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SYSTEMATIC REVIEW and META-ANALYSIS

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Effects of Statins on Bone Mineral Density and Fracture Risk

A PRISMA-compliant Systematic Review and Meta-Analysis

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Abstract: Although observational studies have identified the protective effect of statins on bone health, the effects remain controversial in randomized controlled trials (RCTs). We conducted a meta-analysis of RCTs to evaluate the effects of statins on bone mineral density (BMD) and fracture risk among adults.

We searched electronic databases of Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) and conducted a bibliography review to identify articles published until May, 2015.

Studies included in this meta-analysis should be randomized controlled trials conducted in adults, using statins in the intervention group. Information on changes in BMD or odds ratio, relative risk or hazard ratio (HR) for fracture risk with the corresponding 95% confidence interval (CI) was provided.

Two investigators independently reviewed the title or abstract, further reviewed the full-texts and extracted information on study characteristics and study outcomes. Net change estimates of BMD and pooled HR of fracture risk comparing the intervention group with the control group were estimated across trials using random-effects models.

Of the relevant 334 citations, 7 trials (including 27,900 randomized participants in total) meeting the eligibility criteria were included. Of the 7 trials, 5 were conducted to assess the association of statins use with BMD change and 2 with fracture risk. Compared with the control group, statins use was associated with significant increase in BMD of 0.03 g/cm2 (95% CI: 0.006, 0.053; $P < 0.001$; $I^2 = 99.2\%$), but null association with fracture risk, with the pooled HR of 1.00 (95% CI: 0.87, 1.15; $P = 0.396$; $I^2 = 0$). Sensitivity analyses revealed that the associations were consistent and robust.

The effect of statins use on bone health among subpopulation could not be identified due to limited number of trials.

These findings provide evidence that statins could be used to increase BMD other than decreasing fracture risk in participant with dyslipidemia. In addition, further trials with the primary outcome of bone health-related measurements in subpopulation are warranted to ensure the effect of statins use.

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Abbreviations: BMD = bone mineral density, CI = confidence interval, HR = hazard ratio, RCT = randomized clinical trial.

INTRODUCTION

Osteoporosis, which is defined based on bone mineral density (BMD), is a skeletal disorder characterized by compromised bone strength. It is induced by an imbalance between osteoblastic bone formation and osteoclastic bone resorption.[1] Osteoporosis, which is a process operative in almost all individuals past middle age, will greatly increase the risk of fractures in both men and women.[2,3] Osteoporosis or osteoporotic fracture is also the great disease burden in an aging population due to their association with increased mortality and substantial long-term loss of independence.[4] It has been demonstrated that osteoporosis causes more disability-adjusted life years loss than any type of cancer other than lung cancer.[5] Therefore, a cost-effectiveness of treatment on osteoporosis should be considered.

Cardiovascular diseases are also age-related disease and several epidemiologic studies have identified that they may share common biological pathways.[6,7] The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used for primary prevention of cardiovascular disease.[2,8,9] Previous studies have revealed the positive biologic effects of statins on bone, including simulating bone formation[10] and sharing the same pathway as nitrogen-containing bisphosphonate drugs.[11] In addition, the pleiotropic effect has attracted particular attention of statins on bone metabolism. Therefore, statins might be clinically significant in the prevention and treatment of osteoporosis. Furthermore, some in vitro and in vivo experiments have investigated the mechanism of statins influencing bone metabolism.[12,13] The positive effects of statins on osteoblast differentiation and bone formation[14–16] have been identified to be related with the inhibition of the isoprenoid biosynthetic pathway. Therefore, the depletion of GGPP, especially FPP, may be necessary for statin-induced bone formation.[17] Moreover, simvastatin was proved to be involved in the inhibition of receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast differentiation by preventing the production of reactive oxygen species (ROS).[18]

Several observational studies have found the association of statins use with improved BMD,[19–21] as well as reduced risk of fractures.[22–26] However, some other observational studies and post hoc analysis of randomized clinical trials (RCTs) did not find consistent results.[27–30] Due to controversial results and cumulative reports of RCTs on the association of statins use with osteoporosis-related measurement, we performed the meta-analysis to explore the association of statins use with BMD and fracture risk and provide evidence for the treatment of osteoporosis or improvement of bone health.

METHODS

We conducted the literature search, study selection, data extraction, and results synthesis following the Preferred

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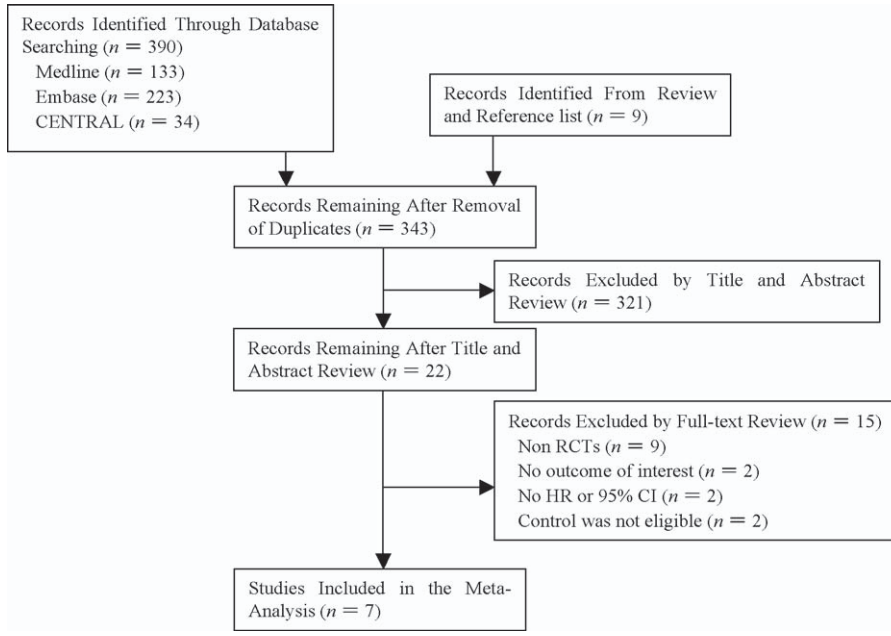

FIGURE 1. Selection of eligible randomized controlled trials examining the association of statins use on bone health.

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[31] The PRISMA checklist is shown in the appendix.

Search Strategy and Study Selection

A literature search was conducted in electronic databases, including PubMed (1966 to May, 2015), Embase (1947 to May, 2015), and the Cochrane Central Register of Controlled Trials (CENTRAL) (issue April, 2015) for articles examining the association of statins use with BMD and bone fracture without language restriction. Detailed search strategies for 3 databases are shown in the Supplementary materials, http://links.lww.com/MD/A955. Briefly, the following search terms were included in our literature search strategy: ''statin,'' ''bone mineral density,'' ''bone fracture,'' and ''osteoporosis.'' In addition, reference lists from all eligible articles, reviews, systematic reviews, and meta-analyses were also searched to identify relevant articles.

After removing duplicates, 2 investigators reviewed the articles independently and discrepancies regarding study eligibility were discussed with another investigator. The inclusion criteria of eligible articles are as follows: adults participants aged 18 years or older; statins were used as the intervention or at least part of the intervention; changes in BMD and corresponding variance or confidence interval (CI) or information which could be used to calculate above indicator were provided, or odds ratio, relative risk, or hazard ratio (HR) with their corresponding 95% CI for fracture risk was provided; and randomization was used to conduct group allocation. Articles with latest information were included, if several articles were generated from the same study. Ethical approval was not necessary for the current meta-analysis.

Data Extraction and Quality Assessment

Two investigators also conducted data extraction and quality assessment independently and further discussed with another investigator for discrepancies. The following data were extracted: title of articles, authors, year of publication, name of the trial, study design (primary outcome of study, randomization, and blinding), participants' characteristics, intervention drug and corresponding dose, information on BMD or bone fracture and outcome measurement, and statistical analysis methods. The Jadad score was used to assess the quality of included studies. The scoring system included randomization, blinding, description of drop-out and withdrawal, and evaluation of randomization and blinding.[32]

Data Synthesis and Statistical Analysis

For each RCT, if net effect size of BMD was not provided, it was calculated as the change in BMD-related measures (from the baseline to the end of intervention) in the intervention group minus the change in BMD in the control group: $(X_{TT} - X_{TB}) - (X_{CT} - X_{CB})$. For studies without variance data, we calculated variance from CIs or test statistics. If the variance for change between baseline and end of intervention (σ_Δ) was not reported, it was calculated from the following equation[33]: $\sigma_\Delta = \sigma^2_{pre} + \sigma^2_{post} - 2\rho\sigma_{pre}\sigma_{post}$, where σ_{pre} corresponds to the variance at baseline, σ_{post} corresponds to the variance at the end of intervention, and an imputed ρ of 0.5 is the correlation coefficient between measurements at baseline and the end of intervention.[34]

We used random-effect models to estimate BMD net change or pooled HR of fracture risk across trials. Heterogeneity across studies was assessed by the Cochrane Q and the I^2 statistics.[35] We conducted influence analysis by removing each trial sequentially to determine its influence magnitude on the overall estimates. To further assess the robustness of our results, we performed several sensitivity analyses by only including trials with Jadad score ≥ 3, using BMD or bone fracture as the primary outcome, and trials using intention-to-treat (ITT) analysis.

Funnel plots were used to inspect publication bias visually and the Egger test was used to assess the asymmetry of the

funnel plot.[36] In addition, we used ''trim-and-fill'' method to examine the influence of publication bias on the overall findings.[37] A two-sided P value less than 0.05 was considered statistically significant and all the analyses were performed with Stata 12.0 (StataCrop LP, College Station, TX).

RESULTS

Of the retrieved 334 relevant citations, 7 trials of 27,900 randomized participants were included in the current meta-analysis (Figure 1). Characteristics of the 7 trials are shown in Table 1. The trials, published between 2001 and 2014, varied from 64 to 17,802 participants. Study durations ranged from 12 months to 6 years. The studies were conducted in the US, Denmark, Australia, and countries from East Asia, as well as multiple centers. Of the 7 trials, 5 were conducted to assess the association of statins use with BMD change[38–42] and 2 with fracture risk.[43,44] A total of 4 trials included participants with osteoporosis or osteopenia. Five trials had the primary outcome of BMD change and the other 2 trials assessed fracture risk as the secondary outcome. Four trials applied ITT analysis and 5 were categorized as high quality (Jadad score ≥ 3).[32] Participants in intervention groups received statins treatment with various dosages daily, including atorvastatin, simvastatin, and rosuvastatin; and participants in control groups received placebo, diet or lifestyle guidance, or nonstatin treatment.

Baseline characteristics of participants in the intervention group and control group were shown Table 2. In both groups, the average age ranged from 58.6 to 80.8 years old with the proportion of males participants from 0% to 100%. Among intervention groups, average BMD ranged from 0.51 to 0.93, with those from 0.58 to 0.91 in their corresponding control groups.

Among 5 trials with the outcome of BMD change, 4 reported comparisons of absolute BMD change and 1 reported percentage of BMD change[38] at various time point. In the current analysis, only information at the end of the study was used (Table 3). In addition, most of the studies reported BMD change of lumbar spine, and Chuengsamarn et al[40] reported that of distal radius. Among the 4 trials reported absolute BMD change, net change ranged from -0.002 to $0.045\,g/cm^2$ in intervention groups and from -0.02 to $0.006\,g/cm^2$ in control groups. As shown in Table 4, 2 trials assessed the association of statins use and fracture risk.

Pooled estimate of the net change of BMD is presented in Figure 2 and pooled HR of fracture risk is presented in Figure 3, respectively. On average, compared with the control group, statins use resulted in significant increases in BMD, with net BMD change of $0.030\,g/cm^2$ (95% CI: 0.006, 0.053; $P < 0.001$; $I^2 = 99.2\%$= but null association with fracture risk, with the pooled HR of 1.00 (95% CI: 0.87, 1.15; $P = 0.396$; $I^2 = 0$). In order to examine the robustness of our findings, we also conducted sensitivity analyses based on restricting BMD location and study population. For example, when we excluded the study that only included males,[39] the pooled net change of BMD was 0.040 (-0.006, 0.085) g/cm^2 and when we further pooled the results of studies conducted only in females,[41,42] the net change was 0.030 (-0.027, 0.088) g/cm^2. The results did not substantially differ from the overall findings. In addition, the influence analysis did not identify any trials' removal would significantly alter the findings. Although the somewhat asymmetrical funnel plot was shown regarding to net BMD change estimates (Figure 4), the Begg test did not indicate significant publication bias ($P = 0.174$).

TABLE 1. Characteristics of 7 Trials Examining the Effect of Statin Use on Net Change in Bone Related Measures Among Adults

First Author, Year	No. of Participants	Country	Study Population	Follow-Up Duration	Blinding	Outcome	Primary Outcome	Intervention	Control	Blood Lipid Level	Measurement	ITT Analysis	Jadad Score
Reid, 2001	9014	Australia	Patients w/MI or UAG	6.0 years	Yes	Fracture	No	Pravastatin 40 mg	Placebo	TC: 4.0–7.0 mmol/L	–	Yes	5
Rejnmark, 2004	82	Denmark	PW w/OP	1.5 years	Yes	BMD	Yes	Simvastatin 40 mg	Placebo	TC: >4.0 mmol, LDL: >2.5 mmol	DXA	Yes	4
Bone, 2007	626	USA	PW	12 months	Yes	BMD	Yes	Atorvastatin 10/20/40/80 mg	Placebo	LDL-C: 130–190 mg/dL	DXA	Yes	4
Chuengsamarn, 2010	212	Thailand	PD w/OP	18 months	No	BMD	Yes	Simvastatin 40–80 mg	Nonstatin*	Dyslipidemia	DXA	NR	2
Zhao, 2013	100	China	PW w/OP	12 months	NR	BMD	Yes	Atorvastatin 10 mg	Diet	LDL-C: ≥190 mg/dL	DXA	No	2
Chen, 2014	64	China	Males w/OP	12 months	No	BMD	Yes	Atorvastatin 10 mg + LG	LG	Mild dyslipidemia	DXA	No	3
Peña, 2014	17,802	26 countries	PD	5 years	Yes	Fracture	No	Rosuvastatin 20 mg	Placebo	–	Radiograph, CT, bone scan, etc.	Yes	5

BMD = bone mineral density, DXA = dual-energy X-ray absorptiometry, ITT = intention-to-treat, LDL = low density lipoprotein, LG = lifestyle guidance, MI = myocardial infraction, OP = osteoporosis or osteopenia, PD = patients with dyslipidemia, PW = postmenopausal women, TC = total cholestoral, UAG = ustable angina.
*Gemfibrozil or fibrate.

TABLE 2. Baseline Information of Study Participants

First Author, Year	Location	Intervention Group N	Age, Years Mean (SD)	Female (n/%)	BMI, kg/m^2	BMD, g/cm^2 or Fracture	Control Group N	Age, years Mean (SD)	Female (n/%)	BMI, kg/m^2	BMD, g/cm^2 or Fracture
Reid, 2001[*]	Multiple sites[†]	4512	62	756/17	78.4 (12.8)	Fracture	4502	62	760/17	78.4 (13.0)	Fracture
Rejnmark, 2004	Lumbar spine	41	64 (61–68)[‡]	41/100	24.8 (0.6)	0.821 (0.083)	41	63 (60–67)[‡]	41/100	26.5 (0.5)	0.820 (0.102)
Bone, 2007[*,§]	Lumbar spine	118	58.6 (6.5)	118/100	72.7 (15.0)	0.92 (0.084)	119	58.8 (7.6)	119/100	73.8 (15.3)	0.91 (0.087)
		121	59.2 (6.5)	121/100	72.6 (13.5)	0.92 (0.079)					
		124	59.4 (7.0)	124/100	74.6 (15.0)	0.93 (0.083)					
		122	57.8 (6.7)	122/100	73.0 (12.6)	0.91 (0.086)					
Chuengsamarn, 2010	Distal radius	106	62.15 (8.8)	74/69.8	26.8 (4.1)	0.51 (0.7)	106	61.65 (8.45)	75/70.8	26.9 (4.5)	0.58 (0.11)
Zhao, 2013	Lumbar spine	50	55.8 (4.2)	50/100	26.3 (2.3)	0.70 (0.13)	50	55.2 (3.2)	50/100	26.5 (2.8)	0.70 (0.13)
Chen, 2014	Lumbar spine	32	80.8 (6.8)	0/0	23.1 (1.4)	0.821 (0.022)	32	79.3 (6.5)	0/0	23.2 (1.8)	0.819 (0.021)
Peña, 2014	Any	8901	66 (60–71)[‡]	3426/38.5	<25.0: 22.9% 25.0–29.9: 39.5% ≥30.0: 37.6%	Fracture	8901	66 (60–71)[‡]	3375/37.9	<25.0: 22.9% 25.0–29.9: 39.5% ≥30.0: 37.6%	Fracture

BMD = bone mineral density, BMI = body mass index, SD = standard deviation.
[*]Only body weight other than BMI was presented in the original article.
[†]Skull and face, wrist, other upper limb, hip, other lower limb, vertebra, neck, and trunk.
[‡]Median (IQR).
[§]Four intervention groups were recorded.
[#]Hip region, forearm, and whole body were also reported.

TABLE 3. Average Change in BMD

First Author, Year	Intervention Group Mean (95% CI)	Control Group Mean (95% CI)	Duration
Rejnmark, 2004	0.006 (0.008)	0.006 (0.011)	12 months
	−0.002 (0.008)	−0.003 (0.011)	18 months
Bone, 2007*	−0.26 (−0.98, 0.45)	0.16 (−0.51, 0.84)	12 months
	−0.38 (−1.05, 0.30)		
	−0.44 (−1.12, 0.23)		
	−0.03 (−0.75, 0.69)		
Chuengsamarn, 2010	0.045 (0.057)	−0.014 (0.046)	18 months
Zhao, 2013	0.02 (0.017)	−0.01 (0.017)	6 months
	0.04 (0.016)	−0.02 (0.018)	12 months
Chen, 2014	0.001 (0.0004)	0.002 (0.0004)	6 months
	0.003 (0.0004)	0.002 (0.0004)	12 months

CI = confidence interval, BMD = bone mineral density.
*Percent change and 4 intervention group were recorded.

DISCUSSION

The current meta-analysis pooled results from 7 RCTs with almost 30,000 participants. We have identified that statins use significantly increased BMD by approximately 0.030 g/cm^2 and was not associated with higher fracture risk, with robust findings across sensitivity analyses. Our findings indicate that statins use could be a potential prevention or treatment for bone health.

Osteoporosis is responsible for 2 million broken bones and $19 billion in related costs every year.[45] It is estimated that osteoporosis will be responsible for approximately 3 million fractures and $25.3 billion in costs each year by 2025 (http://www.nof.org/article/7). As the most important predictor of osteoporotic fractures, the decrease in BMD significantly increased the fracture risk.[46] A previous systematic review suggested that statins use is effective for increasing bone turnover.[47] The current meta-analysis provides important information on quantitative benefits of statins use on BMD from the accumulation evidence of RCTs. Additional study strengths include the inclusion of only RCTs, thereby reducing the likelihood that the observed association statins use with BMD and fracture risk related traits could be explained entirely by bias and confounding. In addition, only 2 of 4 trials of BMD were individually statistically significant, highlighting the benefits of meta-analysis to identify important effect sizes with increased statistical power. In addition, sensitivity analysis did not substantially change the findings.

TABLE 4. Overview of Multivariable-Adjusted Associations of Statin Use With Fracture

First Author, Year	Subgroup	Number of Outcome: Intervention Group	Number of Outcome: Control Group	Adjusted HR	Adjusted Variables
Reid, 2001	Any	175	183	0.94 (0.77, 1.16)	Not mentioned
	Yes	107	101	1.05 (0.80, 1.37)	Not mentioned
	No	84	88	0.94 (0.70, 1.27)	Not mentioned
Peña, 2014	All	221	210	1.06 (0.88,1.28)	Age (continuous), sex, BP status, randomized treatment assignment, current tobacco use, BMI, exercise, race, alcohol use, baseline hemoglobin A1c level, and history of previous fracture.
	Men	99	105	0.97 (0.74, 1.28)	
	Women	122	105	1.16 (0.89, 1.50)	
	Hip	23	14	1.67 (0.85–3.23)	
	Vertebral	22	18	1.23 (0.66–2.30)	
	Upper extremity	72	65	1.12 (0.80–1.56)	
	Lower extremity	71	64	1.13 (0.80–1.58)	
	Skull, face, finger, toe	29	25	1.17 (0.69–2.00)	
	Other	25	35	0.73 (0.43–1.21)	

BMI = body mass index, BP = blood pressure, HR = hazard ratio.

