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Review

The complex associations between late life depression, fear of falling and risk of falls. A systematic review and meta-analysis

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ABSTRACT

Introduction: Depression rates in older people worldwide vary from 10% to 15% of community-dwelling older persons. There are two others problems related to depression in old age, namely the high incidence of falls and the so-called fear of falling (FOF), with a prevalence ranging from 20% to 85%; it was initially considered a post-fall syndrome, which later as a fall-independent event.

Aims: Study aims to conduct a systematic review and meta-analysis to bridge the existing gap in literature about the association between depressive symptomatology, FOF, use of antidepressant therapy and falls, also identifying a possible effect of the study quality on the outcome.

Methods: The selection of studies was carried out between May 20, 2020, and July 27, 2020 and only observational clinical trials, written in English, with participants aged more or equal to 60 years affected by diagnosis of depression or treatment for depression mentioned both as a clinical diagnosis in older patient, and as a predictor/consequence of falls were included. The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting systematic reviews and meta-analysis, and the protocol was recorded in the International Prospective Register of Systematic Reviews (PROSPERO).

Results and discussion: The screening process ultimately led to the inclusion of 18 articles. Many of the included studies showed that depressive symptoms caused the subsequent increase in the number of falls. Results from the meta-analysis had no highlighted association between depression and falls, in contrast to other review and meta-analysis works: our work includes a substantial number of studies, with a relatively recent publication date, including patients diagnosed with depression, clearly evaluating the association between depression and falls. Results all seem to confirm the hypothesis of an interdependent association between the presence of FOF and the risk of fall, despite the high percentage of cross-sectional studies prevents inferring on the direction of the association. Therapeutic interventions aimed at decrease rate of falls reducing depressive symptoms and FOF.

1. Introduction

Depression is a common and important cause of morbidity and mortality in older people worldwide, affecting around 10–15% of community-dwelling older persons. In the geriatric population, depression is associated with functional decline, cognitive impairment, premature death by suicide, increased mortality, decreased quality of life and premature nursing home admission. If left untreated, symptoms

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may persist for years (van Poelgeest et al., 2021). Untreated depression is independently associated with increased fall risk: a meta-analysis showed an OR of 1.63 for depression-associated falling (Deandrea et al., 2010). The pathophysiologic mechanisms underlying the association between depression and falling are complex and difficult to trace back to linear causality patterns. These phenomena seem to be related to complex bidirectional interactions. So far, the well-known high incidence of falls in older patients has been attributed to visual or motor functional changes, as well as balance disorders. Recently some studies have shown a correlation between depressive symptomatology and frequency of falls, leading to the hypothesis that pathways exist which are shared by both pathologies (Kvelde et al., 2013; Stel et al., 2004). Numerous risk factors for falls have been associated with depressive symptoms in older patients, such as cognitive impairment, slow walking, poor balance, increased reaction times and asthenia (Kvelde et al., 2013; Stel et al., 2004). The symptoms most characteristically associated with depressive episodes such as psychomotor retardation, slow gait, slow cognitive processing, low levels of energy and activity can all result in falls, but they themselves can eventually provoke the Fear of Fall (FOF), understood as "low perceived self-efficacy at avoiding falls during essential, nonhazardous activities of daily living" (Tinetti et al., 1990), which in turn can lead to the development of depressive symptoms (Kvelde et al., 2013).

Abnormal gait pattern (Buchner et al., 1996; Herman et al., 2005) and postural abnormalities (Turcu et al., 2004), which can be characteristics of older people with depression, may suggest a physiological rather than psychic or psychological origin of falls. However, some studies show that depression may be an independent factor related to fractures (Whooley et al., 1999), dizziness and FOF (Burker et al., 1995). Both FOF and depressive symptomatology are independently related to stride-to-stride variability, itself an indicator of the risk of falls (Hamacher et al., 2019). It is also possible that falls may lead to the development of depression in the older people, with a reverse causality ratio, reducing the functional state and increasing rates of disability (Kerse et al., 2008).

The action of beginning to walk, and continuing to walk, represent a complex integrated process of a neurological and psychological nature that requires the simultaneous interaction of multiple brain loci. Multiple neurological causes such as cortical and/or subcortical vascular pathology can cause gait changes, while psychopathological causes have been less commonly documented (Peeters et al., 2019). Interestingly, balance disorders and anxiety disorders share central neural circuits involving monoaminergic components and converge in the parabrachial nucleus network, explaining why anxiety is often associated with alterations in balance (Teixeira et al., 2016).

Finally, many of the drugs used in depressive episodes have been associated with an increased risk of falls and fractures. Some psychotropic drugs also have a direct effect on bone mineralization, potentially increasing the risk of fractures in the event of a fall (Kvelde et al., 2013). The trend of the prescription of antidepressants in recent years is constantly increasing (Gualano et al., 2014). The increase of these drugs prescriptions and their association with falls is of particular importance. Many articles, however, generically group all psychoactive drugs, making it unclear which pharmacological class is most associated with the risk of falls (Kvelde et al., 2013). A systematic review and meta-analysis (Kvelde et al., 2013) on depressive symptomatology as a risk factor for falls in older people, included only two studies (Granek et al., 1987; Rosendahl et al., 2003) and reported significant findings from univariate analysis suggesting that antidepressants could be a predictor of subsequent falls. Other articles included in this systematic review reported that the use of psychotropic or psychoactive medications was a predictor of falls, even if the samples consisted of patients taking different classes of medication (including antidepressants, benzodiazepines, and antipsychotics), making it difficult to draw clear conclusions about the relationship between depression, antidepressants, and falls.

Regardless of the specific mechanism involved in the relationship between depression and falls, which is not yet fully clarified, it seems that the presence of falls should prompt an investigation about the possible co-existence of depressive symptomatology and vice versa. Only in this way will it be possible to guarantee personalized and targeted care and the conditions required for healthy aging to an ever-increasing population (Kerse et al., 2008; WHO, 2020).

Our study first aim is to conduct a systematic literature review and meta-analysis on the currently available literature on the topic, to bridge (at least partially) the existing gap in the literature about the two-way correlation between depressive symptomatology, FOF, use of antidepressant therapy and falls.

A secondary aim is to identify a possible effect of the study quality on the outcome, using two different tools to assess the quality.

2. Materials and methods

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting systematic reviews and meta-analysis (Liberati et al., 2009). The protocol of this review has been recorded in the International Prospective Register of Systematic Reviews (PROSPERO) (protocol number CRD42020173678).

2.1. Selection process

On May 16, 2020, the following databases were investigated: PubMed, Scopus, PsycINFO, Embase, and Cochrane, using the search strings showed in appendix.

The selection of studies was carried out between May 20, 2020 and July 27, 2020. Two reviewers (CV and MM) independently evaluated the records extracted from the databases described above. Any discrepancies between reviewers were resolved by a third-party author (EG). After removing duplicates, titles were screened first, followed by the abstract, and then by full-text articles, with the screener taking care to identify any publications related to a single study. The screening search process was performed in the light of the inclusion/exclusion criteria detailed below, and all studies that did not have the assessment of the relationship between fall and/or FOF and depression (and vice versa) as their primary outcome were excluded.

2.2. Inclusion and exclusion criteria

Studies were included when they possessed the following inclusion criteria:

1. Observational
2. Written in English
3. Study participants with age over or equal to 60 years
4. Any setting
5. Diagnosis of depression or treatment for depression mentioned both as a clinical diagnosis in older patient, and as a predictor/consequence of falls

Studies involving older patients with falls related to exclusively somatic problems (balance problems, bone fractures, etc.) were excluded, as well as studies that included populations of patients under the age of 60. Experimental studies, literature reviews, meta-analyses, case reports, editorials, commentaries, and book chapters were also excluded from this systematic review.

2.3. Data collection and analysis

A data collection tool was developed to record and later aggregate information on specific variables of interest, including (i) information related to the study, (ii) information related to the population included

in the study (iii) variables related to depression, FOF and falls. One author (EG) extracted the data from the studies included in the review by examining all the papers. The data extracted from the selected full text was then registered in a database using a standardized and predetermined encoding. The following categorical and numerical variables were recorded:

- General information on the study (author(s), year of publication, duration of the study, country, type of study, sample size, drop-out percentages, setting)
- Information about participants (gender, age, social status, presence or absence of caregiver, presence of medical comorbidities and type, presence of cognitive decline, suicide)
- Information related to the diagnosis of depression (International Classification of Diseases (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM), depressive symptoms, the possible presence of associated psychiatric symptoms, rating scales for depression and for the assessment of other psychiatric symptoms and quality of life)
- Information related to falls (single or multiple falls, the test used for motor function, presence of FOF, therapy that could affect falls and possibly the prescriber, consequences of falling)
- Primary outcome and possible secondary outcomes
- Evaluation of the quality of studies through the Newcastle-Ottawa Scale (NOS) (Ottawa Hospital Research Institute, 2020) and the bias risk assessment tool developed by the Scottish Inter-Collegiate Guidelines Network (SIGN) (Checklists, 2020)

Qualitative data was described in two narrative tables, reporting the description of studies.

2.4. Evaluation of the quality of the studies

Two different tools were used to assess the quality of studies: the NOS (Ottawa Hospital Research Institute, 2020) and the bias risk assessment tool developed by the SIGN (Checklists, 2020). The evaluation was carried out by two evaluators independently. Any discrepancies between evaluators were resolved by a third-party evaluator. The NOS consists of two different checklists: one for the evaluation of cohort studies, and one for case-control studies. Each of the two checklists allows the attribution of scores for selection (maximum score 4), comparability (maximum score 2), and outcome (maximum score 3). As such, the total maximum score for a study is 9 (Ottawa Hospital Research Institute, 2020).

The checklist for observational studies developed by SIGN consists of two sections, each further divided into various sub-sections. Section 1 is focused on study design and methodology; subsections allow evaluation of the risk of selection bias, performance bias, attrition bias and detection bias. Section 2 refers to the overall evaluation of the quality of the article ("high quality," "acceptable quality," or to be "rejected") according to the answers given to the questions in the previous section (Reed, 2007).

To make the scores of the two tools more comparable, the NOS scale scores were converted to categorical variables as follows (Ottawa Hospital Research Institute, 2020): articles that scored 3–4 points in the selection domain, 1–2 points in the comparability domain and 2–3 points in the outcome domain were rated as “high quality”; articles with 2 points in the selection domain, 1–2 points in the comparability domain and 2–3 points in the outcome domain were rated as “acceptable quality”; and last, those with a score of 0–1 in the selection domain, 0 points in the comparability domain and 0 points in the outcome domain were rated as “to reject”.

2.5. Statistical analysis

The quantitative data were analyzed through Stata Statistical Software: Release 13 (StataCorp, 2013) using descriptive statistics, which made it possible to obtain: frequency distributions of dichotomous quantitative variables and divided into classes, standard deviations for continuous variables, and contingency tables.

A random-effects meta-analysis model was computed. Different meta-analytic estimates have been provided for the study outcome. The final pooled estimate was reported in term of Odds Ratio effect with 95% confidence interval. The publication bias assessment has been performed by visually inspecting the funnel plot representation.

The meta-regression estimate was also reported according to identified risk of bias categories in order to identify a possible effect of the study quality on the final outcome.

Results and study level estimates were represented in a forest plot. The statistical significance was set at a p-value < 0.05. The analyses were performed using R 3.3.5 (R Core Team, 2018) with metaphor packages (Viechtbauer, 2010).

3. Results

Search process on PubMed, Scopus, PsycINFO, Embase, and Cochrane identified a total of 11,322 records. At the end of the selection process, 18 studies meeting the inclusion criteria were eventually included in the review, as shown in the PRISMA flow diagram (Fig. 1). The main results emerging from the included articles are summarized below; more information about each article is presented in Table 1.

3.1. Characteristics of the included studies

Half of the studies included in the review were published since 2016 (Atlas et al., 2017; Carrière et al., 2016; Choi et al., 2020; Hajek et al., 2018b; Lee et al., 2017; Lin et al., 2019; Park et al., 2017; Rakhshani et al., 2019), while only two studies were published before 2005 (Gagnon et al., 2005; Miller and Pantel, 2003). As far as geographical distribution is concerned, six of the 18 studies included were conducted in Asia (33.3%) (Chou and Chi, 2008; Ku et al., 2013; Kwan et al., 2012; Lin et al., 2019; Park et al., 2017; Rakhshani et al., 2019), three in Europe (16.7%) (Carrière et al., 2016; Hajek et al., 2018b; van Haastregt et al., 2008), five in America (27.8%) (Choi et al., 2020; Gagnon et al., 2005; Lin et al., 2019; Miller and Pantel, 2003; Quach et al., 2013), and four in Oceania (22.2%)(Anstey et al., 2008; Atlas et al., 2017; Kerse et al., 2008; Lee et al., 2017). The study design was prospective longitudinal in most cases (55.5%) (Anstey et al., 2008; Atlas et al., 2017; Carrière et al., 2016; Chou and Chi, 2008; Hajek et al., 2018b; Kwan et al., 2012; Lee et al., 2017; Lin et al., 2019; Quach et al., 2013), in others cross-sectional in (38.8%) (Gagnon et al., 2005; Kerse et al., 2008; Ku et al., 2013; Lin et al., 2019; Miller and Pantel, 2003; Park et al., 2017; Rakhshani et al., 2019; van Haastregt et al., 2008), and in one retrospective (Choi et al., 2020). Nine studies (52.94%) (Anstey et al., 2008; Hajek et al., 2018b; Kerse et al., 2008; Kwan et al., 2012; Lin et al., 2019; Miller and Pantel, 2003; Park et al., 2017; Rakhshani et al., 2019; van Haastregt et al., 2008) were monocenter, while eight (47.06%) (Carrière et al., 2016: Choi et al., 2020; Chou and Chi, 2008; Gagnon et al., 2005; Kerse et al., 2008; Lee et al., 2017; Quach et al., 2013) were multicenter.

