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Associations between bone mineral density and coronary artery calcification: a systematic review and meta-analysis

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Abstract

Background: The studies about the correlation between bone mineral density (BMD) and coronary arterial calcification (CAC) were still controversial. The aim of this study was to conduct a meta-analysis to evaluate the association between BMD and CAC.

Methods: We systematically searched PubMed, Embase, Google scholar and Cochrane library for observational studies. We pooled odds ratio (OR) or correlation coefficient, and 95% confidence interval (CI) of the studies. Continuous data were pooled by mean difference (MD). Sub-group analysis was applied to investigate sources of heterogeneity. Funnel plots for publication bias was also performed.

Results: Seventeen studies met the inclusion criteria. Pooled ORs for the prevalence of CAC in patients with low BMD versus patients with normal BMD was 2.11 (95% CI: 1.11 - 4.02, $P = 0.02$). The data pooled for comparing CAC score of low BMD and normal BMD patients is 33.77 (95% CI: 23.77 - 43.77, $p = 0.000$). The pooled ORs of multivariate logistic regression to predict the association were 1.00 (95% CI: 0.92 - 1.10, $p = 0.95$, age-adjusted), and 0.95 (95% CI: 0.86 - 1.05, $p = 0.33$, multivariable-adjusted). Cohort category and BMD assessment method were the main sources of heterogeneity.

Conclusions: Low BMD is associated with higher prevalence and severity of CAC, especially in postmenopausal women. But the relation is not significant after adjusting age and other confounding variables. Low BMD and CAC may be two independent processes with aging. More large-scale studies with high-quality design are still needed to increase the understanding of them.

Keywords: bone mineral density, coronary artery calcification, meta-analysis

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Introduction

Coronary artery calcification (CAC) is one of the manifestations of coronary atherosclerosis. Calcification is caused by the incomplete absorption of calcium ions after tissue damage, especially inflammation. CAC reduces vascular compliance and affects myocardial perfusion,[1] and calcified plaque further narrows the lumen of the blood vessels, leading to myocardial ischemia and serious cardiovascular events. CAC is mainly diagnosed by computed tomography coronary angiography (CTCA), the most widely used quantitative index of CAC was Agaston score (CAC score).[2] Epidemiological investigation showed that CAC is related to many factors, including gender, age, calcium metabolism and so on. Among these factors, the abnormal deposit of calcium with low bone mineral density (BMD) is becoming more and more remarkable. Osteoporosis is a systemic bone disease with decreased BMD, which increases the risk of fracture, and hip fracture is the most serious.[3] BMD is usually measured by dual-energy X-ray absorptiometry (DXA) and T score is widely used in clinical trials of osteoporosis. According to WHO criteria, osteopenia was defined as a T-score

between -1 and -2.5 SD, and osteoporosis as T-score less than -2.5 SD.[4]

The mechanism of low BMD and artery calcification share similar pathways. It has been shown that arterial calcification is an active process involving protein molecules. Leopold[5] have found that microRNAs (miRs) is a key factor in vascular calcification, it affects vascular calcification mainly by regulating gene recombination of smooth muscle cells, and another study reported the receptor activator of nuclear factor-kappaB ligand/osteoprotegrin pathway may be a link between osteoporosis and CAC.[6] Moreover, atheroma plaque calcification involves cytokines and growth factors including proinflammatory cytokines (IL-6 and TNF-α), osteoprotegerin, sclerostin, matrix GLA protein, and FGF-23, which also play a role in bone turnover.[7]

Epidemiology study showed that the incidence of CAC is age-dependent and gender-dependent with CAC occurring in more than 90% of men and 67% of women over the age of 70.[8,9] However, it's still conflicting on whether CAC and BMD are related or not. The Copenhagen General Population Study reported that BMD and CAC were inversely related in both men and postmenopausal women, supporting the hypothesis that a direct relation between bone loss and development of atherosclerosis exists irrespective of gender.[10] Xu *et al.*[11] investigated the association between BMD and CAC in postmenopausal women, suggesting that women with low BMD were at a high risk for CAC. However, the Chinese study showed that there was no direct relationship between osteoporosis and CAC in elderly men after adjusting for age and other factors.[12]

Though previous studies have explored the correlation between BMD and CAC, the results were inconsistent, and some of the studies did not exclude age and gender confounders. Thus, it is still unknown whether they are independently related or not. The aim of the study was to perform a meta-analysis to investigate the pooled results of associations between BMD and CAC and whether the correlation is different adjusted by sex, age, or bone region.

Methods

We performed a systematic review and meta-analysis of the existing literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] This study was a part of the work registered in PROSPERO (No. CRD42019124663). All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

Search strategy

We searched the following electronic databases for English literature (up to December 31 of 2020): PubMed, Embase, Google scholar and Cochrane library. The fewer key-words or corresponding Medical Subject Headings (MeSH) were used for searching to avoid article omission headings ((bone (Title/Abstract) AND density (Title/Abstract) AND calcification (Title/Abstract). Our literature search process is shown in Figure 1. We retained 51 articles after reading the titles and abstracts of 846 literatures. By reading the full text, we excluded 34 studies for the reasons: data unavailable; the content is not relevant (the association between BMD and other vascular calcification; intervention research). Finally, seventeen articles were included in the quality assessment and meta-analysis.

Selection criteria

Inclusion criteria were the following:

- observational studies concerning association between BMD and CAC;
- CAC score was calculated according to the Agaston method based on CT scanning of coronary arteries;
- BMD was measured by DXA or quantitative computed tomography (QCT), and the definition of osteopenia and osteoporosis was based on the WHO criteria: T-score based on the WHO criteria: the participants were regarded as normal (T-score $>$ - 1 SD), osteopenic (- 2.5 SD $<$ *T* $<$ - 1 SD), and osteoporotic (T-score $<$ - 2.5 SD).

