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ORIGINAL ARTICLE

Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case–control studies

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Abstract
Summary Studies on use of selective serotonin reuptake inhibitors (SSRIs) and risk of fracture have yielded inconsistent results. This meta-analysis, which pooled results from 13 qualifying cohort and case–control studies, found that SSRIs were associated with a significantly increased risk of fractures.
Introduction This study was conducted to assess whether people who take SSRIs are at an increased risk of fracture.
Methods We conducted a meta-analysis of observational studies. Relevant studies published by February 2010 were identified through literature searches using MEDLINE (from 1966), EMBASE (from 1988), PsycINFO (from 1806), and manual searching of reference lists. Only cohort or case–control studies that examined the association of SSRIs and risk of fracture and bone loss were included. Data were abstracted independently by two investigators using a standardized protocol; disagreements were resolved by consensus. Random effects models were used for pooled analysis due to heterogeneity in the studies.
Results Thirteen studies met inclusion criteria. Overall, SSRI use was associated with a significantly increased risk of fracture (relative risk, RR, 1.72; 95% CI [1.51, 1.95]; $P<0.001$). An increased fracture risk associated with SSRIs also was observed in the three studies that adjusted for bone mineral density (RR, 1.70; 95% CI [1.28, 2.25]; $P<0.001$) and in the four studies that adjusted for depression (RR 1.74; 95% CI [1.28, 2.36]; $P<0.001$). SSRI use was not associated with bone loss in the two cohort studies of women ($P=0.29$). The overall association between SSRI use and fracture risk was weaker (RR, 1.40; 95% CI [1.22, 1.61]), though still significant ($P<0.001$) in analyses that accounted for apparent publication bias.
Conclusions Use of SSRIs is associated with increased risk of fracture. The SSRIs may exert an increased risk of fracture independent of depression and bone mineral density.

Keywords Antidepressant · Bone fractures · Bone mineral density · Depression · Osteoporosis · Serotonin reuptake inhibitors

Abbreviations

BMD	Bone mineral density
CI	Confidence interval
HR	Hazard ratio
MOOSE	Meta-analysis of Observational Studies in Epidemiology
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RR	Relative risk
SSRI	Selective serotonin reuptake inhibitor

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Introduction

Osteoporotic fractures are a major public health problem worldwide, especially in elderly persons. Approximately 13% of white men and 40% of white women sustain an osteoporotic fracture after age 50 years [1]. Furthermore,

the population age is increasing worldwide, with the prevalence of osteoporosis increasing as well. Although standardized hip fracture rates have declined in North America, the absolute number of hip fracture continues to increase [2–4]. Severe disability and excess deaths associated with fractures often lead to an increase in social and economic burden [5].

Antidepressants are one of the most commonly prescribed drugs in the Western world and have been reported to be associated with an increased risk of fractures [6–16]. Selective serotonin reuptake inhibitors (SSRIs) are recommended for first-line pharmacological management of depression because they are considered safer and better tolerated [17] than other types of antidepressants. The use of SSRIs is widespread, and SSRIs account for approximately 62% of all antidepressants prescribed in the USA [18]. Several cohort and case–control studies have examined the association between the use of SSRIs and the risk of fractures [7–15, 19–21]; however, the reported findings have not been consistent. Some studies found a significant positive association between SSRI use and fracture risk [7, 9, 12–15, 19–21]; yet other studies found a nonsignificant association [8, 11]. Several narrative reviews examined the inconsistent results; however, these reviews did not include meta-analyses of the results [22–26].

We conducted a meta-analysis to quantitatively assess all qualified cohort and case–control studies that examined the effect of SSRIs on risk of fractures and bone loss, which allowed us to gather more precise and accurate information about this effect. We also investigated whether the impact varied by sex, study design, sample type, country, and adjustment for depression or bone mineral density (BMD).

Methods

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement were followed [27, 28]. A protocol was developed in advance to specify the objective, primary outcome, inclusion criteria, and method for study selection, data extraction, and data synthesis for our meta-analysis. Data fields were predefined and formatted in Access software (Microsoft Corp., Redmond, WA, USA). Sensitivity analysis and subgroup analysis were also prespecified in the protocol, and the protocol was peer reviewed.