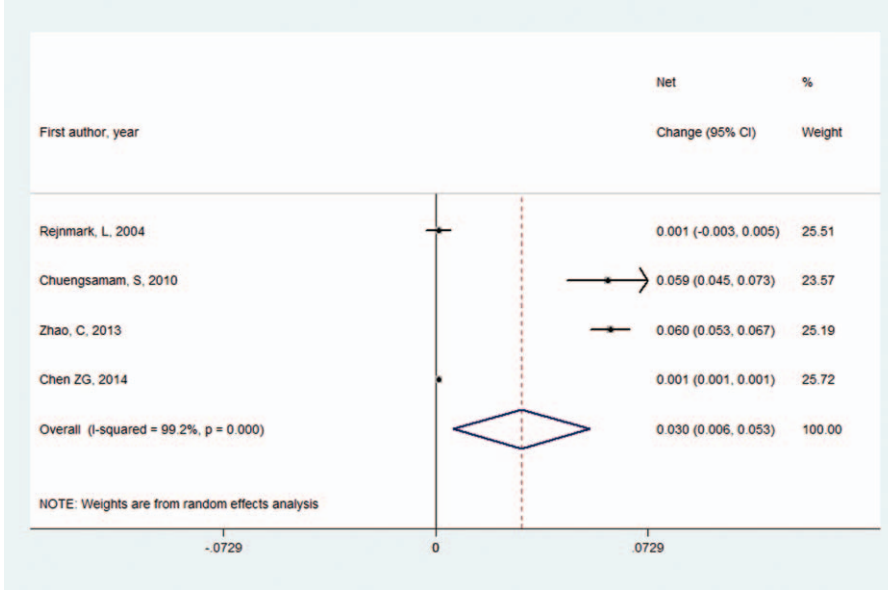

FIGURE 2. Average net change in bone mineral density in randomized controlled trials comparing statins use with control group. The size of each square is proportional to the percent weight that each study contributed in the pooled estimate. The pooled effect size is indicated by the diamond. Bars, 95% confidence interval (CI).

The ''statin for osteoporosis'' hypothesis has drawn great attention and many studies have revealed the mechanism on the protective effect of statins use on the prevention of osteoporosis.[48] A very complex and still incomplete picture showed that statins could increase osteogenesis or suppress osteoblast apoptosis.[49] In addition, other pathways, including reduction of oxidative stress and restoration of NO formation, and antiinflammatory effects of statins also contribute to the protection against osteoporosis. Although BMD significantly increased after statins use, the fracture risk was not reduced otherwise. The potential explanation includes that small changes in BMD might not translate to changes on bone surfaces, which is critical to protect against fracture.[50] Although it might be more cost-effective when treating dyslipidemia and osteoporosis together, the current study did not identify the significant association between statins use and osteoporosis.

Still, certain limitations should be addressed and some of these limitations provided hints for further investigations. First, the number of RCTs regarding to the association of statins use with BMD and fracture risk is very small, which

