



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

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Received: 23 July 2019 / Accepted: 8 May 2020 / Published online: 16 June 2020
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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

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 [7–9]. 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].

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.

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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 [11–13]. 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 women, 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, 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.

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.

Table 1 Characteristics of case-control studies included in the analysis

Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINS-I)	Number of females	Anatomical site of the fracture	SSRI use duration	Clinical risk factor adjusted
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, sex, number of comorbidities, socioeconomic status, anti-Parkinson medicines, benzodiazepine-related medicines, tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, other antidepressants
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-related disease, cardiovascular diseases, chronic kidney diseases, chronic obstructive pulmonary diseases, diabetes mellitus, hyperlipidemia, 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, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol
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, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol
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	Age, sex, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol
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 falls, cardiac diseases, chronic obstructive pulmonary disease, urinary incontinence, Parkinson disease, chronic mental disorders, dementia, depression, liver disease, peripheral vascular disease, arthritis, cerebrovascular disease, arthritis,

Table 1 (continued)

Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINS-I)	Number of females	Anatomical site of the fracture	SSRI use duration	Clinical risk factor adjusted
7. Payne et al. [22]	2013	UK	Retrospective Case-cohort	Scottish general practice dataset	1779	65–≥ 85	Critical	NR	All sites	NR	Sex, age, SIMD, medical history (lifetime), ischemic heart disease, stroke, hypertension falls, fracture, alcohol misuse, dementia, psychosis, affective disorder, primary care activity (recent consultation, recent BP measurement, BMI (kg/m ²), systolic BP (mmHg), number of current medicines (cardiovascular, psychotropic), recent change in medicines (cardiovascular, 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 region, calendar time, other than SSRIs antidepressants, benzodiazepines, antipsychotics, lithium, anti-Parkinson drugs, anticonvulsants, corticosteroids, hormone-replacement therapy, disease-modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs, antiarrhythmic, thiazide, diuretics, beta-blockers, opiates, metoclopramide, anti-diabetic drugs, thyroid hormones; the history of hospitalization.
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 region, other than SSRIs antidepressants, benzodiazepines, antipsychotics, lithium, anti-Parkinson drugs, anticonvulsants, corticosteroids, hormone-replacement therapy, disease-modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs, antiarrhythmic, thiazide diuretics, beta-blockers, opiates, metoclopramide, anti-diabetic drugs; history of hospitalization
10. Abrahamsen and Brixen [25]	2009	Denmark	Case-control	Fracture data from the Danish National Hospital	62,865	Men ≥ 50 years	Critical	NR	Any/hip/spine fracture	NR	Age, previous fracture, modified Charlson comorbidity index, groups of medications

Table 1 (continued)

Author	Year	Country	Design	Sample type	Study size	Age (years)	Overall risk of bias (ROBINS-I)	Number of females	Anatomical site of the fracture	SSRI use duration	Clinical risk factor adjusted
11. Bolton et al. [26]	2008	Canada	Case-control	Discharge Register Manitoba residents computerized outpatient records	41,751	Adults ≥ 50 years	Critical	70.3%	Osteoporotic fracture	120 days	Age, sex, ethnicity, income, residence, comorbidity index of the John Hopkins Ambulatory Care Group system (diabetes, ischemic heart disease, myocardial infarction, hypertension, epilepsy, rheumatoid arthritis, organ transplantation, COPD, home care use, depression, substance abuse, dementia, schizophrenia), medication use such as anticonvulsants, diuretics, anticoagulant, thyroid hormone
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/Collies' spine fracture	ever used during the study duration	Age, sex, psychiatric comorbidity (e.g., schizophrenia, alcoholism), medication use such as anxiolytic, sedative, neuroleptic, corticosteroid, antiepileptic, lithium, hospitalization, prior fracture, income, working status, education, residence, Charlson 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, general practice, duration of available data, previous fracture, cerebrovascular diseases, BMI, diastolic blood pressure, hormone replacement therapy, cardiovascular diseases, eye disorders, peripheral neuropathy, medications such as hypnotics, opiates, nonopioid analgesics, antipsychotics, corticosteroids
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	Age, sex, comorbidities (depression, dementia and other), medications such as sedatives, tranquilizers, cardiac agents, anti-Parkinson drugs, thyroid hormones, anticonvulsants, diabetic agents, corticosteroids, estrogens, etidronate; different exposure categories and doses of antidepressants

