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PhD thesis

"HEALTHY AGING" GOAL: THE COMPLEX ASSOCIATIONS BETWEEN SENILE AGE DEPRESSION, FEAR OF FALLING AND RISK OF FALLS.
A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE LITERATURE.

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Summary

INTRODUCTION

HEALTHY AGING

The themes of old age and ageing have very ancient roots: already in the writings of Publius Terentius Afro (190-185 B.C. about - 159 B.C.) reference was made to old age, wondering if it was not itself a disease "... senectus ipsa est morbus..."; the Roman philosophical approach to old age finds expression in Cicero's "De senectute" (106 a.C. - 43 a.C.), a work in which two opposite models are integrated: the ethical one inspired *by frugalitas and archaic gravitas* and the hedonistic one, sensitive to the pleasures of existence (1,2). In more recent times, we find numerous references to the theme of old age in the works of Carl Gustav Jung (1875-1961): according to the psychoanalyst, in the years of old age individuals tend to shift their attention from the outside world to themselves becoming less dependent on the influence exerted by others and, in general, tend to be more introverted. Quoting his words, during old age "Instead, many older men prefer to be hypochondriacs, stingy, rigid, *laudatores temporis acti*, or eternally young… miserable substitution of self-enlightenment and an inevitable consequence of madness, which would claim that the second half of life was supported by the same principles as the first" (3).

From an epidemiological point of view, in recent decades there has been a global and rapid increase in the elderly population. It is estimated that by 2050 the proportion of elderly people in the world will almost double, from 12% in 2015 to around 22% in 2050. In absolute terms, this is an increase from 900 million to 2 billion people over the age of 60 (4). In this socio-cultural context, therefore, studies on healthy ageing are becoming increasingly important; the concepts of "living well" and "living healthy" however do not always coincide and it is, therefore, necessary to find a balance between the two lifestyles (5): to age well, in psychological terms, it is necessary to heal the negative antithesis *between senex* and *puer* to transform it *into positive conjunction* (1).

Until the 1960s, major ageing theories considered advancing age as a progressive and linear decline that gradually led to death. Of particular importance in this regard is Cumming and Henry's "Theory of Disengagement", according to which, ageing of success was characterized by a progressive detachment from active life in preparation for imminent death (6). In response to these theories, Robert Havighurst developed in the 1960s the "Theory of Activity", also known as the implicit theory of ageing, which

proposes that success in ageing occurs when the elderly remain active and maintain social interactions (7). Following the publication of Havighurst's theory, John W. Rowe and Robert Kahn published an article in Science, still considered a milestone in theories of healthy ageing. In this model, and those elaborated later, Rowe and Kahn identified three main components that contribute to the healthy ageing process (8):

1. Absence of illness
2. Maintenance of physical and cognitive function
3. Active engagement

Rowe & Kahn's model has since received numerous reviews, revisions, and expansions over the years (9).

Currently, the World Health Organization (WHO) defines healthy ageing as "the process of development and maintenance of functional skills that allow well-being in old age" (10). Functional skills are the result of the combination of an individual's intrinsic abilities, environmental characteristics, and the mutual interactions between these two constructs. An individual's inherent abilities include not only the person's mental and physical abilities but also the ability to walk, think, see, listen, and remember. The level of intrinsic capacity is influenced by some factors including the presence of diseases, injuries, and age-related changes. As far as environmental characteristics, they include housing, the community and, more generally, society and all the factors within it (interpersonal relationships, attitudes and codes of values, health, and social policies, etc.). It, therefore, seems that living in environments that support and maintain intrinsic skills and functional skills is the key to healthy ageing (10).

Successful ageing theories are an indispensable tool in scientific research, enabling the identification of functionality predictors, as well as the objectives towards which to aim, both at the individual and population level (11).

SENILE DEPRESSION

Epidemiology

More than 20% of people aged 60 and over suffer from a psychiatric or neurological condition, and 6.6% of Disability Adjusted Life Years (DALY), an indicator for describing the weight of accidents at work, are attributable to these disorders in this age group. Among the most common neuropsychiatric diseases, there are all forms of cognitive impairment and depression, which affect 5% and 7% of the world's population over the age of 60 (12) respectively. Other studies report that rates of depression in the elderly range from about 2% to 10% when patients with minor depression (13) are included. Rates of depression appear considerably higher in elderly patients with concomitant organic diseases and hospitalized patients. Geriatric patients admitted to hospital have rates of depression prevalence of more than 30%, in particular patients hospitalized for stroke, myocardial infarction or neoplasms (prevalence more than 40%) (14).

Depression, therefore, seems to be one of the most frequent causes of suffering in senile age, significantly affecting the quality of life of the elderly (15).

Clinical presentation

The term "senile depression" is nonspecific including elderly patients suffering from a recurrent depressive disease onset at an early stage of life and patients with depressive pathology that arose in senile age (16). However, the distinction between early and late-onset depression is supported by epidemiological, imaging, therapeutic and long-term outcome studies (17).

The symptomatologic constellation in elderly patients may not coincide with the typical constellation observed in young patients; in the elderly, non-specific symptomatology characterized by somatic complaints, insomnia, anorexia, asthenia, and cognitive deficits is more frequently observed. Often this symptomatology can be evaluated as the consequence of organic comorbidity or as a physiological effect of ageing rather than framed in the context of a mood disorder. Also, several physical disorders or their treatments can cause key symptoms of depression such as insomnia, fatigue, lack of interest, anorexia. Depressive episodes in old age are also more likely to become chronic and recovery can be

transient, with frequent relapses. The risk of relapse and chronicity also seems to be accentuated by the presence of comorbidities (17,18).

Depression in the elderly is an important risk factor for suicide: older patients attempt suicide less often than younger patients but are more successful in completing it (19,20). Male seniors have the highest suicide rate (28.9/100,000) (21); in particular, male subjects over the age of 85 have the highest full suicide rate (55/100,000) (19).

Particular attention should be paid to the acute risk of suicide in the elderly patient; predictive factors of suicide are represented by hopelessness, insomnia, agitation or restlessness, cognitive alterations, use of chronic alcohol or acute intoxication, pain not controlled by therapy. Other factors that increase the risk of suicide in the elderly patient include the presence of organic comorbidity, chronic and inadequately treated pain, terminal illness or worsening of organic pathology, social status (widowing and social isolation), previous suicide attempt and family history of suicide (20,22). However, suicidal behaviours can occur independently of a diagnosis of depression or, in broader terms, of any psychiatric diagnosis. The approach to suicide must therefore not neglect the philosophical and existential perspective. (23.24).

Risk factors

In patients who develop the first episode of senile age, the family psychiatric disorders history is found to be much lower than in patients with depression diagnosed at a young age, thus suggesting the presence of other risk factors such as (25,26):

- Female
- Social isolation
- Civil status (widowed, divorced or separated)
- Low socioeconomic status
- Organic comparability / Uncontrolled pain
- Insomnia
- Functional impairment
- Cognitive impairment

Eziopathogenetic hypotheses

The aetiology of depression and the factors influencing its course in the elderly have not yet been fully clarified, however, it is possible to hypothesize some etiopathogenic theories. According to Alexopoulous's theory (27), one of the most cited in the literature, depression in the elderly would seem to represent the clinical expression of dysfunction in reward, salience and cognitive circuits. The degree of impairment of these circuits can explain the intensity of the symptoms of the affective sphere, cognitive and motor behaviour and give the reason for the heterogeneity of clinical presentations. Genetic factors, factors related to ageing and organic pathologies (such as chronic inflammation, cardiovascular diseases, accumulation of amyloid-beta) could directly cause alterations in reward, salience, and cognitive circuits and/or compromise the front-limbic circuits that predispose to depression. Also, many of the etiological factors that affect the etiopathogenic mechanisms of depression tend to develop from middle age (hypertension, diabetes, obesity, vascular and hormonal alterations, amyloid deposition, chronic inflammatory response, alterations in neuroplasticity and synaptogenesis). Finally, senile age is often associated with stressors, both clinical and psychosocial, which can promote pro-inflammatory responses, increased reactive oxygen species, suppression of neurogenesis and dendritic atrophy, contributing to the development of depression directly, promoting front-limbic abnormalities, but also indirectly, triggering alterations in reward, salience and cognitive circuits (27).

This etiopathogenetic model has allowed the formulation of hypotheses about the relationships between etiological and predisposing factors/mechanisms, which mediate behavioural expressions, and the course of depression of the senile age. Based on this model, three depressive syndromes have been described in the elderly, which tend to overlap and recall additional pathogenic mechanisms.

1. *The hypothesis of executive dysfunction related to depression*: From the clinical point of view, it presents itself with anhedonia, psychomotor slowdown, suspiciousness, poorly pronounced depressive conception and mild vegetative symptoms. There are also alterations to verbal fluidity and problem-solving skills, reduced cognitive flexibility, alterations in working memory and ideomotor planning. This symptomatology appears to be related to modifications of subcortical frontal circuits. These depressive forms frequently develop in disorders of

subcortical structures (vascular dementia, Parkinson's disease, Huntington's disease, super-nuclear paralysis, calcification of the basal ganglia and stroke of the caudate) (27).

2. *Vascular depression hypothesis*: The concept of vascular depression appears in 1905, when elderly patients with depression secondary to arteriosclerosis (17.28) were first described. Cerebrovascular diseases can increase an elderly person's vulnerability to the development of depression through multiple neurobiological mechanisms (29). Depression can develop after an acute cerebrovascular event, the so-called "post-stroke depression" (30) or develop in combination with chronic ischemic alterations (actual "vascular depression") (27,31). Two important factors for the development of post-stroke depression are the location of the injury and the time since stroke. Patients with lesions of the left hemisphere, especially the left prefrontal cortex, tend to have more frequent depressive and more severe episodes. The riskiest period seems to be the two years following the event, with a peak prevalence within the first three to six months (30). From a clinical point of view, depending on the location and extent of cerebrovascular lesions, executive dysfunction is frequently highlighted. Depressive symptomatology is also generally characterized by psychomotor slowdown, anhedonia, absence of disease awareness. From a pharmacological point of view, the response to antidepressants is poor or very slow (27).
3. *The hypothesis of inflammation*: This hypothesis postulates that the dysregulation of the immune system related to age and concomitant pathologies can contribute to the aetiology of senile depression (27).

As already pointed out, depressed elderly patients frequently experience a certain degree of cognitive impairment, with deficits in attention and concentration, executive functions and memory that often resemble dementia frameworks. 18-57% of depressed elderly patients have dementia-like symptomatology or "demented depression syndrome", this condition was formerly referred to as "pseudo-dementia" (32). The term pseudo-dementia has historically been used to describe impairment of memory and other cognitive domains similar to dementia but caused by functional psychiatric disorders such as depression (17). Treatment with antidepressants can solve cognitive symptoms (17,33), however, these patients appear to be at greater risk of developing a picture of irreversible dementia in later years (17,34).

Diagnosis

Diagnosing a depressive episode in old age can be particularly challenging and complex because, as already pointed out, the symptoms reported may not be the typical one of a depressive episode that occurs at a young age, and several factors complicate and modify the picture. Clinical, making the diagnostic process even more difficult, such as the presence of numerous organic comorbidities, drug poly-therapy, the difficulty of the elderly patient in effectively verbalizing their suffering.

Several screening tools have been developed and validated for use both in basic medicine and in other contexts, the table below shows the most frequently used tests (35,36).

TABLE 1: SCREENING TOOLS FOR THE ASSESSMENT OF SENILE DEPRESSION (AS AMENDED BY 36)

	Sensitivity (%)	**Specificity (%)**	**Patients Hospitalized**	**Patients Outpatient**	**Comorbidities Organic**	**Cognitive Decay**
Two-question screen	97	67	--	Yes	--	No
Geriatric Depression Scale (5-item)	94	81	Yes	Yes	Yes	--
Patient Health Questionnaire-9 (9-item)	88	88	--	Yes	Yes	--
Cornell Scale for Depression in Dementia (19-item)	90	75	Yes	Yes	--	Yes
Center for Epidemiologic Studies - Depression Scale (20-item)	93	73	No	Yes	--	No

Therapy

Although ageing is a risk factor for a more unfavorable course of depressive forms, there are, however, several effective treatment options. The success of therapy depends on several factors. First of all, it is necessary to treat the comorbidity adequately, it is also necessary to adapt the interventions to the individual patient, thus customizing the treatment as much as possible, finally, it is important to closely

monitor the therapy to evaluate its effectiveness and the possible presence of side effects (27). The main guidelines have highlighted the effectiveness of both psychotherapy and pharmacological treatments: psychotherapy and pharmacotherapy can be used individually or in combination (37,38). Among psychotherapies, problem-solving therapy is particularly important for its effectiveness in older people with cognitive impairment and executive dysfunction (39). Among intervention studies, cognitive-behavioural therapy and interpersonal psychotherapy combined with antidepressant drugs are more effective in treating depression of senile age (38).

It is evident that, in the depressive disorder of this age group, the motto "start low and go slow (and keep going)" is particularly relevant. There are a series of pharmacokinetic changes related to ageing that can decrease the absorption of drugs, change their bioavailability, and increase their half-life. Given the high frequency of poly-therapy, there is an increased risk of pharmacokinetic and pharmacodynamic interactions. Also, rare side effects may be more frequent in the elderly, such as bone demineralization and serotonin syndrome; particular attention should also be paid to falls, hyponatremia and gastrointestinal bleeding associated with SSRI therapy (37). Non-pharmacological therapies include exercise, which is effective in assisting the treatment of depression in the elderly, although it may be difficult for patients with major depression to engage in a physical activity program (40).

Although senile depression is associated with an excess of morbidity and mortality and has a not insignificant weight in economic and health terms, this pathology remains underdiagnosed and often treated inadequately (41,42).

FALLS

Epidemiology

According to the definition most accredited for epidemiological research purposes, a fall is an event which as its final result the fact that a person is inadvertently and suddenly on the ground or at a lower level than he was at (43). Studies have shown that 25-40% of older people over the age of 65 experience at least one episode of fall; among those over the age of 80, it is estimated that about one in two people falls at least once a year. Falls are estimated to be the sixth most common cause of death among people

over 65 and the fifth leading cause of death among people over the age of 75 (43,44). Considering the literature, in Italy, it is estimated that about 28.6% (range 26-31%) of people over 65 fall within a year and, and among them, about 43% present episodes of multiple and recurrent accidental falls, of which 60% takes place inside the home (45).

Etiopathogenesis

The ageing process is associated with a decrease in the ability to maintain balance; sensory and motor alterations typical of old age can adversely affect balance leading to a higher frequency of falls. Although slight alterations in one of the systems responsible for maintaining balance do not cause significant disturbances, the sum of several alterations, albeit minor, can lead to serious deficits in postural stability (46,47). The risk of falls is an important clinical problem, leading to high rates of both morbidity and mortality, significant disability and a reduction in the quality of life of the elderly patient (48).

The causes that may be responsible for falls in elderly patient are manifold; in normal clinical practice, it is very rare to identify a specific one, since, more often, it is a multifactorial event.

TABLE 2: MAIN CAUSES OF FALL IN THE ELDERLY (49)

Cause	Average percentage[1]	Range[2]
Accidental – related to the environment	31%	1-53%
Gait disorder – reduction of muscle strength	17%	4-39%
Dizziness - Vertigo	13%	0-30%
Collapse	9%	0-52%
Confusion	5%	0-14%
Postural hypotension	3%	0-24%
Visual disturbance	2%	0-5%
Syncope	0,3%	0-3%
Other specified causes[3]	15%	2-39%
Unknown causes	5%	0-21%

[1]Average percentage calculated from 3,628 falls in 12 studies; [2]Minimum – maximum; [3]This category includes arthritis, acute diseases, medications, alcohol, pain, epilepsy and falling from bed.

Risk factors

Identifying risk factors for falls seems to be more useful than trying to retrospectively classify specific precipitating causes; early identification of risk factors allows for more effective preventive strategies. Table 3 lists the main risk factors for falls in elderly patients and their relative importance.

TABLE 3: FUNCTIONAL CONDITIONS INCREASING THE RISK OF FALLS IN THE ELDERLY PATIENT (49)

Functional conditions	Significant/Total[1]	RR – OR medium[2]	Range
Weakness	11/11	4.9 (8)	1.9-10.3
Balance deficit	9/9	3.2 (5)	1.6-5.4
Gait deficit	8/9	3.2 (5)	1.7-4.8
Vision deficit	5/9	2.8 (9)	1.1-7.4
Limitations of mobility	9/9	2.5 (8)	1.0-5.3
Cognitive impairment	4/8	2.4 (5)	2.0-4.7
Compromised functional state	5/6	2.0 (4)	1.0-3.1
Postural hypotension	2/7	1.9 (5)	1.0-3.4

1Number of studies in which the association was significant, divided by the number of studies that examined the factor. 2Relative Risk (from prospective studies), Odds Ratios (from retrospective studies). Incidentally, the number of studies reporting RR or OR.

