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Review

Frailty and Multimorbidity: A Systematic Review and Meta-analysis

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Abstract

Background: Multimorbidity and frailty are complex syndromes characteristics of aging. We reviewed the literature and provided pooled estimations of any evidence regarding (a) the coexistence of frailty and multimorbidity and (b) their association.

Methods: We searched PubMed and Web of Science for relevant articles up to September 2017. Pooled estimates were obtained through random effect models and Mantel–Haenszel weighting. Homogeneity (I^2), risk of bias, and publication bias were assessed. PROSPERO registration: 57890.

Results: A total of 48 studies involving 78,122 participants were selected, and 25 studies were included in one or more meta-analyses. Forty-five studies were cross-sectional and 3 longitudinal, with the majority of them including community-dwelling participants ($n = 35$). Forty-three studies presented a moderate risk of bias and five a low risk. Most of the articles defined multimorbidity as having two or more diseases and frailty according to the Cardiovascular Health Study criteria. In meta-analyses, the prevalence of multimorbidity in frail individual was 72% (95% confidence interval = 63%–81%; $I^2 = 91.3\%$), and the prevalence of frailty among multimorbid individuals was 16% (95% confidence interval = 12%–21%; $I^2 = 96.5\%$). Multimorbidity was associated with frailty in pooled analyses (odds ratio = 2.27; 95% confidence interval = 1.97–2.62; $I^2 = 47.7\%$). The three longitudinal studies suggest a bidirectional association between multimorbidity and frailty.

Conclusions: Frailty and multimorbidity are two related conditions in older adults. Most frail individuals are also multimorbid, but fewer multimorbid ones also present frailty. Our findings are not conclusive regarding the causal association between the two conditions. Further longitudinal and well-designed studies may help to untangle the relationship between frailty and multimorbidity.

Keywords: Frailty, Multimorbidity, Older people, Chronic diseases, Personalized medicine

During aging, a number of biological deficits accumulate, which disturb the homeostatic balance of the organism (1–3). This process starts since the life in the womb and follows distinct trajectories and proceeds at a different pace among individuals, variably reducing their resilience to internal and external stressors. The term "frailty" identifies the predisposition of biologically old persons to develop adverse outcomes and experience rapid changes in health status. Chronic diseases have been suggested to contribute to the development of frailty (2).

To a certain extent, diseases may be viewed as the result of an accumulation of specific biological deficits, which, beyond a certain threshold, may present as specific nosological entities (4,5). As we age, we tend to accumulate multiple chronic diseases; this condition is referred to as "multimorbidity" (having two or more diseases), and its prevalence reaches 30% in people younger than 65 years and ranges between 55% and 98% in people older than 65 years (6,7). Population aging and the increased likelihood to survive from events previously fatal are responsible for the worldwide multimorbidity epidemic (6).

Frailty and multimorbidity are considered to be promising clinical biomarkers for studying mechanisms underlying the aging process. Both have been shown to be associated with older people's risk of disability, hospitalization, and mortality, as well as escalating health-related costs (7–9). Indeed, a certain amount of overlap between the two conditions is biologically plausible, and a bidirectional causal relationship between them is probable. Frailty may predispose persons to the development of multiple chronic diseases, but frailty may also stem from the coexistence of multiple diseases (10–12).

The National Institute for Health and Care Excellence (NICE) has recently issued its first guidelines for the clinical assessment and management of multimorbidity (13). In this document, it is clearly stated that not all persons with multimorbidity require additional support beyond standard care, but only those whose multimorbidity-related complexity significantly affects their life. In this regard, frailty is mentioned both as a component of multimorbidity and as a condition to take into account in the management of older adults with multimorbidity (14,15).

Describing the co-occurrence of frailty and multimorbidity and assessing their association may help further decipher the mechanisms governing the aging process, build specific care pathways around these constructs, and inform clinicians (4,16–20). Results from different studies are conflicting, and due to the increasing aging of the population and high prevalence of multimorbidity and frailty, a meta-analysis is necessary to concretely clarify the role that these two conditions have on each other. The aim of the present study is to systematically review the literature and provide pooled estimations of any evidence regarding (a) the coexistence of frailty and multimorbidity and (b) their association in adults and older persons. Describing such evidence across a variety of studies, addressing different populations and using different definitions, may help to bring out the criticisms that need to be resolved in future studies and to put in context the results deriving from single previous and future studies.

Methods

We reviewed studies providing information on the association between frailty and multimorbidity in adult persons (ie, 18 years old or older), regardless of the study setting, study design, or definition of multimorbidity and frailty. No restrictions have been applied in this regard, considering that both multimorbidity and frailty have been described as transversal findings across a wide set of different ages and settings. The protocol of the present study was a priori registered in the international prospective register of systematic reviews PROSPERO (registration number 57890). No significant deviations from the original protocol have been made. This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. For the present study, no ethics committee approval was necessary.

Data Sources and Searching

We searched the PubMed electronic database of the National Library of Medicine and the Web of Science database for relevant articles published from 1 January 2002 to 5 September 2017. Two searches have been carried out, on 21 February 2017, and on 5 September 2017. MeSH terms and free words referring to frailty and multimorbidity were used as keywords. The detailed search queries are reported in Supplementary Material. References from selected papers and other relevant articles were screened for potential additional studies.

Study Selection and Data Extraction

Two assessors (D.L.V. and K.P.) independently screened the title and abstract of the selected studies. Studies that reported information on either the proportion of multimorbid persons among those with frailty, the proportion of frail persons among those with multimorbidity, or cross-sectional/longitudinal measures of association between frailty and multimorbidity were selected. Articles were excluded if they (a) did not investigate the aims of the review; (b) included persons younger than 18 years; (c) did not present original data; (d) did not provide an explicit definition of frailty and/or multimorbidity, and (e) if frailty was evaluated through a single measure (eg, walking speed only). The full text of the articles selected by at least one of the assessors was further evaluated. The same assessors independently extracted information from the selected studies. Any disagreement was resolved through consensus. Most of the studies used the terms multimorbidity and comorbidity interchangeably. However, both in the text and in the table/figures we refer only to multimorbidity for consistency. When more than one measure of association was provided, the most adjusted estimation was used for the present study.

