Title page

Title: Multimorbidity and mortality in older adults: a systematic review and meta-analysis

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Abstract:

Objective: to review literature and provide a pooled effect for the association between multimorbidity and mortality in older adults.

Methods: a systematic review was performed of articles held on the PUBMED database published up until January 2015. Studies which used different diseases and other conditions to define frailty, evaluated multimorbidity related only to mental health or which presented disease homogeneity were not included. A meta-analysis using random effect to obtain a pooled effect of multimorbidity on mortality in older adults was conducted only with studies which reported hazard ratio (HR). Stratified analysis and univariate meta-regression was performed to evaluate sources of heterogeneity.

Results: Out of 5806 identified articles, 26 were included in meta-analysis. Overall, positive association between multimorbidity and mortality [HR: 1.44 (95%CI: 1.34; 1.55] was detected. The number of morbidities was positively related to risk of death [HR: 1.20 (95%CI: 1.10; 1.30)]. Compared to individuals without multimorbidity, the risk of death was 1.73 (95%CI: 1.41; 2.13) and 2.72 (95%CI: 1.81; 4.08) for people with 2 or more and 3 or more morbidities, respectively. Heterogeneity between studies was high (96.5%). The sample, adjustment and follow-up modified the associations. Only nine estimates performed adjustment which included demographic, socioeconomic and behavior variables. Disabilities appear to mediate the effect of multimorbidity on mortality.

Conclusions: Multimorbidity was associated with an increase in risk of death. Multimorbidity measurement standardization is needed to produce more comparable estimates. Adjusted analysis which includes potential confounders might contribute to better understanding of causal relationships between multimorbidity and mortality.

1. Introduction

Multimorbidity is a frequent problem, mainly in the elderly population, among whom prevalence was found to be greater than 60% (Fortin et al., 2012). Although studies of this problem are recent, available data have shown negative consequences related to multimorbidity including an increased risk of disability, frailty and decrease in quality of life, as well as associations with mortality (Fortin et al., 2004; Gijsen et al., 2001; Marengoni et al., 2011; Mello et al., 2014).

The biological plausibility of association between multimorbidity and mortality is analogous to physiologic mechanisms which increase the risk of death in individuals with a specific disease. Moreover, multimorbidity increases the risk of complications and consequences on the physiological system due to interactions between morbidities and disease treatment (American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity, 2012; Guthrie et al., 2012; Mallet et al., 2007; Marengoni et al., 2011; Salisbury, 2012; van Weel and Schellevis, 2006). Some studies have found higher risk of death among elderly people with multimorbidity compared to those without diseases (Landi et al., 2010; Marengoni et al., 2009; Menotti et al., 2001; Wang et al., 2009), while other studies did not find differences (St John et al., 2014; Woo and Leung, 2014). Furthermore, mortality in the elderly is multifactorial and includes environmental (Beelen et al., 2014; Meijer et al., 2012; Silva et al., 2014), demographic (Luy and Gast, 2014) and socioeconomic characteristics (Silva et al., 2014), as well as being influenced by social relationships (Holt-Lunstad et al., 2010), geriatric conditions (Landi et al., 2012; Landi et al., 2010; Shamliyan et al., 2013; Theou et al., 2012; Woo and Leung, 2014) and healthcare actions (Veras et al., 2014).

Despite this context, to the best of our knowledge, a pooled effect on the association between multimorbidity and mortality does not exist. The description of characteristics which modify association might be useful to inform future interventions to measure actions and programs related to elderly (Moraes, 2012; Salisbury, 2012; Salive, 2013). Thus, the objective of this study was, by means of a systematic review and meta-analysis, to evaluate and quantify the association between multimorbidity and mortality in older adults.

2. Methods

2.1. Search strategy and selection criteria

A systematic review of literature held on the PUBMED database published up until January 22nd 2015 was conducted. Manuscripts in English, Portuguese and Spanish were searched. The following terms were used: ("comorbidity" OR "co-morbidity" OR "multimorbidity" OR "multi-morbidity" OR "multiple diseases" OR "multiple morbidities" OR "multimorbid" OR "multiple pathology" OR "disease clustering" OR "Risk Adjustment" OR "Severity of Illness Index") AND ("Mortality" OR "survival rate" OR "cause of death") AND ("aged"). Only studies involving individuals ≥60 years old were included. The manuscript has been modelled on guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement (Moher et al., 2009). Original articles which evaluated mortality risk according to multimorbidity occurrence were included. Studies were not included which used different diseases and other conditions to define frailty or evaluated multimorbidity related only to mental health or which presented disease homogeneity – comorbidity. References cited in the articles were also evaluated. Only studies which reported hazard ratio (HR) or information on obtaining HR were included in the meta-analysis. If necessary the authors were contacted to obtain additional information. Three out of twelve authors contacted answered providing additional estimates.

All titles and abstracts searched were read by the first author. Then, two independent reviewers (BPN and TRF) evaluated the full articles for inclusion in the meta-analysis. The following information was extracted from eligible articles: study country, study design, age group, target population, multimorbidity measurement and operationalization, number of diseases included in the multimorbidity construct, type and

follow-up of mortality. Disagreements (no consensus) were evaluated by others reviewers (LAF and ET).

2.2. Data analysis

Overall and stratified analyses according to multimorbidity operationalization (≥2; ≥3 and continuous) were performed. Co-variables analyzed included: age group (<75/ ≥75); sample size (<500/ 500 to 1000/ >1000); sample studied (population-based/ service-based–hospital–institutionalized); selection bias possibility (no/yes); follow-up (≤1 / 1 to 5/ >5 to 10/ >10 years); disease severity in multimorbidity measurement (no/yes); number of morbidities included (<12; ≥12); comparison group for ≥2 morbidities cut-off (0/ 0-1); comparison group for ≥3 morbidities cut-off point (0/ 0-3); confounding factor adjustment (sex and age; sex, age and socioeconomic variables; sex, age and behavior variables; sex, age, socioeconomic and behavior variables); adjustment for disability (no/yes); and adjustment for self-rated health (no/yes). All variables were selected due to possible influence on association investigated (Fortin et al., 2012; Marengoni et al., 2011; Salive, 2013). Potential selection bias was defined by observed differences between the sample analyzed and losses/refusals, or by response rate <50%. To adjust for confounding factors the following variables were considered as socioeconomic and behavior variables, respectively: income, social class, economic class, assets index, occupation, and smoking, at-risk drinking, and anthropometric or physical activity indicator. Due to the paucity of studies which evaluated the multimorbidity effect on mortality stratified by sex, this variable was not included in the analyses.