Among the most frequent functional conditions related to falls, we find muscle weakness, gait problems and balance. Muscle weakness is an extremely common condition among the elderly population, mostly resulting from illness and inactivity rather than the ageing process itself (49). Case-control studies show a substantial increase in the risk of falls and fractures among subjects with gait disorders and muscle dysfunctions (49). Some screening tests are available to assess gait and balance, such as "timed up and

go" (50) or Tinetti test (51), also useful to identify the risk of falls and document the need for treatment. Drugs, in particular psychoactive drugs, have also been identified as risk factors for falls, although their relative risk is generally between 1.5 and 1.7, just below other factors included in Table 3 (49). It can be seen that the risk factors presented in Table 3 are likely to be improved, which implies the possibility of numerous fall prevention interventions in elderly patient.

FOF

FOF is a common problem in the elderly (52), with prevalence ranging from 20% to 85% depending on the study (53,54). This is a peculiar aspect, which is manifested above all among elderly patients: the fall is fearsome not only for the consequences in terms of disability but also for the psychological repercussions that follow the event itself, including the loss of safety and the FOF again.

Initially, FOF was considered a post-fall syndrome (55), however, subsequent studies have shown that it can also occur independently of falls (52-56); as age increases, the FOF significantly increases, often related to the increase in perceived fragility and not necessarily as a result of a previous fall.

FOF is burdened with a large number of adverse consequences, including limitations on mobility and/or activities resulting in deconditioning, reduction of social interactions, subsequent falls and reduction of quality of life and therefore a further decline in physical and psychological functions (52,56–58).

Multiple risk factors have been associated with the development of FOF, including (56.58–60):

- Advanced age
- Female
- History of previous falls
- Reduction in physical performance
- Depressive disorders
- Impaired cognitive function
- Live alone or have fewer social contacts
- Subjective perception of low health
- Poor level of education or illiteracy
- Chronic diseases

Finally, numerous studies have investigated the presence of FOF as an anticipatory marker of cognitive decay: the results show that it can be considered an indicator of decline in some domains of cognitive functioning, especially those related to executive functions and processing speed; in particular, associations have been found between the presence of FOF and alterations in delayed re-enactment and verbal fluidity (61).

ASSOCIATION BETWEEN SENILE DEPRESSION AND FALLS

The relationship between falls in the elderly and depressive symptomatology is complex and difficult to trace back to linear causality patterns; these phenomena would seem to be related by complex two-way interactions. So far, the well-known high incidence of falls in the elderly patient has been mainly attributed to visual or motor functional changes, as well as balance; recently some studies have shown an association between depressive symptomatology and frequency of falls, leading to hypothesize the existence of pathways common to both pathologies (62,63). Numerous risk factors for falls have been associated with depressive symptoms in elderly patients, such as cognitive impairment, slow walking, poor balance, increased reaction times and asthenia. Besides, the symptoms most characteristically associated with depressive episodes such as psychomotor slowdown, slowing of gait and speed of cognitive processing, reduction of energy levels and low levels of activity, can all result in falls, although they may themselves provoke the FOF, which in turn can lead to the development of depressive symptoms (63).

Elderly people with depression have an abnormal gait pattern (64,65) and have postural abnormalities (66), suggesting a physiological rather than psychological origin of falls. Some studies, on the other hand, show that depression is an independent factor related to fractures (67), dizziness and, as already pointed out in the previous paragraph, FOF (68). Both FOF and depressive symptomatology are independently related to stride-to-stride variability, itself an indicator of the risk of falls. It is also possible that falls may lead to the development of depression, with reverse causality ratio, reducing functional state and causing an increase in disability. (69).

The beginning and continuation of walking 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 (61).

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 (70).

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 (63). The prescription trend of antidepressants in recent years is constantly increasing (71); understanding therefore the mechanisms of the correlation between the use of these drugs and their association with falls is of particular importance. Many articles, however, generically group all psychoactive drugs, making, in fact, uncertain any inference on the pharmacological class most associated with the risk of falls (63).

Regardless of the specific mechanism involved in the relationship between depression and falls, now not yet fully clarified, the presence of falls should prompt to investigate of depressive symptomatology and vice versa. Only in this way will it be possible to offer personalized and targeted care to guarantee an ever-increasing population the conditions for healthy ageing (10,69).

Our study, therefore, aims to bridge, at least partially, the gap currently present in the literature related to the two-way association between depressive symptomatology, FOF, use of antidepressant therapy and falls to develop, in the future, effective intervention models in this field and contribute to the successful ageing process, an aspect of elderly still little investigated in the current scientific landscape.

MATERIALS AND METHODS

This work of systematic review and meta-analysis of the literature is part of the research project "Aging Project" of the Department of Translational Medicine of Università del Piemonte Orientale, funded by the Ministry of Education, University and Research (MIUR) as part of the program "Departments of Excellence 2018-2022". Specifically, this study is in a broader context designed and co-supported by Prof. From Molin, involving the Chair of Psychiatry (Prof. Zeppegno, Prof. Gramaglia), Dr. Campani and Dr Azzolina.

This review of the literature has been recorded in the PROSPERO International Database of systematic reviews (protocol number CRD42020173678) and written by PRISMA guidelines for reporting systematic reviews and meta-analysis (72).

SELECTION OF STUDIES

On 5/16/2020, the following databases were investigated: PubMed, Scopus, PsycINFO, Embase, Cochrane, using the following search strings:

1. **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])

2. **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)

3. **PsychINFO. Records: 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))

4. **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)

5. 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
	#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

The selection of studies to be included was carried out in a period between 20 May 2020 and 27 July 2020. Two reviewers (CV and MM) independently evaluated the items identified by the previously reported search strings. After removing duplicates, all items whose titles were not in line with the purpose of the work were excluded. Subsequently, all abstracts were evaluated and, finally, only full text in line with the inclusion criteria was selected, taking care to identify any publications related to a single study. Any discrepancies between reviewers have been resolved by a third-party Author (EG). Finally, studies that did not have as their primary outcome the assessment of the relationship between fall and/or FOF and depression (and vice versa) were excluded.

INCLUSION AND EXCLUSION CRITERIA

All observational clinical trials published in English in line with the following inclusion criteria have been included:

1. Age greater than or equal to 60 years
2. Any setting
3. Diagnosis of depression or treatment for depression mentioned both as a clinical diagnosis in the elderly patient, and as a predictor/consequence of falls

Studies for elderly patients with exclusively somatic problems related to falls (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-analysis, case reports, editorials, commentary, and book chapters have also been excluded from this revision work.

DATA EXTRACTION AND ANALYSIS

A data collection tool has been developed to document 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 placed in a database using a standardized and predetermined encoding. The following categorical and numerical variables have been 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, average age, social status, presence or absence of caregiver, presence of medical comorbidities and type, presence of cognitive decay, suicide)
- Information related to the diagnosis of depression (International Classification of Diseases -ICD, Diagnostic and Statistical Manual of Mental Disorders - DSM, generic depressive symptoms, the possible presence of associated psychiatric symptoms, evaluation scales used, other rating scales for evaluating psychiatric symptoms and quality of life)
- Information related to falls (single or multiple falls, the test used for motor function, presence of FOF or 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)(73) and the bias risk assessment tool developed by the Scottish Inter-collegiate Guidelines Network (SIGN) (74)

The quantitative data were analyzed through State Statistical Software: Release 13 (75) using descriptive statistics, which made it possible to obtain:

- Frequency distributions of dichotomous quantitative variables and divided into classes.
- Standard déviations for continuous variables.
- Contingency tables.

Also, qualitative data have been analyzed through the construction of two narrative tables (as will be seen in the section on the results), one on the description of studies and a second table on the evaluation of the quality of studies through the SIGN and NOS instruments.

EVALUATION OF THE QUALITY OF STUDIES

Two different tools were used to assess the quality of studies: the NOS (73) and the bias risk assessment tool developed by the SIGN (74).

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 is divided into three further sub-classifications defined as selection, comparability, and outcome.

- <u>Selection: provides a maximum score of 4.</u>

  Sample representativeness and appropriateness in recruitment methods are assessed. Furthermore, case-control studies, it allows evaluating the randomization of the recruited patients.
- <u>Comparability: provides a maximum score of 2.</u>

  The comparability of the intervention arms with the control ones or concerning the cohorts that were selected for demographic characteristics and pre-test measurements of the variables under study is evaluated.
- <u>Outcome: provides for a maximum score of 3.</u>

  The adequacy of the methods adopted for measuring the outcomes and the impact that any patients lost to follow-ups could have on the reliability of the results is verified.

Therefore, each study can total a maximum score of 9 (73).

The checklist for observational studies developed by SIGN consists of two sections, in turn, divided into various sub-sections:

- Section 1: identifies the study, its objectives, and the reviewer. The reviewer is asked to consider several aspects of the study design and to make a judgment on those aspects. Each item from which this section is formed refers to an aspect of the methodology with which the study was conducted that could influence its conclusions. Due to the potential complexity of the design of this type of study, there are relatively few criteria that automatically exclude a study, such as not using validated assessment methods or not adequately managing confounding factors. The checklist is aimed primarily at increasing confidence in the strength of the association between exposure and outcome by identifying how many aspects of a good study design are present, a study that has received poor marks in two or more of the items in this section should almost certainly be rejected. Each subsection allows evaluating the risk of selection bias, performance bias, attrition bias and detection bias.
- Section 2: refers to the overall evaluation of the article. In this section, the reviewer is required to make an overall assessment of the quality of the study based on the answers given to the questions in the previous section. The article can therefore be evaluated as of "high quality", "acceptable quality" or to be "rejected" (74).

To make the scores of the two tools more comparable, the NOS scale scores were converted to categorical variables as follows (73):

- High quality: articles that scored 3-4 points in the selection domain, 1-2 points in the comparability domain and 2 or 3 points in the outcome domain.
- Acceptable quality: 2 points in the selection domain, 1 or 2 points in the comparability domain and 2 or 3 stars in the outcome domain.
- to reject: Items with a score of 0 or 1 in the selection domain or 0 stars in the comparability domain or 0 stars in the outcome domain.

RESULTS

Bibliographic research on PubMed, Scopus, PsycINFO, Embase and Cochrane identified a total of 11,322 articles. At the end of the title selection process, abstracts and full text were found to be 18 articles that met the inclusion criteria, as shown in Prisma's flowchart (Figure 1). The text shows the salient results obtained from the revision of the literature, for a more complete treatment of the individual articles, see Table 4.

Figure 1: SELECT ARTICLES USING PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA 2009 FLOW DIAGRAM): IDENTIFICATION OF 18 ARTICLES TO BE ANALYZED.

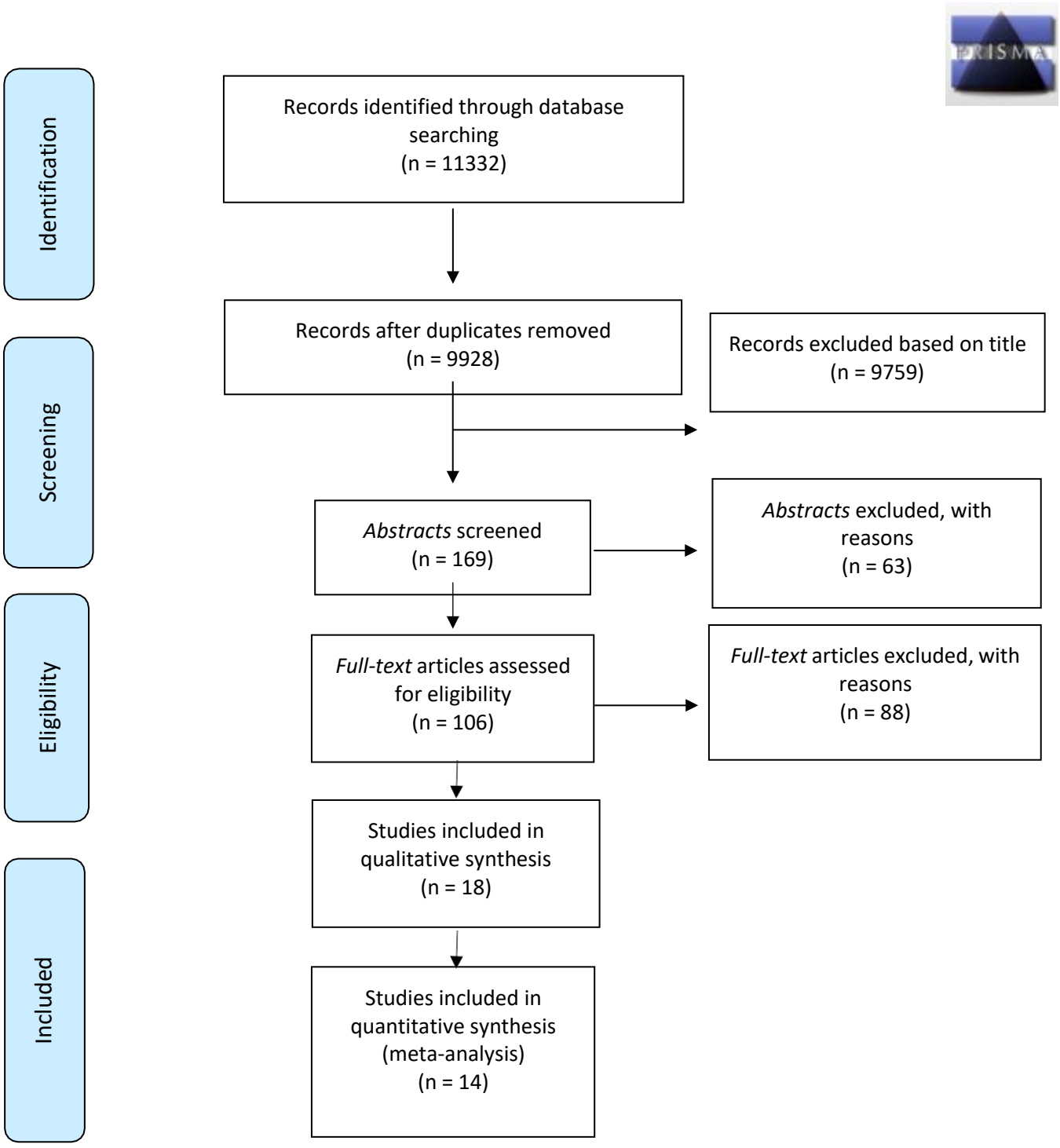


TABLE 4: ANALYSIS OF THE LITERATURE ON THE ASSOCIATION BETWEEN DEPRESSION, ANTIDEPRESSANTS, FALLS AND FOF IN THE ELDERLY.

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(76)	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 (77)	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).

Career 2016 (78)	French (Europe) 1999-2001.	N = 6599: Non-fallers N = 5326; Fallers N = 1273 Average non-fallers age = 73 years Average fallers age = 75 years Drop out = N.S.	Longitudinal cohort study	Home	General depressive symptoms within the story major depressive episode	Fallers N= 1273	Non-fallers: 16.15% Fallers: 27.73% IRR 1.39; CI (1.22-1.57)	Rosow and Breslau mobility scale Instrumental The activity of Daily Living (IADL) The activity of Daily Living (ADL) MMSE CES-D	Cardiovascular diseases (% N.S.) Osteomuscular pathologies (18.9%)	SSRI non-fallers = 130 SSRI fallers N = 71	Examine the associations between the use of SSRIs and the fall or incidence of fractures.	SSRI intake was significantly associated with a higher risk of 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 (79)	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 for major depression, regardless of falls, previous health conditions, and likely previous episodes of major depression.

Chou 2008 (80)	Hong Kong (Asia) 1999-2000	N = 321 Average age = 72.6 years Males = 48% Drop out = 29.8%	Perspective longitudinal study	Health centres 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 (81)	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.

Hajek 2018 (82)	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.	Home	Generic depressive symptoms	20.7% a T1 25% a T2	N.S.	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)	N.S.	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 (69)	Australia (Oceania)	N = 21596 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 (83)	Asia 2009-2010	N = 940 Average age= 85.5 years M = 100% Drop out = N.S.	Cross-sectional Study	Non-sanitary retirement homes	Generic depressive symptoms Depression Fallers (N = 162): 44.4%; Non fallers (N = 778): 33.7%	Falls:17.2% recurring falls: 6.9%	N.S.	GDS	Diabetes (11.09%) Cardiovascular diseases (45.7%) Other (% N.S.)	N.S.	Study the prevalence and frequency of falls and identify factors associated with falling among older Chinese men.	No significant differences in demographic 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 (84)	Taiwan (Asia) Period= 2 years	N= 260 Average = 74.9 years M = 150 (57.7%) Drop out = 6.8%	Perspective 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 (85)	Australia (Oceania) January 2013-September 2014	N = 311 (218 subjects concluded follow-up at 6 months) Average age = 78.4 years M = 42.1% Drop out = N.S.	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 recently discharged from the hospital	Depressive symptoms associated with falls reported in the following month (un fixing OR: 1.20 (1.12, 1.28)) and 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 2020 (86)	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 (β = −0.58) of depression on quality of life consisting of a direct effect (β = −0.51) and an indirect effect (β = −0.07), mediated by family function and the number of falls.

