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META-ANALYSIS

Antidepressant medications in women aged 40 and older and the risk of fragility fractures: a systematic literature review and meta-analysis

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ABSTRACT

Introduction: Antidepressants and menopause are risk factors which are independently associated with an increased risk of fractures. This review aims to investigate the risk of fragility fractures in women aged 40 and older and prescribed antidepressants.

Methods: A literature search was conducted using PubMed, Ovid Embase, Ovid PsychINFO, Web of Science, and Scopus from inception to 1 June 2024. Relevant citations were identified and screened against our inclusion/exclusion criteria. The study population comprised women over 40 years. The risk of fragility fractures was compared between users and non-users of antidepressants. Risk of bias assessment was carried out using the ROBINS-I tool. A meta-analysis of cohort studies was performed to assess fracture risk associated with prescribing of any antidepressant agents, and SSRIs specifically.

Results: Of the 3,676 articles retrieved, five observational studies were found eligible for inclusion ($n = 1{,}240{,}354$). In a meta-analysis of 4 studies, an increased risk of fractures in women was associated with the prescribing of antidepressants (HR = 1.62, 95% CI: 1.15–2.28; $I^2 = 96.50\%$) and SSRIs in particular (HR = 1.36, 95% CI: 1.20–1.55; $I^2 = 40.32\%$).

Conclusions: Findings from this review suggest that prescribing of antidepressants is associated with an increased risk of fractures in women aged 40 and older. Substantial heterogeneity between studies may have affected the results of the meta-analysis.

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Antidepressant; fractures; menopause; SSRI; women

1. Introduction

Osteoporosis is a systemic skeletal condition which is characterized by low bone mineral density (BMD) and microarchitectural deterioration in bone. This leads to bone fragility which, subsequently, results in an increased risk of fractures. Osteoporosis does not present with any symptoms. Sufferers are usually unaware that they have the disease until a fracture occurs, most commonly at the hip, vertebrae in the spine, or wrist [1]. Sex is a non-modifiable risk factor for osteoporosis. Thus, women are more likely to experience this condition, particularly with increasing age. This occurs due to a fall in estrogen production during the menopausal transition. One of the most vital functions of this hormone is the regulation of bone metabolism. Estrogen promotes the activity of osteoblasts whilst suppressing osteoclastic bone resorption; osteoclast activity rises as estrogen levels drop during menopause [2]. Therefore, menopause is associated with a decline in BMD which increases the risk of osteoporosis [3]. Additionally, lower peak bone mass and smaller bones are also linked to a higher incidence of fractures in women [4].

Another risk factor for osteoporosis is mental illness, such as depression [5]. It is estimated that one in six adults will suffer from depression in their lifetime, and this disorder is twice as likely to impact women than men [6]. Symptoms of moderate to severe clinical depression may be treated with antidepressants in combination with psychotherapy [7]. Types of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenaline and specific serotonergic antidepressants (NASSAs), tricyclic antidepressants (TCAs), serotonin antagonists and reuptake inhibitors (SARIs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants [8]. Data published by the CDC in the United States found that females are 2.5 times more likely than males to use antidepressants and, of the female population, antidepressant use is highest amongst women aged 40–59 years [9]. Besides depression, antidepressants may also be prescribed for the treatment of obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and generalized anxiety disorder (GAD); TCAs are used occasionally to manage neuropathic pain [10]. Some antidepressants have proven to be effective in relieving symptoms associated with menopause, though the mechanism by which this occurs is not yet fully understood. There is no conclusive evidence for the use of SSRIs to treat low mood in menopausal women who have not been diagnosed with depression, but some SSRIs can be prescribed for the treatment of vasomotor symptoms (VMS) in cases where menopausal hormone therapy (MHT) is not tolerated [11]. A randomized clinical trial by Joffe, H. et al. in 2014 concluded

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that low dose oral estradiol and venlafaxine (a medication of the SNRI class) are almost equally effective in alleviating VMS in perimenopausal and menopausal women, and the slight difference in efficacy is of uncertain clinical relevance [12]. Likewise, paroxetine (a medication of the SSRI class) is FDA-approved for the treatment of VMS in women who cannot tolerate estrogen [13].

SSRIs are the most preferred and widely prescribed antidepressants because they have a more favorable side-effect profile in comparison to other antidepressants [14]. Use of SSRIs/SNRIs is a risk factor for osteoporosis as these medicines interfere with bone formation and resorption by the activation of 5-HT receptors on osteoblasts and osteoclasts [15]. A review conducted by Rizzoli, R. et al. in 2012 examined the relationship between depression, antidepressants, and osteoporosis [16]. This study found that there is an associated risk of falls and fractures in the management of depression with SSRIs and TCAs, and there is strong evidence to support the impact of these drugs on bone mineral density [16]. Likewise, a study on menopausal women without mental health disorders showed that SSRI use increased the risk of fractures [17].

