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Could Frailty be an Explanatory Factor of the Association between Depression and Other Geriatric Syndromes in Later Life?

Marcus Kiiti Borges MSc(b), Richard C. Oude Voshaar PhD(1,5), Carla Fernanda de Vasconcellos Romanini MSc(3), Fabiana Maria Oliveira BSc(5), Natália Almeida Lima BSc(5), Marina Petrella PhD(1,5), Daniele Lima Costa MD(6), José Eduardo Martinelli PhD(5), Silvana Vieira Bandeira Mingardi BSc(6), Alaise Siqueira BSc(4), Marina Biela MD(8), Rose Collard PhD(8), and Ivan Aprahamian MSc, PhD(2,4,8)

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ABSTRACT

Objectives: This study aimed to investigate whether frailty could be an explanatory factor of the association between depression and the number of geriatric syndromes.

Methods: Cross-sectional baseline data from a cohort study (MIMICS-FRAIL) were analyzed in a sample of 315 older adults. Depression was measured according to DSM-5 criteria and a self-report questionnaire (PHQ-9). Frailty was assessed according to the FRAIL questionnaire and a 30-item Frailty Index (FI). We considered six geriatric syndromes. Multiple linear regression analyses were performed and adjusted for potential confounders.

Results: Multiple linear regression analyses yielded significant associations between depression and geriatric syndromes. These associations decreased substantially in strength when frailty was added to the models. Findings were consistent for different definitions of depression and frailty.

Conclusions: Among depressed patients, frailty may be hypothesized as a causal pathway toward adverse health outcomes associated with depression. Longitudinal studies should explore the causality of this association.

Clinical implications: Frailty should be treated or prevented in order to minimize the impact of other geriatric syndromes among depressed older adults. Screening for frailty would be of utmost importance in mental health care, as frailty is neglected especially in this field. Integrated care models are crucial for clinical practice in mental illness care.

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KEYWORDS
Frailty; depression; geriatric syndromes; multimorbidity; older adults

Introduction

Depression is highly prevalent in older persons, with pooled prevalence rates between 13.5 and 17.1% for clinically relevant depressive symptoms (Luppa et al., 2012). Presumed pathophysiological mechanisms related to depression include metabolic, inflammatory, autonomic, and hypothalamic-pituitary-adrenal dysregulation (Brown et al., 2016; Penninx, Milanessi, Lamers, & Vogelzangs, 2013). Most prospective cohort studies have shown associations between depression and adverse health outcomes, independent of lifestyle characteristics, therefore mechanisms intrinsically related to depressive disorder are also assumed to explain these outcomes (Cuijpers et al., 2013). Since these mechanisms also underlie physical frailty, frailty might be an explanatory factor for many outcomes of late-life depression, e.g. geriatric syndromes. Moreover, late-life depression as well as frailty are independent predictors of other adverse events (e.g. falls, functional dependence, hospitalization, institutionalization, and death) (Atlantis et al., 2012; Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Lohman, Mezuk, & Dumenci, 2017; Prina et al., 2013).

Geriatric syndromes are defined as a specific symptom or complaint which is common in later life (e.g. falls, vertigo, urinary incontinence, fatigue, delirium, etc), has a multifactorial origin (e.g. biological, psychological, environmental), and cannot be ascribed to a single disease (Flacker, 2003). Different from chronic diseases or multimorbidity,
Geriatric syndromes cannot be classified into disease categories or clusters (Salive, 2013). Geriatric syndromes (e.g., cognitive impairment, falls, urinary incontinence) are prevalent among older adults in different settings and are associated with lower quality of life, loss of activities of daily living and death (Liang, Rausch, Laflamme, & Möller, 2018; Sánchez, Vidán, Serra, Fernández-Avilés, & Bueno, 2011). However, most studies have omitted geriatric syndromes when evaluating older patients despite considered relevant in clinical practice (Inouye, Studenski, Tinetti, & Kuchel, 2007).