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 (ROBINS-I)	Number of fractures	Anatomical site of the fracture	Follow-up	Clinical risk factor adjusted
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, race (Black, White, other), marital status, Charlson score, weight category (normal/overweight, obese, morbidly obese), catastrophic disability, alcohol dependence, and tobacco use disorder.
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, fracture, upper gastrointestinal bleed, road traffic accident, adverse drug reaction, and all-cause mortality
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, center, sex, smoking, benzodiazepines, other CNS drugs, osteoarticular pain, time since first depressive episode, anti-osteoporosis drugs, corticosteroids
4	Uddin et al. [33]	2016	UK	Cohort	THIN (The Health Improvement Network) BIFAP	570,139	51 ± 17.78	Serious	NR	Hip/femur	3.7 years	Age, sex, stroke, ischemic heart disease, dementia, history of fractures, mental disorders, anemia, DMARD
5	Uddin et al. [33]	2016	Spain	Cohort	Dutch Modriaan GP database	252,203	51.5 ± 17.3	Serious	NR	Hip/femur	2.7 years	benzodiazepines, antiepileptic drugs, anti-diabetic drugs, glucocorticoids, antihypertensive, ACE inhibitors, angiotensin II antagonists, diuretics, opioids (including morphine), hormone replacement, antipsychotics, vitamin D, anti-Parkinson, statins
6	Uddin et al. [33]	2016	Netherlands	Cohort	Dutch Modriaan GP database	22,474	50 ± 16.85	Serious	NR	Hip/femur	2.2 years	Age, sex, number of acute hospitalizations, number of outpatient visits, Charlson comorbidity index, previous BMD scans, use of hormone replacement therapy, cancer, opiate use, stroke, Parkinson disease, premenopausal symptoms, irritable
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	

Table 2 (continued)

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 risk factor adjusted
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	bowel syndrome, seizures, urinary incontinence, cardiovascular disease, chronic lung disease, history of falls, prior fractures Age, sex, number of acute hospitalizations for non-psychiatric and psychiatric reasons, number of outpatients visits, Charlson comorbidity index, number of hospitalizations for substance abuse, psychiatric comorbidity, suicide ideation and attempts, depression, other psychiatric disorders, cancer, dementia, opiate use, stroke, Parkinson disease.
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, birth year, time 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, race, number of hospitalizations, Charlson index, psychiatric disorders, history of fractures, emergency room visits after fall, use of corticosteroids, bisphosphonates, hormone replacement therapy, diagnosis of osteoporosis, rheumatoid arthritis, hyperparathyroidism
11		2011	USA	Cohort	Community-dwelling women	8057	77.25 ± 5.03 years (only SSRI)	Serious	100%	Non-vertebral; hip; wrist	–	Age, health status, instrumental daily

Table 2 (continued)

