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Published in:
AGING & MENTAL HEALTH

DOI:
10.1080/13607863.2020.1857689

Publication date:
2021

Routledge
Taylor & Francis Group

Aging & Mental Health

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/camh20

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To cite this article: Marcus K. Borges, Ivan Aprahamian, Carla V. Romanini, Fabiana M. Oliveira, Silvana V. B. Mingardi, Natália A. Lima, Juliana F. Cecato, Marina Petrella & Richard C. Oude Voshaar (2021) Depression as a determinant of frailty in late life, Aging & Mental Health, 25:12, 2279-2285, DOI: 10.1080/13607863.2020.1857689

To link to this article: https://doi.org/10.1080/13607863.2020.1857689

AGING & MENTAL HEALTH
2021, VOL. 25, NO. 12, 2279–2285
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Depression as a determinant of frailty in late life

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ABSTRACT

Objectives: Accumulating evidence shows depression as a risk factor for frailty, but studies are mainly population-based and widely differ in their assessment of either depression or frailty. We investigated the association between depression and frailty among geriatric outpatients using different assessment instruments for both conditions.

Method: Among 315 geriatric outpatients (mean age 72.1 years, 68.3% female sex) participating the MiMiCS-FRAIL cohort study, major and subthreshold depression were measured with psychiatric diagnostic interview according to DSM-5 criteria (SCID-5) as well as with instruments to screen and measure severity of depressive symptoms (GDS-15 and PHQ-9). Frailty was assessed according to a screening instrument (FRAIL-BR) and a multidimensional Frailty Index (FI-36 items). Multiple logistic and linear regression were performed to assess the association between depression (independent variable) and frailty (dependent variable) adjusted for confounders.

Results: Frailty prevalence in patients with no, subthreshold or major depressive disorder increases from either 14.5%, 46.5% to 65.1% when using the FRAIL-BR questionnaire, and from 10.2%, 20.9%, to 30.2% when using the FI-36 index. These association remain nearly the same when adjusted for covariates. Both the FRAIL-BR and the FI-36 were strongly associated with major depressive disorder, subthreshold depression, and depressive symptoms by PHQ-9 and GDS-15.

Conclusion: Late life depression and frailty are associated in a dose-dependent manner, irrespective of the used definitions. Nonetheless, to avoid residual confounding, future research on underlying biological mechanisms should preferably be based on formal psychiatric diagnoses and objectively assessment frailty status.

ARTICLE HISTORY
Received 23 May 2020
Accepted 22 November 2020

KEYWORDS
Elderly; depression; frailty; prognosis; cohort

Introduction

Depression and frailty, two geriatric giants, often co-occur in later life. Available prospective studies point to a bidirectional association between these conditions (Nascimento & Batistoni, 2019). Since late-life depression as well as frailty are associated with a variety of adverse health outcomes (Mezuk, Edwards, Lohman, Choi, & Lapane, 2012), this bidirectional association between depression and frailty may lead to a vicious cycle with detrimental consequences for the older persons. Better understanding is warranted, especially in geriatric outpatients who are potentially more frail and more depressed compared to the general population (Satake et al., 2017).

About 7.2% of older persons suffer from a depressive disorder and even 17.1% from clinically significant depressive symptoms (CSDS) (Luppa et al., 2012). Whereas late-life depression increases the risk on adverse health effects including excess mortality (Penninx, Milaneschi, Lamers, & Vogelzangs, 2013; Van den Berg et al., 2019), underlying mechanisms are not elucidated yet. Hypothesized mechanisms include both, an unhealthy lifestyle as well as depression-related physiological abnormalities including immuno-metabolic, autonomic, and endocrine dysregulation (Penninx et al., 2013). These mechanisms are assumed to be also involved in the pathogenesis of frailty. Frailty is a dynamic, clinical condition of increased vulnerability and loss of resistance to stressors, which can be explained by a reduced reserve in several inter-related physiological systems (Fried et al., 2001). Similar to depression, this condition may lead to adverse health outcomes, such as falls, disability, lower quality of life, hospitalization, institutionalization and death (Kojima, Iliffe, & Walters, 2018). Whereas approximately one in ten adults aged 65 and over can be classified as frail, about 3 through 4 in 10 depressed older adults are frail (Collard, Boter, Schoevers, & Oude Voshaar, 2012; Soysal et al., 2017). A spurious association, however, cannot be excluded because both constructs have overlapping criteria (Buigues et al., 2015; Mezuk et al., 2012; Soysal et al., 2017; Vaughan, Corbin, & Goveas, 2015).

