Systematic Review

Osteoporosis and Fracture Risk Associated with Novel Antidepressants: A Systematic Review and Meta-Analysis

Jin Hu[1]
Kailuo Xie[1]
Senxiang Wu[2]
Yiyi Chen[2,*]

[1]Department of Orthopedics, Third Affiliated Hospital of Shanghai University/Wenzhou Third Clinical Institute Affiliated to Wenzhou Medical University/Wenzhou People's Hospital, 325000 Wenzhou, Zhejiang, China
[2]Department of Neurology, Third Affiliated Hospital of Shanghai University/Wenzhou Third Clinical Institute Affiliated to Wenzhou Medical University/Wenzhou People's Hospital, 325000 Wenzhou, Zhejiang, China

Abstract

Background: The use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), has been linked to adverse effects on bone health, but findings are conflicting. This study aimed to quantify the associations between newer antidepressants and bone mineral density (BMD) and fracture risk through a comprehensive meta-analysis.

Methods: Observational studies on the association between the use of novel antidepressants and BMD and hip fracture were systematically searched in PubMed, Embase, CINAHL, Cochrane Library, and Scopus. Random effects meta-analyses were conducted to pool results across the eligible studies. The heterogeneity, publication bias, and influence were assessed extensively.

Results: 14 eligible studies with 1,417,134 participants were identified. Antidepressant use was associated with significantly lower BMD compared to non-use at all skeletal sites examined, with pooled standardized mean differences (SMD) ranging from –0.02 (total hip) to –0.04 (femoral neck). Importantly, antidepressant use was associated with a 2.5-fold increased risk of hip fracture (pooled odds ratio (OR) 2.50, 95% CI 2.26–2.76). While heterogeneity was detected, the overall findings were robust in sensitivity analyses.

Conclusions: This meta-analysis provided strong evidence that novel antidepressants, especially widely used SSRIs, have detrimental impacts on bone health. The observed associations with decreased BMD and doubled hip fracture risk have important clinical implications.

Keywords

novel antidepressants; osteoporosis; fracture; systematic review; meta-analysis

Introduction

Depression and anxiety disorders are commonly treated with antidepressant medications. The older generation of antidepressants includes tricyclic antidepressants (TCAs). However, TCAs have mainly been replaced by serotonin reuptake inhibitors (SSRIs) and other newer-generation antidepressants due to their improved safety and tolerability [1]. Despite their advantages, emerging evidence has suggested that these newer antidepressants may have unintended adverse effects on bone health, including decreased bone mineral density (BMD) and increased fracture risk [2,3]. The proposed mechanisms involve serotonin-mediated inhibition of osteoblast function and hypocortisolism, leading to increased bone resorption [4]. The potential elevated risk of hip fracture with antidepressant use is particularly concerning, given its associated morbidity and mortality in the elderly [5].

While observational studies have reported associations between the use of newer-generation antidepressants, especially SSRIs, and bone health outcomes, the findings are conflicting. For example, a prospective cohort study by

*Corresponding author details: Yiyi Chen, Department of Neurology, Third Affiliated Hospital of Shanghai University/Wenzhou Third Clinical Institute Affiliated to Wenzhou Medical University/Wenzhou People's Hospital, 325000 Wenzhou, Zhejiang, China. Email: cyyinhz@163.com

Rauma *et al*. [6] found accelerated bone loss at the femoral neck with long-term SSRI use in postmenopausal women. In contrast, a cross-sectional study by Ho *et al*. [7] reported no differences in BMD between premenopausal women on SSRIs versus controls. The discrepant results were likely due to differences in study populations, designs, and adjusted confounders.

To rigorously synthesize the current evidence, this study conducted a systematic review and meta-analysis of observational studies examining the relationship between the use of newer-generation antidepressants and bone health outcomes. Given the clinical relevance, the study focused on changes in BMD and the risk of hip fracture.

Materials and Methods

Literature Search Strategies

Relevant studies published between 1995 and 2023 in electronic databases (PubMed, Embase, CINAHL, Cochrane Library, Scopus) and other sources were searched. The search adopted a combination of subject words and free words, and the search terms were antidepressants, citalopram, amitriptyline, paroxetine, desvenlafaxine, bupropion, fluoxetine, fluvoxamine, levomilnacipran, clomipramine, vilazodone, milnacipran, duloxetine, vortioxetine, mirtazapine, venlafaxine, escitalopram, and agomelatine, and reboxetine; fracture, osteoporosis.

Literature Inclusion and Exclusion Criteria

Inclusion Criteria: Observational study design; Novel antidepressants compared with traditional tricyclic antidepressants (TCAs); Reported ORs for hip fracture and BMD associated with the use of antidepressants, including SSRIs and other novel antidepressants.

Exclusion criteria: Conference abstracts, literature not available in full text, proposals; Articles not presented in English or Chinese; Duplicate publications.

Literature Screening, Data Extraction, and Quality Assessment

The title and abstract were read independently by two researchers trained in evidence-based systems. Based on the inclusion and exclusion criteria, literature that met the inclusion criteria was further read, screened, and cross-checked in full text. If there was any inconsistency, a third researcher was invited to arbitrate.

Two reviewers independently extracted information from the included studies into standardized templates. The information extracted included the first author, year, country, study design, antidepressant, sample size, age of patients, and BMD investigation bone site.

Two researchers evaluated the literature independently and cross-checked it when each was finished, with a third researcher asked to adjudicate in case of disagreement. Cohort studies were assessed using tools like the Newcastle-Ottawa Scale, and the articles included were of medium and high quality.

Statistical Analysis

All meta-analyses were conducted in R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $p < 0.05$. This study was reported following the PRISMA guidelines (**Supplementary File 1**).

Meta-Analysis of BMD and novel antidepressant use: The standardized mean differences (SMD) in BMD between antidepressant users and non-users was pooled across studies using DerSimonian-Laird random effects models in the R package "dmetar" [8]. Heterogeneity was quantified using the I^2 statistic. Publication bias was assessed visually using funnel plots and quantitatively using Egger's regression test [9]. The influence of individual studies was examined through a leave-one-out analysis. Clustering techniques were applied to identify potential outlier studies, including k-means, density-based spatial clustering of applications with noise (DBSCAN), and Gaussian mixture models.

Meta-analysis of hip fracture risk and novel antidepressant use: The OR for hip fracture risk was pooled using inverse-variance weighted random effects models with the "rma ()" function in the R package "meta" [10]. The between-study variance was estimated using restricted maximum likelihood. Publication bias was evaluated through Egger's test, Begg's rank correlation test [11], and trim-and-fill analysis [12]. The contribution of each study to heterogeneity and overall effect size was assessed using Baujat plots [13].