Exclusion criteria were the following:

- animal studies, reviews, letters, abstracts, or case reports;
- studies on CAC patients afflicted with other diseases, such as diabetes and kidney disease;

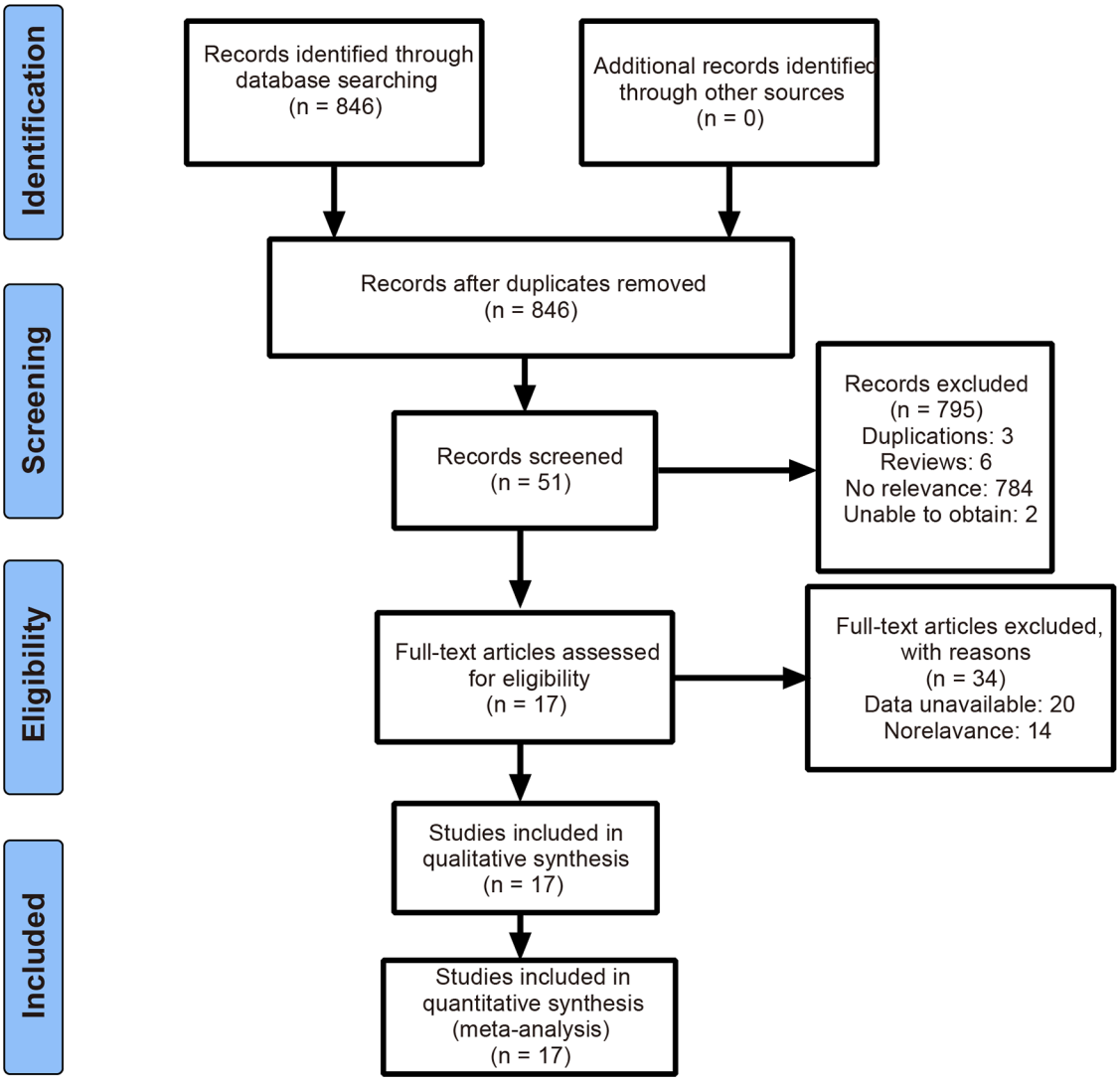

Figure 1. PRISMA flow chart for literature screening.

- studies that provide insufficient data on BMD values (no descriptions of bone location, measurement method or device);
- duplicate reports.

Data extraction and quality assessment

The data were extracted by three reviewers independently and recorded in Excel file, and we discussed and resolved the inconsistencies. The first author's name, year of publication, country, gender and age of participants, sample size, BMD value and location, number of people with low BMD (osteopenia and osteoporosis) and coronary artery calcification score (CAC score) were extracted from each study. We used a six-item table tailored from Newcastle Ottawa Scale (NOS)[14] for quality assessment. The quality assessment graphs are generated by Review Manager (RevMan, version 5.3. Copenhagen: the Nordic Cochrane Center, the Cochrane Collaboration, 2014).

Publication bias

Funnel plots for publication bias were performed, when the meta-analysis contained more than 5 studies. Publication bias is confirmed if the plot is asymmetrical.

Statistical analysis

We used RevMan to pool the categorical data of odds ratio (OR) with 95% confidence interval

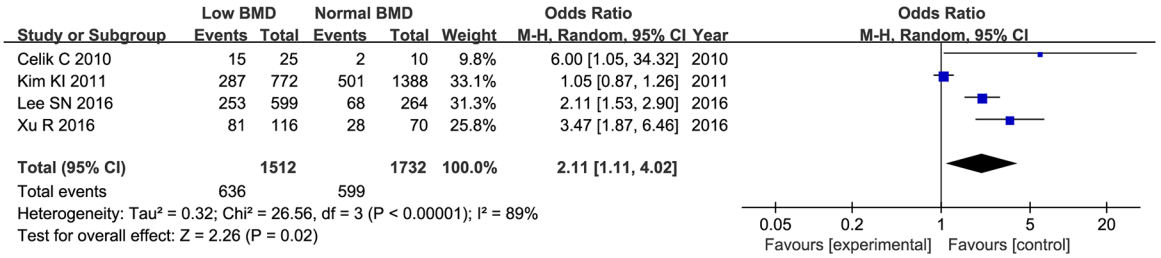

Figure 2. Forest plot of association between bone mineral density and coronary artery calcification.