Studies were included if they were written in English or another European language. One Spanish article and one German article were selected for full-text evaluation. These articles were sent for translation by a native speaker who conducted data extraction.

Assessment of Risk of Bias

Study quality was evaluated independently by the two assessors through Newcastle Ottawa Scale (NOS), a tool for the qualitative evaluation of observational studies. Any disagreement in quality assessment was resolved through consensus. Studies with scores of >7 indicated low risk of bias, scores of 5–7 indicated moderate risk of bias, and scores of <5 indicated high risk of bias. Likelihood of publication bias was assessed (see Statistical analysis).

Data Analysis

For each measure of interest (ie, proportions and estimates of associations), we ran a meta-analysis when at least three studies used the same definition of frailty and multimorbidity (Supplementary Table S2). Considering the observational design of the retrieved studies, and the methodological differences potentially responsible for a significant share of the variance within the measures of interest, pooled estimates were obtained through random effect models and Mantel–Haenszel weighting. Lack of homogeneity within the pooled studies was assessed through the I^2 statistics (significant if ≥50%). I^2 represents the percentage of variability of the pooled estimate which is due to methodological heterogeneity rather than to chance. Analyses are presented according to the different definitions of frailty and multimorbidity. When a sufficient number of studies

was available, secondary analyses were performed: (a) by NOS, to investigate the role of methodological bias in explaining heterogeneity; (b) by sample size, using different cutoffs (100, 500, and 1,000 participants); and (c) by age. Publication bias was assessed by mean of the Egger's and the Begg's tests. All statistical analyses were performed with STATA version 14.0 (StataCorp, College Station, TX). A p value of less than .05 was considered statistically significant.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Through the literature search, we retrieved 2,416 articles (Figure 1). Of them, 2,235 (93%) were excluded based on title and abstract and 133 (6%) after full-text reading. Forty-eight articles were part of the final qualitative assessment, and 25 articles were analyzed in several meta-analyses.

Study Description

Supplementary Table S1 summarizes the main characteristics and findings of the selected studies. The overall number of participants was 78,122, with a mean age spanning from 52 to 85 years and a prevalence of females ranging from 14% to 100%. Notably, out of the 48 selected articles, only three included some people aged less than 60 years and in any case, even in these studies, the majority of participants were older than 60 years. Most studies had a cross-sectional design (n = 45) and included community-dwelling people (11,21–55) (n = 36) or hospitalized people (56–62) (n = 7). Few of them included special populations: patients on hemodialysis (63) (n = 1), HIV patients (64) (n = 1), rehabilitation outpatients (65) (n = 1), or homeless people (66) (n = 1). Finally, one study was based on post hoc analyses of a clinical trial (55). Most of the studies were carried out in Europe (n = 20) and North America (n = 14) and fewer studies in Asia (n = 8), South America (n = 5), and Australia (n = 1).

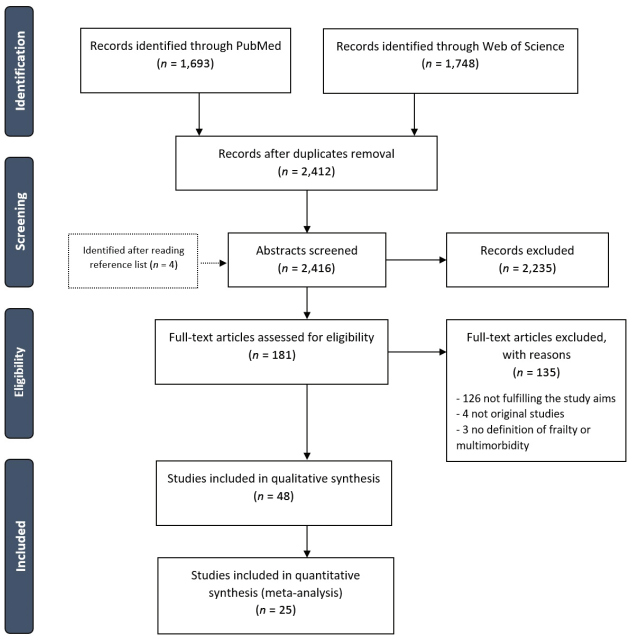

Figure 1. Systematic review and meta-analysis of PRISMA flowchart.

Frailty assessment

Most of the studies (n = 33) defined frailty according to the Cardiovascular Health Study (CHS) criteria, proposed by Fried and colleagues, which define frailty as the presence of at least three of the following: weight loss, low handgrip strength, slow gait speed, exhaustion, and reduced physical activity (11). The rest of the studies evaluated frailty based on a frailty index (n = 6) (1), the Edmonton Frail Scale (EFS; n = 3), the Canadian Study of Health and Ageing (CSHA) scale (n = 2), the Clinical Frailty Scale (CFS; n = 1), the FRAIL scale (n = 1), the Korean FRAIL scale (n = 1), the Short Emergency Geriatric Assessment (SEGA; n = 1), the Frailty Framework among Vulnerable Populations (FFVP; n = 1), and the EASY-Care Two-step Older persons Screening (EASY-Care TOS; n = 1). Within the 48 selected articles, frailty prevalence spanned from 0% to 76%.

Multimorbidity assessment

In the selected studies, 4–28 different conditions were assessed to compute multimorbidity. It is noteworthy that five studies did not report the number of diseases assessed. Different cutoffs were used to define multimorbidity: 2+ diseases (n = 14), 3+ diseases (n = 6), 4+ diseases (n = 1), 5+ diseases (n = 1), and 6+ diseases (n = 1). A continuous scale developed on disease count was analyzed in 14 studies. Alternatively, two indexes of multimorbidity were adopted: the Charlson Comorbidity Index (CCI; n = 12) and the Comorbidity Illness Rating Scale (CIRS; n = 2). Within the 48 selected articles, multimorbidity prevalence spanned from 2% to 70%.