Miller 2003 (87)	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 (88)	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 valid for female participants.
Quach 2013 (89)	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 (90)	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.
Sumika Lin 2019 (91)	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 of falling, regardless of depression and/or frailty.

van Haastregt 2008 (92)	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.

CHARACTERISTICS OF THE STUDIES INCLUDED

Half of the studies included in the work have been published since 2016 (77–79,82,85,88,90,91), while only two studies were published before 2005 (81,87). As far as geographical distribution is concerned, of the eighteen studies included, six were conducted in Asia (33.3%) (80,83,84,86,88.90), three in Europe (16.7%) (78,82,92), five in America (27.8%) (79,81,87,89.91) and four in Oceania (22.2%) (69,76,77,85). Most studies had a prospective longitudinal design (55.5%) (76–78,80,82,84,85,89,91), while just under half were represented by cross-sectional studies (38.8%) (69,81,83,87,88,90–92); there was only one retrospective study (79). Nine studies (76, 82, 84, 86-88, 90-92) were monocenter, eight studies (69, 78-81, 83, 85, 89) were multicenters, respectively 52,94% and 47,06% of the total. The average duration was reported by 12 studies (76, 78-80, 82, 83-85, 88-89, 91) and the complex average duration was 2.29 year (CI:
0,88.5 to 3.71), while for longitudinal studies, the average duration was 2.75 years (SD 2.33), with a minimum duration of 6 months (85) and a maximum of 8 years (76).

Evaluation of the quality of studies

Sufficient agreement was found in the evaluation of the quality of studies through the two instruments used (NOS and SIGN): 61% of studies received the same evaluation through the two scales used (76–80,82,84,85,87,89,91). Also, half of the studies were evaluated by both instruments used, as high quality (76,78–80,82,84,85,89,91), and the subsequent work of meta-analysis focused on these studies. Table 5 compares the overall scores obtained with the NOS and SIGN scale.

By evaluating the results of the NOS scale in more detail, the lowest average scores were highlighted in the comparability domain, three studies, obtained a score of 0 in this field (77,87,90) and only two studies obtained the maximum score (78,85). On the other hand, the selection and outcome domains had more satisfactory average scores, an indication of greater methodological solidity in these domains. About the evaluation carried out through the tool developed by SIGN, the domain with the greatest risk of bias was the measurement of attrition bias. Specifically, half of the studies (77,79,81,83,87–90,92) did not provide sufficient data on drop-out rates or, if these rates were reported, no comparison

analysis was carried out between dropouts and patients who had completed the study, thus resulting in a possible distortion of the final results. As regards the management of confounding agents, three studies (77,86,87) did not provide sufficient information on this subject, the potential confounders in these studies were not taken into account or were not adequately managed in the development of statistical models, so these studies will be eliminated from subsequent meta-analysis work.

TABLE 5. RESULTS OF THE EVALUATION OF THE QUALITY OF STUDIES THROUGH THE USE OF THE NOS AND SIGN SCALES

Author/ Year	**Us**	**SIGN**
Anstey 2008 (76)	High quality	High quality
Atlas 2017 (77)	To be rejected	To be rejected
Career 2016 (78)	High quality	High quality
Choi 2020 (79)	High quality	High quality
Chou 2008 (80)	High quality	High quality
Gagnon 2005 (81)*	High quality	Acceptable
Hajek 2018 (82)	High quality	High quality
*Kerse 2008 (69)**	High quality	Acceptable quality
Ku 2013 (83)*	High quality	Acceptable quality
Kwan 2012 (84)	High quality	High quality
Lee 2017 (85)	High quality	High quality
Lin 2020 (86)*	Acceptable	To be rejected
Miller 2003 (87)	To be rejected	To be rejected
Park 2017 (88)*	Acceptable	To be rejected
Quach 2013 (89)	High quality	High quality
Rakhshani 2019 (90)*	To be rejected	Acceptable
Sumika Lin 2019 (91)	High quality	High quality
Van Haastregt 2008 (92)*	High quality	Acceptable

**Studies with non-coincident evaluation*

Population

The number of study participants included was on average 19,644.60 (SD 72.948.8), ranging from a minimum of 58 subjects (87) to a maximum of 311,218 (84); in particular, most studies (44.5%) had a sample between 500 and 1,000 subjects (76,77,82,83,88,89,91,92), while only two studies examined a cohort of more than 20,000 participants (11.1%) (69,85).

As for the setting, about half of the studies (44.5%) (69,76–78,82,89,91,92) investigated a population of elderly people residing at home; two studies included only subjects residing in health centers for the elderly (80,91); finally, the presence of two articles (81,85) which recruited patients hospitalized in hospitals is of particular importance.

The sample of subjects included was made up of elderly people aged between 71.8 and 88.9 (69,82), mainly women (females 61.1%). Thirteen studies (69, 76, 78, 80, 82, 84-92) reported the percentage of male that was in media about 35,99% (CI: 34.63 to 37.35).

The medium age of the participants was reported by 11 studies (69, 76, 78, 80-81, 83-84, 87-89, 91-92), and the medium values were about 77.8 years (CI: 76.0 to 80.8). About half (44.4%) of the studies assessed drop-out rates (77,78,80,82,84,85,87.89) from a low of 1.1% (92) to a high of 40.55% (77).

Therapy

Some of the studies included (33.3%) assessed the intake of therapy for the treatment of the central nervous system (69,76,78,84,89,91); in particular, most of them focused on the correlation between antidepressant use and the risk of falls (69,78,89,91), the results of which will be reported later in the text. On the other hand, a study managed the intake of psychotropic therapy as a confounding factor and found no correlation between the use of it and the risk of falls (76). About the use of other drugs with action on the central nervous system, the study by Carrière et al. (78) also investigated the use of benzodiazepines, taken from 18.6% of the sample, without finding a significant increase in the risk of falls in patients using these drugs (p =0.14, HR 1.11, CI 0.97;1.26). The study by Kerse et al. (69) evaluated, in addition to the use of antidepressant drugs, also the impact of anxiolytic, hypno-inducing and antipsychotic drugs, taken respectively by 4.4%, 5% and 2.1% of the sample, without however finding a high increase in the risk of a 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 (OR0.90, CI 0.69-1.16; 1.11, CI 0.89-1.38; OR1.33, CI 0.95-1.86).

Comorbidities

About 70% of studies (69,76,78,79,82–84,87–90,92) assessed the concomitant presence of chronic organic comorbidity to be able to manage them as confusing in statistical analysis and reduce any distortions of outcomes related to the presence of such confounders.

More than half of the articles (55.5%) (76,78–82,84,88,89,92) assessed the presence of cognitive impairment through the administration of the Mini-Mental State Examination (MMSE), but using different cut-off values (76,78,81,84,88,89,91) or other tests such as the Global Deterioration Scale (GDS) (82) and Morris Performance Scale (MPS) (82).

As regards the presence of other comorbidities, the most frequently evaluated were cardiovascular diseases were, considered in seven articles (76,78,79,83,84,90,91), in which the overall prevalence of patients with this comorbidity ranges from a minimum of 21.5% (84) to a maximum of 81.1% (91).

Rating scales

A great heterogeneity has been found about rating scales used, so only the scales most frequently used are reported in the text, while reference is made to Table 4 for a more detailed discussion.

The two scales most used for the diagnosis of depressive symptomatology were GDS used in six studies (38.9%) (77,82–85,87,91) and the CES-D used in four studies (22.2%) (78–80,82,87,88,91). Numerous studies have assessed the quality of life, using, in most cases (38.9%), the IADL scale (78–80,82,87,88,91), other studies (16.7%) instead investigated this parameter through the Basic Activities of Daily Living (BADL) scale (78,79,91). For the evaluation of falls and FOF, the Falls Efficacy Scale was mainly used, in its original version (FES) (81.87) or modified (MFES) (84,90).

Associations

The primary objective of this revision work, as explained in the previous sections, is to investigate the existence of an association between the presence of depressive symptomatology, FOF, use of antidepressant therapy and risk of falls. Therefore, the results from the eighteen included studies concerning these associations will be treated individually.

Association between depressive symptomatology and risk of falls

Of the eighteen studies that met the inclusion criteria, eleven showed an association between depressive symptoms and falls from the statistical analysis (69,76,77,82–86,88,89,91); in particular, studies with a prospective design showed that depressive symptomatology was a predictor of future falls (76,77,84,85,89,91). For example, the study of Kwan et al. (84) pointed out that the presence of depressive symptomatology was an independent predictor of recurrent falls; similarly, the article published by Lee et al. (85) indicated that higher levels of depression at the baseline were a predictor of subsequent falls (OR 1.20, CI 1.12-1.28). Also, the results of the work of Quach et al. (89) indicated that the presence of depressive symptomatology increased the risk of falls, in particular, this study showed that depressive symptomatology was related to an increased risk of falls both outside and at home (60% and 62% respectively). The study by Kerse et al. (69) stressed the presence of an association between depression and the risk of a single fall The study by Kerse et al. (69) stressed the presence of an association between depression and the risk of single fall (OR 1.19, CI 0.86-1.64), with an increase in particular in the risk of multiple falls or falls resulting in physical injury (respectively OR 1.70, CI 1.25-2.31; OR 1.71, CI 1.27-2.30); however, due to the cross-sectional nature of the study, the direction of causality of this association is less evident. Finally, the work of Hajek et al. (82) pointed out, on the contrary, that the presence of falls was linked to a greater development of depressive symptoms (β 0.60) while assuming a possible role of FOF as a mediator of this report.

Association between FOF, depression and risk of falls

Seven of the eighteen studies included specifically investigated the construct of FOF (79–81,87,88,90,92). Many of them have found a association between depression and FOF, particularly the recent study by Choi et al. (79) showed a bidirectional association between FOF and depressive symptoms: the presence of FOF at baseline was a predictor of the development of depressive symptoms at follow up (AOR 2.64, CI 1 .98 - 3.51) as well as the presence of depressive symptoms. From the results of the study by Chou et al. (80) it emerged instead that the presence of FOF was predictive of the development of depressive symptoms, but the contrary association was not valid; the authors of this study also hypothesized the presence of social functioning as a mediator of this relation. The work of Rakhshani et al. (90) evaluated the association between anxious/depressive symptoms and the

presence of FOF, finding a significant association between the two variables (AOR 3.7, CI 2.2-6.2), although the cross-sectional design of the study did not allow to infer the directionality of this association. From the results of the study published by van Haastregt et al. (92) instead it emerged that only the presence of depressive symptoms and not the presence of anxiety symptoms was associated to FOF (OR 2.43, CI 1.44-4.13).

Association between the use of antidepressant therapy and the risk of falls

Fewer studies evaluated the association between the use of antidepressant therapy and the risk of falls (69,78,89,91). The study by Kersey et al. (69) found an association between the use of antidepressant therapy and the increased risk of single and multiple falls resulting in physical (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). The article by Carrière et al. (78) found a significant increase in the risk of falls and fractures of approximately 60% in patients using SSRIs at baseline, and, also, observed an even greater increase (80%) in chronic SSRI use. Similarly, Quach et al. (89) showed, among patients in antidepressant therapy, an increased risk of falls of 70% (IRR 1.70, CI 1.16-2.49); in particular, this study showed an association with falls in the external environment rather than an increased risk of falls at home (IRR 1.53, CI 1.05-2-25 respectively; IRR 0.94, CI 0.64-1.37). Finally, also the work published by Sumika et al. (91) attested the presence of an association between the use of SSRIs and the increase in falls, but without finding an additive or multiplicative effect in patients with depression who used SSRI.

META-ANALYSIS

It was possible to conduct the multivariate statistical analysis on 14 studies (69, 76, 78-85, 89-92) reporting ODDS RATIO (OR) statistics. Three studies (86-88) were not included in the meta-analysis because they did not report OR neither Risk Ratio (RR) or absolute risk (AR). There was a low heterogeneity across studies, except for Park (88) that was excluded by meta-analysis for the low quality of the study, not reporting any data about the sample selection, even if it reported a strong association between depression and risk of falls (OR = 16.12, CI: 10.29 to 25.25), for the low quality of the study, not reporting any data about sample selection. Pooling data from 7 observational studies (69, 76, 83-85, 89, 91) showed small but significant pooled effect sizes for depression (random effect = 1.07; 95% CI: 0.95 to 1.21) (Fig 2) on risk of fall. Only one study (82) reported the strong and inverse association between risk of fall and depression (OR = 2.73, CI: 2.54 to 2.94). One study (79) reported a strong association between FOF and depression (OR = 2.64, CI: 1.25 to 5.58), while pooling data from three studies (79, 90, 92) showed the strong and association between depression and FOF (OR = 2.85, CI: 1.66 to 4.90) (Fig. 3). Pooling data from two studies (69,78) showed a moderate association between use of antidepressants drugs and risk of falls (OR = 1.48, CI: 0.88 to 2.49) (fig. 4).

According to the funnel plots (Fig 5, 6, 7) there was no asymmetry for observational studies, both for the studies evaluating the association between depression or use of antidepressant drugs and increased risk of falls, and for the studies that correlated FOF and depression. Visual inspection of the funnel plots for observational studies showed weak indication of publication bias (Fig 5, 6, 7).

Figure 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.

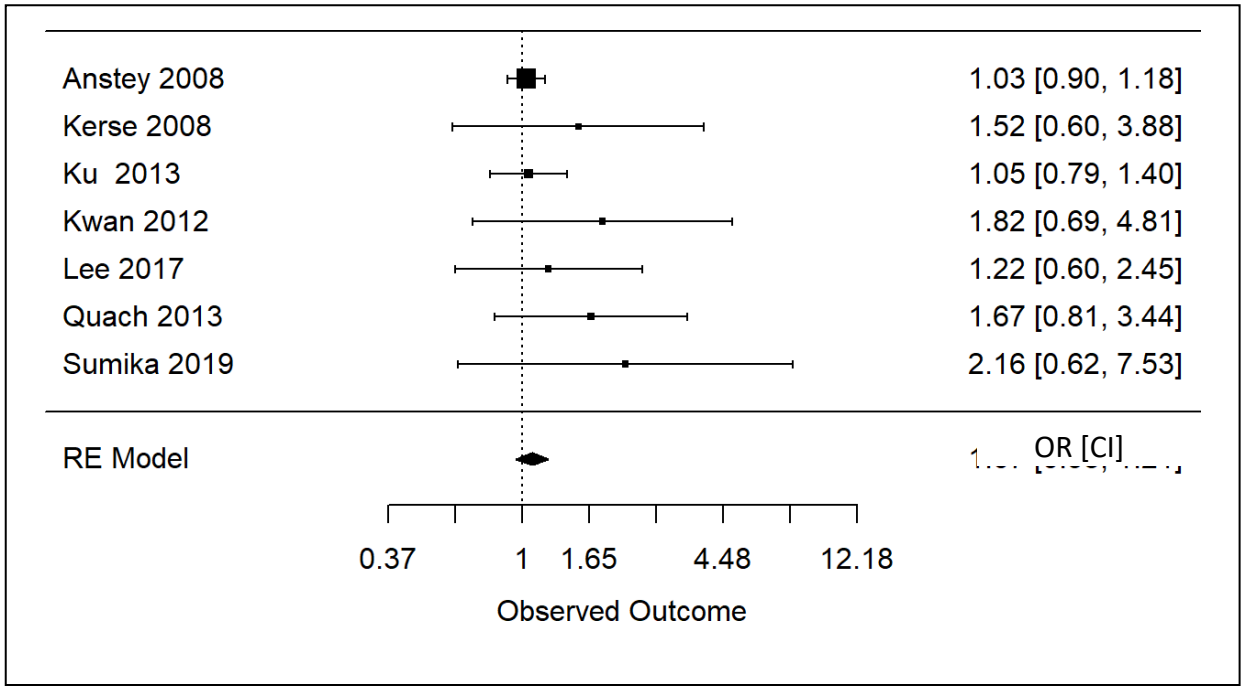


Figure 3. Forest plot – Depression and FOF. Meta-analysis baseline model showing OR (odds ratio) and 95% CI FOF comparing individuals with depression or depressive symptoms to individuals without depression or depressive symptoms in a random-effect model. Random effects model of depression on FOF. The 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.