Results

Characteristics of Included Studies

Fourteen eligible studies with a total of 1,417,134 participants were identified (Fig. 1). The characteristics of the

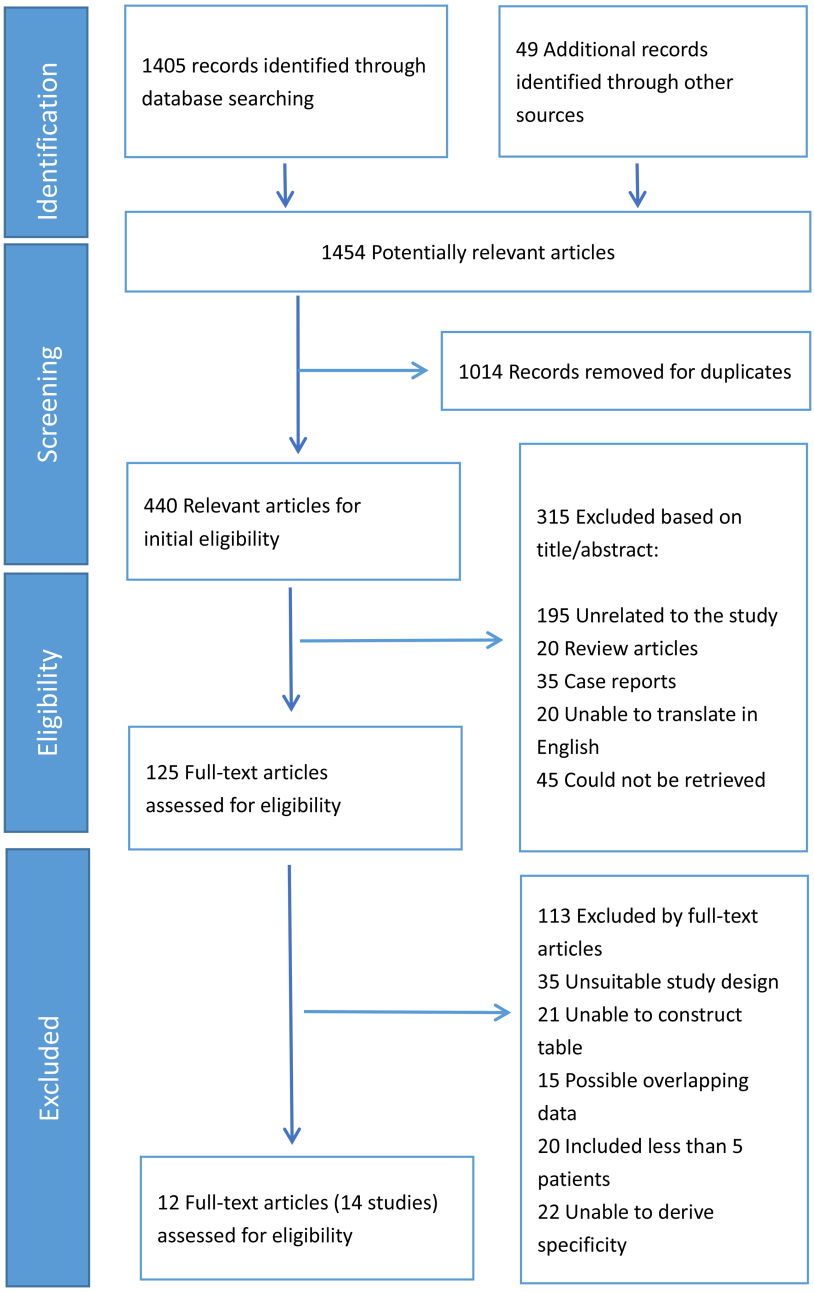

Fig. 1. PRISMA flowchart for search strategy of this systematic review and meta-analysis.

included studies are summarized in Table 1 (Ref. [6,7,14–23]). These studies were conducted in the USA, Australia, Iran, Finland, Sweden, Canada, Singapore, and the Netherlands, including cross-sectional, cohort, and case-control studies. Antidepressant exposure was measured by prescription records, self-reports, or medical records. Criteria defining the outcome of a hip fracture were derived from hospital records, radiological reports, or fracture registries. Confounders were adjusted for age, sex, comorbidities, and other medications.

Meta-Analysis of Lumbar and Total Spine BMD (g/cm^2) and Novel Antidepressant Use

The pooled SMD of BMD (g/cm^2) between the exposed and non-exposed groups was –0.03 (95% CI: –0.04, –0.01), indicating a significant decrease in BMD (g/cm^2) among the novel antidepressant users (Fig. 2A). The studies had substantial heterogeneity ($I^2 = 91\%$, Q = 90.69, $p <$ 0.01). The subgroup analysis by skeletal site showed that the effect was more pronounced in the lumbar spine (SMD

Table 1. Characteristics of included studies for meta-analysis of BMD & hip fracture risk and novel antidepressant use.

Authors, year	Country	Study design	Antidepressant	Sample size	Age of patients (mean ± SD)	BMD investigation of bone site
Saraykar *et al.* [14], 2018	USA	Cross-sectional retrospective study	SSRI	140	78.1 ± 10.5	Femoral neck | spine
Williams *et al.* [15], 2018	Australia	Community-based study	SSRI	128	57.5 ± 5.1	Lumbar spine | femoral neck | ward's triangle | trochanter | total body | distal forearm | mid-forearm
Efendioglu *et al.* [16], 2023	Iran	Cross-sectional retrospective study	SSRI	34	30.6 ± 6.9 | 33.7 ± 2.2	Lumbar
Feuer *et al.* [17], 2015	USA	Cross-sectional study	SSRI	4303	16.1 ± 2.4	lumbar | total femur | femoral neck
Ho *et al.* [7], 2022	Singapore	Cross-sectional study	SSRI	90	37.64 ± 7	Lumbar | Hip
Rauma *et al.* [6], 2016	Finland	Cohort study	SSRI | TCA | Other	1988	63.6 ± 2.9	Femoral neck
Brännström *et al.* [18], 2021	Sweden	Cross-sectional retrospective study	SSRI | TCA | Other	408,144	80.1 ± 7.2	Hip
Liu *et al.* [19], 1998	Canada	Case-Control Study	SSRI | TCA	8239	>65	Hip
Vangala *et al.* [20], 2020	USA	Case-Control Study	SSRI	54,032	71 ± 12.72	Hip
Leach *et al.* [21], 2017	Australia	Case-Control Study	SSRIs | Psychoactive medicines	44,138	>65	Hip
Souverein *et al.* [22], 2016 (BIFAP)	Netherlands	Cohort study	SSRI | TCA	252,203	50.9 ± 16.9	Hip
Souverein *et al.* [22], 2016 (Mondriaan)	Netherlands	Cohort study	SSRI | TCA	22,954	48.8 ± 17.2	Hip
Souverein *et al.* [22], 2016 (THIN)	Netherlands	Cohort study	SSRI | TCA	587,637	49.7 ± 18.5	Hip
Brand *et al.* [23], 2009	Netherlands	Case-Control Study	SSRI | TCA	33,104	75.7 #	Hip

BMD, bone mineral density; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. # Because the standard deviation of age was not shown in this paper, only the average was shown, and only the average of age was extracted.

