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Serotonin receptor inhibitor is associated with falls independent of frailty in older adults

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ABSTRACT

Objectives: To evaluate whether fall risk in older adults is associated with the use of selective serotonin receptor inhibitor (SSRI) monotherapy among geriatric outpatients, and whether this association is moderated by the presence of depressive disorder and/or frailty.

Methods: Prospective cohort study with a 12-month follow-up and including 811 community-dwelling adults aged 60 or older from a university-based Geriatric Outpatient Unit. Major depressive disorder (MDD) was diagnosed according to DSM-5 criteria; subsyndromal depression as not meeting MDD criteria, but a Geriatric Depression Scale 15-item score $\geq$ 6 points. Frailty was evaluated with the FRAIL questionnaire. The association between SSRI use, depression, or both as well as the association between SSRI use, frailty, or both with falls were estimated through a generalized estimating equation (GEE) adjusted for relevant confounders.

Results: At baseline, 297 patients (36.6%) used a SSRI (82 without remitted depression) and 306 (37.7%) were classified as physically frail. Frailty was more prevalent among SSRI users (44.8% versus 33.7%, p =.004). After 12 months, 179 participants had at least one fall (22.1%). SSRI use, depression as well as frailty were all independently associated with falls during follow-up. Nonetheless, patients with concurrent of SSRI usage and non-remitted depression had no higher risk compared to either remitted SSRI users or depressed patients without SSRIs. In contrast, concurrence of SSRI use and frailty increases the risk of falling substantially above those by SSRI usage or frailty alone.

Conclusion: SSRI usage was independently associated with falls. Especially in frail-depressed patients, treatment strategies for depression other than SSRIs should be considered.

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Introduction

Falls in older adults are an important health problem, which may precipitate fractures, functional decline, loss of independence, and death (Phelan & Ritchey, 2018). A meta-analysis of 22 studies showed that antidepressants, including selective serotonin receptor inhibitors (SSRIs), are associated with an increased fall risk (Gebara et al., 2015). Nonetheless, the evidence for a causative effect of antidepressants remains limited when comparing these findings with Bradford Hill's criteria for a causal association (Gebara et al., 2015).

First, many studies failed to adjust for the presence of depression. Depression as well as clinically relevant depressive symptoms are well-known risk factors for falls (Deandrea et al., 2010; Kvelde et al., 2013). This association can at least be partly explained by the motor and cognitive impairment associated with depression, such as slowness in gait and mental processing speed, lower energy levels, sedentary behavior, and poor balance (Caligiuri & Ellwanger, 2000).

Second, none of the studies adjusted their analyses for the presence of frailty. Frailty is considered an independent risk factors for falls (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013), and differs from multimorbidity or disability (Benraad et al., 2016; Fried, Ferrucci, Darer, Williamson, & Anderson, 2004).

Especially in clinical geriatric samples in which both depression and frailty are highly common, it is important to know the fall risk associated with antidepressant drug use (Bloch et al., 2011; Gebara et al., 2015; Kerse et al., 2008; Woolcott, Richardson, & Wiens, 2009). In this regard, SSRI monotherapy should be especially investigated because SSRIs are often the initial drugs prescribed for older adults with depression (Gebara et al., 2015). Unfortunately, comorbidity between depression and frailty is highly common (Aprahamian et al., 2019; Lohman, Dumenci, & Mezuk, 2016; Soysal et al., 2017). In frail patients, psychotropic drugs and other drugs associated with increased fall risk should be avoided whenever possible. In other words, in frail-depressed patients, psychotherapy might be preferred as a first option and if not an realistic option, the risk–benefit ratio of antidepressants should be considered.

Therefore, the aim of this study was to examine whether SSRI use increases fall risk in a large clinical sample of older

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adults. We addressed whether this effect is independent of the presence of depression and frailty and, if so, whether depression or frailty moderates the impact of SSRIs on fall risk over a 12-month follow-up.