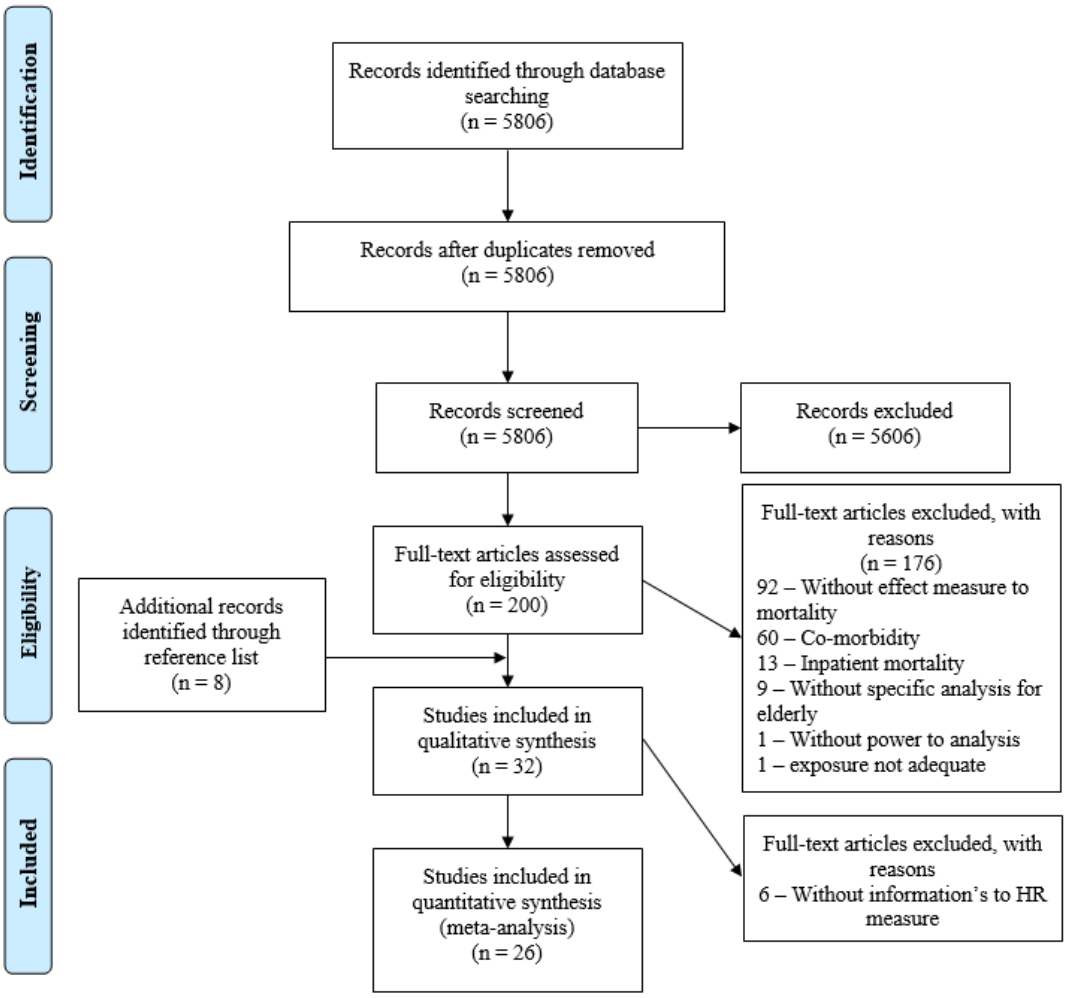
In the case of six studies (Chan et al., 2014; Drame et al., 2008; Gutierrez-Misis et al., 2012; Marengoni et al., 2009; Newman et al., 2008; Tooth et al., 2008), additional pooled effects were calculated based on data in order to increase comparability. Heterogeneity

between studies was evaluated using the I^2 statistic, taking 31% as the cut-off point for using fixed models (Higgins and Thompson, 2002). Articles with different estimates were included independently. Univariate meta-regression was performed to evaluate the pooled effect according to the characteristics of the studies. Funnel plots and the Egger test were used to evaluate publication bias. Analysis was performed using Stata 12.1.

3. Results

The search identified 5806 studies. After title and abstract reading, 200 manuscripts were selected for full-text reading. The majority of these were excluded because they did not have effect measurement for association between multimorbidity and mortality or included comorbidity evaluation (disease index) (Figure 1). Eight additional records were identified through references list of selected papers, reaching 32 papers in qualitative synthesis. Then, 26 articles were included in the meta-analysis and provided 45 estimates for the association being investigated by this study (Chan et al., 2014; Chen et al., 2010; Chwastiak et al., 2010; Dahl et al., 2013; Drame et al., 2008; Fillenbaum et al., 2000; Formiga et al., 2013; Gutierrez-Misis et al., 2012; Helvik et al., 2013; Jakobsson and Hallberg, 2006; Jeong et al., 2013; Landi et al., 2010; Marengoni et al., 2009; Mazzella et al., 2010; Menotti et al., 2001; Minicuci et al., 2003; Newman et al., 2008; Nybo et al., 2003; Rozzini et al., 2002; St John et al., 2014; Theou et al., 2012; Tiainen et al., 2013; Tooth et al., 2008; van Doorn et al., 2001; Wang et al., 2009; Woo and Leung, 2014).