Table 2. Leave-one-out analysis of lumbar and total spine BMD (g/cm^2) and novel antidepressant use.

Leave-One-Out Analysis (Sorted by I^2)					
Study	No.	Effect	LLCI	ULCI	I^2
Feuer *et al.* [17], 2015 (Model_1)	Lumbar	–0.033	–0.036	–0.03	0.736
Feuer *et al.* [17], 2015 (Model_2)	Lumbar.1	–0.024	–0.027	–0.021	0.885
Feuer *et al.* [17], 2015 (Model_3)	Lumbar.6	–0.028	–0.031	–0.026	0.914
Feuer *et al.* [17], 2015 (SSRI_users < 6_months)	Lumbar.4	–0.027	–0.029	–0.024	0.916
Feuer *et al.* [17], 2015 (SSRI_users > 6_months)	Lumbar.2	–0.027	–0.03	–0.024	0.922
Feuer *et al.* [17], 2015 (excluding_those_subjects_with_BMI < 5th_percentile)	Lumbar.3	–0.028	–0.03	–0.026	0.922
Saraykar *et al.* [14], 2018	Lumbar.5	–0.027	–0.03	–0.025	0.922
Efendioglu *et al.* [16], 2023	Total_spine	–0.028	–0.03	–0.025	0.923

LLCI, lower limit confidence interval; ULCI, upper limit confidence interval.

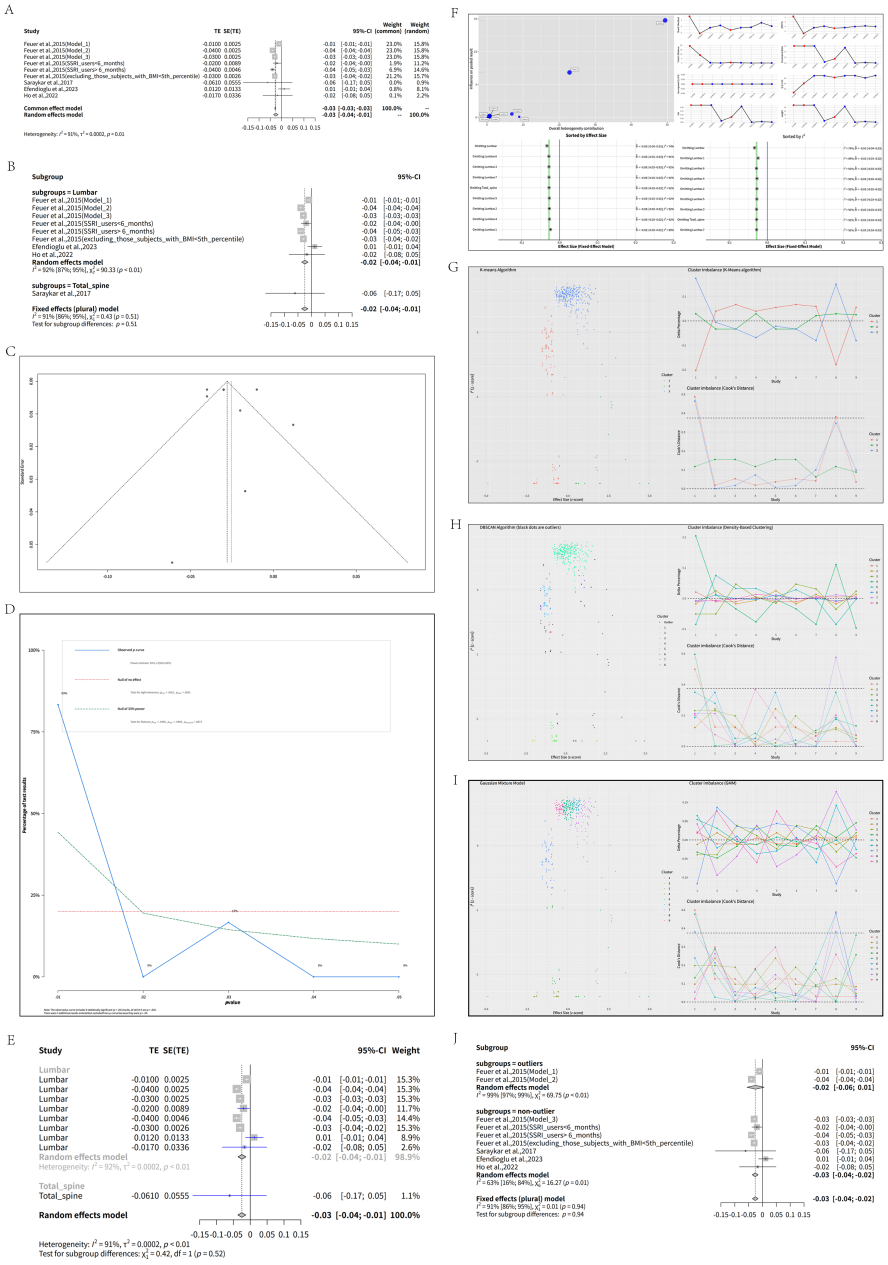

Fig. 2. Results of a meta-analysis of lumbar and total spine BMD (g/cm^2) and novel antidepressant use. (A) Forest plot of the pooled standardized mean differences (SMD) of BMD (g/cm^2) between novel antidepressant users and non-users. (B) Subgroup analysis of the pooled SMD of BMD (g/cm^2) by skeletal site. (C) Funnel plot of the SMD of BMD (g/cm^2) versus standard error. (D) P-curve analysis of the statistical significance of the studies on BMD (g/cm^2). (E) Outlier detection plot of the SMD of BMD (g/cm^2) based on random-effects model estimates. (F) The plot showed the leave-one-out estimates of effect size and heterogeneity for each study on the x-axis and y-axis, respectively. The plot also showed the overall effect size and heterogeneity as black vertical lines and red horizontal lines, respectively. (G) Leave-one-out analysis of BMD (g/cm^2) and novel antidepressant use. (H) Influence diagnostics of BMD (g/cm^2) and novel antidepressant use. (I) Baujat diagnostics of BMD (g/cm^2) and novel antidepressant use. (J) Subgroup analysis of the pooled SMD of BMD (g/cm^2) by outliers and non-outliers.

= –0.02, 95% CI: –0.04, –0.01) than in the total spine (SMD = –0.06, 95% CI: –0.17, 0.05), but the difference was not statistically significant (Q = 0.43, p = 0.51) (Fig. 2B).