Materials and methods

Design, setting, and participants

This is a prospective clinical cohort study, as described previously (Aprahamian et al., 2019) In brief, all patients who attended the geriatric outpatient clinic of a tertiary university-based hospital in São Paulo, Brazil, between March and September 2015 were considered eligible for the present study (see Figure 1). A trained team of geriatricians, psychologists, and medical students performed a baseline assessment by telephone between September and December 2015 to check relevant clinical data and collect additional data (see later). Of the 1112 eligible patients, 298 (26.8%) could not be contacted by telephone (three attempts within 3 weeks). Exclusion criteria were: (1) inconsistencies between the telephonic interview and the electronic medical record regarding drug prescriptions, comorbidities, disability, mood and cognitive evaluations; (3) psychotic depression; (4) electroconvulsive therapy in the last year; (5) use of antidepressants that are not SSRIs or use of two or more antidepressants; (6) refusal to participate in the survey; (7) lack of attendance at routine geriatric evaluations between March and September 2016; and (8) hospitalization and/or severe comorbidity at telephone contact. Between September and December 2016, a one-year follow-up assessment was conducted by telephone.

The study followed the standards established by the National Council of Health and was approved by the local committee on human experimentation. All patients and/or their legal guardians agreed to participate by signing an informed consent form.

Measurements

Baseline data were extracted from electronic medical records regarding the 6 months before the inclusion date and complemented with a telephone interview. Demographic data included age, sex, and education. Physical characteristics included body mass index (BMI) as well as laboratory information including creatinine, fasting glucose, and glycosylated hemoglobin levels. Activities of daily living (ADL) were evaluated by Katz index (Katz, Ford, & Moskowitz, 1963) and Lawton & Brody instrumental ADL scale (Lawton & Brody, 1969). Any need of assistance in the six items of Katz index or the nine items of IADL was considered a disability. Cognitive performance was screened with the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) Clinical comorbidities included hypertension, diabetes mellitus, dyslipidemia, cancer (excluding nonmelanoma skin cancer), coronary heart disease, heart failure, stroke, asthma, chronic obstructive pulmonary disease, dementia, osteoporosis, and chronic renal failure. The baseline assessment of the primary parameters, i.e. depression diagnosis, SSRI use, and frailty are described in more detail below.

Depression diagnosis

Depression was diagnosed according to DSM-5 categorization by trained geriatricians in the absence of suspected dementia diagnosed by the DSM-5 criteria for a major neurocognitive disorder to avoid inclusion of false-positive cases. Depression was operationalized as major depressive disorder (MDD) as well as subthreshold depression or classified as 'another specified depressive disorder' according to DSM-5 and/or scoring about the cut-off ($\geq$6 points) on the 15-item Geriatric Depression Scale (GDS-15) (Almeida & Almeida, 1999) for clinically relevant depressive symptoms combined with any impairment secondary to depressive symptoms and confirmed by proxies. We considered major as well as subthreshold depression as the determinant of interest as subthreshold depression is also associated with same negative outcomes as those associated with MDD (Judd et al., 1998).

Antidepressant use

Pharmacotherapy with antidepressants was based on electronic medical prescriptions and confirmed by patients.

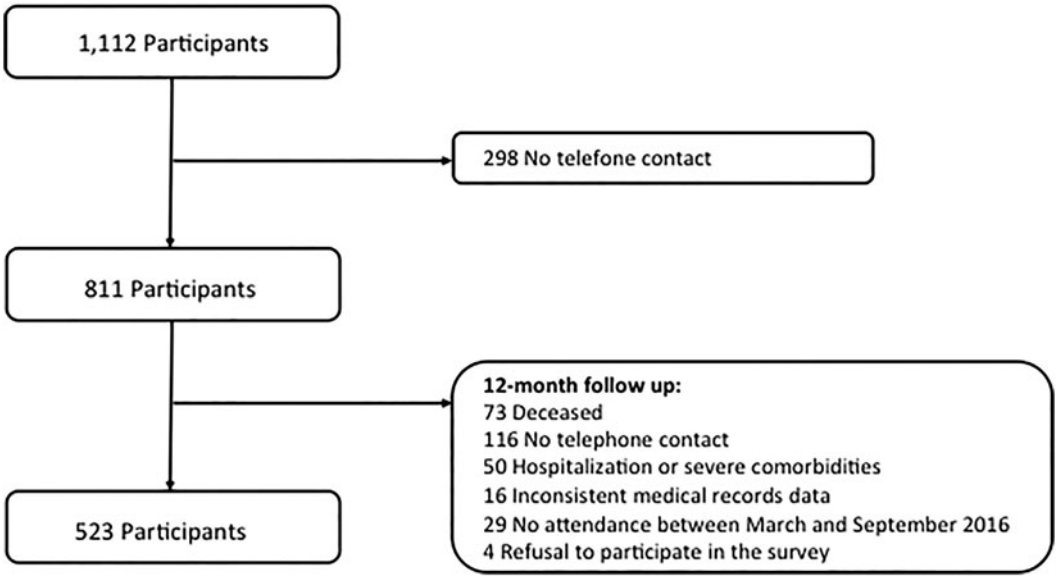

Figure 1. Flow chart of the study.

