and less likely to develop specific chronic diseases such as depression.

With few exceptions, all studies found a significant effect of multimorbidity on disability, quality of life and health care utilization. Multimorbidity and disability along with frailty identify the vulnerable subset of the old population ([Fried et al., 2004](#)). These terms indicate distinct clinical entities, although interrelated. In the Cardiovascular Health Study, of the 2762 participants, 2131 were affected by 2+ chronic conditions, but did not have either disability or frailty ([Fried et al., 2004](#)). Thus, the number of chronic conditions only partially explains disability and functional decline in aging. However, considering merely alone the additive effect of individual diseases on functional status could be inadequate. Clusters of conditions may have a synergistic effect on disability and specific diseases can be associated with difficulty in different functional tasks, suggesting specificity in the etiologic relationship between diseases and a type of disability ([Fuchs et al., 1998](#); [Fried et al., 1994](#)). Indeed, although the role of chronic conditions in causing functional limitation is intuitively important, we still lack consensus on the pathway from disease to disability, mechanisms whereby diseases cause disability, and the degree to which this occurs ([Guralnik, 1994](#)). A recent theory suggests that diseases could be an interface between basic pathophysiological processes (such as inflammation, oxidative stress, and apoptosis) and final health outcomes (e.g., functional disability) ([Yancik et al., 2007](#)). Chronic diseases can be widely different in terms of severity and effects on survival. Indeed, an increasing number of chronic conditions do not necessarily have a major impact on survival. We can reasonably hypothesize that disease severity, disease duration and interactions between acute and chronic conditions are probably much more important than the mere count of chronic morbidities in increasing mortality risk. On the other hand, all studies agree on the fact that persons with multiple diseases have significant medical needs, which raises issues of resource allocation, equality and prioritization.

Some studies have validated care models for persons with multimorbidity, in particular medical home (primary health care), hospital care and their integration with social assistance and few have studied quality of care. Although only some of these studies are included in this review, in general, the data available do not reflect the broader physical, cognitive, and psychological effects of multimorbidity and polytherapy on the old person (Tinetti et al., 2004), in spite of the fact that very old people often experience both medical problems and multiple functional (physical and cognitive) limitations simultaneously. The prevalence of such complex health problems and associated care needs presents a major challenge for both the amount and structure of the provided services (Boyd et al., 2007; Meinow et al., 2006; Fratiglioni et al., 2007). Some innovations have already been suggested, although not yet tested in practice: weighting performance measures based on concurrent diseases, developing additional clinical outcomes (for example, pain control) (Werner et al., 2007), and incorporating the preferences, goals of care, and values of patients and their caregivers in the same measures (Norris et al., 2008). Further some new indicators of such complex health problems have been suggested. Using national representative samples of the Swedish population aged 77+, Meinow et al. (2006) constructed a measure including three health domains: diseases/symptoms, mobility, and cognition/communication. People having serious problems in at least two of the three domains were considered to have complex health problems. Prevalence rates have increased from 19% in 1992 to 26% in 2002 (Meinow et al., 2006); on the other hand, 4-year mortality decreased for men aged 77+ with multimorbidity between 1992 and 2002 (Meinow et al., 2010). Higashi et al. (2007) showed that quality of care increases as the number of medical conditions increase, maybe because of the increased use of health care by patients with multimorbidity, but the study included both adults and elderly people.

4.3. Limitations

First, given the diversity of articles on multimorbidity, it is difficult to identify a comprehensive search strategy. Missed articles would have included those that focused on two or more conditions, but did not include “multimorbidity” (or related terms) in the title, abstract or as Mesh heading.

Second, we focused only on studies about multimorbidity defined as the number of concurrent diseases in the same individual. Studies evaluating multimorbidity from a clinical point of view (i.e., considering also the severity of disease) or a social aspect (i.e., evaluating care needs in people with multimorbidity) were not included in this review.

