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Review

Depression and frailty in old age: a narrative review of the literature published between 2008 and 2018

Priscila Pascarelli Pedrico do Nascimento[a]
<priscila.pascarelli@gmail.com>

Samila Sathler Tavares Batistoni[b]
<samilabatistoni@usp.br>

[a] Pós-Graduanda do Programa de Gerontologia (Doutorado), Faculdade de Ciências Médicas, Universidade Estadual de Campinas. Rua Tessália Vieira de Camargo, 126, Cidade Universitária Zeferino Vaz. Campinas, SP, Brasil. 13083-887.
[b] Departamento de Gerontologia, Escola de Artes, Ciências e Humanidades, Universidade de São Paulo. São Paulo, SP, Brasil.

This article reports a narrative review of the literature on the relationships between depression and frailty in the elderly. We selected 28 articles retrieved from the LILACS, MEDLINE/PubMed and SciELO databases published in the last decade (2008-2018). The literature review revealed the predominance of screening measures for depression and the conceptual model of the frailty phenotype. Variations in the associations between the two conditions mediated by variables related to gender, physical, cognitive and socioemotional aspects, biological markers, use of antidepressants and risk of mortality were observed. The findings corroborate the combined impact of the two syndromes, which promote greater health decline, vulnerability and a high-risk profile. Although considered distinct syndromes, depression and frailty are strongly associated. There is a lack of national data on the combined effect of the phenomena in the Brazilian elderly population.

Keywords: Aged. Depression. Frailty.

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Introduction

Since the early 2000s, observations of the cooccurrence of depression and frailty in older adults have highlighted the need for a multi-disciplinary approach to elucidate this association and guide clinical and psychosocial interventions[1]. These observations coincided with the proposal of two different, but consistent and robust, conceptual models, both of which are currently adopted to operationalize frailty in older adults. The "phenotype of frailty"[2] comprises five objective measurable criteria (unintentional weight loss, self-reported exhaustion, weakness, slowing walking speed and low physical activity) and the "frailty index"[3], based on a multidimensional approach involving the accumulation of physical and psychosocial deficits.

Estimating the cooccurrence of the syndromes is challenging owing to the variety of different models and measures used in studies to identify the prevalence of frailty and depression due to the heterogeneity of the conditions, whose manifestation of signs and symptoms varies with age and socioeconomic situation. In low and middle-income countries, including Brazil, the prevalence of frailty ranges from 3.9% to 51.4%, and is higher in individuals aged > 75 years and among women[4]. In the same context, the prevalence of depression ranges from 0.3% to 13.8%, if assessed using diagnostic criteria, and from 1% to 38.6%, when screening measures are adopted[5]. In Brazil, an estimated 26% of community-dwelling elderly exhibit clinically significant symptoms and 7% have major depression[6].

According to Vaughan et al.[7], one in every ten older adults are frail or present depressive symptoms and a high percentage have both these conditions. Assessments of the cooccurrence of the conditions show that around 4-16% of frail elderly aged ≥ 60 years have severe depression, a rate rising to 35% among older adults > 75 years[8]. A recent metanalysis study suggested that frail elderly are four times more likely to have depression than non-frail or robust individuals, with a similar probability for frailty among depressed versus non-depressed subjects[9].

The associations between frailty and depression are taken to be bidirectional in the clinical and research literature[9]. However, the causal relationships and extent to which the phenomena are overlapping or distinct syndromes remains unclear because few studies investigating the nature of the relationship between the conditions have been conducted. Low quality of life, functional dependence, greater health service use and increased morbidity and mortality are some of the adverse outcomes predicted by both conditions in old age[10,11].

