University of Groningen

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

Borges, Marcus Kiiti; Oude Voshaar, Richard C; Romanini, Carla Fernanda de Vasconcellos; Oliveira, Fabiana Maria; Lima, Natália Almeida; Petrella, Marina; Costa, Daniele Lima; Martinelli, José Eduardo; Mingardi, Silvana Vieira Bandeira; Siqueira, Alaise

Published in:
Clinical gerontologist

DOI:
[10.1080/07317115.2020.1836106](https://doi.org/10.1080/07317115.2020.1836106)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Borges, M. K., Oude Voshaar, R. C., Romanini, C. F. D. V., Oliveira, F. M., Lima, N. A., Petrella, M., Costa, D. L., Martinelli, J. E., Mingardi, S. V. B., Siqueira, A., Biela, M., Collard, R., & Aprahamian, I. (2021). Could Frailty be an Explanatory Factor of the Association between Depression and Other Geriatric Syndromes in Later Life? *Clinical gerontologist*, 44(2), 143–153 . <https://doi.org/10.1080/07317115.2020.1836106>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

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

Marcus Kiiti Borges, Richard C. Oude Voshaar, Carla Fernanda de Vasconcellos Romanini, Fabiana Maria Oliveira, Natália Almeida Lima, Marina Petrella, Daniele Lima Costa, José Eduardo Martinelli, Silvana Vieira Bandeira Mingardi, Alaise Siqueira, Marina Biela, Rose Collard & Ivan Aprahamian

To cite this article: Marcus Kiiti Borges, Richard C. Oude Voshaar, Carla Fernanda de Vasconcellos Romanini, Fabiana Maria Oliveira, Natália Almeida Lima, Marina Petrella, Daniele Lima Costa, José Eduardo Martinelli, Silvana Vieira Bandeira Mingardi, Alaise Siqueira, Marina Biela, Rose Collard & Ivan Aprahamian (2021) Could Frailty be an Explanatory Factor of the Association between Depression and Other Geriatric Syndromes in Later Life?, *Clinical Gerontologist*, 44:2, 143-153, DOI: [10.1080/07317115.2020.1836106](https://doi.org/10.1080/07317115.2020.1836106)

To link to this article: <https://doi.org/10.1080/07317115.2020.1836106>

Published online: 25 Oct 2020.

Submit your article to this journal [↗](#)

Article views: 201

View related articles [↗](#)

View Crossmark data [↗](#)

Citing articles: 2 View citing articles [↗](#)

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

Marcus Kiiti Borges MSc^a, Richard C. Oude Voshaar PhD^b, Carla Fernanda de Vasconcellos Romanini MSc^c, Fabiana Maria Oliveira BSc^c, Natália Almeida Lima BSc^c, Marina Petrella PhD^c, Daniele Lima Costa MD^c, José Eduardo Martinelli PhD^c, Silvana Vieira Bandeira Mingardi BSc^a, Alaise Siqueira BSc^a, Marina Biela MD^a, Rose Collard PhD^d, and Ivan Aprahamian MSc, PhD^{a,b,c}

^aDepartment and Institute of Psychiatry, Faculty of Medicine, University of São Paulo, São Paulo, Brazil; ^bDepartment of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; ^cGeriatrics Division, Internal Medicine Department, Faculty of Medicine of Jundiaí, Group of Investigation on Multimorbidity and Mental Health in Aging (GIMMA), Jundiaí, Brazil; ^dDepartment of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands

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-FRIL) 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 FRIL 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.

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, Milaneschi, 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, multi-disciplinary 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 R^2 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 Jundiaí) 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 (Arahamian 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 $\geq 5\%$ 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 socio-demographic, 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

Figure 1. Flowchart of the study.

Table 1. Clinical characteristics of the sample (n = 315).