Figure 1. Flow chart of article search and selection.



144

145 All papers presented a cohort study design. Most studies were carried out in European
146 countries and had a sample size greater than 500 participants, included 12 or more
147 diseases, used disease count and continuous operationalization for multimorbidity, and
148 had follow-up of less than five years. All studies evaluated overall mortality. Half of them
149 included disease severity measurement. Out of 26 studies included in meta-analysis, 20
150 found positive association between multimorbidity and mortality. Only five studies
151 performed adjustment for sex, age, socioeconomic and behavior variables. Population-
152 based samples were most used and 50% of studies had possible selection bias (Table 1).

153 **Table 1. Articles included in the meta-analysis.**

First author (year)	Country	Age	Proportion of women %	Sample size	Measurement form	Severity	Cut-off for multimorbidity	Number of diseases	Mortality (Follow-up in years)	Confounding adjustment[#]	Association?
Woo, 2014	China	≥65	50.3	3401	Disease count	No	≥2	-	All-cause (9)	No	No
St. John, 2014	Canada	≥65	58.5	1751	Disease count	No	Continuous, ≥2 and ≥3	36	All-cause (5)	No	No/Yes
Frenkel, 2014	Netherlands	≥65	54.2	1,313	Charlson Index	Yes	≥2 and ≥3	15	All-cause (3 months, 1 and 5 years)	No	Yes
Chan, 2014	China	≥65	59.7	2050	Charlson Index	Yes	≥2 and ≥3	13	All-cause (1)	No	Yes
van der Jagt-Willems, 2013	Netherlands	82	66.1	395	Charlson Index	Yes	Continuous	-	All-cause (3)	No	Yes
Tiainen, 2013	Finland	≥90	80.7	888	Disease count	No	≥2	7	All-cause (9)	No	No
Jeong, 2013	Korea	≥65	56.1	1000	Cumulative Illness Rating Scale	Yes	Continuous	-	All-cause (5)	No	No
Helvik, 2013	Norway	≥65	50.2	484	Disease count	Yes	Continuous	-	All-cause (3)	No	Yes
Formiga, 2013	Spain	85*	61.6	328	Disease count	Yes	Continuous	33	All-cause (3)	No	Yes
Dahl, 2013	Sweden	≥65	59.8	882	Disease count	No	Continuous	11	All-cause (18)	Yes	Yes
Theou, 2012	Canada	≥65	62.1	2305	Disease count	No	Continuous	32	All-cause (5)	No	Yes
Gutierrez-Misis, 2012	Spain	≥65	48.1	978	Charlson Index	Yes	≥2	17	All-cause (5)	Yes	Yes
Chan, 2012	China	85.6*	65.3	1129	Charlson Index	Yes	≥2 and ≥3	-	All-cause (5)	Yes	Yes
Mazzella, 2010	Italy	≥65	57.0	1288	Charlson Index	Yes	Continuous	19	All-cause (12)	No	No
Landi, 2010	Italy	≥80	67.0	364	Disease count	No	≥2	13	All-cause (4)	No	Yes
Chwastiak, 2010	USA	64*	4.1	559985	Disease count	No	Continuous	12	All-cause (9)	Yes	Yes
Chen, 2010	Taiwan	81*	All males	559	Charlson Index	Yes	Continuous	-	All-cause (1)	No	Yes
Wang, 2009	USA	≥66	61.6	50000	Charlson Index	Yes	Continuous	19	All-cause (1)	No	Yes

Marengoni, 2009	Sweden	≥77	77.3	1099	Disease count	No	≥2	22	All-cause (2.8)	No	Yes
Tooth, 2008	Australia	73-78	All females	10434	Disease count	No/Yes	≥2 and ≥3	19	All-cause (6)	No	Yes
Newman, 2008	USA	≥65	60.0	2928	Disease count	No	Continuous and ≥3	10	All-cause (1)	No	Yes
Drame, 2008	France	≥75	65.0	1306	Charlson Index	Yes	≥2	-	All-cause (2)	Yes	Yes
Jakobsson, 2006	Sweden	≥65	67.0	626	Disease count	No	Continuous	-	All-cause (3)	No	Yes
Byles, 2005	Australia	≥70	45.0	1303	Charlson Index	Yes	Continuous	25	All-cause (2)	No	No/Yes
Nybo, 2003	Denmark	93 (all)	66.3	463	Disease count	No	Continuous	31	All-cause (1.25)	Yes	No
Minicuci, 2003	Italy	≥65	58.5	429	Disease count	No	Continuous	6	All-cause (1)	No	Yes
Selim, 2002	USA	64*	4.7	31,823	Charlson Index	Yes	Continuous	17	All-cause (1.5)	No	Yes
Rozzini, 2002	Italy	79*	70.8	576	Disease count and Geriatric Index of Comorbidity	No/Yes	Continuous	15	All-cause (1)	No	No/Yes
Buntinx, 2002	Belgium	84*	78.0	2,624	Charlson Index	Yes	≥2	19	All-cause (0.5)	No	Yes
van Doorn, 2001	USA	≥70	56.0	524	Charlson Index and ICD-9-CM	Yes	Continuous	16	All-cause (1)	No	Yes
	Finland			716							Yes
Menotti, 2001	Netherlands	65-84	All males	887	Disease count	No	≥3	7	All-cause (10)	No	Yes
	Italy			682							No
Fillenbaum, 2000	USA	≥65	67.0	4034	Disease count	No	≥2	5	All-cause (6)	No	Yes

154 Legend: *mean age; #adjustment for sex, age, socioeconomic and behavior variables.

The pooled mortality risks, comparing elderly people with multimorbidity versus those with no multimorbidity, were 1.44 (95%CI: 1.34; 1.55, I^2: 96.5%). This effect was 1.20 (95%CI: 1.10; 1.30), 1.73 (95%CI: 1.41; 2.13) and 2.72 (95%CI: 1.81; 4.08) for multimorbidity operationalized as continuous, ≥2 and ≥3, respectively (Figure 2).