Depression and frailty share the same neurovegetative symptoms and risk factors, such as loss of energy (fatigue), psychomotor retardation (slowed gait), decline in physical activity. weight loss, comorbidities and both cognitive and functional impairment[1,11-15]. Underlying physiopathological mechanisms common to both conditions[16,17] have also been implicated, such as hormonal changes activated by the hypothalamus-pituitary-adrenal axis; mitochondrial dysfunction, associated with reduced activity, mobility and increased fatigue[18]; deficit in dopaminergic neurotransmission, which slows cognitive and motor processes[18]; and chronic inflammatory processes as precursor mechanisms of both the conditions in elderly that may combine to make depressed individuals become frail or frail become depressive[19-21].

Mapping the main interests of this research output is important for the recognition, clarification and establishment of better approaches in clinical and research settings, considering the negative outcomes this elderly group is exposed to and the coexistence of different parameters for frailty and also for depression. Thus, the aim of the present narrative review[22] was to provide a general overview of this field of investigation by examining the perspectives and approaches, focusing on the methodological criteria and study designs, as well as the key findings and implications for clinical practice.

Methods

The LILACS, MEDLINE/PubMed and SciELO databases were searched between May and August 2018 for literature in Portuguese or English published in the last decade (2008-2018). The descriptors used were "depression", "depressive symptoms", "frailty", "aged" and their corresponding translations in Portuguese, applying the Boolean operator "and" in the search. The inclusion criteria adopted were: full text available, cross-sectional or longitudinal design and intervention studies published in journals indexed on the above-cited databases, investigating the prevalence of frailty in depressed elderly, prevalence of depression among frail elderly, causal relationship, construct overlap, role of moderating variables and mortality risk. Exclusion criteria were: publication date (prior to 2008), repetition of article in the different databases, and titles and abstract not relevant or pertinent to the article after full reading. The data drawn from the scientific literature selected were analyzed individually for each article and according to their relationship with the other studies retrieved, as opposed to analysis using characteristic quantitative or qualitative techniques.

Results and discussion

Of the 550 publications initially retrieved, 33 were assessed in full and 28 were included in the present study (Figure 1). Fifteen articles provided cross-sectional data, 12 longitudinal and only one yielded intervention data. The information is further described in the ensuing sections. The selected articles revealed a recent increase in scientific output, especially over the last 5 years (see Figure 2).

The majority of the cross-sectional studies[12,23-30], longitudinal studies[11,31-39] and intervention study[40] assessed older adults using screening scales for depression. The most frequently used instruments were the Center for Epidemiologic Studies-Depression (CES-D) and the Geriatric Depression Scale (GDS). Most of the studies whose samples comprised patients clinically diagnosed with depression were cross-sectional[41-46] while a few were longitudinal[47,48].

Regarding frailty assessment, the conceptual model most commonly adopted by the cross-sectional[12,23,25,28,29,41-45], longitudinal[11,31-34,36,37,47] and intervention studies[40] was the phenotype of Fried et al.[2].