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 risk factor adjusted
Diem et al. [38]												
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	activities, ability to rise from a chair, MMSE, smoking, alcohol use, hormone replacement therapy, bisphosphonate use, benzodiazepine use, thiazide use, proton pump inhibitor use, corticosteroid use, weight, depression, walk for exercise, prior fracture, BMD
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, sex, depression during the follow-up period, disability category, lower-limb disability
14	Lewis et al. [41]	2007	USA	Prospective multi-center cohort	MeOS is a multicenter prospective study population	5995	75.5	Serious	0%	Non-spine fracture	4.1 years	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
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, BMI, smoking, activities of the daily living score, cognitive impairment, and Rosow-Breslau physical impairment scale
16	Ensrud et al. [43]	2003	USA	Prospective cohort	Study of Osteoporotic fracture	8127	77.1 ± 4.8 years	Serious	100%	Hip/any Non-spine fracture	4.4, 4.8 years	Age, health status, use of ≥ 1 medication, walking for exercise, functional impairment, fall in the previous year, cognitive function, weight change, gait speed, inability to rise from a chair, femoral neck BMD
17		2016	Taiwan	Cohort		139,110	46.5 ± 17.8	Serious	62.20%	Hip fracture	9 years	

Table 2 (continued)

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 risk factor adjusted
	Cheng et al. [44]				NHRI research database							Age, sex, urbanization, osteoporosis, Charlson comorbidity 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, BMI, socioeconomic status, depression, smoking, hormone replacement therapy use, diabetes, benzodiazepine use, primary care physician visits
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, BMI, smoking status, use of alcohol, history of fracture before diagnosis, history of falls within 3–12 months before the diagnosis, history of chronic diseases (asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, thyroid disorders, renal disease, cancer, congestive heart failure, cerebrovascular disease, diabetes, inflammatory bowel disease, dementia), prescription in the last 6 months for medications such as antidepressants, anxiolytics/hypnotics, anticonvulsants, corticosteroids, antipsychotics, opioids, immunosuppressants
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, total hip BMD, modified Charlson index, prevalent vertebral deformity, prevalent fragility fractures at baseline, cumulative lifetime estrogen use in 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, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of

Table 2 (continued)

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 risk factor adjusted
22	Souverein et al. [20]	2016	Dutch	Cohort	National Prescriptions Database	22,954	18–104	Serious	63.60%	Hip or femur fracture	8 years	bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol Age, sex, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol
23	Souverein et al. [20]	2016	Spain	Cohort	National Prescriptions Database	252,203	18–106	Serious	72.70%	Hip or femur fracture	8 years	Age, sex, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol

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 [39–41, 43], 3 were retrospective cohort [30, 45, 46], and others were classical cohort studies.

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.

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 1.52 (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.