Characteristics	Values	
<i>Socio-demographics:</i>		
● Age (years)	Mean (SD)	72.1 (8.4)
● Female sex	n (%)	215 (68.3%)
● Education (years)	Mean (SD)	5.0 (4.0)
● Living alone	n (%)	45 (14.3%)
<i>Lifestyle characteristics:</i>		
● Smoking (yes)	n (%)	13 (4.1%)
● Alcohol use (yes)	n (%)	16 (5.1%)
● Rigorous physical activity	n (%)	89 (28.3%)
● Body mass index (kg/m ²)	Mean (SD)	28.4 (5.8)
● Polypharmacy	n (%)	161 (51.1%)
● Multimorbidity	n (%)	199 (63.2%)
<i>Psychopathology:</i>		
● Depression severity (PHQ-9)	Mean (SD)	6.2 (6.3)
● Depressive disorder:		
• Subthreshold depression	n (%)	86 (27.3%)
• Major depression	n (%)	63 (20.0%)
<i>Burden of disease:</i>		
● Clusters of clinical diseases (number)	Mean (SD)	1.8 (1.0)
● Geriatric syndromes (number)	Mean (SD)	0.9 (0.1)
<i>Frailty:</i>		
● FRAIL-BR	Mean (SD)	1.7 (1.6)
● Frailty index	Mean (SD)	0.15 (0.08)

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

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

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

Number of Disease Clusters n (%)	Geriatric Syndromes n (%)	
0	32 (10.2%)	145 (46.1%)
1	84 (26.6%)	91 (28.9%)
2	130 (41.3%)	47 (14.9%)
3	57 (18.1%)	22 (7.0%)
4	11 (3.5%)	8 (2.5%)
5	1 (0.3%)	2 (0.6%)
Disease clusters:		
<i>Cardiovascular disease, n (%)</i>		
• Hypertension	241 (76.5%)	
• Heart failure	225 (71.4%)	
• Myocardial infarction	45 (14.3%)	
• Atrial fibrillation	26 (8.3%)	
• Coronary disease	21 (6.7%)	
• Valvulopathy	14 (4.4%)	
• Cerebrovascular disease, n (%)	3 (0.9%)	
• Stroke	28 (8.9%)	
<i>Endocrino-metabolic disease, n (%)</i>		
• diabetes	169 (53.7%)	
• dyslipidemia	108 (34.3%)	
• hypothyroidism	56 (17.8%)	
• Kidney disease, n (%)	52 (16.5%)	
• chronic kidney failure	24 (7.6%)	
<i>Lung disease, n (%)</i>		
• Asthma	22 (7.0%)	
• COPD	10 (3.2%)	
<i>Liver disease, n (%)</i>		
• cirrhosis, chronic liver failure	12 (3.8%)	
<i>Rheumatic disease, n (%)</i>		
• osteoarthritis	3 (0.9%)	
	77 (24.4%)	

COPD = Chronic Obstructive Pulmonary Disease.

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[¶] with geriatric syndromes as dependent variable and the FRAIL as explanatory factor.

	Number of Geriatric Syndromes			
	B(SE)	beta	VIF	p-value
[†] Model 1:				
• Subthreshold depression	0.424 (0.127)	0.174	1.170	0.001*
• Major depression	0.654 (0.141)	0.237	1.170	< 0.001**
[‡] Model 2:				
• Frailty (FRAIL-BR)	0.342 (0.031)	0.497	1.186	< 0.001**
[§] Model 3:				
• Subthreshold depression	-0.032 (0.122)	-0.013	1.395	0.793
• Major depression	-0.038 (0.145)	-0.014	1.588	0.794
• Frailty (FRAIL-BR)	0.349 (0.038)	0.506	1.695	< 0.001**
[†] Model 1:				
• Severity of depressive symptoms (PHQ-9)	0.046 (0.008)	0.262	1.054	< 0.001**
[‡] Model 2:				
• Frailty (FRAIL-BR)	0.342 (0.031)	0.497	1.186	< 0.001**
[§] Model 3:				
• Depressive symptoms	0.001 (0.009)	0.005	1.519	0.927
• Frailty (FRAIL-BR)	0.340 (0.038)	0.494	1.708	< 0.001**

VIF = variance inflation factor.

[†]Model 1: Depression as independent variable and the number of geriatric syndromes as the dependent variable, adjusted for covariates.

[‡]Model 2: Frailty as independent variable and the number of geriatric syndromes as the dependent variable, adjusted for covariates.

[§]Model 3: Depression as well as frailty as simultaneously included in one model as independent variables with the number of geriatric syndromes as the dependent variable, adjusted for covariates.

[¶]Adjusted for age, sex, level of education (years), living alone, BMI, physical activity, alcohol, smoking, polypharmacy and multimorbidity.

