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Alliance between selective serotonin reuptake inhibitors and fracture risk: an updated systematic review and meta-analysis

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Abstract

Purpose

In the past few years, several fracture-related events have been reported with chronic use of selective serotonin reuptake inhibitors (SSRIs) throughout the globe. Hence, an updated systematic review and meta-analysis was necessary to ascertain the risk involved. The present work evaluated the association of SSRIs with the risk of fracture in adults.

Methods

We systematically searched PubMed, Cochrane library, and Google Scholar for observational studies on the same from inception to April 2019. Screening, data extraction, and risk of bias assessment were conducted independently by 2 authors.

Results

We assessed 69 studies out of which 37 (14 case-control, 23 cohorts) were included. Our results showed that SSRIs were significantly associated with an increased fracture risk (relative risk of 1.62, 95% CI 1.52–1.73; $P < 0.000$; $I^2 = 90.8\%$). The relative risk values for case-control and cohort studies were found to be 1.80 (95% CI 1.58–2.03; $P < 0.000$; $I^2 = 93.2\%$) and 1.51 (95% CI 1.39–1.64; $P < 0.000$; $I^2 = 88.0\%$) respectively. Subgroup analysis showed that association of risk of fracture persisted regardless of geographical location, study design, risk factors, defined daily dose, SSRI use duration, site of the fracture, period of study and after adjusting for depression, physical activity, gender, and age group. The sensitivity analysis data shows that the studies adjusted for bone mineral density and osteoporosis show lesser fracture risk.

Conclusion

Our findings suggests that SSRIs may be associated with an increased fracture risk; hence, bone health should be taken into consideration while prescribing this class of drugs.

Keywords

Selective serotonin reuptake inhibitors
SSRI
Fracture risk
Systematic review
Meta-analysis
Antidepressants

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00228-020-02893-1) contains supplementary material, which is available to authorized users.

Introduction

In a lifetime, more than 50% of women and 25% of men experience at least one fragility fracture [1]. The mortality rates are higher for the fracture of the hip and vertebrae in both sexes [2]. Osteoporosis is a condition in which the bones become porous and their mineral density and quality are reduced, so there is an increased fracture. Osteoporosis remains undetected until the occurrence of fracture [3]. Out of the many causes of osteoporosis, the use of medication is one of the important factors leading to bone loss [4].

A recent study on the prescribing trends of antidepressants revealed that the prescription of antidepressants has been increased many folds and that selective serotonin reuptake inhibitors (SSRIs) constitute 51% of the total antidepressant prescriptions [5]. This is because of their better safety and efficacy profiles [6]. It has been evidenced that the chronic administration of SSRIs for the treatment of psychiatric conditions in humans is associated with osteoporosis [7, 8, 9]. It has also been reported that SSRIs play a dual role in bone primarily due to opposing effects of serotonin on the bone turnover where gut-derived serotonin is reportedly associated with bone loss while brain-derived serotonin causes bone formation [10].

The three meta-analyses evaluating fracture risk with the use of SSRIs in adults concluded a significant risk associated with these drugs with the possibility of a major clinical impact [11, 12, 13]. However, this meta-analysis was published in 2012 and 2013 and studies included were carried out until April 2011. There has been a lot of observational studies reported on this aspect after 2010, thus necessitating an updated analysis of data. Further, the most recent meta-analysis incorporated studies on two categories of antidepressants including both serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs up to the period of November 2016. The meta-analysis concluded that SSRIs are associated with an increased risk of fracture irrespective of age [14]. Contrary to the results on fracture risk, a recent meta-analysis on four studies on woman, with bone mineral density as outcome, concluded that antidepressants including tricyclic antidepressants (TCAs) or SSRIs do not have any impact on bone mineral density at all three measured sites including lumbar spine, femoral neck, and total hip [15]. Based on this contradiction and the fact that various high-quality studies have been added after 2016, there was a need for an updated meta-analysis.

In the present systematic review and meta-analysis, we have evaluated the association of the SSRI uses and the fracture risk for case-control and cohort studies (as the randomized clinical trial could not have been possible with this kind of outcome) carried out from inception until April 2019. The study is expected to provide a better picture of the possible association between SSRI use and risk of fracture with updated literature and can help guide the physician in selecting antidepressant for those patients with existing risk factors.

Material and methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for reporting of data [16]. The protocol of the review was registered in PROSPERO reference no CRD42018086090.

Literature search

We have performed computational data search of the electronic libraries on the search engines like PubMed, Cochrane library, and Google Scholar for relevant studies by using individual keywords or combination of the keywords like selective serotonin reuptake inhibitor, fracture, osteoporosis, osteopenia, bone loss, SSRIs, SSRI's, and fracture risk. An extensive data search was done from the first known literature of SSRI use with fracture outcome until April 2019 of the data published in the English language. The first search was started on 15 September 2018 and then updated on 30 April 2019. In addition to the above search plan, the references of the relevant literature were checked manually for any missing eligible studies.

Eligibility criteria

We have included studies if they fulfill the following criteria:

1. Population - the adult population.
2. Intervention - observational study design with SSRIs (sertraline, fluoxetine, escitalopram, citalopram, paroxetine, and fluvoxamine) as treatment regardless of indication, dose, and duration of the usage.
3. Comparison - SSRI non-users as controls.
4. Outcome - fractures as the primary outcome regardless of the site of fracture which is self-reported, recorded, or diagnosed.

We have excluded animal studies, any duplicate studies, studies with other adjuvant therapies that interfere with bone turnover, abstracts, and non-English literature.

Study selection and assessment of the quality

The data were independently reviewed by two impartial reviewers (MK, ARS) for the inclusion of the studies as per the eligibility criteria. The literature was first looked for the title and abstract followed by a full article for relevant literature. In case of any discrepancy, it was resolved by mutual consensus of both the reviewers.

The quality of the eligible studies was assessed by the ROBINS-I scale [17] as applicable for the case-control and cohort study by the two 2 reviewers (MK, ARS) independently. The study was defined as low, moderate, serious, critical, or no information.