The publication bias assessment showed no evidence of asymmetry in the funnel plot (Fig. 2C) or significant Egger's test (p = 0.87). The P-curve analysis indicated

Table 3. Influence diagnostics of lumbar and total spine BMD (g/cm^2) and novel antidepressant use.

Influence Diagnostics									
Study	No.	rstudent	dffits	cook.d	cov.r	QE.del	hat	weight	infl
Feuer *et al.* [17], 2015 (Model_1)	Lumbar	8.011	4.38	19.183	1.299	26.521	0.23	23.015	*
Feuer *et al.* [17], 2015 (Model_2)	Lumbar.1	–5.45	–2.98	8.881	1.299	60.984	0.23	23.015	*
Feuer *et al.* [17], 2015 (Model_3)	Lumbar.2	–0.963	–0.527	0.277	1.299	89.762	0.23	23.015	
Feuer *et al.* [17], 2015 (SSRI_users < 6_months)	Lumbar.3	0.886	0.122	0.015	1.019	89.905	0.019	1.856	
Feuer *et al.* [17], 2015 (SSRI_users > 6_months)	Lumbar.4	–2.72	–0.742	0.551	1.074	83.293	0.069	6.929	*
Feuer *et al.* [17], 2015 (excluding_those_subjects_with_BMI < 5th_percentile)	Lumbar.5	–0.913	–0.473	0.224	1.268	89.857	0.212	21.157	
Saraykar *et al.* [14], 2018	Total_spine	–0.597	–0.013	0	1	90.334	0	0.048	
Efendioglu *et al.* [16], 2023	Lumbar.6	3.001	0.275	0.076	1.008	81.683	0.008	0.835	
Ho *et al.* [7], 2022	Lumbar.7	0.323	0.012	0	1.001	90.586	0.001	0.131	

* the study is considered as an influential study.

Table 4. Baujat diagnostics of lumbar and total spine BMD (g/cm^2) and novel antidepressant use.

Baujat Diagnostics (sorted by Heterogeneity Contribution)			
Study	No.	HetContrib	Influence Effect Size
Feuer *et al.* [17], 2015 (Model_1)	Lumbar	49.401	14.768
Feuer *et al.* [17], 2015 (Model_2)	Lumbar.1	22.87	6.837
Feuer *et al.* [17], 2015 (Model_3)	Lumbar.6	8.933	0.075
Feuer *et al.* [17], 2015 (SSRI_users < 6_months)	Lumbar.4	6.885	0.513
Feuer *et al.* [17], 2015 (SSRI_users > 6_months)	Lumbar.3	0.771	0.015
Feuer *et al.* [17], 2015 (excluding_those_subjects_with_BMI < 5th_percentile)	Lumbar.2	0.715	0.214
Saraykar *et al.* [14], 2018	Lumbar.5	0.657	0.176
Efendioglu *et al.* [16], 2023	Total_spine	0.356	0
Ho *et al.* [7], 2022	Lumbar.7	0.104	0

that there was an evidential value present in the studies with $p < 0.05$ (k = 6, power estimate = 99%) and no evidential value absent or inadequate (Fig. 2D). The outlier detection did not identify any outliers based on random-effects model estimates (Fig. 2E). The leave-one-out analysis showed that omitting any study from the meta-analysis changed the overall effect size and heterogeneity. The most significant changes were observed when omitting Feuer *et al.* [17], 2015 (Model_1) or Feuer *et al.* [17], 2015 (Model_2), which decreased the overall effect size by 0.008 and 0.0013, respectively, and reduced the heterogeneity by 0.187 and 0.038, respectively (Fig. 2F and Table 2). The influence diagnostics provided several indicators to identify potential outliers or influential studies. Feuer *et al.* [17], 2015 (Model_1) and Feuer *et al.* [17], 2015 (Model_2) were outliers or had large weights, as they had high values of rstudent, dffits, cook.d, cov.r, QE.del, hat, weight, and infl (marked with * in Table 3). The Baujat diagnostics showed the contribution of each study to both heterogeneity and effect size estimates. The studies with high contributions to heterogeneity and effect size were considered influential. Based on this criterion, Feuer *et al.* [17], 2015 (Model_1) and Feuer *et al.* [17], 2015 (Model_2) were considered influential studies because they had high values of HetContrib and InfluenceEffectSize (Fig. 2F and Table 4). Three cluster algorithms were used: K-means, DBSCAN, and Gaussian Mixture Model (GMM). The number of clusters detected by each algorithm was: K-means 3 clusters (Fig. 2G), DBSCAN 8 clusters (Fig. 2H), and GMM 9 clusters (Fig. 2I). Some potential outliers or anomalous data points that deviate from the rest of the data were also identified. The outliers detected by each algorithm were Feuer *et al.* [17], 2015 (Model_1) and Efendioglu *et al.* [16], 2023.