3.2. Population

The mean number of study participants was 19,644.60 (SD 72.948.8), ranging from a minimum of 58 subjects (Miller and Pantel, 2003) to a maximum of 311,218 (Kwan et al., 2012); a majority of studies (44.5%) had a sample size between 500 and 1000 subjects (Anstey et al., 2008; Atlas et al., 2017; Hajek et al., 2018b; Ku et al., 2013; Lin et al., 2019; Park et al., 2017; Quach et al., 2013; van Haastregt et al., 2008), while only two studies examined a cohort of more than 20,000 participants (11.1%) (Kerse et al., 2008; Lee et al., 2017).

Regarding the setting, about half the studies (44.5%) (Anstey et al., 2008; Atlas et al., 2017; Carrière et al., 2016; Hajek et al., 2018b; Kerse et al., 2008; Lin et al., 2019; Quach et al., 2013; van Haastregt et al., 2008) investigated a population of older people living at home (Gagnon

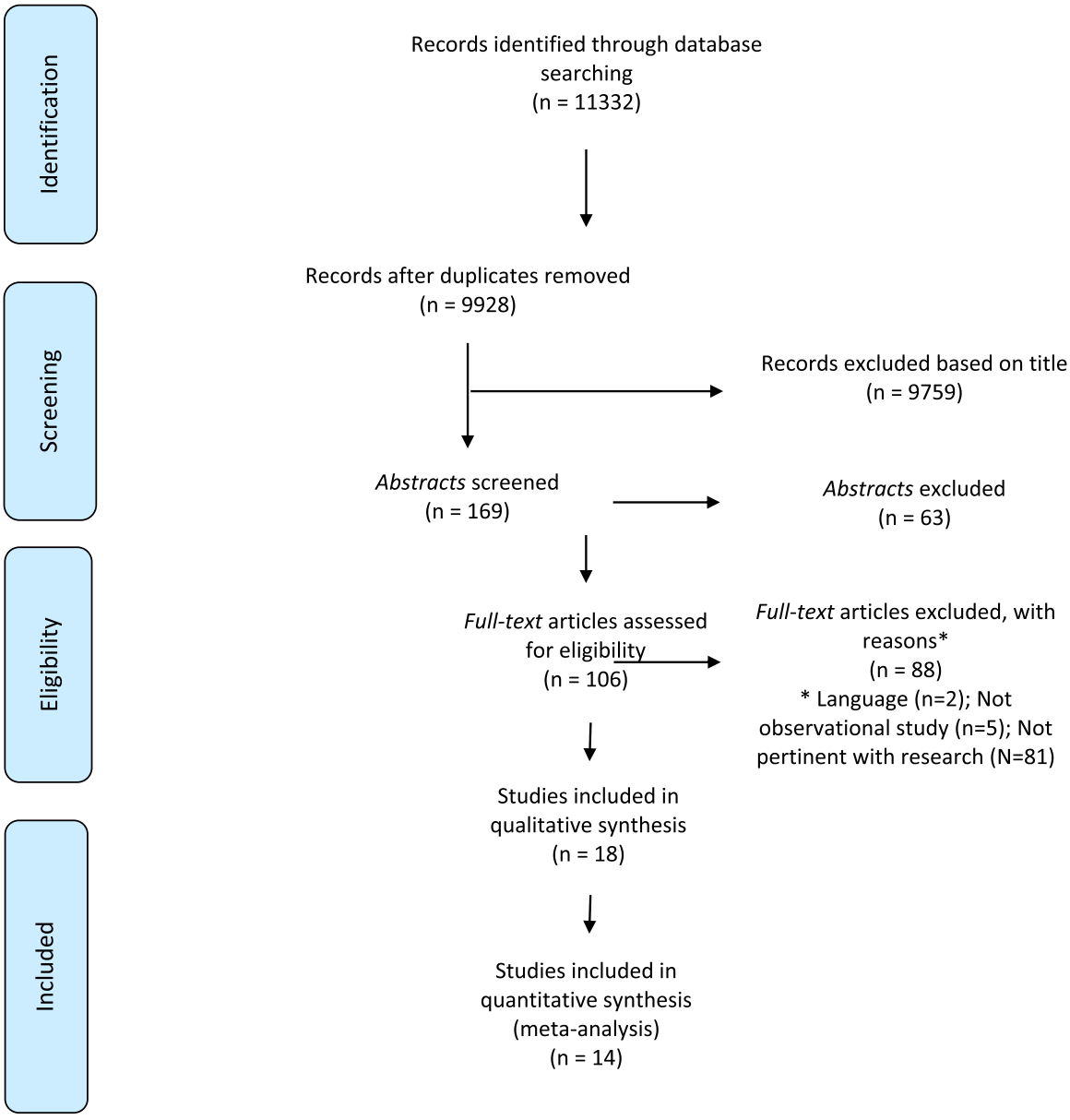

Fig. 1. Select articles using preferred reporting items for systematic reviews and meta-analyses (PRISMA 2009 Flow Diagram): Identification of 18 articles to be analyzed.

et al., 2005; Lee et al., 2017); two studies included only subjects living in long-term care facilities for senior citizens (Chou and Chi, 2008; Lin et al., 2020), and another two articles (Gagnon et al., 2005; Lee et al., 2017) reported on patients in a hospital setting.

Overall, the samples included older people aged between 71.8 and 88.9 years (Hajek et al., 2018b; Kerse et al., 2008), mainly females (61.1%). Thirteen studies (Kerse et al., 2008; Anstey et al., 2008; Carrière et al., 2016; Chou and Chi, 2008; Hajek et al., 2018b; Kwan et al., 2021; Lee et al., 2017; Lin et al., 2019; Miller and Pantel, 2003; Park et al., 2017; Quach et al., 2013; Rakhshani et al., 2019; Lin et al., 2020; van Haastregt et al., 2008) reported the percentage of male; overall, the mean rate of male participants was 35.99% (CI: 34.63–37.35).

Participants' mean age was reported by 11 studies (Kerse et al., 2008; Anstey et al., 2008; Carrière et al., 2016; Chou and Chi, 2008; Gagnon et al., 2005; Ku et al., 2013; Kwan et al., 2012; Miller and Pantel, 2003; Park et al., 2017; Quach et al., 2013; Lin et al., 2021; van Haastregt et al., 2008), and was 77.8 years (CI: 76.0–80.8). About half (44.4%) of the studies assessed drop-out rates (Atlas et al., 2017; Carrière et al., 2016; Chou and Chi, 2008; Hajek et al., 2018b; Kwan et al., 2012; Lee et al., 2017; Miller and Pantel, 2003; Quach et al., 2013) which ranged from 1.1% (van Haastregt et al., 2008) to 40.55% (Atlas et al., 2017).

3.3. Therapy

Some of the studies (33.3%) assessed whether the participants were taking medication that acted on the central nervous system (Anstey et al., 2008; Carrière et al., 2016; Kerse et al., 2008; Kwan et al., 2012; Lin et al., 2019; Quach et al., 2013); in particular, most of them focused on the correlation between antidepressant use and the risk of falls (Carrière et al., 2016; Kerse et al., 2008; Lin et al., 2019; Quach et al., 2013; see later in the text for details). Only one study assessed the intake of psychotropic therapy as a confounding factor, and it found no correlation between medications and the risk of falls (Anstey et al., 2008). Kerse and colleagues (2008) evaluated the use of antidepressants, as well as that of anxiolytic, hypno-inducing and antipsychotic

Table 1
Analysis of the literature on the correlation between depression, antidepressants, falls and FOF in the elderly.

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
Anstey 2008	Australia (Oceania) 1992–2000	N = 787 Average age = 75.6 years M = 42,2% Drop out = N.S.	Prospective cohort study	Home	Generic depressive symptoms	T1 0 drops = 591 1 fall = 121 Multiple drops = 75	N.S.	Mini-Mental State Examination (MMSE) Center for Epidemiologic Studies - Depression scale (CES-D) Desired Control Measures (DCM) Self-Rated Health (SRH)	Diabetes (6.2%) Cardiovascular diseases (25.9%) Other pathologies (% N.S.)	N.S. psychotropic	(I) Evaluate the association between moral, depressive symptoms, the expectation of control and increased risk of falling. (II) Evaluate whether the decline in welfare indices is associated with an increase in the sink rate. (III) Evaluate whether there is a reduction in the effect size after adjustment for the confounders	Depressive symptoms, reduced expectation of control, and low morale are risk factors for a subsequent fall. Depressive symptoms, reduced thymic tone and the psychological dimension of control predict the rate of decline over the next 8 years.
Atlas 2017	New Zealand (Oceania) 2010–2016	N = 937 Average age = 83.6 years M = 414 (44.2%) Drop out = 83.6%	Prospective cohort study	Home	Generic depressive symptoms	N = 492 (52.5%) Of those who fell: 27%: 2 falls; 17%: 3 falls; 23%: 4 or more.	N.S.	Geriatric Depression Scale (GDS) Falls: self-reported	N.S.	N.S.	Examine the association between falls and depression in Maori and non-Maori octogenarians	Fewer falls among Māori (47%) than non-Māori (57%); 19% of non-Māori and 20% of Maori obtained an indicative GDS score of depression. In the entire study population, people with depression were more likely to fall than Maori who was not diagnosed with depression (OR 2.72, CI 1.65–4.48 for non-Māori and OR 2.01, CI 1, 25–3.25 for the Māori).
Carrière, 2016	French (Europe) 1999–2001.	N = 6599: Non-fallers N = 5326; Fallers N =	Longitudinal cohort study	Home	General depressive symptoms within the	Fallers N = 1273	Non-fallers: 16.15% Fallers: 27.73%	Rosow and Breslau mobility scale Instrumental	Cardiovascular diseases (% N. S.) Osteomuscular	SSRI non-fallers = 130 SSRI fallers N = 71	Examine the associations between the use of SSRIs and the fall or	SSRI intake was significantly associated with a higher risk of

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Table 1 (*continued*)

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
		1273 Average non-fallers age = 73 years Average fallers age = 75 years Drop out = N.S.			story major depressive episode		IRR 1.39; CI (1.22–1.57)	The activity of Daily Living (IADL) The activity of Daily Living (ADL) MMSE CES-D	pathologies (18.9%)		incidence of fractures.	falls (OR, 95%, CI = 1.58 (1.23–2.03)) and fractures (OR, 95%, CI = 1.61 (1.16–2.24)). Risks had increased by 80% in patients chronically taking SSRI
Choi 2020	USA (North America) 2015–2016	N = 6299 Average years age (over or equal to 65) = N.S. M = 45%	Retrospective cohort study	Own domicile or residential care facilities	Generic depressive symptoms	Number of T1 falls: Multiple 13.26%; Single 17.47%; None 69.28% Number of T2 drops: Multiple 13.80%; Single 17.94%; None 68.26%	Concern to fall limit activity to T1: 8.30%; No activity restrictions: 17.5% No fear: 73.6% Concern to fall limiting T2 activity: 9.68%; No activity restrictions: 19.8%; No fear: 70.5%	Patient health questionnaire (PHQ-2) ADL IADL Concern to fall and concern that limited activities measured with two questions	Diabetes (% N. S.) Cardiovascular diseases (46.7%) Stroke sequelae (% N.S.) Osteomuscular pathologies (% N.S.) Oncological diseases (% N. S.) Other (% N.S.)	N.S.	Examine the relationship between likely major depression and the concern to fall that limits activity.	Subjects with activity limitation due to concern of falling to T2 were significantly more likely to experience depression than those without limitation of activity (OR = 2.64, IC 95% = 1.98–3.51) Subject with probable depression greater than T2 was more likely to limit activity due to concern to fall (AOR = 2.42, 95% IC = 1.66–3.52). Subjects with probable prolonged major depression were more likely to have T2 Activity limitations due to concern to fall than those with no likely major depression (AOR = 2.31, IC 95% = 1.62–3.29). Increased FOF is associated with an increased risk

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Table 1 (*continued*)

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
												for major depression, regardless of falls, previous health conditions, and likely previous episodes of major depression.
Chou 2008	Hong Kong (Asia) 1999–2000	N = 321 Average age = 72.6 years Males = 48% Drop out = 29.8%	Prospective longitudinal study	Health centers for elderly	Generic depressive symptoms	N.S.	18.1%	Minimum Data Set for Home Care (MDS-HC) IADL	N.S.	N.S.	(I) Evaluate the association between FOF and depression (II) Investigating the mutual relationship between FOF and depression (III) Examining the media role of physical disability and withdrawal from social activity	The FOF at T1 predicted the presence of depression at T2; the presence of depression at T1 did not predict the FOF at T2. Social functioning has the role of mediator between FOF and depression.
Gagnon 2005	Canada (North America) N.S. period	N = 105 Average age = 78.2 years F = 91 (86.7%) M = 14 (13.3%) Drop out = N.S.	Retrospective cohort study	Hospital wards (internal medicine/ orthopaedics	DSM N = 20 (19%)	Average: 2.7 falls	N = 57 (54.3%) No/ slight fear N = 48 (45.7%) moderate/ severe fear	Modified Falls Efficacy Scale (MFES) MMSE Hospital Anxiety and Depression Scale (HADS) Structured Clinical Interview for DSM-IV (SCID) Physical Illness Rating Scale Philadelphia Geriatric Centre Pain Intensity Scale Timed Up and Go test Bedford Life Events and Difficulties Schedule modified for elderly subjects	N.S.	N.S.	Determine whether clinically significant depression and anxiety were independently associated with FOF	Depressive disorders, the severity of depression and anxiety associated independently with FOF. Found greater association with depression.
				Home			N.S.			N.S.		