Study selection

We conducted a comprehensive literature search of MEDLINE (from January 1966) by OVID, without language restrictions and with the search terms *serotonin uptake inhibitor*, *antidepressant*, *fluoxetine*, *fluvoxamine*, *sertraline*, *citalopram*, *escitalopram*, *paroxetine*, *fractures*, *osteoporosis*, *osteopenia*, *bone density*, and *bone loss* (Appendix). The search strategy was peer reviewed. Using the same strategy, we also searched the databases of EMBASE (from 1988) and PsycINFO (from 1806). The last search was run on February 22, 2011. The literature search was updated to March 18, 2011, with automatic Ovid alerts. We also searched Dissertation Abstracts Online and the proceedings of the International Osteoporosis Foundation World Conference on Osteoporosis from 2000 to 2010. Medical librarians were consulted during the literature search. A manual search was conducted by two investigators (Q.W. and A.F.B.) independently by examining reference lists from the original studies [7–15, 19–21, 29] and review articles [22–26] obtained during the electronic search.

For the initial screening stage, two investigators (Q.W. and A.F.B.) independently reviewed each title and abstract of articles to exclude only the obviously irrelevant citations on which both investigators agreed. We used simple relevance criteria: (1) human participants, (2) SSRI, and (3) BMD or fracture which resulted in a total of 44 qualifying articles. Agreement was only modest between the two investigators at this initial stage (κ=0.67). For the second screening stage, the same two researchers independently evaluated the full contents of the 44 articles, using predetermined selection criteria and assessment methods. Areas of uncertainty or disagreement were resolved by consensus. Agreement between the two investigators was good at this second stage (κ=0.91).

Study selection flow is illustrated in Fig. 1. The present meta-analysis included only cohort and case–control studies that reported data on individuals with a fracture or BMD who were either exposed to SSRIs or not exposed to antidepressants. Cross-sectional studies were excluded. We included studies that reported the hazard ratio (HR), relative risk (RR), or odds ratio (OR) of fracture or decreased rate of BMD associated with SSRI use. Thirteen studies met the inclusion criteria [7–15, 19–21, 29] and were included in our meta-analysis.

We assessed study quality using a 10-point scale adapted from a published quality scale for observational studies [30]. Quality assessment scoring was performed independently by two investigators (Q.W. and A.F.B.). Using the Bland and Altman limits-of-agreement approach [31], the average disagreement was close to 0 (0.15), and the 95% confidence interval (CI) included zero (−0.33, 0.64), suggesting no evidence of a systematic disagreement bias between the two reviewers. As recommended by the MOOSE study group [27], the quality scores were not used as weights in the analyses; they were used in the sensitivity analysis by excluding articles with a score below 7. This threshold was derived from a meta-analysis by Etminan et al. [32].

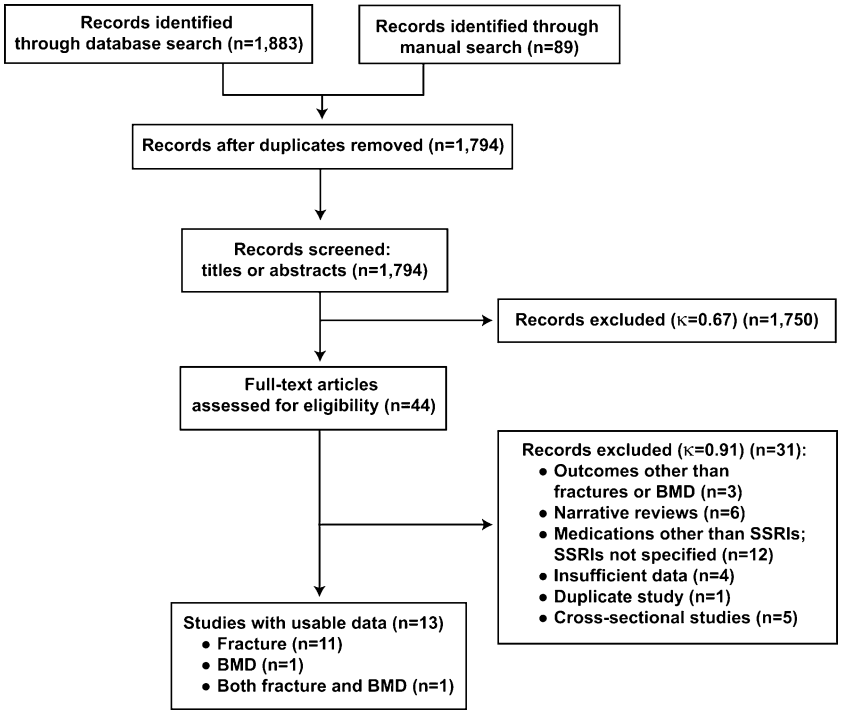

Fig. 1 Study selection for meta-analysis. *BMD* indicates bone mineral density; *SSRI*, selective serotonin receptor inhibitor