In spite of many population-based studies, the association between depression and frailty has hardly been studied in clinical samples (Soysal et al., 2017). A recent meta-analysis identified only five studies in clinical samples (Soysal et al., 2017). Four out of these five studies were cross-sectional analyses in either psychiatric outpatients (Arts et al., 2016; Collard, Comijs, Naarding, & Oude Voshaar, 2014), renal transplant patients (McAdams-DeMarco et al., 2017), and geriatric inpatients (Dent & Hoogendijk, 2014). The only prospective study in clinical patients, showed that among 33,324 non-frail woman aged 65–79 participating in the Women's Health Initiative-

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Observational Study (WHI-OS), the use of antidepressants as well as depressive symptoms at baseline had an increased odds of frailty according to the Fried Frailty Phenotype at three-year follow-up (Lakey et al., 2012). Nonetheless, participants in the WHI-OS were probably classified as 'clinical patients' based on the specific recruitment sites of the WHI-OS and not on the presence of a specific disease or condition. Furthermore, the presence of depression was based on a screening instrument and not a formal diagnostic interview.

Interpretation of the association between depression and frailty is hampered by two problems. First, most studies only assessed self-report depressive symptoms instead of depressive disorders according to formal diagnostic criteria (Nascimento & Batistoni, 2019). Symptoms due to comorbid somatic conditions may be picked up by self-report depression questionnaires as being a symptom of depression (Koenig, George, Peterson, & Pieper, 1997; Thombs et al., 2010), therefore, symptoms or signs due to frailty might inflate a self-report depressive symptom score in the absence of clinical depression. Secondly, the assessment of frailty widely differs between studies, although most studies assessed frailty according to frailty phenotype (Soysal et al., 2017). The five criteria of the Frailty Phenotype might be confounded by the presence of depression, i.e. feelings of exhaustion might be mixed up with depressed feelings by patients and performance tests assessing muscle strength and walking speed might be affected by motivational problems due to depression. To our knowledge, no studies on the association between depression and frailty have assessed frailty according to the widely used Frailty Index (FI) based on the deficit accumulation model (Chu, Chang, Ho, & Lin, 2019; Soysal et al., 2017). The FI may be less confounded by depression as at least 30 age-related health deficits are included. Moreover, the FI has a higher predictive ability of adverse events than other frailty measurements in both hospital and community settings (Dent & Hoogendijk, 2014).

Since geriatric outpatient clinics are generally devoted to maintaining well-being and the ability to manage one-self, targeting depression and frailty are key priorities to reduce their actual disease burden and adverse health outcomes. Understanding the dynamics of these geriatric syndromes is of utmost importance. Therefore, the objectives of the present study were to examine the association between depression and frailty in a geriatric outpatient sample using different assessment instruments for both conditions.

Methods

Study design, participants and procedure

The present study is based on the baseline data of the first 315 patients included in the Multimorbidity and Mental health Cohort Study in Frailty and Aging (MiMiCS-FRAIL). This ongoing, prospective cohort study was set up to examine the interaction between multimorbidity, frailty and psychopathology and their consequences among geriatric outpatients.

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

All patients who consented to participate received a baseline assessment according to a comprehensive geriatric assessment protocol with structured diagnostic interviews, a complete physical examination and validated self-report questionnaires. Subsequently, patients are followed-up every 12 months with respect to all variables amenable to change as well as the primary study outcomes falls, hospital admissions, and death.

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 boards and local committee of medical institutes (University of São Paulo and Jundiai Medical School) approved this study. Written informed consent was obtained from all participants.

Patient recruitment started in January 2018 (and is still ongoing). For the present study, we selected the 315 patients who completed their baseline assessment in 2019.

Measures

Depression (explanatory factor)

The primary determinant was the presence of a depressive disorder at baseline assessed with the mood section of the Structured Clinical Interview for DSM-5 disorders (SCID-5). Depressive disorder was defined as either a Major Depressive disorder (MDD) according to DSM-5 criteria or subthreshold depression (STD) defined as 'another specified depressive disorder' according to DSM-5 criteria (APA, 2013). Eligible patients were clinically evaluated for the exclusion of a bipolar disorder as well as a depressive syndrome secondary to a somatic condition by two geriatric psychiatry specialists.