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Table 1 (*continued*)

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
Hajek 2018	Germany (Europe) January 2014- February 2015; September 2015- July 2016.	N = 547 Average age = 88.9 years M = 44% Drop out = 9.3% Individuals recruited by the AgeQualiDe study	A multicenter longitudinal study. Individuals recruited by the AgeQualiDe study.		Generic depressive symptoms	20.7% a T1 25% a T2		Global Deterioration Scale (GDS) Lubben social network scale (LS) The instrumental rental activity of daily living (IADL) GDS Comparative analysis of Social Mobility in Industrial nations Barthel Index	Comorbidity (not-specified pathologies)		Investigating the impact of falls on depressive symptoms among people ages > 85	The occurrence of falls was associated with an increase in depressive symptoms, regardless of changes in civil status, social support, functional decline, cognitive impairment, and increased chronic diseases, depressive symptoms were associated with functional impairment.
Kerse 2008	Australia (Oceania)	N = 21,596 Average age = 71.8 years M = 9522 (41.6%) Drop out = NA	Cross-sectional study	Home	Generic depressive symptoms	47.3%: 1 fall 27.1%: 2 falls	N.S.	PHQ-9 36-item Short-Form health survey (SF 36)	Stroke sequelae (% N.S.) Osteomuscular pathologies (57.0%) Obesity (% n.s) Other pathologies (% N.S.)	Antidepressants 12% Anxiolytics 5% Antipsychotics 2% Other drugs in action on CNS	Evaluate whether the use of medical therapy is associated with the risk of damaged or indistinctive fall.	The use of antidepressants (especially SSRIs) was strongly associated with falls regardless of the presence of depressive symptoms. Both depression and its treatment are independently associated with an increased risk of falls. Depression is independently associated with multiple drops while antidepressants are associated with falls (1 fall, 2 or + drops) and post-fall injuries.
Ku 2013	Asia 2009–2010	N = 940 Average age= 85.5	Cross-sectional Study	Non-sanitary retirement homes	Generic depressive symptoms	Falls:17.2% recurring falls: 6.9%	N.S.	GDS	Diabetes (11.09%) Cardiovascular	N.S.	Study the prevalence and frequency of falls	No significant differences in demographic

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Table 1 (*continued*)

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
		years M = 100% Drop out = N.S.			Depression Fallers (N = 162): 44.4%; Non fallers (N = 778): 33.7%				diseases (45.7%) Other (% N.S.)		and identify factors associated with falling among older Chinese men.	factors between those who had recurrent falls and those who had non-recurring falls. Those who had recurrent falls had a significantly higher rate of depression than those who had single falls. The only depressive state was associated with recurrent falls [OR: 1.22; CI: 1.12 and 1.32;).
Kwan 2012	Taiwan (Asia) Period= 2 years	N = 260 Average = 74.9 years M = 150 (57.7%) Drop out = 6.8%	Prospective longitudinal study	Home	Generic depressive symptoms	N = 86 (33.1%) one or more falls	N.S.	GDS-15 MMSE Make Incidental and Planned Exercise Questionnaire (IPEQ) Items from SF12 Timed Up and Go test	Diabetes (21.5%) Cardiovascular diseases (21.5%) Stroke sequelae (2.3%) Osteomuscular pathologies (16.9%) Obesity (% n.s)	Excluded patients in antidepressant therapy	Determine the incidence of falls in Taiwanese home-based seniors not on antidepressant therapy. Examine the extent to which a wide range of psychological, physiological, logical and functional factors influence the risk of falling.	Depressive symptoms are prevalent in patients with recurrent falls (40.0%) and in those who fell only once (27.5%) compared to those who did not fall (16.1%). Depressive symptoms, poor depth perception, reduced lower limb strength and increased instability independent and significant predictors of falls.
Lee 2017	Australia (Oceania) January 2013-September 2014	N = 311 (218 subjects concluded follow-up at 6 months) Average age = 78.4 years	Prospective cohort study	Hospital	Generic depressive symptoms	11% a T0	N.S.	Cognitive Impairment Test GDS Phone-FITT household and recreational subscales	N.S.	N.S.	Investigate the temporal relationships between depressive symptoms, fall and participation in physical activities in elderly people	Depressive symptoms associated with falls reported in the following month (un fixing OR: 1.20 (1.12, 1.28) and

(*continued on next page*)

Table 1 (*continued*)

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
		M = 42.1% Drop out = N.S.									recently discharged from the hospital	physical activity levels were associated with reported falls in the following month (undead OR: 0.97 (0.96, 0.99). Falls, physical activity and depressive symptoms were associated with each other, and depressive symptoms and low levels of physical activity preceded falls.
Lin 2019	Brazil (South America) 2015–2016	N = 811 Average age = 81.65 years Males = 27.1% Drop out = N.S.	Prospective cohort study	Home	DSM-5	179 falls after 12 months follow up	N.S.	MMSE IADL Basic ADL GDS Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight (FRAIL)	Diabetes (31.7%) Cardiovascular diseases (81.1%) Stroke sequelae (% N.S.) Respiratory diseases (% N.S.) Osteomuscular pathologies (34.6%) Obesity (% N.S.)	SSRI	Assess whether the risk of elderly falls is associated with the use of SSRI in monotherapy; assess whether this association was mediated by the presence of depressive disorder and/or fragility.	The use of SSRIs, depression and frailty were independently associated with an increased risk of falls during follow-up. Patients with unhealed depression and concomitant use of SSRIs did not show an increase in falls compared to depressive states in remission using SSRIs or depressed patients not on SSRIs. Conversely, the concomitant use of SSRIs and frailty increases the risk of falling. The use of SSRIs among elderly people is associated with an increased risk

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Table 1 (*continued*)

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
												of falling, regardless of depression and/ or frailty.
Lin 2020)	China (Asia) July to November 2018	N = 335 Age = 60–69 years N = 165 (49.25%); Age = 70–79 years: N = 124 (37.01%); Age ≥ 80: N = 46 (13.73%) M = 47.47% Drop out = N.S.	Cross-sectional study	Home	Generic depressive symptoms	Yes	N.S.	Self-Depression Scale (SDS) SF-12 Family APGAR Score (APGAR)	N.S.	N.S.	Explore the state of psychological health and quality of life, probe the interrelationships between depression, family function, number of falls and quality of life.	Significant effect ($\beta = -0.58$) of depression on quality of life consisting of a direct effect ($\beta = -0.51$) and an indirect effect ($\beta = -0.07$), mediated by family function and the number of falls.
Miller 2003	USA (North America) N.S. period	N = 61 (58 complete and reported). Average age = 79.2 years Males = 25.86% Drop out = N.S.	Observational study	Non-sanitary retirement homes	Generic depressive symptoms	N.S.	Yes (31%)	Time Get Up and Go test GDS MFES Beck Anxiety Inventory (BAI) Modified Falls Interview Schedule-Worry (MFIS-W) ADL	Chronic comorbidities	N.S.	Explore the association between depression/anxiety and concern to fall/ worry about falling while performing specific daily life activities.	Impaired walking and balance were related to worry about falling as measured on MFIS-W. While difficulties in gait and balance, high scores on the GDS and BAI scale were not correlated with the fear of falling as measured on MFES.
Park 2017	Korea (Asia) September 2005 – August 2006	N = 977 Age = 77.2 years M = 431 (44.1%) Drop out = N.S.	Longitudinal cohort study	Inhabitants of the city of Seongnam (over 65 years of age)	Generic depressive symptoms	Average drops: 1.65	Medium FOF: 2.22	SF-36 MMSE CES STAI Performance-Oriented Assessment of Mobility Assessment (POMA) ADL IADL	Yes (N.S. pathologies)	N.S.	Evaluate the association between falls and depressive symptoms in elderly people living in communities. Also, evaluate how gender influences the association between falls and depressive symptoms.	Depressive symptoms have shown a significant correlation with the previous number of falls; depression was strongly associated with falling even after checking for other variables, including FOF. However, this result was only

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Table 1 (*continued*)

Study (author/ year)	Country/ period of study	Population (number, age, gender, drop out)	Type of study	Setting (**Own** domicile, nursing home)	Diagnosis (ICD or DSM, depressive symptoms)	Falls	FOF	Scales of assessment	Comorbidity	Patient therapy	Main outcomes	Results
												valid for female participants.
Quach 2013	USA (North America) September 2005- April 2009	N = 7663 Average = 78 years M = 274 (36%) Drop out = 1%	Perspective longitudinal study	Home	DSM	Fall rate: 26/100 people/ year	N.S.	CES-D revisited MMSE Trails B (executive function)	Generic chronic diseases with only obesity specified (% N. S.)	Antidepressants N = 93 (12%)	Examine the association between depression and antidepressant therapy, with internal and external falls.	Depression associated with indoor and outdoor falls. Use of antidepressants associated with an increased risk of caution outdoors but not indoors.
Rakhshani 2019 (31)	Iran (Asia) N.S. period	N = 500 Age 60–64: 34.38% Ages 65–69: 21.19% Ages 70–74: 17.15% Age 75 + : 27.28% M = 51.2% Drop out = 0	Cross-sectional study	Home	Generic depressive symptoms	N.S. number of falls	Low FOF: 64.44% Medium FOF: 5.63% High FOF: 3.05%	HADS (FES) Physical evaluation	Diabetes (19.29%) Cardiovascular diseases (32.36%) Osteomuscular pathologies (23.58%)	N.S.	(I) Examine the association between depression/anxiety and FOF (II) Evaluate sociodemographic variables and explore whether physical and mental conditions were predictors of FOF.	Besides, having physical or mental disorders is more associated with FOF or the risk of falling. The association between physical health conditions with the development of anxiety/ depression disorders and FOF in the elderly can be the result of functional impairment and loss of confidence.
van Haastregt 2008 (33)	Netherlands (Europe) November 2002- July 2003	N = 540 Age = 77.6 years M = 28% Drop out = 0	Cross-sectional study	Home	Generic depressive symptoms	Yes	Moderate FOF: 55% Severe FOF: 45%	HADS Specific questions to analyze the FOF Medical Outcome Study Short Form-20	N.S.	N.S.	(I) Assess the presence of anxiety and depression among older people who avoid activity due to FOF. (II) Assess whether anxiety and depression are independently associated with the severity of FOF and the avoided activities related to it.	Anxiety and depression most common in people with severe FOF. Depressive symptoms more closely associated with FOF than anxious symptoms.

medications, which were taken respectively by 4.4%, 5% and 2.1% of the sample, and found no increase in the risk of a single fall (respectively: OR 1.04, CI 0.79–1.37; OR 1.16, CI 0.94–1.43; OR 1.06 CI 0.76–1.48) or multiple falls (OR 0.90, CI 0.69–1.16; 1.11, CI 0.89–1.38; OR1.33, CI 0.95–1.86).

3.4. Comorbidities

About 70% of the included studies (Anstey et al., 2008; Carrière et al., 2016; Choi et al., 2020; Hajek et al., 2018b; Kerse et al., 2008; Ku et al., 2013; Kwan et al., 2012; Miller and Pantel, 2003; Park et al., 2017; Quach et al., 2013; Rakhshani et al., 2019; van Haastregt et al., 2008) assessed chronic organic comorbidity and accounted for comorbidities as possible confounding factors in the statistical analysis to reduce bias. Among comorbidities, cardiovascular diseases was the most frequently assessed (Anstey et al., 2008; Carrière et al., 2016; Choi et al., 2020; Ku et al., 2013; Kwan et al., 2012; Lin et al., 2019; Rakhshani et al., 2019); its prevalence among participants ranged from a minimum of 21.5% (Kwan et al., 2012) to a maximum of 81.1% (Lin et al., 2019).

3.5. Rating scales

A great heterogeneity was found in the psychometric rating scales used. The most frequently used are described below, while more details are available in Table 1.

The most-used scales for the assessment of depressive symptomatology were the Geriatric Depression Scale (GDS) and the Center for Epidemiological Studies-Depression (CES-D) scale, which were used in six (38.9%)(Atlas et al., 2017; Hajek et al., 2018b; Ku et al., 2013; Kwan et al., 2012; Lee et al., 2017; Lin et al., 2019; Miller and Pantel, 2003) and four studies (22.2%) respectively (Carrière et al., 2016; Choi et al., 2020; Chou and Chi, 2008; Hajek et al., 2018b; Lin et al., 2019; Miller and Pantel, 2003; Park et al., 2017). Several studies (38.9%) assessed functional status, in most cases (38.9%) with the Instrumental activities daily living (IADL) scale (Carrière et al., 2016; Choi et al., 2020; Chou and Chi, 2008; Hajek et al., 2018b; Lin et al., 2019; Miller and Pantel, 2003; Park et al., 2017), with others (16.7%) investigated that parameter with the Basic Activities of Daily Living (BADL) scale (Carrière et al., 2016; Choi et al., 2020; Lin et al., 2019). The Falls Efficacy Scale in its original (FES) (Gagnon et al., 2005; Miller and Pantel, 2003) or modified (MFES) version (Kwan et al., 2012; Rakhshani et al., 2019) was mainly used for the evaluation of falls and FOF.

3.6. Association

The primary objective of this review was to investigate the potential association between the presence of depressive symptomatology, FOF, use of antidepressant therapy and risk of falls. Each correlation will be discussed below.

3.6.1. Association between depressive symptomatology and risk of falls

Eleven of the 18 studies included in the systematic review found an association between depressive symptoms and falls (Anstey et al., 2008; Atlas et al., 2017; Hajek et al., 2018b; Kerse et al., 2008; Ku et al., 2013; Kwan et al., 2012; Lee et al., 2017; Lin et al., 2019; Lin et al., 2019; Park et al., 2017; Quach et al., 2013), with depressive symptomatology being a predictor of future falls (Anstey et al., 2008; Atlas et al., 2017; Kwan et al., 2012; Lee et al., 2017; Lin et al., 2019; Quach et al., 2013). For example, The study of Kerse et al. (2008) highlights the association between depression and the risk of a single fall (OR 1.19, CI 0.86–1.64) as well as the fact that the increased risk of multiple falls or falls resulted in physical injury (respectively OR 1.70, CI 1.25–2.31; OR 1.71, CI 1.27–2.30); due to the cross-sectional nature of the study, however, the direction of causality of this relationship is unclear. Finally, Hajek and colleagues (2018) linked falls to a greater development of depressive symptoms (R^2: 0.03), suggesting a possible role of FOF as a mediator.