Data abstraction

The data abstraction form was tested on three randomly selected studies and refined accordingly. All data were independently abstracted by two investigators (Q.W. and A. F.B.) using the standard protocol and data abstraction form. No major discrepancies arose between abstractors; minor errors were resolved by rechecking the original reports. The following study characteristics were recorded:

- Name of first author
- Publishing year
- Country in which the study was conducted
- Study setting and design
- Study population and baseline characteristics
- Inclusion and exclusion criteria
- Measures of outcomes and exposure
- Duration of follow-up
- Confounding factors that were controlled by matching or multivariate adjustment
- RR, HR, or OR of fracture associated with SSRI use and its 95% CI
- Mean (SD) difference of BMD change associated with SSRI use

When multiple estimates of fracture risk from nested models were presented in the original studies, the estimate that adjusted for the largest number of confounders was used; when estimates of fracture risk were presented for both current and previous SSRI users, the estimate from current SSRI users was used [7, 15, 21]. Vestergaard et al. [13] presented estimates of fracture risk at multiple levels of SSRI defined daily doses, and the estimate from the SSRI level closest to one defined daily dose was used. Spangler et al. [20] presented adjusted HRs for different anatomical sites of fracture, and the overall adjusted HR from all anatomical sites was used for overall analysis. Verdel et al. [21] presented risk estimates for both osteoporotic fracture and nonosteoporotic fracture, and the estimate from osteoporotic fracture was used. No authors were contacted since no further study detail was needed.

Statistical analysis

The primary outcome was the risk of any fracture associated with use of SSRIs. The confounder-adjusted RR was used as a measure of the association between SSRI use and fracture risk. The second outcome was the risk of bone loss associated with SSRI use. The confounder-adjusted mean percentage difference between a patient who took an SSRI and a patient who did not take an SSRI was used as a measure of association between SSRI use and loss of BMD. In case–control studies, the OR was used as a surrogate measure of the corresponding RR. Because the absolute risk of fracture is low, the ORs approximated the RRs. For studies that reported outcomes stratified by subgroups only, the overall effect size across subgroups in each individual study was estimated with meta-analysis. To stabilize the variance and normalize the distributions, we

transformed HRs or RRs into their natural logarithms [33] before pooling the data. The variance of the natural logarithm of HR or RR was derived from the CI, which was either provided in the study or calculated with standard formulas [34]. To estimate the overall effect size, each study was weighted by the reciprocal of its variance. The percentage of BMD change over different follow-up periods was standardized as an annual percentage of BMD change by dividing this outcome by years of follow-up. Variances for the percentage BMD decrease by SSRI use in each study were calculated by using CIs or by pooling the individual variances.

We conducted prespecified sensitivity analyses to estimate the robustness of our findings under different assumptions. The effects of SSRIs were examined by the fracture definition and quality score. We conducted one post hoc sensitivity analysis by including studies with participants aged ≥50 years only. We used both a fixed effects model and a random effects model to calculate the pooled relative risk. Both approaches yielded statistically significant estimates, and the variation between estimates was small. Cochran Q statistics were used to assess heterogeneity [35, 36]. Heterogeneity was expected because these individual studies were conducted among participants with different races/ethnicities, sexes, ages, and durations of SSRI use and in different settings with different study designs. Cochran Q statistics indicated that heterogeneity was present ($P<0.001$). Therefore, we presented results obtained with the random effects model instead of the fixed effects. The random effects model also provided a conservative approach that accounted for any differences among studies [37].

We prespecified a list of subgroup analyses in order to assess whether the effect of SSRIs on fracture risk was modified by demographic or clinical variables. These variables were selected on the basis of known risk factors or biological plausibility, such as sex, race/ethnicity, age, study design, study location, and whether the study controlled for depression or BMD. One post hoc subgroup analysis was also conducted by sample type. We were not able to conduct subgroup analysis for race/ethnicity because some original studies did not specify the variable and others used multiethnic groups. Age was included in the sensitivity analysis because most studies ($n=9$) reported participants who were older than 50 years. Multivariate meta-regression analysis was not performed because of the limited number of studies that qualified for inclusion in the present meta-analysis and the unavailability of some important variables, such as sex and race/ethnicity, in the original studies.

The potential for publication bias was examined by constructing a funnel plot, in which log RRs were plotted against their standard errors [38], by using the Begg's rank correlation test [39], and by using the trim-and-fill method [40], which estimated and adjusted for the potential effect that nonpublished studies might have on the measured outcome.