Frailty is a dynamic condition of greater vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes (Hoogendijk et al., 2019). Frailty can be thus hypothesized to predict the onset of chronic clinical (physical) diseases and presumably other geriatric syndromes (besides frailty). This makes sense as frailty is conceptualized as an accelerated decrease of reserve in several physiological systems that are interrelated (Morley et al., 2013). According to a systematic review, approximately one in ten adults aged 65 and over is frail (Collard, Boter, Schoevers, & Oude Voshaar, 2012), while 3 through 4 in 10 depressed older adults can be classified as frail (Soysal et al., 2017). Centering medical care around one specific disease has been shown highly effective (Boult et al., 2009), especially for otherwise healthy persons. Nonetheless, as aging come along with the emergence of several chronic diseases, single-disease centered care might fail and thus integrated, multidisciplinary care is needed (Boult et al., 2009; Briggs & Araujo de Carvalho, 2018; WHO, 2019).

As depression and frailty share pathophysiological mechanisms such as higher inflammatory activation and hormonal dysfunction (Brown et al., 2016), frailty might be a causal pathway from depression to geriatric syndromes. This hypothesis fits with a recent systematic review, which showed that most frail individuals present also multimorbidity, while the inverse relation is not proportional (Vetrano et al., 2019). However, only indirect information regarding geriatric syndromes can be estimated since they were not considered in this study (Vetrano et al., 2019). To our knowledge, only one study has examined whether frailty may mediate the association between depression and chronic clinical diseases (Collard et al., 2015). This study was conducted in a primarily psychiatric sample and showed that frailty indeed could explain the association between depression and the number of clinical diseases. However, no study evaluated the association between depression, frailty and other geriatric syndromes.

Finally, our objective was to investigate whether frailty could explain the association between depression and the number of geriatric syndromes in a general, geriatric outpatient sample.

**Methods**

**Study design and procedures**

We conducted a cross-sectional study with baseline data of the Multimorbidity and Mental health Cohort Study in Frailty and Aging (MiMiCS-FRAIL). The overall aim of the MiMiCS-FRAIL study is to increase our understanding of the (reciprocal) associations between multimorbidity, frailty and psychopathology within a clinical population of geriatric outpatients. Recruitment for this study has started in January 2018 (and is still ongoing). For the present study, patients were included until July 2019. All participants received an extensive assessment at baseline by a well-trained team of geriatricians, psychiatrists, and physical and nutritional therapists. The baseline assessment included a comprehensive geriatric assessment protocol (which included the evaluation of sociodemographic, multimorbidity, functional disability, frailty, sarcopenia, polypharmacy, cognitive performance, depressive symptomatology, anthropometric measurement and gait speed variables) and a structured psychiatric diagnostic interview, using validated observer-based and self-report questionnaires. Subsequently, patients will be followed-up every year with respect to all variables amenable to change.

The primary outcome parameter of the MiMiCS-FRAIL is mortality, which is estimated between 25% and 40% during a 5-year follow-up in our clinic. Based on meta-analyses, the hazard ratio (95% confidence interval) of dichotomous measures of either frailty, multimorbidity (2 or more diseases versus no morbidity) and depressive disorder is estimated at 2.34 (1.77–3.09), 1.73 (1.41–2.13), and 1.60 (1.37–1.86),
respectively (Brandão, Fontenelle, da Silva, Menezes, & Pastor-Valero, 2019; Cuijpers et al., 2014; Nunes, Flores, Mielke, Thumé, & Facchini, 2016), corresponding to a regression coefficient of B ranging from Ln(1.60) = 0.47 through Ln(2.34) = 0.85. Assuming a power of 80% (beta = 0.2), an alpha of 5% (0.05), and an R2 between the predictor and all covariates of 0.20 (to adjust for covariates as well as examining mediating effects), requires a sample size between 136 and 711 patients to detect a statistically significant effect.

The study followed the standards established by the Brazilian National Council of Health. All procedures were conducted in accordance with the ethical precepts governing research with humans stipulated by the Helsinki Convention. The ethical review board and local committee of Medical Institutes (University of São Paulo and Faculty of Medicine of Jundiai) approved this study with protocol number (CAAE: 12,535,218.5.0000.0065). Written informed consent was obtained from all participants and patient anonymity was preserved.

**Participants**

Eligible patients were all new referrals to a secondary care (university-based) geriatric outpatient clinic in southwest of Brazil. Geriatric outpatient clinics in Brazil are open to referrals from general practitioners as well as self-referrals by patients themselves. Inclusion criteria were: (a) ≥ 60 years, (b) adherence to clinical follow-up, including at least one visit every 12 months, and (c) signing of the informed consent.