Antidepressants of all classes were evaluated, and the total number of medications was recorded. Fluoxetine, sertraline, paroxetine, and escitalopram were the available SSRIs, and they were delivered soon after the routine geriatric evaluation according to the prescription or delivered to the patient home on a monthly basis for free as a routine service of the hospital assistance program. The number of pills dispensed monthly was evaluated, and adherence to the treatment was checked by the medical staff during the next routine clinical evaluation.

Frailty measurement

The diagnosis of frailty was based on the FRAIL questionnaire classifying each participant as robust (0 points), prefrail (1 to 2 points), or frail (3 or more points) (van Kan et al., 2008). The FRAIL scale was developed by a research group composed of members of the International Association of Nutrition and Aging. The instrument is based on self-reporting of answers to five questions, with one point assigned for each affirmative answer (dichotomic answers, yes or no). The instrument assesses the presence of fatigue, muscle resistance, ambulation, disease burden, and weight loss with 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.

Advantages of the FRAIL scale are the lack of any specialized training or equipment requirements, very fast speed, and the ability to perform without review of medical charts and physical exams or maneuvers (Aprahamian, Lin, & Suemoto, 2017; Aprahamian et al., 2019). Previously, we have validated two subdomains of the FRAIL questionnaire regarding physical capacity, named Physical Performance, and a general health measure, named Health Status (Aprahamian, Lin, & Suemoto, 2017). Moreover, the FRAIL questionnaire facilitates the assessment of frailty and presents similar prognostic accuracy as more complex instruments based on performance-based measures (Lin et al., 2018).

Falls assessment

Finally, information about the number of falls during the last 12 months was included in the longitudinal assessment. Falls were defined as any unintended event in which the subject suffered a sudden impact on a surface lower than he/she previously was. Any fall during the period reported by the proxy in the case of cognitively impaired individuals or by the patient was considered an adverse outcome.

Statistical analysis

Comparison of categorical variables (sex, comorbidities, frailty status, and FRAIL components) was performed using the Pearson chi-square test. Continuous variables (age, education, BMI, number of medications, MMSE score, GDS-15 score, FRAIL score, serum glycemia, serum creatinine, glycated hemoglobin) were not normally distributed (Kolmogorov–Smirnov test and graphical analysis of skewness and kurtosis) and therefore compared with the Mann–Whitney test.

First, the association between the use of SSRIs and falls was an estimated odds ratio (OR) obtained through a generalized estimating equation (GEE). Participants were stratified into four groups: (0) asymptomatic and no SSRI use ($n = 332$); (1) GDS-15 $<= 5$ and SSRI use (remitted depression) ($n = 156$); (2) symptomatic, but no SSRI use (MDD or minor depression included) ($n = 45$); and (3) symptomatic (MDD or minor depression) and SSRI use ($n = 56$). To explore the potential impact of frailty, we present unadjusted results (model 1) as well as adjusted results including age, sex, education, total number of medications, number of comorbidities, BMI, and basic ADL as covariates (models 2–4). In model two, we adjusted for the presence of frailty (yes/no), in model three for the physical performance subdomain of the FRAIL questionnaire, and finally in model four, the health status subdomain of the FRAIL questionnaire.

Second, the interaction between SSRI use and frailty was tested through the GEE. In the first model, results were only adjusted for depression. In the second model, we adjusted for depression, age, sex, education, total number of medications, number of comorbidities, BMI, and basic ADL.

Data analysis was performed using IBM SPSS version 21 for IOS/Mac, Armonk, NY, USA. All statistical tests were two-tailed with an alpha level of 0.05.