All data analyses were conducted with Stata 10.0 (StataCorp, College Station, TX, USA) statistical software. Statistical significance was set at a P value of 0.05 or less.

Results

Of the 13 studies included in our meta-analysis, 11 studies reported fracture as an outcome [7–15, 20, 21], one study reported BMD as an outcome [29], and one study reported both outcomes [19]. All 13 studies were published in the English language. The characteristics of the study participants and the designs of the cohort studies are presented in Table 1. Of the seven cohort studies, five were conducted on persons in the USA, three were conducted on mixed-sex groups, and four either did not specify race or were conducted on groups of mixed race. Four studies were conducted on persons aged ≥65 years and three on persons aged ≥50 years. The number of study participants ranged from 2,722 in the Study of Osteoporotic Fractures [29] to 93,676 in the Women's Health Initiative Observational Study [20]. SSRI use was verified from containers [8, 9, 19, 20, 29] or pharmacy dispensing records [10] in six studies. Self-reported fractures were confirmed by radiographic reports [8, 9, 11] or medical reports [20] in four studies; one study assessed fractures through general practitioner reports from a computerized system [10], and one study identified fracture through face-to-face interviews by trained interviewers [19]. The mean follow-up period ranged from 4.0 to 8.4 years. The potential confounding effects of age and sex (if applicable) were controlled for in six cohort studies, whereas BMD was controlled for in only five cohort studies.

All six case–control studies [7, 12–15, 21] were conducted outside the USA and on mixed-sex groups. The number of case subjects enrolled in these six studies ranged from 6,763 [15] to 124,655 [13]; the corresponding number of control subjects ranged from 26,341 to 373,962. In all the case–control studies, cases were identified with clinical diagnoses or hospital records, and exposure was assessed with prescription records. Matching or adjustment was performed for various potential confounders (Table 2).

Figure 2 shows RR (and 95% CIs) of fractures associated with SSRI use in each study and overall. All RRs were greater than one, but only ten RRs were statistically significant. Compared with patients who had taken no SSRI, those who had taken an SSRI had an overall RR of fractures of 1.72 (95% CI [1.51, 1.95], $P<0.001$). To explore how adjustment for confounders influenced the risk estimate, we pooled crude RR from eight studies that were available. The overall crude RR was 2.25 (95% CI [1.90, 2.68], $P<0.001$), and the corresponding overall adjusted RR from the eight studies was 1.76 (95% CI [1.51, 1.95], $P<0.001$).

Table 1 Characteristics of seven cohort studies of SSRI use associated with fracture risk and bone loss

Author, year, location	Study population	Exposure assessment	Outcome assessment	Outcomes	Duration of follow-up, years	Variables controlled
Ensrud et al. 2003 [8], USA	8,127 white women aged ≥65 years in the Study of Osteoporotic Fractures	Interview, with verification of SSRI use from containers	Postcard or phone interview confirmed with radiographic report	Nonspine fracture Hip fracture	4.4 4.8	Age, health status, use of ≥1 medication, walking for exercise, functional impairment, fall in previous year, cognitive function, weight change, gait speed, inability to rise from chair, femoral neck BMD
Schneeweiss and Wang, 2004 [19], USA	7,126 men and women aged ≥65 years in MCBS	Interview, with verification of SSRI use from containers	Face-to-face interview by trained interviewers	Hip fracture	4.0	Age, sex, BMI, smoking, activities of daily living score, cognitive impairment, and Rosow–Breslau physical impairment scale
Diem et al. 2007 [29], USA	2,722 women aged ≥65 years in the Study of Osteoporotic Fractures	Interview, with verification of SSRI use from containers	BMD measured with DEXA	BMD	4.9	Age; race; health status; functional status; walking speed; ability to rise from a chair; Mini-Mental State Examination score; smoking status; use of calcium supplement, vitamin D supplement, estrogen, thiazide, bisphosphonate; BMI; change in weight; total hip BMD at visit 6 examination; Geriatric Depression Scale score
Lewis et al. 2007 [11], USA	5,995 men aged ≥65 years in MrOS	Interview by trained staff	Triannually mailed questionnaires adjusted with medical report or radiographic report	Nonspine fracture	4.1	Age, BMD
Richards et al. 2007 [9], Canada	5,008 men and women aged ≥50 years in CaMos	Interview, with verification of SSRI use from containers	Annually mailed questionnaires confirmed radiographically	Clinical fragility fracture	5.0	Age, total hip BMD, modified Charlson index, prevalent vertebral deformity, prevalent fragility fractures at baseline, cumulative lifetime estrogen use in women
Ziere et al. 2008 [10], Netherlands	7,983 men and women aged ≥55 years in Rotterdam Study	Pharmacy dispensing records	Reported by general practitioners through a computerized system	Nonvertebral fracture	8.4	Age, sex, depression during follow-up period, disability category, lower-limb disability
Spangler et al. 2008 [20], USA	93,676 women aged 50–79 years in Women's Health Initiative Observational Study	Interview, with verification of SSRI use from containers	Self-report, with hip fracture adjudicated by medical records	Fracture, BMD	7.4	Age, height, ethnicity, years since menopause, physical function, exercise, current smoking, depression. Additional adjustment for BMD: baseline BMD, log weight, oral hormone therapy. Additional adjustment for fracture: previous fracture, weight, CVD, use of analgesic or narcotic