For the present study, we excluded those individuals with (1) a clinical diagnosis of dementia; (2) refusal to participate; (3) bipolar disorder; (4) psychotic disorder; (5) delirium or hospitalization in the last month; (6) electroconvulsive therapy; (7) wheelchair dependent; (8) severe sensory impairment; (9) severe limb paresis due to stroke; (10) unstable clinical condition (e.g., decompensated heart failure, current infection); (11) terminal illness.

**Measures**

**Depression**

The primary determinant of our study was the presence of a depressive disorder according to DSM-5 criteria (APA, 2013) as assessed with the Structured Clinical Interview Clinical Version for DSM-5 (SCID-5) (First, Williams, Karg, & Spitzer, 2016). Six researchers were trained to apply the SCID-5. We considered a major depressive disorder (MDD) as well as subthreshold depression defined as “another specified depressive disorder” according to DSM-5 as our primary determinant of interest.

The severity of depressive symptoms with the Patient Health Questionnaire (PHQ) 9-item version was a secondary determinant of interest (Kroenke, Spitzer, & Williams, 2001). The 9 items correspond to the DSM-5 criteria for a depressive episode and have to be rated on a Likert scale ranging from 0 to 3 corresponding to “not at all”, “several days”, “more than half the days” and “nearly every day”. A higher score indicates a higher severity; a score of 1 to 4 points is considered normal; whereas 5 to 9 as mild, 10 to 14 as moderate, 15 to 19 as moderately severe, and 20 to 27 as severe depression (Kroenke et al., 2001). PHQ-9 has been validated among Brazilian older people (Santos et al., 2013). PHQ-9 has shown a sensitivity of 0.88 and a specificity of 0.85 to detect MDD according to meta-analysis (Levis, Benedetti, & Thombs, 2019).

**Frailty**

Frailty was assessed according to the two common criteria, i.e. the FRAIL questionnaire Brazilian version (Aprahamian et al., 2017) and the deficit accumulation model (Rockwood & Mitnitski, 2007).

The FRAIL-BR questionnaire is a self-report frailty screening scale aimed to measure frailty mainly based on variables from Fried Frailty Phenotype (Morley et al., 2013). The FRAIL-BR assesses the presence of fatigue, muscle resistance, ambulation, disease burden, and loss of weight based on the following criteria: (1) Fatigue: the answers “all the time” or “most of the time” to the question “How much of the time during the past 4 weeks did you feel tired?”; (2) Resistance: “yes” to the question “By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?”; (3) Ambulation: “yes” to the question “By yourself and not using aids, do you have any difficulty walking several hundred yards?”; (4) Illness: presence of 5 or more illnesses out of 11
(hypertension, diabetes mellitus, cancer (excluding basal cell carcinoma skin or equivalent), chronic obstructive pulmonary disease, angina or coronary artery disease, heart attack or myocardial infarction, congestive heart failure, asthma, arthritis, stroke, chronic renal failure); and (5) Loss of weight: respondents with a weight loss ≥5% of their total weight within one year. Each affirmative answer results in 1 point. The classification consists of 0 points: robust; 1–2: prefrail; and 3–5: frail (Morley et al., 2013). Data collection is very fast, as this instrument does not require specialized training or equipment and can be performed without reviewing medical records and physical maneuvers (Aprahamian et al., 2017). A cutoff of 3 points in the FRAIL-BR presented a sensitivity of 28% and specificity of 90% when compared to the phenotype model (Aprahamian et al., 2017). Although a low sensitivity, clinimetric properties were frequently evaluated for the FRAIL questionnaire showing consistent results across different populations and settings (Faller et al., 2019).