Results

This outpatient cohort consisted of 811 patients in the baseline analysis as shown in the flowchart of Figure 1. The mean age was 81.65 ± 7.26 years, with a predominance of females (72.9%), low education (4.19 ± 3.88 years), and the presence of polypharmacy (8.35 ± 3.26 drugs) and multimorbidity (mean of 2.29 ± 1.16 diseases). Additionally, the mean BMI was 26.68 ± 5.08 kg/m^2, the mean MMSE score was 20.13 ± 6.41 points, 14.3% had at least one instrumental activity of daily living (IADL) dysfunction, and 16.4% had disability in basic activities of daily living (BADL). Of 363 cases diagnosed with depression (not related to dementia), 148 (18.7%) were diagnosed with current depression (66 with a history of over 30 days without SSRI use, 82 with symptoms and use of an SSRI). A total of 215 participants used an SSRI as a maintenance treatment and were classified as remitted. A total of 306 participants were classified as frail (37.7%), 395 as prefrail (48.7%), and 110 as robust (13.6%). There were 179 falls after 12 months of follow-up [number of falls: 1 ($n = 82$); 2 ($n = 38$); 3 ($n = 34$); 4 ($n = 7$); 5 ($n = 7$); 6 ($n = 1$); 8 ($n = 1$); 9 ($n = 1$); 10 ($n = 6$); 12 ($n = 1$); 25 ($n = 1$)].

The SSRI group had a lower education, a higher number of medications in use, a higher BMI, and lower BADL independency, as described in Table 1. Frailty components were also compared in these two groups and are presented in Table 2. The frequency of the fatigue and disease burden components were significantly higher among SSRI

Table 1. Baseline characteristics of the sample ($n = 811$).

Variables	SSRI users ($n = 297$)	Nonusers ($n = 514$)	p*
Age (years), mean (SD)	81.2 (6.9)	81.9 (7.4)	.277
Female, %	23.9	29.0	.117‡
Education (years), mean (SD)	3.8 (4.0)	4.4 (3.8)	.028
Number of medications in use	9.2 (2.3)	7.8 (3.3)	<.001
Comorbidities	2.3 (1.1)	2.2 (1.1)	.247
Hypertension, %	81.1	81.1	.996‡
Diabetes, %	32.6	31.2	.671‡
Cancer, %	12.4	8.5	.075‡
COPD, %	5.8	5.8	.997‡
Coronary artery disease, %	8.6	8.0	.789‡
Heart failure, %	2.4	3.0	.614‡
Asthma, %	4.5	3.2	.369‡
Stroke, %	2.1	2.2	.888‡
Chronic renal failure, %	16.8	19.5	.350‡
Osteoporosis, %	33.3	35.4	.554‡
BMI (kg/m^2), mean (SD)	27.6 (5.5)	26.1 (4.7)	.002
MMSE, mean (SD)	19.8 (6.0)	20.2 (6.6)	.404
GDS-15, mean (SD)	6.0 (3.3)	4.7 (3.2)	<.001
Basic ADL	0.8 (1.6)	0.6 (1.4)	.044
Instrumental ADL	3.7 (2.7)	3.6 (3.0)	.415

Note: SSRI: selective serotonin receptor inhibitor; SD: standard deviation; COPD: chronic obstructive pulmonary disease; BMI: body mass index; MMSE: Mini Mental State Examination; GDS-15: Geriatric Depression Scale 15 items; ADL: activities of daily living.
*Mann–Whitney test, except ‡Pearson chi-square;

Table 2. Prevalence of frailty status, components, and FRAIL items between SSRI users and nonusers.

	SSRI users ($n = 297$)	Nonusers ($n = 514$)	p*
FRAIL components			
Weight loss	124 (41.9%)	210 (40.9%)	.773
Fatigue	241 (81.1%)	345 (67.1%)	<.001
Muscle resistance	98 (33.0%)	142 (27.6%)	.107
Ambulation	110 (37.0%)	158 (30.7%)	.066
Disease burden	119 (40.1%)	155 (30.2%)	.004
Number of components			.013
0	31 (10.4%)	79 (15.4%)	
1	64 (21.5%)	126 (24.5%)	
2	69 (20.9%)	136 (26.2%)	
3	64 (21.5%)	99 (19.3%)	
4	49 (16.5%)	57 (11.1%)	
5	20 (6.7%)	17 (3.3%)	
Frailty status			.004
Robust	31 (10.4%)	79 (15.4%)	
Prefrailty	133 (44.8%)	262 (51.0%)	
Frailty	133 (44.8%)	173 (33.7%)	

Note: SSRI: selective serotonin receptor inhibitor.
*Pearson chi-square test.

users than in the nonuser group (81.1% *versus* 57.1%, $p <$ .001 and 40.1% *versus* 30.2%, $p =$.004, respectively). Frailty prevalence was higher among SSRI users than nonusers (44.8% *versus* 33.7%, $p =$.004), and robustness and prefrailty were more commonly associated with nonusers (10.4% *versus* 15.4%, and 44.8% *versus* 51%, respectively, $p =$.004).