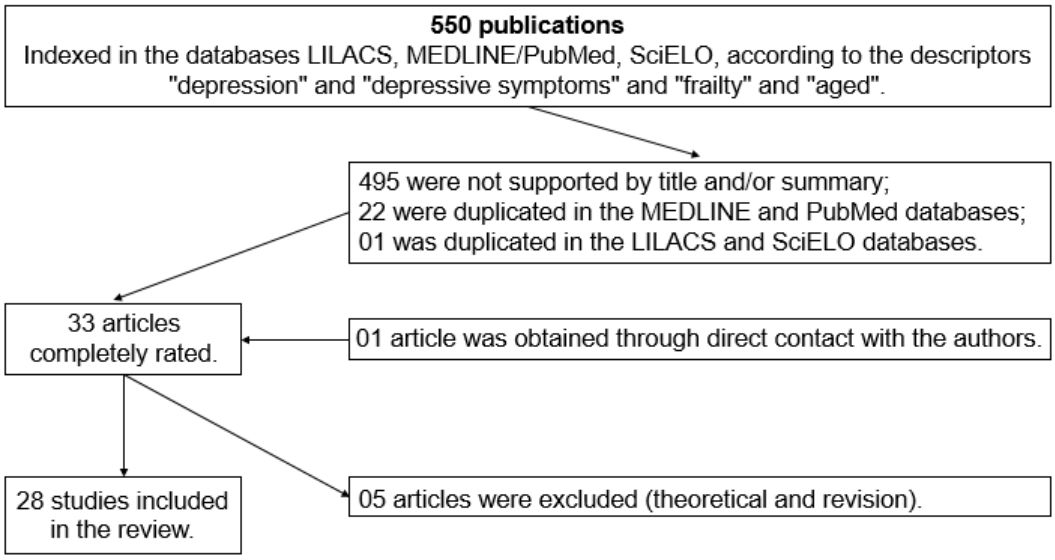

Figure 1. Flow diagram depicting the search and inclusion strategy for the literature on the relationship between depression and frailty syndromes.

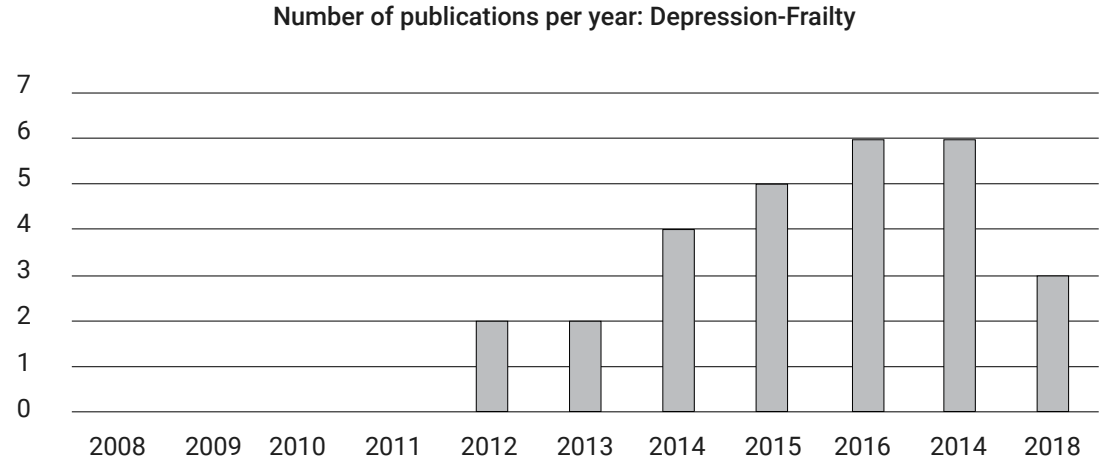

Figure 2. Scientific output on the depression-frailty relationship (2008-2018).

Main focus of cross-sectional studies

Prevalence of frailty in depressed versus non-depressed elderly

The studies revealed that, irrespective of the conceptual model adopted for detecting frailty and screening tools or diagnostic criteria for depression, the syndromes were strongly associated[30,42]. The occurrence of frailty was significantly greater among depressed elderly than among subjects without depression.

Collard et al.[42] found that the prevalence of physical frailty, according to the phenotype of Fried et al.[2], was around 25% higher among clinically depressed elderly than non-depressed subjects. Older age and depressive symptom severity were independently associated with frailty in the depressed group. According to the authors, most patients with severe depression, secondary to lifestyle and physiological disorders or autonomous nervous system problems related to this condition, were more prone to developing frailty; frailty can also be accompanied by severe depression due to its association with somatic diseases and functional limitations; and lastly, the common underlying processes found in both frailty and depression are also relevant.

Ge et al.[30] estimated the prevalence of frailty in community-dwelling older adults using the Clinical Frailty Scale (based on clinical judgement), and investigated the independent association between frailty, classified into 4 levels, and depressive symptoms. The results showed that higher frailty levels, i.e. more severe, were significantly associated with greater depressive symptoms.