The FI is expressed as a ratio and involves the accumulation of 30 or more co-morbidities, symptoms, diseases, disabilities or any deficiency in health (Hoogendijk et al., 2019). The FI is a stronger predictor for adverse health outcome than the sum of the predictive values or its single components (Rockwood & Mitnitski, 2007). The FI Score is the sum of health deficits present divided by the total number of deficits measured (Hoogendijk, 2019). In this study, we considered a 30-item Frailty Index (FI) as the proportion of health deficits derived from a count of 30 health deficits across different health domains (range 0–1). For instance, if an older adult has 12 of these 30 deficits, the FI is 0.4. We assessed the following 30 health deficits: anemia, arthritis, visual impairment, diabetes, dyspnea, chronic renal disease, sleep disorder, peripheral vascular diseases, urinary tract disorders, thyroid disease, respiratory disease, cerebrovascular disease, ischemic heart disease, atrial fibrillation, fracture, hypertension, syncope, heart failure, disability in activities of daily living (ADLs), care dependency, osteoporosis, parkinsonism and related disorders, polypharmacy, foot injuries (e.g. plantar fasciitis, heel spurs, bunions, Achilles tendinitis, ankle sprains), obesity, hearing loss, valvulopathy, social vulnerability, pressure ulcers, peptic ulcers. The FI can be interpreted as follows: a score <0.15 indicates robustness, a score of 0.15–0.25 as prefrail, and a score ≥0.25 as frail (Rockwood & Mitnitski, 2007). According to clinimetric properties, the FI has a great capacity to predict several adverse outcomes (Faller et al., 2019; Kojima, Iliffe, & Walters, 2018).

**Geriatric syndromes**

Geriatric syndromes are a heterogeneous cluster of clinical problems with one central symptom (e.g. dizziness, cognitive impairment). Definitions and specifications to diagnosis are variable among them (Inouye et al., 2007). A comprehensive geriatric assessment is the most recommended strategy to identify geriatric syndromes, which are usually detected clinically, and it was used in our study with this objective (Inouye et al., 2007). The number of geriatric syndromes was operationalized as the sum of 6 recognized geriatric syndromes, namely cognitive impairment, urinary incontinence, falls, weight loss/anorexia, mobility problems, and dizziness. Geriatric syndromes were not considered in the FI model or in the conceptualization of multimorbidity or in the sum of clinical disease clusters.

**Clinical disease clusters**

The prevalence of chronic clinical diseases and disease clusters were compared to the percentage of geriatric syndromes. The presence of single diseases and disease clusters or groups was dichotomized (by present yes/no). Clusters of clinical diseases was operationalized as a count of 7 common chronic clinical disease groups, namely cardiovascular disease (hypertension, atrial fibrillation, heart failure, valvulopathy, myocardial infarction, coronary disease), cerebrovascular disease (stroke), endocrinometabolic disease (diabetes, dyslipidemia, hypothyroidism), lung disease (asthma and COPD), kidney disease (chronic kidney failure), liver disease (cirrhosis, chronic liver failure), and rheumatic disease (osteoarthritis). A geriatrician evaluated each diagnosis both clinically and according to patient’s medical record.

**Covariates**

An update review identified potential risk factors for the onset of frailty across a wide range of socio demographic, clinical, lifestyle-related and biological
factors (Hoogendijk et al., 2019). Potential confounders were selected a priori, based on their relationship with characteristics associated with depression, frailty (Chu, Chang, Ho, & Lin, 2019; Hoogendijk et al., 2019; Soysal et al., 2017) or geriatric syndromes (Liang et al., 2018).

We included demographic as well as lifestyle characteristics as covariates in the analyses: age, sex, years of education, living alone (yes/no), body mass index (as indicated by the weight (in kg) of the patient divided by its squared length in meter), involvement in vigorous physical activity (based on estimated time dedicated to physical activity during the week), self-report regular use of alcohol (how many drinks and type of beverage consumed per week), currently smoking (yes/no), polypharmacy (5 or more chronic prescribed medications) and multimorbidity (two or more chronic diseases; all diseases evaluated are those above mentioned in clinical disease clusters).

**Statistical analyses**

Descriptive statistics were performed for the characterization of the sample. All continuous variables had a normal distribution after histogram analysis, Shapiro-Wilk and Kolmogorov–Smirnov test. The prevalence of several chronic diseases and clinical disease cluster were reported as percentages. The number of clinical disease clusters were compared to the number of geriatric syndromes.

Multiple linear regression analyses were conducted to assess the association between depression (independent variable) and geriatric syndromes (dependent variable) adjusted for potential confounders as described (model 1). Separate models were run for depressive disorder according to DSM-5 criteria or depressive symptom severity as assessed with the PHQ9 as well as with both frailty indicators (FRAIL-BR and FI). The association between frailty (independent variable) and geriatric syndromes (dependent variable) was assessed by linear regression adjusted for confounders (model 2). In the final model (model 3), frailty was added as an independent variable to model 1 in order to examine to what extent the association between depression and geriatric syndromes would be reduced in strength. In case the strength (B-value) between depression and geriatric syndromes was reduced by more than 10%, we considered as a clinically relevant level for an explanatory factor (Collard et al., 2015).