Secondary determinants of interest were depressive symptoms at baseline assessed with the 15-item geriatric depression scale (GDS-15) (Sheikh & Yesavage, 1986) and the Patient Health Questionnaire (PHQ) 9-item version (Kroenke, Spitzer, & Williams, 2001). These self-report questionnaires have been validated among Brazilian people (Almeida & Almeida, 1999; Santos et al., 2013). The GDS-15 was developed as a depression screening tool and contains 15 items which have been rated in a dichotomous format (yes/no). The nine items of the PHQ correspond to the DSM-5 criteria for a depressive episode and have to be rated in a Likert scale ranging from 0 to 3. Items 1–9 are added to yield a total score ranging from 0 to 27. On this scale, a score of 1–4 points is considered non-depressed; whereas a score of 5–9 as mild, 10–14 as moderate, 15–19 as moderately severe, and 20–27 as severe depression (McCarron, Vanderlip, & Rado, 2016).

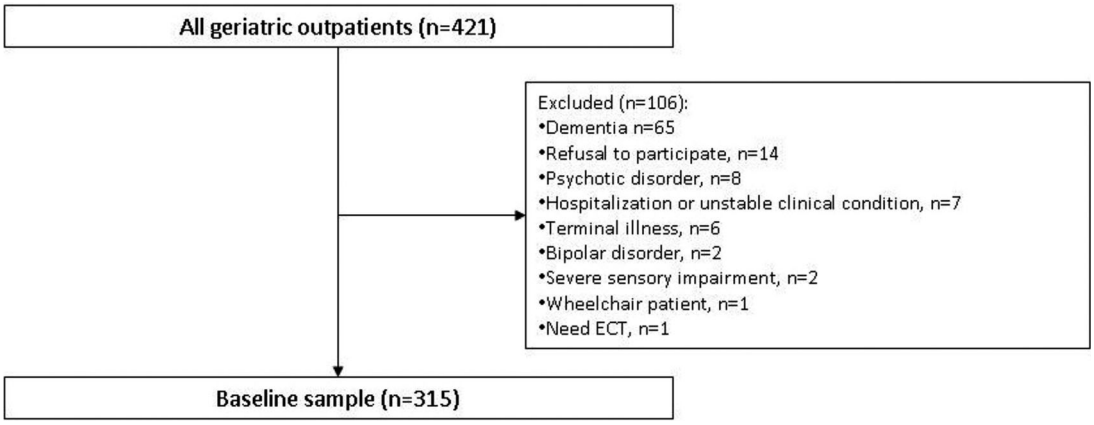

Figure 1. Flowchart of the study.

Frailty (dependent variable)

Frailty was assessed according to two commonly used instruments, i.e. a simple screening test (FRAIL-BR questionnaire) (Aprahamian et al., 2017) and a multidimensional frailty model (Frailty Index) (Rockwood & Mitnitski, 2007).

- The FRAIL-BR questionnaire is a self-report scale for screening frailty based on the Fried Frailty Phenotype (Fried et al., 2001) and the Frailty Index models (Rockwood & Mitnitski, 2007). 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 five or more illnesses out of 11; 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 yielding a total score between 0 and 5; a score of $\geq$3 points represents frailty (Morley et al., 2013). Data collection is very fast, does not require specialized training or equipment, and can be performed without reviewing medical records and physical manoeuvres (Aprahamian et al., 2017, 2019). Moreover, prognostic accuracy is comparable to that of more complex instruments (Lin et al., 2018).
- A 36-item Frailty Index (FI-36) is the proportion of health deficits derived from a count of 36 health deficits across different health domains (range 0–1). The FI is a stronger predictor for adverse health outcome than the sum of the predictive values of its single components (Mitnitski, Mogilner, & Rockwood, 2001). We assessed the following 36 health deficits: anemia, arthritis, cognitive impairment, 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, urinary incontinence, disability, care dependency, osteoporosis, falls, parkinsonism and related disorders, loss of appetite or anorexia, polypharmacy, foot disorders, mobility problems, obesity, hearing loss, valvulopathy, dizziness, social vulnerability, pressure ulcers, peptic ulcers. Patients having an FI of $\geq$0.25 are considered as frail (Rockwood, Andrew, & Mitnitski, 2007).