Specificities of depression in the context of frailty

Some authors[24,28,29] noted that certain items from the depressive symptom screening scales were more related to pre-frailty conditions and the transition to frailty. St. John et al.[24] investigated the gradient effect across the range of depressive symptoms measured using the CES-D scale and the association of specific symptoms with frailty. They identified a strong correlation between the syndromes, and an association of somatic complaints, positive affects and negative affects with frailty.

Nascimento et al.[28] investigated the relationships between the presence of depression and specific depressive symptoms based on the total score of the GDS-15 and its constituent items, respectively, with the conditions of pre-frailty and frailty, assessed according to the phenotype of frailty in 2,402 Brazilian community-dwelling older adults. The authors observed that the prevalence of depression was greater in frail than pre-frail subjects, and differed significantly from robust elderly. Depressive symptoms characteristic of each frailty profile were identified: in pre-frail individuals symptoms included lower positive affects, somatic perception and interpersonal sensitivity, whereas among frail subjects symptoms were somatic perception and anhedonia (loss of interest or pleasure in everyday activities).

The study by Ribeiro et al.[29] explored the relationship between physical frailty, assessed according to the phenotype of frailty, and depression as measured by the GDS scale, and the most characteristic depressive symptoms associated with frailty in centenarians. The risk of depression was higher in frail subjects than pre-frail elderly. Consistent with the findings of Nascimento et al.[28], the results suggested that specific depressive symptoms can differentiate the frailty profiles. Among frail individuals, the key items identified indicate that loss of ability to experience joy and pleasure can constitute an important characteristic among individuals with accumulated vulnerability.

Specificities of overlap between depression and frailty

In a study analyzing the relationship and concordance between depression and frailty, Mezuk et al.[41] identified different groups of people, profiles underpinned by

similar symptoms, based on confirmatory latent class analyses. The results suggested that the conditions are indeed interrelated, but represent distinct syndromes rather than a single construct. The symptoms of both tend to coaggregate, and their operational criteria identify substantively overlapping subpopulations.

Along the same lines, Lohman et al.[25] sought to determine the degree of diagnostic overlap between frailty and depression. Using latent class analysis, their findings indicated a substantially overlapping subpopulations, particularly between the group of severely depressed elderly, where almost three-quarters were classified as moderately frail or frail with exhaustion, compared to elderly with fewer depressive symptoms, with no difference for gender.

Lohman et al.[26] examined the correlation between frailty, based on three different conceptual models (biological syndrome, frailty index and functional domains) and depression, and an approach with latent variables. The authors showed that, irrespective of the concept used, frail status was significantly associated with the presence of depression. Even after controlling for shared symptomology, the association remained significant, i.e. the significantly consistent correlation was not fully explained by differences in definitions, overlapping symptoms or sociodemographic covariables. The authors highlighted that, despite the fact that the frailty models focus on physical and functional indicators, psychological vulnerability, measured by depression, may be an inherent component of frailty.

Relationships between depression-frailty in the presence of other variables and outcomes

Some authors investigated the relationship of frailty and depression with other variables. Ní Mhaoláin et al.[23] explored the relationship between frailty, clinically significant anxiety and depression. The study identified high scores on depression and anxiety scales among groups of frail and pre-frail elderly compared to robust elders. It was suggested that physical frailty is accompanied by psychological frailty, with higher likelihood of emotional disorders. Anxiety appears to increase morbidity and mortality, acting as a driver of frailty[23].

Arts et al.[43] found a relationship between inflammatory markers and specific frailty criteria among depressive elderly. C-Reactive Protein (CRP) and Interleukin (IL-6) were significantly associated with handgrip strength and neutrophil gelatinase-associated lipocalin (NGAL) with gait speed. The study pointed to the possibility of a characteristic depressive subtype underpinned by these specific inflammatory mechanisms.

Collard et al.[44] examined whether depression and physical frailty act independently and/or synergistically in their association with somatic diseases. The results showed both common and unique pathways. Frailty appears to mediate, at least in part, the association between depression and somatic diseases, particularly via the criteria "exhaustion/low energy" and "slowness" (or gait speed). Slowness was an unexpected finding, given its association was fully independent of the presence of depression, suggesting that gait speed has an underlying physiopathologic mechanism that leads to somatic diseases or vice-versa, unlike mechanisms associated with depression[44].