3.6.2. Association between FOF and depression

Seven of the 18 included studies specifically investigated the construct of FOF (Choi et al., 2020; Chou and Chi, 2008; Gagnon et al., 2005; Miller and Pantel, 2003; Park et al., 2017; Rakhshani et al., 2019; van Haastregt et al., 2008van Haastregt et al., 2008), and most of those studies (Choi et al., 2020; Chou et al., 2008; Rakhshani et al., 2019; van Haastregt et al., 2008) found a relationship between depression and FOF. In more detail, the study of Choi et al. (Choi et al., 2020) found a bidirectional association between FOF and depressive symptoms; the presence of FOF at baseline predicted the development of depressive symptoms at follow-up (AOR 2.64, CI 1.98–3.51) and vice versa. In the study of Chou et al. (Chou and Chi, 2008), it emerged instead that the presence of FOF was predictive of the development of depressive symptoms, while the inverse relationship was not observed.

A couple of studies (Rakhshani et al., 2019; van Haastregt et al., 2008) assessed the relationship between anxious and depressive symptoms and FOF. Rakhshani et al. (2019) found a significant association between the two variables (AOR: 3.7; CI: 2.2–6.2), but, in the study by van Haastregt et al. (2008).

3.6.3. Association between the use of antidepressants and the risk of falls

Few studies evaluated the association between the use of antidepressant therapy and the risk of falls (Carrière et al., 2016; Kerse et al., 2008; Lin et al., 2019; Quach et al., 2013). Kerse et al. (2008) examined the risk of single and multiple falls resulting in physical injury (respectively OR 1.43, CI 1.16–1.56; OR 1.46, CI 1.25–1.70; OR 1.29, CI 1.12–1.49). Quach et al. (2013)reported a similar risk of falls (70%; IRR 1.70, CI 1.16–2.49) in patients taking antidepressants and describe an association of antidepressants with falls in the external environment rather than at home (IRR 1.53, CI 1.05–2–25 respectively; IRR 0.94, CI 0.64–1.37). Finally, the work of Lin et al. (2019) also confirms that SSRI use did not increase the fall risk associated with depression without frailty, but, in cases of frailty, it significantly increased the fall risk associated with it.

3.7. Meta-analysis

The meta-analysis included 14 studies (Anstey et al., 2008; Carrière et al., 2016; Choi et al., 2020; Chou and Chi, 2008; Gagnon et al., 2005; Hajek et al., 2018b; Kerse et al., 2008; Ku et al., 2013; Kwan et al., 2012; Lee et al., 2017; Quach et al., 2013; Rakhshani et al., 2019; Lin et al., 2020; van Haastregt et al., 2008) reporting odds ratio (OR) statistics. As regards three studies (Atlas et al., 2017; Lin et al., 2019; Miller and Pantel, 2003; Park et al., 2017) the confounding agents were not adequately managed in the development of the statistical models, such as OR, risk ratio (RR), or absolute risk (AR); therefore, these studies were not included in the meta-analysis, such as the Park et al.'s study (2017) which was excluded from the meta-analysis because of its low quality, and the fact that it did not report any data about sample.

There was a low heterogeneity across the studies, except for the study by Park et al. (2017) which reported a strong association between depression and the risk of falls (OR = 16.12, CI: 10.29–25.25). Pooling the data of seven observational studies (Kerse et al., 2008; Anstey et al., 2008; Ku et al., 2013; Kwan et al., 2012; Lee et al., 2017; Quach et al., 2013; Lin et al., 2020) did not reveal pooled effect sizes for depression (random effect = 1.07; 95% CI: 0.95–1.21) (Fig. 2) on the risk of fall. Only one study (Hajek et al., 2018b) reported a strong and inverse

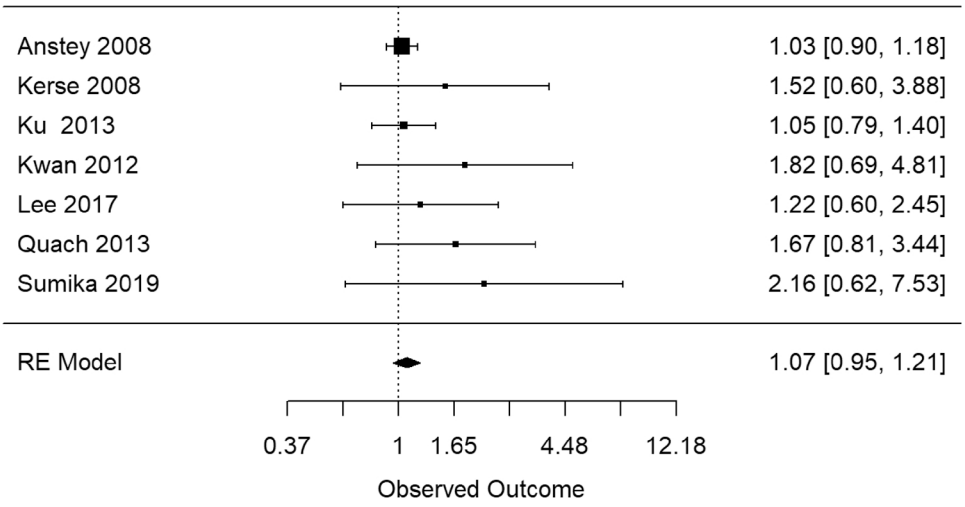

Fig. 2. Forest plot – depression and risk of falls (OR). Meta-analysis baseline model showing OR (odds ratio) and 95% CI risk of falls comparing individuals with depression or depressive symptoms to individuals without depression or depressive symptoms in a random-effect model. Random effects model of depression on risk of falls. The summary estimates were obtained using a random-effects model. The data markers indicate the Observed Outcome in depressed participants compared with non- depressed individuals. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data markers indicate the pooled OR. CI indicates confidence interval.

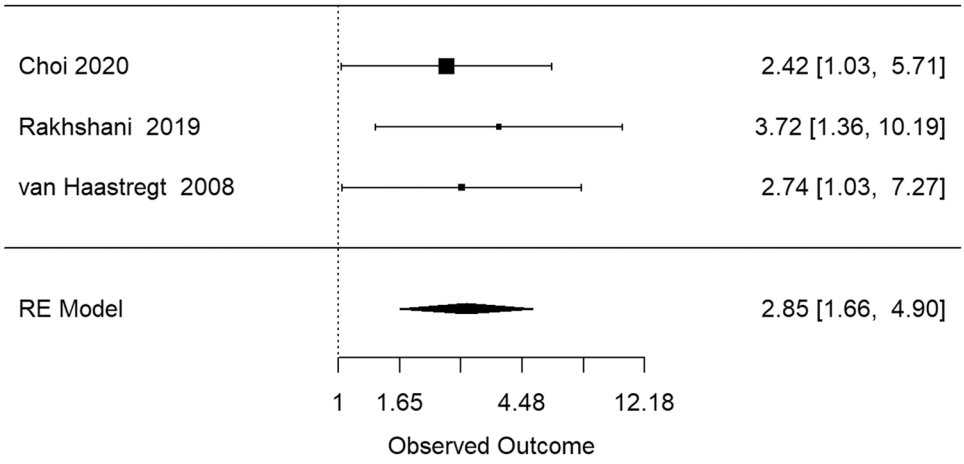

Fig. 3. Forest plot – depression and FOF. Meta-analysis baseline model showing OR (odds ratio) and 95% CI FOF comparing individuals with depression or depressive symptoms to individuals without depression or depressive symptoms in a random-effect model. Random effects model of depression on FOF. The summary estimates were obtained using a random-effects model. The data markers indicate the Observed Outcome of development of fof. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data markers indicate the pooled OR. CI indicates confidence interval.

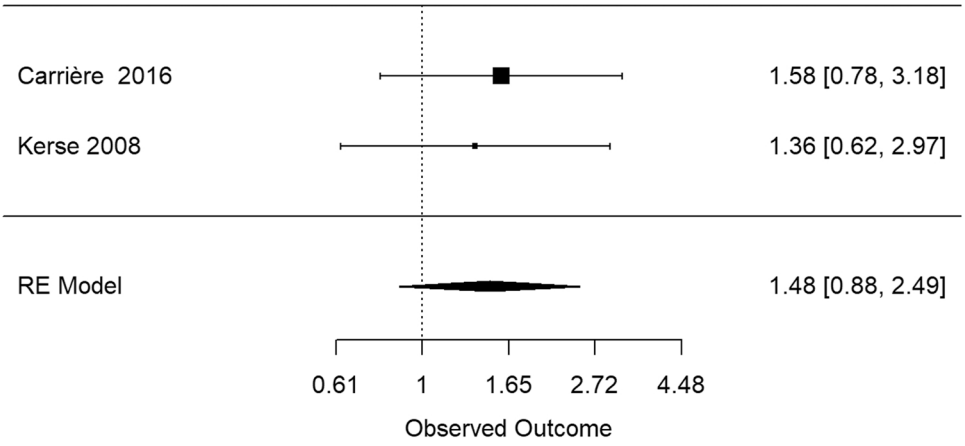

Fig. 4. Forest plot – antidepressants and risk of falls. Meta-analysis baseline model showing OR (odds ratio) and 95% CI risk of falls comparing individuals who use antidepressants to individuals without individuals who do not use antidepressants in a random-effect model. Random effects model of antidepressants on risk of falls. The summary estimates were obtained using a random-effects model. The data markers indicate the Observed Outcome in individuals who take antidepressants compared with individuals who do not take antidepressants. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data markers indicate the pooled OR. CI indicates confidence interval.

association between the risk of fall and depression (OR = 2.73, 95% CI: 2.54–2.94). One study (Choi et al., 2020) reported a strong association between FOF and depression (OR = 2.64, CI: 1.25–5.58), while pooling data from three studies (Choi et al., 2020; Rakhshani et al., 2019; van Haastregt et al., 2008) showed a strong association between depression and FOF (OR = 2.85, CI: 1.66–4.90) (Fig. 3). Pooling data from two studies (Kerse et al., 2008; Carrière et al., 2016) did not show any association between the use of antidepressants drugs and the risk of falls (OR = 1.48, CI: 0.88–2.49) (Fig. 4).

According to the funnel plot (Fig. 5), there was no asymmetry among the observational studies, neither for the studies evaluating the association between depression or the use of antidepressant drugs and increased risk of falls nor for the studies that correlated FOF and depression. A visual inspection of the funnel plots of observational studies shows a weak indication of publication bias (Fig. 5).

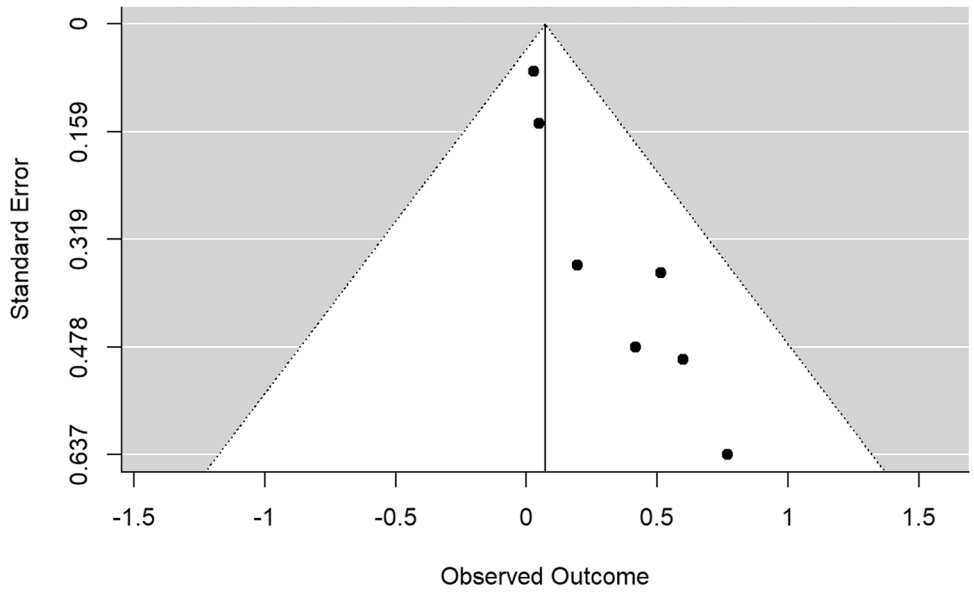

Fig. 5. Funnel plot of depression and risk of falling studies for evaluation of publication bias.

3.8. Evaluation of the studies' quality

The two instruments used (NOS and SIGN) found sufficient agreement in the evaluation of the studies' quality, with 61% of the studies receiving the same evaluation according to the two scales (Anstey et al., 2008; Atlas et al., 2017; Carrière et al., 2016; Choi et al., 2020; Chou and Chi, 2008; Hajek et al., 2018b; Kwan et al., 2012; Lee et al., 2017; Lin et al., 2019; Miller and Pantel, 2003; Quach et al., 2013). (Table 2).

Regarding the results of the NOS scale, the lowest average scores were found in the comparability domain; three studies obtained a score of 0 in this field (Atlas et al., 2017; Miller and Pantel, 2003; Rakhshani et al., 2019), and only two studies obtained the maximum score (Carrière et al., 2016; Lee et al., 2017). By contrast, the selection and outcome domains had more satisfactory average scores.

In the SIGN assessment is concerned, the domain with the greatest risk of bias was the measurement of attrition bias. Specifically, half of the studies (Atlas et al., 2017; Choi et al., 2020; Gagnon et al., 2005; Ku et al., 2013; Miller and Pantel, 2003; Park et al., 2017; Quach et al., 2013; Rakhshani et al., 2019; van Haastregt et al., 2008) did not provide sufficient data on dropout rates or, if those rates were reported, no comparison analysis was carried out between dropouts and patients who completed the study, resulting in a possible distortion of the final results.