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

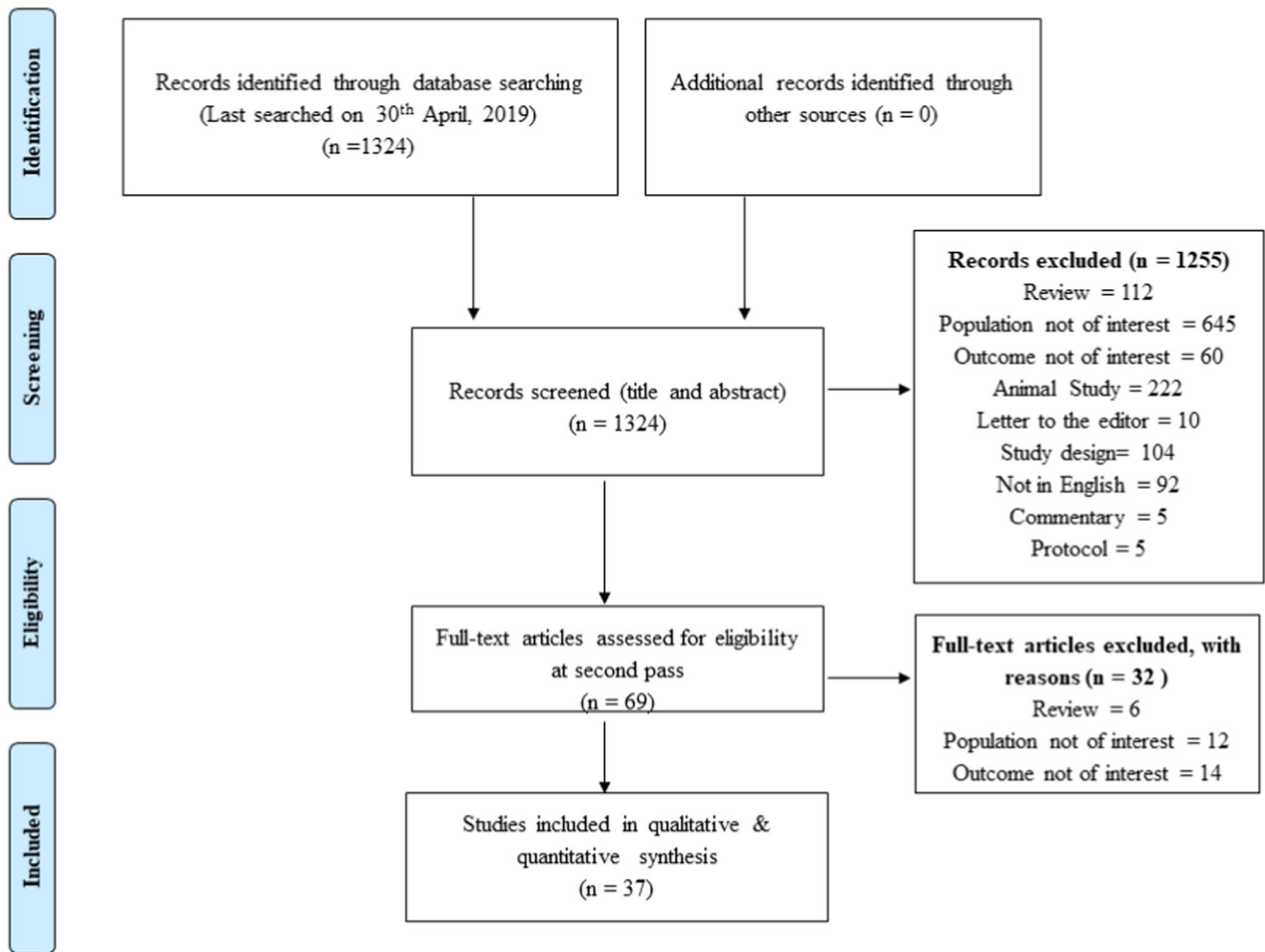
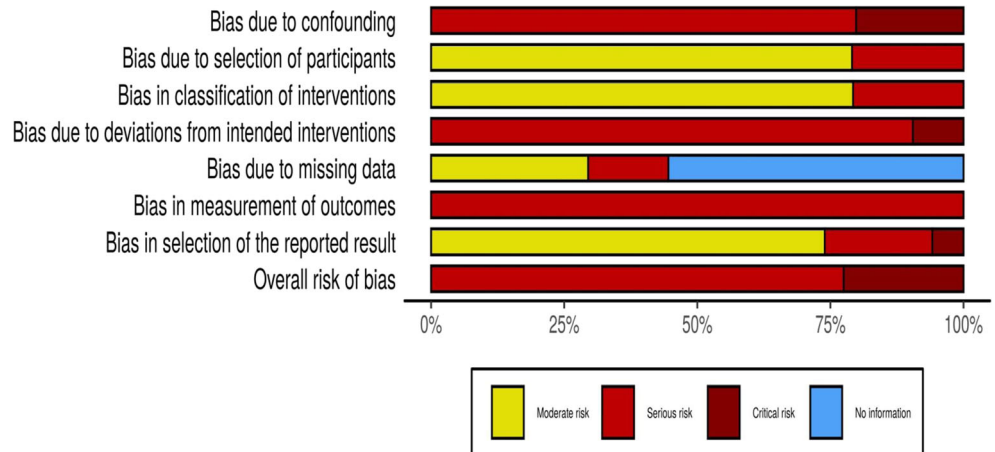


Fig. 1 PRISMA flowchart of the studies selection

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 $\geq 60\%$ ($P < 0.001$), and mean age