* $p < 0.05$; ** $p < 0.001$

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

	Number of Geriatric Syndromes			
	B(SE)	beta	VIF	p-value
[†] Model 1:				
• Subthreshold depression	0.424 (0.127)	0.174	1.170	0.001*
• Major depression	0.654 (0.141)	0.237	1.170	< 0.001**
[‡] Model 2:				
• Frailty (Frailty Index)	5.533 (0.774)	0.430	1.737	< 0.001**
[§] Model 3:				
• Subthreshold depression	0.343 (0.120)	0.139	1.184	0.005*
• Major depression	0.432 (0.138)	0.157	1.255	0.002*
• Frailty (Frailty Index)	4.850 (0.787)	0.377	1.866	< 0.001**
[†] Model 1:				
• Severity of depressive symptoms (PHQ-9)	0.046 (0.008)	0.262	1.054	< 0.001**
[‡] Model 2:				
• Frailty (Frailty Index)	5.533 (0.774)	0.430	1.737	< 0.001**
[§] Model 3:				
• Depressive symptoms	0.031 (0.008)	0.178	1.159	< 0.001**
• Frailty (Frailty Index)	4.651 (0.795)	0.361	1.909	< 0.001**

VIF = variance inflation factor.

[†]Model 1: Depression as independent variable and the number of geriatric syndromes as the dependent variable, adjusted for covariates.

[‡]Model 2: Frailty as independent variable and the number of geriatric syndromes as the dependent variable, adjusted for covariates.

[§]Model 3: Depression as well as frailty as simultaneously included in one model as independent variables with the number of geriatric syndromes as the dependent variable, adjusted for covariates.

[¶]Adjusted for age, sex, level of education (years), living alone, BMI, physical activity, alcohol, smoking, polypharmacy and multimorbidity.

* $p < 0.05$; ** $p < 0.001$

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, Karunanathan, 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 maybe 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.

Acknowledgments

Prof Aprahamian received a national public grant level two from the National Council for Scientific and Technological Development (Ministry of Science, Technology, Innovation and Communications, Brazil).

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.

Funding

This study was financed in part by the “Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (Capes)” – Finance Code 001.