Data extraction

The data of the eligible studies were further summarized in a tabular form with the information regarding author detail, year, country, study design, sample type, study size, age, number of females, overall risk of bias~~study quality score~~, site of fracture,follow-up period (in cohort studies), clinical risk factor adjustment, adjustment of physical activity, adjustment of calcium intake, adjustment of depression, number of exposed cases, and number of exposed cases in control, as shown in Tables 1 and 2.

Table 1

Characteristics of case-control studies included in the analysis

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	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINN-I)	Number of females	Anatomical site of the fracture	SSRI use duration	Clinical risk adjuste
A												
1.	Leach et al. [18]	2017	Australia	Case-control	Australian Government Department of Veterans' Affairs	44,138	88 years (median)	Critical	46.70%	Hip	180 days	Patients' age number of comorbidities socioeconom status, anti-Parkinson medicines, benzodiazepi related medic tricyclic antidepressar serotonin and noradrenaline reuptake inhi other antidepressar
2.	Hung et al. [19]	2017	Taiwan	Case-control	Taiwan Longitudinal Health Insurance Database	9782	78.9 ± 6.9 years	Critical	62.50%	Hip	Greater than 6 months	Age, alcohol- disease, cardiovascul diseases, chr kidney diseas chronic obstr pulmonary di diabetes mell hyperlipidem hypertension osteoporosis
3.	Souverein et al. [20]	2016	UK	Nested case-control	National Prescriptions Database	18,773	19–103	Serious	76.80%	Hip or femur fracture	90 days	Age, sex, pre fracture, corticosteroic rheumatoid a smoking, alc use, BMI, osteoporosis, history of bo diseases, pre use of bisphosphona other bone protecting dr raloxifene, strontium ran parathyroid hormone, cal vitamin D, calcitonin, ca
4.	Souverein et al. [20]	2016	Dutch	Nested case-control	National Prescriptions Database	384	29–96	Serious	83.50%	Hip or femur fracture	90 days	Age, sex, pre fracture, corticosteroic rheumatoid a smoking, alc use, BMI, osteoporosis, history of bo diseases, pre use of bisphosphona other bone protecting dr raloxifene, strontium ran parathyroid hormone, cal vitamin D, calcitonin, ca

	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINN-I)	Number of females	Anatomical site of the fracture	SSRI use duration	Age, sex, pre fracture, corticosteroi rheumatoid a smoking, alc use, BMI, osteoporosis, history of bo diseases, prev use of bisphosphon other bone protecting dr raloxifene, strontium ran parathyroid hormone, cal vitamin D, calcitonin, ca
5.	Souverein et al. [20]	2016	Spain	Nested case-control	National Prescriptions Database	7662	22–100	Serious	81.40%	Hip or femur fracture	90 days	Clinical risk adjuste
6.	Wang et al. [21]	2016	Taiwan	Nested case-control	NHIRD, LHID	41,250	79.9 years	Serious	59.84%	All sites	NR	Age, sex, hypertension, diabetes, osteoporosis, history of fal cardiac disea chronic obstr pulmonary di urinary incontinence, Parkinson dis chronic ment disorders, de depression, li disease, perip vascular dise cerebrovascu disease, arthr chronic kidn diseases, glau use of medica (opiates, non analgesics, antipsychotic anxiolytics, sedatives, corticosteroi hormone replacement therapy, antiepileptics tricyclics
7.	Payne et al. [22]	2013	UK	Retrospective Case-cohort	Scottish general practice dataset	1779	65–≥ 85	Critical	NR	All sites	NR	Sex, age, SIM medical histo (lifetime), isc heart disease, stroke, hyper falls, fracture alcohol misu dementia, psychosis, af disorder, prin care activity consultation, BP measuren BMI (kg/m^2) systolic BP (mmHg), nur current medi (cardiovascul psychotropic change in me (cardiovascul psychotropic
8.	Verdel et al. [23]	2010	Netherlands	Case-control	PHARMO RLS	46,302	≥ 18	Critical	66.00%	All osteoporotic fracture	NR	Age, sex, geographical calendar time than SSRIs antidepressar benzodiazepi antipsychotic lithium, anti-Parkinson dr anticonvulsar corticosteroi hormone-replacement therapy, disea modifying an rheumatic dr non-steroidal inflammatory antiarrhythm thiazide, diur beta-blockers opiates, metoclopram anti-diabetic thyroid horm the history of hospitalizatic

	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINN-I)	Number of females	Anatomical site of the fracture	SSRI use duration	Clinical risk adjust
9.	Van den Brand et al. [24]	2009	Netherlands	Case-control	PHARMO-RLS database.	897	≥ 18	Serious	53.01%	Hip/femur fracture	1 month	Age, sex, geographical other than SS antidepressa benzodiazepi antipsychotic lithium, anti-Parkinson dru anticonvulsan corticosteroic hormone-replacement therapy, disea modifying an rheumatic dru non-steroidal inflammatory antiarrhythm thiazide diure beta-blockers opiates, metoclopram anti-diabetic history of hospitalizatic
10.	Abrahamsen and Brixen [25]	2009	Denmark	Case-control	Fracture data from the Danish National Hospital Discharge Register	62,865	Men ≥ 50 years	Critical	NR	Any/hip/spine fracture	NR	Age, previou fracture, mod Charlson comorbidity i groups of medications
11.	Bolton et al. [26]	2008	Canada	Case-control	Manitoba residents computerized outpatient records		Adults ≥ 50 years	Critical	70.3%	Osteoporotic fracture	120 days	Age, sex, eth income, resid comorbidity i of the John H Ambulatory (Group systen (diabetes, isc heart disease, myocardial infarction, hypertension, epilepsy, rheumatoid a organ transplantatic COPD, home use, depressi substance abu dementia, schizophreni medication u as anticonvul diuretics, anticoagulant thyroid horm
12.	Vestergaard et al. [27]	2006	Denmark	Case-control	National Hospital Discharge Register	41,751	43.44_27.39 years	Critical	51.80%	Any/hip/Colles' /spine fracture	ever used during the study duration	Age, sex, psychiatric comorbidity (schizophreni alcoholism), medication u as anxiolytic, sedative, neuroleptic, corticosteroic antiepileptic, lithium, hospitalizatic prior fracture income, work status, educat residence, Ch index
13.	Hubbard et al. [28]	2003	United Kingdom	Case-control	UK General Practice Research Database	1847	79 ± 12 years	Serious	79%	Hip fracture	within 15 days	Age, sex, ger practice, dura available data previous frac cerebrovascu diseases, BM diastolic bloc pressure, hor replacement therapy, cardiovascula diseases, eye disorders, per neuropathy, medications s hypnotics, op nonopioid analgesics, antipsychotic corticosteroic