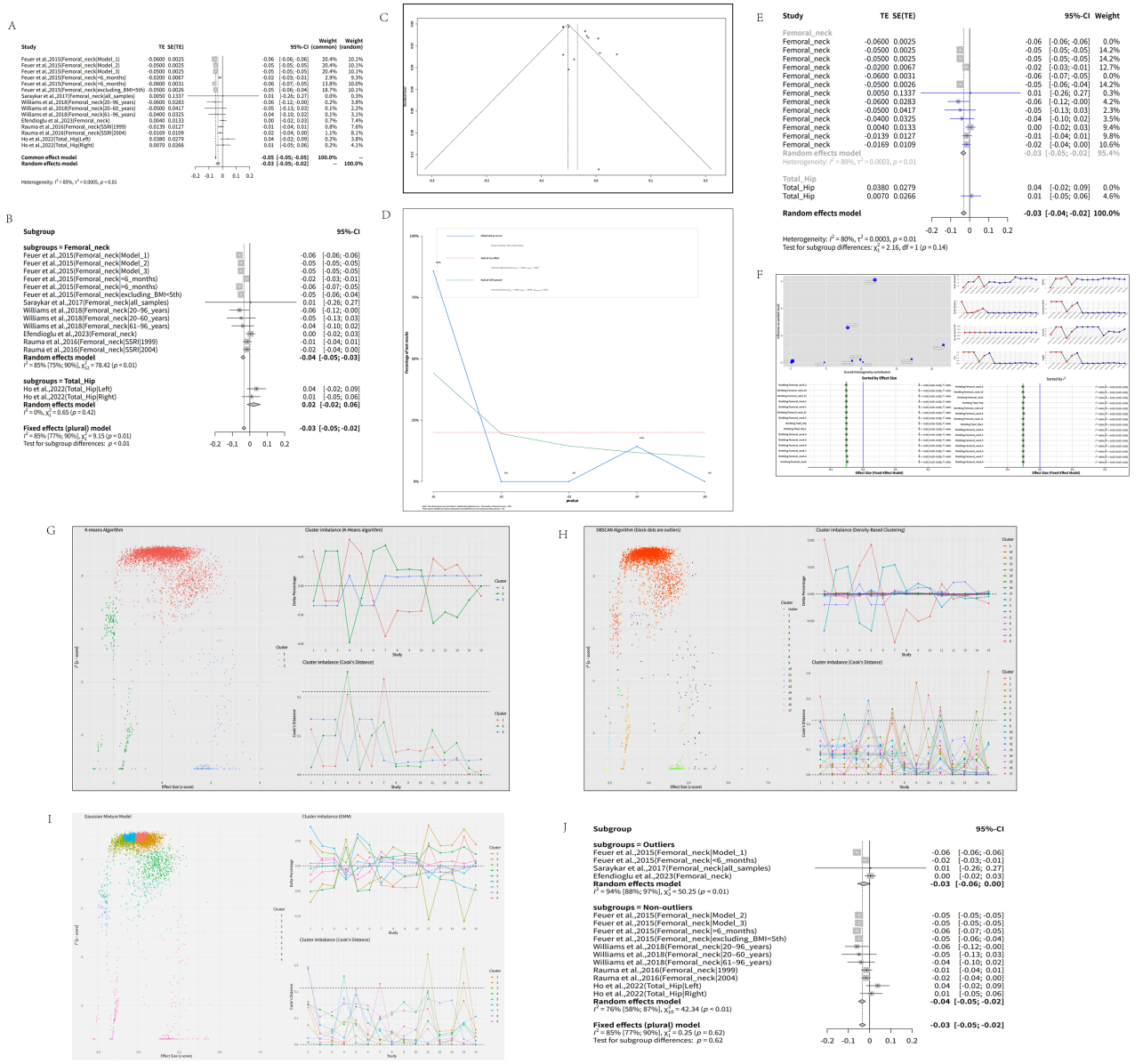

Fig. 3. Results of a meta-analysis of femoral neck and total hip BMD (g/cm^2) and novel antidepressant use. (A) Forest plot of the pooled SMD of BMD (g/cm^2) between novel antidepressant users and non-users. (B) Subgroup analysis of the pooled SMD of BMD (g/cm^2) by skeletal site. (C) Funnel plot of the SMD of BMD (g/cm^2) versus standard error. (D) P-curve analysis of the statistical significance of the studies on BMD (g/cm^2). (E) Outlier detection plot of the SMD of BMD (g/cm^2) based on random-effects model estimates. (F) The plot showed the leave-one-out estimates of effect size and heterogeneity for each study on the x-axis and y-axis, respectively. The plot also showed the overall effect size and heterogeneity as black vertical lines and red horizontal lines, respectively. (G) Leave-one-out analysis of BMD (g/cm^2) and novel antidepressant use. (H) Influence diagnostics of BMD (g/cm^2) and novel antidepressant use. (I) Baujat diagnostics of BMD (g/cm^2) and novel antidepressant use. (J) Subgroup analysis of the pooled SMD of BMD (g/cm^2) by outliers and non-outliers.

Finally, this analysis showed the results of a meta-analysis on the effect of SSRI use on BMD (g/cm^2) in two subgroups: non-outlier and outlier studies (Fig. 2J). The non-outlier studies were not identified as outliers by any outlier detection or cluster analysis methods. The outlier studies were the studies that were identified as outliers by at least one of these methods. The outlier studies were Feuer *et al.* [17], 2015 (Model_1) and Feuer *et al.* [17], 2015

Table 5. Leave-one-out analysis of femoral neck and total hip BMD (g/cm^2) and novel antidepressant use.

Leave-One-Out Analysis (Sorted by I^2)					
Study	No.	Effect	LLCI	ULCI	I^2
Feuer *et al.* [17], 2015 (Femoral_neck|< 6_months)	Femoral_neck.3	–0.052	–0.054	–0.05	0.817
Efendioglu *et al.* [16], 2023 (Femoral_neck)	Femoral_neck.10	–0.052	–0.054	–0.049	0.829
Feuer *et al.* [17], 2015 (Femoral_neck|Model_1)	Femoral_neck	–0.049	–0.052	–0.046	0.834
Rauma *et al.* [6], 2016 (Femoral_neck|2004)	Femoral_neck.12	–0.052	–0.054	–0.049	0.844
Ho *et al.* [7], 2022 (Total_Hip|Left)	Total_Hip	–0.051	–0.054	–0.049	0.844
Feuer *et al.* [17], 2015 (Femoral_neck|> 6_months)	Femoral_neck.4	–0.05	–0.052	–0.047	0.845
Rauma *et al.* [6], 2016 (Femoral_neck|1999)	Femoral_neck.11	–0.052	–0.054	–0.049	0.847
Ho *et al.* [7], 2022 (Total_Hip|Right)	Total_Hip.1	–0.051	–0.054	–0.049	0.853
Feuer *et al.* [17], 2015 (Femoral_neck|Model_2)	Femoral_neck.1	–0.052	–0.054	–0.049	0.861
Feuer *et al.* [17], 2015 (Femoral_neck|Model_3)	Femoral_neck.2	–0.052	–0.054	–0.049	0.861
Feuer *et al.* [17], 2015 (Femoral_neck|excluding_BMI < 5th)	Femoral_neck.5	–0.052	–0.054	–0.049	0.861
Saraykar *et al.* [14], 2018 (Femoral_neck|all_samples)	Femoral_neck.6	–0.051	–0.053	–0.049	0.861
Williams *et al.* [15], 2018 (Femoral_neck|20–96_years)	Femoral_neck.7	–0.051	–0.053	–0.049	0.861
Williams *et al.* [15], 2018 (Femoral_neck|20–60_years)	Femoral_neck.8	–0.051	–0.053	–0.049	0.861
Williams *et al.* [15], 2018 (Femoral_neck|61–96_years)	Femoral_neck.9	–0.051	–0.053	–0.049	0.861

Table 6. Influence diagnostics of femoral neck and total hip BMD (g/cm^2) and novel antidepressant use.