ORCID

Marcus Kiiti Borges MSc <http://orcid.org/0000-0001-8441-9519>

Richard C. Oude Voshaar PhD <http://orcid.org/0000-0003-1501-4774>

Marina Petrella PhD <http://orcid.org/0000-0003-1769-9113>

Ivan Aprahamian MSc, PhD <http://orcid.org/0000-0003-2399-8208>

References

- Alexopoulos, G. S. (2019). Mechanisms and treatment of late-life depression. *Translational Psychiatry*, 9(1), 188. doi:10.1038/s41398-019-0514-6
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). Washington, DC: American Psychiatric Publishing.
- Aprahamian, I., Lin, S. M., Suemoto, C. K., Apolinario, D., Oiring de Castro Cezar, N., Elmadjian, S. M., ... Yassuda, M. S. (2017). Feasibility and factor structure of the FRAIL scale in older adults. *Journal of the American Medical Directors Association*, 18(4), 367.e11–367.e18. doi:10.1016/j.jamda.2016.12.067
- Atlantis, E., Shi, Z., Penninx, B. J., Wittert, G. A., Taylor, A., & Almeida, O. P. (2012). Chronic medical conditions mediate the association between depression and cardiovascular disease mortality. *Social Psychiatry and Psychiatric Epidemiology*, 47(4), 615–625. doi:10.1007/s00127-011-0365-9
- Boult, C., Green, A. F., Boult, L. B., Pacala, J. T., Snyder, C., & Leff, B. (2009). Successful models of comprehensive care for older adults with chronic conditions: Evidence for the institute of medicine's "retooling for an aging America" report. *Journal of the American Geriatrics Society*, 57(12), 2328–2337. doi:10.1111/j.1532-5415.2009.02571.x
- Brandão, D. J., Fontenelle, L. F., da Silva, S. A., Menezes, P. R., & Pastor-Valero, M. (2019). Depression and excess mortality in the elderly living in low- and middle-income countries: Systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, 34(1), 22–30. doi:10.1002/gps.5008
- Briggs, A. M., & Araujo de Carvalho, I. (2018). Actions required to implement integrated care for older people in the community using the World Health Organization's ICOPE approach: A global Delphi consensus study. *PLoS One*, 13(10), e0205533. doi:10.1371/journal.pone.0205533
- Brown, P. J., Rutherford, B. R., Yaffe, K., Tandler, J. M., Ray, J. L., Pott, E., ... Roose, S. P. (2016). The depressed Frail phenotype: The clinical manifestation of increased biological aging. *The American Journal of Geriatric Psychiatry*, 24(11), 1084–1094. doi:10.1016/j.jagp.2016.06.005
- Canevelli, M., Raganato, R., Remiddi, F., Quarata, F., Valletta, M., Bruno, G., & Cesari, M. (2020). Counting deficits or diseases? The agreement between frailty and multimorbidity in subjects with cognitive disturbances. *Aging Clinical and Experimental Research*, 32(1), 179–182. doi:10.1007/s40520-019-01161-2
- Chu, W., Chang, S. F., Ho, H. Y., & Lin, H. C. (2019). The relationship between depression and frailty in community-dwelling older people: A systematic review and meta-analysis of 84,351 older adults. *Journal of Nursing Scholarship*, 51(5), 547–559. doi:10.1111/jnu.12501
- Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *Lancet*, 381(9868), 752–762. doi:10.1016/S0140-6736(12)62167-9
- Collard, R. M., Arts, M., Comijs, H. C., Naarding, P., Verhaak, P. F., de Waal, M. W., & Oude Voshaar, R. C. (2015). The role of frailty in the association between depression and somatic comorbidity: Results from baseline data of an ongoing prospective cohort study. *International Journal of Nursing Studies*, 52(1), 188–196. doi:10.1016/j.ijnurstu.2014.07.007
- Collard, R. M., Boter, H., Schoevers, R. A., & Oude Voshaar, R. C. (2012). Prevalence of frailty in community-dwelling older persons: A systematic review. *Journal of the American Geriatrics Society*, 60(8), 1487–1492. doi:10.1111/j.1532-5415.2012.04054.x
- Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., & Penninx, B. W. (2013). Differential mortality rates in major and subthreshold depression: Meta-analysis of studies that measured both. *The British Journal of Psychiatry: The Journal of Mental Science*, 202(1), 22–27. doi:10.1192/bjp.bp.112.112169
- Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., & Penninx, B. W. (2014). Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *American Journal of Psychiatry*, 171(4), 453–462. doi:10.1176/appi.ajp.2013.13030325
- de Groot, V., Beckerman, H., Lankhorst, G. J., & Bouter, L. M. (2003). How to measure comorbidity. a critical review of available methods. *Journal of Clinical Epidemiology*, 56(3), 221–229. doi:10.1016/s0895-4356(02)00585-1
- Faller, J. W., Pereira, D., de Souza, S., Nampo, F. K., Orlandi, F. S., & Matumoto, S. (2019). Instruments for the detection of frailty syndrome in older adults: A systematic review. *PLoS One*, 14(4), e0216166. doi:10.1371/journal.pone.0216166
- First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2016). *Structured clinical interview for DSM-5 disorders, clinician version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association.
- Flacker, J. M. (2003). What is a geriatric syndrome anyway? *Journal of the American Geriatrics Society*, 51(4), 574–576. doi:10.1046/j.1532-5415.2003.51174.x
- Hoogendijk, E. O., Afilalo, J., Ensrud, K. E., Kowal, P., Onder, G., & Fried, L. P. (2019). Frailty: Implications for clinical practice and public health. *Lancet*, 394(10206), 1365–1375. doi:10.1016/S0140-6736(19)31786-6