	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINN-I)	Number of females	Anatomical site of the fracture	SSRI use duration	Age, sex, comorbidities (depression, dementia), clinical risk adjusted medications sedatives, tranquilizers, cardiac agent Parkinson dr thyroid horm anticonvulsa diabetic agen corticosteroi estrogens, etidronate; di exposure cat and doses of antidepressa
14.	Liu et al. [29]	1998	Canada	Case-control	hospital discharge data of Canadian Institute for Health Information	1688	Adults ≥ 66 years	Serious	NA	Hip fracture	within 30 days	

Table 2

Characteristics of cohort studies included in the analysis

S. no.	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINN-I)	Number of females	Anatomical site of the fracture	Follow-up	Clinica a
1	Brinton et al. [30]	2019	USA	Retrospective cohort	US Veterans Health Administration patients	45,03,390	18–75 years	Serious	6.10%	Hip fracture	10 years	Sex, rac White, status, C score, w category (normal obese, n obese), disabilit depende tobacco
2	Coupland et al. [31]	2018	UK	Cohort	Egton Medical Information Systems	238,963	39.5 ± 11.1	Serious	61%	Vertebral, rib, pelvis, upper limb, lower limb, distal radius, hip and skull fractures	5 years	Falls, fr gastroin road tra adverse reaction cause m
3	Carriere et al. [32]	2016	France	Cohort	3-C cohort (Bordeaux, Dijon, and Montpellier)	6823	66.8 ± 12.9 years	Serious	66.50%	All body sites	4 years	Age, ce smoking benzodi other C osteoart time sin Age, se depressi ischemi anti-ost disease drugs, c history
4	Uddin et al. [33]	2016	UK	Cohort	THIN (The Health Improvement Network)	570,139	51 ± 17.78	Serious	NR	Hip/femur	3.7 years	mental anemia, benzodi antiepil anti-dia glucoco antihyp ACE inh angiote antagon opioids morphin replacer antipsyc vitamin Parkins
5	Uddin et al. [33]	2016	Spain	Cohort	BIFAP	252,203	51.5 ± 17.3	Serious	NR	Hip/femur	2.7 years	
6	Uddin et al. [33]	2016	Netherlands	Cohort	Dutch Modriaan GP database	22,474	50 ± 16.85	Serious	NR	Hip/femur	2.2 years	
7	Sheu et al. [34]	2015	USA	Cohort	PharMetrics Claims Database	373,325	40–64 years	Serious	100%	Hip, humerus, radius, and ulna	6 months	Age, se acute hospital number visits, C comorbi previous use of h replacer cancer, stroke, I disease, premen symptor bowel s seizures

S. no.	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINS-I)	Number of females	Anatomical site of the fracture	Follow-up	Clinical
												incontin cardiova disease, disease, falls, pr
												Age, sex
8	Lanteigne et al. [35]	2015	USA	Cohort	PharMetrics claims database	396,758	50–99	Serious	64.20%	Hip, humerus, radius, and ulna	2 years	acute ho for non- and psy reasons, outpatie Charlso index, n hospital substan psychiat comorbi ideation depressi psychiat cancer, opiate u Parkinso
9	Bakken et al. [36]	2013	Norway	Cohort	Norwegian Prescription Database (NorPD), Norwegian Hip Fracture Registry and the Central Population Registry	906,422	72.8 ± 8.9 years	Serious	56%*	Hip	5 years	Sex, bir period
10	Gagne et al. [37]	2011	USA	Cohort	Medicare beneficiaries	73,072	77.7 ± 10.8 (only SSRI)	Serious	80.70%	hip, humerus, pelvis, or wrist	over 2 year	Age, sex number hospital Charlso psychiat history emerger visits af corticos bisphos hormon therapy, osteopo rheumat hyperpa
11	Diem et al. [38]	2011	USA	Cohort	Community-dwelling women	8057	77.25 ± 5.03 years (only SSRI)	Serious	100%	Non-vertebral; hip; wrist	–	Age, he instrum activitie rise fro MMSE, alcohol replacer bisphos benzodi thiazide pomp in corticos weight, walk fo prior fra
12	Ziere et al. [39]	2008	Netherlands	Prospective cohort	participants of the Rotterdam study	7983	77.0 ± 9.5	Serious	61%	Non-vertebral fracture	8.4 years	Age, sex during t period, category disabilit
13	Spangler et al. [40]	2008	USA	Prospective cohort	Participants from the Women's Health Initiative (WHI) Observational Study	93,676	64 ± 7	Critical	100%	Any/hip/spine/wrist/other site fracture	7.4 years	Age, he ethnicity menopa function current depressi Additio adjustm baseline weight, therapy. adjustm fracture fracture CVD, u analgesi
14	Lewis et al. [41]	2007	USA	Prospective multi-center cohort	MrOS is a multicenter prospective study population	5995	75.5	Serious	0%	Non-spine fracture	4.1 years	Age, BM
15	Schneeweiss and Wang [42]	2004	USA	Cohort	MCBS Medicare Current Beneficiary Survey,	7126	greater than and equal to 65 years	Serious	65%	Hip fracture	4.0 years	Age, sex smoking the daily cognitiv and Ros physical scale
												Age, he use of ≥