Clinical conditions involving cognitive impairment and dementias are often associated with frailty, increasing vulnerability and directly impacting the well-being of this elderly population. Arts et al.[45] investigated the association between physical frailty and cognitive functioning in depressed older adults. Frailty was associated with poorer cognitive performance on the domains verbal memory, processing speed and working memory, independently of the severity of depression, especially on three criteria: muscle weakness, slowness and low physical activity. The authors drew attention to the negative health effects associated with depression in late-life, which may be potentialized by the cooccurrence of physical frailty and cognitive impairment. Also, the study of Potter et al.[46] investigated the relationship of physical frailty with neurocognitive performance in depressed elderly and revealed that frailty was strongly associated with executive dysfunction and verbal fluency. The results showed that slowed processing speed may be a central characteristic of cognitive frailty, similarly to the way motor slowing is a core feature of physical frailty.

The study by Lau et al.[27] analyzed how moderate depression moderates the relationship between frailty and self-rated health. The presence of depressed mood and negative cognitions, such as feelings of sadness and hopelessness, appear to promote poor perceived health among frail older adults. Among the very old, the mechanism of lateral or upward social comparison influences their self-rated health, but is negatively affected in the presence of depression. Depressed elderly tend to make harsher assessment of themselves and their health, perceive themselves as having less control and are less optimist about health issues, translating to poorer self-rating[27].

Brown et al.[12] investigated the effect of the presence of frailty and its criteria on death as an outcome in elders with different degrees of depressive symptoms. The results for men and women differed. The combined effect of depression and frailty, particularly the criteria of fatigue and slowed gait, proved more deleterious for women, who had higher mortality risk.

Main focus of the longitudinal studies

Direction of the relationship between the phenomena: frailty as a predictor of depression over time

Most of the studies were based on the observation of frailty in baseline measures of investigations to predict the incidence of depressive symptoms over the long term. Feng et al.[11], for instance, analyzed the prospective relationship of frailty and the incidence of depression at 2 and 4-month follow-ups, based on data for 1,827 community-dwelling Chinese aged ≥55 years, participants in the Singapore Longitudinal Aging Study-I (SLAS-I). The results of the study support the hypothesis that frailty and depression are comorbid conditions, while frailty represents a risk factor for the development and persistence of depressive symptoms. The components of frailty which proved individual predictors of depression were exhaustion, weakness, slowness and low level of physical activity. The authors cited the use of a screening scale for depressive symptoms (GDS) as a strength of the study. The GDS was more suitable because it does not include the somatic symptoms associated with the phenotype of frailty.

In line with these results, the study by Collard et al.[33], analyzing data on 888 frail older adults (≥65 years), participants in the Invecchiare in Chianti, aging in the Chianti area (InCHIANTI), involving follow-ups of 3, 6 and 9 years, 30.6% of the non-depressed participants developed depression during the follow-up, and the presence of frailty conferred a significant risk for the onset of depression in adjusted models. The separate analysis of components of frailty showed that only low level of physical activity significantly increased the risk of incidence of depressive symptoms. The authors also concluded that, among the individuals who had depression at baseline and symptom remission during follow-up, the presence of frailty was associated with lower remission of the depressive symptoms. The finding confirmed that the severity of frailty negatively impacts both the emergence and remission of depression. Similarly, Makizako et al.[31] showed that, among elderly people without depressive symptoms at baseline, frail individuals were twice as likely to develop depressive symptoms during a 15-month follow-up. Frailty and poor self-rated health were independent predictors of the incidence of depressive symptoms among the community-dwelling elderly investigated.