(CI) and continuous data by mean difference (MD). We used GetData Graph Digitizer Version 2.26 to extract the data from the studies with only graph displaying results. We combined the sample's mean and standard deviation by the method of Altman DG *et al.*[15] Some continuous variables were transformed by the methods of Luo D *et al.*[16] and Wan X *et al.*[17] Correlation coefficients of BMD and CAC score were pooled using Medcalc (ver. 19.0) software. When $I^2 \geqslant 50\%$ or $p \leqslant 0.05$ (significant heterogeneity),[18] random-effects model was used to combine HRs, or else fixed-effects model was applied. Sub-group analysis was applied to investigate sources of heterogeneity. p-value < 0.05 was considered statistically significant.

Results

Study characteristics

Seventeen studies published from March 1998 to October 2020 were included in our meta-analysis (S_Table 1), and the articles were all published in English. The studies were conducted in the United States (7 studies, 41.2%),[19–25] China (3 studies, 17.6%),[11,12,26] Korea (4 studies, 23.5%),[27–30] Turkey (1 study, 5.9%),[31] Denmark (1 study, 5.9%)[32] and Sweden (1 study, 5.9%).[33] Nine studies recruited both male and female participants, five studies only recruited postmenopausal women and one study only recruited men. Most of studies measured BMD by dual-energy X-ray absorptiometry (DXA), six studies measured BMD by QCT.

Quality assessment

The quality assessment of the included studies is shown in S_Figure 1. Ludmila N. Bakhireva's recruited middle-class and upper-class individuals, we labeled it as high-risk bias of representativeness of the cases. C. Celik's study included a small sample (35 women), we marked it as unclear risk bias of representativeness of the cases. Only four studies reported whether CAG readers were blinded to the BMD results, other studies that did not mention it were regarded as unclear risk of bias. Six studies explained why the patients were excluded from the statistical analysis. In summary, most of the studies were mid-grade or high-grade quality.

Association between BMD and CAC

Four articles[11,28,30,31] reported the prevalence of CAC in different levels of BMD, and the BMDs values were all measured by DXA. The pooled OR for the prevalence of CAC in patients with low BMD versus patients with normal BMD was 2.11 (95% CI: 1.11 – 4.02, $p = 0.02$, $I^2 = 89\%$; random-effects model; Figure 2). The prevalence of CAC in patients with low BMD was higher than that in patients with normal BMD.

CAC score difference in low BMD and normal BMD

Five articles[11,21,28,29,31] reported CAC score in low and normal BMD, and the BMD values were all measured by DXA. The data pooled for comparing CAC score in patients with low BMD and normal BMD were 19.82 (95% CI: 18.73–20.90, $p = 0.000$, $I^2 = 0\%$; Figure 3) in women, 68.10 (95% CI: 60.19–76.02, $p = 0.000$, $I^2 = 0\%$; Figure 2) in postmenopausal women, 24.21 (95% CI: -2.16–50.58, $p = 0.07$, $I^2 = 75\%$) in men, and 33.77 (95% CI: 23.77– 43.77, $p = 0.000$, $I^2 = 97\%$; random-effects model) in total. There was no significant difference in men subgroup. CAC score in low BMD patients was much higher than that in normal BMD ones, especially in postmenopausal women.

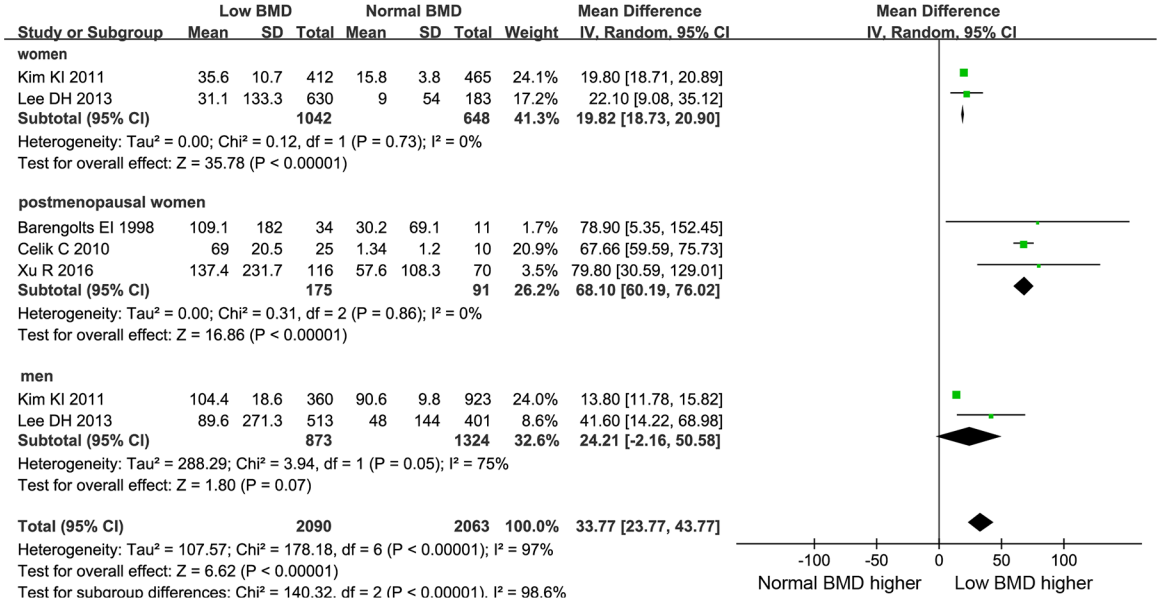

Figure 3. Forest plot of coronary artery calcification score comparison between low bone mineral density and normal bone mineral density.