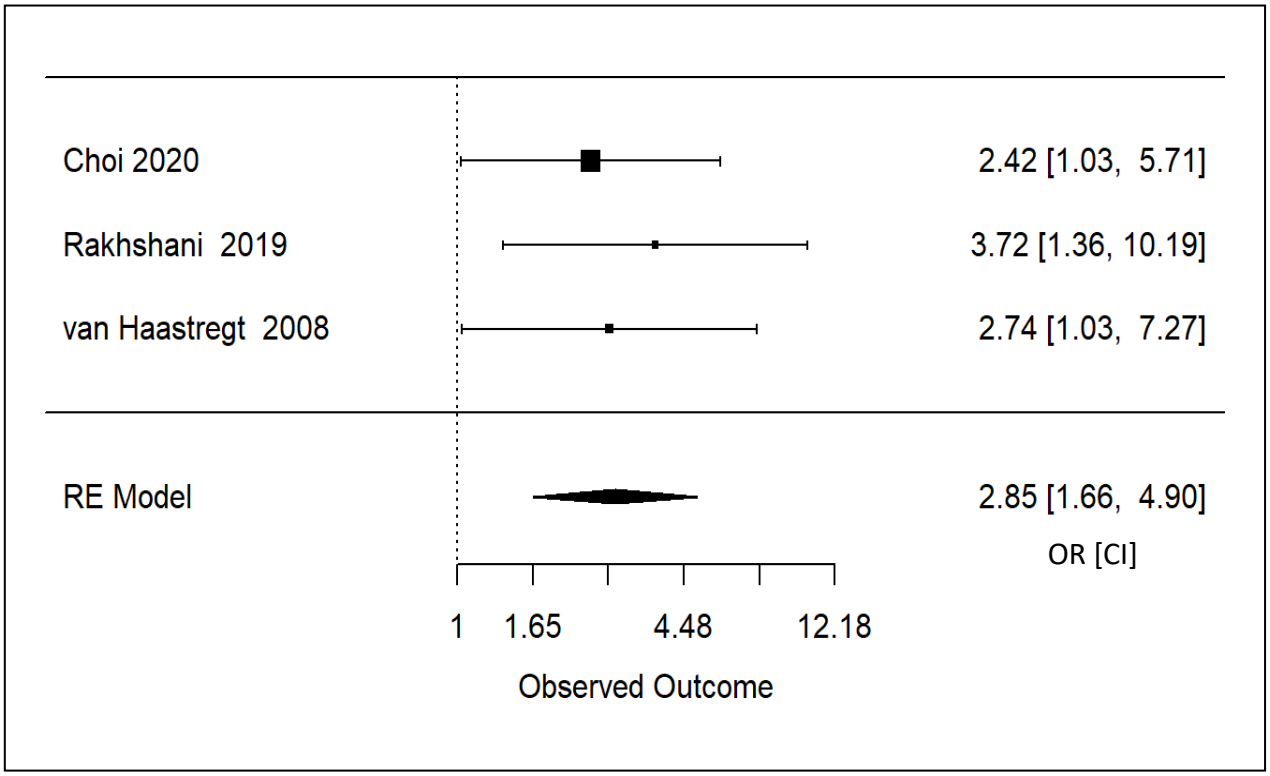


FIGURE 4. FOREST PLOT – ANTIDEPRESSANTS AND RISK OF FALLS. META-ANALYSIS BASELINE MODEL SHOWING OR (ODDS RATIO) AND 95% CI RISK OF FALLS COMPARING INDIVIDUALS WHO USE ANTIDEPRESSANTS TO INDIVIDUALS WITHOUT INDIVIDUALS WHO DO NOT USE ANTIDEPRESSANTS IN A RANDOM-EFFECT MODEL. RANDOM EFFECTS MODEL OF ANTIDEPRESSANTS 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.

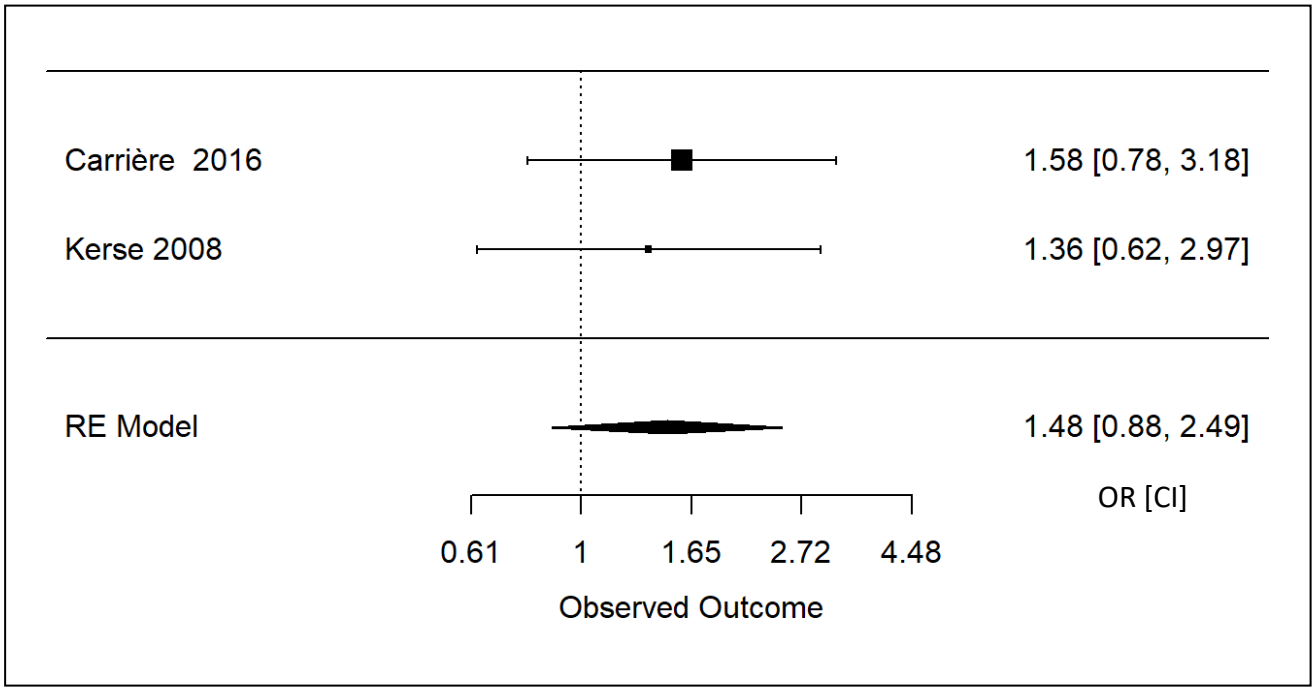


FIG 5. FUNNEL PLOT OF DEPRESSION AND RISK OF FALLING STUDIES FOR EVALUATION OF PUBLICATION BIAS.

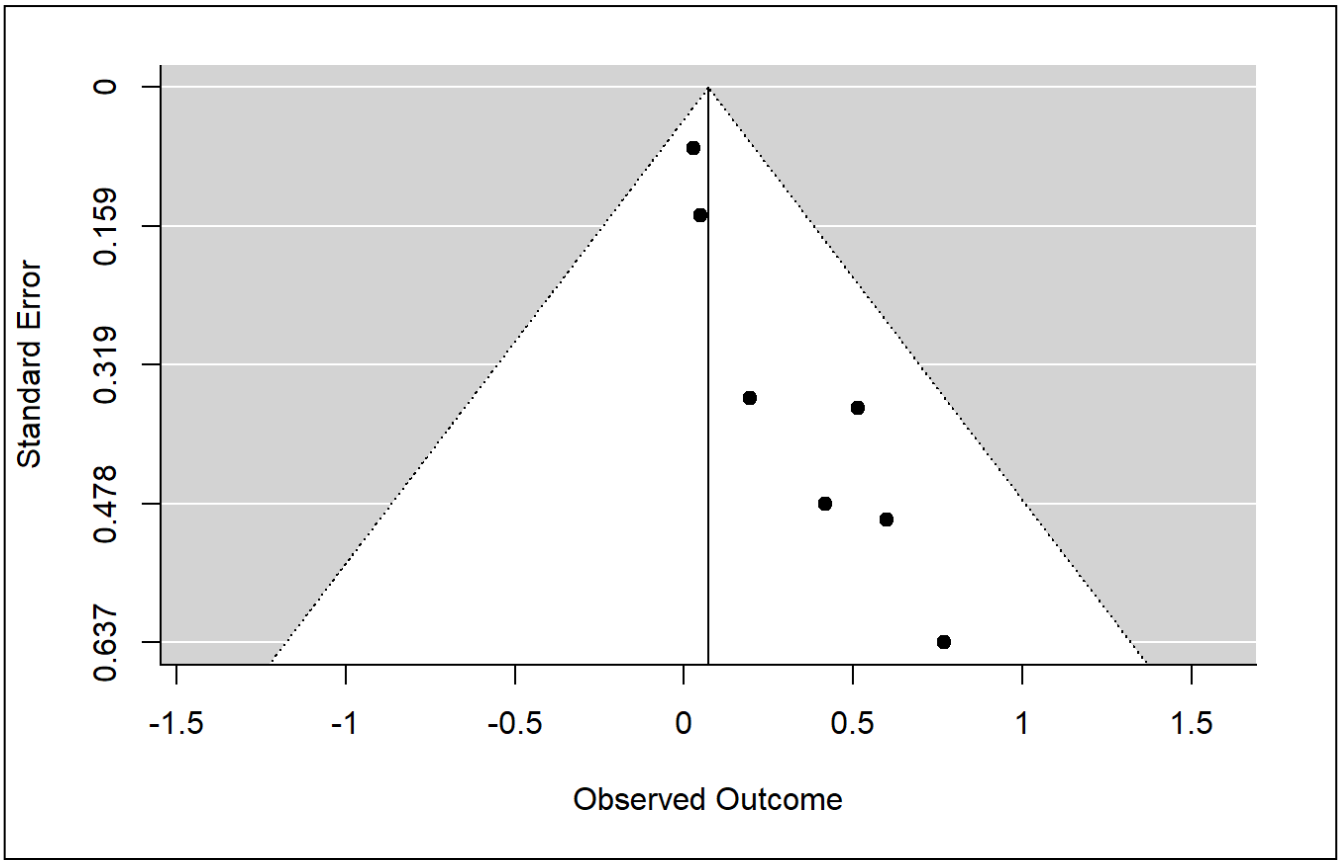


FIGURE 6. FUNNEL PLOT – DEPRESSION AND FOF FOR EVALUATION OF PUBLICATION BIAS

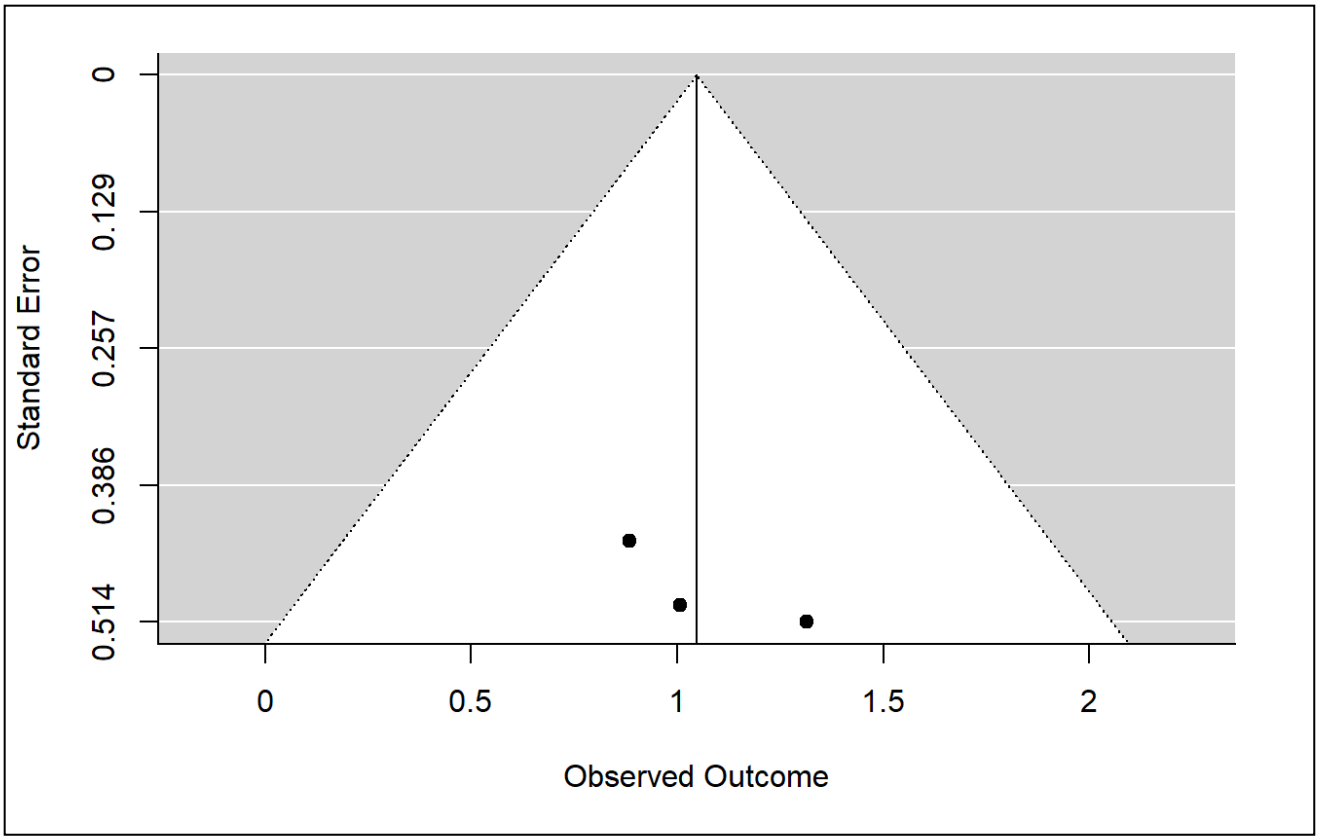
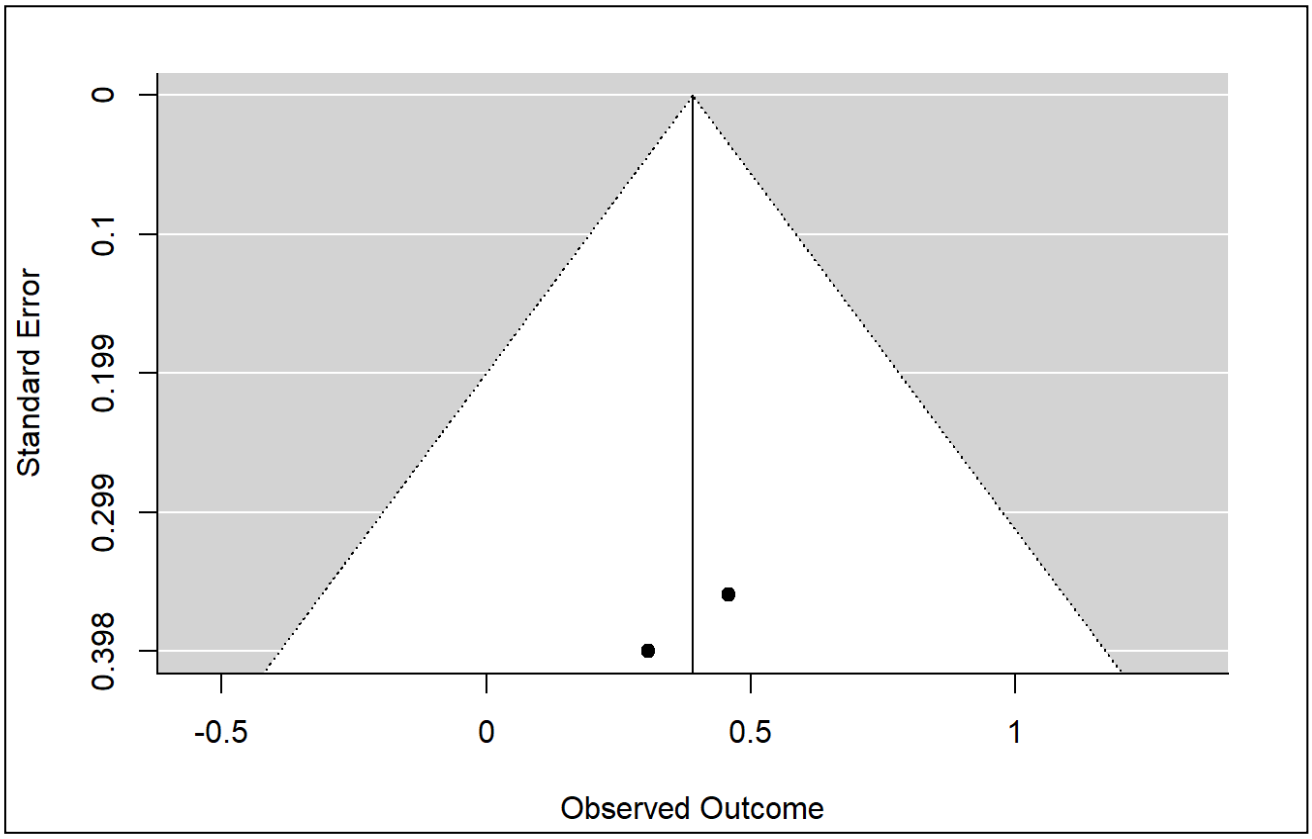


FIGURE 7. FUNNEL PLOT – ANTIDEPRESSANTS AND RISK OF FALLS FOR EVALUATION OF PUBLICATION BIAS



Moderator metaregression analysis

As highlighted in the table 6, the joint estimation of the quality of the scientific evidence included in the selection process of the current systematic review did not have a significant effect on moderator meta regression. This applies to the studies that analyzed the association between depression and the risk of falls (p-value = 0.59; 95% CI: 0.75 to 1.66) and to the studies that analyzed the association between and FOF (p-value = 0; 95% CI: 1.58 to 6.41).