Assessment of Risk of Bias

The majority of the studies (n = 43) presented a moderate risk of bias, and five studies presented a low risk according to the NOS. In most cases, the self-reported nature of information was responsible for a lower score. In general, many studies applied a modified version of the frailty tools to adapt the assessment to the available data. Finally, according to the Egger's and the Begg's tests, no strong evidence of publication bias was detected in our meta-analyses (p = .324 and p = .450, respectively).

Overlap of Frailty and Multimorbidity

Nine studies, all of them involving community-dwelling persons, reported data on the overlap between frailty (CHS criteria by Fried and colleagues) and multimorbidity (2+ diseases), for a total of 14,704 individuals (Figure 2) (11,23,26,31,33,37,40,49,51). According to these data, 868 (6%) persons presented both multimorbidity and frailty, 403 (3%) presented only frailty, and 6,213 (42%) presented only multimorbidity. As shown in Figure 3A, the pooled prevalence of multimorbidity in community-dwelling frail people was 72% (95% confidence interval [95% CI] = 63%–81%; I^2 = 91.3%). After stratifying the analysis by NOS, the I^2 for studies presenting a lower risk of bias decreased to 29.8% with a slight decrease in the prevalence of multimorbidity (67%; 95% CI = 63%–70%) (11,31,40,49). After restricting the analysis to the three studies including the majority of participants aged 80 years and older, the pooled prevalence of multimorbidity among frail individuals was 63% (95% CI = 41%–85%; I^2 = 97.0%) (26,37,49). As shown in Figure 3B, the pooled prevalence of multimorbidity in community-dwelling frail people was 16% (95% CI = 12%–21%; I^2 = 96.5%).

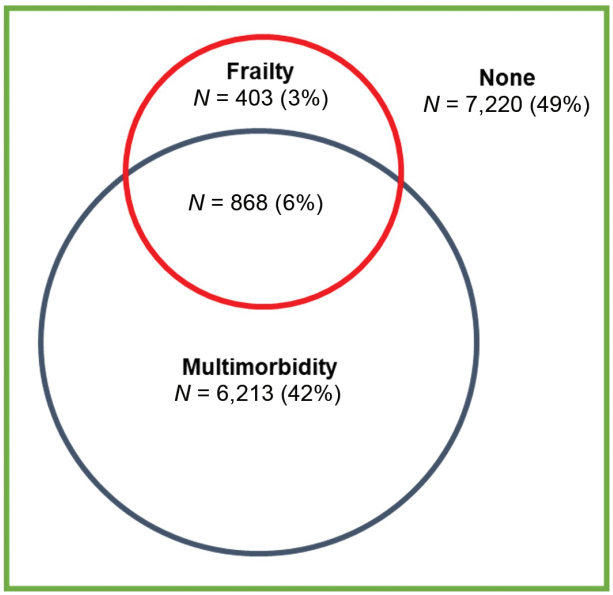

Figure 2. Overlap of frailty and multimorbidity (pooled data from nine studies including community-dwelling people; *N* = 14,704). Frailty was defined according to the Cardiovascular Health Study (CHS) criteria (by Fried and colleagues) and multimorbidity as 2+ diseases.

Stratification for NOS and sample size did not reduce heterogeneity. By restricting the analysis to the three studies including the majority of participants aged 80 years and older, the pooled prevalence of frailty in multimorbid people was 27% (95% CI = 9%–45%; I^2 = 98.3%) (26,37,49).

When the CCI was used to estimate multimorbidity burden (seven studies; Figure 4), nonfrail participants, when compared with those with frailty, presented a lower CCI (ΔCCI = 0.66; 95% CI = 0.75–0.45; I^2 = 62.0%) (56,59,61–63,65,67). To note, all these studies included hospitalized (*n* = 6) or dialysis (*n* = 1) patients.

The studies not included in the meta-analysis because they used more heterogeneous measures of frailty and multimorbidity generally reported a higher number of diseases or a higher comorbidity score within frail participants (Supplementary Table S1).

Association Between Frailty and Multimorbidity

Cross-sectional studies

Sixteen studies assessed the cross-sectional association between multimorbidity and frailty. Four studies defined multimorbidity as the presence of 2+ diseases and frailty according to the CHS criteria (22,23,34,37). Noticeably, among them, one study reported the estimations separately for five different countries (22). Three studies defined multimorbidity as the presence of 3+ diseases and frailty according to the CHS criteria (30,41,47). The remaining nine studies used alternative or nonconsistent definitions of both multimorbidity and frailty, so they were not included in the meta-analysis. The model adjustments carried out in the individual studies are reported in Supplementary Table S1. When multimorbidity was defined as the presence of 2+ diseases we found a significant pooled association with frailty in community-dwelling people (odds ratio = 2.27; 95% CI = 1.97–2.62; I^2 47.7%; Figure 5A), with consistent results after stratification for low or moderate risk of bias and larger sample size (data not shown). When multimorbidity was defined as the presence of 3+ diseases, we found a nonsignificant pooled association

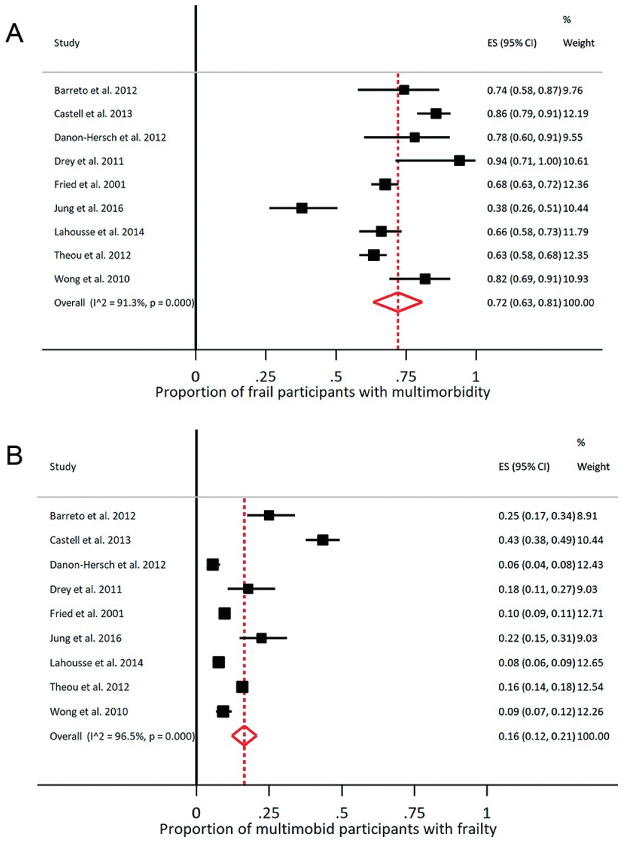

Figure 3. Proportion of (**A**) community-dwelling participants presenting with multimorbidity among those with frailty and (**B**) community-dwelling participants presenting with frailty among those with multimorbidity. Frailty was defined according to the Cardiovascular Health Study (CHS) criteria (by Fried and colleagues) and multimorbidity as the presence of 2+ diseases.