Fig. 2 Overall quality assessment of studies using ROBINS-I scale



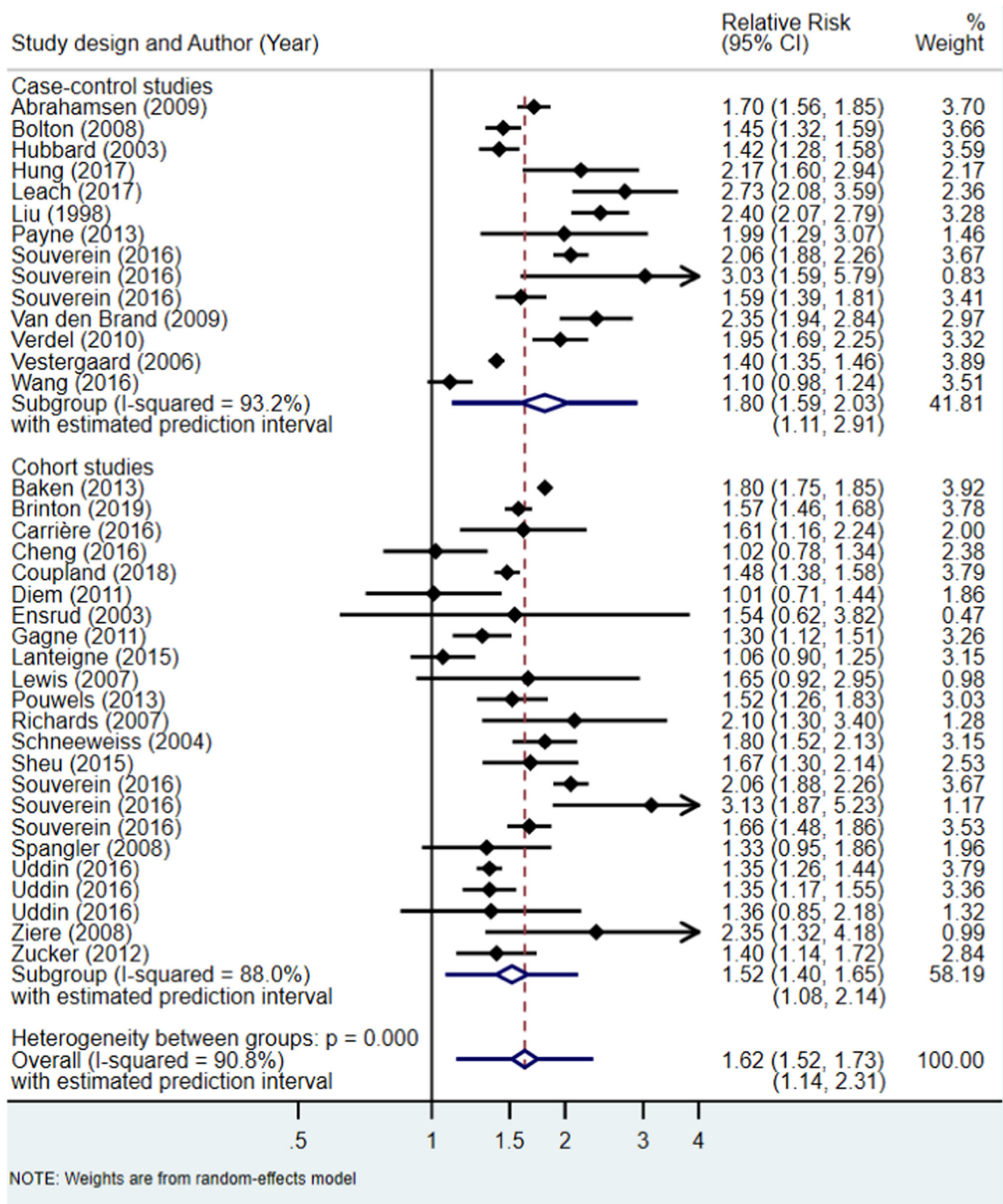


Fig. 3 Risk of fracture associated with the selective serotonin reuptake inhibitor (SSRI) use according to the study design using random-effects meta-analysis

< 50 ($P < 0.001$), mean age ≥ 50 ($P < 0.001$), age ≥ 50 ($P < 0.001$), and age ≥ 18 ($P < 0.001$).