Studies conducted in previous years have examined the link between antidepressant prescribing and fracture risk, often without reporting the effect separately for men and women. Whilst these studies do give insight into how these medicines may affect the prevalence of fracture events in general, it is difficult to determine what risk is posed to older women more specifically. Given that fragility fractures are more common in older women, and antidepressant prescribing rates are higher for older women [18,19], it is prudent to explore the safety of the use of such medicines in a patient population already at risk of fragility fractures. Thus, the purpose of this systematic review and meta-analysis was to investigate the risk of fragility fractures as it pertains to women aged 40 years and above who are prescribed antidepressant medications.

2. Methods

2.1. Information sources and search strategy

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [20]. A structured search was conducted using five databases from their inception dates to 1 June 2024. Databases used include Ovid Embase, Ovid PsycINFO, PubMed, Web of Science, and Scopus. The complete search strategy is detailed in APPENDIX-1. The search strategy was supplemented by an investigation of reference lists from relevant research articles. This review research question was prospectively registered on PROSPERO (CRD42023403391) [21].

2.2. Inclusion and exclusion criteria

Observational studies were selected based on the following inclusion and exclusion criteria:

2.2.1. Inclusion criteria

- The study **population** included women aged 40 and above, or women who have reached menopause. *Menopause* describes the absence of one's menstrual period for at least 12 months [22]. Perimenopausal women, postmenopausal women, and women experiencing premature menopause also fell under the inclusion criteria. Studies on special populations such as women with osteoporosis were excluded. Studies which investigated fracture risk in both older men and women were included if effect measures were reported independently for women.
- The **intervention** was antidepressant agents (SSRIs, TCAs, MAOIs, NASSAs, SNRIs and atypical antidepressants).
- The **comparator** was nonuse of antidepressants.
- The **outcome** was fragility fractures (including but not limited to, the following sites: hip, arm, wrist, and spine) (APPENDIX 1).

2.2.2. Exclusion criteria

- Studies were excluded if premenopausal women were included in the population group, and studies which did not assess and independently record the outcome for the female population (aged 40 and older) were excluded.
- Any reports of non-prescription use of medication were excluded.
- Non-fragility fracture outcomes were excluded (APPENDIX 1).

2.3. Screening and data extraction

Search results from the five databases were combined in EndNote. Duplicate titles were removed using EndNote. The identified titles and abstracts were screened by M.J and D.A using Rayyan, an online tool for screening systematic reviews [23]. Full text versions of the papers were retrieved, and reviews were carried out by M.J and D.A independently using a pre-developed checklist. Any discrepancies were resolved by discussion. The data of interest were extracted from each study using a data collection table. Data were extracted by M.J and verified by D.A. The following data were extracted: first author's name, publication year, country, study design, data source, participant's description, mean follow-up (years, SD), number of participants and age range of the participants (years). Where possible, the mean age of participants was extracted. Intervention, comparator, and outcome were also extracted. These data were exported to a table of study characteristics (Table 1).

2.4. Quality assessment

The quality of the studies included in this systematic review was independently assessed by the D.A. and E.T. using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [24]. The ROBINS-I tool comprises seven domains which enable users to ascertain the overall risk of bias in each of the non-randomized studies selected for inclusion. The risk of bias is categorized into low, moderate, serious, and critical risk; studies which were deemed to have a critical risk of bias were not included in the meta-analysis.

Table 1. Characteristics of the included studies.

Authors	Publication Year	Country	Study design	Data source	Participants	Mean Follow-up (years)	No. participants	Age Range (years)	Intervention	Comparator	Outcome
Bakken, M. S. et al. [25]	2013	Norway	Prospective cohort study	Norwegian Prescription Database (NorPD) + Norwegian Hip Fracture Registry + the Central Population Registry	Men and women ≥60 years-old	5.2 ± 1.7	906,422 [56% women]	≥68	SSRI TCA Other antidepressant agents	Non-exposure to any antidepressant agent	Hip fracture
Brannstrom et al. [45]	2019	Sweden	Retrospective cohort study	Prescribed Drugs Register of Sweden's National Board of Health and Welfare	Men and women ≥65 years-old	1 year	408,144 [63.1% women]	≥65	Any antidepressant agent	Non-antidepressant users	Hip fracture
Diem, S. J. et al. [29]	2011	United States	Prospective cohort study	prospective Study of Osteoporotic Fractures.	Women ≥65 years-old	7.93 ± 4.64	8,217	≥69	SSRI TCA	Non-SSRI users Non-TCA users	Non-spine fracture
Sheu, Y. et al. [17]	2015	United States	Cohort study	PharMetrics Claims Database, IMS Health	Women aged 40–64 years-old	5	373,325	40-64	SSRI	H2A/PPI users	Hip, humerus, radius and ulna fracture
Spangler, L. et al. [28]	2008	United States	Prospective cohort study	Women's health initiative	Women aged 50–79 years	7.4	93,676	50-79	Any antidepressant agent	Non-antidepressant users	Hip, spine, wrist and 'other' skeletal fracture

SSRIs= selective serotonin inhibitors, TCA= tricyclic antidepressants, H2A= H2 antagonists, PPI= proton-pump inhibitors.