BMD bone mineral density, *BMI* body mass index, *CaMos* Canadian Multicentre Osteoporosis Study, *CVD* cardiovascular disease, *DEXA* dual energy x-ray absorptiometry, *MCBS* Medicare Current Beneficiary Survey, *MrOS* Osteoporotic Fractures in Men Study, *SSRI* selective serotonin reuptake inhibitor

Table 2 Characteristics of six case–control studies of SSRI use associated with risk of fracture

Author, year, location	Fracture cases	Controls	Case assessment	Exposure assessment	Controlled variables
Liu et al. 1998 [7], Canada	8,239 men and women aged ≥66 years with a hip fracture in an Ontario acute-care hospital	41,195 individuals in Registered Person Database	Clinical diagnosis	Prescription claim	Age, sex, comorbidity (e.g., depression, dementia, osteoporosis), previous drug exposure (e.g., sedative, tranquilizer, cardiac drug, anti-Parkinson agent, thyroid-replacement drug, anticonvulsant, insulin, glucocorticoid, estrogen, etidronate)
Hubbard et al. 2003 [12], UK	16,341 men and women with mean (SD) age of 79 years (12) with a hip fracture or fractured neck of femur in GPRD	29,889 patients in GPRD	Clinical diagnosis	Computerized recordings of prescription	Age, sex, general practice, duration of available GPRD data, history of falls and prescriptions for hypnotics and antipsychotics
Vestergaard et al. 2006 [13], Denmark	124,655 men and women with mean (SD) age of 43.4 years (27.4) with a fracture, in Danish population	373,962 residents in Civil Registration System	Radiographic and clinical diagnosis	Prescription history in database	Age; sex; psychiatric comorbidity (e.g., manic depression, schizophrenia, alcoholism, eating disorder); medication use (e.g., anxiolytic, sedative, neuroleptic, corticosteroid, antiepileptic, cardiovascular agent, lithium); hospital stay; prior fracture; income; working, educational, and residential status; Charlson index
Bolton et al. 2008 [14], Canada	15,796 men and women aged ≥50 years with an osteoporotic fracture in Manitoba Health	47,289 Manitoba residents aged ≥50 years	Recorded clinical diagnosis in database	Prescription codes in database	Age, sex, ethnicity, demographic characteristics (e.g., income quintile, region of residence), physical diagnoses (e.g., diabetes mellitus, ischemic heart disease, myocardial infarction, hypertension, epilepsy, rheumatoid arthritis, solid organ transplant, COPD, home care use), mental diagnoses (e.g., substance abuse, depression, dementia, schizophrenia), medication use (e.g., anticonvulsant, diuretic, anticoagulant, thyroid hormone)
van den Brand et al. 2009 [15], Netherlands	6,763 men and women aged ≥18 years with a hip or femur fracture in Dutch PHARMO RLS	26,341 hospitalized patients	Hospital record for a first fracture of the hip or femur	Reviewing prescription information	Age; sex; geographical region; other antidepressant; use of benzodiazepine, antipsychotic, lithium, anti-Parkinson agent, anticonvulsant, oral–inhaled corticoid, bronchodilator, HRT, antiarrhythmic, thiazide diuretic, β-blocker, drug for diabetes mellitus, metoclopramide, morphine/opiate, or ≥2 NSAIDs; history of hospitalization
Verdel et al. 2010 [21], Netherlands	16,717 men and women aged ≥18 years with a fracture in PHARMO RLS	61,517 patients in PHARMO RLS	Recorded clinical diagnosis in database	Reviewing prescription information	Age; sex; geographical area; calendar time; cancer; cardiovascular disease; cerebrovascular disease; inflammatory bowel disease; mental disorder; obstructive airway disease; use of antidiabetic, antiepileptic, anti-Parkinson drug, antipsychotic, benzodiazepine, β-blocking agent, DMARD, HRT, NSAID, oral glucocorticoid, opioid