We reported forest plots of the pooling data from studies evaluating the association between depression and risk of falls, the association between depression and FOF, the association between antidepressant use and risk of falls, based on the quality of the studies, obtained by SIGN scale.

As regards the association between depression and risk of falls (Fig. 8), two studies with acceptable quality (69, 83) reported a low but positive association between depression and risk of falls (OR = 1.088, CI: 0.82 to 1.43), while five studies with high quality (776, 84-85, 89, 91) reported a little stronger association (OR = 1.23, CI: 0.91 to 1.66). Figure 9 shows the association between depression and FOF: two studies with acceptable quality (90, 92) reported a strong association between depression and fall (OR = 3.18, CI: 1.58 to 6.41), one study with high quality (79) reported a little weaker but still significant association (OR = 2.42, CI: 1.03 to 5.71) between antidepressant use and risk of falls. Finally, one study with high quality (69) reported association between antidepressants and risk of falls (OR = 1.36, CI: 0.62 to 2.97), while one study with high quality (78) reported a little stronger association (OR = 1.58, CI: 0.78 to 3.18) (Fig 10).

TABLE 6. 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	**Intercept**	1.11	1.23	0.53	0.59	0.75	1.66
	SIGN high quality	1.08	1.28	0.32	0.75	0.67	1.76
DEPRESSION AND FOF	**Intercept**	3.18	1.43	3.23	0	1.58	6.41
	SIGN high quality	3.18	1.43	3.23	0	1.58	6.41

FIGURE 8. FOREST PLOT – DEPRESSION AND RISK OF FALLS (OR). DIFFERENTIATION BASED ON QUALITY EVALUATION THROUGH SIGN AND NOS SCALE.

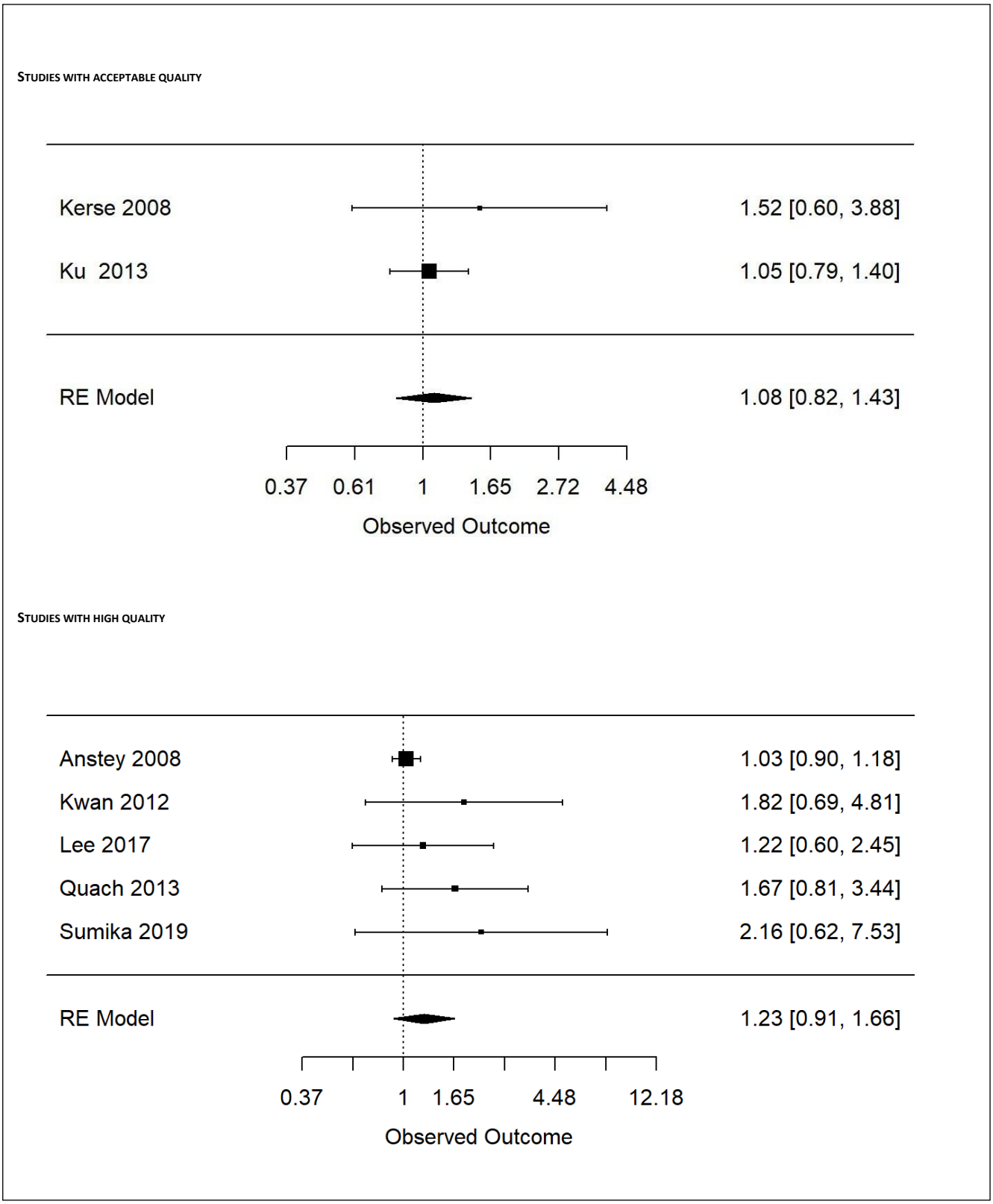


FIGURE 9. FOREST PLOT – DEPRESSION AND FOF. DIFFERENTIATION BASED ON QUALITY EVALUATION THROUGH SIGN AND NOS SCALE.

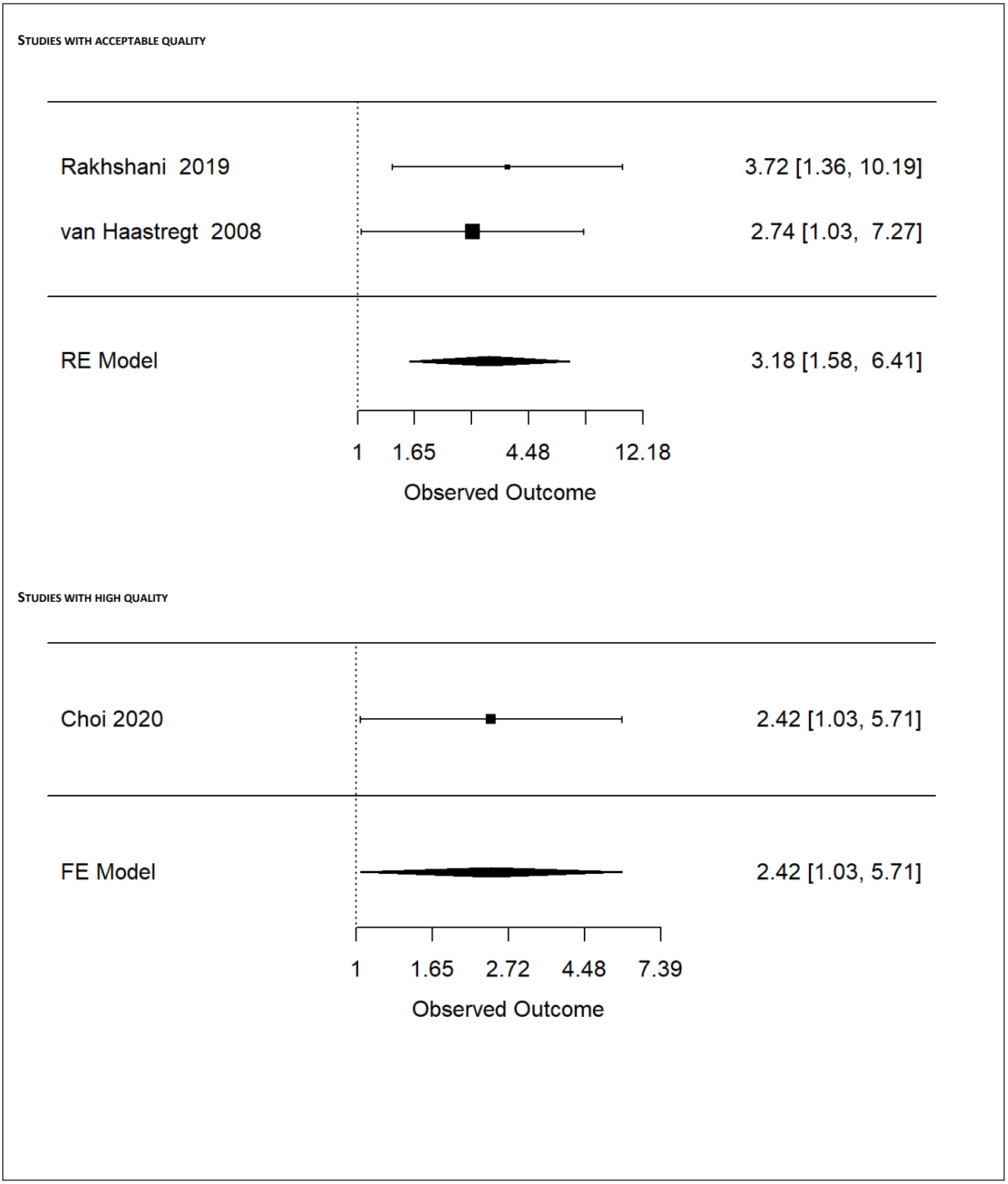
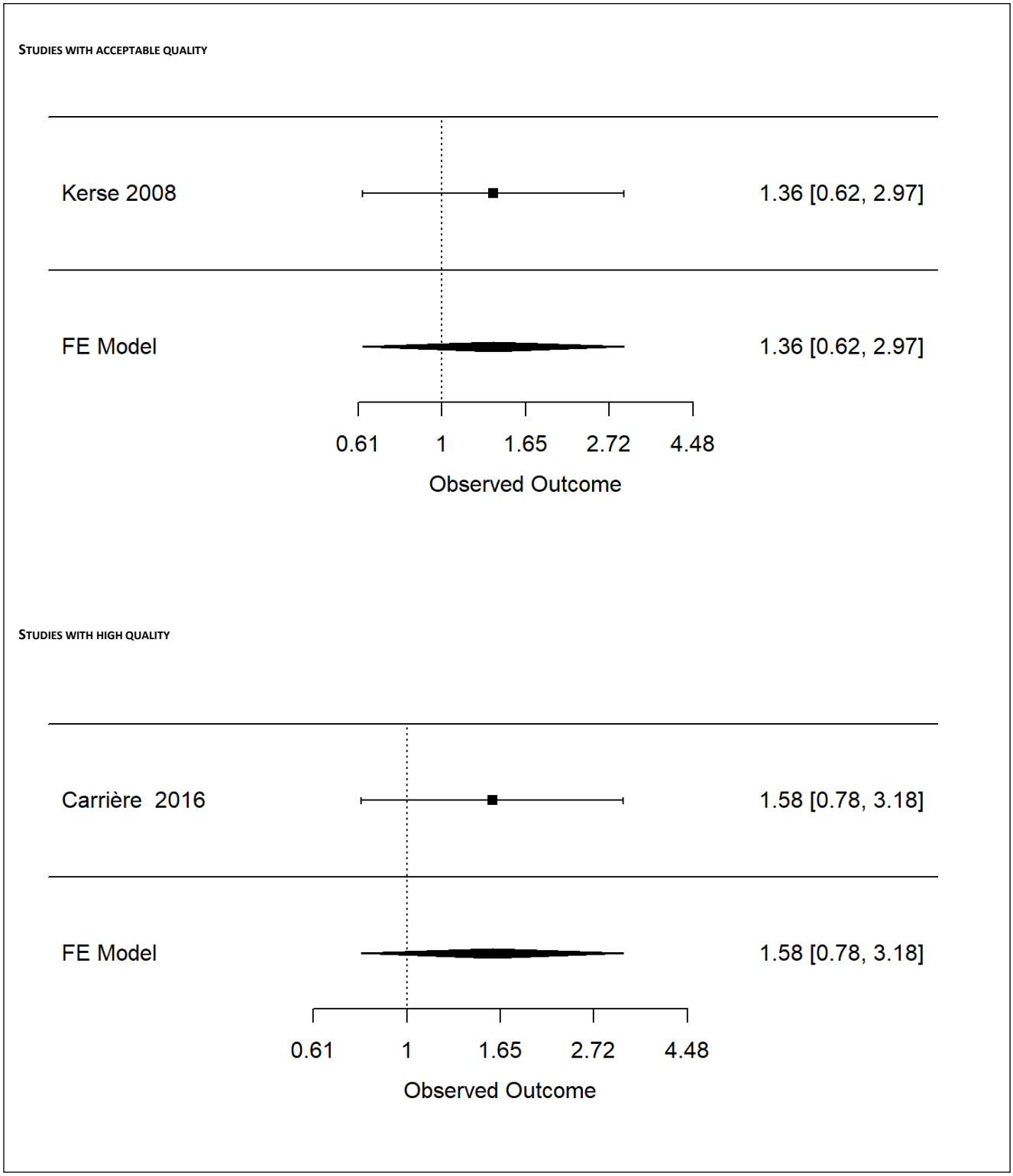


FIGURE 10. FOREST PLOT – ANTIDEPRESSANTS AND RISK OF FALLS (OR). DIFFERENTIATION BASED ON QUALITY EVALUATION THROUGH SIGN AND NOS SCALE.



DISCUSSION

This work of systematic review and meta-analysis of the literature presents data from eighteen studies that evaluated the association between depressive symptomatology, FOF, use of antidepressant therapy and risk of falls in subjects over the age of 60. As evidenced in the previous section, the majority of the studies included have been published since 2016 (77–79,82,85,88,90,91), an indication of a progressive and growing interest in this topic.

Despite the obvious methodological differences between the included studies, the results all appear confirm the hypothesis of an interdependent association between the finding of depressive symptoms and use of antidepressant therapy, the presence of FOF and the risk of falls. The directionality of such associations, however, do not appear unambiguous, also considering the high percentage of cross studies sectional which prevents inferring on the direction of the association.

In reference to the association between depressive symptoms and falls, many of the included studies have highlighted how depressive symptoms caused the subsequent increase in the number of falls (76,77,84,85,89,91), lies only the study by Hajek et al. (82) instead showed an association in the reverse direction. The results obtained in this area agree with other review works systematics and meta-analyzes present in the literature, such as the meta-analysis published by Kvelde et al. in 2013 (93), which highlighted an association between depressive symptoms and falls. Also, one 2015 review underlines how the presence of depressive pictures in subjects over the age of 55 years is strongly correlated to an increase in the patient's frailty, leading, inevitably, to an increased risk of accidental falls (94).

Although the precise mechanisms underlying the association between depressive symptoms and the risk of falls are not yet fully understood, there are many possible explanations for this association. Numerous epidemiological evidence points out that depressive symptoms in the elderly are associated with a very high number of known risk factors for falls, first of all, the psychomotor slowdown which can lead to a reduction in walking speed and less balance (95, 96); elderly people suffering from depression, moreover, tend to present postural abnormalities and alterations in gait patterns, suggesting the physiological, rather than psychological, the origin of falls (96). Depressive symptoms

are also associated with a characteristic pattern of cognitive deficits that affect attention, executive functions and the processing speed, all factors that can cause an increased risk of falls. Geriatric depression is also frequently accompanied by a reduction in appetite with consequent loss of weight and muscle mass, which can consequently increase the risk of falls.

Another systematic review and exploratory meta-analysis of prospective studies on falls in older adults with major depressive disorder (MDD) (97) showed an increased risk of falls in old adults affected by MDD (OR = 4.0, CI: 2.0 to 8.1), even if older adults with MDD lived in long-term care facilities (OR = 3.3, CI: 1.6 to 6.8). The review of Stubbs et al. identified only three prospective studies investigating the association between MDD and falls finding that there was a greater risk of falls among people affect MDD rather than those with subthreshold depressive symptoms.