2.5. Statistical analysis

A pooled estimate of the hazard ratio (HR) of individual papers was generated to summarize the association between antidepressant use in women aged 40 and older and fragility fractures. The results from four studies identified in the systematic review were meta-analyzed. Besides the main meta-analysis, which focused on any antidepressant use, we conducted another meta-analysis for SSRIs versus those not prescribed antidepressants. A random effects model under the restricted maximum likelihood (REML) method was employed for calculating a pooled HR with 95% confidence interval (CI). The statistical analysis was carried out using the Stata software version 17.

3. Results

3.1. Study selection

The search strategy identified 3,676 studies, of which 239 were duplicates (Figure 1). Most commonly, titles were excluded if they had little to no relevance to the research question. Thus, 41 full texts were sought for retrieval and subsequently assessed for eligibility under the inclusion criteria. The most common reason for excluding studies at the full-text review was that the population did not include menopausal women ($n = 17$). Furthermore, studies were excluded because of how 'exposure' was defined, or because the outcome did not match our inclusion criteria. Five cohort studies met the criteria and were included in the review [17,25–28].

3.2. Study characteristics

The characteristics of the studies included in this review are summarized in Table 1. Publications were between 2008 and 2019, and the studies carried out were based in the United States ($n = 3$), Sweden ($n = 1$) and Norway ($n = 1$), with a total of 1,240,354 female participants. Sample sizes ranged from 6,627 to 373,325 and the minimum age of the participants ranged from 40 to 69 years. Three studies primarily included women older than 60 years [25,26,29]. Women going through the menopausal transition and in the early postmenopausal period were included in two studies [28,30]. The mean follow-up duration for studies included in this review ranged from 1 to 7.4 years. Finally, the fracture outcomes assessed in the studies included hip, humerus, radius, ulna, wrist, spine, non-spine and 'other' skeletal fractures.

3.3. Quality assessment

The quality of all five included studies was assessed using the ROBINS-I tool. Based on the outcome of this assessment, Brannstrom et al. [26] and Diem et al. [27] were deemed to be at a low risk of bias, whereas Sheu et al. [17] and Spangler et al. [28] both had a moderate risk of bias. Bakken et al. [25] was found to have a serious risk of bias. Overall, none of the studies were found to have a critical risk of bias, thus all were included in the review. Results of ROBINS-I are illustrated in Figure 2.