COPD chronic obstructive pulmonary disease, *DMARD* disease-modifying anti-rheumatic drug, *GPRD* General Practice Research Database, *HRT* hormone replacement therapy, *NSAID* nonsteroidal anti-inflammatory drug, *PHARMO RLS* PHARMO Record Linkage System, *SSRI* selective serotonin reuptake inhibitor

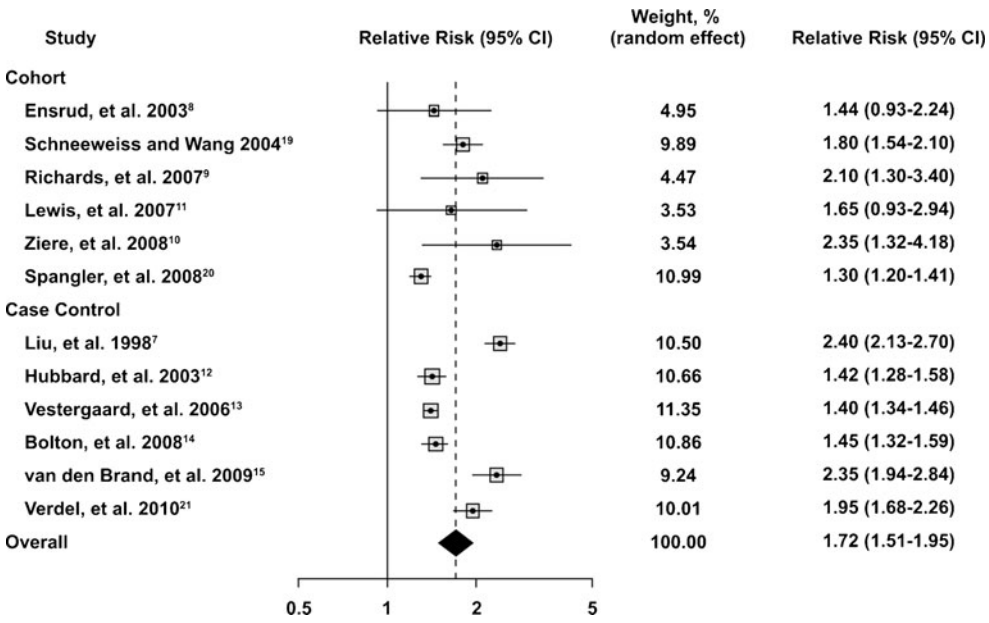

Fig. 2 Risk of fracture associated with selective serotonin reuptake inhibitor use by individual study and by all studies combined. *CI* indicates confidence interval

The estimated fracture risk changed little when studies with different criteria were excluded (Table 3). For example, when the analysis was confined to the ten studies that adjusted for important fracture risk factors such as age, sex, major comorbidity, and medications known to increase fracture risk, the overall RR decreased slightly to 1.70. After the exclusion of three studies that included persons younger than 50 years, the overall RR decreased slightly to 1.68. When the analysis was confined to the 11 studies for which the quality score was at least 7, the overall RR decreased slightly to 1.63. After the exclusion of four studies that included vertebral fracture as the outcome, the overall RR increased slightly to 1.78. Finally, when the analysis was confined to studies that used hip fracture as the outcome, the overall RR was 1.70.

Table 4 summarizes the pooled estimates of RR associated with SSRI use in subgroups of cohort and case–control studies according to study design, study location, sex, study sample type, and adjustment for depression or BMD. Overall, an increase in fracture risk associated with SSRI use was observed in all subgroups, particularly in studies with case–control design, population-based sample, adjustment for depression, adjustment for BMD, and conducted outside the USA.

Only two studies [20, 29] that reported BMD as the outcome met the inclusion criteria. Both were cohort studies and were conducted with women only. The increased annual bone loss of 0.19% (95% CI [−0.15%, 0.53%]) at the hip by SSRI use was not significant (P=0.29).