Other authors have instead highlighted how falls can have an impact on many domains involved in the development of depressive symptoms, first by increasing the FOF (98–100), thus reducing the perception of one's independence and subjectively perceived well-being (82,100, 101). The most likely bidirectional association between depressive symptoms and falls therefore appears to be very complex. Referring to the Bradford Hill criteria (102), published in 1965 to determine whether the observed epidemiological associations are of a causal type, it would seem that the direction of causality of the association between depression and falls is globally satisfied in both directions, although there are no studies that allow to clarify the biological gradient, so for example whether more severe forms of depression cause a greater number of falls or, conversely, if multiple falls can cause more severe forms of depression. Moving on to examine the construct of FOF, the results of this revision work all seem to agree in highlighting an association between the presence of FOF and depressive symptomatology; once again, however, the direction of this association does not appear to be entirely clear due to the presence of some cross-sectional studies (87,88,90,92) and conflicting evidence: from the results of the Choi et al. study (79), it emerges that this association can be read in both directions; on the contrary, the study by Chou et al. (80) suggests a association between FOF and depression, but not an association in the reverse direction. The presence of FOF could therefore increase the risk of falls as a mediator in the association between falls and depressive symptomatology, as pointed out by some literature reviews (96,103). Other evidence, on the other hand, point to a direct association between FOF and increased risk of falls. According to these studies, FOF is associated with an increased risk of future falls, probably due to their effect on gait and balance: subjects with FOF tend to make disproportionate

changes to gait speed in response to a postural threat, an excessively slowed gait is maladaptive, reducing, instead of improving, stability (52,104,105). Of course, the reverse causality also seems to be valid: in fact, the development of FOF following a first fall (96,103) seems to be valid, thus triggering a vicious circle that leads to increase the risk of subsequent falls both directly and indirectly according to the mechanisms reported above. Similar to the association between depression and the risk of falls, again, referring to the Bradford Hill criteria (102), they seem to be generally satisfied in both directions, although, as has already been observed for the association between depression and falls, the criterion of the biological gradient is more difficult to prove.

Finally, as regards the association between the use of antidepressant therapy and falls resulting from this review work, less heterogeneity seems to emerge, with all the studies indicating a association between the use of antidepressant therapy, SSRI in particular, and increased risk of falls (69,78,89,91). The works of Kerse et al. (69) and Carrière et al. (78) indicate the presence among SSR users, in addition to a general major risk of falls, an increase in falls resulting in physical injuries and fractures. Data from previous literature reviews and meta-analyzes confirm the findings of this work, also highlighting a correlation, in particular between the use of SSRIs and the risk of falls (96,106). Again, the mechanism underlying the association between SSRIs and falls is multiple and not yet complete. Many potential factors could explain this association: firstly, the use of SSRIs could increase the risk of falls due to possible cardiovascular effects, and how they could lead to insomnia or sedation and alterations in gait (107–109). Finally, the role of serotonin in bone metabolism can account for the association between fractures and SSRI use. It is well known that serotonin transporters are present on bone cells; serotonin, also, has a central role in regulating bone mass through the sympathetic system thus causing demineralization (96). In this case, however, there may be some confounders factors; for example, depressed symptoms themselves have been associated with reduced bone mineral density (110) and with a consequent increased risk of fractures (111). These injuries could be caused by a reduction in motor activity and an increase in inflammatory processes occurring during the depression (96). The systematic revision of Gebara et al. (106) refers explicitly to the Bradford Hill criteria, pointing out that, although with some uncertainty, they can confirm the directionality of the association between SSRIs and falls. Further confirmation of this association is also provided by the publication by the American Geriatrics Society in 2012 of the updates of the Beers criteria. These criteria, which are designed to promote a safe and effective prescription of medicines to elderly patients through the identification of

inappropriate drugs, have classified SSRIs as potentially inappropriate drugs for elderly patients with anamnestic evidence of falls or fractures (112).

Figure 11 aims to provide an outline of the main associations highlighted by this study by explaining some of the physio-pathological mechanisms underlying these associations.

It should be considered that not all people who assume SSRI are affected by MDD. As emphasized by Quach et al. (89), although there was an association between SSRI and risk of falls, more than half of the population taking antidepressants had no clinically significant depressive symptoms. At first Gebara et al. (106), then Stubbs (113) showed that SSRI may cause falls, but both emphasized that only high-quality prospective research could clearly untangle these associations, because depressive symptomatology, ache and mobility restrictions, closely interlined and associated with risk of falls, influencing the observed results. Stubs noted that studies analyzing the association between SSRI and falls used different study design or methods to collect falls data and adjusted for a range of differing cofounders in their results, so stated that '*associationdoes not certainly imply causation, but SSRI medications certainly remain implicated as a key risk factor for falls in older adults'*.

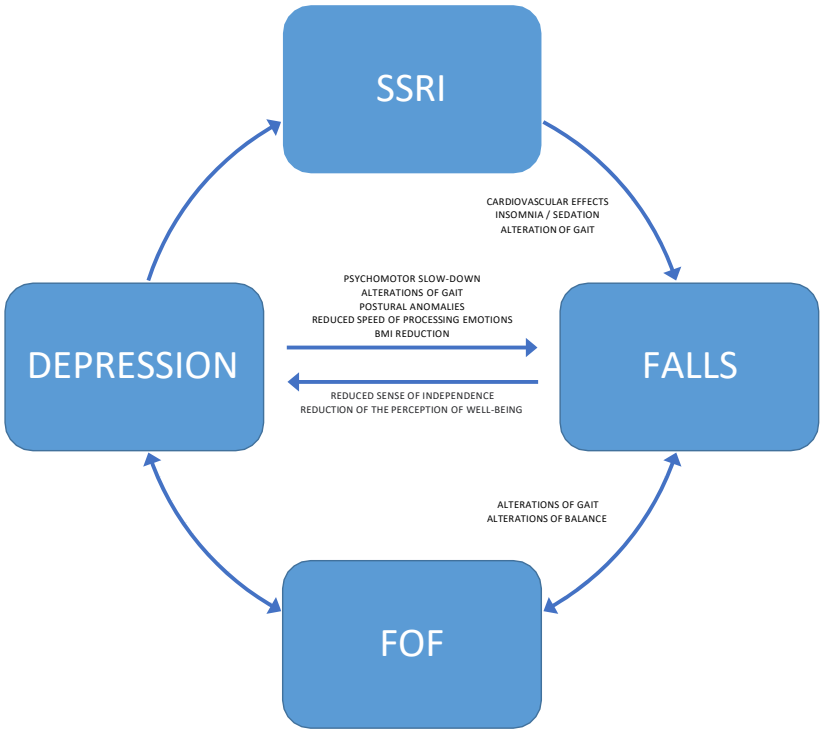


FIGURE 11. ASSOCIATION BETWEEN DEPRESSION, FOF, SSRI USE AND RISK OF FALLS

STRENGTHS AND LIMITATIONS OF THE STUDY

This work is one of the few that aims to analyze the complex and two-way associations existing between different constructs, such as depression, use of antidepressant therapy, FOF and risk of falls; other revisions and meta-analysis works (96,104,107,114) in fact, they concentrated on the analysis of a single association between these constructs, with the limit therefore of having a vision, certainly very detailed, but potentially less global, of the possible interrelationships existing between the different parameters evaluated in this study. The double evaluation of the studies using the NOS and SIGN scales also allowed to have a clear view of the strengths and 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 quality, thus leading to the hypothesis of sufficient reliability of the results obtained. As already highlighted in the previous section, however, it appears necessary to remember the possible interference of distortions due to attrition and confounding bias on the results obtained.

Great heterogeneity was also found as regards the type of 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 and whether there is a linear association between the severity of the clinical depression and risk of falls. A substantial heterogeneity was also found in the measurement of falls and their classification: some studies have investigated the presence of single falls, others of multiple falls or even falls resulting in physical injuries. Finally, the same measurement heterogeneity was found for FOF.

CLINICAL IMPLICATIONS AND FUTURE DEVELOPMENTS

This literature review and meta-analysis, born from the collaboration between the Chair of Psychiatry (Prof. Zeppegno, Prof. Gramaglia), Prof. Dal Molin, Dr. Campisi and Dr. Azzolina, is part of the numerous research projects aimed at implementing the management of the frail elderly patient of the "Aging Project" program of the Department of Translational Medicine of this University.

The evidence available under this review and meta-analysis shows that the problem of the association between depression, FOF, use of antidepressant therapy and falls is of primary importance in the elderly patient. The routine assessment of the risk of falls in subjects above 60 years should therefore also investigate the presence of depression, FOF and the use of antidepressant therapy; conversely, in the evaluation of the patient suffering from old age depression, an in-depth assessment of the risk of falls would be desirable.

The results presented here allow to hypothesize how therapeutic interventions aimed at reducing depressive symptoms may have the additional benefit of reducing the rate of falls. Given the associationfound between the use of antidepressants and the increased risk of falls, and in the light of the reporting of inappropriate SSRIs use among elderly patients in the Beers criteria, it may be preferable, in the treatment of geriatric depression, to use non-drug therapies (114). Moreover, there is proven evidence from the literature that highlights how exercise programs can prevent falls in older adults (115); exercise can also have the dual effect of improving depressive symptomatology (116).

In conclusion, it is evident, from the analysis of the results discussed so far, that further studies are needed with the primary objective of investigating and disentangling the mechanisms underlying the associations found in this work, to be able to develop targeted and specific intervention programs, prevention strategies that allow empowerment of the ageing process, thus belonging to the more global concept of healthy ageing.

BIBLIOGRAPHY

1. Torre E. Invecchiare bene a Novara. In Novara: Università del Piemonte Orientale; 2017.
2. Barucci M. Psicogeriatria. Mente, vecchiaia, educazione. UTET. 2005.
3. Jung CG. Opere. Bollati Boringhieri; 1997.
4. WHO. 10 Facts on ageing and the life course [Internet]. [cited 2021 March 6]. Available at: https://www.who.int/features/factfiles/ageing/ageing_facts/en/
5. Torre E, Filiberti A, Usai C, Gramaglia C, Zeppegno P. Il male nella sofferenza psichica. Aracne; 2018.
6. Coleman P. Cumming E. and Henry W., Growing Old: The Process of Disengagement. Basic Books, New York, 1961. (Reprint: Arno, New York, 1979, ISBN 0405 118147.). Ageing Soc. giugno 1991;11(2):217–20.
7. Havighurst RJ. Successful aging. The Gerontologist. 1961;1:8–13. https://doi.org/10.1093/geront/1.1.8
8. Rowe JW, Kahn RL. Human aging: usual and successful. Science. 1987 Jul 10;237(4811):143-9. doi: 10.1126/science.3299702.
9. Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr Psychiatry. 2006 Jan;14(1):6-20. doi: 10.1097/01.JGP.0000192501.03069.bc. PMID: 16407577.
10. WHO. What is Healthy Ageing? [Internet]. [cited 2020 August 12]. Available at: https://www.who.int/ageing/healthy-ageing/en/
11. Cosco TD, Howse K, Brayne C. Healthy ageing, resilience and wellbeing. Epidemiol Psychiatr Sci. 2017 Dec;26(6):579-583. doi: 10.1017/S2045796017000324.
12. WHO. Mental health of older adults [Internet]. [cited 2020 August 12]. Available at: https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults.
13. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. Br J Psychiatry. 1999 Apr;174:307-11. doi: 10.1192/bjp.174.4.307.
14. Koenig HG, George LK, Peterson BL, Pieper CF. Depression in medically ill hospitalized older adults: prevalence, characteristics, and course of symptoms according to six diagnostic schemes. Am J Psychiatry. 1997 Oct;154(10):1376-83. doi: 10.1176/ajp.154.10.1376.

15. Blazer DG. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci. 2003 Mar;58(3):249-65. doi: 10.1093/gerona/58.3.m249.

16. Taylor WD. Clinical practice. Depression in the elderly. N Engl J Med. 2014 Sep 25;371(13):1228-36. doi: 10.1056/NEJMcp1402180.

17. Roose SP, Sackeim HA. Clinical trials in late-life depression: revisited. Am J Geriatr Psychiatry. 2002 Sep-Oct;10(5):503-5.

18. Birrer RB, Vemuri SP. Depression in later life: a diagnostic and therapeutic challenge. Am Fam Physician. 2004 May 15;69(10):2375-82.

19. Murphy SL, Xu J, Kochanek KD, Curtin SC, Arias E. Deaths: Final Data for 2015. National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2017 Nov;66(6):1-75.

20. Waern M, Runeson BS, Allebeck P, Beskow J, Rubenowitz E, Skoog I, Wilhelmsson K. Mental disorder in elderly suicides: a case-control study. Am J Psychiatry. 2002 Mar;159(3):450-5. doi: 10.1176/appi.ajp.159.3.450.

21. Centers for Disease Control and Prevention. National Violent Death Reporting System (NVDRS) Coding Manual Revised [Online] 2020 National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (producer). Available from URL: www.cdc.gov/injury

22. Szanto K, Mulsant BH, Houck P, Dew MA, Reynolds CF 3rd. Occurrence and course of suicidality during short-term treatment of late-life depression. Arch Gen Psychiatry. 2003 Jun;60(6):610-7. doi: 10.1001/archpsyc.60.6.610.

23. Gramaglia C, Feggi A, Bergamasco P, Bert F, Gattoni E, Marangon D, et al. Clinical Characteristics Associated with Suicide Attempts in Clinical Settings: A Comparison of Suicidal and Non-Suicidal Depressed Inpatients. Front Psychiatry. 2016;7:109. doi: 10.3389/fpsyt.2016.00109

24. Torre E, Usai C, Zeppegno P. Lezioni di psichiatria e psicologia clinica. Aracne; 2010.

25. Hybels CF, Blazer DG. Epidemiology of late-life mental disorders. Clin Geriatr Med. 2003 Nov;19(4):663-96, v. doi: 10.1016/s0749-0690(03)00042-9.

26. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. Am J Psychiatry. 2003 Jun;160(6):1147-56. doi: 10.1176/appi.ajp.160.6.1147.

27. Alexopoulos GS. Mechanisms and treatment of late-life depression. Transl Psychiatry. 2019 Aug 5;9(1):188. doi: 10.1038/s41398-019-0514-6. PMID: 31383842.

28. Roth M. The Significance of Affective Symptoms in Old Age. By F. Post, Maudsley Monograph No. 10. London, New York, Toronto: Oxford University Press. Pp. 106. 1962. Price 30s. Br J Psychiatry. 1964 january;110(464):118–9.

29. Kales HC, Maixner DF, Mellow AM. Cerebrovascular disease and late-life depression. Am J Geriatr Psychiatry. 2005 Feb;13(2):88-98. doi: 10.1176/appi.ajgp.13.2.88.

30. Robinson RG. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. Biol Psychiatry. 2003 Aug 1;54(3):376-87. doi: 10.1016/s0006-3223(03)00423-2.

31. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas. 2014 Oct;79(2):184-90. doi: 10.1016/j.maturitas.2014.05.009. Epub 2014 May

32. Lavretsky H, Siddarth P, Kepe V, et al. Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older nondemented adults. Am J Geriatr Psychiatry. 2009;17(6):493-502. doi:10.1097/jgp.0b013e3181953b8233.

33. Banerjee S, Hellier J, Dewey M, Romeo R, Ballard C, Baldwin R, Bentham P, Fox C, Holmes C, Katona C, Knapp M, Lawton C, Lindesay J, Livingston G, McCrae N, Moniz-Cook E, Murray J, Nurock S, Orrell M, O'Brien J, Poppe M, Thomas A, Walwyn R, Wilson K, Burns A. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. Lancet. 2011 Jul 30;378(9789):403-11. doi: 10.1016/S0140-6736(11)60830-1. Epub 2011 Jul 19. P

34. Butters MA, Whyte EM, Nebes RD, Begley AE, Dew MA, Mulsant BH, Zmuda MD, Bhalla R, Meltzer CC, Pollock BG, Reynolds CF 3rd, Becker JT. The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry. 2004 Jun;61(6):587-95. doi: 10.1001/archpsyc.61.6.587. 35. Löwe B, Spitzer RL, Gräfe K, Kroenke K, Quenter A, Zipfel S, Buchholz C, Witte S, Herzog W. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. J Affect Disord. 2004 Feb;78(2):131-40. doi: 10.1016/s0165-0327(02)00237-9.

36. Diagnosis and management of late-life unipolar depression - UpToDate [Internet]. [cited 2020l August12]. Available at: https://www-uptodate-com.bvsp.idm.oclc.org/contents/diagnosis-and-management-of-late-life-unipolar-

epression?search=late%20life%20depression&source=search_result&selectedTitle=1~19&usage_type=default&display_rank=1

37. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments [published correction appears in Can J Psychiatry. 2017 May;62(5):356]. Can J Psychiatry. 2016;61(9):540-560. doi:10.1177/0706743716659417.