Influence Diagnostics									
Study	No.	rstudent	dffits	cook.d	cov.r	QE.del	hat	weight	infl
Feuer *et al.* [17], 2015 (Femoral_neck|Model_1)	Femoral_neck	–3.871	–1.958	3.836	1.256	78.504	0.204	20.383	*
Feuer *et al.* [17], 2015 (Femoral_neck|Model_2)	Femoral_neck.1	0.542	0.274	0.075	1.256	93.192	0.204	20.383	*
Feuer *et al.* [17], 2015 (Femoral_neck|Model_3)	Femoral_neck.2	0.542	0.274	0.075	1.256	93.192	0.204	20.383	*
Feuer *et al.* [17], 2015 (Femoral_neck|< 6_months)	Femoral_neck.3	4.725	0.82	0.672	1.03	71.164	0.029	2.922	*
Feuer *et al.* [17], 2015 (Femoral_neck|> 6_months)	Femoral_neck.4	–3.062	–1.225	1.501	1.16	84.113	0.138	13.805	*
Feuer *et al.* [17], 2015 (Femoral_neck|excluding_BMI < 5th)	Femoral_neck.5	0.514	0.247	0.061	1.231	93.222	0.187	18.737	
Saraykar *et al.* [14], 2018 (Femoral_neck|all_samples)	Femoral_neck.6	0.421	0.004	0	1	93.309	0	0.007	
Williams *et al.* [15], 2018 (Femoral_neck|20–96_years)	Femoral_neck.7	–0.31	–0.013	0	1.002	93.389	0.002	0.164	
Williams *et al.* [15], 2018 (Femoral_neck|20–60_years)	Femoral_neck.8	0.029	0.001	0	1.001	93.485	0.001	0.075	
Williams *et al.* [15], 2018 (Femoral_neck|61–96_years)	Femoral_neck.9	0.345	0.012	0	1.001	93.366	0.001	0.124	
Efendioglu *et al.* [16], 2023 (Femoral_neck)	Femoral_neck.10	4.157	0.359	0.129	1.007	76.204	0.007	0.74	
Rauma *et al.* [6], 2016 (Femoral_neck|SSRI|1999)	Femoral_neck.11	2.962	0.269	0.073	1.008	84.714	0.008	0.821	
Rauma *et al.* [6], 2016 (Femoral_neck|SSRI|2004)	Femoral_neck.12	3.158	0.333	0.111	1.011	83.51	0.011	1.101	
Ho *et al.* [7], 2022 (Total_Hip|Left)	Total_Hip	3.202	0.132	0.017	1.002	83.234	0.002	0.169	
Ho *et al.* [7], 2022 (Total_Hip|Right)	Total_Hip.1	2.188	0.094	0.009	1.002	88.696	0.002	0.185	

* the study is considered as an influential study.

(Model_2). The results showed that SSRI use had a significant negative effect on BMD (g/cm^2) in the non-outlier subgroup but not in the outlier subgroup. The pooled effect size for the non-outlier subgroup was –0.03, with a 95% confidence interval of [–0.04, –0.02] and a *p*-value of 0.01. This means SSRI users had lower BMD (g/cm^2) than non-users by 0.02 standard deviations in the non-outlier subgroup. The pooled effect size for the outlier subgroup was –0.03, with a 95% confidence interval of [–0.06, 0.01] and a *p*-value < 0.01. This means there was no significant difference in BMD (g/cm^2) between SSRI users and non-users in the outlier subgroup. The results also showed moderate to high heterogeneity within each subgroup but no significant heterogeneity between the subgroups. The I^2 statistic for the non-outlier subgroup was 0.63, with a 95% confidence interval of [0.16, 0.84], indicating that 63% of the variation in effect sizes within this subgroup was due to heterogeneity rather than chance. The I^2 statistic for the outlier subgroup was 0.99, with a 95% confidence interval of [0.97, 0.99], indicating that 99% of the variation in effect sizes within this subgroup was due to heterogeneity rather than chance. The Q statistic for testing the difference between the subgroups was 0.01, with a *p*-value of 0.94, indicating no significant difference in effect sizes between the subgroups.

Table 7. Baujat diagnostics of femoral neck and total hip BMD (g/cm^2) and novel antidepressant use.

Baujat Diagnostics (sorted by Heterogeneity Contribution)			
Study	No.	HetContrib	InfluenceEffectSize
Feuer *et al.* [17], 2015 (Femoral_neck|Model_1)	Femoral_neck	11.928	3.054
Feuer *et al.* [17], 2015 (Femoral_neck|Model_2)	Femoral_neck.1	0.233	0.06
Feuer *et al.* [17], 2015 (Femoral_neck|Model_3)	Femoral_neck.2	0.233	0.06
Feuer *et al.* [17], 2015 (Femoral_neck|< 6_months)	Femoral_neck.3	21.669	0.652
Feuer *et al.* [17], 2015 (Femoral_neck|> 6_months)	Femoral_neck.4	8.079	1.294
Feuer *et al.* [17], 2015 (Femoral_neck|excluding_BMI < 5th)	Femoral_neck.5	0.215	0.049
Saraykar *et al.* [14], 2018 (Femoral_neck|all_samples)	Femoral_neck.6	0.177	0
Williams *et al.* [15], 2018 (Femoral_neck|20–96_years)	Femoral_neck.7	0.096	0
Williams *et al.* [15], 2018 (Femoral_neck|20–60_years)	Femoral_neck.8	0.001	0
Williams *et al.* [15], 2018 (Femoral_neck|61–96_years)	Femoral_neck.9	0.119	0
Efendioglu *et al.* [16], 2023 (Femoral_neck)	Femoral_neck.10	17.154	0.128
Rauma *et al.* [6], 2016 (Femoral_neck|SSRI|1999)	Femoral_neck.11	8.7	0.072
Rauma *et al.* [6], 2016 (Femoral_neck|SSRI|2004)	Femoral_neck.12	9.865	0.11
Ho *et al.* [7], 2022 (Total_Hip|Left)	Total_Hip	10.235	0.017
Ho *et al.* [7], 2022 (Total_Hip|Right)	Total_Hip.1	4.781	0.009

Meta-Analysis of Femoral Neck and Total Hip BMD (g/cm^2) and Novel Antidepressant Use

A systematic review and meta-analysis was conducted to examine the association between novel antidepressants and BMD (g/cm^2) in different skeletal sites, namely the femoral neck and total hip. The overall pooled SMD of BMD (g/cm^2) was –0.03 (95% CI: –0.05, –0.02), indicating that antidepressant users had significantly lower BMD (g/cm^2) than non-users or controls across all skeletal sites (Fig. 3A). However, the studies had substantial heterogeneity (I^2 = 85%, $p < 0.01$). The subgroup analyses showed that the effect of antidepressants was more pronounced in the femoral neck than in the total hip, with SMDs of –0.04 (95% CI: –0.05, –0.03) and 0.02 (95% CI: –0.02, 0.06), respectively (Fig. 3B). The difference between subgroups was statistically significant ($p < 0.01$).

Several methods were used to explore the sources of heterogeneity and potential outliers in this meta-analysis. A funnel plot was constructed to visually inspect the symmetry of the studies around the pooled effect size (Fig. 3C). Egger's test was also performed to detect any small-study effects or publication bias, with no evidence of bias (p = 0.91). A P-curve analysis was also conducted to assess the evidential value of this meta-analysis (Fig. 3D). Seven datasets with p-values less than 0.05 in the analysis were included, and the P-curve was right-skewed, indicating evidential value in this meta-analysis. The power estimate was 99%, suggesting that this meta-analysis had sufficient statistical power to detect a true effect.