- Inouye, S. K., Studenski, S., Tinetti, M. E., & Kuchel, G. A. (2007). Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *Journal of the American Geriatrics Society*, 55(5), 780–791. doi:10.1111/j.1532-5415.2007.01156.x
- Kojima, G., Iliffe, S., & Walters, K. (2018). Frailty index as a predictor of mortality: A systematic review and meta-analysis. *Age and Ageing*, 47(2), 193–200. doi:10.1093/ageing/afx162
- Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, 16(9), 606–613. doi:10.1046/j.1525-1497.2001.016009606.x
- Levis, B., Benedetti, A., & Thombs, B. D.; DEPRESSion Screening Data (DEPRESSD) Collaboration. (2019). Accuracy of patient health questionnaire-9 (PHQ-9) for screening to detect major depression: Individual participant data meta-analysis. *BMJ*, 365, 11476. doi:10.1136/bmj.11476
- Liang, Y., Rausch, C., Laflamme, L., & Möller, J. (2018). Prevalence, trend and contributing factors of geriatric syndromes among older Swedes: Results from the Stockholm county council public health surveys. *BMC Geriatrics*, 18(1), 322. doi:10.1186/s12877-018-1018-6
- Lohman, M. C., Mezuk, B., & Dumenci, L. (2017). Depression and frailty: Concurrent risks for adverse health outcomes. *Aging & Mental Health*, 21(4), 399–408. doi:10.1080/13607863.2015.1102199
- Luppa, M., Sikorski, C., Luck, T., Ehreke, L., Konnopka, A., Wiese, B., ... Riedel-Heller, S. G. (2012). Age- and gender-specific prevalence of depression in latest-life—systematic review and meta-analysis. *Journal of Affective Disorders*, 136(3), 212–221. doi:10.1016/j.jad.2010.11.033
- Marques, A., & Queirós, C. (2018). Frailty, sarcopenia and falls. In Hertz, K., & Sainty-Tomlinson, J. (Eds.). *Fragility fracture nursing: Holistic care and management of the orthogeriatric patient* (pp. 15–26). Chan, Switzerland: Springer International Publishing.
- Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., ... Walston, J. (2013). Frailty consensus: A call to action. *Journal of the American Medical Directors Association*, 14(6), 392–397. doi:10.1016/j.jamda.2013.03.022
- Nunes, B. P., Flores, T. R., Mielke, G. I., Thumé, E., & Facchini, L. A. (2016). Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Archives of Gerontology and Geriatrics*, 67, 130–138. doi:10.1016/j.archger.2016.07.008
- Penninx, B. W., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. *BMC Medicine*, 11, 129. doi:10.1186/1741-7015-11-129
- Prina, A. M., Huisman, M., Yeap, B. B., Hankey, G. J., Flicker, L., Brayne, C., & Almeida, O. P. (2013). Association between depression and hospital outcomes among older men. *CMAJ: Canadian Medical Association Journal = Journal De l'Association Médicale Canadienne*, 185(2), 117–123. doi:10.1503/cmaj.121171
- Read, J. R., Sharpe, L., Modini, M., & Dear, B. F. (2017). Multimorbidity and depression: A systematic review and meta-analysis. *Journal of Affective Disorders*, 221, 36–46. doi:10.1016/j.jad.2017.06.009
- Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 722–727. doi:10.1093/gerona/62.7.722
- Salive, M. E. (2013). Multimorbidity in older adults. *Epidemiologic Reviews*, 35(1), 75–83. doi:10.1093/epirev/mxs009
- Sánchez, E., Vidán, M. T., Serra, J. A., Fernández-Avilés, F., & Bueno, H. (2011). Prevalence of geriatric syndromes and impact on clinical and functional outcomes in older patients with acute cardiac diseases. *Heart*, 97(19), 1602–1606. doi:10.1136/hrt.2011.227504
- Santos, I. S., Tavares, B. F., Munhoz, T. N., Almeida, L. S., Silva, N. T., Tams, B. D., ... Matijasevich, A. (2013). Sensibilidade e especificidade do Patient Health Questionnaire-9 (PHQ-9) entre adultos da população geral [Sensitivity and specificity of the patient health questionnaire-9 (PHQ-9) among adults from the general population]. *Cadernos De Saude Publica*, 29(8), 1533–1543. doi:10.1590/0102-311x00144612
- Soysal, P., Veronese, N., Thompson, T., Kahl, K. G., Fernandes, B. S., Prina, A. M., ... Stubbs, B. (2017). Relationship between depression and frailty in older adults: A systematic review and meta-analysis. *Ageing Research Reviews*, 36, 78–87. doi:10.1016/j.arr.2017.03.005
- Sternberg, S. A., Wershof Schwartz, A., Karunanathan, S., Bergman, H., & Mark Clarfield, A. (2011). The identification of frailty: A systematic literature review. *Journal of the American Geriatrics Society*, 59(11), 2129–2138. doi:10.1111/j.1532-5415.2011.03597.x
- Vetrano, D. L., Palmer, K., Marengoni, A., Marzetti, E., Lattanzio, F., Roller-Wirnsberger, R., ... Onder, G.; Joint Action ADVANTAGE WP4 Group. (2019). Frailty and multimorbidity: A systematic review and meta-analysis. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 74(5), 659–666.
- Walston, J., Buta, B., & Xue, Q. L. (2018). Frailty screening and interventions: Considerations for clinical practice. *Clinics in Geriatric Medicine*, 34(1), 25–38. doi:10.1016/j.cger.2017.09.004
- World Health Organization. (2019). *Integrated care for older people (ICOPE): Guidance for person-centred assessment and pathways for primary care*. Retrieved from <https://apps.who.int/iris/handle/10665/326843>