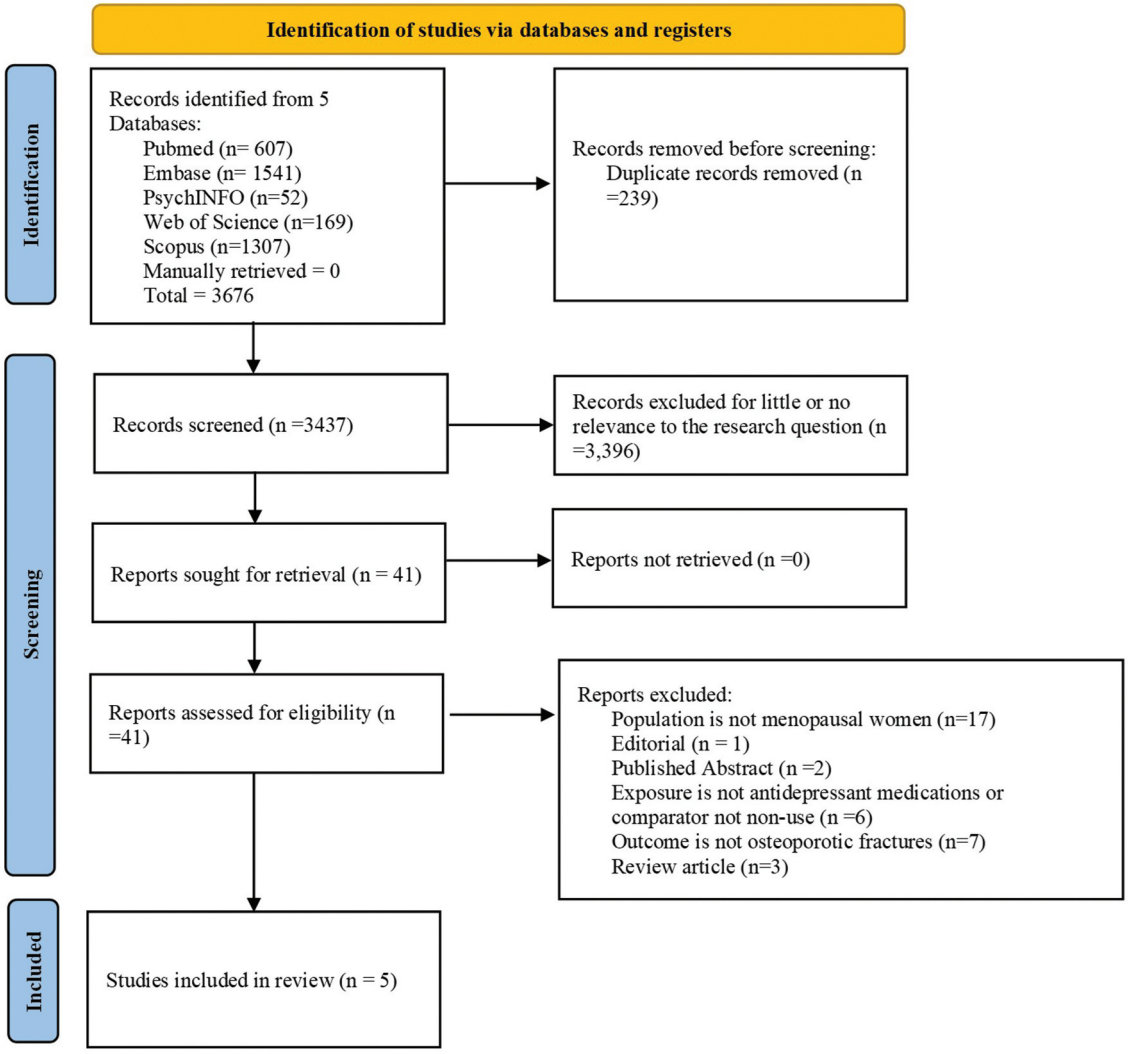

Figure 1. PRISMA flow-diagram for study selection criteria.

3.4. Results of individual studies

The results of the studies included in this review are summarized in Table 2. The results of the retrospective cohort study conducted by Brannstrom et al. [26] in 2019 indicate a 156% increased risk of hip fracture occurrence in women over the age of 65 years who are users of any antidepressant agents compared to those who are not (OR = 2.56, 95% CI: 2.30–2.84). This value corresponds to exposure to antidepressant medication for longer than six months. The mean follow-up duration in this study was one year. Covariates adjusted to include age, sex; alcohol intoxication, depression, dementia, and the use of antidementia drugs, antipsychotic drugs, benzodiazepines, bisphosphonates, and prednisolone. The full list of confounding variables is detailed in Table 2. The results of the prospective cohort study conducted by Spangler et al. [28] in the United States show that the risk of self-reported skeletal fracture is 22% greater in women between the ages of 50–79 years who use any antidepressant compared to non-users (HR = 1.22, 95% CI: 1.15–1.30). This study also observed the incidence of skeletal fractures with the use of SSRIs specifically and found a 30% increased risk (HR = 1.30, 95% CI: 1.20–1.55). The mean follow-up duration in this study was 7.4 years. Spangler et al. adjusted their analyses for age, weight, height, ethnicity, years since menopause, physical function, exercise, current smoking, cardiovascular disease, analgesic, or narcotics, previous fracture, and depressive symptoms.

The cohort study carried out by Sheu et al. [17] in the United States investigated hip, humerus, radius, and ulna fracture risk with use of SSRIs in women aged 40–64 years. Sheu et al. [17] excluded women with mental disorders. Women without mental health disorders who were prescribed SSRIs were compared to those prescribed H2-receptor antagonists (H2A) or proton pump inhibitors (PPI). It is important to note that PPIs are associated with an increased risk of fractures [31]. Therefore, comparing SSRIs with PPIs is likely to underestimate the extent of increased risk of fractures associated with antidepressants. The results show a 67% increased risk of fracture outcomes (HR = 1.67, 95% CI: 1.30–2.14). The mean follow-up duration in this study was five years. Covariates adjusted for include age, sex, specific drugs that may affect the risk of fractures, use of HRT, Parkinson's disease, perimenopausal symptoms, seizure disorders, a history