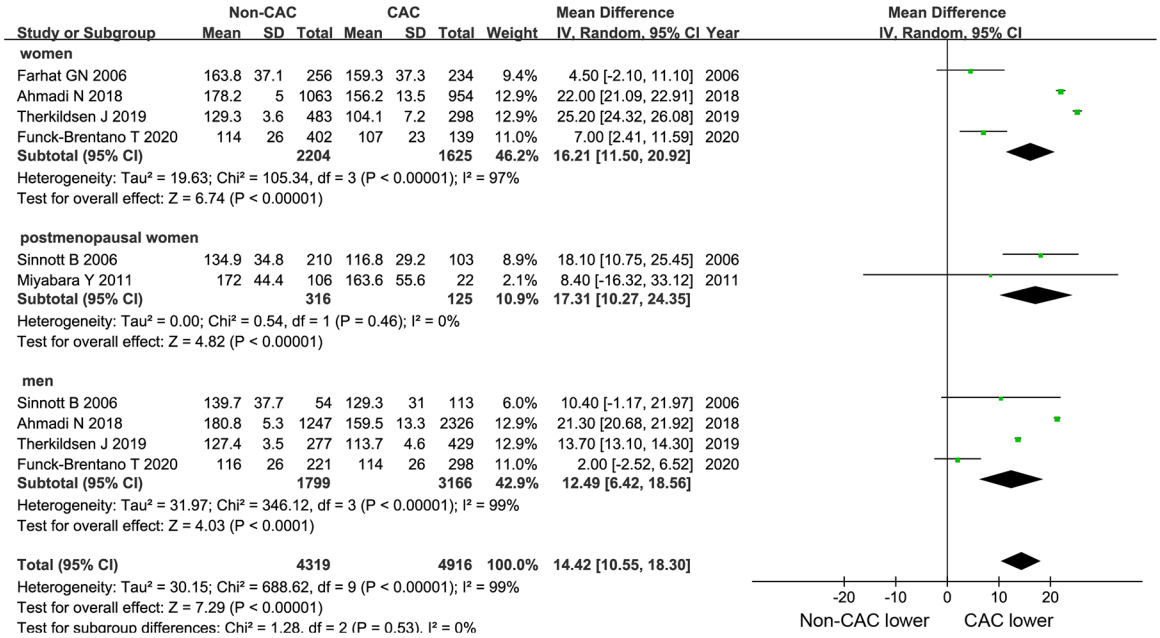

Figure 4. Forest plot of bone mineral density difference in non- coronary artery calcification and coronary artery calcification.

BMD difference in non-CAC and CAC

Six articles[22–25,32,33] reported the BMD in non-CAC and CAC, and BMD values were derived from QCT (the unit of BMD is mg/cm^3). The data pooled for comparing BMD difference in patients with Non-CAC and CAC were 16.21 (95% CI: 11.50 - 20.92, $p=0.000$, I^2 = 97%; Figure 4) in women, 17.31 (95% CI: 10.27 - 24.35, $p=0.000$, I^2 = 0%) in postmenopausal women, 12.49 (95% CI: 6.42–18.56, $p=0.000$,

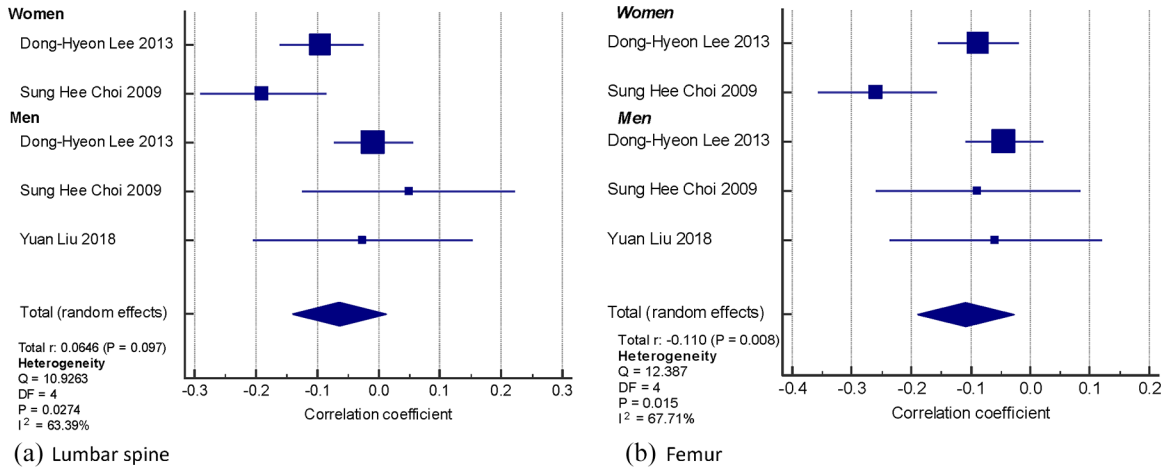

Figure 5. Forest plot of relationship between bone mineral density (BMD) and coronary artery calcification score (Correlation coefficient). (a) The pooled correlation coefficient of lumbar spine BMD and CAC score and (b) The pooled correlation coefficient of femur BMD and CAC score.

I^2 = 99%) in men, and 14.42 (95% CI: 10.55–18.30, p=0.000, I^2 = 99%; random-effects model) in total, respectively. The BMD of patients with CAC was lower than the BMD of non-CAC people.

Relationship between BMD and CAC score (Correlation coefficient)

Three articles[26,27,29] reported the results of correlation analysis (r value), and the BMD values were all measured by DXA. The pooled correlation coefficient of BMD of lumbar spine and CAC score was - 0.07 (p=0.10, I^2 = 63.39%; random-effects model; Figure 5(a)), and the pooled correlation coefficient of BMD of femur and CAC score was - 0.11 (p=0.01, I^2 = 67.71%; random-effects model; Figure 5(b)). BMD of femur was inversely correlated with CAC; no correlation was found between lumbar BMD and CAC.

Multivariate logistic regression analysis of the relationship between low BMD of different locations and CAC

Four articles[12,19,20,22] reported the ORs of multiple logistic regression analysis of the relationship between low BMD (lumbar spine or femoral neck) and CAC. The covariates adjusted for analysis include: waist, systolic blood pressure, fasting plasma sugar, triglyceride, HDL-C, cholesterol, BMI, smoking, LDL-C, hs-CRP, and alkaline phosphatase in Lin T 2011's study; age, fat-free mass, HDL, smoking and use of cholesterol lowering medications in Bakhireva LN's study; age, total cholesterol: HDL cholesterol ratio, hypertension, smoking history, diabetes status, and hormone therapy (women only) in Hyder JA 2007's study; age, race, study site, menopause status, alcohol drinking, physical activity score, weight, height, diastolic blood pressure, LDL, and triglyceride level in Farhat GN 2006's study.

The pooled OR (age-adjusted) was 1.00 (95% CI: 0.92 - 1.10, p=0.95, I^2 = 23%; fix-effects model; Figure 6), the pooled ORs of subgroup were 0.98 (95% CI: 0.86–1.13, p=0.35, I^2 = 9%) in lumbar spine (DXA), 1.25 (95% CI: 1.01–1.55, p=0.58, I^2 = 0%) in lumbar spine (QCT) and 0.93 (95% CI: 0.81 - 1.07, p=0.31, I^2 = 17%) in femoral neck. The pooled OR (multivariable-adjusted) was 0.95 (95% CI: 0.86–1.05, p=0.33, I^2 = 38%; fix-effects model; Figure 7). The pooled ORs of subgroup were 0.96 (95% CI: 0.83–1.12, p=0.48, I^2 = 0%) for low lumbar spine (DXA), 1.30 (95% CI: 0.95 - 1.79, p=0.11, I^2 = 0%) for lumbar spine (QCT) and 0.86 (95% CI: 0.74–1.01, p=0.07, I^2 = 61%) for low femoral neck. The pooled data showed that no relation was found between low BMD and CAC by age or multivariable adjustment.

Sources of heterogeneity

The meta-analyses of CAC comparison of low BMD vs normal BMD and BMD difference of non-CAC vs CAC showed obvious heterogeneity

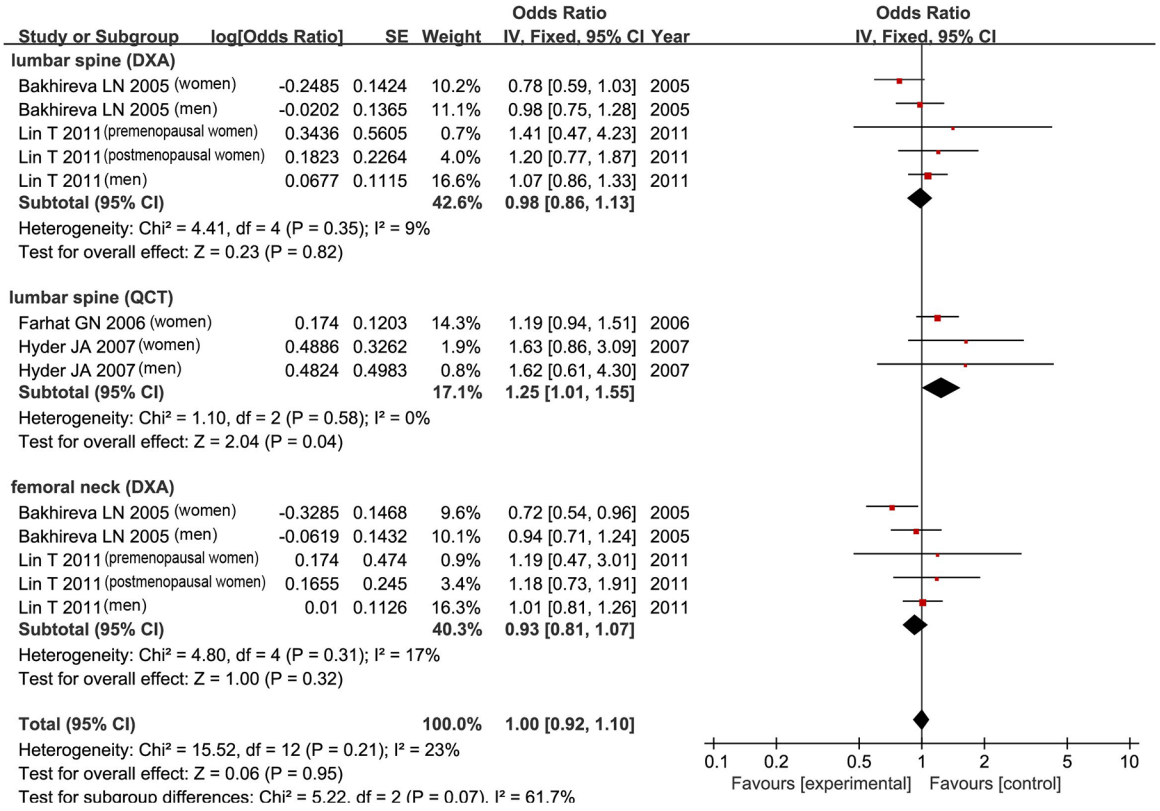

Figure 6. Forest plot of Logistic regression analysis of the relationship between low bone mineral density in different locations and coronary artery calcification (age-adjusted).

(Figures 3 and 4). Sub-group analyses by sex and postmenopause revealed that the heterogeneity appeared in men sub-group (I^2 = 75%) from the meta-analysis of CAC comparison of low BMD vs normal BMD, and in women (I^2 = 97%) and men (I^2 = 99%) sub-groups from the meta-analysis of BMD difference of non-CAC vs CAC, respectively. While, the results from the studies of postmenopausal women were homogeneous (I^2 = 0%). For the pooled data of multivariate logistic regression analysis (age-adjusted), the heterogeneity of sub-groups divided by DXA or QCT decreased (Figure 6), which meant the assessment method for BMD was also the source of heterogeneity.