The overall association between the fracture risk and the reported study characteristics was assessed by univariable and

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	<i>P</i> value
Geographic location					
Australia	1	2.73 (2.08–3.59)	–	–	<i>P</i> < 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	<i>P</i> < 0.001
USA and Canada	12	1.52 (1.33–1.75)	84.4	0.95–2.43	<i>P</i> < 0.001
Study design					
Case-control	14	1.80 (1.59–2.03)	93.2	1.11–2.91	<i>P</i> < 0.001
Cohort	23	1.52 (1.40–1.65)	88.0	1.08–2.14	<i>P</i> < 0.001
No. of clinical risk factors adjusted					
< 5	13	1.64 (1.44–1.87)	94.3	1.00–2.69	<i>P</i> < 0.001
≥ 5	24	1.62 (1.50–1.75)	85.2	1.17–2.24	<i>P</i> < 0.001
Defined daily dose					
No	22	1.56 (1.51–1.61)	89.7	0.98–2.60	<i>P</i> < 0.001
Yes	15	1.63 (1.60–1.67)	92.2	1.19–2.32	<i>P</i> < 0.001
SSRI use duration					
≤ 6 months	7	1.81 (1.53–2.14)	93.4	1.00–3.26	<i>P</i> < 0.001
> 6 months	22	1.55 (1.43–1.69)	88.2	1.10–2.18	<i>P</i> < 0.001
Not reported	8	1.64 (1.36–1.99)	91.8	0.87–3.10	<i>P</i> < 0.001
Anatomical site of the fracture					
Hip	8	1.77 (1.56–2.01)	90.3	1.17–2.68	<i>P</i> < 0.001
All sites	12	1.50 (1.38–1.64)	81.4	1.14–1.98	<i>P</i> < 0.001
Hip/femur	10	1.80 (1.54–2.11)	91.9	1.05–3.08	<i>P</i> < 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	<i>P</i> < 0.001
2011 or after	24	1.57 (1.44–1.71)	91.4	1.07–2.31	<i>P</i> < 0.001
Adjusted for depression					
No	28	1.69 (1.57–1.82)	92.0	1.17–2.44	<i>P</i> < 0.001
Yes	9	1.38 (1.21–1.58)	76.6	0.94–2.03	<i>P</i> < 0.001
Adjustment for physical activity					
No	33	1.64 (1.53–1.76)	91.6	1.15–2.34	<i>P</i> < 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	<i>P</i> < 0.001
% of females < 60%	8	1.53 (1.35–1.74)	95.3	1.01–2.33	<i>P</i> < 0.001
% of females ≥ 60%	26	1.70 (1.55–1.87)	87.5	1.09–2.65	<i>P</i> < 0.001
Age groups (years)					
Mean age < 50	7	1.32 (1.20–1.45)	74.5	1.01–1.73	<i>P</i> < 0.001
Mean age ≥ 50	10	1.469 (1.30–1.66)	86.2	1.02–2.12	<i>P</i> < 0.001
Age ≥ 50	9	1.787 (1.50–2.13)	89.5	0.98–3.25	<i>P</i> < 0.001
Age ≥ 18	11	1.844 (1.64–2.07)	86.6	1.23–2.77	<i>P</i> < 0.001

PI prediction interval, CI confidence interval

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 ($|z|_{\text{corrected}} = 0.92$, $P = 0.360$). Similar results were also found for case-control ($|z|_{\text{corrected}} = 0.77$, $P = 0.443$) and cohort ($|z|_{\text{corrected}} = 1.27$, $P = 0.205$) studies.