Figure 2. Meta-analysis comparing multimorbidity and mortality (random effect) according to multimorbidity cut-off point.

Univariate meta-regression analysis found a greater effect of ≥2 (p=0.021) and ≥3 diseases (p<0.001) operationalization compared to continuous. There was a difference between ≥3 and ≥2 diseases operationalization (p=0.030). Effect modification was not observed in the analyses according to the independent variables, with the exception of multimorbidity cut-off. The stratified analysis by multimorbidity cut-off point showed a similar pattern compared to overall analysis. Moreover, a tendency towards reduction as follow-up increased was more evident in continuous and ≥2 morbidities operationalization. Estimates using disease severity presented higher effect for multimorbidity evaluated as continuous (p=0.059). Association was attenuated in estimates which compare the elderly with 0-1 (p<0.001) and 0-2 (p=0.003). The adjustment for socioeconomic level decreases the strength of association (Table 2).

173 **Table 2. Univariate meta-regression stratified by multimorbidity cut-off point.**

Variables	≥2				≥3				Continuous			
	n	HR (IC95%)	p	R2	n	HR (IC95%)	p	R2	n	HR (IC95%)	p	R2
Age												
<75	7	1.62 (1.27; 2.06)	index	-10.1	7	1.87 (1.63; 2.14)	index	33.9	7	1.22 (1.10; 1.36)	index	-6.6
≥75	8	1.90 (1.34; 2.69)	0.598		2	5.01 (3.57; 7.03)	0.072		14	1.15 (0.96; 1.38)	0.582	
Sample size												
<500	3	1.25 (0.90; 1.72)	index	0.4	-	-	-		6	1.14 (0.97; 1.35)	index	-11.9
500 a 1000	3	1.51 (1.06; 2.16)	0.626		3	3.07 (2.36; 3.99)	index	-14.1	8	1.28 (1.10; 1.49)	0.558	
>1000	9	2.10 (1.48; 2.96)	0.372		6	2.66 (1.55; 4.59)	0.851		7	1.16 (1.01; 1.33)	0.888	
Sample												
Population	13	1.61 (1.31; 1.97)	index	10.9	8	2.04 (1.79; 2.33)	index	-7.0	14	1.11 (1.01; 1.22)	index	26.5
Service-based	2	2.79 (1.73; 4.49)	0.244		1	4.00 (2.49; 6.43)	0.515		7	1.64 (1.12; 2.39)	0.007	
Selection bias												
No	7	1.65 (1.24; 2.20)	index	-9.7	4	1.89 (1.17; 3.07)	index	38.7	11	1.23 (1.06; 1.42)	index	-7.6
Yes	8	1.82 (1.31; 2.53)	0.815		5	3.70 (2.70; 5.10)	0.076		10	1.12 (1.06; 1.19)	0.798	
Follow-up (years)												
≤1	1	3.36 (2.25; 5.02)	index	-5.0	2	3.10 (1.84; 5.22)	index	91.5	7	1.53 (1.19; 1.98)	index	14.1
1 a 5	7	1.68 (1.23; 2.30)	0.264		2	1.27 (1.06; 1.53)	0.024		9	1.05 (1.00; 1.10)	0.021	
>5 a 10	5	1.83 (1.21; 2.78)	0.311		5	3.70 (2.70; 5.10)	0.581		3	1.23 (0.95; 1.58)	0.257	
>10	2	1.29 (0.98; 1.70)	0.154		-	-	-		2	1.15 (1.09; 1.22)	0.177	
Disease severity												
No	8	1.53 (1.22; 1.93)	index	-5.6	7	1.87 (1.63; 2.15)	index	11.2	10	1.08 (1.01; 1.14)	index	18.6
Yes	7	1.92 (1.30; 2.82)	0.619		2	4.24 (3.10; 5.80)	0.235		11	1.37 (1.15; 1.63)	0.059	
Number of morbidities included												
<12	2	1.19 (1.05; 1.34)	index	5.5	4	2.91 (2.30; 3.67)	index	-16.7	3	1.24 (1.12; 1.39)	index	-7.2
≥12	11	1.99 (1.48; 2.69)	0.206		5	1.89 (1.62; 2.20)	0.978		13	1.19 (1.05; 1.33)	0.491	
Comparison group (≥2)												
0	5	3.46 (2.73; 4.39)	index	92.7		-	-			-	-	
0-1	10	1.30 (1.15; 1.48)	<0.001			-	-			-	-	

Comparison group (≥3)												
0		-	-	-	6	3.73 (3.09; 4.51)	index	86.5		-	-	
0-2		-	-		3	1.36 (1.14; 1.61)	0.003			-	-	
Confounding adjustment												
Sex and age (1)	3	3.28 (2.09; 5.15)	index	82.7	2	5.01 (3.57; 7.03)	index	100.0	12	1.30 (1.12; 1.51)	index	-5.8
Socioeconomic variable (2)	6	1.27 (1.10; 1.46)	0.314		2	1.27 (1.06; 1.53)	<0.001		3	1.07 (0.98; 1.17)	0.307	
Adjust 1 + behavior variable	1	3.36 (2.25; 5.02)	0.442		5	3.10 (2.51; 3.82)	0.057		2	1.35 (1.04; 1.76)	0.739	
Adjust 1 + 2 + behavior variable	5	1.41 (1.07; 1.86)	0.385		-	-	-		4	1.09 (1.01; 1.17)	0.154	
Adjustment for disability												
No	5	2.25 (1.38; 3.66)	index	6.6	7	2.46 (2.11; 2.87)	index	-6.4	12	1.28 (1.11; 1.47)	Index	3.1
Yes	10	1.51 (1.22; 1.88)	0.236		2	1.58 (1.26; 1.98)	0.501		9	1.07 (1.02; 1.12)	0.309	
Adjustment for self-rated health												
No	10	2.09 (1.52; 2.87)	index	16.6	9	2.15 (1.89; 2.44)	-	-	18	1.21 (1.11; 1.33)	Index	-2.5
Yes	5	1.27 (1.04; 1.55)	0.103		-	-	-		3	1.07 (0.78; 1.47)	0.494	

The funnel plot and Egger's test showed publication bias possibility for multimorbidity classified as ≥2 (p=0.001) and ≥3 diseases (p=0.021). The possibility of selection bias was not found in continuous operationalization of multimorbidity (p=0.899) (supplementary file 1).