4.4. Future perspectives

Better understanding of the development and natural history of multimorbidity has become one of the most urgent issues in public health and clinical practice. Which are the underlying mechanisms leading to the co-occurrence of apparently unrelated diseases in the same individuals? Can we identify these subjects before the whole chain of events has taken place? Or at least can we stop the process and decrease the dramatic consequences of multimorbidity? Further, are we able to identify better models for caring persons with multiple health problems? These are the major research questions that we have addressed in this review, and at the moment, in spite of the efforts in the last few years, our knowledge is very limited. In the future we need to further explore relevant topics such as:

- *Risk factors and pathogenetic mechanisms leading to multimorbidity* (Gijzen et al., 2001): Attention should be paid to genetic factors and biological factors, lifestyles, social determinants of multimorbid-

ity, and their interactions. Underlying pathological mechanisms such as chronic inflammation, oxidative stress and metabolic syndrome needs to be investigated in relation to disease clustering. This can hopefully lead to identify prevention strategies, including early recognition of secondary diseases. Identifying common clusters of conditions would be an important first step.

- *Influences of contextual factors on the natural history of multimorbidity*: We lack investigations concerning the possible modulator effect of factors such as social support, socio-economic status and environmental context on the adverse outcomes due to multimorbidity (e.g., functional decline and mortality). A life course perspective in relation to the time of onset and duration of diseases should be adopted, and the role of factors such as personality, resiliency, and stress should be taken into account.
- *Clinical trials/interventions and development of specific guidelines for multimorbidity*: Clinical trials and treatment guidelines should include persons with multimorbidity that represents the majority of older populations. Patients with several coexisting conditions are treated with a combination of medications prescribed in compliance with disease-specific guidelines. Vitry and colleagues showed that only one Australian clinical guideline for a chronic disease addressed treatment for older persons with multimorbidity (Vitry et al., 2008). Fried and colleagues recently reported that practicing clinicians struggle with the uncertainties of applying disease-specific guidelines to their older persons with multiple conditions (Fried et al., 2011). Yet most research and clinical practice is still based on a single disease paradigm, which may not be appropriate for patients with complex and overlapping health problems.
- *Health care models and care organisation for persons with multimorbidity*: Elderly people with multimorbidity need care that involves a holistic approach, continuous collaboration across specialties, and over professional and organizational boundaries, including both medical care and social services. A primary research agenda should be the validation of quality measures for existing or new care models for persons with multimorbidity.

Recently, research of multimorbidity in primary care has been moving up the international agenda (Mercer et al., 2009). Fortin and colleagues in Quebec have called for international collaboration and have set up a dedicated website to facilitate communication through a virtual research community (https://www.med.usherbrooke.ca/cirmo/mission_anglais.htm). In Scotland, there are new funds provided to support research of multimorbidity and development of complex primary care-based interventions to help patients with multimorbidity in deprived areas (Mercer et al., 2009). In the Netherlands, the Dutch ‘National Care for the Elderly Programme’ is designed to improve care of older people with multimorbidity and complex care needs (<http://www.nationaalprogrammaouderenzorg.nl/english/the-national-care-for-the-elderly-programme/>). In Sweden several studies aimed to validate different models of interventions are ongoing e.g. the Sahlgrenska academy at Gothenburg University is conducting an ongoing interventional study on the care of elderly people with multimorbidity. The overall objective is to create a coherent care for frail, multimorbid older people, from the emergency department to their own homes (<http://www.sahlgrenska.se/sv/SU/Omraden/3/Verksamhetsomraden/Geriatrik/Projekt-Vardkedja-fran-akutmottagning-till-egget-boende/>) (Wänell, 2007; Fratiglioni et al., 2010).

This review intends to be a contribution to all these efforts to better identify priorities in research and to serve as the base of a new insight of the needs of care of the growing older population in the 21st century.

5. Conclusions

The main findings of this review can be summarized as follows; Multimorbidity affects more than half of the elderly population with increasing prevalence in very old persons, women and people from lower social classes. Very little is known about risk factors for multimorbidity, such as genetic background, biological causes, life styles, or environmental factors, whereas major consequences of multimorbidity are functional impairment, poor quality of life and high health care utilization and costs. Data available are insufficient to provide scientific basis for evidence-based care of patients affected by multimorbidity.

Funding

This study was funded by research grants from the Loo and Hans Osterman Foundation. The authors' work was independent of the funders.

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