For all linear regression models, the assumption of homoscedasticity was tested by the Breusch–Pagan test, and we explicitly checked whether all models met the assumption of normally distributed errors. Furthermore, potential problems of multicollinearity (assuming the FRAIL-BR, FI, multimorbidity and geriatric syndromes could present overlapped variables) were explored by calculating the variance inflation factor (VIF), with a value of 1 pointing to no multicollinearity, a value between 1 and 5 to some multicollinearity and a value above 5 as substantial multicollinearity. P-values lower than 5% were considered statistically significant. Data were analyzed using Statistical Package of the Social Sciences (SPSS), version 25.0.

**Results**

**Sample characteristics**

A total of 106 out of the 421 study participants met the exclusion criteria (Figure 1). Mean age of the 315 participants included was 72.1 years and 68.3% was female. A total of 63/315 (20%) patients had major depression and 86/315 (27%) subthreshold depression.

Table 1 presents the clinical characteristics of the 315 patients. Based on validated cutoff values for frailty, 105/315 (33.3%) scored three or more on the FRAIL-BR questionnaire, and 45/315 (14.3%) had a FI of 0.25 or above. Furthermore, a total of 199/315 (63.2%) patients had two or more chronic diseases and 170/315 (54.0%) had at least one geriatric syndrome. Table 2 shows the proportion of the number of chronic diseases and geriatric syndromes.

**Associations between depression and other geriatric syndromes**

Multiple regression analyses adjusted for sociodemographic, lifestyle characteristics and multimorbidity showed that major depressive disorder (beta = 0.237, p < .001) as well as subthreshold depression (beta = 0.174, p = .001) were associated with the number of geriatric syndromes. Additionally, depressive symptoms measured by PHQ-9 were also associated (beta = 0.262, p < .001) (model 1 in
Table 1. Clinical characteristics of the sample (n = 315).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographics:</strong></td>
<td></td>
</tr>
<tr>
<td>● Age (years)</td>
<td>Mean (SD) 72.1 (8.4)</td>
</tr>
<tr>
<td>● Female sex</td>
<td>n (%) 215 (68.3%)</td>
</tr>
<tr>
<td>● Education (years)</td>
<td>Mean (SD) 5.0 (4.0)</td>
</tr>
<tr>
<td>● Living alone</td>
<td>n (%) 45 (14.3%)</td>
</tr>
<tr>
<td><strong>Lifestyle characteristics:</strong></td>
<td></td>
</tr>
<tr>
<td>● Smoking (yes)</td>
<td>n (%) 13 (4.1%)</td>
</tr>
<tr>
<td>● Alcohol use (yes)</td>
<td>n (%) 16 (5.1%)</td>
</tr>
<tr>
<td>● Rigorous physical activity</td>
<td>n (%) 89 (28.3%)</td>
</tr>
<tr>
<td>● Body mass index (kg/m²)</td>
<td>Mean (SD) 28.4 (5.8)</td>
</tr>
<tr>
<td>● Polypharmacy</td>
<td>n (%) 161 (51.1%)</td>
</tr>
<tr>
<td>● Multimorbidity</td>
<td>n (%) 199 (63.2%)</td>
</tr>
<tr>
<td><strong>Psychopathology:</strong></td>
<td></td>
</tr>
<tr>
<td>● Depression severity (PHQ-9)</td>
<td>Mean (SD) 6.2 (6.3)</td>
</tr>
<tr>
<td>● Depressive disorder:</td>
<td></td>
</tr>
<tr>
<td>- Subthreshold depression</td>
<td>n (%) 86 (27.3%)</td>
</tr>
<tr>
<td>- Major depression</td>
<td>n (%) 63 (20.0%)</td>
</tr>
<tr>
<td><strong>Burden of disease:</strong></td>
<td></td>
</tr>
<tr>
<td>● Clusters of clinical diseases (number)</td>
<td>Mean (SD) 1.8 (1.0)</td>
</tr>
<tr>
<td>● Geriatric syndromes (number)</td>
<td>Mean (SD) 0.9 (0.1)</td>
</tr>
<tr>
<td><strong>Frailty:</strong></td>
<td></td>
</tr>
<tr>
<td>● FRAIL-BR</td>
<td>Mean (SD) 1.7 (1.6)</td>
</tr>
<tr>
<td>● Frailty index</td>
<td>Mean (SD) 0.15 (0.08)</td>
</tr>
</tbody>
</table>

Polypharmacy = 5 or more prescribed medications in use; Multimorbidity = 2 or more chronic clinical diseases.