S. no.	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINN-I)	Number of females	Anatomical site of the fracture	Follow-up	Clinica
	Endo et al. [43]	2005	USA	Prospective cohort	Study of Osteoporotic fracture	8137	77.1 ± 4.8 years	Serious	100%	Hip/any Non-spine fracture	4.4, 4.8 years	medicat for exer function impairm the prev cognitiv weight c
												speed, i rise fror femoral
17	Cheng et al. [44]	2016	Taiwan	Cohort	NHRI research database	139,110	46.5 ± 17.8	Serious	62.20%	Hip fracture	9 years	Age, sex urbaniz osteopo Charlso index
18	Zucker et al. [45]	2012	Israel	retrospective cohort study	Prescription information from the database	10,621	Women of 40 years and older	Serious	100%	Hip, wrist, rib, lumbar or thoracic spine compression fracture	3 years	Age, BM socioec depressi hormon therapy benzodi primary physicia
19	Pouwels et al. [46]	2013	UK	retrospective cohort study	National Prescriptions Database	4687	40 years and older	Serious	42%	Osteoporotic fracture of the radius/ulna, humerus, rib, femur/ hip, pelvis or vertebrae	4 years	Sex, BM status, u history before d history 3–12 mo the diag of chron (asthma obstruct pulmona rheumat thyroid renal dis congesti failure, cerebrov disease, inflamm disease, prescrip last 6 m medicat antidepr anxiolyt anticonv corticos antipsyc opioids, immuno
20	Richards et al. [47]	2007	Canada	prospective cohort study	community-dwelling adults	5008	50 years and older	Serious	83.20%	Fragility fracture	5 years	Age, tot modifie index, p vertebra prevalen fracture cumulat estroger women
21	Souverein et al. [20]	2016	UK	Cohort	National Prescriptions Database	587,637	18–106	Serious	63.70%	Hip or femur fracture	8 years	Age, sex fracture corticos rheumat smoking BMI, os history diseases of bisph other bo drugs: r strontiu parathyr calcium calciton
22	Souverein et al. [20]	2016	Dutch	Cohort	National Prescriptions Database	22,954	18–104	Serious	63.60%	Hip or femur fracture	8 years	Age, sex fracture corticos rheumat smoking BMI, os history diseases of bisph other bo drugs: r strontiu parathyr calcium calciton

S. no.	Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINN-I)	Number of females	Anatomical site of the fracture	Follow-up	Age, se fracture corticos rheumat smokin BMI, os history diseases of bisph other bo drugs: r strontiu parathy calcium calciton
23	Souverein et al. [20]	2016	Spain	Cohort	National Prescriptions Database	252,203	18–106	Serious	72.70%	Hip or femur fracture	8 years	

AQ2

Apart from other factors known to interfere with bone loss, depression itself is a major confounder. Hence, the "adjustment for depression" was extracted from various studies and on this basis, we divided the studies into two groups: studies that have considered depression as a biasing parameter and studies that have not considered depression as a biasing parameter.

Data synthesis and analysis

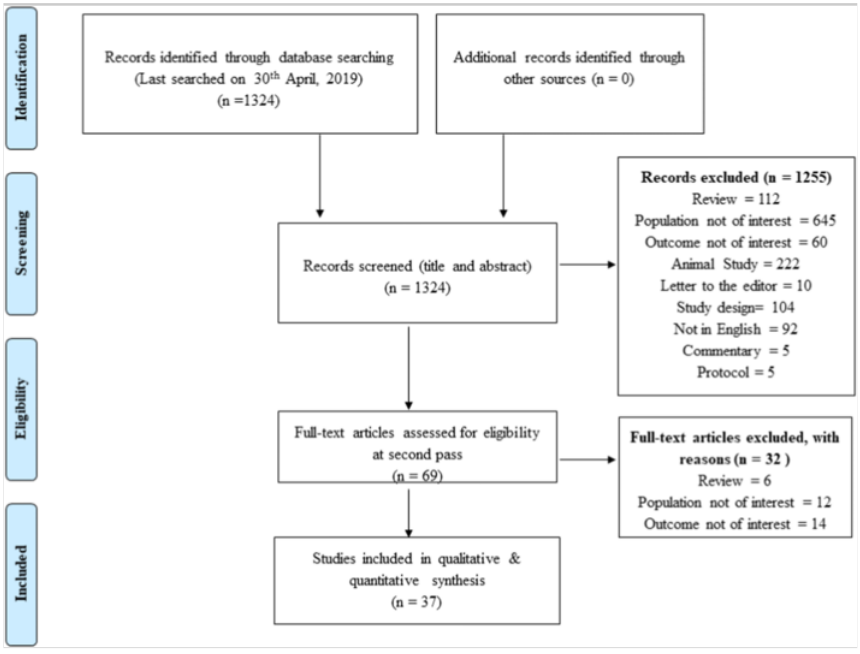
Data were extracted in a pre-designed excel template and the reference was updated in endnote version X9. We computed pooled relative risk and 95% confidence interval (CI) from confounder adjusted ORs/RRs/HRs and corresponding 95% CIs as reported in the studies. We considered the odds ratio (OR) as a surrogate measure of the corresponding risk ratio (RR)/hazard ratio (HR) in longitudinal studies because the absolute risk of fracture is low. To stabilize the variance and normalize the distributions, we transformed ORs, RRs, and HRs into their natural logarithms before pooling the data (and therefore, a variation could be possible when converting back to relative risk; however, it did not change any interpretation of results) [48]. The standard error (SE) of the natural logarithm of OR/HR/RR was derived from the corresponding CI, which was either provided in the study or calculated with standard formulas [49]. To estimate the overall effect size, each study was weighted by the reciprocal of its variance. In studies where only subgroup estimates were reported for the outcome, the overall effect size across subgroups in each individual study was estimated with meta-analysis. Random-effects meta-analysis, using DerSimonian and Laird method [50], was employed on individual study estimates to obtain a pooled summary estimates for relative risk. Heterogeneity between studies was assessed using the Cochrane Q statistic ($P < 0.1$ considered as the presence of heterogeneity) and I-squared (I^2) statistics (> 50% representing moderate heterogeneity) [51], and a number of subgroup analyses were conducted to identify potential sources of heterogeneity. A 95% prediction interval for the random-effects distribution was also calculated to understand the possible range of relative risk if a new study is conducted as suggested by Higgins and Thompson [52]. Publication bias was assessed by funnel plot and its asymmetry was tested by the Begg and Mazumdar rank correlation test ($P < 0.10$ was considered as an indication of publication bias) [53]. To determine whether there is a relation between fracture risk and subgroup variables (i.e., study design, with defined daily dose, year of reporting, number of adjusted risk factors, other key risk factors such as depression, physical activity, osteoporosis, and bone mineral density (BMD)), we used univariable and multivariable meta-regression analysis using the maximum likelihood method ($P < 0.10$ considered significant given the low power of these tests). We were able to add age into the regression analysis due to high disparity in reporting. Further, a sensitivity analysis was also carried out by adjusting the risk-factors such as BMD and osteoporosis. All statistical analyses were conducted on Stata statistical software (version 15.2, StataCorp LLC, College Station, TX, USA) using user-written *admetan*, *metafunnel*, *metabias*, and *metareg* commands. A P value of < 0.05 was considered statistically significant for the effect of study-level covariates on the estimated relative risks.