4. Discussion

Multimorbidity increases the risk of death regardless of its operationalization. High heterogeneity between studies was observed. A positive gradient between number of diseases and mortality was found, and ≥3 diseases as the cut-off point showed the strongest association with risk of death. Small samples, population-based studies, more comprehensive adjustment, multimorbidity without disease severity measurement and multimorbidity comparison groups were characteristics that appear to reduce the strength of association. Follow-up seems to modify association. In addition the possibility of selection bias was found for multimorbidity defined as ≥2 and ≥3 morbidities.

The biological plausibility of association investigated here is strengthened by greater physiological wear due to multiple diseases and complications related to interactions between morbidities and medications used in treatment (Calderon-Larranaga et al., 2012; Moraes, 2012) which can cause negative effects on target organs, either by themselves or owing to prescription error (Calderon-Larranaga et al., 2012). Also, multimorbidity is one of the main determinants of disability (Marengoni et al., 2011; Marengoni et al., 2009), frailty (Mello et al., 2014) and quality of life (Fortin et al., 2004), giving rise to a series of pathophysiological, social and health care events which increase the risk of death. The relationships between these mechanisms are complex and suffer effect modification by contextual (Beelen et al., 2014), demographic (Luy and Gast, 2014) and social characteristics (Holt-Lunstad et al., 2010), although mainly by socioeconomic attributes (Silva et al., 2014).

Furthermore, multimorbidity promotes the need for different health actions capable of influencing the risk of death (Veras et al., 2014). Elderly people with multiple health problems require more access to health services, this being the first barrier which may

increase the risk of death. Even if access is guaranteed, the quality of care provided may reflect poor outcomes. The lack of quality care, mainly related to communication difficulties between health professionals and patients, as well as to inadequate guidance, expose older adults to greater risk of complications in the management of their health problems. Even if treatment is appropriate, inadequate use of medication and polypharmacy may increase the risk of death (Calderon-Larranaga et al., 2012; Moraes, 2012) owing to two main reasons: elderly people having difficulty in understanding medication administration; and interactions between drugs. To a large extent these reasons are explained by fragmented care provided to older adults (Veras et al., 2014) who are monitored by health professionals and services unable to coordinate care without considering other morbidities, medications and treatments used by the elderly (Salisbury, 2012). Also, the low inclusion of older adults and individuals with multimorbidity in randomized clinic trials (American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity, 2012; Hempenius et al., 2013; Marengoni, 2013; Smith et al., 2012) reinforces the difficulty faced by health systems in creating appropriate clinical protocols for patient management.

In this meta-analysis, hospitalized-based samples showed stronger estimates compared to population-based studies. This result may be explained by higher capacity of diagnosis for hospitalized and institutionalized individuals. Moreover, these studies tend to use disease severity and this increases the strength of association.

Longer follow-up seems to decrease the effect of multimorbidity on mortality because the lack of measurement of elderly people's health status tends to dilute associations. Therefore, more frequent measurement of multimorbidity can contribute to a more detailed evaluation of associations (Wang et al., 2009).

The definition of reference group is fundamental for the comparison of studies of multimorbidity effect on mortality and to also for guiding health services (Fortin et al., 2012; Harrison et al., 2014). Studies evaluating multimorbidity as continuous do not seem to be the most appropriate, since associations with mortality can present a non-linear relationship, apart from efforts to estimate the severity of each disease (Marengoni et al., 2009; Tooth et al., 2008). Thus, that form of operationalization could hamper its applicability to health service actions. Operationalization with ≥3 morbidities showed the greatest strength of association with mortality. Moreover, six out of nine results of this form of operationalization used elderly people without diseases as reference group, differing from studies with ≥2 morbidities as their cut-off point and the reference group of which more frequently includes elderly people with zero and one morbidity. Thus, in order to facilitate comparability between studies and inform health service actions, studies should use reference groups which include individuals below the cut-off (0 and 1 for ≥2 and 0 to 2 for ≥3 diseases) (Fortin et al., 2012; Harrison et al., 2014).

Few studies performed full control of confounding including demographic, behavior and socioeconomic variables, recognized determinants of mortality (Silva et al., 2014) and multimorbidity (Barnett et al., 2012; Salive, 2013). Effect measurement tended to be smaller when adjustment included socioeconomic level, suggesting an overestimation of effect measurement in studies not using this analysis strategy.

The adjustment for physical disabilities as confounder might be a mistake in analyses, given that it may be a mediator in association between multimorbidity and mortality rather than a confounding variable. Occurrence of multiple health problems as a determinant of disabilities (Marengoni et al., 2011; Marengoni et al., 2009) revealed a mediator role (St John et al., 2014) or effect modification in associations studied. Combination of multimorbidity and physical disabilities can increase the predictive effect of mortality

(Landi et al., 2010; Marengoni et al., 2009). For instance, Marengoni et al. (2009) found risk of death 7.7 (95%CI: 4.7; 12.6) times greater for elderly adults with both multimorbidity and physical disability compared to individuals without these characteristics. When the exposed group was elderly people with multimorbidity but without disability, risk of death decreased to 2.5 (95%CI: 1.6; 3.8) (Marengoni et al., 2009).