The longitudinal association between depression, SSRI use, and falls after 12 months of follow-up is shown in Table 3. In the first adjusted model, which included the FRAIL instrument, depression and SSRI use had a significant association with falls (OR = 2.51, confidence interval (CI) 95% = 1.34–4.69, $p =$.004), as well as in the remitted depression group with SSRI use (OR = 2.00, CI 95% = 1.05–4.00, $p =$.034), but not in the depression group without SSRI use (OR = 2.16, CI 95% = 0.97–4.77, $p =$.056). In the second adjusted model, which evaluated the Physical Performance subdomain of the FRAIL instrument, this association was also observed in the depression with or without SSRI use group and in remitted depression with SSRI use group (OR 2.09–2.60). In the third adjusted model that evaluated the Heath Status subdomain of the FRAIL questionnaire, an association between current or remitted depression with or without SSRI use and falls was observed (OR 2.06–2.75).

Table 4 shows the interaction between SSRI use and frailty with falls. The use of SSRIs without frailty was associated with falls in the adjusted model (OR = 1.65, CI 95% = 1.26–2.15, $p <$ .001). Among frail individuals that do not use SSRIs, there was also a positive association (OR = 1.57, CI 95% = 1.05–2.32, $p =$ .025) with falls. In patients with frailty and SSRI use, the association was stronger (OR = 2.97, CI 95% = 2.30–3.82, $p <$ .001).

Discussion

This current study shows that SSRI usage among older persons is associated with an increased fall risk, independent of depression and/or frailty status. Interestingly, SSRI usage did not increase the fall risk associated with depression, but in case of frailty, it significantly increased the fall risk associated with it.

As stated in the introduction, the current evidence on the association between SSRI use and falls do not comply the Bradford Hill epidemiological criteria for causality (Gebara et al., 2015). Especially as most studies included were observational and cross-sectional, bias due to unknown and/or unmeasured confounders cannot be excluded. The reasons for the association between depression and fall risk are also still debatable. A systematic review and meta-analysis focused on all (independent) risk factors of falls showed that depression is associated with a 44% increase in fall risk after multivariate analyses (Deandrea et al., 2010). These results were confirmed by a more recent meta-analysis restricted to the association between depression and falls (Kvelde et al., 2013). This latter study, however, also pointed to the lack of knowledge of the underlying pathophysiology, generally needed to firmly establish causality (Kvelde et al., 2013). In the present study, we confirmed that depression and SSRI usage were both associated with falls, but we neither found an additive, nor a multiplicative effect in the presence of both depression and SSRI usage. This might indicate that depression and SSRI usage may share the same underlying mechanism, although other explanations can still be true like SSRI counteracting the specific mechanism by which depression increases fall risk or simply a ceiling effect.

Adjusted for depression, we observed a significant association between SSRI use and falls when stratified for the presence of frailty. Moreover, the impact of SSRI on fall risk significantly increases in the presence of frailty. This is highly important, as up till now geriatric characteristics have rarely been taken into account in clinical trials on antidepressant medications in patients with late-life depression according to a systematic review (Benraad et al., 2016).

Recently, the presence of sarcopenia and low muscle strength was proposed as one possible mechanism explaining the increased fall risk associated with frailty (Hayashi et al., 2019; Kokkeler, Berg, Comijs, Oude Voshaar, & Marijnissen, 2019; Szlejf, Suemoto, & Brunoni, 2018). The interaction between SSRI usage and frailty might be explained by the biological effects of the antidepressants on the central nervous system, such as sedation (Ray, 1992), the cardiovascular system, causing postural

Table 3. Longitudinal association between depression, SSRI use, and falls after 12 months of follow-up.