Results

A total of 1324 studies were identified; out of which, we have assessed the full text of 69 articles to further include 37 eligible studies in the analysis as shown in Fig. 1. The studies extracted were published from the period 1998 to 2019 (Tables 1 and 2). Out of 37 eligible studies, 14 were case-control and 23 were cohort studies. Among the eligible case-control studies, 2 were nested case-control [20, 21] and one was retrospective in nature [22], whereas others were prospective case-control studies. In the cohort studies, 4 were prospective cohort [39, 40, 41, 43], 3 were retrospective cohort [30, 45, 46], and others were classical cohort studies.

Fig. 1

PRISMA flowchart of the studies selection

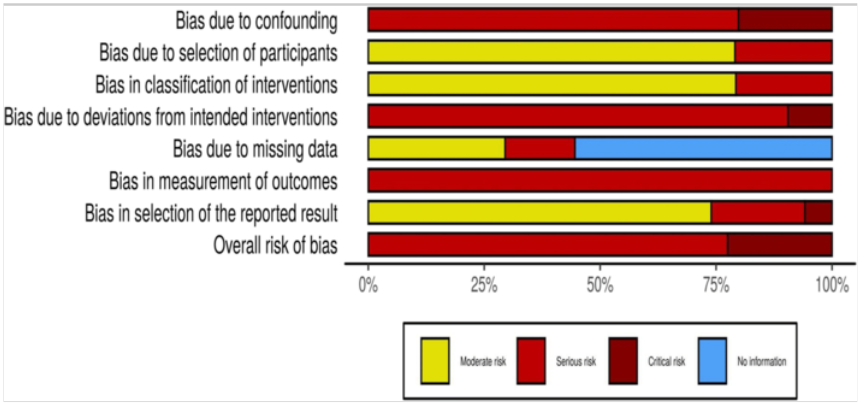


Quality of the studies

The ROBINS-I tool assesses risk of bias in seven domains and an overall risk of bias according to the highest level of risk in any one domain. If a study is assessed to have a serious risk of bias in one domain, but low risk of bias in all others, the overall risk of bias for the study will be serious. Risk of bias within the seven domains, and overall, is displayed for all 37 studies in Fig. 2.We deemed the overall risk of bias to be critical for 8 studies and serious for the remaining 29 studies. We deemed all studies to have a serious risk of bias in the measurement of outcomes and critical or serious risk of bias in confounding because of the study designs.

Fig. 2

Overall quality assessment of studies using ROBINS-I scale



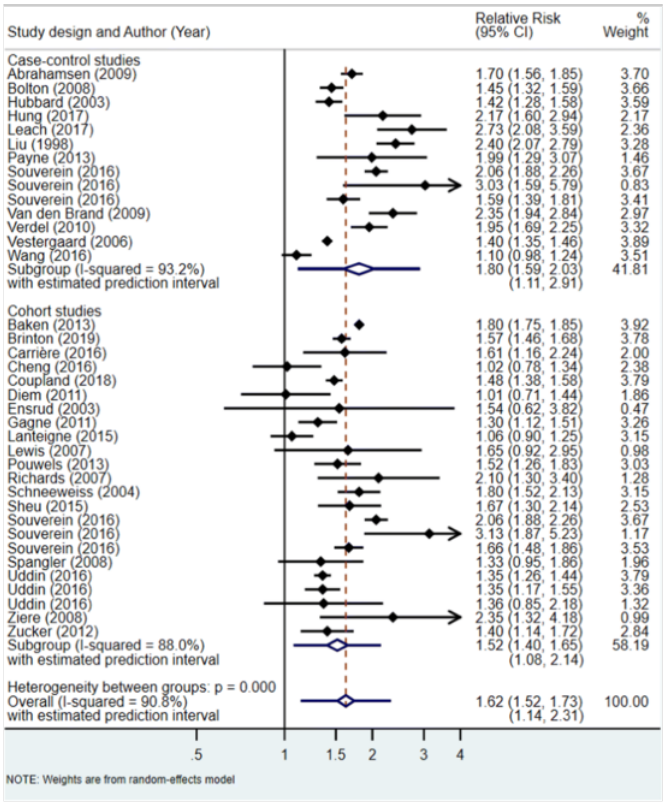
Meta-analysis for fracture risk

The main outcome of the meta-analysis of both case-control and cohort studies is that SSRIs are significantly associated with the increase in the fracture risk with a relative risk of 1.62 (95% CI 1.52–1.73; $P < 0.000$; $I^2 = 90.8\%$). In case-control studies, when considered alone, the fracture risk was significantly associated with SSRIs with a relative risk of 1.80 (95% CI 1.59–2.03; $P < 0.000$; $I^2 = 93.2\%$), while cohort studies also show the same trend of increased fracture risk with a relative risk of ~~1.51~~ 1.52 (95% CI 1.40–1.65; $P < 0.000$; $I^2 = 88.0\%$). Figure 3 shows the forest plot of the combined effect of 14 case-control and 23 cohort studies. As shown, heterogeneity between groups was significantly associated; hence, random-effects analysis was carried out for the pooled analysis.