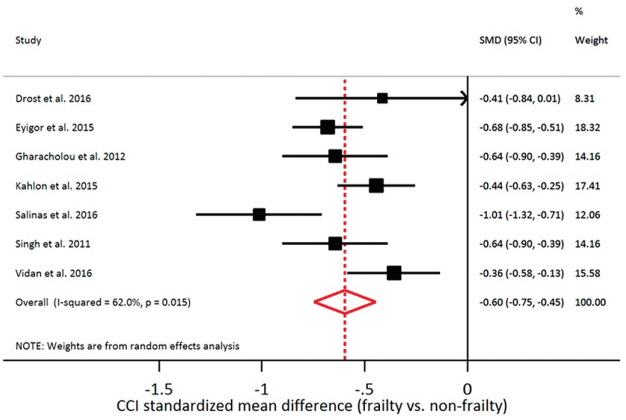

Figure 4. Charlson Comorbidity Index (CCI) mean difference between frail and nonfrail participants. All these studies included hospitalized (*n* = 6) or dialysis (*n* = 1) patients.

with frailty (odds ratio = 2.16; 95% CI = 0.94–4.97; I^2 = 86.7%; Figure 5B).

Among the nine studies not included in the meta-analysis, only one did not show a significant association between frailty and multimorbidity (24). The remaining studies constantly reported a

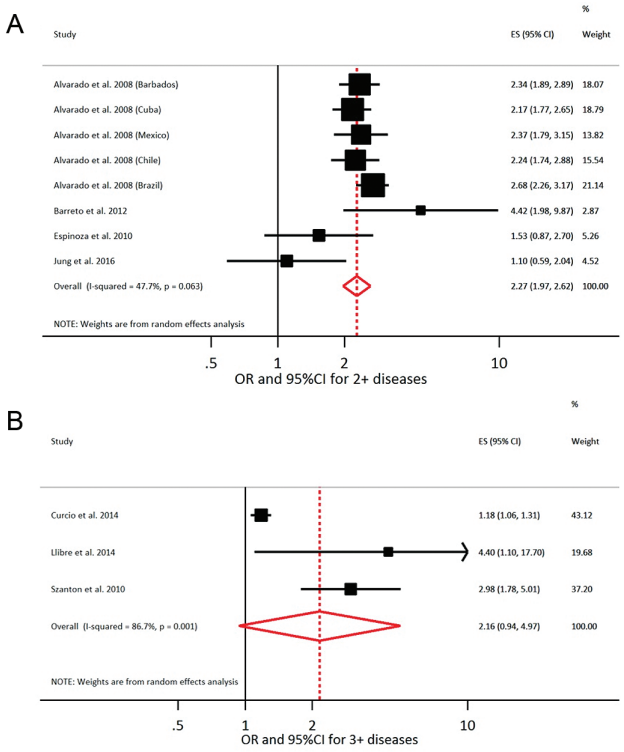

Figure 5. Cross-sectional association of frailty (Cardiovascular Health Study [CHS] criteria by Fried and colleagues) with multimorbidity defined as the presence of (**A**) 2+ diseases and (**B**) 3+ diseases in community-dwelling people.

significant association, up to fourfolds, between the two measures, as defined in several different ways across the studies (Supplementary Table S1) (21,27,28,38,42,53,63,65).

Longitudinal studies

Three studies reported measures of longitudinal association between multimorbidity and frailty (Supplementary Table S1). However, the different methodology across them did not allow us to perform a meta-analysis. Two studies described a positive association between multimorbidity and the development of frailty. Namely, Hejek and colleagues showed that the multimorbidity score, computed by weighting diseases according to their severity, was associated with a nonsignificant increase in frailty score ($\beta = 0.013$; $p > .05$) (36). Zheng and colleagues reported a significant association between multimorbidity (3+ diseases) and risk of developing frailty (odds ratio = 6.24; $p < .05$) (54). Finally, Guaraldi and colleagues addressed the relationship between frailty at baseline (measured with a frailty index) and incident multimorbidity (2+ diseases), in HIV outpatients, finding a significant association (incidence rate ratio = 1.98; 95% CI = 1.65–2.36) (64).

Discussion

In this systematic review and meta-analysis of 48 observational studies, we found that 7 out of 10 frail adults present with multimorbidity and that almost a fifth of adults with multimorbidity also present with frailty. In addition, multimorbidity increases the likelihood of being frail almost twofold. Finally, according to longitudinal studies, multimorbidity is associated with an increasing risk of developing frailty and vice versa, suggesting a bidirectional association between the two conditions. In general, a significant heterogeneity has been found across studies regarding the definition of both multimorbidity and frailty. This is the first systematic review and meta-analysis investigating the relationship between frailty and multimorbidity in the adult population.