38. Areán PA, Cook BL. Psychotherapy and combined psychotherapy/pharmacotherapy for late life depression. Biol Psychiatry. 2002 Aug 1;52(3):293-303. doi: 10.1016/s0006-3223(02)01371-9. P

39. Huang AX, Delucchi K, Dunn LB, Nelson JC. A systematic review and meta-analysis of psychotherapy for late-life depression. Am J Geriatr Psychiatry. 2015 Mar;23(3):261-73. doi: 10.1016/j.jagp.2014.04.003. Epub 2014 Apr 23.

40. Sjösten N, Kivelä SL. The effects of physical exercise on depressive symptoms among the aged: a systematic review. Int J Geriatr Psychiatry. 2006 May;21(5):410-8. doi: 10.1002/gps.1494.

41. Unützer J. Clinical practice. Late-life depression. N Engl J Med. 2007 Nov 29;357(22):2269-76. doi: 10.1056/NEJMcp073754.

42. Alexopoulos GS. Depression in the elderly. Lancet. 2005 Jun 4-10;365(9475):1961-70. doi: 10.1016/S0140-6736(05)66665-2.

43. World Health Organization WHO [GLobal report on falls prevention in older age] [Internet]. [cited 2020 August 14]. Available at: https://apps.who.int/iris/handle/10665/43811

44. Milat AJ, Watson WL, Monger C, Barr M, Giffin M, Reid M. Prevalence, circumstances and consequences of falls among community-dwelling older people: results of the 2009 NSW Falls Prevention Baseline Survey. N S W Public Health Bull. 2011 Jun;22(3-4):43-8. doi: 10.1071/NB10065.

45. PRIME PubMed | [Epidemiology of falls among the elderly] [Internet]. [cited 2020 August 14]. Available at: https://www.unboundmedicine.com/medline/citation/17206182/[Epidemiology_of_falls_among_the_elderly]_

46. Matsumura BA, Ambrose AF. Balance in the elderly. Clin Geriatr Med. 2006 May;22(2):395-412; x. doi: 10.1016/j.cger.2005.12.007.

47. Tinetti ME, Williams CS, Gill TM. Dizziness among older adults: a possible geriatric syndrome. Ann Intern Med. 2000 Mar 7;132(5):337-44. doi: 10.7326/0003-4819-132-5-200003070-00002.

48. Ćwirlej-Sozańska A, Wilmowska-Pietruszyńska A, Sozański B, Wiśniowska-Szurlej A. Analysis of Chronic Illnesses and Disability in a Community-Based Sample of Elderly People in South-Eastern Poland. Med Sci Monit. 2018;24:1387-1396. Published 2018 Mar 7. doi:10.12659/msm.904845

49. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing. 2006 Sep;35 Suppl 2:ii37-ii41. doi: 10.1093/ageing/afl084.

50. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991 Feb;39(2):142-8. doi: 10.1111/j.1532-5415.1991.tb01616.x.

51. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. Am J Med. 1986 Mar;80(3):429-34. doi: 10.1016/0002-9343(86)90717-5.

52. Friedman SM, Munoz B, West SK, Rubin GS, Fried LP. Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. J Am Geriatr Soc. 2002 Aug;50(8):1329-35. doi: 10.1046/j.1532-5415.2002.50352.x.

53. Fear of Falling among the Community-Dwelling Elderly - Jonathan Howland, Elizabeth Walker Peterson, William C. Levin, Lise Fried, Dorothy Pordon, Sharon Bak, 1993 [Internet]. [cited 2020 August 2020]. Available at: https://journals.sagepub.com/doi/abs/10.1177/089826439300500205

54. Uemura K, Shimada H, Makizako H, Doi T, Tsutsumimoto K, Lee S, Umegaki H, Kuzuya M, Suzuki T. Effects of Mild Cognitive Impairment on the Development of Fear of Falling in Older Adults: A Prospective Cohort Study. J Am Med Dir Assoc. 2015 Dec;16(12):1104.e9-13. doi: 10.1016/j.jamda.2015.09.014.

55. Bhala RP, O'Donnell J, Thoppil E. Ptophobia. Phobic fear of falling and its clinical management. Phys Ther. 1982 Feb;62(2):187-90. doi: 10.1093/ptj/62.2.187.

56. Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. Age Ageing. 2008 Ja Murphy SL, Dubin JA, Gill TM. The development of fear of falling among community-living older women: predisposing factors and subsequent fall events. J Gerontol A Biol Sci Med Sci. 2003;58(10):M943-M947. doi:10.1093/gerona/58.10.m943

58. Chang HT, Chen HC, Chou P. Factors Associated with Fear of Falling among Community-Dwelling Older Adults in the Shih-Pai Study in Taiwan. PLoS One. 2016 Mar 2;11(3):e0150612. doi: 10.1371/journal.pone.0150612.

59. Oh E, Hong GS, Lee S, Han S. Fear of falling and its predictors among community-living older adults in Korea. Aging Ment Health. 2017 Apr;21(4):369-378. doi: 10.1080/13607863.2015.1099034. Epub 2015 Oct 19.

60. Clemson L, Kendig H, Mackenzie L, Browning C. Predictors of injurious falls and fear of falling differ: an 11-year longitudinal study of incident events in older people. J Aging Health. 2015 Mar;27(2):239-56. doi: 10.1177/0898264314546716. Epub 2014 Aug 12.

61. Peeters G, Feeney J, Carey D, Kennelly S, Kenny RA. Fear of falling: A manifestation of executive dysfunction? Int J Geriatr Psychiatry. 2019 Aug;34(8):1275-1282. doi: 10.1002/gps.5133. Epub 2019 May 10.

62. Stel VS, Smit JH, Pluijm SM, Lips P. Consequences of falling in older men and women and risk factors for health service use and functional decline. Age Ageing. 2004 Jan;33(1):58-65. doi: 10.1093/ageing/afh028.

63. Kvelde T, McVeigh C, Toson B, Greenaway M, Lord SR, Delbaere K, Close JC. Depressive symptomatology as a risk factor for falls in older people: systematic review and meta-analysis. J Am Geriatr Soc. 2013 May;61(5):694-706. doi: 10.1111/jgs.12209. Epub 2013 Apr 25.

64. Buchner DM, Cress ME, Esselman PC, Margherita AJ, de Lateur BJ, Campbell AJ, Wagner EH. Factors associated with changes in gait speed in older adults. J Gerontol A Biol Sci Med Sci. 1996 Nov;51(6):M297-302. doi: 10.1093/gerona/51a.6.m297.

65. Herman T, Giladi N, Gurevich T, Hausdorff JM. Gait instability and fractal dynamics of older adults with a "cautious" gait: why do certain older adults walk fearfully? Gait Posture. 2005 Feb;21(2):178-85. doi: 10.1016/j.gaitpost.2004.01.014.

66. Turcu A, Toubin S, Mourey F, D'Athis P, Manckoundia P, Pfitzenmeyer P. Falls and depression in older people. Gerontology. 2004 Sep-Oct;50(5):303-8. doi: 10.1159/000079128.

67. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS. Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1999 Mar 8;159(5):484-90. doi: 10.1001/archinte.159.5.484.

68. Burker EJ, Wong H, Sloane PD, Mattingly D, Preisser J, Mitchell CM. Predictors of fear of falling in dizzy and nondizzy elderly. Psychol Aging. 1995 Mar;10(1):104-10. doi: 10.1037//0882-7974.10.1.104

.69. Kerse N, Flicker L, Pfaff JJ, Draper B, Lautenschlager NT, Sim M, Snowdon J, Almeida OP. Falls, depression and antidepressants in later life: a large primary care appraisal. PLoS One. 2008 Jun 18;3(6):e2423. doi: 10.1371/journal.pone.0002423.

70. Teixeira AR, Wender MH, Gonçalves AK, Freitas Cde L, Santos AM, Soldera CL. Dizziness, Physical Exercise, Falls, and Depression in Adults and the Elderly. Int Arch Otorhinolaryngol. 2016 Apr;20(2):124-31. doi: 10.1055/s-0035-1566304. Epub 2015 Nov 6.

71. Gualano MR, Bert F, Mannocci A, La Torre G, Zeppegno P, Siliquini R. Consumption of antidepressants in Italy: recent trends and their significance for public health. Psychiatr Serv. 2014 Oct;65(10):1226-31. doi: 10.1176/appi.ps.201300510.

72. Li Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700. doi: 10.1136/bmj.b2700.

73. Ottawa Hospital Research Institute [Internet]. [citated 2020 August 20. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

74. Checklists [Internet]. SIGN. [citated 2020 November 9]. Available at: https://testing36.scot.nhs.uk

75. StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP. 2013.

76. Anstey KJ, Burns R, von Sanden C, Luszcz MA. Psychological well-being is an independent predictor of falling in an 8-year follow-up of older adults. J Gerontol B Psychol Sci Soc Sci. 2008 Jul;63(4):P249-P257. doi: 10.1093/geronb/63.4.p249.

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

78. Carrière I, Farré A, Norton J, Wyart M, Tzourio C, Noize P, Pérès K, Fourrier-Réglat A, Ancelin ML. Patterns of selective serotonin reuptake inhibitor use and risk of falls and fractures in community-dwelling elderly people: the Three-City cohort. Osteoporos Int. 2016 Nov;27(11):3187-3195. doi: 10.1007/s00198-016-3667-7. Epub 2016 Jun 16.

79. Choi NG, Gell NM, DiNitto DM, Marti CN, Kunik ME. Depression and activity-limiting fall worry among older adults: longitudinal reciprocal relationships. *International Psychogeriatrics*. 2020;32(4):495-504. doi:10.1017/S1041610219000838.

80. Chou KL, Chi I. Reciprocal relationship between fear of falling and depression in elderly Chinese primary care patients. Aging Ment Health. 2008 Sep;12(5):587-94. doi: 10.1080/13607860802343068.

81. Gagnon N, Flint AJ, Naglie G, Devins GM. Affective correlates of fear of falling in elderly persons. Am J Geriatr Psychiatry. 2005 Jan;13(1):7-14. doi: 10.1176/appi.ajgp.13.1.7.

82. 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 SG, König HH; AgeCoDe & AgeQualiDe Study Groups. Impact of falls on depressive symptoms among the oldest old: Results from the AgeQualiDe study. Int J Geriatr Psychiatry. 2018 Oct;33(10):1383-1388. doi: 10.1002/gps.4949. Epub 2018 Jul 19.

83. Ku Y-C, Liu M-E, Tsai Y-F, Liu W-C, Lin S-L, Tsai S-J. Associated Factors for Falls, Recurrent Falls, and Injurious Falls in Aged Men Living in Taiwan Veterans Homes. Int J Gerontol. 2013;7(2):80-84. doi:https://doi.org/10.1016/j.ijge.2012.07.004

84. Kwan MM, Lin SI, Close JC, Lord SR. Depressive symptoms in addition to visual impairment, reduced strength and poor balance predict falls in older Taiwanese people. Age Ageing. 2012 Sep;41(5):606-12. doi: 10.1093/ageing/afs065. Epub 2012 May 29.

85. Lee D-CA, Lalor AF, Russell G, et al. Understanding temporal relationships between depression, falls, and physical activity in a cohort of post-hospitalized older adults – a breakthrough or a conundrum? *International Psychogeriatrics*. 2017;29(10):1681-1692. doi:10.1017/S104161021700103X

86. Lin WQ, Huang TY, Liu L, Yang YO, Li YH, Sun MY, Qin FJ, Yang QY, Shen JC. Prevalence and related factors of depression and falls among the elderly living in rural communities of Guangzhou. Psychol Health Med. 2020 Sep;25(8):980-988. doi: 10.1080/13548506.2020.1714064. Epub 2020 Jan 22.

87. Miller PA, Pantel ES. Toward a More Comprehensive Understanding of the Etiology of Falls: Identifying Depression and Anxiety in Community-Dwelling Elders. Top Geriatr Rehabil. 2003;19(3). https://journals.lww.com/topicsingeriatricrehabilitation/Fulltext/2003/07000/Toward_a_More_Comprehensive_Understanding_of_the.8.aspx

88. Park Y, Paik NJ, Kim KW, Jang HC, Lim JY. Depressive Symptoms, Falls, and Fear of Falling in Old Korean Adults: The Korean Longitudinal Study on Health and Aging (KLoSHA). J Frailty Aging. 2017;6(3):144-147. doi: 10.14283/jfa.2017.21.

89. Quach L, Yang FM, Berry SD, Newton E, Jones RN, Burr JA, Lipsitz LA. Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. J Gerontol A Biol Sci Med Sci. 2013 Dec;68(12):1575-81. doi: 10.1093/gerona/glt084. Epub 2013 Jul 1.

90. Rakhshani T, Ansari MH, Ebrahimi M, Ebrahimi MR, Pearson SK. Fear of falling and its association with anxiety and depression disorders among community-dwelling older adults. Int J Heal Promot Educ. 2019;57(6):303-315. doi:10.1080/14635240.2019.1632731g.

91. Lin SM, Borges MK, de Siqueira ASS, Biella MM, Jacob-Filho W, Cesari M, Voshaar RCO, Aprahamian I. Serotonin receptor inhibitor is associated with falls independent of frailty in older adults. Aging Ment Health. 2021 Feb;25(2):219-224. doi: 10.1080/13607863.2019.1675143. Epub 2019 Oct 11.

92. van Haastregt JC, Zijlstra GA, van Rossum E, van Eijk JT, Kempen GI. Feelings of anxiety and symptoms of depression in community-living older persons who avoid activity for fear of falling. Am J Geriatr Psychiatry. 2008 Mar;16(3):186-93. doi: 10.1097/JGP.0b013e3181591c1e.

93. Kvelde T, Pijnappels M, Delbaere K, Close JC, Lord SR. Physiological and cognitive mediators for the association between self-reported depressed mood and impaired choice stepping reaction time in older people. J Gerontol A Biol Sci Med Sci. 2010 May;65(5):538-44. doi: 10.1093/gerona/glp195. Epub 2009 Dec 21.

94. Vaughan L, Corbin AL, Goveas JS. Depression and frailty in later life: a systematic review. Clin Interv Aging. 2015 Dec 15;10:1947-58. doi: 10.2147/CIA.S69632.

95. Lord SR, Clark RD, Webster IW. Physiological factors associated with falls in an elderly population. J Am Geriatr Soc. 1991 Dec;39(12):1194-200. doi: 10.1111/j.1532-5415.1991.tb03574.x.

96. Iaboni A, Flint AJ. The complex interplay of depression and falls in older adults: a clinical review. Am J Geriatr Psychiatry. 2013 May;21(5):484-92. doi: 10.1016/j.jagp.2013.01.008. Epub 2013 Feb 6.

97. Stubbs B, Stubbs J, Gnanaraj SD, Soundy A. Falls in older adults with major depressive disorder (MDD): a systematic review and exploratory meta-analysis of prospective studies. Int Psychogeriatr. 2016 Jan;28(1):23-9. doi: 10.1017/S104161021500126X. Epub 2015 Aug 3.

98. Austin N, Devine A, Dick I, Prince R, Bruce D. Fear of falling in older women: a longitudinal study of incidence, persistence, and predictors. J Am Geriatr Soc. 2007 Oct;55(10):1598-603. doi: 10.1111/j.1532-5415.2007.01317.x..

99. Deshpande N, Metter EJ, Bandinelli S, Lauretani F, Windham BG, Ferrucci L. Psychological, physical, and sensory correlates of fear of falling and consequent activity restriction in the elderly: the InCHIANTI study. Am J Phys Med Rehabil. 2008;87(5):354-362. doi:10.1097/PHM.0b013e31815e6e9b.

100. Bruce ML, Hoff RA. Social and physical health risk factors for first-onset major depressive disorder in a community sample. Soc Psychiatry Psychiatr Epidemiol. 1994 Jul;29(4):165-71. doi: 10.1007/BF00802013.

101. Reyes-Ortiz CA, Al Snih S, Markides KS. Falls among elderly persons in Latin America and the Caribbean and among elderly Mexican-Americans. Rev Panam Salud Publica. 2005 May-Jun;17(5-6):362-9. doi: 10.1590/s1020-49892005000500008.

102. Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION?. Proc R Soc Med. 1965;58(5):295-300.

103. Payette MC, Bélanger C, Léveillé V, Grenier S. Fall-Related Psychological Concerns and Anxiety among Community-Dwelling Older Adults: Systematic Review and Meta-Analysis. PLoS One. 2016 Apr 4;11(4):e0152848. doi: 10.1371/journal.pone.0152848.

