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Association Between Coronary Artery Calcium and Thoracic Spine Bone Mineral Density: Multiethnic Study of Atherosclerosis

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Abstract

Background and aims: Previously, osteoporosis and coronary artery disease were considered unrelated. However, beyond age, these two conditions appear to share common etiologies that are not yet fully understood. We examined the relationship between thoracic spine bone mineral density (BMD) and severity of coronary artery calcium (CAC) score.

Methods and results: MESA is a prospective cohort study of 6,814 men and women between the ages of 45 and 84 years, without clinical cardiovascular disease. This study included participants who underwent non-contrast chest CT scans to determine CAC score and thoracic spine BMD. The thoracic spine BMD was categorized into osteoporosis (defined as T score: ≤ −2.5), osteopenia (T-score between: −2.5 to −1) and normal BMD (T-score ≥ −1). There were 3,392 subjects who had CAC >0 at baseline. The prevalence of CAC >0 was 36% in normal BMD group, 49% in the osteopenia and 68% in osteoporosis group. After adjusting for risk factors of atherosclerosis, in multivariate regression models we found a significant association between CAC and osteoporosis (OR:1.40, 95% CI 1.16–1.69, p value<0.0004). Furthermore, we stratified our results by gender and found a statistically significant association in both men and women.

Conclusion: Results from this cross-sectional analysis of a large population based ethnically diverse cohort indicate a significant inverse relationship between thoracic BMD and CAC in

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both genders independent of other cardiovascular risk factors. Future studies need to explore the underlying pathophysiological mechanisms relating BMD and coronary artery calcification.

Keywords

Osteoporosis; CVD; Coronary calcium; BMD; atherosclerosis; CT

1.0 Introduction:

Coronary artery disease (CAD) and osteoporosis are common among the general population in the United States, and their prevalence is growing.(1, 2) Previously, osteoporosis and atherosclerotic CAD were considered unrelated, and their coexistence was attributed to independent age-related processes. However, there is increasing epidemiologic and biologic evidence supporting a link between these two entities, which is independent of age.(3–5) It is now recognized that calcification in arteries is an organized process regulated by similar mechanisms involved in bone mineralization.(6) The mineral detected in atherosclerotic calcium plaque has an almost identical chemical composition compared with hydroxyapatite crystals that form the inorganic bone matrix.(7) Calcified plaques also express several bone matrix proteins, suggesting a common pathway between cardiovascular disease and osteoporosis.(8)

Coronary artery calcium (CAC) is a marker of subclinical atherosclerosis and a strong predictor of future cardiovascular events.(9) Similarly, low bone mineral density (BMD) is the hallmark of osteoporosis and a well-established risk marker for future fractures.(10) Numerous research studies have been conducted to examine the association between CAC and BMD, however, the results have been inconsistent, and the majority of the studies are limited by sample size.(11–16)

For instance, recent meta-analyses, have found discrepant results regarding the link between CAD and BMD. Khandkar et al. performed a meta-analysis with 4156 patients from ten cross-sectional studies. In this study, a pooled analysis revealed a significant link between low BMD and CAD.(17) Conversely, Zhang et al. showed that low bone mineral density was not linked with the prevalence of coronary artery disease in a meta-analysis that included 11 studies and 4170 participants.(18) These findings remain inconsistent and necessitate large-scale epidemiological research to better investigate the relationship between BMD and CAD.

In a large population-based sample, we aimed to evaluate the relationship between thoracic spine BMD and CAC, independent of other atherosclerotic risk factors. In addition, given the discrepancies in results between genders in previous studies,(11–16) we examined this relationship in men and women specifically. A better understanding of the relationship between these two major diseases could ultimately lead to improved detection, earlier treatment, and even refine prevention strategies for these disorders.

2.0 Materials and Methods:

2.1 Study population:

This current study is a cross sectional analysis of the participants from the multiethnic study of atherosclerosis (MESA). MESA is a prospective observational cohort of 6,814 men and women from six communities across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St Paul, MN). MESA was launched in July 2000 to explore the prevalence and progression of subclinical cardiovascular disease. The study enrolled men and women between the ages of 45 and 84 who did not have a history of clinical cardiovascular disease. At each recruitment site, an equal proportion of men and women from two or more racial/ethnic groups were recruited. Approximately 38% were White, 28% African-American, 23% Hispanic, and 11% Asian (of Chinese descent). All procedures were conducted under institutionally approved protocols of six field centers for human subject research. Written informed consent was obtained from each patient included in the study. The details of MESA study design are previously described elsewhere.(19) An institutional review board approval was sought for this retrospective analysis.

The MESA cohort is a large population-based sample representing a range of racial and ethnic groups. In addition, it includes individuals who have both CAC scores and quantitative thoracic spine BMD measurements obtained from a single gated cardiac CT scan. The MESA cohort appropriately represents the general population. Therefore, we sought to test our hypothesis using MESA participants.