Frailty stems from the progressive accumulation of biological deficits that pile up with passing time as an expression of the aging process. It can be considered as a global and transversal measure able to capture both clinical and subclinical impairments (2,68). Multimorbidity may be thought of as the accumulation of biological abnormalities deemed as clinically relevant and that define overt disease diagnoses (2,4,69). However, even if conceptually they are close concepts, the proportion of the community-dwelling population presenting both conditions is quite low, only 6%, with a huge discrepancy between those presenting only multimorbidity (42%) and those presenting only frailty (3%). Noticeably, our meta-analysis highlights two important elements: (a) the majority of frail people are also multimorbid and (b) very few people with multimorbidity are also frail. On the one hand, this evidence corroborates the hypothesis that chronic diseases are major determinants of the frailty syndrome (2,69,70). This is also confirmed by the fact that multimorbidity was associated with a twofold increased likelihood of being frail, even though, in cross-sectional studies, this association may be interpreted as bidirectional. On the other hand, the low prevalence of frailty in multimorbid people suggests that only a small proportion of those suffering from multiple diseases also develop a condition of frailty. According to previous studies, multimorbidity becomes evident in the fifth decade of life and its prevalence continues increasing into very old age. Conversely, frailty becomes evident only later in life (71,72). Such a temporal gap might be interpreted as an individual's resilience to cope with multimorbidity before it has a relevant impact on health (ie, frailty). In support of this hypothesis, after restricting our prevalence analyses to studies including the oldest participants, we observed that the proportion of frailty in multimorbid people and that of multimorbidity in frail people became closer (63% and 27%, respectively). Further studies addressing such an association in different age groups are warranted.

It is possible that frailty and multimorbidity are clearly connected by shared mechanisms but that they rarely overlap due to differences in the way they are defined, operationalized, and measured (4,12). This may also contribute to the relevant heterogeneity found in the present study. The bidirectional results of the few longitudinal studies, even if not always significant, seem to support this view. We found many different ways to define frailty and multimorbidity in our review, and different sets of diseases to define multimorbidity, with almost all of the studies applying modified versions of the original frailty tools to exploit the available data. Such a methodological heterogeneity does not allow us to draw any conclusion on the actual relationship underlying these two conditions and calls for more rigorous and standardized definitions of both multimorbidity and frailty (4,6). We should also consider the use of arbitrary cutoffs for the definition of multimorbidity. Most of the studies retrieved in our review defined multimorbidity as the presence of 2+ concurrent diseases (4,6). It is likely that such a strict cutoff is affected by a ceiling effect that does not take into account the huge variability of disease burden existing between a person suffering from two diseases and, for example, someone suffering from five or more diseases. In this regard, using a continuous measure of multimorbidity is warranted (4,6).

Strengths and Limitations

The major strength of the present study is its comprehensive literature search that, together with the careful study selection and quality

assessment, provides a reliable overview of the evidence in the field. Moreover, the generalizability of our findings is enhanced by the representativeness of the retrieved studies that mainly involved community-dwelling adults and older persons. Another strength is that we included articles in English and any other European language. However, there are several limitations to discuss. First, we detected a significant heterogeneity among the studies that was only partially buffered by subgroup analyses. The different definitions of frailty and multimorbidity, the use of adapted tools, the different adjustment carried out in multivariate models, and the demographic differences might explain such a high level of heterogeneity. Moreover, cross-country differences regarding disease-coding systems may further hinder comparability of the results (73). Similarly, poor development and limited access to health services may affect the validity the disease measurements. In this regards, the scarce representativeness of Asian, South American, Australian, and African countries may limit the generalizability of our results to these contexts. Furthermore, overmedicalization and excessive diagnostic testing, which is more frequent in high-income countries, could lead to an overestimation of multimorbidity. However, the absence of evident publication bias and the low-to-moderate risk of methodological bias increase the reliability of our findings. Second, the cross-sectional design of the majority of studies limits the opportunity to generate hypotheses regarding a causal link between the conditions of interest. At the same time, the three longitudinal studies retrieved by our literature search suggest a bidirectional relationship between frailty and multimorbidity, indeed not always statistically significant. However, the weak methodology, which does not take into account the potential competing risk of mortality, calls for more rigorous studies testing the longitudinal association of frailty and multimorbidity. Third, in our meta-analyses, we included only studies defining frailty according to the CHS criteria as proposed by Fried and colleagues. The low number of studies using alternative definitions prevented us from running additional pooled estimations. Finally, due to the specific aim of the present review, we did not take into consideration the role played by disability, which, beyond—and often simultaneously—frailty and multimorbidity, represents the most frequent finding in the older population.

Relevance and Future Perspective

Researchers, clinicians, and policymakers strive to find effective models that may help to understand the aging process, assist in the design of personalized treatments, and build efficient health systems for the care of complex older adults (4,19). Frailty and multimorbidity have been demonstrated to be helpful prognostic conditions, and are the focus of interest of many health professionals and international bodies, to the point that huge investments have recently been provided to investigate them (74,75). The recently issued NICE guidelines for the clinical assessment and management of multimorbidity clearly warrant the assessment of frailty in complex older adults, considering it a steering condition in the person-centered vision of care offered to multimorbid patients (13–15). Our systematic review and meta-analysis provide, for the first time, a comprehensive picture of the available evidence regarding the relationship between frailty and multimorbidity. It appears to be a close relationship, suggesting the need for comprehensive assessment of both conditions in complex adults. Both frailty and multimorbidity have been demonstrated to be burdensome conditions, and the co-occurrence of the two may be associated with an even higher burden (52). However, the investigation of the impact of these two conditions on people's health was beyond the aim of the present study.

We believe that the results of our review can be informative for leveraging further efforts in the fields of research, clinical practice, and public health. The following issues are worth addressing in the near future: First, a shared definition of both frailty and multimorbidity should be reached, considering not only the scientific validity of the two constructs but also the feasibility of their assessment in real-world settings, also optimizing the information currently available in clinical practice (4,6,12). This may help to buffer the significant heterogeneity found in our study. Second, despite stemming from similar processes, the limited overlap of frailty and multimorbidity raises several concerns regarding the validity of their current operationalization (12). The adoption of continuous measures, instead of rigid categories, may provide the methodological flexibility that would help untangle the actual link between the two conditions (2,6). Third, more studies need to investigate the shared pathways leading to frailty and multimorbidity. In this regard, a more holistic approach, encompassing the use of biomarkers (eg, inflammatory cytokines and in general -omics) and longitudinal study designs, may help generate new hypotheses on the nature of their association. Finally, pragmatic studies need to be designed to test the clinical validity of these two concepts, eventually suggesting the best strategies to set up preventive practices and dedicated care paths (4).