Table 3 Relative risk of fracture associated with use of SSRIs according to different exclusion criteria

Studies included	Relative risk		
	No. of studies	(95% CI)	*P* value
All studies	12	1.72 (1.51, 1.95)	<0.001
Studies that scored ≥7[a]	11	1.63 (1.46, 1.81)	<0.001
Studies that controlled for important fracture risk factors[b]	10	1.70 (1.48, 1.94)	<0.001
Studies that included persons aged ≥50 years only[c]	9	1.68 (1.41, 2.00)	<0.001
Studies with nonvertebral fractures as outcome[d]	8	1.78 (1.43, 2.21)	<0.001
Studies that used hip fractures as outcome[e]	7	1.70 (1.48, 1.95)	<0.001

CI confidence interval, *SSRI* selective serotonin reuptake inhibitor

[a] Excludes Liu et al. [7]

[b] Excludes Lewis et al. [11] and Ziere et al. [10]

[c] Excludes Vestergaard et al. [13], van den Brand et al. [15], and Verdel et al. [21]

[d] Excludes Vestergaard et al. [13], Richards et al. [9], Bolton et al. [14], and Verdel et al. [21]

[e] Excludes Richards et al. [9], Lewis et al. [11], Ziere et al. [10], Bolton et al. [14], and Verdel et al. [21]

Table 4 Relative risk of fracture associated with use of SSRIs in subgroups defined by characteristics of study design, sex, confounder adjustment, sample type, and study location

Studies included	No. of studies	Relative risk (95% CI)	*P* value
Study design			
Cohort	6	1.65 (1.33, 2.05)	<0.001
Case–control	6	1.76 (1.47, 2.12)	<0.001
Sex			
Women	3	1.30 (1.20, 1.41)	<0.001
Men and women	9	1.81 (1.55, 2.12)	<0.001
Adjusted for BMD			
Yes	3	1.70 (1.28, 2.25)	<0.001
No	9	1.72 (1.49, 1.98)	<0.001
Adjusted for depression			
Yes	4	1.74 (1.28, 2.36)	<0.001
No	8	1.72 (1.48, 2.00)	<0.001
Sample type			
Population-based	3	1.79 (1.32, 2.43)	<0.001
Convenience	9	1.70 (1.42, 2.03)	<0.001
Study location			
USA	5	1.58 (1.27, 1.98)	<0.001
International	7	1.79 (1.50, 2.15)	<0.001

BMD bone mineral density, *CI* confidence interval, *SSRI* selective serotonin reuptake inhibitor

Publication bias was suspected in our meta-analysis, as indicated by the funnel plot (Fig. 3) and Begg's rank correlation test (t=2.00, P=0.07). However, after trim-and-fill correction for missing data, the effect size was still significant (RR, 1.40; 95% CI [1.22, 1.61]; P<0.001).

Discussion

Overall, our meta-analysis showed a 72% increased relative risk of fracture for SSRI users compared to non-SSRI users. This increased risk was consistent in sensitivity analyses, in which data were pooled from studies on the basis of different inclusion criteria, and in subgroup analyses. These findings strongly suggest that patients who take an SSRI have an increased risk of osteoporotic fractures. However, SSRI use was not significantly associated with bone loss (P=0.29). Furthermore, adjusting for BMD had no effect on the strength of association between SSRI use and risk of fracture. These results suggest that SSRIs may exert an increased risk of fracture independent of BMD.

Previous reviews have summarized the association between SSRIs and fracture and have tried to address the inconsistent findings regarding this association [22–26]. However, these reviews have neither provided an overall estimation of the effect of SSRIs on fracture nor systematically reviewed the subgroups of study design, study location, sex, and controlled confounders. Use of meta-analysis to examine and pool these results provides unique insight into the relationship between SSRI use and fracture risk. To our knowledge, the present study is the first meta-analysis to examine the impact of SSRI use on bone fracture comprehensively.

Both bone loss and a higher propensity to fall contribute to increased fracture risk. The underlying mechanism for the relationship between SSRIs and osteoporotic fractures remains unclear. In this meta-analysis, SSRI use was not significantly associated with bone loss (P=0.29); adjusting for BMD had no effect on the strength of association between SSRI use and risk of fracture. These results suggest that SSRIs may exert an increased risk of fracture independent of BMD reduction. Other pathways, such as impaired bone architecture by SSRIs leading to decreased bone strength, cannot be excluded. Previous studies have identified antidepressant use as a risk factor for falls in elderly patients [41–43]. The association