Table 2
Results of the evaluation of the quality of studies through the use of the NOS and SIGN scales.

Author/ Year	NOS	SIGN
Anstey 2008	High quality	High quality
Atlas 2017	To be rejected	To be rejected
Carrière *2016*	High quality	High quality
Choi 2020	High quality	High quality
Chou 2008	High quality	High quality
Gagnon 2005[a]	High quality	Acceptable
Hajek 2018	High quality	High quality
Kerse 2008[a]	High quality	Acceptable quality
Ku 2013[a]	High quality	Acceptable quality
Kwan 2012	High quality	High quality
Lee 2017	High quality	High quality
Lin 2020[a]	Acceptable	To be rejected
Miller 2003	To be rejected	To be rejected
Park 2017[a]	Acceptable	To be rejected
Quach 2013	High quality	High quality
Rakhshani 2019[a]	To be rejected	Acceptable
Van Haastregt 2008[a]	High quality	Acceptable

[a] The asterisk indicates the discrepancy between the result of the NOS and SIGN assessment tool.

3.8.1. Moderator meta-regression analysis

As highlighted in Table 3, the joint estimation of the quality of the scientific evidence included in the current systematic review did not have a significant effect on moderator meta-regression. This applies to the studies that analyzed the correlation between depression and the risk of falls (p-value = 0.75; 95% CI: 0.75–1.66) and to the studies that analyzed the association between and FOF (p-value = <0.001; 95% CI: 1.58–6.41).

Based on the quality of the studies as assessed by the SIGN scale, we report forest plots of the pooling data from studies evaluating the association between depression and the risk of falls, the association between depression and FOF, and the association between antidepressant use and the risk of falls.

As regards the association between depression and the risk of falls (Fig. 6), two studies with acceptable quality (Kerse et al., 2008; Ku et al., 2013) reported a weak but positive association between depression and the risk of falls (OR = 1.088, CI: 0.82–1.43), while five studies with high quality (Anstey et al., 2008; Kwan et al., 2012; Lee et al., 2017; Quach et al., 2013; Lin et al., 2020) reported a stronger association (OR = 1.23, CI: 0.91–1.66). Fig. 7 shows the association between depression and FOF; two studies with acceptable quality (Rakhshani et al., 2019; van Haastregt et al., 2008) report a strong association between depression and falls (OR = 3.18, CI: 1.58–6.41), while one study with high quality (Choi et al., 2020) reports a weaker but still significant association (OR = 2.42, CI: 1.03–5.71) between depression and the risk of falls. Finally,

Table 3
moderator metaregression of the association between depression with risk of fall and FOF through the evaluation of the quality of studies with the sign scale.

		estimate	se	zval	pval	ci.lb	ci.ub
DEpression and Risk of Falls	**SIGN high quality**	1.08	1.28	0.32	0.75	0.67	1.76
DEPRESSION AND FOF	**SIGN high quality**	3.18	1.43	3.23	< 0.01	1.58	6.41

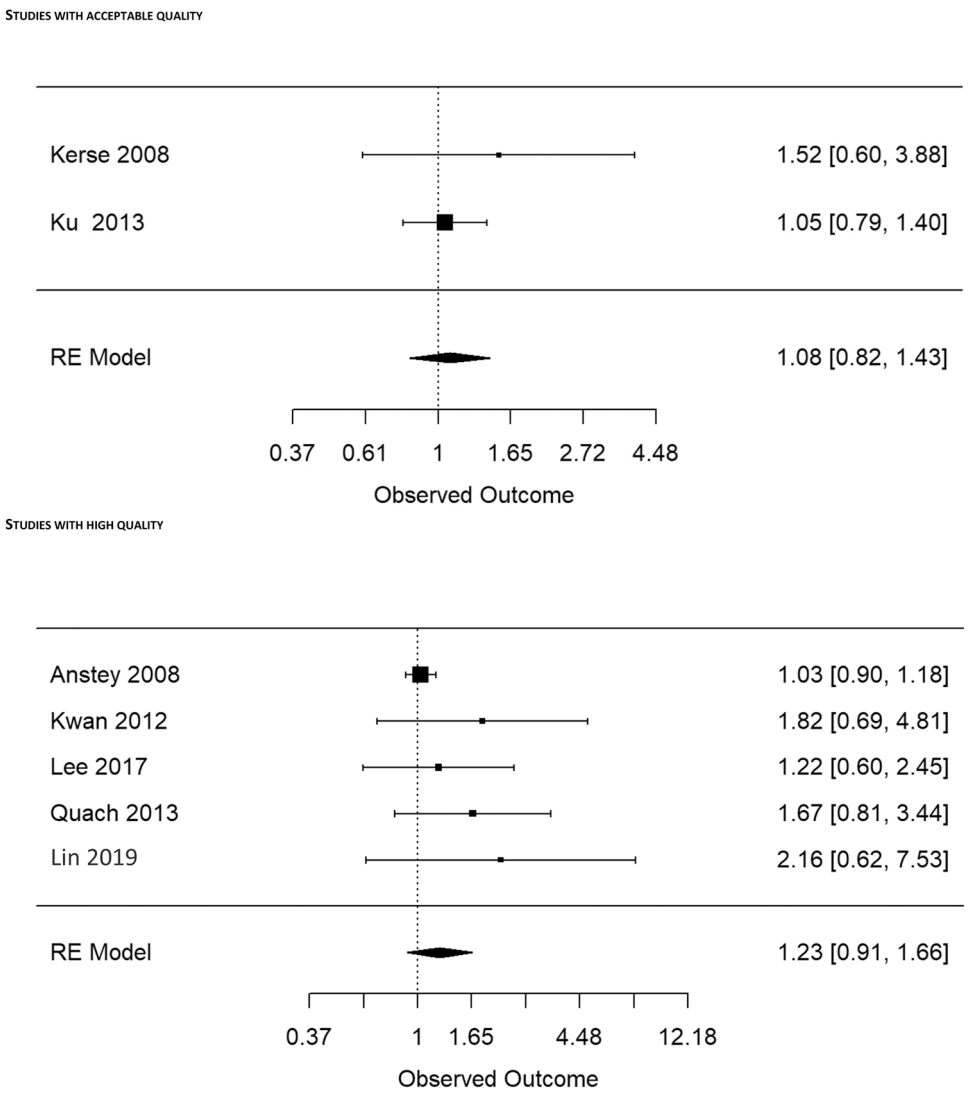

Fig. 6. Forest plot – depression and risk of falls (OR). Differentiation based on quality evaluation through sign and NOS scale.

figure 10 shows the association between antidepressants use and the risk of falls. Specifically, one study with high quality (Kerse et al., 2008) reports an association between antidepressants and the risk of falls (OR = 1.36, CI: 0.62–2.97), while another study with high quality (Carrière et al., 2016) reports a somewhat stronger association (OR = 1.58, CI: 0.78–3.18) (Fig. 8).

4. Discussion

This systematic review and meta-analysis of the literature presents data from 18 studies that evaluated the association between depressive symptomatology, FOF, the use of antidepressant therapy, and the risk of falls in people over the age of 60 years. Most of the included studies have been published after 2016 (Atlas et al., 2017; Carrière et al., 2016; Choi et al., 2020; Hajek et al., 2018b; Lee et al., 2017; Lin et al., 2019; Park et al., 2017; Rakhshani et al., 2019), which suggests a progressively growing interest on this topic.

Despite the obvious methodological differences between these included studies, their results support the hypothesis of an interdependent association between the depressive symptoms and use of antidepressant therapy, the presence of FOF, and the risk of falls. The directionality of such correlations, however, was not unambiguous, particularly considering the high percentage of cross-sectional studies, which prevents inferring the direction of the association. However, the meta-analysis shows only a significant association between FOF and depression, and no between antidepressants or depression and risk of falls.

Overall, the results from the meta-analysis unveil the lack of association between depression and falls, in contrast to other revision and meta-analysis works (Kvelde et al., 2010; Stubbs et al., 2016; Vaughan et al., 2015). This could be motivated by the fact that our work includes a substantial number of studies, with a relatively recent publication date (year of publication between 2003 and 2021), which included exclusively patients diagnosed with depression and not with depression as comorbidity as a sample of the study, and that clearly evaluate the association between depression and falls and not between depression and frailty and only consequently falls.

Many of the included studies have suggested that depressive symptoms caused the subsequent increase in the number of falls (Anstey et al., 2008; Atlas et al., 2017; Kwan et al., 2012; Lee et al., 2017; Quach et al., 2013; Lin et al., 2020). Only the study by Hajek et al. (2018a) reported a correlation in the reverse direction. Overall, these results are consistent with other previous reviews and meta-analyses, such as that published by Kvelde et al. in 2010 (2010), which highlighted the correlation between depressive symptoms and falls. Another review found that depressive disorders in subjects over the age of 55 years were strongly correlated with an increase in patient's frailty, which inevitably leads to an increased risk of accidental falls (Vaughan et al., 2015).

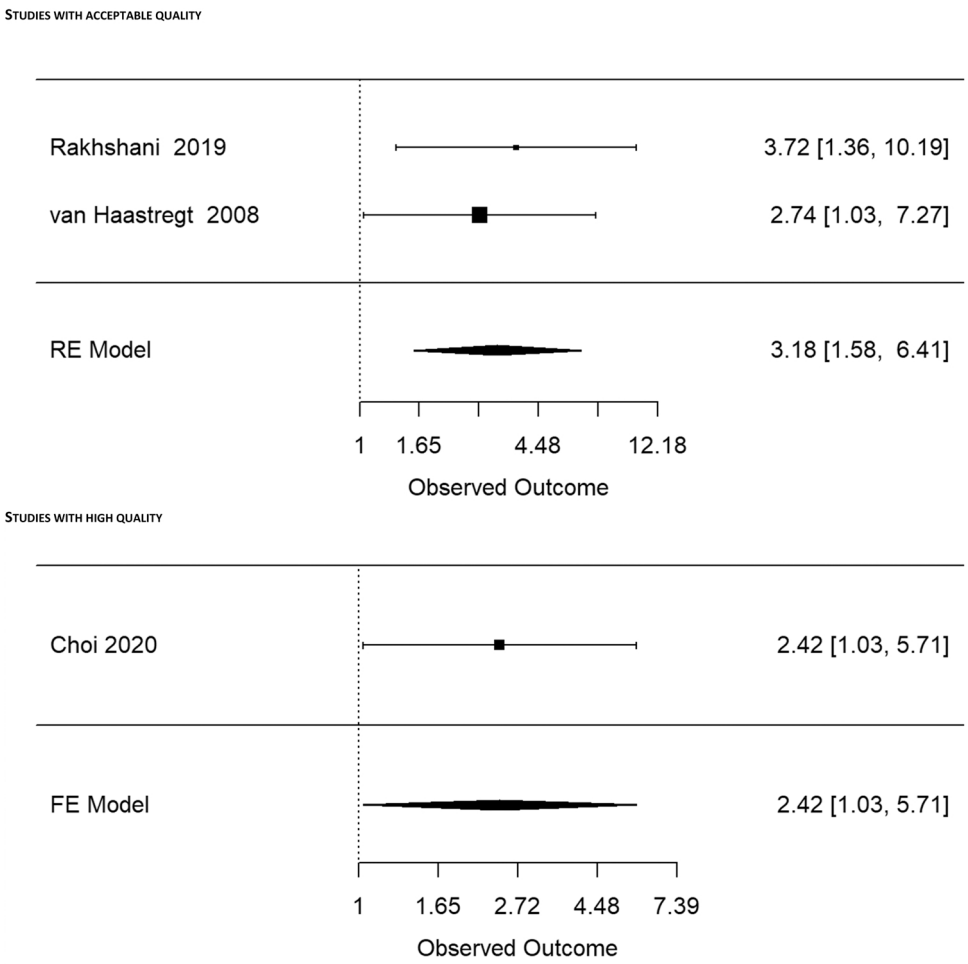

Fig. 7. Forest plot – depression and FOF. Differentiation based on quality evaluation through sign and NOS scale.

Although the precise mechanisms underlying the correlation between depressive symptoms and the risk of falls are not yet fully understood, there are many possible explanations for this relationship. Epidemiological evidence suggests that depressive symptoms in older people are associated with a very high number of known risk factors for falls, including psychomotor retardations, which can lead to a reduction in walking speed and poor balance (Iaboni and Flint, 2013; Lord et al., 1991). People with depression also tend to present with postural abnormalities and alterations in gait patterns, suggesting a possible role of physiological, rather than psychological, factors in the origin of falls. Depressive symptoms are also associated with a characteristic pattern of cognitive deficits that affect attention, executive functions, and processing speed, which can all contribute to an increased risk of falls. Geriatric depression is often frequently accompanied by a reduction in appetite with a consequent loss of weight and muscle mass, which may also increase the risk of falling.

Another systematic review and exploratory meta-analysis of 3 prospective studies (Iaboni and Flint, 2013) revealed an increased risk of falls in older adults affected by major depressive disorder (MDD) (odds ratio [OR] = 4.0, confidence interval [CI]: 2.0–8.1) and also in those living in long-term care facilities (OR = 3.3, CI: 1.6–6.8). The review of Stubbs et al. (Stubbs et al., 2016) identified only three prospective studies that had investigated the relationship between MDD and falls, which suggested a greater risk of falls among people affected by MDD compared with those who had subthreshold depressive symptoms.