CONCLUSION

Frailty and multimorbidity are two related conditions in older adults. Most frail individuals are also multimorbid, but few multimorbid older adults also present frailty. Overall, in the general adult population, only 6% present with both conditions. Our findings are inconclusive regarding the causal association between the two conditions. However, a bidirectional association seems plausible. The wide set of tools used for the assessment of frailty and multimorbidity further limits speculation on the nature and significance of the association. Further studies, including more rigorous and agreed definitions of the two conditions, involving the assessment of specific biomarkers, and adopting longitudinal designs, are necessary to untangle the relationship between frailty and multimorbidity.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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D.L.V. and K.P. authors contributed equally to the study. D.L.V., K.P., and G.O. contributed to the study conception. D.L.V. and K.P evaluated the article. D.L.V. analyzed the data and drafted the article. All the authors interpreted the results, revised, and approved the final manuscript. All the authors fulfilled the ICMJE criteria for authorship.

Conflict of Interest

None reported.

References

1. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62:722–727.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752–762. doi:10.1016/S0140-6736(12)62167-9
3. Rodriguez-Manas L, Fried LP. Frailty in the clinical scenario. *Lancet (London, England)*. 2015;385:e7–e9. doi:10.1016/S0140-6736(14)61595–6
4. Vetrano DL, Calderón-Larrañaga A, Marengoni A, et al. An international perspective on chronic multimorbidity: approaching the elephant in the room. *J Gerontol A Biol Sci Med Sci*. 2017. doi:10.1093/gerona/glx178
5. Fabbri E, An Y, Zoli M, et al. Aging and the burden of multimorbidity: associations with inflammatory and anabolic hormonal biomarkers. *J Gerontol A Biol Sci Med Sci*. 2015;70:63–70. doi:10.1093/gerona/glu127
6. Calderón-Larrañaga A, Vetrano DL, Onder G, et al. Assessing and measuring chronic multimorbidity in the older population: a proposal for its operationalization. *J Gerontol A Biol Sci Med Sci*. 2017;72:1417–1423. doi:10.1093/gerona/glw233
7. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10:430–439. doi:10.1016/j.arr.2011.03.003
8. Vetrano DL, Rizzuto D, Calderón-Larrañaga A, et al. Trajectories of functional decline in older adults with neuropsychiatric and cardiovascular multimorbidity: a Swedish cohort study. *PLoS Med*. 2018;15:e1002503. doi:10.1371/journal.pmed.1002503
9. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. *BMJ*. 2015;350:h1059. doi:10.1136/bmj.h1059
10. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004;59:255–263.
11. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156.
12. Cesari M, Pérez-Zepeda MU, Marzetti E. Frailty and multimorbidity: different ways of thinking about geriatrics. *J Am Med Dir Assoc*. 2017;18:361–364. doi:10.1016/j.jamda.2016.12.086
13. National Institute for Health and Care Excellence (NICE). *Multimorbidity: Clinical Assessment and Management*. United Kingdom: NICE, 2016. https://www.nice.org.uk/guidance/ng56/resources/multimorbidity-clinical-assessment-and-management-pdf-1837516654789. Accessed January 5, 2018.
14. Guthrie B, Payne K, Alderson P, McMurdo ME, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. *BMJ*. 2012;345:e6341. doi:10.1136/bmj.e6341
15. Farmer C, Fenu E, O'Flynn N, Guthrie B. Clinical assessment and management of multimorbidity: summary of nice guidance. *BMJ*. 2016;354:i4843. doi:10.1136/bmj.i4843
16. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380:37–43. doi:10.1016/S0140-6736(12)60240-2
17. Bierman AS, Tinetti ME. Precision medicine to precision care: managing multimorbidity. *Lancet*. 2016;388:2721–2723. doi:10.1016/S0140-6736(16)32232-2
18. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition – multimorbidity. *JAMA*. 2012;307:2493–2494. doi:10.1001/jama.2012.5265
19. Onder G, Cesari M, Maggio M, Palmer K. Defining a care pathway for patients with multimorbidity or frailty. *Eur J Intern Med*. 2017;38:1–2. doi:10.1016/j.ejim.2017.01.013