Covariates

Covariates were chosen based on their association with both depression and frailty (Aprahamian et al., 2018; Arts et al., 2016; Hajek et al., 2016; Lakey et al., 2012; Lohman, Dumenci, & Mezuk, 2014; Ribeiro, Duarte, Teixeira, & Paúl, 2018; St John, Tyas, & Montgomery, 2013; Woods et al., 2005). Age, sex and education were included as socio-demographic characteristics. Body mass index (as indicated by the weight (in kg) of the patient divided by its squared length in meter), cognitive performance (10-Cognitive Screener test), multimorbidity ($\geq$2 chronic diseases), and polypharmacy ($\geq$5 medications in current use) were included as clinical factors.

Statistical analyses

Descriptive statistics were performed for the characterization of the sample. All continuous variables had a normal distribution. According to the classification of depressive disorders at baseline, group differences were tested by ANOVA (dimensional variables) or Chi-square test (χ2) (categorical variables).

Binary logistic regression was used to estimate the odds for presence of frailty (dependent variable) in older people with depression *versus* non-depressed (independent variable) at baseline. The presence (yes/no) of frailty was either defined as $\geq$3 points on the FRAIL-BR or $\geq$0.25 on the FI-36 (Rockwood & Mitnitski, 2007). Linear regression models were performed to investigate the association between depression (independent variable) and frailty severity (dependent variable). Frailty severity was either based on the number positive criteria of the FRAIL-BR (range 0–5) or the dimensional FI-36 (range 0–1). Separate models were run for the different definitions of depression (depressive disorder according to DSM-5 criteria or severity of depressive symptoms that were assessed with the PHQ-9 and GDS-15) (Sjöberg et al., 2017) and frailty (the FRAIL-BR questionnaire and multidimensional FI-36) (Rockwood et al., 2007). Both, the logistic as well as the linear multivariate regression models were adjusted for all covariates described above. Multicollinearity problems were checked using the variance inflation factor (which appeared to be at most 1.57).

Table 1. Socio-demographic and clinical characteristics according to depression status ($n = 315$).

Characteristics		Depression status			
		Non-depressed ($n = 166$)	Subthreshold depression ($n = 86$)	Major depressive disorder ($n = 63$)	p
Demographics					
Age (years)	Mean (SD)	71.1 (8.5)	74.5 (8.0)	71.6 (8.2)	**.009**
Female	*n* (%)	104 (62.7)	60 (69.8)	51 (81)	**.028**
Education (years)	Mean (SD)	5.4 (4.2)	4.5 (3.9)	4.5 (3.4)	.146
Clinical characteristics					
BMI (kg/m^2)	Mean (SD)	28.0 (5.5)	27.8 (5.7)	30.1 (6.2)	**.030**
Cognitive functioning (10-CS)	Mean (SD)	7.7 (2.1)	6.6 (2.7)	6.9 (2.5)	**.001**
Multimorbidity	*n* (%)	87 (52.4)	57 (66.3)	42 (66.7)	**.041**
Polypharmacy	*n* (%)	77 (46.4)	45 (52.3)	39 (61.9)	.107
Depression					
Screening (GDS-15)	Mean (SD)	8.4 (1.6)	10.2 (2.0)	10.6 (2.0)	**<.001**
Severity of depressive symptoms (PHQ-9)	Mean (SD)	1.4 (1.4)	9.0 (3.7)	15.1 (4.9)	**<.001**
Frailty					
Screening (FRAIL-BR)	*n* (%)	24 (14.5)	40 (46.5)	41 (65.1)	**<.001**
Frailty index (FI-36)	Mean (SD)	0.13 (0.08)	0.17 (0.09)	0.19 (0.09)	**<.001**

Abbreviations: SD, standard deviation; BMI, body mass index; 10-CS, 10-point cognitive screening; GDS-15, Geriatric Depression Scale-15 item version; PHQ-9, Patient Health Questionnaire-9 item version; FRAIL-BR, Scale of physical frailty-Brazil; FI-36, Frailty Index-36 items; *p*, *p*-value calculated by ANOVA (in case mean (SD) are presented) or χ^2 test (in case *n* (%) are presented).
Bold valuessignifies $p < .05$

Table 2. Cross-sectional associations between two definitions of frailty severity (dependent variable) and different definitions of depression (independent variable) by linear regression ($n = 315$) at baseline.