104. Delbaere K, Sturnieks DL, Crombez G, Lord SR. Concern about falls elicits changes in gait parameters in conditions of postural threat in older people. J Gerontol A Biol Sci Med Sci. 2009 Feb;64(2):237-42. doi: 10.1093/gerona/gln014. Epub 2009 Feb 4.

105. Menz HB, Lord SR, Fitzpatrick RC. A structural equation model relating impaired sensorimotor function, fear of falling and gait patterns in older people. Gait Posture. 2007 Feb;25(2):243-9. doi: 10.1016/j.gaitpost.2006.04.005. Epub 2006 May 12.

106. Gebara MA, Lipsey KL, Karp JF, Nash MC, Iaboni A, Lenze EJ. Cause or Effect? Selective Serotonin Reuptake Inhibitors and Falls in Older Adults: A Systematic Review. Am J Geriatr Psychiatry. 2015;23(10):1016-1028. doi:10.1016/j.jagp.2014.11.004.

107. Pacher P, Ungvari Z. Selective serotonin-reuptake inhibitor antidepressants increase the risk of falls and hip fractures in elderly people by inhibiting cardiovascular ion channels. Med Hypotheses. 2001 Oct;57(4):469-71. doi: 10.1054/mehy.2001.1366.

108. Darowski A, Chambers SA, Chambers DJ. Antidepressants and falls in the elderly. Drugs Aging. 2009;26(5):381-94. doi: 10.2165/00002512-200926050-00002.

109. Hegeman J, van den Bemt B, Weerdesteyn V, Nienhuis B, van Limbeek J, Duysens J. Unraveling the association between SSRI use and falls: an experimental study of risk factors for accidental falls in long-term paroxetine users. Clin Neuropharmacol. 2011 Nov-Dec;34(6):210-5. doi: 10.1097/WNF.0b013e31823337d1.

111. Yirmiya R, Bab I. Major depression is a risk factor for low bone mineral density: a meta-analysis. Biol Psychiatry. 2008 Dec; 66(5):423–32. doi: https://doi.org/10.1016/j.biopsych.2009.03.016

112. Spangler L, Scholes D, Brunner RL, Robbins J, Reed SD, Newton KM, Melville JL, Lacroix AZ. Depressive symptoms, bone loss, and fractures in postmenopausal women. J Gen Intern Med. 2008 May;23(5):567-74. doi: 10.1007/s11606-008-0525-0. Epub 2008 Feb 20.

113. Stubbs B. A Meta-Analysis Investigating Falls in Older Adults Taking Selective Serotonin Reuptake Inhibitors Confirms an Association but by No Means Implies Causation. The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry. 2015 Oct;23(10):1098. https://doi.org/10.1016/j.jagp.2015.02.004

114. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 Apr;60(4):616-31. doi: 10.1111/j.1532-5415.2012.03923.x. Epub 2012 Feb 29.

115. Denkinger MD, Lukas A, Nikolaus T, Hauer K. Factors associated with fear of falling and associated activity restriction in community-dwelling older adults: a systematic review. Am J Geriatr Psychiatry. 2015 Jan;23(1):72-86. doi: 10.1016/j.jagp.2014.03.002. Epub 2014 Mar 15.

116. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc. 2008 Dec;56(12):2234-43. doi: 10.1111/j.1532-5415.2008.02014.x.

117. Singh NA, Stavrinos TM, Scarbek Y, Galambos G, Liber C, Fiatarone Singh MA. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. J Gerontol A Biol Sci Med Sci. 2005 Jun;60(6):768-76. doi: 10.1093/gerona/60.6.768.

ANNEX

Methodology Checklist 3: Cohort studies

Study identification

Anstey et al.

Psychological Well-Being Is an Independent Predictor of Falling in an 8-Year Follow-Up of Older Adults, Journal of Gerontology: PSYCHOLOGICAL SCIENCES 2008, Vol. 63B, No. 4, P249–P257

Guideline topic: mutual relationship between depression and falls in the elderly population	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** ☐ No ☐ Can't say ☐
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** ☐ No ☐ Can't say ☐ Does not apply ☐
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes ☐ No ☐ **Does not apply** ☐

1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ Can't say □	No □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	NOT ASESSED	
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	**Yes** □ Can't say □	No □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			

1.14	Have confidence intervals been provided?	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	**High quality (++)** □ Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. The results of this study supported the hypothesis that between-person differences in depressive symptoms, morale, and control all predict subsequent fall rate over 8 years in older adults. This effect is confirmed after adjusting for all covariates, indicating that well-being is an independent predictor of falling over at least 8 years of follow-up.		

SIGN	Methodology Checklist 3: Cohort studies	
Study identification Atlas et al. Falls and depression in octogenarians - life and living in advanced age: a cohort study in New Zealand J PRIM HEALTH CARE 2017;9(4):311–315		
Guideline topic: mutual relationship between depression and falls in the elderly population	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

3. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
4. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Arm 1 □ 30.62% drop out

		Arm 2 □ 53.4% drop out
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ **No** □ Can't say □ Does not apply □

ASSESSMENT		
1.7	The outcomes are clearly defined.	Yes □ **No** □ Can't say □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ No □ Can't say □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ No □ Can't say □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ No □ Can't say □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ **No** □ Can't say □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ No □ Can't say □ Does not apply □
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes □ **No** □ Can't say □
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	**Yes** □ No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ Acceptable (+) □

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes □ Can't say □	**No** □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes □	**No** □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. The results are not so easily generalizable; thestudy does not take into consideration possible sources of confounders, drop outs rate are too high (more than 20%) and there is no comparison between full participants and those lost at follow up.		

Methodology Checklist 3: Cohort studies

Study identification Carrière et al. Patterns of selective serotonin reuptake inhibitor use and risk of falls and fractures in community-dwelling elderly people: the Three-City cohort 2016, Osteoporos Int DOI 10.1007/s00198-016-3667-7

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

5. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
6. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □

1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	13.75% drop out in totale
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	**Yes** □ No □ Can't say □ Does not apply □

ASSESSMENT		
1.7	The outcomes are clearly defined.	**Yes** □ No □ Can't say □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ No □ Can't say □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ No □ Can't say □
1.10	The method of assessment of exposure is reliable.	**Yes** □ No □ Can't say □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ No □ Can't say □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ No □ Can't say □ Does not apply □
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ No □ Can't say □
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	**Yes** □ No □

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise the risk of bias or confounding?	**High quality (++)** □ Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. A very significant increase in the 4-year risk of falls and fractures for participants taking SSRIs at baseline and an even greater increase (around 80 %) in chronic users. These associations remained significant after adjustment for a large range of other confounders. Conversely, the risk was not significant after treatment discontinuation		

Methodology Checklist 3: Cohort studies

Study identification Choi et al. Depression and activity-limiting fall worry among older adults: longitudinal reciprocal relationships International Psychogeriatrics: page 1 of 10 © International Psychogeriatric Association 2019 doi:10.1017/S1041610219000838

Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

7. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
8. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ **No** □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □

1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Not specified
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ **No** □ Can't say □ Does not apply □

ASSESSMENT		
1.7	The outcomes are clearly defined.	**Yes** □ No □ Can't say □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ No □ Can't say □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ No □ Can't say □
1.10	The method of assessment of exposure is reliable.	Yes □ **No** □ Can't say □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ **No** □ Can't say □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ No □ Can't say □ Does not apply □
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes □ **No** □ Can't say □
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	Yes □ No □

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. Activity limiting fall worry strongly influence probable major depression and vice versa. The study had some limitations: it does'nt use validated scale to measure depression, it is not clear if confounders had been taken ointo account and there's o clear evidence of the number of dropout		

Methodology Checklist 3: Cohort studies

Study identification Chou et al. Fear of falling and depressive symptoms in Chinese elderly living in nursing homes: Fall efficacy and activity level as mediator or moderator? Aging & Mental Health, 9:3, 255-261

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

9. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
10. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	0%

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	No □ **Does not apply** □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	No □ **Does not apply** □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □	**No** □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □	

		Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. Older adults who expressed a high level of fear of falling reported depressive symptoms more frequently; the effect is statistically independent of a number of sociodemographic variables as well as several health related variables		

Methodology Checklist 3: Cohort studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

11. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
12. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	29.8%

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	**Yes** □ Can't say □	No □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	**Yes** □ Can't say □	No □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □	**No** □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	**High quality (++)** □ Acceptable (+) □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. Results suggest that fear of falling causes depression but depression does not cause fear of falling. Role of social functioning as a mediator from FOF to depression		

Methodology Checklist 3: Cohort studies

Study identification Gagnon et al. Affective Correlates of Fear of Falling in Elderly Persons 2005 Am J Geriatr Psychiatry 13:1, January

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

13. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
14. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ **No** □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Not specified

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	**No** □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	**No** □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □	**No** □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above. Not only were depressive disorders and depression severity independently associated with fear of falling, but depression had the strongest association with this fear among all the variables that we measured.		

Methodology Checklist 3: Cohort studies

Study identification Hajek et al Impact of falls on depressive symptoms among the oldest old: Results from the AgeQualiDe study Int J Geriatr Psychiatry. 2018;1–6 (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

15. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
16. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ **No** □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □

1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Not specified
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ No □ Can't say □ **Does not apply** □

ASSESSMENT		
1.7	The outcomes are clearly defined.	**Yes** □ No □ Can't say □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ **No** □ Can't say □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ No □ Can't say □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ No □ Can't say □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ No □ Can't say □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ No □ Can't say □ Does not apply □
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ No □ Can't say □
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	Yes □ **No** □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □

		Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised abov		
	The occurrence of falls is associated with an increase in depressive symptoms.		

Methodology Checklist 3: Cohort studies

Study identification Kerse et al Falls, Depression and Antidepressants in Later Life: A Large Primary Care Appraisal 2008 PLoS ONE 3(6): e2423

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

17. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
18. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ **No** □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Not specified

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ **Can't** say □	No □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	**No** □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	Yes □ **Can't say** □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ Can't say □	**No** □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	**No** □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised abov		
	Presence of depressive symptoms and antidepressant use were independently associated with multiple falls and injury but not having sustained a single fall. Falls risk accumulated for those with a combination of risk factors		

Methodology Checklist 3: Cohort studies

Study identification Ku et al		
Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

19. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
20. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ **No** □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Not specified

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ **No** □ Can't say □ Does not apply □

ASSESSMENT		
1.7	The outcomes are clearly defined.	**Yes** □ No □ Can't say □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ No □ Can't say □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes □ **No** □ Can't say □
1.10	The method of assessment of exposure is reliable.	**Yes** □ No □ Can't say □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ No □ Can't say □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ **No** □ Can't say □ Does not apply □
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ No □ Can't say □
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	**Yes** □ No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above		
	The independent variables for predicting falls were increasing age, depression, stroke, gouty arthritis and cataract. Recurrent fallers have a greater percentage of depression compared to single fallers		

Methodology Checklist 3: Cohort studies

Kerse et al

Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

21. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
22. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	6.8

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	**Yes** □ Can't say □	No □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	**No** □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	**No** □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	**High quality (++)** □ Acceptable (+) □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised abov		
	Depression is an independent prediction of falls.		

Methodology Checklist 3: Cohort studies

Study identification Lee et al.		
Guideline topic:	Key Question No:	Reviewer:CV

Before completing this checklist, consider:

23. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
24. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

	In a well conducted cohort study:	***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
	SELECTION OF SUBJECTS	
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	17%

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	**Yes** □ Can't say □	No □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	**No** □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised abov		
	Falls and depression are associated; having higher levels of depressive symptoms precede falls.		

Methodology Checklist 3: Cohort studies

Study identification Lin et al		
Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

25. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
26. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	0

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	No □ **Does not apply** □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	**No** □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes □ Can't say □	**No** □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	**No** □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes □ Can't say □	**No** □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □	**No** □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised abov		
	Depression influenced falls directly and indirectly trough QOL and Family function		

Methodology Checklist 3: Cohort studies

Study identification: Park		
Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

27. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
28. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ **No** □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Not specified

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	**No** □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	**No** □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □	**No** □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above		
	Depressive symptoms showed a correlation to number of falls experienced in the past, this result is only valid in female participants		

Methodology Checklist 3: Cohort studies

Study identification: Quach et al.

Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

29. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
30. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	10% (non specificato nell'articolo ma nei precedent articoli relative allo studio)

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	**No** □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	**No** □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	**High quality (++)** □ Acceptable (+) □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above		
	Depression significantly increase the risk of falls (indoor and outdoor); the relationship between outdoor falls and depression could be mediated by antidepressant use		

Methodology Checklist 3: Cohort studies

Study identification: Rakhshani et al.		
Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

31. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
32. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ **Does not apply** □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ **No** □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Not specified

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	**No** □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	**No** □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ **Acceptable (+)** □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above		
	FOF is related to anxiety and depression trough a complex relationship		

Methodology Checklist 3: Cohort studies

Study identification: Sumika		
Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

33. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
34. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	0%

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	No □ **Does not apply** □

ASSESSMENT			
1.7	The outcomes are clearly defined.	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	**Yes** □ Can't say □	No □
1.10	The method of assessment of exposure is reliable.	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	**Yes** □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	**High quality (++)** □ Acceptable (+) □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above		
	Depression and SSRI are associated with falls, but there is no additional effect in the presence of both. The impact of SSRI increases in presence of frailty.		

Methodology Checklist 3: Cohort studies

Study identification: Van Haastregt		
Guideline topic:	Key Question No:	Reviewer: CV

Before completing this checklist, consider:

35. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
36. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.[i]	**Yes** □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.[ii]	**Yes** □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.[iii]	**Yes** □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.[iv]	**Yes** □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.[v]	1.11%

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.[vi]	Yes □ Can't say □	**No** □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.[vii]	**Yes** □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.[viii]	Yes □ Can't say □	No □ **Does not apply** □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.[ix]	**Yes** □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.[x]	**Yes** □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.[xi]	**Yes** □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.[xii]	Yes □ Can't say □	**No** □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.[xiii]	**Yes** □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?[xiv]	**Yes** □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?[xv]	High quality (++) □ **Acceptable (+)** □	

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	**Yes** □ Can't say □	No □
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	**Yes** □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above		
	Both anxiety and symptoms of depression were independently associated with fear of falling when adjusted for covariates.		

[i] Unless a clear and well defined question is specified in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question you are trying to answer on the basis of the conclusions.

[ii] This relates to **selection bias**.* It is important that the two groups selected for comparison are as similar as possible in all characteristics except for their exposure status, or the presence of specific prognostic factors or prognostic markers relevant to the study in question.

[iii] This relates to **selection bias**.* The participation rate is defined as the number of study participants divided by the number of eligible subjects, and should be calculated separately for each branch of the study. A large difference in participation rate between the two arms of the study indicates that a significant degree of **selection bias*** may be present, and the study results should be treated with considerable caution.

[iv] If some of the eligible subjects, particularly those in the unexposed group, already have the outcome at the start of the trial the final result will be subject to **performance bias.*** A well conducted study will attempt to estimate the likelihood of this occurring, and take it into account in the analysis through the use of sensitivity studies or other methods.

[v] This question relates to the risk of **attrition bias**.*The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop out rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher drop out rate is to be expected. A decision on whether to downgrade or reject a study because of a high drop out rate is a matter of judgement based on the reasons why people dropped out, and whether drop out rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study.

[vi] For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. This relates to the risk of **attrition bias**.* Any unexplained differences should lead to the study results being treated with caution.

[vii] This relates to the risk of **detection bias**.* Once enrolled in the study, participants should be followed until specified end points or outcomes are reached. In a study of the effect of exercise on the death rates from heart

disease in middle aged men, for example, participants might be followed up until death, or until reaching a predefined age. **If outcomes and the criteria used for measuring them are not clearly defined, the study should be rejected.**

[viii] This relates to the risk of **detection bias.*** If the assessor is blinded to which participants received the exposure, and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done, or not done adequately.

[ix] This relates to the risk of **detection bias.*** Blinding is not possible in many cohort studies. In order to asses the extent of any bias that may be present, it may be helpful to compare process measures used on the participant groups - e.g. frequency of observations, who carried out the observations, the degree of detail and completeness of observations. If these process measures are comparable between the groups, the results may be regarded with more confidence.

[x] This relates to the risk of **detection bias.*** A well conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study

[xi] This relates to the risk of **detection bias.*** The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected.** Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.

[xii] This relates to the risk of **detection bias.*** Confidence in data quality should be increased if exposure level is measured more than once in the course of the study. Independent assessment by more than one investigator is preferable.

[xiii] Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate which potential confounders have been considered, and how they have been assessed or allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected, depending on how serious the risk of confounding is considered to be. **A study that does not address the possibility of confounding should be rejected.**

[xiv] Confidence limits are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution.

[xv] Rate the overall methodological quality of the study, using the following as a guide: **High quality** (++): Majority of criteria met. Little or no risk of bias. Results unlikely to be changed by further research. **Acceptable** (+): Most criteria met. Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies. **Low quality** (0): Either most criteria not met, or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies.