Osteoporosis International (2018) 29:1243–1251
https://doi.org/10.1007/s00198-018-4413-0

REVIEW

Effect of selective serotonin reuptake inhibitors on bone mineral density: a systematic review and meta-analysis

C. Zhou[1,2,3] · L. Fang[1] · Y. Chen[1] · J. Zhong[1] · H. Wang[2,3] · P. Xie[1,2,3,4]

Received: 25 September 2017 / Accepted: 24 January 2018 / Published online: 12 February 2018

Abstract

Our work is the first systematic meta-analysis to investigate the effect of selective serotonin reuptake inhibitor (SSRI) medication on bone mineral density. Through meta-analyzed 11 studies, our findings suggested that compared with nonusers, use of SSRIs was significantly associated with lumbar spine BMD reduction, particularly for old people. The use of selective serotonin reuptake inhibitors (SSRIs) has already been associated with bone mass loss. Their effects on bone mineral density (BMD) for the different bone sections have, however, thus been inconsistent. Here, we aim to assess the effects of SSRIs on BMD using a meta-analysis. We searched PubMed, Scopus, ISI Web of Knowledge, the Cochrane Library, and PsycINFO for all English-written studies investigating the effects of SSRIs on BMD and published before November 2017. BMD was compared between non-SSRI users and SSRI users using a random-effect model with standardized mean differences (SMD) and 95% confidence intervals (CIs). Furthermore, subgroup analyses were performed based on study design, age, and sex in order to find the origins of high heterogeneity. Eleven studies met the inclusion criteria and were used for the meta-analysis. Our study demonstrated that the use of SSRIs was significantly associated with lower BMD values (SMD − 0.40; 95% CI − 0.79 to 0.00; $p = 0.05$) and BMD Z-scores (SMD − 0.28; 95% CI − 0.50 to − 0.05; $p = 0.02$) of the lumbar spine, but not of the total hip and femoral neck. In addition, SSRI use was associated with a greater bone loss in older people. SSRI use is a risk factor of lower BMD of the lumbar spine, especially for older people. Future studies into the relationship between SSRI use and bone metabolism and bone mass need to be conducted with larger sample sizes for both men and women at different bone sites.

Keywords Antidepressant · Bone mineral density · Meta-analysis · Selective serotonin reuptake inhibitors

Introduction

Selective serotonin reuptake inhibitors (SSRIs), which inhibit the reuptake of both serotonin and noradrenaline, are the most commonly prescribed class of antidepressants worldwide [1]. Recently, several clinical human studies reported that the use of SSRIs may (in)directly influence bone metabolism and increase the risk of osteoporotic fractures and osteoporosis [2–5].

A possible explanation for SSRIs-induced osteoporosis and fracturing has been proposed and relates to the ability of SSRIs to reduce bone mineral density (BMD). Since then, the effect of SSRIs use on BMD has been investigated in more depth but has yielded contradictory results. While some studies associated SSRI use with low BMD [6–8], others reported no difference [9, 10]. Arguably, factors such as

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-018-4413-0) contains supplementary material, which is available to authorized users.

✉ P. Xie
xiepeng@cqmu.edu.cn

[1] Department of Neurology, Yongchuan Hospital of Chongqing Medical University, Chongqing, China

[2] Institute of Neuroscience, Chongqing Medical University, Chongqing, China

[3] Chongqing Key Laboratory of Neurobiology, Chongqing Medical University, Chongqing, China

[4] Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuzhong District, Chongqing 400016, China

weight, age, gender, and race of the patients enrolled into each of these studies may have obscured the results. In fact, these factors may be important covariants of changes to a patient's bone metabolism when treated with antidepressants [11–14]. As only a few meta-analyses specifically focus on the effects of SSRIs on BMD, the aim of the meta-analysis presented herein was to examine if the use of SSRIs could influence BMD and to identify the impact of individual factors on BMD during SSRI treatment.

Methods

The study was designed and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidelines (Table S1).

Search strategy

The original studies, from their date of publication until November 2017, were systematically searched for in English electronic databases including PubMed, Scopus, ISI Web of Knowledge, the Cochrane Library, and PsycINFO. In addition, book chapters, bibliographies of relevant studies, and gray literature (conference papers, working papers, and reports in institutional series) were searched in Google Scholar, Embase, Science Direct, EconLit, and AgEcon. A combination of the following medical terms and keywords were used for the searches: [(antidepressants OR selective serotonin reuptake inhibitors OR SSRIs) AND (bone mineral density OR BMD)]. The final search results were limited to human studies and the English language using the filters provided by the databases.

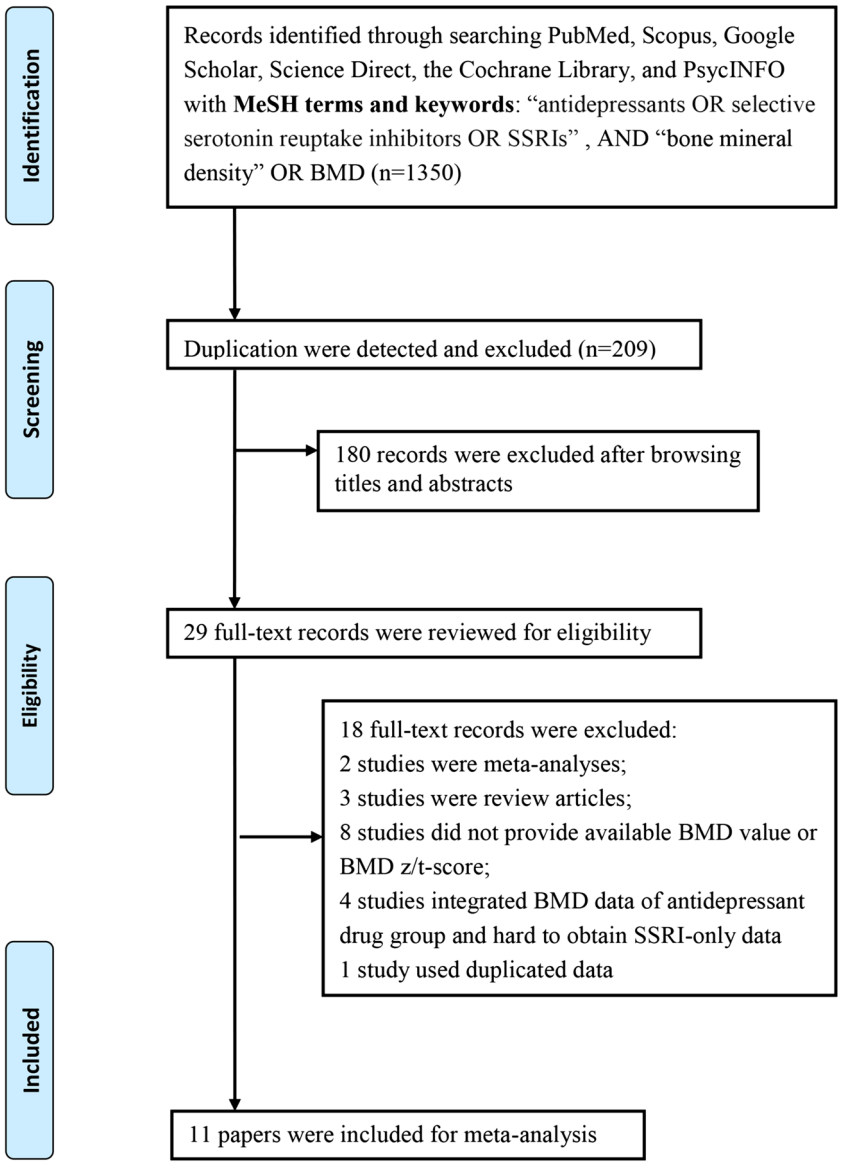

Fig. 1 Flowchart of study selection

Table 1 Study characteristics of included 11 researches

Author	Year	Country	Study design	Cohorts	*N* (m/f)	BMI	Age	Outcomes	Bone site
Saraykar et al.	2017 [10]	USA	Cross-sectional	SSRI-use Non-SSRI use	22 (0/22) 118 (0/118)	25.33 26.18	78.09 77.36	BMD, BMD T-score	Lumbar spine, femoral neck
Rauma et al.	2016 [33]	Australia	Cohort	SSRI-use Non-SSRI use	118 (0/118) 1669 (0/1669)	28.1 27.7	63.4 63.7	BMD	Femoral neck
Feuer et al.	2015 [28]	USA	Cross-sectional	SSRI-use Non-SSRI use	62 (20/42) 4232 (2265/1967)	23.45 23.97	16.06 15.65	BMD	Lumbar spine, femoral neck, total femur
Ak	2015 [30]	Turkey	Cross-sectional	SSRI-use Non-SSRI use	60 (0/60) 40 (0/40)	27.4 28.8	56.0 56.5	BMD T-score, BMD Z-score	Lumbar spine, femoral neck, total femur
Couturier et al.	2013 [27]	Canada	Cross-sectional	SSRI-use Non-SSRI use	31 (0/31) 31 (0/31)	18.4 18.3	16.2 16.0	BMD Z-score	Lumbar spine
Diem et al.	2013 [29]	USA	Cohort	SSRI-use Non-SSRI use	311 (0/311) 1590 (0/1590)	– –	49.6 49.7	BMD	Lumbar spine, femoral neck, total hip
Diem et al.	2011 [31]	USA	Cohort	Non-SSRI use SSRI-use	91 (0/91) 7626 (0/7626)	– –	77.25 77.01	BMD	Total hip
Misra et al.	2010 [32]	USA	Cross-sectional	SSRI-use Non-SSRI use	60 (0/60) 95 (0/95)	17.38 16.98	17.5 16.6	BMD Z-score	Lumbar spine, femoral neck, total hip
Richards et al.	2007 [8]	Canada	Cohort	SSRI-use Non-SSRI use	137 (114/23) 4871 (3462/1409)	28.2 27.1	65.1 65.7	BMD	Lumbar spine, total hip
Williams	2008 [34]	Australia	Cross-sectional	SSRI-use Non-SSRI use	26 (0/26) 102 (0/102)	29.9 27.7	57.5 51.0	BMD	Lumbar spine, femoral neck
Haney et al.	2007 [7]	USA	Cross-sectional	SSRI-use Non-SSRI use	137 (137/0) 5708 (5708/0)	28.3 27.4	73.2 73.6	BMD	Lumbar spine, femoral neck, total hip

BMD bone mineral density, *SSRI* selective serotonin reuptake inhibitor

Study selection strategy

Three authors independently screened and selected eligible studies for analysis; the procedure is shown in Fig. 1. Cross-sectional, case-control, and cohort studies examining the effects of SSRIs use on BMD were considered for our meta-analysis. Furthermore, SSRI users were required to have confirmed a history of exposure to SSRIs up to the point of their BMD measurement. SSRI non-users were subjects not exposed to SSRIs.

Data extraction and outcome measures

Three authors independently extracted the data from all of the included studies to minimize extraction errors. Any discrepancies were checked and resolved by consensus according to the included original article. If necessary, a fourth reviewer was consulted to ensure the accuracy of the extracted data. BMD measurements were expressed in g cm^{-2} and included the BMD T-score or Z-score. Other parameters such as the first author, publication year, country of origin, number of patients, diagnosis, BMD measuring regions, and mean age were also reported herein.

Statistical methods

Statistical analyses were performed using Cochrane Review Manager (Rev. Man. 5.1.1). BMD measurements were assessed using standardized mean differences (SMDs) and 95% confidence intervals (CIs) for each study. For the subgroup analyses, the studies were compared in terms of their design, mean subject age, and sex. Two-tailed p values of < 0.05 were considered statistically significant. A Q-statistic test based on chi-square was used to detect heterogeneity among the studies. A random-effects model was assumed that the true treatment effects would vary between the included studies.

Study quality assessment

The Newcastle-Ottawa quality assessment scale was used to assess the quality of the included studies, as recommended by Cochrane. Three areas were evaluated: selection, comparability, and exposure. The maximum total score was nine; studies with a score ≥ 5 were considered of sufficient quality using robust methods.

Table 2 Study quality of included studies based on the Newcastle-Ottawa scale

Study	Selection				Comparability	Outcome		Scores
	Representativeness of the exposed cohorts	Selection of the non-exposed cohorts	Ascertainment of exposure	Demonstrate that outcome of interest was not present at start of study	Comparability of controls on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts?	
Saraykar et al. 2017 [10]	☆	☆	☆	☆	☆☆	☆	–	–	7
Rauma et al. 2016 [33]	☆	☆	☆	☆	☆☆	☆	☆	–	8
Feuer et al. 2015 [28]	☆	☆	☆	☆	☆☆	☆	–	–	7
Ak 2015 [30]	☆	–	☆	☆	☆	☆	–	–	6
Couturier et al. 2013 [27]	☆	☆	☆	–	☆☆	☆	–	–	7
Diem et al. 2013 [29]	☆	☆	☆	☆	☆☆	☆	–	–	7
Diem et al. 2011 [31]	☆	☆	☆	☆	☆☆	☆	–	–	7
Misra et al. 2010 [32]	☆	☆	☆	☆	☆☆	☆	–	–	7
Richards et al. 2007 [8]	☆	☆	☆	☆	☆☆	☆	☆	–	8
Williams 2008 [34]	☆	☆	☆	☆	☆☆	☆	–	–	7
Haney et al. 2007 [7]	☆	–	☆	☆	☆	☆	–	–	6

Sensitivity analysis and publication bias

Sensitivity analyses were conducted using the leave-one-out method to assess the extent by which each individual study influenced the results of the overall analysis. Publication bias, the tendency of small studies to report large effect sizes, was assessed by Egger's funnel plots in STATA 12.0 (StataCorp, Texas, USA).

Results

A total of 1350 studies were initially identified as potentially relevant. Following a rigorous screening, 209 studies were kept after detecting duplication, of which 180 were removed after comparing the titles and abstracts. Of the remaining 29 articles, 18 studies were excluded for the following reasons: (i) Two studies were meta-analyses [4, 5]; (ii) three studies were review articles [2, 3, 15]; (iii) eight studies did not provide available BMD values or BMD Z/T-scores [9, 16–22]; (iv) four studies reported integrated BMD data of the antidepressant drug group where it was hard to obtain SSRIs-only data for [23–26]; and (v) one study used previously published data [6]. Eleven studies [7, 8, 10, 27–34] were ultimately included in our meta-analysis, of which the characteristics are displayed in Table 1. Of the 11 studies, seven reported BMD values, three reported the BMD Z-scores, and only two reported the BMD T-score at the different bone sections (lumbar spine, femoral neck, total femur, and total hip). Given the little data we had on T-scores, the meta-analysis predominantly focused on the comparison of BMD value and BMD Z-score between SSRI users and non-SSRI users. The BMD data, obtained from each of the studies and used for the meta-analysis, is summarized in Supplementary Table S2.

Quality of evidence

The Newcastle-Ottawa scores of the 11 studies ranged between six and eight (Table 2). These scores were indicative of a reasonably good overall methodological quality and that there were no studies without a response.

Meta-analyses of included studies

Lumbar spine

Of the 11 studies included, six and three studies reported the respective BMD values and BMD Z-scores at the lumbar spine for SSRI and non-SSRI users. Figure 2a shows that SSRI users had a lower BMD than non-SSRI users (SMD − 0.40; 95% CI − 0.79 to 0.00; $p = 0.05$). The mean difference of the spine Z-score was less than 0 with an SMD of − 0.28

(95% CI − 0.50 to − 0.05; $p = 0.02$; Fig. 2b) and was significantly different between SSRI and non-SSRI users. Significant heterogeneity was found when comparing spine BMD values ($I^2 = 95\%$; $\text{Tau}^2 = 0.22$; $p < 0.00001$), but not for the spine BMD Z-scores ($I^2 = 0\%$; $\text{Tau}^2 = 0.00$; $p = 0.38$).

Femoral neck

Femoral neck BMD values were obtained from six studies of which the meta-analysis showed no adverse effects for SSRIs (SMD − 2.73; 95% CI − 6.53 to 1.07; $p = 0.16$; Fig. 3). Significantly high heterogeneity was found when comparing femoral neck BMD values ($I^2 = 100\%$; $\text{Tau}^2 = 22.50$; $p < 0.00001$).

Total hip

Three studies evaluated the effects of SSRI use on BMD values of the total hip. According to the meta-analysis, total hip BMD values of SSRI users and non-SSRI users were not significantly different (SMD, -3.50; 95% CI, -8.17 to 1.16; $p = 0.14$; Fig. 4). Significant heterogeneity was found when comparing total hip BMD values ($I^2 = 100\%$; $\text{Tau}^2 = 22.67$; $p < 0.00001$).

Subgroup analysis of BMD

To analyze the impact of demographic heterogeneity and find the source of high heterogeneity between the studies, all included studies were also subject to age, sex, and study design subgroup analysis (Table 3).

Study design

Of the 11 included studies, seven ($n_{\text{meta}} = 4$) were cross-sectional studies and four ($n_{\text{meta}} = 3$) were cohorts-based studies. The meta-subgroup analysis of the cross-sectional studies identified a significant increase in bone loss of the lumbar spine after SSRIs were used (SMD − 0.62; 95% CI − 0.99 to − 0.26; $p = 0.0008$), but not of the femoral neck and total hip. No significant differences in BMD values were observed for the lumbar spine, femoral neck, and total hip regions in the cohort studies.

Sex

Four studies tested BMD values in women. No significant differences between female SSRI users and non-users were observed when comparing BMD values at all regions. There was not enough data to perform a similar analysis for the male patients.

Age

Based on the age of the patient, the following subgroups were used: old age (> 55 years), adult age (18–55 years), and adolescence (< 18 years). Seven studies ($n_{\text{meta}} = 5$) used subjects with a mean age of > 55 years. For one study, all of the participants were of adult age. The mean age of each of the remaining three studies was < 18 years. The age subgroup analysis showed that the lower bone mass was strongly related to SSRI use in the older population at the lumbar spine (SMD − 0.76; 95% CI − 1.30 to − 0.21; $p = 0.007$), but not at the femoral neck and total hip. There was not enough data to perform the same analysis for adults and adolescents.

Sensitivity analysis and publication bias

Sensitivity analyses were conducted using the leave-one-out method to assess the degree by which each individual study influenced the results of the overall analysis. It was concluded that no single study influenced the pooled SMDs. Furthermore,

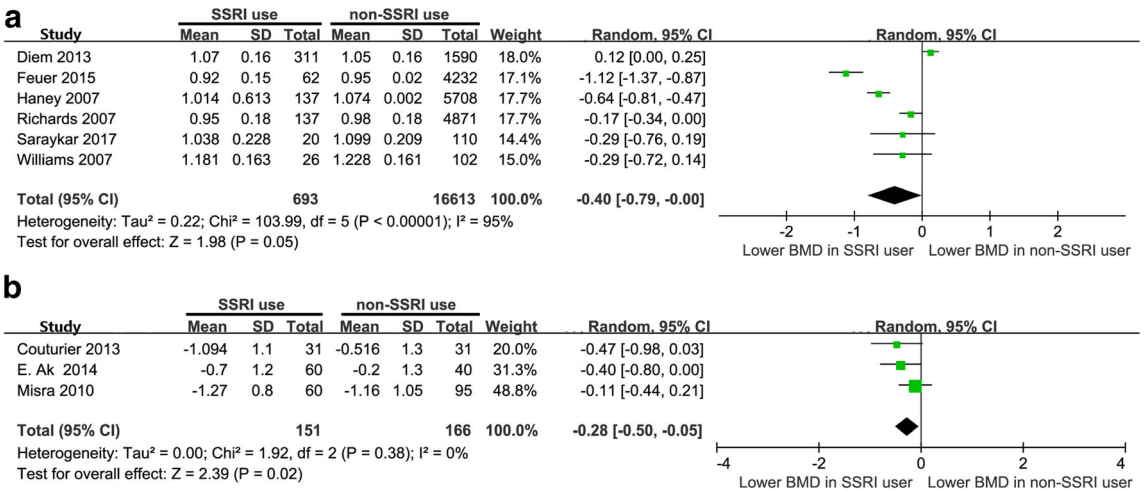

Fig. 2 Meta-analysis of BMD at lumbar spine **a** BMD value and **b** BMD *Z*-score between SSRIs users and non-SSRIs users

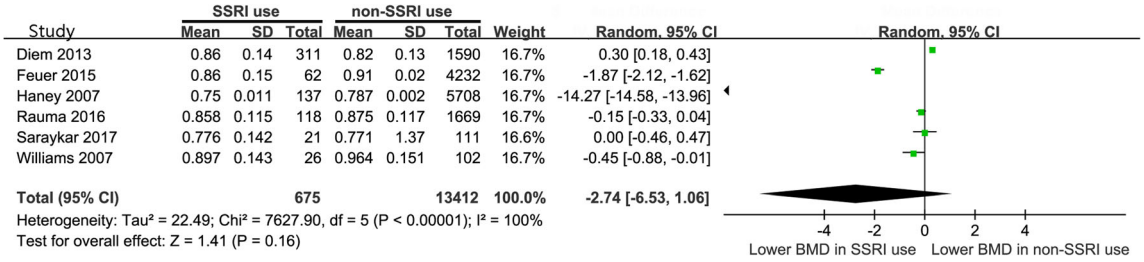

Fig. 3 Meta-analysis of BMD value at femoral neck BMD status between SSRIs users and non-SSRIs users

no strong statistical evidence for publication bias was observed for all the meta-analysis based on the Egger's test results (all $p > 0.05$).

Discussion

To the best of our knowledge, there is currently no consensus within the research community on the relationship between bone mass loss and the use of SSRIs. Our study is the first meta-analysis to investigate the effects of SSRI medication on BMD. These analyses have demonstrated that SSRI usage is associated with a significantly lower BMD of the lumbar spine but not of the total hip and femoral neck region, as compared to non-SSRI use. Our age subgroup analysis confirmed that particularly older people treated with SSRIs had a lumbar spine bone mass deficiency. In brief, these findings suggest that subjects taking SSRIs, especially the elderly, might have a significant decrease in bone mass at the lumbar spine.

Osteoporosis is a chronic skeletal disease and a decrease in BMD has become a strong predictor of osteoporosis. During recent years, there have been discussions about the pathogenesis of osteoporosis and bone loss by SSRIs. SSRIs act as antidepressants by antagonizing the serotonin transporter (5-HTT) and block the reuptake of serotonin (5-HT), and researchers are now also aware of a functional 5-HT system in the bones [2, 3, 35, 36]. Indeed, in vitro and in vivo studies have confirmed that 5-HTT activity is required for osteoclast differentiation [37–39]. Hence, one possible reason for osteoporosis caused by SSRI use is that SSRIs might block the 5-HTT in the bone and consequently also reduce osteoclast differentiation. Indeed, a recent animal study discovered that a long-term treatment with fluoxetine (Flx), one of the most frequently prescribed SSRIs, could cause bone loss in mice and directly impair osteoclast differentiation and function through a brain-serotonin-dependent rise in the sympathetic output mechanism [40].

Further, the effects of individual factors (age and sex) on BMD during SSRIs treatment were analyzed by subgroup meta-analyses. According to the age-related subgroup analyses, SSRI-use-related lower BMD was greater in older subjects at the lumbar spine. This result is consistent with some reports where SSRI use has been associated with lower bone density in older men and women [7, 31]. As an example, a cross-sectional analysis conducted on 5995 men aged about 65 years showed a 5.9% lower lumbar spine BMD for SSRI users compared with those not using antidepressants [26]. Nevertheless, some studies have opposed these observations. Saraykar et al., for example, did not observe any significant differences in BMD of elderly women but observed a tendency for a reduction in BMD at the spine level in SSRI users [10]. It is, therefore, possible that this tendency was in all likelihood associated with an increased risk of osteoporosis with age, even in the absence of further bone loss [10]. Our observations are believed to encourage clinicians to consider SSRI prescriptions more carefully for the older patients given the increased risk of bone mineral loss.

Interestingly, the data presented herein showed no difference in spine, hip, and femoral neck BMD values for women using SSRIs, as compared to non-users. SSRIs have, however, previously been associated with an increased bone mass loss in female patients. While most of the SSRI-use-related bone loss was observed in postmenopausal elderly women(> 57 years) [30, 31, 33], contradictory observations have been made in studies investigating SSRI use and BMD in middle-