Other authors have instead highlighted how falls can have an impact on many domains involved in the development of depressive symptoms, such as by increasing the FOF (Austin et al., 2007; Deshpande et al., 2008; Stubbs et al., 2016) and thus reducing the perception of one's independence and subjectively perceived well-being (Gramaglia et al., 2016; Reyes-Ortiz et al., 2005). The most likely bidirectional relationship between depressive symptoms and falls therefore appears to be very complex and may possibly be mediated by FOF. Based on the Bradford Hill criteria (Hill, 1965a, 1965b), which can be used to determine whether the observed epidemiological associations are of a causal type, it would seem that the direction of causality of the relationship between depression and falls was globally satisfied in both directions. Nonetheless, no studies have clarified the biological gradient (dose-response relationship), shown whether more severe forms of depression could cause a greater number of falls or, conversely, whether multiple falls may lead to more severe forms of depression.

After examining the FOF construct, the results of this review were consistent at highlighting an association between the presence of FOF and depressive symptomatology; however, the direction of this relationship did not appear to be entirely clear due to the cross-sectional nature of some of the available studies (Miller and Pantel, 2003; Park et al., 2017; Rakhshani et al., 2019; van Haastregt et al., 2008). The Choi et al. study (Choi et al., 2020) suggested a bi-directional correlation, while the results of Chou et al. (Chou and Chi, 2008) supported a correlation between FOF and depression, but not in the reverse direction. The presence of FOF could therefore increase the risk of falls by either acting as a mediator in the relationship between falls and depressive symptomatology (Iaboni and Flint, 2013; Payette et al., 2016) or via a direct relationship. FOF could be associated with an increased risk of future falls (Pena et al., 2019), which is likely due to its effect on gait and balance. People with a FOF tend to make disproportionate changes to

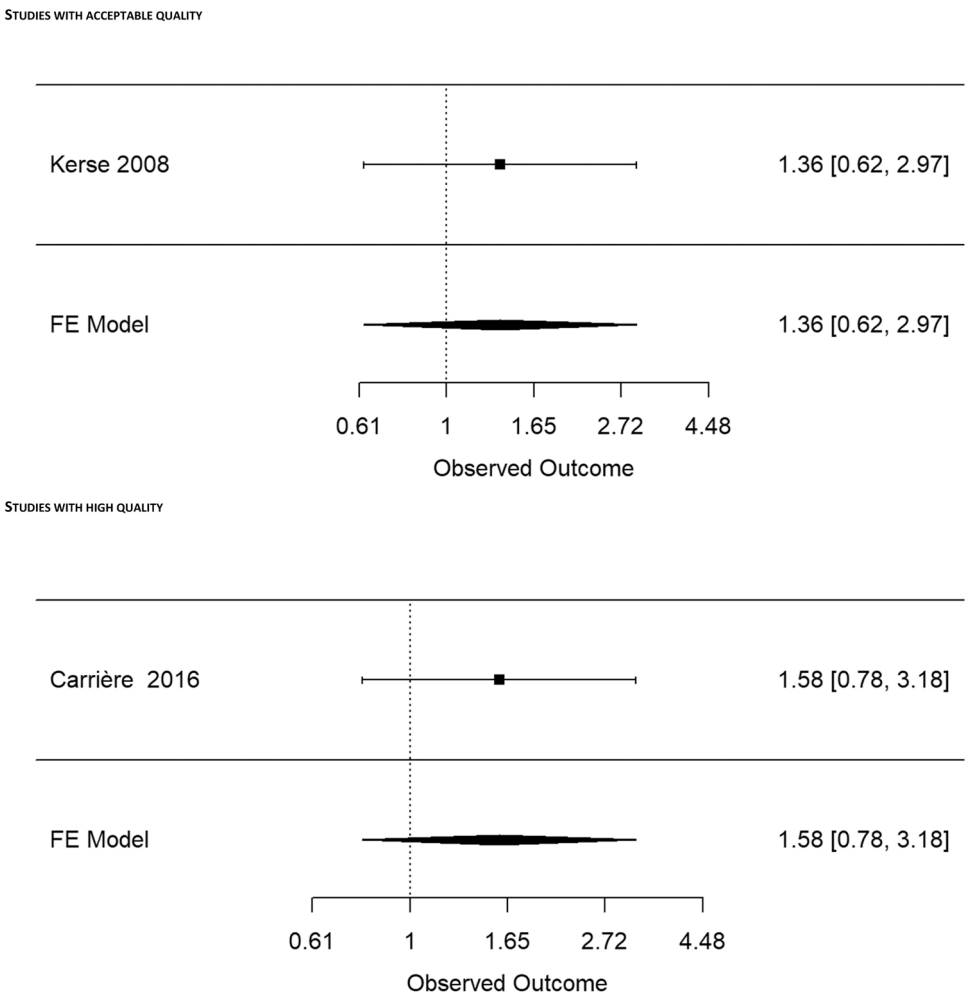

Fig. 8. Forest plot – antidepressants and risk of falls (OR). Differentiation based on quality evaluation through sign and NOS scale.

gait speed in response to a postural threat, and an excessively slowed gait can be maladaptive because it reduces stability rather than improving it (Delbaere et al., 2009; Friedman et al., 2002; Menz et al., 2007). Of course, the reverse could also be possible; in fact, the development of FOF following a first fall (Iaboni and Flint, 2013; Payette et al., 2016) seems to be true and may trigger a vicious circle of direct and indirect mechanisms (as described above) that eventually leads to an increase in the risk of subsequent falls. Similar to the relationship between depression and the risk of falls, again, referring to the Bradford Hill (Hill, 1965a, 1965b) to prove.

Finally, even if the meta-analysis did not confirm the association between the use of antidepressants in older patients and falls, all the studies included in this systematic review suggested a relationship between SSRIs in particular and an increased risk of falls (Carrière et al., 2016; Kerse et al., 2008; Lin et al., 2019; Quach et al., 2013). The studies by Kerse et al. (2008) and Carrière et al. (Carrière et al., 2016) indicated that in addition to a general major risk of falls, an increase in falls resulting in physical injuries and fractures was also present in SSRI users. Data from previous literature reviews and meta-analyses appear to support these findings (Gebara et al., 2015; Iaboni and Flint, 2013). The mechanism underlying the relationship between SSRIs and falls is likely complex and is still far from being thoroughly understood. Potential factors involved in this association include the following: possible cardiovascular effects of SSRIs; antidepressant-induced insomnia or sedation and alterations in gait (Darowski et al., 2009; Hegeman et al., 2011; Pacher and Ungvari, 2001); and the role of serotonin in bone metabolism and demineralization (Spangler et al., 2008), which can specifically account for the relationship between fractures and SSRI use. Nonetheless, some confounding factors should be mentioned, such as medical comorbidities and concomitant therapies; for example, depressive symptoms themselves have been associated with reduced bone mineral density (Yirmiya and Bab, 2009) and with a consequent increased risk of fractures (Spangler et al., 2008). These injuries could be caused by a reduction in motor activity and an increase in the inflammatory processes that occur in depression (Iaboni and Flint, 2013). The systematic revision of Gebara et al. (2015) refers explicitly to the Bradford Hill criteria and points out that they can confirm the directionality of the association between SSRIs and falls, although with some uncertainty. Further confirmation of this association is also provided by a publication of the American Geriatrics Society in 2012 that updated of the Beers criteria. These criteria, which are designed to promote the safe and effective prescription of medications to older patients, have classified SSRIs as potentially inappropriate drugs for older patients with anamnestic evidence of falls or fractures (American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012).

Fig. 9 offers an outline of the main correlations we highlighted and explains some of the physio-pathological mechanisms underlying these relationships.

It should be considered that not all people who are prescribed an SSRI have been diagnosed with MDD. As emphasized by Quach et al. (2013), although there was an association between SSRI use and the risk of falls, more than half of the population taking antidepressants had no clinically significant depressive symptoms. First Gebara et al. (2015) and then Stubbs (2015) showed that SSRIs may cause falls, but both

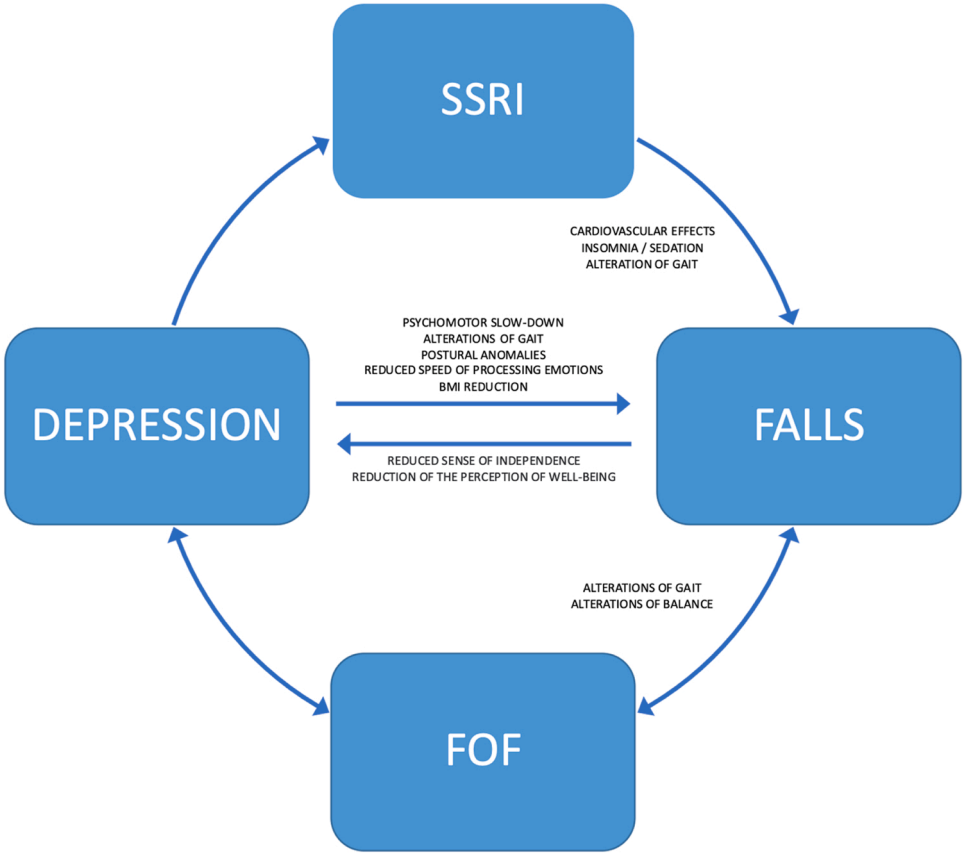

Fig. 9. Correlation between depression, FOF, SSRI use and risk of falls.

emphasized that only high-quality prospective research could clearly untangle these associations. Stubbs (2015) noted that studies analyzing the association between SSRIs and falls used different study designs or methods to collect fall data and had adjusted for a range of differing confounders in their results. The author noted that, even if SSRI medications seem to play a clear role in determining an increased risk of falls in the older people, their use in the older people would seem to correlate but not cause falls.

4.1. Strengths and limitations of the study

This work adds to the existing literature's analysis of the complex and two-way relationships that exist between different constructs: depression, use of antidepressant therapy, FOF, and the risk of falls. Indeed, other reviews and meta-analyses (Denkinger et al., 2015; Gebara et al., 2015; Kvelde et al., 2010; Payette et al., 2016) have focused on a single relationship between these constructs we have described in detail. Therefore, our approach in the current review allows a more global view of the topic and of the possible interrelationships between the constructs detailed above. The double evaluation of the studies using the NOS and SIGN scales also allowed to have a clear view of the strengths and of the issues related to the development of the study design of each of the included articles. Overall, the quality of the studies was assessed as being of high or acceptable, thus leading to the hypothesis of the sufficient reliability of the obtained results. As previously discussed, it appears necessary to consider possible interference with the obtained results due to the presence of attrition and confounding bias.

Great heterogeneity was also found regarding the type of assessment scales used. Different tools were used to measure depressive symptoms; moreover, not all studies referred to the diagnostic criteria of DSM 5 or ICD 10. Therefore, it is not completely clear to what extent it is possible to generalize from depressive symptoms to clinical depression or whether there is a linear association between the severity of the clinical depression and the risk of falling. A substantial heterogeneity was also found in the measurement of falls and their classification. Some studies have investigated the presence of single falls, while others explored multiple falls or even falls that resulted in physical injuries. Finally, the same heterogeneity was found for FOF. The authors of the studies, with the exception of Park et al. (2017), to whom we asked for the full text of the article, were not contacted. However, where available, other articles related to the single study were consulted to fill in the missing data.

5. Conclusion

The evidence available from this review and meta-analysis shows that the problem of the correlation between depression, FOF, the use of antidepressant therapy, and falls is of primary importance in older patients. The routine assessment of the risk of falls in patients older than 60 years of age should therefore also investigate the presence of depression, FOF, and any current medications. Conversely, in the evaluation of the patient suffering from late life depression, an in-depth assessment of the risk of falls should also be recommended.

The strongest association, resulting by meta-analysis, seems to be between FOF construct and depressive symptomatology, even if not entirely clear due to the cross-sectional design of some of the available studies. The presence of FOF acts as mediator in the relationship between falls and depressive symptomatology (Iaboni and Flint, 2013; Payette et al., 2016), or via direct relationship, finally increasing the risk of falls. The effect on gait and balance of FOF could be associated with an increased risk of future falls, due to the fact that subjects with FOF tend to make disproportionate changes to gait speed, and an excessively slowed gait can be maladaptive, as it reduces stability, rather than improving it (Delbaere et al., 2009; Friedman et al., 2002; Menz et al., 2007). Of course, the reverse could also be possible: in fact, the

development of FOF following a first fall (Iaboni and Flint, 2013; Payette et al., 2016) seems to be truthful, thus triggering a vicious circle of direct and indirect mechanisms (as described above) that eventually leads to an increase the risk of subsequent falls.

The results presented here indicate that therapeutic interventions to address depressive symptoms might have the additional benefit of reducing the rate of falls. Given the correlation between the use of antidepressants and the increased risk of falls, and in the light of the report of inappropriate SSRIs use among older patients based on the Bradford Hill criteria, it may be preferable to use non-pharmacological approaches for the treatment of geriatric depression (Sherrington et al., 2008). Moreover, evidence highlights how exercise programs can prevent falls in older adults (Hopewell et al., 2020) while also having a beneficial effect on depressive symptomatology (Singh et al., 2005).

Further studies with the primary objective of investigating and disentangling the mechanisms underlying the associations found in this work are needed to develop targeted and specific prevention and intervention programs, that allow empowerment of the aging process in the perspective of healthy aging, an aspect that remains poorly investigated.

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CRediT authorship contribution statement

Eleonora Gambaro: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Carla Gramaglia:** Conceptualization, Supervision, Writing – review & editing. **Danila Azzolina:** Statistical analysis. **Daiana Campani:** Conceptualization, Supervision, Writing – review & editing. **Alberto Dal Molin:** Supervision, Visualization. **Patrizia Zeppegno:** Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

Search strategy

I. **PUBMED. Records: 2643**
(aged [MeSH] OR aged [text word] OR elderly [text word] OR frail elderly [MeSH]) AND (accidental falls [MeSH] OR accidental falls [text word] OR fall [text word] OR falls [text word] OR FOF [text word]) AND (depression [MeSH] OR depression [text word] OR depress* [text word] OR depressive symptoms [text word] OR emotional depression [text word] OR depressive disorder [MeSH] OR depressive disorder [text word] OR depressive disorder, major [MeSH] OR major depression [text word] OR MDD [text word] OR major depressive disorder [text word])

II. **SCOPUS. Records: 1823**
(TITLE-ABS-KEY ("Elderly") OR TITLE-ABS-KEY ("Frail Elderly") OR TITLE-ABS-KEY ("Aged")) AND (TITLE-ABS-KEY ("accidental fall*") OR TITLE-ABS-KEY ("Falling") OR TITLE-ABS-KEY ("Fall*") OR TITLE-ABS-KEY ("Slip*") OR TITLE-ABS-KEY ("Fracture*") OR TITLE-ABS-KEY ("Fear") OR TITLE-ABS-KEY ("FOF") OR TITLE-ABS-KEY ("Fear of fall*") OR TITLE-ABS-KEY ("Prevention of falling") OR TITLE-ABS-KEY ("Prevention of fall*")) AND (TITLE-ABS-KEY ("Depression") OR TITLE-ABS-KEY ("Depressive symptoms") OR TITLE-ABS-KEY ("Emotional depression") OR TITLE-ABS-KEY ("Depressive disorder") OR TITLE-ABS-KEY ("Major depression") OR TITLE-ABS-KEY ("MDD") OR TITLE-ABS-KEY ("Major depressive disorder") OR TITLE-ABS-KEY ("Depress*")) AND NOT INDEX (medline)

III.
690. ((aged OR elderly OR frail elderly)) AND ((accidental falls OR fall OR falls OR FOF)) AND ((depression OR Depression (Emotion) OR depress* OR depressive symptoms OR emotional depression OR depressive disorder OR depressive disorder OR depressive disorder, major OR major depression OR MDD OR major depressive disorder))

IV. **EMBASE. Records: 5448**
('aged'/exp OR 'aged':ti,ab OR 'aged patient':ti,ab OR 'aged people':ti,ab OR 'aged person':ti,ab OR 'aged subject':ti,ab OR 'elderly':ti,ab OR 'elderly patient':ti,ab OR 'elderly people':ti,ab OR 'elderly person':ti,ab OR 'elderly subject':ti,ab OR 'senior citizen':ti,ab OR 'senium':ti,ab OR 'very elderly'/exp OR 'aged, 80 and over':ti,ab OR 'centenarian':ti,ab OR 'centenarians':ti,ab OR 'nonagenarian':ti,ab OR 'nonagenarians':ti,ab OR 'octogenarian':ti,ab OR 'octogenarians':ti,ab OR 'very elderly':ti,ab OR 'very old':ti,ab OR 'frail elderly'/exp OR 'frail elderly':ti,ab OR 'older adults'/exp OR 'frail older adults':ti,ab) AND ('depression'/exp OR 'depression':ti,ab OR 'Depressive symptoms '/exp OR 'Depressive symptoms':ti,ab OR 'Emotional depression'/exp OR ' Emotional depression ':ti,ab OR ' Depressive disorder '/exp OR ' Depressive disorder ':ti,ab OR 'depress*':ti,ab OR ' Major depression '/exp OR ' Major depression ':ti,ab OR ' MDD '/exp OR ' MDD ':ti,ab OR ' Major depressive disorder '/exp OR ' Major depressive disorder ':ti,ab) AND ('falling'/exp OR 'fall':ti,ab OR 'falling':ti,ab OR 'accidental falls':ti,ab OR 'falls'/exp OR 'falls accidental':ti,ab OR 'slip and fall*':ti,ab OR 'balance postural':ti,ab OR 'body equilibrium'/exp OR 'body equilibrium':ti,ab OR 'body sway':ti,ab OR 'equilibrium, body':ti,ab OR 'musculoskeletal equilibrium':ti,ab OR 'postural balance':ti,ab OR 'postural equilibrium':ti,ab OR 'fracture'/exp OR 'bone cement fracture':ti,ab OR 'bone fracture':ti,ab OR 'closed fracture':ti,ab OR 'fracture':ti,ab OR 'fractures':ti,ab OR 'fractures, bone':ti,ab OR 'fractures, closed':ti,ab OR 'skeleton fracture':ti,ab OR 'unstable fracture':ti,ab OR 'FOF'/exp OR 'basophobia':ti,ab OR 'FOF':ti,ab OR 'fear of walking':ti,ab)

V. **Cochrane. Records: 768 (26 revisions and 742 trials)**

	#	Research
Population	#1	MeSH descriptor: [Aged] explode all trees
	#2	("Aged"):ti,ab,kw OR ("Elderly"):ti,ab,kw OR ("Frail Elder*"):ti,ab,kw OR ("Functionally-Impaired Elderly"):ti,ab,kw OR ("Aged, 80 and over"):ti,ab,kw
	#3	#1 OR #2
Intervention	#4	MeSH descriptor: [Depression] explode all trees
	#5	MeSH descriptor: [Depressive disorder] explode all trees

(*continued on next page*)

(*continued*)

	#	Research
	#6	MeSH descriptor: [Depressive disorder, major] explode all trees
	#7	("Depression "):ti,ab,kw OR ("Depressive symptoms"):ti,ab,kw OR ("Emotional depression "):ti,ab,kw OR ("Depressive disorder"):ti,ab,kw OR ("Major depression"):ti,ab,kw OR ("MDD "):ti,ab,kw OR ("Major depressive disorder "):ti,ab,kw OR ("Depress*"):ti,ab,kw
	#8	#4 OR #5 OR #6 OR #7
OUTCOME	#9	MeSH descriptor: [Accidental Falls] explode all trees
	#10	("Accidental Fall*"):ti,ab,kw OR ("Falling"):ti,ab,kw OR ("Slip*"):ti,ab,kw OR ("Fall*"):ti,ab,kw OR ("Slip* and Fall*"):ti,ab,kw
	#11	MeSH descriptor: [Fractures, Bone] explode all trees
	#12	MeSH descriptor: [Fear] explode all trees
	#13	("FOF"):ti,ab,kw OR ("Fear of Fall*"):ti,ab,kw OR ("FOF"):ti,ab,kw OR ("Prevention of Fall*"):ti,ab,kw OR ("Prevention of Falling"):ti,ab,kw
	#14	MeSH descriptor: [Accident Prevention] explode all trees
	#15	#9 OR #10 OR #11 OR #12 OR #13 OR #14
	#16	#3 AND #8 AND #15

References

American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. 60 (4), 616–631. https://doi.org/10.1111/j.1532-5415.2012.03923.x.

Anstey, K.J., Burns, R., von Sanden, C., Luszcz, M.A., 2008. Psychological well-being is an independent predictor of falling in an 8-year follow-up of older adults. J. Gerontol. Ser. B, Psychol. Sci. Soc. Sci. 63 (4), P249–P257. https://doi.org/10.1093/geronb/63.4.p249.

Atlas, A., Kerse, N., Rolleston, A., Teh, R., Bacon, C., 2017. Falls and depression in octogenarians - life and living in advanced age: a cohort study in New Zealand. J. Prim. Health Care 9 (4), 311–315. https://doi.org/10.1071/HC17012.

Austin, N., Devine, A., Dick, I., Prince, R., Bruce, D., 2007. Fear of falling in older women: a longitudinal study of incidence, persistence, and predictors. J. Am. Geriatr. Soc. 55 (10), 1598–1603. https://doi.org/10.1111/j.1532-5415.2007.01317.x.

Buchner, D.M., Cress, M.E., Esselman, P.C., Margherita, A.J., de Lateur, B.J., Campbell, A.J., Wagner, E.H., 1996. Factors associated with changes in gait speed in older adults. J. Gerontol. Ser. A, Biol. Sci. Med. Sci. 51 (6), M297–M302. https://doi.org/10.1093/gerona/51a.6.m297.

Burker, E.J., Wong, H., Sloane, P.D., Mattingly, D., Preisser, J., Mitchell, C.M., 1995. Predictors of fear of falling in dizzy and nondizzy elderly. Psychol. Aging 10 (1), 104–110. https://doi.org/10.1037//0882-7974.10.1.104.

Carrière, I., Farré, A., Norton, J., Wyart, M., Tzourio, C., Noize, P., Pérès, K., Fourrier-Réglat, A., Ancelin, M.L., 2016. Patterns of selective serotonin reuptake inhibitor use and risk of falls and fractures in community-dwelling elderly people: the Three-City cohort. Osteoporos. Int.: A J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA 27 (11), 3187–3195. https://doi.org/10.1007/s00198-016-3667-7.

Checklists , 2020. SIGN. ⟨https://testing36.scot.nhs.uk⟩ (Accessed 9 November 2020) .

Choi, N.G., Gell, N.M., DiNitto, D.M., Marti, C.N., Kunik, M.E., 2020. Depression and activity-limiting fall worry among older adults: longitudinal reciprocal relationships. Int. Psychogeriatr. 32 (4), 495–504. https://doi.org/10.1017/S1041610219000838.

Chou, K.-L., Chi, I., 2008. Reciprocal relationship between fear of falling and depression in elderly Chinese primary care patients. Aging Ment. Health 12 (5), 587–594. https://doi.org/10.1080/13607860802343068.

Darowski, A., Chambers, S.-A.C.F., Chambers, D.J., 2009. Antidepressants and falls in the elderly. Drugs Aging 26 (5), 381–394. https://doi.org/10.2165/00002512-200926050-00002.

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). ⟨https://journals.lww.com/epidem/Fulltext/2010/09000/Risk_Factors_for_Falls_in_Community_dwelling_Older.20.aspx⟩.

Delbaere, K., Sturnieks, D.L., Crombez, G., Lord, S.R., 2009. Concern about falls elicits changes in gait parameters in conditions of postural threat in older people. J. Gerontol. Ser. A, Biol. Sci. Med. Sci. 64 (2), 237–242. https://doi.org/10.1093/gerona/gln014.

Denkinger, M.D., Lukas, A., Nikolaus, T., Hauer, K., 2015. Factors associated with fear of falling and associated activity restriction in community-dwelling older adults: a systematic review. Am. J. Geriatr. Psychiatry 23 (1), 72–86. https://doi.org/10.1016/j.jagp.2014.03.002.

Deshpande, N., Metter, E.J., Bandinelli, S., Lauretani, F., Windham, B.G., Ferrucci, L., 2008. Psychological, physical, and sensory correlates of fear of falling and consequent activity restriction in the elderly: the InCHIANTI study (PubMed). Am. J. Phys. Med. Rehabil. 87 (5), 354–362. https://doi.org/10.1097/PHM.0b013e31815e6e9b.

Friedman, S.M., Munoz, B., West, S.K., Rubin, G.S., Fried, L.P., 2002. Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. J. Am. Geriatr. Soc. 50 (8), 1329–1335. https://doi.org/10.1046/j.1532-5415.2002.50352.x.

Gagnon, N., Flint, A.J., Naglie, G., Devins, G.M., 2005. Affective correlates of fear of falling in elderly persons. Am. J. Geriatr. Psychiatry: Off. J. Am. Assoc. Geriatr. Psychiatry 13 (1), 7–14. https://doi.org/10.1176/appi.ajgp.13.1.7.

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. Am. J. Geriatr. Psychiatry: Off. J. Am. Assoc. Geriatr. Psychiatry 23 (10), 1016–1028. https://doi.org/10.1016/j.jagp.2014.11.004.

Gramaglia, C., Feggi, A., Bergamasco, P., Bert, F., Gattoni, E., Marangon, D., Siliquini, R., Torre, E., Zeppegno, P., 2016. Clinical characteristics associated with suicide attempts in clinical settings: a comparison of suicidal and non-suicidal depressed inpatients, 109–109. PubMed. Front. Psychiatry 7 https://doi.org/10.3389/fpsyt.2016.00109.

Granek, E., Baker, S.P., Abbey, H., Robinson, E., Myers, A.H., Samkoff, J.S., Klein, L.E., 1987. Medications and diagnoses in relation to falls in a long-term care facility. J. Am. Geriatr. Soc. 35 (6), 503–511. https://doi.org/10.1111/j.1532-5415.1987.tb01395.x.

Gualano, M.R., Bert, F., Mannocci, A., La Torre, G., Zeppegno, P., Siliquini, R., 2014. Consumption of antidepressants in Italy: recent trends and their significance for public health. Psychiatr. Serv. 65 (10), 1226–1231. https://doi.org/10.1176/appi.ps.201300510.

Hajek, A., Brettschneider, C., van den Bussche, H., Lühmann, D., Oey, A., Wiese, B., Weyerer, S., Werle, J., Fuchs, A., Pentzek, M., Stein, J., Luck, T., Bickel, H., Mösch, E., Heser, K., Wagner, M., Scherer, M., Maier, W., Riedel-Heller, S.G., AgeCoDe, AgeQualiDe Study Groups, 2018a. Impact of falls on depressive symptoms among the oldest old: results from the AgeQualiDe study. Int. J. Geriatr. Psychiatry 33 (10), 1383–1388. https://doi.org/10.1002/gps.4949.

Hajek, A., Brettschneider, C., van den Bussche, H., Lühmann, D., Oey, A., Wiese, B., Weyerer, S., Werle, J., Fuchs, A., Pentzek, M., Stein, J., Luck, T., Bickel, H., Mösch, E., Heser, K., Wagner, M., Scherer, M., Maier, W., Riedel-Heller, S.G., for the AgeCoDe & AgeQualiDe Study Groups, 2018b. Impact of falls on depressive symptoms among the oldest old: results from the AgeQualiDe study. Int. J. Geriatr. Psychiatry 33 (10), 1383–1388. https://doi.org/10.1002/gps.4949.

Hamacher, D., Liebl, D., Hödl, C., Heßler, V., Kniewasser, C.K., Thönnessen, T., Zech, A., 2019. Gait Stability and Its Influencing Factors in Older Adults. Front. Physiol. 9 (1955) https://doi.org/10.3389/fphys.2018.01955.

Hegeman, J., van den Bemt, B., Weerdesteyn, V., Nienhuis, B., van Limbeek, J., Duysens, J., 2011. Unraveling the association between SSRI use and falls: an experimental study of risk factors for accidental falls in long-term paroxetine users. Clin. Neuropharmacol. 34 (6), 210–215. https://doi.org/10.1097/WNF.0b013e31823337d1.

Herman, T., Giladi, N., Gurevich, T., Hausdorff, J.M., 2005. Gait instability and fractal dynamics of older adults with a 'cautious' gait: why do certain older adults walk fearfully? Gait Posture 21 (2), 178–185. https://doi.org/10.1016/j.gaitpost.2004.01.014.

Hill, A.B., 1965a. The environment and disease: association or causation? Proc. R. Soc. Med. 58 (5), 295–300 (PubMed).

Hill, A.B., 1965b. The environment and disease: association or causation? Proc. R. Soc. Med. 58 (5), 295–300.

Hopewell, S., Copsey, B., Nicolson, P., Adedire, B., Boniface, G., Lamb, S., 2020. Multifactorial interventions for preventing falls in older people living in the community: a systematic review and meta-analysis of 41 trials and almost 20 000 participants. Br. J. Sports Med. 54 (22), 1340–1350. https://doi.org/10.1136/bjsports-2019-100732.

Iaboni, A., Flint, A.J., 2013. The complex interplay of depression and falls in older adults: a clinical review. Am. J. Geriatr. Psychiatry: Off. J. Am. Assoc. Geriatr. Psychiatry 21 (5), 484–492. https://doi.org/10.1016/j.jagp.2013.01.008.

Kerse, N., Flicker, L., Pfaff, J.J., Draper, B., Lautenschlager, N.T., Sim, M., Snowdon, J., Almeida, O.P., 2008. Falls, depression and antidepressants in later life: a large primary care appraisal. PloS One 3 (6), e2423. https://doi.org/10.1371/journal.pone.0002423.

Ku, Y.-C., Liu, M.-E., Tsai, Y.-F., Liu, W.-C., Lin, S.-L., Tsai, S.-J., 2013. Associated factors for falls, recurrent falls, and injurious falls in aged men living in Taiwan veterans homes. Int. J. Gerontol. 7 (2), 80–84. https://doi.org/10.1016/j.ijge.2012.07.004.

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. J. Am. Geriatr. Soc. 61 (5), 694–706. https://doi.org/10.1111/jgs.12209.

Kvelde, T., Pijnappels, M., Delbaere, K., Close, J.C.T., Lord, S.R., 2010. Physiological and cognitive mediators for the association between self-reported depressed mood and impaired choice stepping reaction time in older people. J. Gerontol. Ser. A, Biol. Sci. Med. Sci. 65 (5), 538–544. https://doi.org/10.1093/gerona/glp195.

Kwan, M.M.-S., Lin, S.-I., Close, J.C.T., Lord, S.R., 2012. Depressive symptoms in addition to visual impairment, reduced strength and poor balance predict falls in older Taiwanese people. Age Ageing 41 (5), 606–612. https://doi.org/10.1093/ageing/afs065.

Lee, D.C.A., Lalor, A.F., Russell, G., Stolwyk, R., Brown, T., McDermott, F., Haines, T.P., 2017. Understanding temporal relationships between depression, falls, and physical activity in a cohort of post-hospitalized older adults—a breakthrough or a conundrum? Int. Psychogeriatr. 29 (10), 1681–1692. https://doi.org/10.1017/S104161021700103X.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339, b2700. https://doi.org/10.1136/bmj.b2700.

Lin, S.M., Borges, M.K., de Siqueira, A.S.S., Biella, M.M., Jacob-Filho, W., Cesari, M., Voshaar, R.C.O., Aprahamian, I., 2019. Serotonin receptor inhibitor is associated with falls independent of frailty in older adults. Aging Ment. Health 1–6. https://doi.org/10.1080/13607863.2019.1675143.

Lin, W.-Q., Huang, T.-Y., Liu, L., Yang, Y.-O., Li, Y.-H., Sun, M.-Y., Qin, F.-J., Yang, Q.-Y., Shen, J.-C., 2020. Prevalence and related factors of depression and falls among the elderly living in rural communities of Guangzhou. Psychol., Health Med. 25 (8), 980–988. https://doi.org/10.1080/13548506.2020.1714064.

Lord, S.R., Clark, R.D., Webster, I.W., 1991. Physiological factors associated with falls in an elderly population. J. Am. Geriatr. Soc. 39 (12), 1194–1200. https://doi.org/10.1111/j.1532-5415.1991.tb03574.x.

Menz, H.B., Lord, S.R., Fitzpatrick, R.C., 2007. A structural equation model relating impaired sensorimotor function, fear of falling and gait patterns in older people. Gait Posture 25 (2), 243–249. https://doi.org/10.1016/j.gaitpost.2006.04.005.

Miller, P., Pantel, E., 2003. Toward a more comprehensive understanding of the etiology of falls: identifying depression and anxiety in community-dwelling elders. Top. Geriatr. Rehabil. 19, 212–219. https://doi.org/10.1097/00013614-200307000-00008.

Ottawa Hospital Research Institute , 2020. ⟨http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp⟩ (Accessed 20 August 2020) .

Pacher, P., Ungvari, Z., 2001. Selective serotonin-reuptake inhibitor antidepressants increase the risk of falls and hip fractures in elderly people by inhibiting cardiovascular ion channels. Med. Hypotheses 57 (4), 469–471. https://doi.org/10.1054/mehy.2001.1366.

Park, Y., Paik, N.-J., Kim, K.W., Jang, H.-C., Lim, J.Y., 2017. Depressive symptoms, falls, and fear of falling in old Korean adults: the korean longitudinal study on health and aging (KLoSHA). J. Frailty Aging 6 (3), 144–147. https://doi.org/10.14283/jfa.2017.21.

Payette, M.-C., Bélanger, C., Léveillé, V., Grenier, S., 2016. Fall-related psychological concerns and anxiety among community-dwelling older adults: systematic review and meta-analysis. PloS One 11 (4), e0152848. https://doi.org/10.1371/journal.pone.0152848.

Peeters, G., Feeney, J., Carey, D., Kennelly, S., Kenny, R.A., 2019. Fear of falling: a manifestation of executive dysfunction? Int. J. Geriatr. Psychiatry 34 (8), 1275–1282. https://doi.org/10.1002/gps.5133.

Pena, S.B., Guimarães, H.C.Q.C.P., Lopes, J.L., Guandalini, L.S., Taminato, M., Barbosa, D.A., Barros, A.L.B.L. de, 2019. Medo de cair e o risco de queda: Revisão sistemática e metanálise. Acta Paul. De. Enferm. 32, 456–463.

Quach, L., Yang, F.M., Berry, S.D., Newton, E., Jones, R.N., Burr, J.A., Lipsitz, L.A., 2013. Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. J. Gerontol. Ser. A, Biol. Sci. Med. Sci. 68 (12), 1575–1581. https://doi.org/10.1093/gerona/glt084.

Rakhshani, T., Ansari, M.H., Ebrahimi, M., Ebrahimi, M.R., Pearson, S.K., 2019. Fear of falling and its association with anxiety and depression disorders among community-dwelling older adults. Int. J. Health Promot. Educ. 57 (6), 303–315. https://doi.org/10.1080/14635240.2019.1632731.

Reed, M.W.R., 2007. Scottish Intercollegiate Guidelines Network (SIGN) 84—National Clinical Guideline for the Management of Breast Cancer in Women1. Clin. Oncol. 19 (8), 588–590. https://doi.org/10.1016/j.clon.2007.06.006.

Reyes-Ortiz, C., Snih, S.A., Markides, K., 2005. Falls among elderly persons in Latin America and the Caribbean and among elderly Mexican-Americans. Rev. Panam. De. Salud Publica = Pan Am. J. Public Health 17 (5–6), 362–369.

Rosendahl, E., Lundin-Olsson, L., Kallin, K., Jensen, J., Gustafson, Y., Nyberg, L., 2003. Prediction of falls among older people in residential care facilities by the Downton index. Aging Clin. Exp. Res. 15 (2), 142–147. https://doi.org/10.1007/BF03324492.

R Core Team , 2018. R: a language and environment for statistical computing. R Foundation for Statistical Computing.

Sherrington, C., Whitney, J.C., Lord, S.R., Herbert, R.D., Cumming, R.G., Close, J.C.T., 2008. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J. Am. Geriatr. Soc. 56 (12), 2234–2243. https://doi.org/10.1111/j.1532-5415.2008.02014.x.

Singh, N.A., Stavrinos, T.M., Scarbek, Y., Galambos, G., Liber, C., Fiatarone Singh, M.A., 2005. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. J. Gerontol. Ser. A, Biol. Sci. Med. Sci. 60 (6), 768–776. https://doi.org/10.1093/gerona/60.6.768.

Spangler, L., Scholes, D., Brunner, R.L., Robbins, J., Reed, S.D., Newton, K.M., Melville, J.L., Lacroix, A.Z., 2008. Depressive symptoms, bone loss, and fractures in postmenopausal women (PubMed). J. Gen. Intern. Med. 23 (5), 567–574. https://doi.org/10.1007/s11606-008-0525-0.

StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP. (Version 13). (2013). [Computer software].

Stel, V.S., Smit, J.H., Pluijm, S.M.F., Lips, P., 2004. Consequences of falling in older men and women and risk factors for health service use and functional decline. Age Ageing 33 (1), 58–65. https://doi.org/10.1093/ageing/afh028.

Stubbs, B., 2015. A meta-analysis investigating falls in older adults taking selective serotonin reuptake inhibitors confirms an association but by no means implies causation. Late-Life Depress Antidepressants 23 (10), 1098. https://doi.org/10.1016/j.jagp.2015.02.004.

Stubbs, B., Stubbs, J., Gnanaraj, S.D., Soundy, A., 2016.). Falls in older adults with major depressive disorder (MDD): A systematic review and exploratory meta-analysis of prospective studies (Cambridge Core). Int. Psychogeriatr. 28 (1), 23–29. https://doi.org/10.1017/S104161021500126X.

Teixeira, A.R., Wender, M.H., Gonçalves, A.K., Freitas, C., de, L.R., Santos, A.M.P.V.D., Soldera, C.L.C., 2016. Dizziness, physical exercise, falls, and depression in adults and the elderly. Int. Arch. Otorhinolaryngol. 20 (2), 124–131. https://doi.org/10.1055/s-0035-1566304.

Tinetti, M.E., Richman, D., Powell, L., 1990. Falls efficacy as a measure of fear of falling. J. Gerontol. 45 (6), P239–P243. https://doi.org/10.1093/geronj/45.6.P239.

Turcu, A., Toubin, S., Mourey, F., D'Athis, P., Manckoundia, P., Pfitzenmeyer, P., 2004. Falls and depression in older people. Gerontology 50 (5), 303–308. https://doi.org/10.1159/000079128.

van Haastregt, J.C.M., Zijlstra, G.A.R., van Rossum, E., van Eijk, J.T.M., Kempen, G.I.J.M., 2008. Feelings of anxiety and symptoms of depression in community-living older persons who avoid activity for fear of falling. Am. J. Geriatr. Psychiatry: Off. J. Am. Assoc. Geriatr. Psychiatry 16 (3), 186–193. https://doi.org/10.1097/JGP.0b013e3181591c1e.

van Poelgeest, E.P., Pronk, A.C., Rhebergen, D., van der Velde, N., 2021. Depression, antidepressants and fall risk: therapeutic dilemmas – a clinical review (PubMed). Eur. Geriatr. Med. 12 (3), 585–596. https://doi.org/10.1007/s41999-021-00475-7.

Vaughan, L., Corbin, A.L., Goveas, J.S., 2015. Depression and frailty in later life: a systematic review (PubMed.). Clin. Interv. Aging 10, 1947–1958. https://doi.org/10.2147/CIA.S69632.

Viechtbauer, W., 2010. Conducting meta-analyses in R with The metafor Package. J. Stat. Softw. 36. https://doi.org/10.18637/jss.v036.i03.

WHO, 2020. What is Healthy Ageing?. ⟨https://www.who.int/ageing/healthy-ageing/en/⟩ (Accessed 12 August 2020) .

Whooley, M.A., Kip, K.E., Cauley, J.A., Ensrud, K.E., Nevitt, M.C., Browner, W.S., 1999. Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. Arch. Intern. Med. 159 (5), 484–490. https://doi.org/10.1001/archinte.159.5.484.

Yirmiya, R., Bab, I., 2009. Major depression is a risk factor for low bone mineral density: a meta-analysis. Biol. Psychiatry 66 (5), 423–432. https://doi.org/10.1016/j.biopsych.2009.03.016.