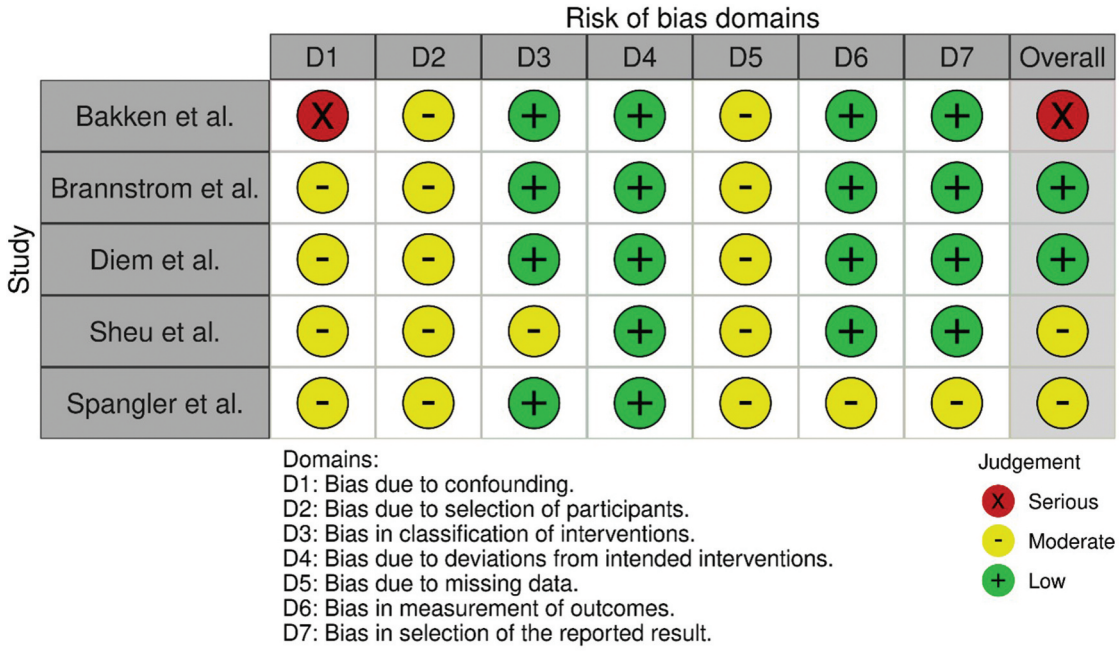

Figure 2. Results of ROBBINS-I tool for risk of bias in included studies.

of falls and prior hip and humerus and/or radius fracture. The full list of confounding variables is detailed in Table 2. The prospective cohort study carried out by Diem et al. [27] in the United States explored the risk of non-spine fracture occurrence in women above the age of 65 who were prescribed either SSRIs or TCAs, and this was compared to those not prescribed SSRIs or TCAs, respectively. Women prescribed other antidepressants were excluded from this study. Their results suggest that prescribing of SSRIs increases fracture risk by 30% (HR = 1.30, 95% CI: 1.04–1.62), and prescribing of TCAs increases fracture risk by 16% (HR = 1.16, 95% CI: 0.95–1.41). Diem et al. controlled for depression in their analysis models as a contributing factor to fractures. Other covariates adjusted for in this study include age, health status, cognitive function, alcohol use, estrogen use, bisphosphonate use, benzodiazepine use, proton pump inhibitor use, oral steroid use, and weight. The mean follow-up duration was 7.93 ± 4.64 years. Finally, the results of the prospective cohort study performed by Bakken et al. [25] in Norway show a 70% greater risk of hip fractures in women above the age of 60 years who were prescribed any antidepressant agent compared to non-users of antidepressants (standardized incidence ratios (SIR) = 1.7, 95% CI: 1.6–1.7). The authors also examined this risk across different antidepressant classes including SSRIs, TCAs and 'other' antidepressants. In women prescribed SSRIs, a 70% increase in fracture incidence was observed in the study population (SIR = 1.7, 95% CI: 1.7–1.8). In women prescribed TCAs, fracture incidence was a 40% increase, and with the use of other antidepressant medications, fracture incidence was 60% greater in the study population (SIR = 1.6, 95% CI: 1.5–1.7). The mean follow-up duration for this study was 5.2 ± 1.7 years; covariates adjusted to include sex, birth year, and time period (in 2-month intervals).

3.5. Analysis of pooled effect (meta-analysis)

The study by Bakken et al. [25] was not included in the meta-analysis because the results reported a standardized incidence ratio, which cannot be combined with effect estimates of odds and hazard ratios. Of the five eligible studies, two studies reported on the risk of fractures associated with prescribing of any antidepressant agents without further specifying the class of antidepressants [26,28] whilst three reported on the risk of fractures associated with prescribing of SSRIs specifically [17,28,29]. Brannstrom [26] et al. reported several effect measures for the year before and after initiation of antidepressants. We opted to include the odds ratio which corresponds to exposure to SSRIs for greater than six months as this is the recommended duration of use according to clinical practice guidelines [32]. The pooled result showed that prescribing of antidepressants to menopausal women increased the risk of fractures by 62% compared with those not prescribed antidepressants (HR = 1.62, 95% CI: 1.15–2.28, p-value = 0.00) (Figure 3). However, the Higgins I^2 test indicated that, across the results, there was considerable heterogeneity ($I^2 = 96.50\%$) [33]. The pooled result for prescribing of SSRIs shows an increased risk of fragility fractures by 36% compared to those not prescribed SSRIs (HR = 1.36, 95% CI: 1.20–1.55, p-value = 0.00) (Figure 4). The pooled estimate was heavily weighted toward the study by Spangler et al. [28] with moderate heterogeneity ($I^2 = 40.32\%$) [33]. The results of the meta-analysis suggest there is an association between prescribing of antidepressants, especially SSRIs, and increased risk of fracture events compared to menopausal women not prescribed antidepressants.