Fig. 3

Risk of fracture associated with the selective serotonin reuptake inhibitor (SSRI) use according to the study design using random-effects meta-analysis

AQ4



Subgroup analysis

The subgroup analysis, as shown in Table 3, indicated that the fracture risk remained consistent after taking into consideration the geographical location (Australia ($P < 0.001$), Asia ($P < 0.038$), Europe ($P < 0.001$), the USA and Canada ($P < 0.001$)) and study design (case-control ($P < 0.001$), cohort ($P < 0.001$)) and after adjusting for clinical risk factors (< 5 ($P < 0.001$), ≥ 5 ($P < 0.001$)); studies with defined daily dose (Yes ($P < 0.001$), No ($P < 0.001$)), SSRI use duration (≤ 6 months ($P < 0.001$), > 6 months ($P < 0.001$)); anatomical site of fracture (hip ($P < 0.001$); all sites ($P < 0.001$); hip/femur ($P < 0.001$); hip, humerus, radius, and ulna ($P < 0.002$)); and the period of study (before 2011 ($P < 0.001$) and 2011 or after ($P < 0.001$)). Further, the fracture risk also remained

significant after adjusting for depression ($P < 0.001$), physical activity (no ($P < 0.001$), yes ($P = 0.034$)), gender males ($P < 0.001$), % of females < 60% ($P < 0.001$), % of females ≥ 60% ($P < 0.001$), and mean age < 50 ($P < 0.001$), mean age ≥ 50 ($P < 0.001$), age ≥ 50 ($P < 0.001$), and age ≥ 18 ($P < 0.001$).

Table 3

Relative risk of fracture associated with the use of SSRIs in subgroups defined by study characteristics using the random-effects model

Subgroup factors	No. of studies	Relative risk (95% CI)	I^2 statistics (%)	95% PI	*P* value
Geographic location					
Australia	1	2.73 (2.08–3.59)	–	–	$P < 0.001$
Asia	4	1.34 (1.02–1.76)	85.2	0.38–4.67	0.038
Europe	20	1.70 (1.57–1.84)	92.1	1.22–2.37	$P < 0.001$
USA and Canada	12	1.52 (1.33–1.75)	84.4	0.95–2.43	$P < 0.001$
Study design					
Case-control	14	1.80 (1.59–2.03)	93.2	1.11–2.91	$P < 0.001$
Cohort	23	1.52 (1.40–1.65)	88.0	1.08–2.14	$P < 0.001$
No. of clinical risk factors adjusted					
< 5	13	1.64 (1.44–1.87)	94.3	1.00–2.69	$P < 0.001$
≥ 5	24	1.62 (1.50–1.75)	85.2	1.17–2.24	$P < 0.001$
Defined daily dose					
No	22	1.56 (1.51–1.61)	89.7	0.98–2.60	$P < 0.001$
Yes	15	1.63 (1.60–1.67)	92.2	1.19–2.32	$P < 0.001$
SSRI use duration					
≤ 6 months	7	1.81 (1.53–2.14)	93.4	1.00–3.26	$P < 0.001$
> 6 months	22	1.55 (1.43–1.69)	88.2	1.10–2.18	$P < 0.001$
Not reported	8	1.64 (1.36–1.99)	91.8	0.87–3.10	$P < 0.001$
Anatomical site of the fracture					
Hip	8	1.77 (1.56–2.01)	90.3	1.17–2.68	$P < 0.001$
All sites	12	1.50 (1.38–1.64)	81.4	1.14–1.98	$P < 0.001$
Hip/femur	10	1.80 (1.54–2.11)	91.9	1.05–3.08	$P < 0.001$
Hip, humerus, radius, and ulna	7	1.35 (1.11–1.63)	62.7	0.79–2.30	0.002
Period of study					
Before 2011	13	1.74 (1.55–1.96)	88.2	1.16–2.61	$P < 0.001$
2011 or after	24	1.57 (1.44–1.71)	91.4	1.07–2.31	$P < 0.001$
Adjusted for depression					
No	28	1.69 (1.57–1.82)	92.0	1.17–2.44	$P < 0.001$
Yes	9	1.38 (1.21–1.58)	76.6	0.94–2.03	$P < 0.001$
Adjustment for physical activity					
No	33	1.64 (1.53–1.76)	91.6	1.15–2.34	$P < 0.001$
Yes	4	1.40 (1.03–1.91)	68.3	0.39–4.96	0.034
Gender					
Males	3	1.35 (1.27–1.43)	0.00	0.92–1.99	$P < 0.001$
% of females < 60%	8	1.53 (1.35–1.74)	95.3	1.01–2.33	$P < 0.001$
% of females ≥ 60%	26	1.70 (1.55–1.87)	87.5	1.09–2.65	$P < 0.001$
Age groups (years)					
Mean age < 50	7	1.32 (1.20–1.45)	74.5	1.01–1.73	$P < 0.001$
Mean age ≥ 50	10	1.469 (1.30–1.66)	86.2	1.02–2.12	$P < 0.001$
Age ≥ 50	9	1.787 (1.50–2.13)	89.5	0.98–3.25	$P < 0.001$
Age ≥ 18	11	1.844 (1.64–2.07)	86.6	1.23–2.77	$P < 0.001$

PI prediction interval, *CI* confidence interval

The overall association between the fracture risk and the reported study characteristics was assessed by univariable and multivariable mixed-effect meta-regression analysis. We found no independent statistically significant association on fracture risk in the multivariable meta-regression for study design ($P = 0.405$), with defined daily dose ($P = 0.919$), the total number of adjusted variables ($P = 0.420$), year of reporting ($P = 0.787$), and other key factors (such as depression ($P = 0.142$), physical activity ($P = 0.525$), osteoporosis ($P = 0.241$), and BMD ($P = 0.698$)).