In clinically depressed elderly, Collard et al.[47] observed that frail-depressed patients had significantly less remission of depression during the 2-year follow-up, compared to their pre-frail and robust peers. According to the authors, the higher level of physical frailty was responsible for the non-remission of the disease. In addition, the higher level of physical frailty was also associated with greater severity of depressive symptoms over time.

The study by De Rui et al.[32], involving 891 community-dwelling elderly from the Progetto Veneto Anziani Longitudinal Study without either of the two conditions at baseline, assessed whether pre-frailty was associated with greater risk for depression, and whether changes in frailty status during follow-up affected the incidence of depression. Results showed that worsening frailty status almost doubled the risk of the incidence of depression during the 4-year follow-up. Pre-frailty *per se*, was not a predictor for the onset of depression, but suggested greater risk with worsening frailty.

Veronese et al.[36] found contrasting data to that outlined thus far. The authors investigated whether pre-frailty, frailty and its specific criteria were associated with greater risk of depression in a 2-year follow-up, failing to find a significant association after adjusting for confounding factors. However, the analysis of the specific criteria for frailty found that only one was associated with the incidence of depression during the follow-up: slow gait speed, which increased the risk by 85%.

The above-mentioned studies indicate that the presence of frailty appears to contribute in a more severely depressed, vulnerable and high-risk group. The authors cited a significant association of some specific criteria of the syndrome, which appear to increase the risk of depression, in particular slowed gait and low physical activity[49]. Slowed gait is associated with dopaminergic dysfunction in the basal ganglia, which may result from, or be aggravated by, the inflammatory processes underlying frailty and depression[50]. In addition, this represents an important risk factor for worsening of depressive symptoms[49] and, in the context of depression, is also associated with higher mortality risk[12]. Low physical activity also shows a significant association with depression, because both share inflammatory processes that can influence the onset

of depression[49]. Slowed gait can promote low physical performance and contribute to social withdrawal, resulting in a vicious circle, with greater risk of depression[49].

Depression as a predictor of frailty over time

Two studies found that the presence of depression at baseline predicted frailty[37,48]. Both studies investigated depression together with the use of antidepressants and concluded an association with frailty after the follow-up period.

Lakey et al.[37], in a 3-year follow-up study of robust adult older women (≥ 65 years) found that depressive symptoms were associated with greater risk of becoming pre-frail and frail over time. There was greater risk (almost double) of frailty among elderly in use of antidepressants and exhibiting depressive symptoms. The statistically significant variables for the incidence of frailty were low score on the Mini-Mental State Exam (MMSE) and scores on the subitems of negative affects of the CES-D depression scale. The elderly who were depressed and in use of antidepressants had more health problems, chronic comorbidities and were more likely to rate their health as regular or poor. The data suggest that treating depression with drugs alone fails to reduce the risk of frailty, where a more comprehensive approach is required.

Results of a Brazilian study conducted in a geriatric outpatient clinic[48] assessing the association between depression treated with SSRI (selective serotonin reuptake inhibitors) and frailty showed a positive association between the syndromes at baseline and after 12-month follow-up. From the baseline analysis, the authors identified a significant association between depression and the two subdomains making up the frailty scale used (FRAIL): physical performance (muscle resistance and ambulation), and health status (fatigue, weight loss and number of illnesses). The association with frailty in depressed patients using SSRI remained similarly significant. After the 12-month follow-up, depression in association with SSRI use remained significantly associated with frailty. The treated depressed group showed a significant association with the two subdomains of the FRAIL scale, whereas the group also treated with SSRI, but with no significant depressive symptoms, showed a significant association only with the health status subdomain. The study emphasized the possible adverse effects and negative outcomes that treatment with SSRI can have over time, independently contributing to the risk of frailty.