20. Palmer K, Marengoni A, Forjaz MJ, et al.; Joint Action on Chronic Diseases and Promoting Healthy Ageing Across the Life Cycle (JA-CHRODIS). Multimorbidity care model: recommendations from the consensus meeting of the Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS). *Health Policy*. 2018;122:4–11. doi:10.1016/j.healthpol.2017.09.006
21. Alcalá MV, Puime AO, Santos MT, Barral AG, Montalvo JI, Zunzunegui MV. Prevalence of frailty in an elderly Spanish urban population: relationship with comorbidity and disability. *Aten Primaria*. 2010;42:520–527. doi:10.1016/j.aprim.2009.09.024
22. Alvarado BE, Zunzunegui MV, Béland F, Bamvita JM. Life course social and health conditions linked to frailty in Latin American older men and women. *J Gerontol A Biol Sci Med Sci*. 2008;63:1399–1406.
23. Barreto Pde S, Greig C, Ferrandez AM. Detecting and categorizing frailty status in older adults using a self-report screening instrument. *Arch Gerontol Geriatr*. 2012;54:e249–e254. doi:10.1016/j.archger.2011.08.003
24. Boeckxstaens P, Vaes B, Legrand D, Dalleur O, De Sutter A, Degryse JM. The relationship of multimorbidity with disability and frailty in the oldest patients: a cross-sectional analysis of three measures of multimorbidity in the BELFRAIL cohort. *Eur J Gen Pract*. 2015;21:39–44. doi:10.3109/13814788.2014.914167
25. Cakmur H. Frailty among elderly adults in a rural area of turkey. *Med. Sci. Monit*. 2015;21:1232–1242
26. Castell MV, Sánchez M, Julián R, Queipo R, Martín S, Otero Á. Frailty prevalence and slow walking speed in persons age 65 and older: implications for primary care. *BMC Fam Pract*. 2013;14:86. doi:10.1186/1471-2296-14-86
27. Chang CI, Chan DC, Kuo KN, Hsiung CA, Chen CY. Prevalence and correlates of geriatric frailty in a northern Taiwan community. *J Formos Med Assoc*. 2011;110:247–257. doi:10.1016/S0929-6646(11)60037-5
28. Chang SS, Weiss CO, Xue QL, Fried LP. Association between inflammatory-related disease burden and frailty: results from the Women's Health and Aging Studies (WHAS) I and II. *Arch Gerontol Geriatr*. 2012;54:9–15. doi:10.1016/j.archger.2011.05.020
29. Chen CY, Wu SC, Chen LJ, Lue BH. The prevalence of subjective frailty and factors associated with frailty in Taiwan. *Arch Gerontol Geriatr*. 2010;50(suppl 1):S43–S47. doi:10.1016/S0167-4943(10)70012-1
30. Curcio CL, Henao GM, Gomez F. Frailty among rural elderly adults. *BMC Geriatr*. 2014;14:2. doi:10.1186/1471-2318-14-2
31. Danon-Hersch N, Rodondi N, Spagnoli J, Santos-Eggimann B. Prefrailty and chronic morbidity in the youngest old: an insight from the Lausanne cohort Lc65+. *J Am Geriatr Soc*. 2012;60:1687–1694. doi:10.1111/j.1532-5415.2012.04113.x
32. Diaz de Leon Gonzalez E, Gutierrez Hermosillo H, Martinez Beltran JA, et al. Validation of the frail scale in Mexican elderly: results from the Mexican health and aging study. *Aging Clin Exp Res*. 2016;28:901–908. doi:10.1007/s40520-015-0497-y
33. Drey M, Wehr H, Wehr G, et al. The frailty syndrome in general practitioner care: a pilot study. *Z Gerontol Geriatr*. 2011;44:48–54. doi:10.1007/s00391-010-0136-3
34. Espinoza SE, Jung I, Hazuda H. Lower frailty incidence in older Mexican Americans than in older European Americans: the San Antonio Longitudinal Study of Aging. *J Am Geriatr Soc*. 2010;58:2142–2148. doi:10.1111/j.1532-5415.2010.03153.x
35. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA. Allostatic load and frailty in older adults. *J Am Geriatr Soc*. 2009;57:1525–1531. doi:10.1111/j.1532-5415.2009.02389.x
36. Hajek A, Brettschneider C, Posselt T, et al. Predictors of frailty in old age – results of a longitudinal study. *J Nutr Health Aging*. 2016;20:952–957. doi:10.1007/s12603-015-0634-5
37. Jung HW, Jang IY, Lee YS, et al. Prevalence of frailty and aging-related health conditions in older Koreans in rural communities: a cross-sectional analysis of the Aging Study of Pyeongchang Rural Area. *J Korean Med Sci*. 2016;31:345–352. doi:10.3346/jkms.2016.31.3.345
38. Jürschik P, Nunin C, Botigué T, Escobar MA, Lavedán A, Viladrosa M. Prevalence of frailty and factors associated with frailty in the elderly