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).

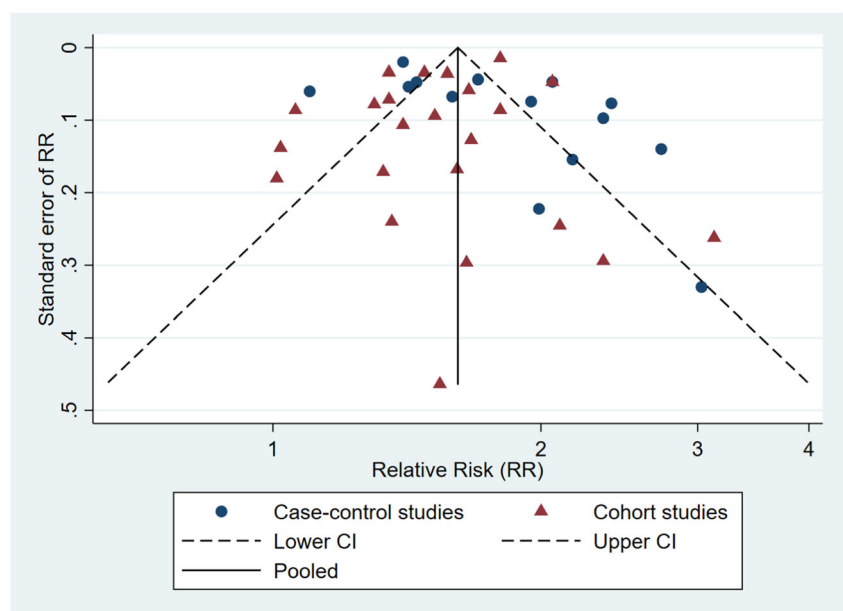
Discussion

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 [11–13]. 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 [11–13]. 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

Fig. 4 Funnel plot of relative risk with 95% pseudo-confidence limits according to the study design