Table 2. Prevalence of clinical disease clusters and geriatric syndromes (n = 315).

<table>
<thead>
<tr>
<th>Number of Disease Clusters</th>
<th>Geriatric Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0</td>
<td>32 (10.2%)</td>
</tr>
<tr>
<td>1</td>
<td>84 (26.6%)</td>
</tr>
<tr>
<td>2</td>
<td>130 (41.3%)</td>
</tr>
<tr>
<td>3</td>
<td>57 (18.1%)</td>
</tr>
<tr>
<td>4</td>
<td>11 (3.5%)</td>
</tr>
<tr>
<td>5</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

**Disease clusters:**

- Cardiovascular disease, n (%) 241 (76.5%)
- Hypertension 225 (71.4%)
- Heart failure 45 (14.3%)
- Myocardial infarction 26 (8.3%)
- Atrial fibrillation 21 (6.7%)
- Coronary disease 14 (4.4%)
- Valvulopathy 3 (0.9%)
- Endocrine-metabolic disease, n (%) 169 (53.7%)
- Diabetes 108 (34.3%)
- Dyslipidemia 56 (17.8%)
- Hypothyroidism 52 (16.5%)
- Kidney disease, n (%) 24 (7.6%)
- Stroke 3 (0.9%)
- Cirrhosis, chronic liver failure 4 (1.3%)
- Rheumatic disease, n (%) 77 (24.4%)
- Osteoarthritis 12 (3.8%)

COPD = Chronic Obstructive Pulmonary Disease.

Tables 3 and 4). No significant multicollinearity (VIF) was found in all the association analyses done (Tables 3 and 4).

Frailty as a potential explanatory factor

We examined whether frailty was independently associated with both markers of geriatric syndromes (model 2 in Tables 3 and 4). Multiple regression analyses adjusted for confounders showed that frailty according to the FRAIL-BR (Table 3) as well as the FI (Table 4) was associated with the number of geriatric syndromes (model 2). In order to examine whether frailty was an explanatory factor of the association between depression and geriatric syndromes, frailty was added to the different (fully adjusted) regression models (model 3 in Tables 3 and 4). Adding the FRAIL-BR scale to any linear regression models shown in Table 3, the association between depression (DSM-5 criteria as well as according to the PHQ-9) with the number of geriatric syndromes...
Table 3. Linear regression analyses adjusted for confounders\(^4\) with geriatric syndromes as dependent variable and the FRAIL as explanatory factor.

<table>
<thead>
<tr>
<th>Number of Geriatric Syndromes</th>
<th>B(SE)</th>
<th>beta</th>
<th>VIF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subthreshold depression</td>
<td>0.424 (0.127)</td>
<td>0.174</td>
<td>1.170</td>
<td>0.001*</td>
</tr>
<tr>
<td>Major depression</td>
<td>0.654 (0.141)</td>
<td>0.237</td>
<td>1.170</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty (FRAIL-BR)</td>
<td>0.342 (0.031)</td>
<td>0.497</td>
<td>1.186</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subthreshold depression</td>
<td>−0.032 (0.122)</td>
<td>−0.013</td>
<td>1.395</td>
<td>0.793</td>
</tr>
<tr>
<td>Major depression</td>
<td>−0.038 (0.145)</td>
<td>−0.014</td>
<td>1.588</td>
<td>0.794</td>
</tr>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of depressive symptoms (PHQ-9)</td>
<td>0.046 (0.008)</td>
<td>0.262</td>
<td>1.054</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty (FRAIL-BR)</td>
<td>0.342 (0.031)</td>
<td>0.497</td>
<td>1.186</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.001 (0.009)</td>
<td>0.005</td>
<td>1.519</td>
<td>0.927</td>
</tr>
<tr>
<td>Frailty (FRAIL-BR)</td>
<td>0.340 (0.038)</td>
<td>0.494</td>
<td>1.708</td>
<td>&lt; 0.001**</td>
</tr>
</tbody>
</table>

VIF = variance inflation factor.