Variables	Odds Ratio (95% confidence interval)							
	Unadjusted Model	*p*	Adjusted Model 1[a]	*p**	Adjusted Model 2[b]	*p**	Adjusted Model 3[c]	*p**
No depression or SSRI use	1 (ref.)	–	1 (ref.)	–	1 (ref.)	–	1 (ref.)	–
Depression and SSRI use	2.46 (1.45–4.19)	.001	2.51 (1.34–4.69)	.004	2.60 (1.40–4.80)	.002	2.75 (1.50–5.00)	.001
Depression without SSRI use	2.41 (1.05–5.50)	.037	2.16 (0.97–4.77)	.056	2.20 (1.01–4.80)	.046	2.27 (1.06–4.86)	.033
SSRI use in remitted depression	2.06 (1.01–4.25)	.048	2.00 (1.05–4.00)	.034	2.09 (1.05–4.14)	.034	2.06 (1.06–4.06)	.036

Note: Falls as a dependent variable. SSRI: selective serotonin receptor inhibitor.
*Generalized Estimating Equation with Poisson regression model.
[a–c]Adjusted for age, sex, educational level, number of drugs in use, number of comorbidities, body mass index, basic activities in daily life.
[a]Adjusted frailty.
[b]Adjusted for Physical Performance subdomain of FRAIL questionnaire.
[c]Adjusted for Health Status subdomain of FRAIL questionnaire.

Table 4. Interaction between SSRI use and frailty associated with falls after 12 months of follow-up.

Variables	Odds Ratio (95% confidence interval)			
	Unadjusted Model[a]	*p**	Adjusted Model[b]	*p**
No SSRI use or frailty	1 (ref.)	–	1 (ref.)	–
SSRI use and frailty	2.48 (2.14–2.87)	<.001	2.97 (2.30–3.82)	<.001
Frailty, no SSRI use	1.17 (1.04–1.32)	.007	1.57 (1.05–2.32)	.025
SSRI use, no frailty	1.43 (1.27–1.63)	<.001	1.65 (1.26–2.15)	<.001

Note: Falls as a dependent. SSRI: selective serotonin receptor inhibitor.
*Generalized Estimating Equation with Poisson regression model.
[a]Adjusted for depression.
[b]Adjusted for age, sex, educational level, body mass index, basic activities in daily life, number of drugs in use, number of comorbidities, and depression.

hypotension (Halper & Mann, 1988) and anticholinergic activity (Fick, Semla, Beizer, & American Geriatrics Society, 2015), affecting the capability to maintain the integrity of one's gait and motor function and increasing the risk of falls.

Limitations

Despite controlling for the most important confounders, we cannot exclude residual confounding due to the design of the study. Moreover, due to lack a genetic variance within the Brazilian population (Durso et al., 2014; Pena, Bastos-Rodrigues, Pimenta, & Bydlowski, 2009), we could not control for race/ethnicity, which also restrict the generalizability of our results. Second, despite our large sample size, the number of fallers who used SSRIs was still relatively small. The validity of fall reporting also represents a significant limitation. The accuracy of fall reporting is higher when prospectively assessing adverse effects as opposed to spontaneous reporting (Wernicke, Faries, Milton, & Weyrauch, 2005) and the number of reported falls increases with direct assessment (Nelson, Delucchi, & Schneider, 2013). Nonetheless, previous studies also mostly relied on medical record reviews or self-reports (Gebara et al., 2015). Finally, frailty determination was based on the FRAIL questionnaire, which presents low sensitivity and high specificity with a moderate correlation with the phenotypic physical criteria (Almeida & Almeida, 1999).

Conclusions and implications for clinical practice or research

Given the importance of falls at the individual as well as societal level, knowledge on amenable risk factors for falls are highly warranted. As the current literature is still not conclusive, replication studies in relevant clinical population samples as the present study are highly warranted. Our results suggest that SSRI usage does not increase the fall risk association with depression, but it does significantly add to the fall risk associated with frailty. Therefore, the distinction between depression and frailty is particularly relevant in clinical care. In case of frail-depressed patients, physical exercise for frailty and psychotherapy for depression might be preferred over antidepressant drug treatment. In addition to well-known psychotherapies for late-life depression like cognitive behavioral therapy and problem-solving treatment (Cuijpers, van Straten, Smit, & Andersson, 2009; Cuijpers, Karyotaki, Reijnders, & Huibers, 2018), one should also consider therapies related to the movement of positive psychology. Especially acceptance and commitment therapy, mindfulness-based stress reduction, and life review are promising therapies in case of frailty associated with depression (Fillit & Butler, 2009).