Bidirectional relationship between the syndromes

Despite identifying data in the current literature supporting the notion that the presence of frailty increases the risk for depression, with similar probability for the inverse, this relationship remains unclear. This relationship has been assumed bidirectional. Based on this premise, Monin et al.[34] studied elderly spouses to determine whether frailty status and the presence of depressive symptoms interacted over time. The authors identified a bidirectional and potentially overlapping relationship between the syndromes. On the individual analysis of the elderly, frailty was a predictor of depressive symptoms, while depressive symptoms were predictors of frailty, corroborating the findings reported by previous studies. Also among spouses, the greater frailty status of one partner predicted greater frailty status of the other, and likewise for the presence of depressive symptoms.

Moderators of the depression-frailty relationship

Some authors have analyzed the relationship of the phenomena in the presence of other variables to elucidate their roles or determine the extent they mediate the impact of cooccurrence, guiding the clinical approach. Regarding use of antidepressants, the study by Lakey et al.[37] cited above showed that, despite treatment for depression, the elderly patients still exhibited risk of frailty, i.e. medication alone did not suffice.

Almeida et al.[38], for example, investigated the relationship of mortality associated with current or previous depression, considering effect of frailty, and found that a substantial percentage of elderly men (85%) with more severe depressive symptoms were also frail. In a bid to better understand the transition path between the conditions, Almeida et al.[39] investigated a cohort of non-frail elderly men to determine whether depression was prospectively associated with physical impairment and functional capacity in a 9-year follow-up. The study revealed an association, suggesting that functional decline may represent an intermediate state between depression and frailty risk, and ultimately, death. Depression may be an initial sign of a trajectory of declining health, i.e. a trigger for a chain of events that lead to progressive impairment in functional capacity, increasing the risk of frailty. Functional impairment thus appears to be a mediator between the conditions.

The findings of the study by Lohman et al.[35] help shed light on the multifactorial determinants of functional decline in old age. The results show that both frailty and depression are associated with an increased likelihood of two adverse and costly health outcomes over the long-term: hospital admissions and serious falls. The authors highlighted the dynamic nature of frailty and its relationship with depression and showed that the trajectories of the development of frailty are themselves predictors of unfavorable outcomes. Depression seems to play a key role toward explaining the risks conferred by frailty, and can be taken as an important feature of frailty.

Findings of the intervention study

Randomized clinical trials assessing the effects of a multimodal intervention on depression in frail elderly are scarce. The only such study retrieved in this review was that of Ng et al.[40], which identified greater effectiveness of a combined intervention, encompassing a joint approach addressing nutritional, physical and cognitive aspects, on depressive symptoms in frail and pre-frail community-dwelling elderly at 6 and 12-month follow-ups. The findings revealed significant correlation of changes in frailty parameters, especially gait speed and energy level, with positive changes in GDS scores, indicating that reversing frailty can mediate improvements in mood. The multiple approach appears to improve psychological well-being, but further studies are needed.

Final considerations

Investigations into the prevalence of concomitant frailty and depression over the last decade have strengthened the concept of confluence between the two conditions and their serious repercussions on the functioning and quality of life of the elderly. Studies have predominantly been cross-sectional in population-based samples,

affording a broader understanding of the distribution of the phenomenon beyond clinical settings. Most of the longitudinal studies have reported observations based on the prevalence of frailty to identify the incidence of depression. However, the findings preclude confirmation of causality or the existence of a "frail-depressed" phenotype as a distinct group, where studies on the close relationship between the phenomenon are very recent.

Although most studies used the phenotype of frailty and screening scales for depression, measures are highly heterogeneous, hampering the development of intervention programs and investigation of risk factors and other associated conditions, given the quality of the scales.

There is also a marked dearth of national studies elucidating the relationship between the two phenomena in the Brazilian population. In the clinical setting, comprehensive, multiple, personalized, differentiated assessment should be introduced to improve diagnosis, care planning and management, given that the relationship between these highly prevalent conditions remains unclear and poorly understood.

Authors´ contributions

Priscila Pascarelli Pedrico do Nascimento was involved in study conception, literature review, data interpretation, writing, editing and review of the paper. Samila Sathler Tavares Batistoni oversaw the study, critically reviewed the intellectual content and approved the final draft of the article.

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