This study found that three studies were outliers with identification of outliers based on the random-effects model, and the results with outliers removed: Feuer *et al.* [17], 2015 (Femoral neck|Model 1), Feuer *et al.* [17], 2015 (Femoral neck|< 6_months), and Ho *et al.* [7], 2022 (Total hip). These studies had very large or small effect sizes compared to the other studies and large standard errors. Removing these studies reduced the heterogeneity from 85% to 79.6% and increased the precision of the pooled effect size from –0.03 [–0.05; –0.02] to –0.03 [–0.04; –0.02] (Fig. 3E). The influence analysis results are shown in Fig. 3F and Tables 5,6,7. The Table 6 shows each study's standardized residuals, DFFITS, Cook's distance, covariance ratio, Q statistic, leverage, weight, and influence flag. This study found that Feuer *et al.* [17], 2015 (Femoral neck|Model_1) had the highest influence on the overall pooled effect size and heterogeneity, as indicated by its large DFFITS, Cook's distance, and influence flag. Removing this study increased the pooled effect size from –0.034 to –0.031 and reduced the heterogeneity from 85% to 79.6%. Other studies that had some influence on the results were Feuer *et al.* [17], 2015 (Femoral neck|< 6_months) and Saraykar *et al.* [14], 2018 (Femoral neck|all_samples). However, none of these studies changed the main conclusion of our meta-analysis. The results of the GOSH diagnostics show the number of clusters detected by three different clustering algorithms: K-means (Fig. 3G), DBSCAN (Fig. 3H), and Gaussian Mixture Model (Fig. 3I). The study found that different clustering algorithms produced different results, indicating no clear consensus on which studies were outliers. However,

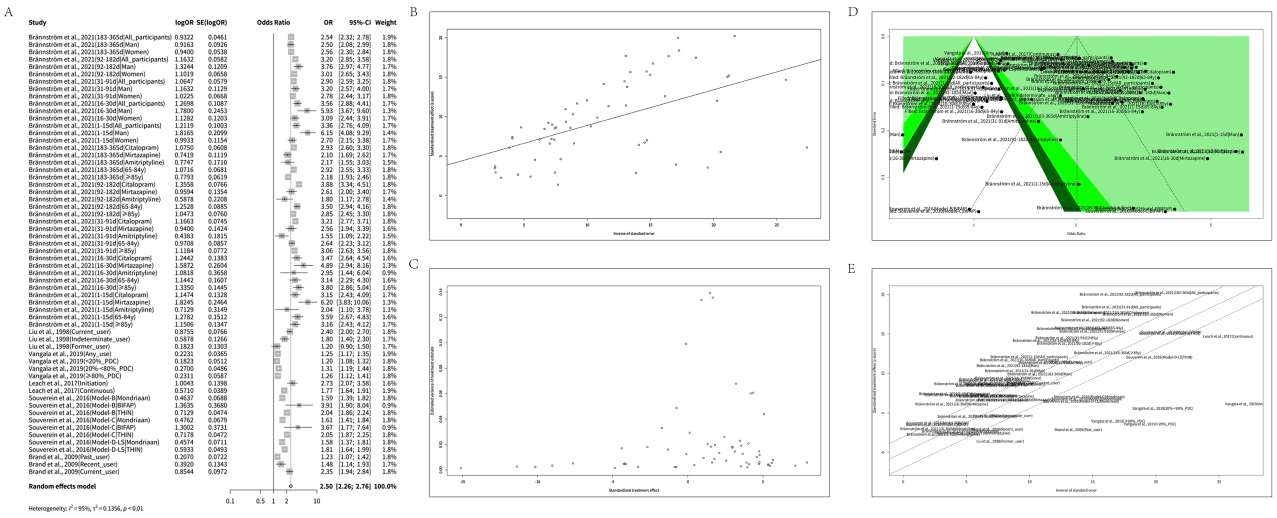

Fig. 4. Results of a meta-analysis of hip fracture risk and novel antidepressant use. (A) Forest plot of the association between antidepressant use and hip fracture risk. (B) Funnel plot with Egger's regression line for publication bias assessment. (C) Funnel plot with Begg's rank correlation test for publication bias assessment. (D) Trim-and-fill analysis of the association between antidepressant use and hip fracture risk. (E) Baujat plot of the influence of individual studies on the meta-analysis results.

some studies appeared to be outliers in more than one algorithm, such as Feuer *et al.* [17], 2015 (Femoral neck|Model 1), Feuer *et al.* [17], 2015 (Femoral neck|< 6_months), and Efendioglu *et al.* [16], 2023 (Femoral neck). Compared to the other studies, these studies had large effect sizes, large standard errors, or both.

Finally, the results of the subgroup analysis of outlier and non-outlier according to the GOSH diagnostics are shown in Fig. 3J. The study found no significant difference between the effect sizes of outliers and non-outliers (Q = 0.25, $p = 0.62$). However, the results of non-outliers were more consistent and reliable than those of outliers. The non-outliers subgroup consisted of 11 datasets with a negative effect size of –0.036 [–0.052; –0.020], indicating that SSRI use was associated with lower BMD than non-use. The standard error of this effect size was 0.008, suggesting that it was precise and had a narrow confidence interval. The heterogeneity within this subgroup was high (I^2 = 76%) but lower than that of outliers (I^2 = 94%). This suggested that the non-outliers subgroup captured most of the variation among studies and that the outliers did not represent the overall population.

Meta-Analysis of Hip Fracture Risk and Novel Antidepressant Use

The overall pooled OR estimating the association between antidepressant use and risk of hip fracture was 2.50 (95% CI 2.26–2.76, $p < 0.01$) using a random-effects model. This indicated antidepressant use was associated with a 2.5-fold increased risk of hip fracture. There was substantial heterogeneity among the included studies (I^2 = 95%, $p < 0.01$) (Fig. 4A). The between-study variance (tau2) was estimated at 0.26 (95% CI 0.19–0.39). The 95% prediction interval for the effect size in a new study was 0.44 to 9.11.

Two tests, including Egger's test and Begg's test, were performed to assess the publication bias in this meta-analysis. Egger's test is a linear regression test of funnel plot asymmetry, which uses the standard error as the predictor and the effect size as the outcome. The test result showed a significant intercept (0.45, $p < 0.01$), indicating a positive relationship between the standard error and the effect size and, thus, evidence of publication bias. The bias coefficient was 4.38, which means that for every unit increase in the standard error, the effect size increased by 4.38 units on average (Fig. 4B). Begg's test is a rank correlation test of funnel plot asymmetry, which uses Kendall's rank correlation coefficient to measure the association between the effect size and its variance. The test result showed a non-significant correlation (z = 0.66, $p = 0.51$), indicating that there was no evidence of publication bias. The rank correlation coefficient was 104, indicating a weak positive relationship between the effect size and its variance (Fig. 4C). The two tests gave inconsistent results, which may be due to different assumptions and sensitivities of the tests. Egger's test is more powerful than Begg's test, but it also assumes that the effect size follows a normal distri-

bution, which may not be true in our case. Begg's test is more robust to non-normality, but it also has lower statistical power and may fail to detect publication bias when it exists.