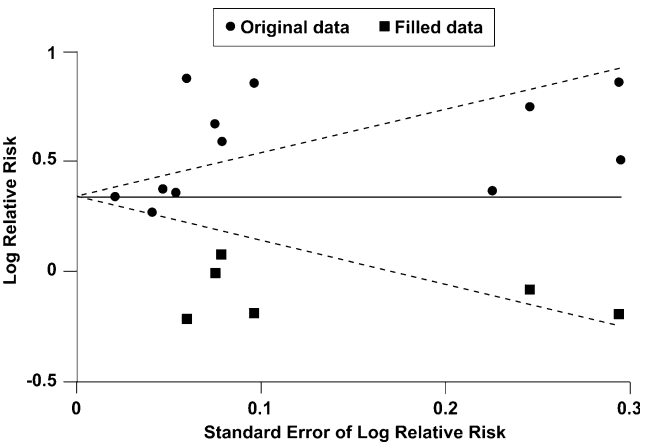

Fig. 3 Funnel plot of RR vs standard error of the log RR

between psychotropic medications and falls in elderly persons may explain the relationship with osteoporotic fractures. SSRIs have CNS effects that may lead to disturbed sleep, insomnia, nocturia, and thus daytime sleepiness [43], which may slow reaction times. SSRIs may also cause sedation, orthostatic hypotension, tremulousness, and arrhythmias [43], which have the potential to increase propensity to falls and increase fracture risk. Therefore, patients taking SSRIs should be targeted for fall prevention.

Our previous meta-analyses showed that depression is a risk factor for fracture and bone loss [44, 45]. Confounding by indication may contribute to an increased risk of fracture in SSRI users. In our subgroup analysis, there also was a significant elevated risk of fracture in the studies that adjusted for depression, indicating that SSRIs may exert an increased risk of fracture independent of depression. However, confounding by indication cannot be excluded, since various methods for assessing depression were used in the studies and some studies may not account for severity and chronicity of prior depression. Additionally, those depressed individuals with SSRI treatment may not currently exhibit symptoms of depression, yet prior depression could have increased risk of fracture.

Our study has limitations. Because of the limited number of studies (n=12 for fracture outcome) that qualified for inclusion in our meta-analysis, we could not perform a multivariate meta-regression analysis to investigate sources of heterogeneity presented in this study. However, subgroup analyses were performed with available key variables such as sex, study design, study location, and whether the study controlled for depression or BMD. Heterogeneity may be partially explained by subgroup differences in sex and study location, but little variation was found between cohort and case–control studies, and adjusting for BMD and depression did not affect the estimates. Important sources of heterogeneity such as variation in SSRI dosage, duration of use, and by indication (discussed above) could not be assessed, because they were not available or were mixed in most studies. Other medications also have the potential to affect bone strength. Anticonvulsants [46] and glucocorticoids [47, 48] have been reported to be associated with risk of fracture. However, some studies included in our meta-analysis did not adjust for these medications, and therefore, we cannot rule out the possibility that the association was confounded by other medications. We pooled estimates from studies which adjusted for different confounders, which may have created imbalances and impacted precision of the overall estimate. However, the crude and adjusted RRs from the same studies were only slightly different, and the overall estimates were consistently significant in all sensitivity analyses and subgroup analyses. Furthermore, some studies in our meta-analysis used claims data [7], which may lack information on cognition, physical functioning, and other important potential confounders. Additional studies are warranted to account for these potential confounders when examining the relationship between SSRIs and fracture. In addition, the results of our meta-analysis were based on data from patients who were currently being treated with SSRIs and may not generalize to patients with a history of SSRI treatment. Often SSRIs are used to treat discrete depressive episodes, and the risk of fracture may decrease upon discontinuation of SSRI therapy. Finally, lack of assessment of risks for falls is another limitation of this study. We could not assess it because so few of studies accounted for falls; however, it remains an important potential etiology for the association between SSRI treatment and fractures.

Summary

Our findings indicate that use of SSRIs is associated with an increased risk of fracture and that SSRIs may exert an increased risk of fracture independent of depression and BMD.

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Conflicts of interest None.

Appendix

Search strategy for MEDLINE (OVID)

001 exp Serotonin Uptake Inhibitors/
002 serotonin uptake inhibitor#.mp.
003 exp Antidepressive Agents/
004 antidepressant#.mp.
005 exp Fluoxetine/or fluoxetine.mp.
006 ssri#.mp.
007 fluvoxamine.mp. or exp Fluvoxamine/
008 sertraline.mp. or exp Sertraline/
009 citalopram.mp. or Citalopram/
010 escitalopram.mp. or exp Citalopram/
011 paroxetine.mp. or exp Paroxetine/
012 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
013 exp Fractures, Bone/
014 fracture#.mp.
015 exp Osteoporosis/or osteoporosis.mp.
016 osteopenia.mp. or exp Bone Diseases, Metabolic/
017 bone mineral density.mp. or exp Bone Density/
018 bone density.mp.
019 bone loss.mp.
020 bone#.mp.
021 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
022 12 and 21

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