The use of physical disabilities has been suggested as an important indicator of active elderly people and an outcome for health service interventions (Kalache and Kickbusch, 1997; Veras, 2009) due to its power of predicting health outcomes and the physiological condition of the elderly (Landi et al., 2010). Therefore, the use of disabilities as an indicator of multimorbidity severity among elderly adults may replace comorbidity indices which take into account the number and severity of diseases in order to predict mortality (Charlson et al., 1987). These indices, some proposed as long ago as the 1970s (Kaplan and Feinstein, 1974), have been important for predicting mortality. Notwithstanding, in this review the pooled effect observed was not so different between studies regardless of the measurement of disease severity. Usually, these indices ascribe weight to morbidities through their effects on mortality, and this is susceptible to advances in diagnosis and therapeutic resources for disease treatment (Peterson et al., 2012). Furthermore, the indices selected in this review were not validated for elderly population (Martinez-Velilla et al., 2014).

Those disease severity measurements which are less susceptible to temporal and health effectiveness changes can improve adequacy and comparability among studies. Both disease count and physical disabilities are measures commonly evaluated in epidemiological surveys (Lima-Costa et al., 2012) and health services as they are

277 relatively easy to obtain. Moreover, changes in physical disability may better reflect
278 living conditions and quality of life of elderly people.

279 The self-rated health adjustment used in some studies seems inadequate because this
280 variable indicates, synthetically, the health condition of elderly adults which is usually
281 determined by the number and severity of diseases. Besides its importance in mortality
282 prediction (DeSalvo et al., 2006), self-rated health mediates the association between
283 multimorbidity and mortality, thus explaining the reduction of effect observed. As well
284 as physical disabilities, future studies can evaluate the role of self-rated health in
285 association studied here (Diederichs et al., 2011; McDaid et al., 2013), but without
286 considering it as a confounding variable.

287 Some limitations of this review should be considered. Firstly, huge heterogeneity was
288 observed, which may be explained by methodological differences between studies,
289 mainly related to measurement and operationalization of multimorbidity. Secondly, we
290 only searched the PUBMED database. However, PUBMED is considered to be one of the
291 largest databases in the health area and we also performed additional searches on
292 references cited in selected articles. Thirdly, eight studies initially selected used odds
293 ratios to evaluate the association between multimorbidity and mortality. These articles
294 were excluded because the authors did not respond our request for additional information.
295 In order to minimize this limitation, additional analyses (data not shown) were performed
296 including the odds ratio together with hazard ratios to calculate the pooled effect.
297 Although this procedure produces skewed estimates, the analyses presented similar
298 results, minimizing the possibility of bias.

299 Strengths of this meta-analysis include the calculation of a pooled effect of
300 multimorbidity on mortality taking many variables into consideration. Given a

controversial relationship present in the literature (Landi et al., 2010; St John et al., 2014; Woo and Leung, 2014), this meta-analysis contributes to understanding the effect of multimorbidity on mortality.

Further research is needed to increase comparability between studies to produce more robust estimates of the effect of multimorbidity on mortality. Also, efforts in order to obtain better understanding the determinants of multimorbidity can help potential confounders to be identified. Wider-ranging descriptions of associations are needed, including different multimorbidity cut-off points, the effect of disease clusters on risk of death and longitudinal analysis to comprehend the role of disabilities on association between multimorbidity and mortality.

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Conflict of interest statement

The authors declare that they have no competing interests

References

American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity, 2012. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. Journal of the American Geriatrics Society 60, E1-e25.

Barnett, K., Mercer, S.W., Norbury, M., Watt, G., Wyke, S., Guthrie, B., 2012. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 380, 37-43.

Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B., Wolf, K., Samoli, E., Fischer, P., Nieuwenhuijsen, M., Vineis, P., Xun, W.W., Katsouyanni, K., Dimakopoulou, K., Oudin, A., Forsberg, B., Modig, L., Havulinna, A.S., Lanki, T., Turunen, A., Oftedal, B., Nystad, W., Nafstad, P., De Faire, U., Pedersen, N.L., Ostenson, C.G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Overvad, K., Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Sugiri, D., Kramer, U., Heinrich, J., de Hoogh, K., Key, T., Peters, A., Hampel, R., Concin, H., Nagel, G., Ineichen, A., Schaffner, E., Probst-Hensch, N., Kunzli, N., Schindler, C., Schikowski, T., Adam, M., Phuleria, H., Vilier, A., Clavel-Chapelon, F., Declercq, C., Grioni, S., Krogh, V., Tsai, M.Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorronsoro, M., Katsoulis, M., Trichopoulou, A., Brunekreef, B., Hoek, G., 2014. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383, 785-795.

Calderon-Larranaga, A., Poblador-Plou, B., Gonzalez-Rubio, F., Gimeno-Feliu, L.A., Abad-Diez, J.M., Prados-Torres, A., 2012. Multimorbidity, polypharmacy, referrals, and adverse drug events: are we doing things well? The British journal of general practice : the journal of the Royal College of General Practitioners 62, e821-826.

Chan, T.C., Luk, J.K., Chu, L.W., Chan, F.H., 2014. Validation study of Charlson Comorbidity Index in predicting mortality in Chinese older adults. Geriatrics & gerontology international 14, 452-457.

Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases 40, 373-383.

Chen, L.K., Peng, L.N., Lin, M.H., Lai, H.Y., Hwang, S.J., Lan, C.F., 2010. Predicting mortality of older residents in long-term care facilities: comorbidity or care problems? Journal of the American Medical Directors Association 11, 567-571.

Chwastiak, L.A., Rosenheck, R.A., Desai, R., Kazis, L.E., 2010. Association of psychiatric illness and all-cause mortality in the National Department of Veterans Affairs Health Care System. Psychosomatic medicine 72, 817-822.

Dahl, A.K., Fauth, E.B., Ernsth-Bravell, M., Hassing, L.B., Ram, N., Gerstof, D., 2013. Body mass index, change in body mass index, and survival in old and very old persons. Journal of the American Geriatrics Society 61, 512-518.

DeSalvo, K.B., Bloser, N., Reynolds, K., He, J., Muntner, P., 2006. Mortality prediction with a single general self-rated health question. A meta-analysis. Journal of general internal medicine 21, 267-275.