---

Table 4. Linear regression analyses adjusted for confounders\(^5\) with geriatric syndromes as dependent variable and the frailty index (30 items) as explanatory factor.

<table>
<thead>
<tr>
<th>Number of Geriatric Syndromes</th>
<th>B(SE)</th>
<th>beta</th>
<th>VIF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subthreshold depression</td>
<td>0.424 (0.127)</td>
<td>0.174</td>
<td>1.170</td>
<td>0.001*</td>
</tr>
<tr>
<td>Major depression</td>
<td>0.654 (0.141)</td>
<td>0.237</td>
<td>1.170</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty (FRAIL Index)</td>
<td>5.533 (0.774)</td>
<td>0.430</td>
<td>1.737</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subthreshold depression</td>
<td>0.343 (0.120)</td>
<td>0.139</td>
<td>1.184</td>
<td>0.005*</td>
</tr>
<tr>
<td>Major depression</td>
<td>0.432 (0.138)</td>
<td>0.157</td>
<td>1.255</td>
<td>0.002*</td>
</tr>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of depressive symptoms (PHQ-9)</td>
<td>0.046 (0.008)</td>
<td>0.262</td>
<td>1.054</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty (FRAIL Index)</td>
<td>5.533 (0.774)</td>
<td>0.430</td>
<td>1.737</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Model 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.031 (0.008)</td>
<td>0.178</td>
<td>1.159</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>Frailty (FRAIL Index)</td>
<td>4.651 (0.795)</td>
<td>0.361</td>
<td>1.909</td>
<td>&lt; 0.001**</td>
</tr>
</tbody>
</table>

VIF = variance inflation factor.

---

was reduced to a non-significant value (Table 3). When combining frailty (Frailty Index) and depression in the linear regression model, the association between depression (subthreshold depression, major depression and depressive symptoms) and other geriatric syndromes was reduced by 17.6%, 33.4% and 30.7%, respectively. Thus, frailty could explain a substantial part of the association between these variables (Table 4). Moreover, the strength of frailty association with geriatric syndromes did not change when frailty was combined to depression.

**Discussion**

According to our results, depressive disorders as well as depressive symptom severity were significantly
associated with the number of geriatric syndromes in a geriatric outpatient sample. Frailty was also significantly associated with other geriatric syndromes. This association remained significant even after adjustment for relevant confounders. Nonetheless, frailty consisted in a possible explanatory variable in these associations since both frailty models interfered with the strength of the association between depression and other geriatric syndromes.

Our findings showed a substantial association with similar power between depression based on DSM-5 criteria as well as according to the PHQ-9 scale and geriatric syndromes in older adults. Geriatric syndromes are an essential part of geriatric rational in clinical practice. A systematic review and meta-analysis about the relation between depression and multimorbidity showed that longitudinal studies have been based on depressive symptoms scales, and only few studies have assessed depression using formal diagnostic criteria (Read, Sharpe, Modini, & Dear, 2017). In this meta-analysis, the relationship between depressive disorder and the number of chronic clinical conditions appears to be more robust than the correlation found between multimorbidity and depressive symptoms (Read et al., 2017). The main empirical justification for this finding is that self-report measures are more likely to be affected by shared-method variance due to overlap of between symptoms of depression and somatic (clinical) diseases (Collard et al., 2015). However, no previous study has addressed geriatric syndromes instead of multimorbidity.

Our results also reported that frailty was not only associated with the number of other geriatric syndromes, it also appears to explain the association between depression and geriatric syndromes. The relationship between late life depression, frailty and other geriatric syndromes might be complex (Chu et al., 2019; Soysal et al., 2017). Geriatric syndromes have by definition a multifactorial origin. Since depression and frailty are associated with aging-related physiological disturbances, especially low-grade inflammation and hormonal dysregulation (Brown et al., 2016), these pathophysiological mechanisms may contribute to the origin of more specific geriatric syndromes. Moreover, the behavioral consequences of either depression (reduced appetite, loss of physical activity) or frailty (reduced mobility) may further culminate in the emergence of other geriatric syndromes. Reciprocal associations between depression and frailty at the population level may lead to a vicious circle of functional impairment (Lohman et al., 2017), and may reinforce each other increasing incident rates of morbidity, including the onset of geriatric syndromes (Prina et al., 2013). Moreover, depressive symptoms discourage engagement in healthy behavior as well as medical and self-care aimed for successful aging, which could reinforce the progression of this process and rise of geriatric syndromes and functional disability (Alexopoulos, 2019). We assume that frailty might be a potential mediator in the relationship between depression and geriatric syndromes since both depression and frailty were combined in regression analysis and frailty associations with geriatric syndromes did not change.