population of Lleida, Spain: the FRALLE survey. *Arch Gerontol Geriatr*. 2012;55:625–631. doi:10.1016/j.archger.2012.07.002
39. Kiely DK, Cupples LA, Lipsitz LA. Validation and comparison of two frailty indexes: the MOBILIZE Boston Study. *J Am Geriatr Soc*. 2009;57:1532–1539. doi:10.1111/j.1532-5415.2009.02394.x
40. Lahousse L, Maes B, Ziere G, et al. Adverse outcomes of frailty in the elderly: the Rotterdam Study. *Eur J Epidemiol*. 2014;29:419–427. doi:10.1007/s10654-014-9924-1
41. Llibre JDE J, López AM, Valhuerdi A, et al. Frailty, dependency and mortality predictors in a cohort of Cuban older adults, 2003–2011. *MEDICC Rev*. 2014;16:24–30. doi:10.6061/clinics/2013(07)15
42. Moreira VG, Lourenço RA. Prevalence and factors associated with frailty in an older population from the city of Rio de Janeiro, Brazil: the FIBRA-RJ Study. *Clinics (Sao Paulo)*. 2013;68:979–985. doi:10.6061/clinics/2013(07)15
43. Ng TP, Feng L, Nyunt MS, Larbi A, Yap KB. Frailty in older persons: multisystem risk factors and the Frailty Risk Index (FRI). *J Am Med Dir Assoc*. 2014;15:635–642. doi:10.1016/j.jamda.2014.03.008
44. Ottenbacher KJ, Ostir GV, Peek MK, Snih SA, Raji MA, Markides KS. Frailty in older Mexican Americans. *J Am Geriatr Soc*. 2005;53:1524–1531. doi:10.1111/j.1532-5415.2005.53511.x
45. Oubaya N, Mahmoudi R, Jolly D, et al. Screening for frailty in elderly subjects living at home: validation of the Modified Short Emergency Geriatric Assessment (SEGAm) instrument. *J Nutr Health Aging*. 2014;18:757–764. doi:10.1007/s12603-014-0466-8
46. Serra-Prat M, Sist X, Saiz A, et al. Clinical and functional characterization of pre-frailty among elderly patients consulting primary care centres. *J Nutr Health Aging*. 2016;20:653–658. doi:10.1007%2Fs12603-016-0684-3
47. Szanton SL, Seplaki CL, Thorpe RJ Jr, Allen JK, Fried LP. Socioeconomic status is associated with frailty: the Women's Health and Aging Studies. *J Epidemiol Community Health*. 2010;64:63–67. doi:10.1136/jech.2008.078428
48. Tang Z, Wang C, Song X, et al. Co-occurrence of cardiometabolic diseases and frailty in older Chinese adults in the Beijing Longitudinal Study of Ageing. *Age Ageing*. 2013;42:346–351. doi:10.1093/ageing/aft004
49. Theou O, Rockwood MR, Mitnitski A, Rockwood K. Disability and comorbidity in relation to frailty: how much do they overlap? *Arch Gerontol Geriatr*. 2012;55:e1–e8. doi:10.1016/j.archger.2012.03.001
50. van Kempen JA, Schers HJ, Melis RJ, Olde Rikkert MG. Construct validity and reliability of a two-step tool for the identification of frail older people in primary care. *J Clin Epidemiol*. 2014;67:176–183. doi:10.1016/j.jclinepi.2013.08.008
51. Wong CH, Weiss D, Sourial N, et al. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. *Aging Clin Exp Res*. 2010;22:54–62. doi:10.3275/6675
52. Woo J, Leung J. Multi-morbidity, dependency, and frailty singly or in combination have different impact on health outcomes. *Age (Dordrecht, Netherlands)*. 2014;36:923–931. doi:10.1007/s11357-013-9590-3
53. Woo J, Zheng Z, Leung J, Chan P. Prevalence of frailty and contributory factors in three Chinese populations with different socioeconomic and healthcare characteristics. *BMC Geriatr*. 2015;15:163. doi:10.1186/s12877-015-0160-7
54. Zheng Z, Guan S, Ding H, et al. Prevalence and incidence of frailty in community-dwelling older people: Beijing Longitudinal Study of Aging II. *J Am Geriatr Soc*. 2016;64:1281–1286. doi:10.1111/jgs.14135
55. Bennett JA, Winters-Stone KM, Dobek J, Nail LM. Frailty in older breast cancer survivors: age, prevalence, and associated factors. *Oncol Nurs Forum*. 2013;40:E126–E134. doi:10.1188/13.ONF.E126-E134
56. Gharacholou SM, Roger VL, Lennon RJ, et al. Comparison of frail patients versus nonfrail patients ≥65 years of age undergoing percutaneous coronary intervention. *Am J Cardiol*. 2012;109:1569–1575. doi:10.1016/j.amjcard.2012.01.384
57. Hewitt J, McCormack C, Tay HS, et al. Prevalence of multimorbidity and its association with outcomes in older emergency general surgical patients: an observational study. *BMJ Open*. 2016;6:e010126. doi:10.1136/bmjopen-2015-010126
58. Hilmer SN, Perera V, Mitchell S, et al. The assessment of frailty in older people in acute care. *Australas J Ageing*. 2009;28:182–188. doi:10.1111/j.1741-6612.2009.00367.x
59. Kahlon S, Pederson J, Majumdar SR, et al. Association between frailty and 30-day outcomes after discharge from hospital. *CMAJ*. 2015;187:799–804. doi:10.1503/cmaj.150100
60. Perna S, Francis MD, Bologna C, et al. Performance of Edmonton Frail Scale on frailty assessment: its association with multi-dimensional geriatric conditions assessed with specific screening tools. *BMC Geriatr*. 2017;17:2. doi:10.1186/s12877-016-0382-3
61. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes*.2011;4:496–502.doi:10.1161/CIRCOUTCOMES.111.961375
62. Vidan MT, Blaya-Novakova V, Sanchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail*. 2016;18:869–875. doi:10.1002/ejhf.518
63. Drost D, Kalf A, Vogtlander N, van Munster BC. High prevalence of frailty in end-stage renal disease. *Int Urol Nephrol*. 2016;48:1357–1362. doi:10.1007/s11255-016-1306-z
64. Guaraldi G, Brothers TD, Zona S, et al. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. *AIDS*. 2015;29:1633–1641. doi:10.1097/QAD.0000000000000753
65. Eyigor S, Kutsal YG, Duran E, et al.; Turkish Society of Physical Medicine and Rehabilitation, Geriatric Rehabilitation Working Group. Frailty prevalence and related factors in the older adult-FrailTURK Project. *Age (Dordr)*. 2015;37:9791. doi:10.1007/s11357-015-9791-z
66. Salem BE, Nyamathi A, Brecht ML, et al. Constructing and identifying predictors of frailty among homeless adults – a latent variable structural equations model approach. *Arch Gerontol Geriatr*. 2014;58:248–256.
67. Salinas GLA, Fernandez MS, Izco MP, et al. Frailty is a short-term prognostic marker in acute coronary syndrome of elderly patients. *Eur Heart J Acute Cardiovasc Care*. 2016;5:434–440. doi:10.1177/2048872616644909
68. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14:392–397. doi:10.1016/j.jamda.2013.03.022
69. Fabbri E, Zoli M, Gonzalez-Freire M, Salive ME, Studenski SA, Ferrucci L. Aging and multimorbidity: new tasks, priorities, and frontiers for integrated gerontological and clinical research. *J Am Med Dir Assoc*. 2015;16:640–647. doi:10.1016/j.jamda.2015.03.013
70. Chang SS, Weiss CO, Xue QL, Fried LP. Patterns of comorbid inflammatory diseases in frail older women: the Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci*. 2010;65:407–413. doi:10.1093/gerona/glp181
71. Marengoni A, Angleman S, Meinow B, et al. Coexisting chronic conditions in the older population: variation by health indicators. *Eur J Intern Med*. 2016;31:29–34. doi:10.1016/j.ejim.2016.02.014
72. Santoni G, Angleman S, Welmer AK, Mangialasche F, Marengoni A, Fratiglioni L. Age-related variation in health status after age 60. *PLoS One*. 2015;10:e0120077. doi:10.1371/journal.pone.0120077
73. Welch HG, Sharp SM, Gottlieb DJ, Skinner JS, Wennberg JE. Geographic variation in diagnosis frequency and risk of death among Medicare beneficiaries. *JAMA*. 2011;305:1113–1118. doi:10.1001/jama.2011.307
74. Onder G, Palmer K, Navickas R, et al.; Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS). Time to face the challenge of multimorbidity: A European perspective from the Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS). *Eur J Intern Med*. 2015;26:157–159. doi:10.1016/j.ejim.2015.02.020
75. World Health Organization. World report on ageing and health. 2015. http://apps.Who.Int/iris/bitstream/10665/186463/1/9789240694811_eng.Pdf. Accessed January 5, 2018.