Diederichs, C.P., Wellmann, J., Bartels, D.B., Ellert, U., Hoffmann, W., Berger, K., 2011. How to weight chronic diseases in multimorbidity indices? Development of a new method on the basis of individual data from five population-based studies. Journal of clinical epidemiology 65, 679-685.

Drame, M., Novella, J.L., Lang, P.O., Somme, D., Jovenin, N., Laniece, I., Couturier, P., Heitz, D., Gauvain, J.B., Voisin, T., De Wazieres, B., Gonthier, R., Ankri, J., Jeandel, C., Saint-Jean, O., Blanchard, F., Jolly, D., 2008. Derivation and validation of a mortality-risk index from a cohort of frail elderly patients hospitalised in medical wards via emergencies: the SAFES study. European journal of epidemiology 23, 783-791.

Fillenbaum, G.G., Pieper, C.F., Cohen, H.J., Cornoni-Huntley, J.C., Guralnik, J.M., 2000. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. The journals of gerontology. Series A, Biological sciences and medical sciences 55, M84-89.

Formiga, F., Ferrer, A., Chivite, D., Montero, A., Sanz, H., Pujol, R., 2013. Utility of geriatric assessment to predict mortality in the oldest old: the Octabaix study 3-year follow-up. Rejuvenation research 16, 279-284.

Fortin, M., Lapointe, L., Hudon, C., Vanasse, A., Ntetu, A., Maltais, D., 2004. Multimorbidity and quality of life in primary care: a systematic review. Health and quality of life outcomes 2, 51.

Fortin, M., Stewart, M., Poitras, M.E., Almirall, J., Maddocks, H., 2012. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. Annals of family medicine 10, 142-151.

Gijsen, R., Hoeymans, N., Schellevis, F.G., Ruwaard, D., Satariano, W.A., van den Bos, G.A., 2001. Causes and consequences of comorbidity: a review. Journal of clinical epidemiology 54, 661-674.

Guthrie, B., Payne, K., Alderson, P., McMurdo, M.E.T., Mercer, S.W., 2012. Adapting clinical guidelines to take account of multimorbidity.

Gutierrez-Misis, A., Sanchez-Santos, M., Otero, A., 2012. [Use of a proxy to the Charlson index to study the short and long-term comorbidity and mortality in the elderly]. Atencion primaria / Sociedad Espanola de Medicina de Familia y Comunitaria 44, 153-161.

Harrison, C., Britt, H., Miller, G., Henderson, J., 2014. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. BMJ Open 4.

Helvik, A.S., Engedal, K., Selbaek, G., 2013. Three-year mortality in previously hospitalized older patients from rural areas--the importance of co-morbidity and self-reported poor health. BMC geriatrics 13, 17.

Hempenius, L., Slaets, J.P.J., Boelens, M.A.M., van Asselt, D.Z.B., de Bock, G.H., Wiggers, T., van Leeuwen, B.L., 2013. Inclusion of frail elderly patients in clinical trials: Solutions to the problems. Journal of geriatric oncology 4, 26-31.

Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Statistics in medicine 21, 1539-1558.

Holt-Lunstad, J., Smith, T.B., Layton, J.B., 2010. Social Relationships and Mortality Risk: A Meta-analytic Review. PLoS medicine 7, e1000316.

Jakobsson, U., Hallberg, I.R., 2006. Mortality among elderly receiving long-term care: a longitudinal cohort study. Aging clinical and experimental research 18, 503-511.

Jeong, H.G., Lee, J.J., Lee, S.B., Park, J.H., Huh, Y., Han, J.W., Kim, T.H., Chin, H.J., Kim, K.W., 2013. Role of severity and gender in the association between late-life depression and all-cause mortality. International psychogeriatrics / IPA 25, 677-684.

Kalache, A., Kickbusch, I., 1997. A global strategy for healthy ageing. World Health 50, 4-5.

Kaplan, M.H., Feinstein, A.R., 1974. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. Journal of chronic diseases 27, 387-404.

Landi, F., Liperoti, R., Fusco, D., Mastropaolo, S., Quattrociocchi, D., Proia, A., Tosato, M., Bernabei, R., Onder, G., 2012. Sarcopenia and mortality among older nursing home residents. Journal of the American Medical Directors Association 13, 121-126.

Landi, F., Liperoti, R., Russo, A., Capoluongo, E., Barillaro, C., Pahor, M., Bernabei, R., Onder, G., 2010. Disability, more than multimorbidity, was predictive of mortality among older persons aged 80 years and older. Journal of clinical epidemiology 63, 752-759.

Lima-Costa, M.F., De Oliveira, C., Macinko, J., Marmot, M., 2012. Socioeconomic Inequalities in Health in Older Adults in Brazil and England. American journal of public health 102, 1535-1541.

Luy, M., Gast, K., 2014. Do women live longer or do men die earlier? Reflections on the causes of sex differences in life expectancy. Gerontology 60, 143-153.

Mallet, L., Spinewine, A., Huang, A., 2007. The challenge of managing drug interactions in elderly people. The Lancet 370, 185-191.

Marengoni, A., 2013. Guidelines for elderly patients with multimorbidity: how to cope with a dark night without fear. Aging clinical and experimental research 25, 703-705.

Marengoni, A., Angleman, S., Melis, R., Mangialasche, F., Karp, A., Garmen, A., Meinow, B., Fratiglioni, L., 2011. Aging with multimorbidity: a systematic review of the literature. Ageing research reviews 10, 430-439.

Marengoni, A., von Strauss, E., Rizzuto, D., Winblad, B., Fratiglioni, L., 2009. The impact of chronic multimorbidity and disability on functional decline and survival in

elderly persons. A community-based, longitudinal study. Journal of internal medicine 265, 288-295.