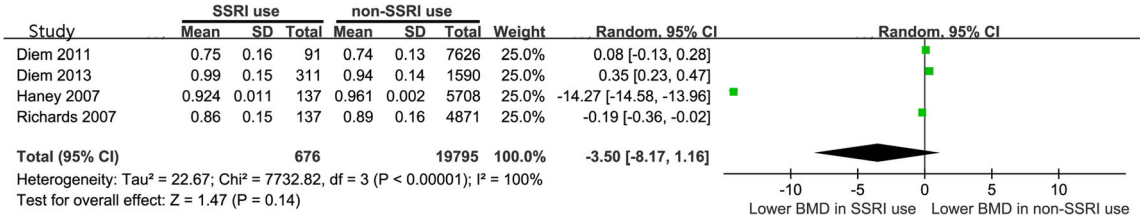

Fig. 4 Meta-analysis of BMD value at total hip between SSRIs users and non-SSRIs users

Table 3 Subgroup analysis of BMD alteration

Study included	Lumbar BMD		Femoral neck BMD		Total hip BMD	
	SMD (95% CI)	*p*	SMD (95% CI)	*p*	SMD (95% CI)	*p*
Age						
Old age	− 0.36 (− 0.66, − 0.06)	0.02	− 3.71 (− 11.07, 3.64)	0.32	− 4.79 (− 12.22, 2.64)	0.21
Sex						
Women	− 0.09 (− 0.41, 0.24)	0.60	− 0.04 (− 0.38, 0.30)	0.81	0.08 (− 0.26, 0.43)	0.63
Study design						
Cross-sectional	− 0.62 (− 0.99, − 0.26)	0.0008	− 4.15 (− 11.18, 2.89)	0.25	–	–
Cohort	− 0.01 (− 0.30, 0.27)	0.92	0.08 (− 0.35, 0.52)	0.71	0.08 (− 0.26, 0.43)	0.63

aged or young women [9, 27–29]. This is likely due to the higher number of risk factors for osteoporosis, besides SSRI use, in older postmenopausal women, such as lower estrogen levels and calcium loss [41]. The mean age of the female patients enrolled into the studies in our subgroup analysis ranged between 49.6 and 78.1 years. Since they included both pre- and postmenopausal ages, the lack of a change in BMD in response to SSRIs use was perhaps not surprising. It is concluded that the relationship between SSRIs use and BMD in female patients merits further investigation.

Further, the effects of SSRIs on BMD were found to be treatment-time-dependent. An animal study by Ortuño et al. found that a long-term (6 weeks) treatment with Flx induced a bone mass loss in mice, whereas when they were treated for a shorter time, they built up a higher bone volume (measured as bone volume over tissue volume) [41]. In human studies, Feuer et al. reported that only when adolescents received more than 6 months of SSRI therapy, the total femur and femoral neck BMD values became significantly reduced [28]. Furthermore, subjects who had taken SSRIs more than 6 months had significantly lower spine and femoral neck Z-scores than subjects who had been on an SSRI for less than 6 months [32]. Given the small number of studies that examined the effect of SSRI treatment time on BMD, we could, unfortunately, not perform a subgroup analysis. The effect of SSRI treatment time on BMD, thus, needs to be further addressed with clinical SSRI trials.

There were several limitations to our meta-analyses. Firstly, the sample sizes and the number of included studies were limited. BMD T- and Z-scores were calculated as bone markers in the studies. To, for example, analyze the relationship between SSRI use and the BMD of the spine and femoral neck, only the Z-scores of three studies could be used as there was not enough data to perform a T-score analysis. Secondly, also the sample size and number of the clinical and demographic subgroups were small. This may have limited the statistical power to detect the effects of individual factors on BMD and make a comprehensive analysis of BMD and SSRI use for a particular subgroup. Thirdly, only English-written studies were included in the meta-analysis.

Conclusion

The meta-analyses presented herein have indicated that the use of SSRIs is associated with a lower spine BMD, particularly for elderly patients. The effect of SSRIs use on hip and femoral neck BMD was not significant but still warrants further investigation. Future studies with larger sample sizes are necessary to fully understand the impact of individual factors, like sex, bone region, age, and treatment time, on the BMD of SSRI users. As such, this research will improve the clinical use of SSRIs.

Acknowledgements The work was supported by The National Key Research and Development Program of China (Grant No. 2017YFA0505700), National Natural Science Foundation of China (Grant No. 81701361), and China Postdoctoral Science Foundation funded project (Project No. 2017M612924).

Compliance with ethical standards

Conflicts of interest None.

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