	FRAIL-BR			Frailty index		
	B (SE)	Beta	*p*	*B* (SE)	Beta	*p*
Depressive disorders (DSM-5)						
Unadjusted						
Subthreshold depression	1.49 (0.18)	0.42	<.001	4.17 (1.08)	0.22	<.001
Major depressive disorder	2.12 (0.20)	0.53	<.001	6.43 (1.21)	0.30	<.001
*Fully adjusted**						
Subthreshold depression	1.24 (0.17)	0.35	<.001	1.81 (0.86)	0.09	.037
Major depressive disorder	1.92 (0.19)	0.48	<.001	2.14 (0.96)	0.19	<.001
Depressive symptoms:						
Unadjusted						
Patient Health Questionnaire-9 items	0.15 (0.01)	0.57	<.001	0.47 (0.07)	0.35	<.001
Geriatric Depression Scale-15 items	0.27 (0.04)	0.35	<.001	1.04 (0.23)	0.25	<.001
*Fully adjusted**						
Patient Health Questionnaire-9 items	0.13 (0.01)	0.50	<.001	0.30 (0.06)	0.22	<.001
Geriatric Depression Scale-15 items	0.23 (0.04)	0.29	<.001	0.67 (0.18)	0.16	<.001

Abbreviations: *B*, coefficient of regression; SE, standard error; beta, standardized coefficient of regression.
*Adjusted for age, sex, education, BMI, cognition, multimorbidity and polypharmacy.

All *p*-values were tested and *p* values <0.05 were considered statistically significant. Data were analyzed using Statistical Package of the Social Sciences (SPSS), version 25.0.

Results

Characteristics of the sample

Of the 421 patients willing to participate, 106 met the exclusion criteria (see Figure 1). The mean age of the 315 participants was 72.1 years, and 68.3% were women. A total of 105/315 (33.3%) participants were classified as frail according to the FRAIL-BR, and 54/315 (17.1%) according to the FI-36. Furthermore, 63/315 (20.0%) participants had major depression (MDD) and 86/315 (27.3%) subthreshold depression (STD). Table 1 presents all baseline characteristics, stratified by depression status.

Cross-sectional association between depression and frailty

The occurrence of frailty was significantly higher among patients with a depressive disorder according to DSM-criteria. According to the FRAIL-BR screening, the proportion of frailty was 24/166 (14.5%), 40/86 (46.5%), and 41/63 (65.1%) among non-depressed participants, patients with STD, and patients with MDD, respectively ($\chi^2 = 62.9$, df = 2, $p < .001$). According to the Frailty Index-36 (FI-36), these figures were respectively 17/166 (10.2%), 18/86 (20.9%), and 19/63 (30.2%) ($\chi^2 = 14.0$, df = 1, $p = .001$). Except for the association between STD and the FI-36, depression status remained significantly associated with frailty when adjusted for covariates. Regarding the association with the FRAIL-BR screening, the odds ratio (OR) for STD was 4.3 [95% CI: 2.3–8.2] ($p < .001$) and for MDD was 11.0 [95% CI: 5.3–23.0] ($p < .001$). With respect to the FI-36, the OR was 1.6 [95% CI: 0.7–3.8] for STD ($p = .309$) and 3.4 [95% CI: 1.4–8.6] for MDD ($p = .009$).

Table 2 shows the cross-sectional linear regression analyses for the association between the two-dimensional operationalizations of frailty with both depressive disorders (according to DSM-criteria) as well as depressive symptoms (PHQ-9 and GDS-15). The strongest associations were found between self-report measures, i.e. regarding frailty the stronger associations with depression were found for the FRAIL-BR compared to the FI-36 and regarding depression stronger associations were found for the PHQ-9 and GDS-15 compared to the DSM-5 defined depressive disorders (see Table 2).

Discussion

Main findings

In a geriatric outpatient sample, depression was cross-sectionally associated with frailty. Irrespective of the operationalization of either depression or frailty, higher levels of depression were associated with more severe frailty independent of potential confounders like socio-demographic and clinical characteristics, including multimorbidity and polypharmacy. Our results fit with two Bradford–Hill criteria for causality, namely a dose–response relationship and consistency across methodology (different criteria for depression and frailty). Furthermore, associations between both conditions were much stronger when these conditions were based on self-report measures (GDS-15, PHQ-9, FRAIL-BR) compared to observer-rated (SCID-5) or objective measures (FI-36).

Assessment of depression

Although major depressive disorder was associated with frailty, self-report assessments of depressive symptom severity were more strongly associated with frailty. This finding may suggest confounding due to self-report measures of depressive symptom severity. Frail older persons, who suffer from fatigue and exhaustion, might report inflated depressive symptom scores on these scales in the absence of formal depression from a psychiatric perspective. This is important as most studies on the relationship between depression and frailty thus far have been based on cross-sectional studies using depressive symptoms scales (self-report questionnaires), and only a few studies have assessed depression using a formal diagnostic criteria (Buigues et al., 2015; Chu et al., 2019; Soysal et al., 2017; Vaughan et al., 2015).