To adjust for potential publication bias, the trim-and-fill analysis identified 20 hypothetically missing studies. After imputing these studies, the overall pooled OR for the association between antidepressant use and hip fracture risk was attenuated from 2.50 (95% CI 2.26–2.76) to 2.01 (95% CI 1.79–2.26) but remained statistically significant. The added studies had OR ranging from 0.61 to 1.20. Despite the adjustment, substantial heterogeneity remained (I^2 96%). The trim-and-fill method suggested possible under-reporting of smaller studies showing less pronounced associations. However, the overall findings support an increased risk of hip fracture with antidepressant use (Fig. 4D).

The Baujat plot shows that several studies had a high influence on this meta-analysis results, such as Vangala *et al*. [20], 2020 (Any use), Brand *et al*. [23], 2009 (Past user), and Brännström *et al*. [18], 2021 (92-182d|Citalopram). These studies had large circles in the upper right quadrant, indicating high heterogeneity and effect size contributions. On the other hand, several studies had a low influence on our meta-analysis results, such as Brännström *et al*. [18], 2021 (183-365d|Mirtazapine), Souverein *et al*. [22], 2016 (Model-D-LS|Amitriptyline), and Brand *et al*. [23], 2009 (Current user). These studies had small circles in the lower left quadrant, indicating low heterogeneity and low effect size contributions (Fig. 4E).

Discussion

This comprehensive meta-analysis of 14 observational studies, including over 1.4 million participants, provided persuasive evidence that newer-generation antidepressants, particularly SSRIs, had detrimental impacts on bone health outcomes. The main finding was a significant reduction in BMD at multiple skeletal sites, including the lumbar spine, femoral neck, and total hip, and a 2.5-fold increased risk of hip fracture among antidepressant users compared to non-users.

The negative associations between antidepressant exposure and bone density and strength are likely explained by several biological mechanisms disrupting bone metabolism. Antidepressants like SSRIs can increase synaptic serotonin levels, which is known to stimulate osteoclast differentiation and bone resorption while inhibiting osteoblast function, thereby adversely affecting bone remodeling [24,25]. Antidepressants may also suppress adrenal glucocorticoid production, leading to reduced BMD through effects on calcium absorption and bone formation. Additionally, these psychoactive agents have been associated with increased risks of falls and fractures through sedation, arrhythmias, and other side effects, providing another pathway for elevated bone fragility. The detrimental skeletal effects appeared more pronounced at certain sites like the femoral neck, which may relate to differences in cortical versus trabecular bone composition across anatomical locations.

The consistent associations between antidepressant use and worsened bone health have important clinical implications given the widespread and growing utilization of these agents, especially SSRIs, for treating depression and anxiety disorders. Prescribers should carefully weigh the potential harms of bone loss and heightened fracture risk against mental health benefits when considering antidepressant therapy for individual patients, particularly vulnerable populations like the elderly who already suffer from compromised bone strength and high baseline fracture risks. Greater awareness and regular monitoring of BMD and fracture risk factors could help enable early detection of skeletal damage in patients on long-term antidepressant regimens. Additionally, preventative strategies, including weight-bearing exercise, calcium, vitamin D, and anti-resorptive medications, may help mitigate progressive bone loss in those requiring antidepressants [26]. Further research is critically needed to clarify optimal approaches for safe antidepressant prescribing and fracture prevention among exposed patients across various risk groups.

A recent study suggested that the effects of antidepressants on bone health may vary depending on the type, dose, duration, and timing of use, as well as the patient's age, sex, menopausal status, and genetic factors [27]. These studies also proposed some potential mechanisms to explain how antidepressants may modulate the serotonin system in both the central nervous system and the peripheral tissues, affecting not only mood but also bone homeostasis [18,27,28]. However, these studies also acknowledged the limitations of observational data, such as residual confounding by indication, severity of depression, lifestyle factors, and comorbidities. Meanwhile, the results showed that Feuer *et al*. [17], 2015 (Model_1) and Feuer *et al*. [17], 2015 (Model_2) were consistently identified as outliers by all methods. These two studies were based on the same data set but used different models to adjust for potential confounders. Model 1 was adjusted for age, gender, ethnicity, and height z-score, while Model 2 was adjusted for age, gender, ethnicity, height z-score, and weight z-score. Model 3 was adjusted for age, gender, ethnicity, height z-

score, weight z-score, physical activity, serum cotinine, and PIR. One possible reason why these two studies were outliers was that they had a very small effect size compared to other studies. The effect size is the difference in BMD (g/cm^2) between SSRI users and non-users. The effect size of Feuer *et al.* [17], 2015 (Model_1) is –0.01, while the effect size of Feuer *et al.* [17], 2015 (Model_2) is –0.04. These values are much lower than the overall effect size of –0.07. This means these two studies show a weak or no association between SSRI use and BMD (g/cm^2). Another possible reason these two studies are outliers is that they have a very small standard error compared to other studies. The standard error measures the uncertainty or variability of the effect size estimate. The standard error of Feuer *et al.* [17], 2015 (Model_1) is 0.002540049, while the standard error of Feuer *et al.* [17], 2015 (Model_2) is 0.002540049. These values are much lower than the overall standard error of 0.007. This means the two studies have a very precise or confident estimate of the effect size. Therefore, more rigorous studies with randomized controlled trials or Mendelian randomization are needed to establish causal inference between antidepressant use and bone health outcomes.

Conclusions

This meta-analysis synthesizing results across 14 observational studies and over 1.4 million participants provided strong and consistent evidence that newer generation antidepressants, especially widely used SSRIs, have negative impacts on bone health. The statistically significant associations with decreased BMD at all sites examined and a doubled risk of highly morbid hip fractures raise significant concerns about skeletal safety with chronic use of these medications. Healthcare providers should carefully consider the risks of adverse bone effects and fracture when weighing the psychiatric benefits against the side effects risks of antidepressant therapy for individual patients. Close monitoring of bone health and preventative strategies to preserve skeletal integrity may be warranted for patients requiring long-term antidepressant treatment. Further investigations into optimal care approaches for maintaining bone strength and minimizing fracture risk in the many patients now using newer antidepressants are critically needed.

Availability of Data and Materials

The datasets used to support the findings of this study are available from the corresponding author on reasonable request.

Author Contributions

YYC and JH conceptualized and designed the study, and drafted the article. JH and KLX independently performed the search databases. JH, KLX and SXW contributed to the analysis and interpretation of data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.v52i3.1560.

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