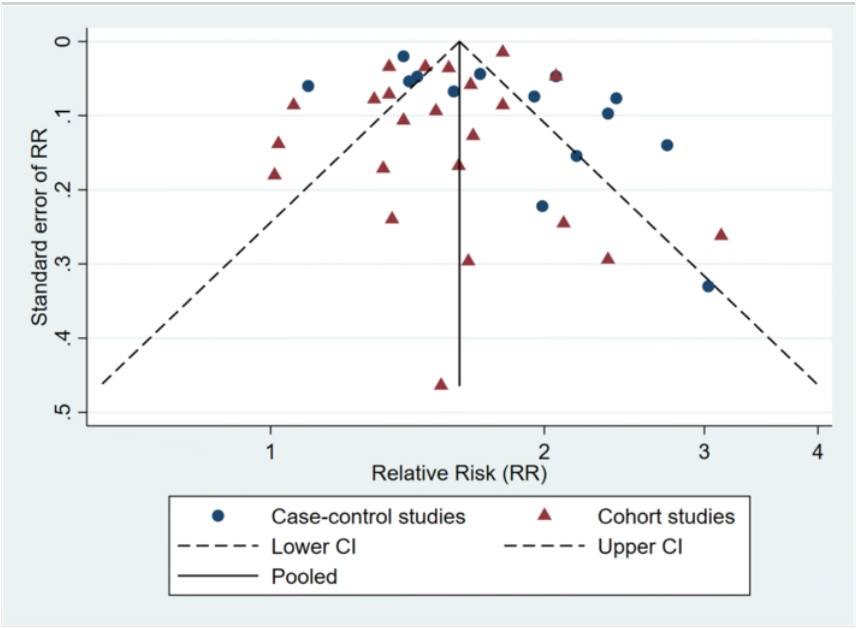
Publication bias

We used a funnel plot (Fig. 4) to assess publication bias. In the figure, the vertical line represents the summary estimate, i.e., RR of the risk of fracture due to SSRI treatment. The diagonal lines represent the 95% confidence limits around the summary treatment effect. These show the expected distribution of studies in the absence of heterogeneity or selection biases. The funnel plot was almost symmetric and indicated none of the missing potential studies. The funnel plot

asymmetry was assessed by Begg and Mazumdar's rank correlation test for publication bias that showed no significant publication bias ($|z|_{corrected} = 0.92$, $P = 0.360$). Similar results were also found for case-control ($|z|_{corrected} = 0.77$, $P = 0.443$) and cohort ($|z|_{corrected} = 1.27$, $P = 0.205$) studies.

Fig. 4

Funnel plot of relative risk with 95% pseudo-confidence limits according to the study design



Sensitivity analysis

A sensitivity analysis is carried out to estimate the risk of fracture by adjusting risk factors such as bone mineral density (BMD) (Fig. 5) and osteoporosis (Fig. 6). Studies adjusted for BMD showed a 17% lower risk of fracture compared with unadjusted studies (for adjusted, RR 1.47, 95% CI 1.19–1.82; for unadjusted, RR 1.64, 95% CI 1.53–1.76). similarly, studies adjusted for osteoporosis showed a 19% lower risk of fracture compared with unadjusted studies (for adjusted, RR 1.54, 95% CI 1.39–1.70; for unadjusted, RR 1.73, 95% CI 1.57–1.90).

Fig. 5

Sensitivity analysis showing the risk estimate by adjusting bone mineral density (BMD)

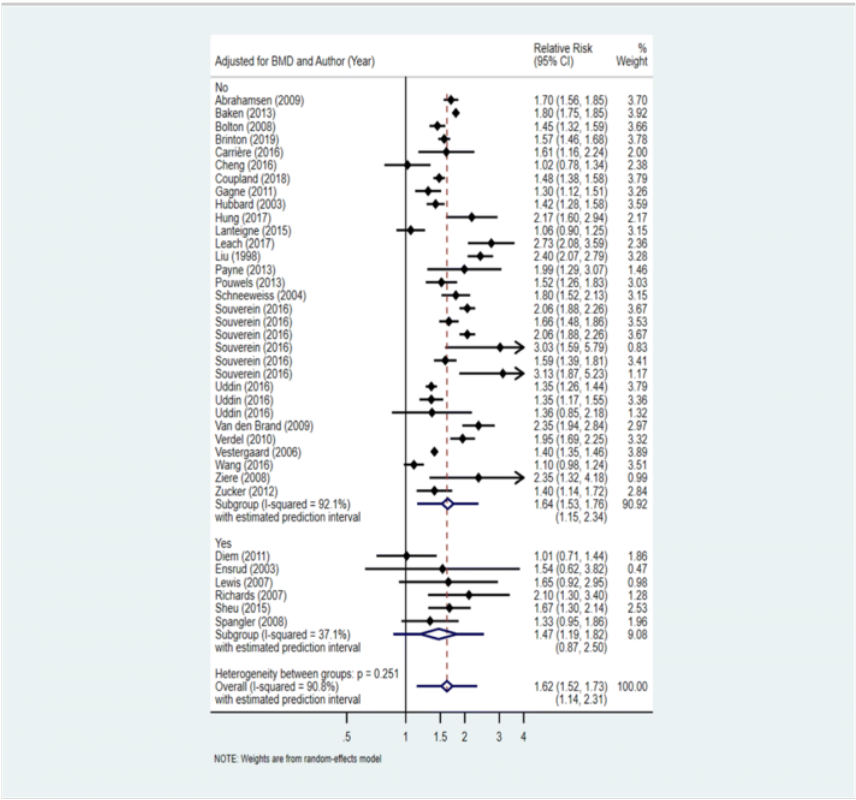
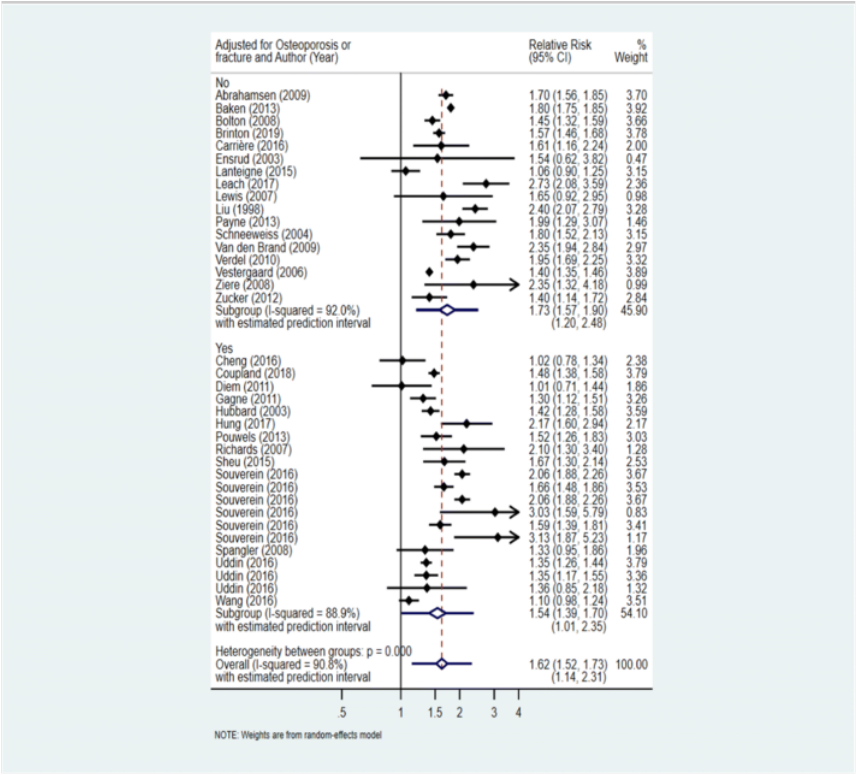