Interestingly, many aging studies publishing on the impact of late-life depression rely on self-report depression scales (e.g. the Canadian Longitudinal Study of Aging (CLSA), the Longitudinal Aging Study Amsterdam (LASA), and the Invecchiare in Chianti (InCHIANTI) study) (Brailean et al., 2016; Collard et al., 2015; Davison et al., 2019). Based on depressive symptom severity scales or cut-off scores, researchers often argue that subthreshold or minor depression has similar (negative) health consequences compared to major depressive disorder (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011). However, hardly any of these studies on the negative health effects of depression have adjusted their results for frailty. In addition, the hazard risk (HR) of 4.3 for mortality of depressed older adults decreased substantially when adjusted for frailty (Almeida et al., 2017). Therefore, the statement that subthreshold depression has similar consequences as major depression should be nuanced. Interestingly, the association between the FI-36 and subthreshold depression according to DSM criteria was almost lost when adjusted for covariates in our study.

Assessment of frailty

The proportion of frailty is markedly higher when assessed with the FRAIL-BR compared to a cut-off of $\geq$0.25 on the FI-36. Among non-depressed patients, the prevalence doubled when applying the FRAIL-BR to assess frailty instead of the FI-36, whereas among patients with either STD or MDD the prevalence of frailty even tripled. While prevalence rates widely vary with the use of the specific frailty instrument, recently the prevalence of the Fried frailty phenotype (27.4%), on which the FRAIL-BR is partially based, was even lower compared to a FI (33%) (Prina et al., 2019). The discrepancy rates we found suggest that the FRAIL-BR screening tool might be falsely inflated due to the presence of depression. This could for example be explained by cognitive biases of depressed patients when evaluating their health status (Everaert, Podina, & Koster, 2017).

In a recent meta-analysis, most cross-sectional studies assessed depression using self-report screening scales and revealed a pooled OR = 3.0 for the association with physical frailty (Chu et al., 2019). This meta-analysis also suggested that the odds of frailty due to depression is significantly higher in men than women (OR for men and women is 4.8 and 2.3, respectively) (Chu et al., 2019). Collard et al. (2014) identified an OR of 2.7 for the frailty phenotype in a case–control study on older patients suffering from depressive disorder when compared to non-depressed control group. Our study extends these findings by showing that depressive disorder is also associated with the FI-36 (in addition to the frailty phenotype).

Strengths and limitations

In addition to the use of different instruments to assess depression and frailty, other strengths include the use of a geriatric outpatient sample instead of population-based sample. Nonetheless, since self-referrals by patient themselves were also accepted, the final sample constitute of a mixed primary and secondary health care sample. In addition, our results were adjusted for important confounding factors: age, sex, education, cognition, BMI, polypharmacy and multimorbidity.

Nonetheless, some limitations should also be acknowledged. First, the FI has been criticized as being merely an indicator of multimorbidity than of frailty (Morley et al., 2013). This may have attenuated the strengths of the effects found using the FI. Nonetheless, as the FRAIL-BR also include the presence of chronic somatic diseases as one of its five components, it is not likely that the differential results between both instruments can be explained this adjustment. Thus far, many studies on frailty neglect multimorbidity and polypharmacy as important geriatric constructs which may be closely related with frailty. For example, polypharmacy is recognized as a major contributor to the pathogenesis of frailty and the assessment of inappropriate drug use appears beneficial for the prevention of frailty status (Aprahamian et al., 2018).

Conclusions and implications

The association between frailty and depression deserves more attention in clinical practice, regarding the negative health consequences of frailty (Kojima et al., 2018), especially among depressed patients (Brown et al., 2016; Collard et al., 2015, 2017; Lin et al., 2019). Our findings confirm the assumed association between depression and frailty

irrespective of the instruments used to assess frailty or depression. Nonetheless, since the strongest associations were found between self-report depressive symptom severity and self-report frailty instruments, suggest that self-report measures may easily confound each other. Therefore, when studying the underlying biological mechanisms of the association between depression and frailty, we strongly advocate to perform formal psychiatric diagnostic interviews and to objectively assess frailty status. Nonetheless, as time-investment and patient burden is significantly less when using self-report measures, these measures may still be relevant for usage in a primary care setting or (very) large scale epidemiological studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

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

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