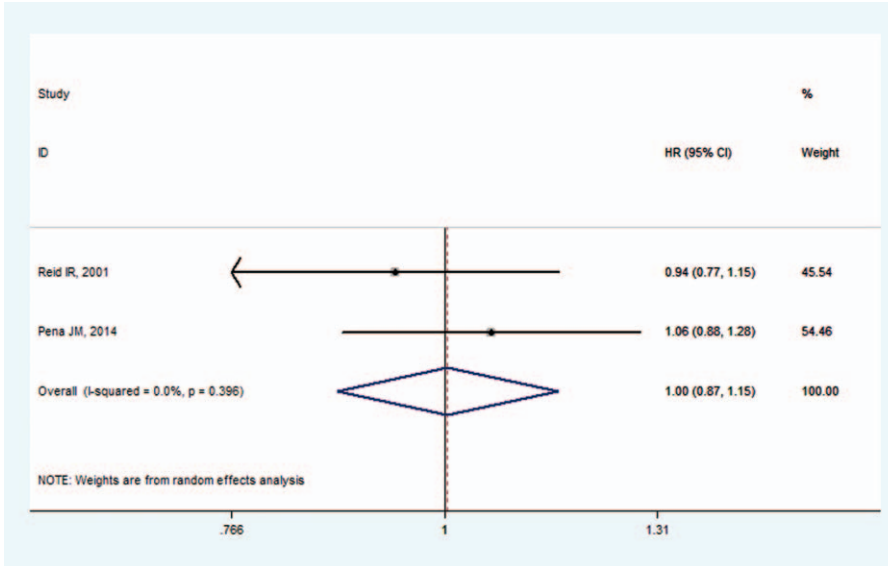

FIGURE 3. The association of statins use with bone fracture in randomized controlled trials comparing statin use with control group. The size of each square is proportional to the percent weight that each study contributed in the pooled estimate. The pooled effect size is indicated by the diamond. Bars, 95% confidence interval (CI).

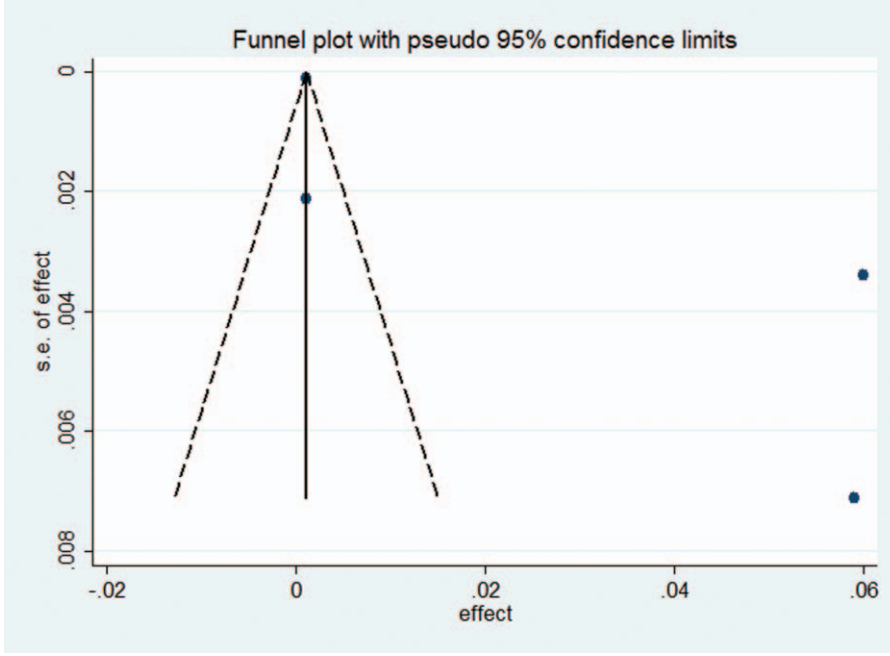

FIGURE 4. Funnel plot of the meta-analysis on the association of statins use with bone mineral density.

has limited subgroup analysis and further limited to identify subgroup population who were more susceptible to statins therapy on both dyslipidemia and osteoporosis. Therefore, more research is needed to determine whether statins intervention can present its benefits among participants with various lipid levels or different disease status, etc. Second, most of the included studies were conducted in females, which have limited the generality of the results to male patients. The prevalence of osteoporosis was more prevalent in females, about 40% of females in developed countries will experience an osteoporosis-related fracture through their lifetime, while males experiencing approximately one-third to one-half the risk of females.[51,52] In despite of this, the effect of statins use on bone health in males should not be ignored. Third, although we searched for ''gray literature,'' none of them was in accordance with our inclusion criteria. Therefore, there was some indication of possible publication bias for the BMD trait. In addition, most of trials in this meta-analysis did not use BMD as its primary outcome, which highlighted the need for relevant RCTs.

In conclusion, this meta-analysis provides evidence that statins are an effective strategy for bone health. Although these findings are encouraging, further trials to better understand the effect of statins use on BMD in certain subgroups are warranted. Research will also be needed to assess the cost-effectiveness of statins use on bone health. In aggregate, results of the current meta-analysis suggested that statins use could contribute to meaningful increments in BMD at the population level.

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