Fig. 6

Sensitivity analysis showing the risk estimate by adjusting osteoporosis or risk factors for osteoporotic fractures



Discussion

This pooled meta-analysis shows that the SSRIs are significantly associated with fracture risk. We reported a 1.62-fold increase in fracture risk (95% CI 1.52–1.73) for SSRI users as compared with non-users for the combined case-control and cohort studies. Our results are in agreement with previous meta-analyses conducted in 2012 and 2013 showing an increase in fracture risk with SSRI users [11, 12, 13]. Randomized clinical trials cannot be possible for fracture as an outcome; hence; we included observational studies in our analysis. Among the studies included in the analysis, though the quality of most of the studies was found to be serious (29) while others were critical (8) as per the ROBINS-I tool, we adjusted for various risk factors that may bias the results. We reported that the risk of fracture remained consistent on subgroup analysis when adjusted for geographical location, study design, number of clinical risk factors adjusted, anatomical site of the fracture, defined daily dose, SSRI use duration, period of study, adjustment for depression, adjustment for physical activities, gender, and age group of the population included in the groups. Additionally, no previous meta-analysis has performed sensitivity analysis to adjust studies for osteoporosis and BMD which elucidate that studies adjusted for both the parameters show lesser fracture risk. Hence, the history of BMD and osteoporosis must be taken into consideration while interpreting fracture risk with SSRIs. Our study did not find any statistical evidence for publication bias. However, we cannot rule out that there are some small studies that found no harm with SSRIs and in the same may not have been published.

The previous meta-analysis conducted in 2012 and 2013 included studies from Western countries only and hence, the results could not be generalized to all other populations [11, 12, 13]. Our study, however, showed that a significant risk persisted across geographical locations with higher fracture risk reported in the case of Australia, Europe, the USA, and Canada as compared with Asia. This could also be due to fewer studies available from Asia as compared with other continents. We also observed that cohort studies showed lesser fracture risk as compared with case-control design. The reason could be due to differences in the study design. The trend of increase in the fracture risk was also seen in case-control studies by previous meta-analysis [11, 12, 14], but only one of them [11] actually reported this observation that case-control studies are significantly associated with the fracture risk as compared with the cohort study design.

The strength of the present meta-analysis is that it consists of 37 studies that accommodate most of the recent literature for SSRIs and fracture risk. Our study has limitations. We observed that adjustment for depression did not show any lesser risk of fracture as compared with studies that were not adjusted which shows that depression was not the confounder in the analyzed studies. However, previous studies have reported that depression itself causes bone loss leading to a reduction in bone mineral density [54]. The reason could be that we could not adjust for depression at an individual or patient level as this information was not available to us. Depression was mentioned in studies for the entire population but not individually at a patient level. Further, the majority of the studies did not report adequate data for sun exposure or vitamin D status or concomitant medications such as glucocorticoids that may have significant effects on bone. Another important limitation of all available studies in this area is that fracture risk could not be ascertained for individual SSRI and most of the studies report effects as a category. This is important as it was earlier shown by Hodge et al. that different drugs of SSRI class behave differently on bone cell lines with sertraline being the most potent to inhibit the bone cell line while citalopram did not have any effect [55]. In addition to the above, a placebo randomized clinical trial conducted on one of the SSRI, escitalopram, demonstrated that 8 weeks of treatment of the drug did not alter the serum bone turnover markers when compared with the placebo group [56]. The same was also seen in our preclinical study showing how fluoxetine and escitalopram, when given orally for 40 days to rats, differ in altering the bone micro-architecture with fluoxetine deteriorating the bone micro-architecture and escitalopram having no effect on the same [57]. The above evidence clearly points towards the need to have future research focus on how different SSRIs behave on the bone which may have clinical implications of showing one drug to be safer than another drug.

To conclude, the results from this meta-analysis suggest the SSRI users may have an increased risk of fractures as compared with non-SSRI users; hence, bone health should be taken into consideration while prescribing this class of drugs particularly for those having existing risk factors for the same. However, the included studies were at serious or critical risk of bias and therefore, the conclusions on fracture risk must be interpreted in the context of any potential bias. Further, the lack of a clear mechanistic effect of SSRIs on BMD and opposing effects of gut and brain serotonin on bone makes the interpretation less certain. It is possible that the SSRI patients may have more fractures as the drug makes them fall over and sustain trauma as serotonin syndrome by SSRIs at higher doses manifests as ataxia. Future research could investigate these aspects and can target on determining the effect of individual SSRIs on fracture risk and bone health in general.

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Authors' contributions

MK and DV conceived the original idea. DV supervised the project. SS, MK, and ARS searched databases and performed the selection of the studies; MK and ARS completed the data extraction; MK and ARS performed the quality assessment of the included studies; MK, RB, ARS, and DV wrote the manuscript; RB analyzed and interpreted the data. All authors provided crucial feedback and helped to shape the investigation, analysis, and preparation of the manuscript.

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Data availability

The authors declare that the data supporting the findings of this study are available within the article (and its Supplementary Information files).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Electronic supplementary material

ESM 1

(XLSX 20 kb)

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