Table 2. Results of the included studies.

Authors	Publication Year	Intervention	Comparator	Outcome	Total no. fracture events	Unadjusted Effect Estimate [95% CI]	Adjusted Effect Estimate [95% CI]	Confounders
Bakken, M. S. et al. [25]	2013	Any antidepressant agent	Not prescribed antidepressants	Hip fracture	39,938	NR	Any: SIR: 1.7 [1.6-1.7] SSRI: SIR: 1.7 [17-1.8] TCA: SIR: 1.4 [1.3-1.6] Others: SIR: 1.6 [1.5-1.7]	Sex, birth year, time period (in 2-month intervals)
Brannstrom et al. [45]	2019	Any antidepressant agent	Not prescribed antidepressants	Hip fracture	NR	NR	OR: 2.56 [2.30-2.84]	Age, sex; marital status, level of education, and early retirement at the index date, renal failure, chronic obstructive pulmonary disease, malignant disease, alcohol intoxication, depression, diabetes, myocardial infarction, ischemic stroke, hemorrhagic stroke, dementia, and the use of antidementia drugs, antipsychotic drugs, benzodiazepines, bisphosphonates, and prednisolone
Diem, S. J. et al. [29]	2011	SSRI TCA	No t prescribed SSRIs Not prescribed TCAs	Non-spine fracture	2,809	SSRI: HR 1.36* [1.11-1.67] TCA: HR 1.38* [1.16-1.64] *Age-adjusted	SSRI: HR 1.30 [1.04-1.62] TCA: HR: 1.16 [0.95-1.41]	Age, health status, functional status, walking for exercise, ability to rise from chair, cognitive function (m-MMSE score), smoking status, alcohol use, estrogen use, bisphosphonate use, benzodiazepine use, thiazide use, proton pump inhibitor use, oral steroid use, weight, total hip BMD at Year 6, history of prior fracture, GDS score, total hip BMD and history of falls in the previous year
Sheu, Y. et al. [17]	2015	SSRI	H2A/PPI users	Hip, humerus, radius and ulna fracture	NR	NR	HR: 1.67 [1.30-2.14]	Age, sex, number of acute hospitalizations for any reasons, number of outpatient visits, constituents of the Charlson Comorbidity Index score, number of distinct generic drugs filled, specific drugs that may affect the risk of fractures, previous bone mineral density scans, use of HRT, malignant neoplasms, opiate use, stroke and transient ischemic attack, Parkinson's disease, perimenopausal symptoms, irritable bowel syndrome, seizure disorders, urinary incontinence, cardiovascular disease and chronic lung disease, a history of falls and prior hip and humerus and/or radius fracture
Spangler, L. et al. [28]	2008	Any antidepressant agent SSRI	Not prescribed antidepressants Not prescribed SSRIs	Hip, spine, wrist/ lower arm and 'other' skeletal fracture	14,982	NR	HR: 1.22 [1.15-1.30] HR: 1.30 [1.20-1.55]	Age, weight, height, ethnicity, years since menopause, physical function, exercise, current smoking, CVD, analgesic or narcotics, previous fracture, and depressive symptoms

HR= hazard ratio, SSRIs= selective serotonin inhibitors, TCA= tricyclic antidepressants, CI= confidence interval, SIR= standardized incidence ratio, H2A= H2 antagonists, PPI= proton-pump inhibitors, HRT= hormonal replacement therapy, NR= not reported.

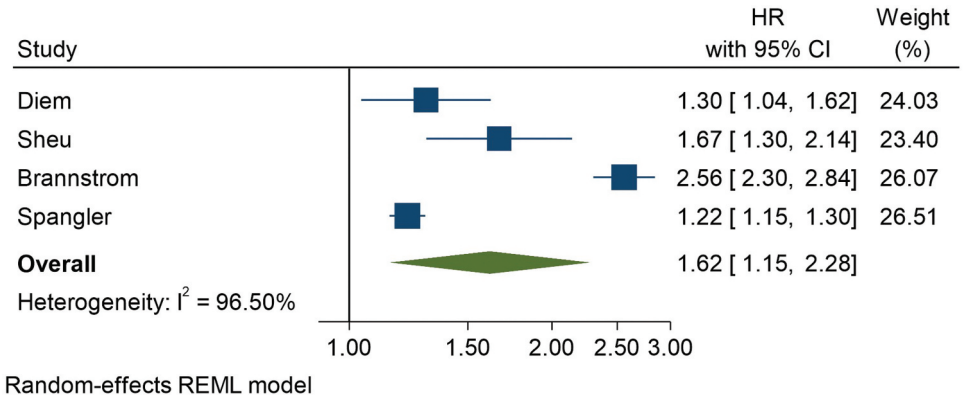

Figure 3. Forest plot for the association between risk of fragility fractures and prescribing of any antidepressants.