A strength of the present study is that frailty has been measured according to two different, but widely used frailty instruments (Sternberg, Wershof Schwartz, Karunananthan, Bergman, & Mark Clarfield, 2011). Both were highly correlated with other geriatric syndromes. Since both instruments revealed comparable results, this adds credibility to our findings. However, the two instruments showed different effects between the association of depression and geriatric syndromes. The strength of this effect was stronger and significant for the FI. The continuous nature of the FI may be more sensitive and a better predictor of the adverse outcomes related to frailty (Kojima et al., 2018). This could explain why we observed a loss of a significant association between depression and geriatric syndromes when the FRAIL-BR was added. Nonetheless, in our study we adjusted our regression models for multimorbidity in order to reduce collinearity, which is in line with previous studies on the association between the FI and multimorbidity (Canevelli et al., 2020). On the other hand, the FRAIL-BR is mainly based on the physical phenotype model of frailty (Morley et al., 2013) and sarcopenia could be directly associated to almost half of the geriatric syndromes considered in our study (namely falls, mobility problems and dizziness) (Marques & Queirós, 2018). Conversely, the multidimensional FI could be associated to most of the syndromes or to the effect on the sum of them.
The present study has some strengths to be highlighted. First, it was performed in a general geriatric sample warranting the assessment of frailty and fundamental issues in geriatrics. Second, geriatric syndromes were added as an outcome variable, which is uncommon in studies involving late life depression. Third, by assessing depressive disorder by a semi-structured diagnostic interview confounding due to overlapping criteria between depression and frailty is minimized, whereas results are still comparable to previous studies by including also a self-report scale. Fourth, we were careful about potential overlap of constructs and formally tested for multicollinearity, which yielded non-significant findings.

Some limitations should also be mentioned. First, frailty and other geriatric syndromes are age-related and possibly highly correlated by the fact that frailty can be a final pathway for several geriatric syndromes (Walston, Buta, & Xue, 2018). Despite this inevitable overlap, it is important to keep the distinction between them. In this study, care was taken to avoid overlapping geriatric syndromes in the used definitions of frailty. Yet, to enhance the external validation and generalizability, we have explicitly mentioned all chronic diseases that have been taken into account individually. Secondly, in the present study, we adjusted for multimorbidity defined as the presence of two or more disease or disease clusters (as specified in the methods). A simple count of disease does not adjust for severity of diseases, which is a clear limitation of our analyses. Indices of morbidity burden using differential weights for specific diseases and condition might have overcome this problem (de Groot, Beckerman, Lankhorst, & Bouter, 2003). Nonetheless, as morbidity indices are generally developed and validated for specific outcome (e.g. mortality) and include aspects of geriatric syndromes, these indices would potentially have confounded our results. Finally, our study has a cross-sectional design, which does not allow causal interpretation for our findings. Nonetheless, justified, these hypotheses are hardly tested thus far and need a long follow-up in order to detect the onset of geriatric syndromes and to perform well-powered analyses.

Conclusions

Although cross-sectional, our findings provide greater understanding and original contribution on the relationship between depression, frailty and other geriatric syndromes in later life. Among depressed patients, frailty may be hypothesized as a causal pathway toward a rise of geriatric syndrome and other adverse health outcomes associated with depression. However, whether frailty could be a consequence of severe depression or an independent process of biological accelerated aging remains to be elucidated. Future longitudinal studies should explore the causality of this association.

Clinical implications

- Frailty should be treated or prevented in order to minimize the impact of other geriatric syndromes among depressed older adults.
- Screening for frailty would be of utmost importance in mental health care, as frailty is neglected especially in this field.
- Integrated care models are crucial for clinical practice in mental illness care.

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Disclosure statement

The authors declare no conflict of interest.

Role of the funder

The funder of this research did not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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