Acknowledging the limitations of our study, future research should be directed to multisite large prospective cohort studies that surpass those obtained by smaller single-center observational studies. Moreover, geriatric characteristics should be taken into account when designing pharmacological treatment studies on late-life depression (van Kan et al., 2008). Such studies are urgently needed, to inform clinical guidelines, in order to establish firm evidence of the risk–benefit ratio of SSRIs that can be discussed with patients and their families when alternative treatment options are not realistic before starting SSRIs treatment to target late-life depression.

Disclosure statement

There are no conflicts of interest.

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References

Almeida, O. P., & Almeida, S. A. (1999). Reliability of Brazilian version of the abbreviated form of geriatric depression scale (GDS) short form [Confiabilidade da versão brasileira da Escala de Depressão em Geriatria (GDS) versão reduzida]. *Arquivos de Neuro-Psiquiatria*, *57*(2B), 421–426.

Aprahamian, I., Lin, S. M., & Suemoto, C. K. (2017). Feasibility and factor structure of the FRAIL scale in older adults. *Journal of the American Medical Directors Association*, *18*, 367.e311–367.e318. doi:10.1016/j.jamda.2016.12.067

Aprahamian, I., Suemoto, C. K., Lin, S. M., de Siqueira, A. S. S., Biella, M. M., de Melo, B. A. R., & Jacob-Filho, W. (2019). Depression is associated with self-rated frailty in older adults from an outpatient clinic: A prospective study. *International Psychogeriatrics*, *31*(3), 425–434.

Benraad, C. E. M., Kamerman-Celie, F., van Munster, B. C., Oude Voshaar, R. C., Spijker, J., & Olde Rikkert, M. G. M. (2016). Geriatric characteristics in randomised controlled trials on antidepressant drugs for older adults: A systematic review. *International Journal of Geriatric Psychiatry*, *31*(9), 990–1003.

Bloch, F., Thibaud, M., Dugué, B., Brèque, C., Rigaud, A.-S., & Kemoun, G. (2011). Psychotropic drugs and falls in the elderly people: Updated literature review and meta-analysis. *Journal of Aging and Health*, *23*(2), 329–346.

Caligiuri, M. P., & Ellwanger, J. (2000). Motor and cognitive aspects of motor retardation in depression. *Journal of Affective Disorders*, *57*(1–3), 83–93.

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *The Lancet*, *381*(9868), 752–762.

Cuijpers, P., Karyotaki, E., Reijnders, M., & Huibers, M. (2018). Who benefits from psychotherapies for adult depression? A meta-analytic update of the evidence. *Cognitive Behaviour Therapy*, *47*(2), 91–106.

Cuijpers, P., van Straten, A., Smit, F., & Andersson, G. (2009). Is psychotherapy for depression equally effective in younger and older adults? A meta-regression analysis. *International Psychogeriatrics*, *21*(01), 16–24.

Deandrea, S., Lucenteforte, E., Bravi, F., Foschi, R., La Vecchia, C., & Negri, E. (2010). Risk factors for falls in community-dwelling older people: A systematic review and meta-analysis. *Epidemiology*, *21*(5), 658–668.

Durso, D. F., Bydlowski, S. P., Hutz, M. H., Suarez-Kurtz, G., Magalhães, T. R., & Pena, S. D. (2014). Association of genetic variants with self-assessed color categories in Brazilians. *PLoS One*, *9*(1), e83926.

Fick, D. M., Semla, T. P., Beizer, J., Brandt, N., Dombrowski, R., DuBeau, C. C., ... Steinman, M. B. (2015). Updated beers criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *63*(11), 2227–2246. doi:10.1111/jgs.13702

Fillit, H., & Butler, R. N. (2009). The frailty identity crisis. *Journal of the American Geriatrics Society*, *57*(2), 348–352.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198.

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *59*(3), M255–M263.

Gebara, M. A., Lipsey, K. L., Karp, J. F., Nash, M. C., Iaboni, A., & Lenze, E. J. (2015). Cause or effect? Selective serotonin reuptake inhibitors and falls in older adults: A systematic review. *The American Journal of Geriatric Psychiatry*, *23*(10), 1016–1028.