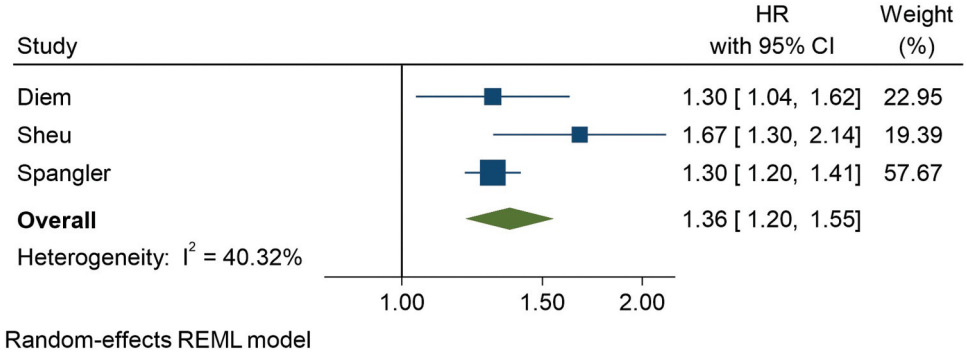

Figure 4. Forest plot for the association between risk of fragility fractures and prescribing of SSRIs.

4. Discussion

4.1. Summary and interpretation of results

The aim of this systematic review was to combine evidence on the association between the prescribing of antidepressants and the risk of fragility fractures amongst women aged 40 and older. The pooled results showed that, compared to women not exposed to antidepressants, antidepressants increase the risk of fracture events by 62%. Women prescribed SSRIs had a 36% higher risk of fractures compared to women not prescribed antidepressants. The mechanism by which antidepressants increase fracture risk is not fully understood, though a possible reason for this could be the direct effect of SSRIs on BMD [15,34]. As mentioned previously, osteoporosis is characterized by low BMD and bone fragility, both of which are linked to skeletal fracture incidence. In this systematic review, two of the included studies controlled for lowered bone mineral density measurement before prescribing of antidepressants [17,27]. Not controlling for bone mineral density and the use of medications that may increase the risk of fractures such as thiazide diuretics or proton pump inhibitors might have introduced bias to the results of studies included in the meta-analysis. Brannstrom et al. [26] showed that the risk of fractures is sustained through the first year after initiating SSRIs. The authors reported a 3-fold increased risk (OR = 3.09, 95% CI: 2.44–3.91) between 16 and 30 days after initiation and 2.5 fold increased risk (OR = 2.56, 95% CI: 2.30–2.84) in days 183–365 after initiation. The risk of fractures soon after drug initiation could be explained by an increased risk of falls due to adverse drug-effects, such as orthostatic hypotension whereas, the risk of fractures in the second period (183–365) suggests that the effect of SSRI exposure on fractures risk may be due to an underlying association with osteoporosis. In Sheu et al. [17], the risk of fractures associated with use of SSRIs accumulated over time, indicating that a shorter duration of treatment could reduce the risk. Though the results of this study show that the rate of fracture incidence could be related to the dosage or the amount of time the patient is on SSRI therapy, more evidence will be needed to establish the presence of a dose–response relationship and determine whether duration of exposure to these agents impacts the relationship observed between use of antidepressants and risk of fractures.

The adverse effects of antidepressant agents may give rise to increased fracture risk. Dizziness is common with the use of SSRIs, particularly upon initiation of drug therapy [35]. TCAs and MAOIs may also induce low blood pressure [35], of which the most prominent symptoms are light-headedness or dizziness. This could increase the risk of falls and, subsequently, the risk of fractures. Frailty, cognitive impairment, and old age may also be contributing factors to studies included in our review. All the studies included women older than 60 years [25,26,29]. Rates of fragility fractures increase with increasing age, particularly in women [36]. Another contributing factor to fractures in older women is weight loss, particularly fracture sites termed 'frailty fractures' which are the proximal humerus, pelvis, and hip [37].

An important factor to consider when assessing the association between prescribing of SSRIs and the risk of fragility fractures is the underlying depression and severity of depression. Literature shows that depression is a confounder for the risk of fractures as it is associated with an increased risk of falls and vitamin D deficiency [38–40]. Indeed, Brannstrom et al. [26] showed that the risk of fractures was highest in the months preceding antidepressant use. This could indicate that depression itself, rather than antidepressant therapy, is a driving factor behind the increased risk of fractures. In contrast, Sheu et al. excluded women diagnosed with mental illness and the results of this study showed a strong effect of SSRI use on the risk of fragility fractures.