Martinez-Velilla, N., Cambra-Contin, K., Ibanez-Beroiz, B., 2014. Comorbidity and prognostic indices do not improve the 5-year mortality prediction of components of comprehensive geriatric assessment in hospitalized older patients. BMC geriatrics 14, 64.

Mazzella, F., Cacciatore, F., Galizia, G., Della-Morte, D., Rossetti, M., Abbruzzese, R., Langellotto, A., Avolio, D., Gargiulo, G., Ferrara, N., Rengo, F., Abete, P., 2010. Social support and long-term mortality in the elderly: role of comorbidity. Archives of gerontology and geriatrics 51, 323-328.

McDaid, O., Hanly, M.J., Richardson, K., Kee, F., Kenny, R.A., Savva, G.M., 2013. The effect of multiple chronic conditions on self-rated health, disability and quality of life among the older populations of Northern Ireland and the Republic of Ireland: a comparison of two nationally representative cross-sectional surveys. BMJ Open 3.

Meijer, M., Rohl, J., Bloomfield, K., Grittner, U., 2012. Do neighborhoods affect individual mortality? A systematic review and meta-analysis of multilevel studies. Social science & medicine (1982) 74, 1204-1212.

Mello, A.d.C., Engstrom, E.M., Alves, L.C., 2014. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. Cadernos de saude publica 30, 1143-1168.

Menotti, A., Mulder, I., Nissinen, A., Giampaoli, S., Feskens, E.J., Kromhout, D., 2001. Prevalence of morbidity and multimorbidity in elderly male populations and their impact on 10-year all-cause mortality: The FINE study (Finland, Italy, Netherlands, Elderly). Journal of clinical epidemiology 54, 680-686.

Minicuci, N., Maggi, S., Noale, M., Trabucchi, M., Spolaore, P., Crepaldi, G., 2003. Predicting mortality in older patients. The VELCA Study. Aging clinical and experimental research 15, 328-335.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.

Moraes, E.N., 2012. Health care for the elderly: conceptual aspects. Pan American Health Organization, Brasília, p. 98.

Newman, A.B., Boudreau, R.M., Naydeck, B.L., Fried, L.F., Harris, T.B., 2008. A physiologic index of comorbidity: relationship to mortality and disability. The journals of gerontology. Series A, Biological sciences and medical sciences 63, 603-609.

Nybo, H., Petersen, H.C., Gaist, D., Jeune, B., Andersen, K., McGue, M., Vaupel, J.W., Christensen, K., 2003. Predictors of mortality in 2,249 nonagenarians--the Danish 1905-Cohort Survey. Journal of the American Geriatrics Society 51, 1365-1373.

Peterson, J.C., Paget, S.A., Lachs, M.S., Reid, M.C., Charlson, M.E., 2012. The risk of comorbidity. Annals of the rheumatic diseases 71, 635-637.

Rozzini, R., Frisoni, G.B., Ferrucci, L., Barbisoni, P., Sabatini, T., Ranieri, P., Guralnik, J.M., Trabucchi, M., 2002. Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity. Age and ageing 31, 277-285.

Salisbury, C., 2012. Multimorbidity: redesigning health care for people who use it. The Lancet 380, 7-9.

Salive, M.E., 2013. Multimorbidity in Older Adults. Epidemiologic reviews.

Shamliyan, T., Talley, K.M.C., Ramakrishnan, R., Kane, R.L., 2013. Association of frailty with survival: A systematic literature review. Ageing research reviews 12, 719-736.

Silva, V.d.L., Cesse, E.Â.P., Albuquerque, M.d.F.P.M.d., 2014. Social determinants of death among the elderly: a systematic literature review. Revista Brasileira de Epidemiologia 17, 178-193.

Smith, S.M., Soubhi, H., Fortin, M., Hudon, C., O'Dowd, T., 2012. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. The Cochrane database of systematic reviews 4, Cd006560.

St John, P.D., Tyas, S.L., Menec, V., Tate, R., 2014. Multimorbidity, disability, and mortality in community-dwelling older adults. Canadian family physician Medecin de famille canadien 60, e272-280.

Theou, O., Rockwood, M.R., Mitnitski, A., Rockwood, K., 2012. Disability and co-morbidity in relation to frailty: how much do they overlap? Archives of gerontology and geriatrics 55, e1-8.

Tiainen, K., Luukkaala, T., Hervonen, A., Jylha, M., 2013. Predictors of mortality in men and women aged 90 and older: a nine-year follow-up study in the Vitality 90+ study. Age and ageing 42, 468-475.

Tooth, L., Hockey, R., Byles, J., Dobson, A., 2008. Weighted multimorbidity indexes predicted mortality, health service use, and health-related quality of life in older women. Journal of clinical epidemiology 61, 151-159.

van Doorn, C., Bogardus, S.T., Williams, C.S., Concato, J., Towle, V.R., Inouye, S.K., 2001. Risk adjustment for older hospitalized persons: a comparison of two methods of data collection for the Charlson index. Journal of clinical epidemiology 54, 694-701.

van Weel, C., Schellevis, F.G., 2006. Comorbidity and guidelines: conflicting interests. The Lancet 367, 550-551.

Veras, R., 2009. Population aging today: demands, challenges and innovations. Revista de saude publica 43, 548-554.

Veras, R.P., Caldas, C.P., Motta, L.B.d., Lima, K.C.d., Siqueira, R.C., Rodrigues, R.T.d.S.V., Santos, L.M.A.M., Guerra, A.C.L.C., 2014. Integration and continuity of Care in health care network models for frail older adults. Revista de saude publica 48, 357-365.

Wang, C.Y., Baldwin, L.M., Saver, B.G., Dobie, S.A., Green, P.K., Cai, Y., Klabunde, C.N., 2009. The contribution of longitudinal comorbidity measurements to survival analysis. Medical care 47, 813-821.

Woo, J., Leung, J., 2014. Multi-morbidity, dependency, and frailty singly or in combination have different impact on health outcomes. Age (Dordrecht, Netherlands) 36, 923-931.