Halper, J. P., & Mann, J. J. (1988). Cardiovascular effects of antidepressant medications. *British Journal of Psychiatry*, *153*(S3), 87–98.

Hayashi, T., Umegaki, H., Makino, T., Cheng, X. W., Shimada, H., & Kuzuya, M. (2019). Association between sarcopenia and depressive mood in urban-dwelling older adults: A cross-sectional study. *Geriatrics & Gerontology International*, *19*(6), 508–512.

Judd, L. L., Akiskal, H. S., Maser, J. D., Zeller, P. J., Endicott, J., Coryell, W., … Keller, M. B. (1998). A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Archives of General Psychiatry*, *55*(8), 694–700.

Katz, S., Ford, A. B., & Moskowitz, R. W. (1963). Studies of illness in the aged. The Index of Adl: A standardized measure of biological and psychosocial function. *JAMA*, *185*(12), 914–919.

Kerse, N., Flicker, L., Pfaff, J. J., Draper, B., Lautenschlager, N. T., Sim, M., … Almeida, O. P. (2008). Falls, depression and antidepressants in later life: A large primary care appraisal. *PLoS One*, *3*(6), e2423.

Kokkeler, K. J. E., Berg, K. S., Comijs, H. C., Oude Voshaar, R. C., & Marijnissen, R. M. (2019). Sarcopenic obesity predicts nonremission of late-life depression. *International Journal of Geriatric Psychiatry*, *34*(8):1226–1234.

Kvelde, T., McVeigh, C., Toson, B., Greenaway, M., Lord, S. R., Delbaere, K., & Close, J. C. T. (2013). Depressive symptomatology as a risk factor for falls in older people: Systematic review and meta-analysis. *Journal of the American Geriatrics Society*, *61*(5), 694–706.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*(3 Part 1), 179–186.

Lohman, M., Dumenci, L., & Mezuk, B. (2016). Depression and frailty in late life: Evidence for a common vulnerability. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *71*(4), 630–640.

Lin, S. M., Aliberti, M. J. R., Fortes-Filho, S. D Q., Melo, J. D A., Aprahamian, I., Suemoto, C. K., & Jacob Filho, W. (2018). Comparison of 3 frailty instruments in a geriatric acute care setting in a low-middle income country. *Journal of the American Medical Directors Association*, *19*(4), 310–314.e313.

Nelson, J. C., Delucchi, K. L., & Schneider, L. S. (2013). Moderators of outcome in late-life depression: A patient-level meta-analysis. *American Journal of Psychiatry*, *170*(6), 651–659.

Pena, S. D., Bastos-Rodrigues, L., Pimenta, J. R., & Bydlowski, S. P. (2009). DNA tests probe the genomic ancestry of Brazilians. *Brazilian Journal of Medical and Biological Research*, *42*(10), 870–876.

Phelan, E. A., & Ritchey, K. (2018). Fall prevention in community-dwelling older adults. *Annals of Internal Medicine*, *169*(11), ITC81–ITC96.

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.

Szlejf, C., Suemoto, C. K., & Brunoni, A. R. (2018). Depression is associated with sarcopenia due to low muscle strength: Results from the ELSA-Brasil study. *Journal of the American Medical Directors Association*, *S1525–S8610*(18), 30511–30515.

Ray, W. A. (1992). Psychotropic drugs and injuries among the elderly: A review. *Journal of Clinical Psychopharmacology*, *12*(6), 386–396. doi:10.1097/00004714-199212000-00004

van Kan, G. A., Rolland, Y., Bergman, H., Morley, J. E., Kritchevsky, S. B., & Vellas, B. (2008). The I.A.N.A task force on frailty assessment of older people in clinical practice. *The Journal of Nutrition Health and Aging*, *12*(1), 29–37.

Wernicke, J. F., Faries, D., Milton, D., & Weyrauch, K. (2005). Detecting treatment emergent adverse events in clinical trials: A comparison of spontaneously reported and solicited collection methods. *Drug Safety*, *28*(11), 1057–1063.

Woolcott, J. C., Richardson, K. J., & Wiens, M. O. (2009). Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of Internal Medicine*, *169*(21), 1952–1960.