The use of menopausal hormone therapy (MHT) by women in two of the studies focused on a younger age group (age 40 to 60) may have been a significant confounding variable and raises the question of what possible effect MHT could have on fracture risk in menopausal women prescribed antidepressant medication. In our systematic review study, Sheu et al. controlled for use of MHT as a potential confounder. There is a link between low estrogen levels and osteoporosis, which is why MHT is effective in preventing fractures [41]. Therefore, all studies examining the risk of fragility fractures in women aged 40–60 years need to account for the confounding effect of MHT. It is also important to consider the use of bisphosphonates, calcium, and vitamin D supplementation for their effect on bone health and potential to reduce the chance of fracture events. Of the included studies, two studies [26,29] controlled for use of bisphosphonates and other medications for treatment of osteoporosis.

4.2. Comparison with other studies

A systematic review and meta-analysis published in 2022 by Filippis et al. examined the relationship between the use of antidepressants and vertebral and hip fracture risk in the general population [42]. Most of the inclusion criteria were similar, but our inclusion criteria narrowed the population to women above 40 years only. This accounts for the stark difference in reports found eligible for inclusion in the reviews (26 vs 5) and highlights the lack of studies which investigate the fracture risk in older women prescribed antidepressant medications. The authors also commented on the fact that only a few studies reported gender ratio and when reported, they were mostly males. Although the authors of Filippis et al. review pooled results using Cohen's d, which is difficult to interpret [43], the pooled results show a higher risk of hip fractures associated with SSRI treatment. This supports the results of the meta-analysis in this systematic review which also showed an increased risk of fractures in women prescribed SSRIs.

4.3. Strengths and limitations

One of the strengths of this review is that the literature search sought studies from PubMed, Ovid EMBASE, Ovid PsycINFO, Web of Science, and Scopus since most literature is accessible from these databases. In addition, the studies included in this review had large sample sizes, with a mean of 248,071 included participants. Having large sample sizes reduces the margin of error in the study, and large sample sizes are considered more representative of the target population. Likewise, the mean follow-up years for the cohort studies ranged from 1 to 7.93 years which was ample time for fracture outcomes to occur. Not only does this speak toward the validity of the included studies but also allows us to make comparisons between exposure durations and see how fracture risk varies with time. However, as mentioned previously, this is an area which requires further investigation.

We have pooled the results for the risk of fractures associated with prescribing of antidepressants in menopausal women compared to women who are not prescribed antidepressants. Antidepressants increased the risk of fractures by 62% and SSRIs in particular increased the risk of fractures by 36%. It is important to interpret these results carefully due to the high heterogeneity found between studies. Differences in follow-up time, data source, and indication for antidepressants between the five studies included in our review may explain the high heterogeneity observed in the meta-analysis [33]. The mean age of women was different across all studies and this may have also contributed to the high heterogeneity. Age-related factors, such as muscle strength and balance play a role in the risk of fragility fractures, and as a result, the fracture risk for women in their 40s is lower compared with older women. Further, the pooled risk of fractures associated with the prescribing of SSRIs was associated with lower heterogeneity compared with heterogeneity associated with antidepressants due to the variability between users of antidepressant classes. Antidepressant classes such as TCA have limited acceptability and are usually reserved as second-line options [44]. Thus, the risk of fractures associated with prescribing of TCA is possibly higher compared with the risk of fractures associated with SSRIs in particular due to confounding by severity of the indicated mental illness. Another limitation is that our study defined menopause on the basis of one year without menses, which may be the results of other factors such as hormonal contraception or hypothalamic dysfunction.

This review is limited by inadequate representation of female populations beyond the Western population as the included studies were based in the United States, Norway, and Sweden. There is also no exploration of potential differences in fracture risk between women of different ethnicities. The studies included in this review either didn't report race [17] or the sample populations comprised of majority white females [28]; black women were even excluded from one of the studies [29]. This limits the generalizability of our results. There is a need for more research to investigate whether fracture risk is the same for women over 40 years taking prescribed antidepressants of different ethnic backgrounds and, if so, what the possible reasons for these differences may be.

Finally, the studies included in this review mostly discussed SSRIs, and there was little to no data on other classes of antidepressant medications. A possible reason for this could be that there is already an established link between SSRI use and fracture risk, and this is an area of interest which researchers have chosen to explore further in relation to a more specific patient population. However, this does highlight another gap in the research. Current literature fails to examine

the impact of a broader range of antidepressants on fracture risk and to make direct comparisons between antidepressant classes, particularly other antidepressants such as SNRIs.

5. Conclusion

This systematic review and meta-analysis provide evidence that the prescribing of antidepressant medications in women aged 40 and older positively correlates with an increased risk of fracture events. Future research should be directed toward studying the effect of antidepressants in women with mental health diseases, assess for dose-response, duration of use, and investigate how this risk potentially differs between different antidepressant classes and different ethnicities.

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Declaration of interest

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