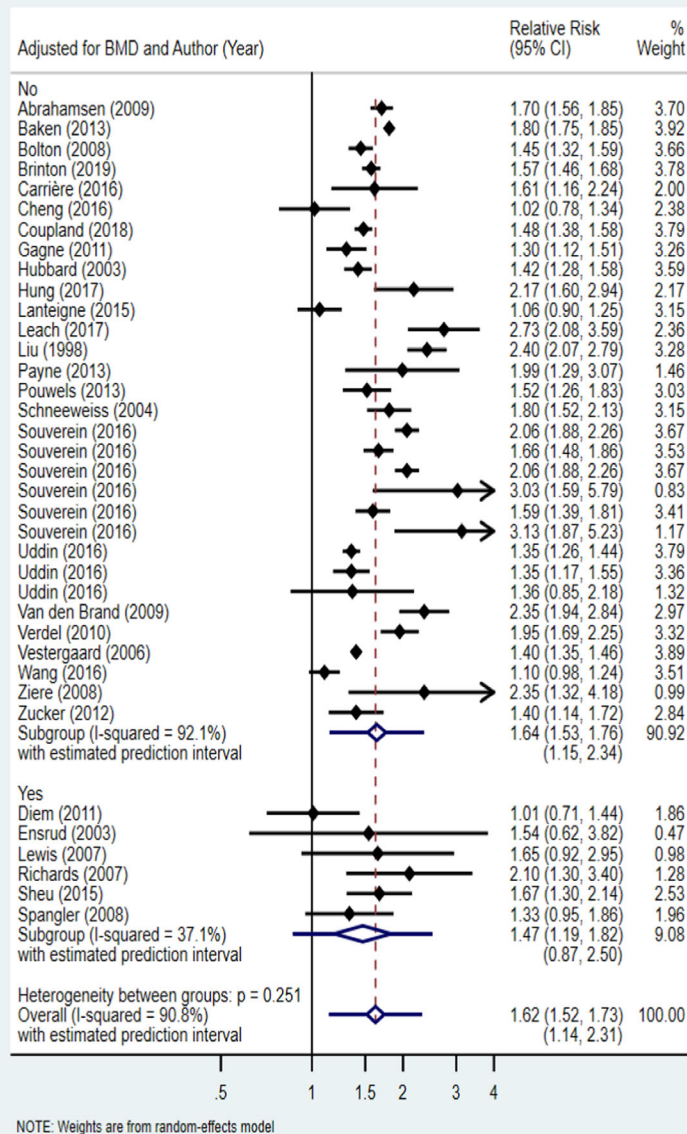


Fig. 5 Sensitivity analysis showing the risk estimate by adjusting bone mineral density (BMD)

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

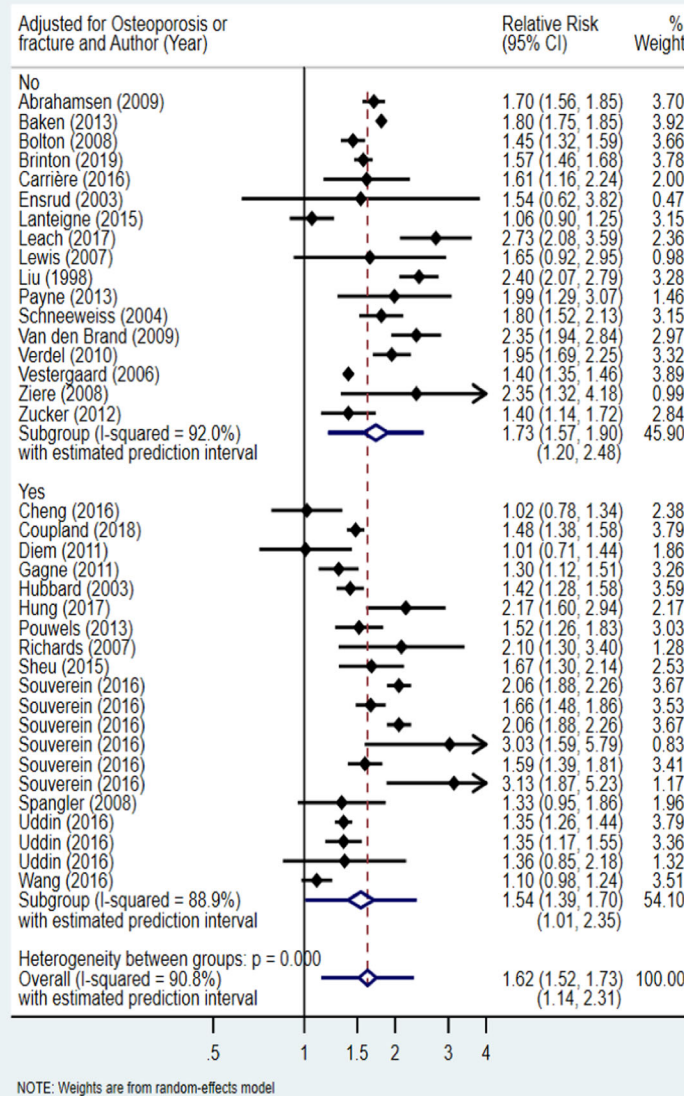


Fig. 6 Sensitivity analysis showing the risk estimate by adjusting osteoporosis or risk factors for osteoporotic fractures

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.

Acknowledgments We are grateful to UGC-SAP DRS-II, DST-FIST program of Department of Pharmacology, and the Jamia Hamdard Pharmaceutical Medicine Program in collaboration with Sun Pharma Ltd. for financial support.

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.

Funding information The financial support was provided by Sun Pharmaceutical Industries Ltd. in the form of fellowship.

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.

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