Publication bias

Four meta-analyses including more than 5 studies conducted publication bias exploration (S_Figure 2). The funnel plots of CAC comparison between low BMD and normal BMD and logistic regression analysis of the relationship between low BMD and CAC (age-adjusted) were asymmetric, showing that these two meta-analyses may exist publication bias. The funnel plots of BMD difference in non-CAC and CAC and logistic regression analysis of the relationship between low BMD and CAC (multivariable-adjusted) did not display any publication bias.

Discussion

Without confounders adjustment, our study results indicated that the prevalence of CAC in patients with low BMD was higher than that in patients with normal BMD, and CAC score in low BMD patients was much higher than that in normal BMD ones. Pooled multiple regression analysis results showed that no relation was found between low BMD at femoral neck or lumbar spine and CAC after adjusting age only or other risk factors, which means that osteoporosis and CAC may be two independent processes with aging. We formerly performed the meta-analysis to explore the association of coronary artery

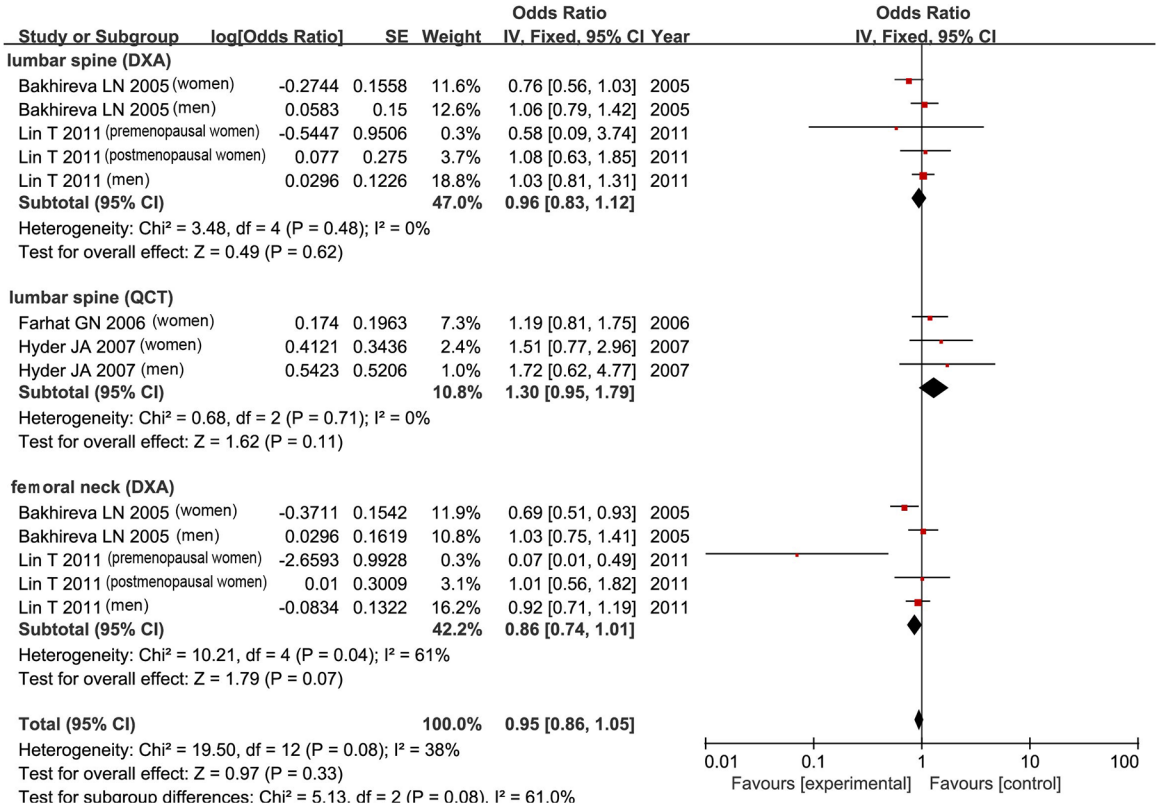

Figure 7. Forest plot of Logistic regression analysis of the relationship between low bone mineral density in different locations and coronary artery calcification (multivariable-adjusted).

disease (CAD) with BMD, and concluded that low BMD was not found to be associated with prevalence of CAD.[34] CAC as one of the manifestations of CAD, is proposed to be related to the metabolic disorder of calcium. The increased coexistence of bone loss and vascular calcification is called the 'calcification paradox', which suggested that the risk of CAC be higher in people with low BMD.[35] Moreover, another confounding for the different results of trials on this issue may be calcium supplementation for osteoporosis/osteopenia.[36] There are some evidences that calcium/vitamin D supplementation augments coronary calcification. a large cohort study involving 2742 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) without cardiovascular disease found that calcium supplement use was associated with a 22% increase in risk of incident CAC (RR, 1.22; 95% CI, 1.07–1.39).[37] An intravascular ultrasound study also found that oral calcium supplementation may increase calcium deposition in the coronary vasculature independent of changes in atheroma volume.[38] However, the Women's Health Initiative Calcium/vitamin D Supplementation Study (WHI CaD) reported that calcium carbonate and vitamin D supplementation had no adverse effect on any cardiovascular endpoints or on coronary artery calcification.[39] Also, the Framingham study does not support the hypothesis that high calcium intake increases coronary artery calcification.[40] Disparities results in trials of calcium metabolism, coronary calcification and reposition of calcium in different doses should be investigated in the future.

The beneficial effects of estrogen on the coronary bed have been reported in women, because estrogen plays a role in vascular calcification inhibition.[41] Campos-Obando *et al*'.s[41] finding suggest that endogenous estradiol deficiency might underlie both pathological processes and thus be a shared risk factor for BMD loss and CAC. Previous studies had found that the prevalence of CAC in men was significantly higher than that in women, and the prevalence of CAC increased with age. Then, postmenopausal women with decreasing estrogen are at risk of CAC and low

BMD. Many epidemiological surveys supported the hypothesis,[10,11,31,42] and some studies suggested that estrogen was involved in bone metabolism and had a certain effect on CAC.[42,43] Our pooled data also revealed the same results on the gender difference in CAC, but whether the age of men and women is comparable was still unknown.

Choi *et al*'.s[27] study showed that lower BMD of the femur area and lumbar spine could be a marker for subclinical atherosclerosis in females. Hyder *et al.*[20] demonstrated a significant negative correlation between BMD in lumbar spine and aortic calcification. Bakhireva *et al*'.s[19] univariate and multivariate logistic regression analyses showed that there was a significant inverse correlation between hip BMD and CAC. On the contrary, Lin *et al.*[12] found no significant correlation between CAC and low BMD at lumbar spine, femur neck, and proximal femur after adjusted for age and other risk factors. Our meta-analysis also showed that there was no significant difference in the correlation between CAC and BMD after adjust the confounding factors.

Although our combined results showed that there was no statistical difference in the effect of low BMD in lumbar spine or femoral neck and CAC, the BMD at other locations such as thoracic vertebrae or hip may be different, for example, three studies have shown that there was an inverse relationship between BMD of thoracic vertebrae (T - 7 to T - 10) and CAC.[10,25,32] Unfortunately, we were unable to include them for the meta-analysis because the heterogenous data are unavailable to pool. If the difference is definite, we assume that because the thoracic bones are close to the coronary arteries, the relationship may be stronger than other sites. The location difference is an interesting finding, and need to be explored in the future. In addition, the sub-group analysis in the present study found assessment method for BMD was one of the sources of heterogeneity. The future study may compare accuracy of BMD assessment methods such as DXA and QCT.

Three studies reported the correlation coefficients of relationship between BMD of different sites and CAC score. Our combined results showed that there was a significant inverse correlation between BMD of femur and CAC score. Therefore, bone loss in the femur is more associated with the severity of CAC. A significant negative correlation was also found between carotid intima media thickness and the T score of lumbar spine (r = -0.35; $p < 0.001$) and femoral neck (r = -0.23, $p < 0.001$), as well as Z score of the lumbar spine in postmenopausal women.[44] But these studies could not exclude the influence of age and other key confounding factors, so the association of the severity of CAC and BMD is still necessary to explore. More large-scale studies with high-quality design are still needed to understand the relationship of these two processes by excluding confounders.

Limitations

Several limitations of our meta-analysis are as follows. First, some of the studies does not directly provide the available data we need. Although we try our best to transformed them to appropriate data for meta-analysis, for example, used the sample's mean and standard deviation combining method of Altman DG *et al.*,[15] some of the data that couldn't be transformed have been dropped. The drop of these data may cause biases and misleading. Second, each meta-analysis could only include a small number of original studies because of data diversity. Then, it influenced the evidence to support the conclusion, for example, only four studies performed multivariate analysis. Third, the quality of the studies included may cause biases. More than half of the studies didn't explain how missing data. Some meta-analyses also revealed publication bias. Besides, there are no studies from Africa, affecting the sample representativeness in terms of ethnicity and region. Fourth, all of the included studies are cross-sectional design, and it cannot determine whether there are any causes underlying this association.

Conclusions

Low BMD is associated with higher prevalence and severity of CAC, especially in postmenopausal women. But no relation is found after adjusting age and other confounding variables. Low BMD and CAC may be two independent processes with aging. More large-scale studies with high-quality design are still needed to increase the understanding of these two processes.

Author contributions

Peiyu Zhang: Data curation; Formal analysis; Methodology; Software; Writing – review & editing.

Liu Yang: Conceptualization; Methodology; Software; Writing – review & editing.
Qingwen Xu: Methodology; Supervision; Writing – review & editing.
Yidi Zeng: Writing – review & editing.
Yipin Yu: Supervision; Validation; Writing – review & editing.
Qinghua Peng: Funding acquisition; Supervision; Validation.
Hao Liang: Conceptualization; Formal analysis; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

References

1. Wang L, Jerosch-Herold M, Jacobs DR, *et al.* Coronary artery calcification and myocardial perfusion in asymptomatic adults: the MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2006; 48: 1018–1026.
2. Agatston AS, Janowitz WR, Hildner FJ, *et al.* Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15: 827–832.
3. Coughlan T and Dockery F. Osteoporosis and fracture risk in older people. *Clin Med* 2014; 14: 187–191.
4. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. *Osteoporos Int* 1994; 4: 368–381.
5. Leopold JA. MicroRNAs regulate vascular medial calcification. *Cells* 2014; 3: 963–980.
6. Demer LL and Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. *Circulation* 2008; 117: 2938–2948.
7. Laroche M, Pécourneau V, Blain H, *et al.* Osteoporosis and ischemic cardiovascular disease. *Joint Bone Spine* 2017; 84: 427–432.
8. Liu W, Zhang Y, Yu CM, *et al.* Current understanding of coronary artery calcification. *J Geriatr Cardiol* 2015; 12: 668–675.
9. Goel M, Wong ND, Eisenberg H, *et al.* Risk factor correlates of coronary calcium as evaluated by ultrafast computed tomography. *Am J Cardiol* 1992; 70: 977–980.
10. Wiegandt YL, Sigvardsen PE, Sørgaard MH, *et al.* The relationship between volumetric thoracic bone mineral density and coronary calcification in men and women – results from the Copenhagen General Population Study. *Bone* 2019; 121: 116–120.
11. Xu R, Yang HN, Li YQ, *et al.* Association of coronary artery calcium with bone mineral density in postmenopausal women. *Coron Artery Dis* 2016; 27: 586–591.
12. Lin T, Liu JC, Chang LY, *et al.* Association between coronary artery calcification using low-dose MDCT coronary angiography and bone mineral density in middle-aged men and women. *Osteoporos Int* 2011; 22: 627–634.
13. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603–605.
15. Altman DG, Machin D, Bryant TN, *et al. Statistics with confidence*. 2nd ed. London: SAGE, 2000.
16. Luo D, Wan X, Liu J, *et al.* Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018; 27: 1785–1805.

17. Wan X, Wang W, Liu J, *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14: 135.
18. Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
19. Bakhireva LN, Barrett-Connor EL, Laughlin GA, *et al.* Differences in association of bone mineral density with coronary artery calcification in men and women: the Rancho Bernardo Study. *Menopause* 2005; 12: 691–698.
20. Hyder JA, Allison MA, Criqui MH, *et al.* Association between systemic calcified atherosclerosis and bone density. *Calcif Tissue Int* 2007; 80: 301–306.
21. Barengolts EI, Berman M, Kukreja SC, *et al.* Osteoporosis and coronary atherosclerosis in asymptomatic postmenopausal women. *Calcif Tissue Int* 1998; 62: 209–213.
22. Farhat GN, Cauley JA, Matthews KA, *et al.* Volumetric BMD and vascular calcification in middle-aged women: the study of women's health across the nation. *J Bone Miner Res* 2006; 21: 1839–1846.
23. Sinnott B, Syed I, Sevrukov A, *et al.* Coronary calcification and osteoporosis in men and postmenopausal women are independent processes associated with aging. *Calcif Tissue Int* 2006; 78: 195–202.
24. Miyabara Y, Camp J, Holmes D 3rd, *et al.* Coronary arterial calcification and thoracic spine mineral density in early menopause. *Climacteric* 2011; 14: 438–444.
25. Ahmadi N, Mao SS, Hajsadeghi F, *et al.* The relation of low levels of bone mineral density with coronary artery calcium and mortality. *Osteoporos Int* 2018; 29: 1609–1616.
26. Liu Y, Fu S, Bai Y, *et al.* Relationship between age, osteoporosis and coronary artery calcification detected by high-definition computerized tomography in Chinese elderly men. *Arch Gerontol Geriatr* 2018; 79: 8–12.
27. Choi SH, An JH, Lim S, *et al.* Lower bone mineral density is associated with higher coronary calcification and coronary plaque burdens by multidetector row coronary computed tomography in pre- and postmenopausal women. *Clin Endocrinol (Oxf)* 2009; 71: 644–651.
28. Kim KI, Suh JW, Choi SY, *et al.* Is reduced bone mineral density independently associated with coronary artery calcification in subjects older than 50 years? *J Bone Miner Metab* 2011; 29: 369–376.
29. Lee DH, Youn HJ, Yi JE, *et al.* Gender difference in bone loss and vascular calcification associated with age. *Korean Circ J* 2013; 43: 453–461.
30. Lee SN, Cho JY, Eun YM, *et al.* Associations between osteoporosis and coronary artery disease in postmenopausal women. *Climacteric* 2016; 19: 458–462.
31. Celik C, Altunkan S, Yildirim MO, *et al.* Relationship between decreased bone mineral density and subclinical atherosclerosis in postmenopausal women. *Climacteric* 2010; 13: 254–258.
32. Therkildsen J, Winther S, Nissen L, *et al.* Sex differences in the association between bone mineral density and coronary artery disease in patients referred for cardiac computed tomography. *J Clin Dens* 2021; 24: 55–66.
33. Funck-Brentano T, Grahnemo L, Hjelmgren O, *et al.* Associations of trabecular and cortical volumetric bone mineral density with coronary artery calcification score: the Swedish cardiopulmonary bioimage study pilot study. *JAMA Cardiol* 2021; 6: 238–240.
34. Zhang Y, He B, Wang H, *et al.* Associations between bone mineral density and coronary artery disease: a meta-analysis of cross-sectional studies. *Arch Osteoporos* 2020; 15: 1–8.
35. Persy V and D'Haese P. Vascular calcification and bone disease: the calcification paradox. *Trends Mol Med* 2009; 15: 405–416.
36. Tankeu AT, Ndip Agbor V and Noubiap JJ. Calcium supplementation and cardiovascular risk: a rising concern. *J Clin Hypertens (Greenwich)* 2017; 19: 640–646.
37. Anderson JJB, Kruszka B, Delaney JAC, *et al.* Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the multi-ethnic study of atherosclerosis (MESA). *J Am Heart Assoc* 2016; 5: e003815.
38. Bazarbashi N, Kapadia SR, Nicholls SJ, *et al.* Oral calcium supplements associate with serial coronary calcification. *JACC Cardiovasc Imaging* 2021; 14: 259–268.
39. Manson JE, Allison MA, Carr JJ, *et al.* Calcium/vitamin D supplementation and coronary artery calcification in the women's health initiative. *Menopause* 2010; 17: 683–691.
40. Samelson EJ, Booth SL, Fox CS, *et al.* Calcium intake is not associated with increased coronary artery calcification: the Framingham study. *Am J Clin Nutr* 2012; 96: 1274–1280.

41. Campos-Obando N, Kavousi M, Roeters van Lennep JE, *et al*. Bone health and coronary artery calcification: the Rotterdam study. *Atherosclerosis* 2015; 241: 278–283.

42. Tankò LB, Bagger YZ and Christiansen C. Low bone mineral density in the hip as a marker of advanced atherosclerosis in elderly women. *Calcif Tissue Int* 2003; 73: 15–20.

43. Mendelsohn ME and Karas RH. The protective effects of estrogen on the cardiovascular system. *New Engl J Med* 1999; 340: 1801–1811.

44. Mohammadi A, Shateri K, Behzadi F, *et al*. Relationship between intima-media thickness and bone mineral density in postmenopausal women: a cross-sectional study. *Int J Clin Exp Med* 2014; 7: 5535–5540.