All MESA participants who had undergone a gated cardiac CT scan at baseline that evaluated CAC and who had available thoracic spine BMD measurements were eligible for inclusion. Ten participants were excluded from this study due to the inability to obtain thoracic BMD. Other exclusion criteria at the time of participant enrollment included: clinical cardiovascular disease, pregnancy, active treatment for cancer, weight > 300 pounds, cognitive inability, and living in a nursing home.

2.2 CT image acquisition:

All the participants had undergone chest CT scans at six different sites. On three of the six sites, the C150 electron-beam CT scanner (GE Imatron, Milwaukee, Wis.) was employed, one site used a LightSpeed Plus multi–detector row CT scanner (GE Medical Systems, Milwaukee, Wis), while the other two sites used a Volume Zoom multi–detector row CT scanner (Sensation 4; Erlangen, Germany). When scans from different subjects and sites were compared, attenuation differences (ie, differences in Hounsfield units) were expected due to the different scanning protocols used in the MESA and the different size and composition of each participant’s chest. To compensate for these discrepancies and to ensure standardize measurements, images were recalibrated to a uniform attenuation. This necessitated the employment of identical calibration phantoms beneath each participant during the scanning process. The technical aspects and scan acquisition details are as previously described.(20)

2.3 Coronary artery calcium scoring:

All the scans were ECG gated chest CT scans. Cardiac ECG gating lowers measurement errors by timing the acquisition of images for each level of the scan to a certain phase of the heart cycle. The Harbor UCLA Research and Education Institute in Los Angeles served as the core laboratory that analyzed all CT images and determined the quantity of calcified coronary artery plaque. The threshold for a calcified lesion was set at a computed tomography density of ≥130 Hounsfield units (modified to adjust for section thickness), and the coronary artery calcium was calculated using Agatston method (Figure 1).(21) Previous studies have described this process and the protocol used in significant detail.(21) Calcium scoring in the MESA study was performed by blinded CT reviewers, and there was excellent intraobserver and interobserver agreement for the presence and amount of calcified plaque among CT image analysts.(20, 22)

2.4 Thoracic spine bone mineral density measurement:

The thoracic spine BMD in the MESA study was assessed using the same non-contrast CT chest images used for calculating the coronary calcium score. The chest CT protocols used to quantify the CAC score also image the midthoracic spine (T5 to T10),(23) making the evaluation of thoracic spine density possible in MESA.(24) Previous research has demonstrated the precision with which phantom less thoracic BMD can be determined from CAC CT scans acquired using a variety of different scanners.(23) Multiple studies have found that phantom less thoracic BMD results correspond well with the more traditional phantom-based CT lumbar BMD results.(23, 25–27)

We will briefly outline the method of measuring quantitative thoracic BMD in this section. In all the scans, thoracic BMD was measured in three consecutive thoracic spine vertebrae. These three measurements started caudally at the left main coronary artery level. The center of vertebrae was considered the region of interest, with at least 2 mm distance from the spinal cortical bone (Figure 1b). The manual free tracing approach eliminated the cortical bone, bone island, fractures, major vascular regions, and calcified herniated discs. The mean BMD for three thoracic vertebrae was computed in all participants. Quantitative thoracic BMD evaluation methods have been previously described by Budoff et al in significant detail.(23, 25)

Scans were read centrally at the MESA CT core lab at Harbor-UCLA (Los Angeles, California) by trained readers blinded to coronary artery calcium scoring. The quantitative thoracic BMD assessment protocol has been extensively used in previous studies designed by the CT core lab.(23–25) There has been excellent intraobserver and interobserver agreement reported for quantitative thoracic BMD evaluation.(25) The standardized BMD values and normalized T scores for quantitative thoracic BMD measurement were computed using the novel method previously published.(25) BMD was considered normal if the T score ≥ −1. We categorized osteopenia as a T score between −2.5 and −1. Osteoporosis was categorized as ≤ −2.5.

2.5 Demographic and Clinical variables:

We used the existing covariate data from MESA in our analysis.(19) The variables utilized for the study were as follows, age, sex, race/ethnicity, income level, menopause, smoking history, minutes per week of moderate conditioning activity and family history of myocardial infarction. Additionally, body mass index (BMI), hypertension, diabetes mellitus, LDL cholesterol, and triglycerides and current medication use based on self-report and examination of pill bottles, lipid lowering medications, vitamin D supplementation, calcium supplementation, menopause and hormone replacement therapy were also recorded.

2.6 Statistical analysis:

Continuous variables are presented as mean +/− standard deviation. Categorical variables are presented as frequencies (percentages). A two-tailed p-value <0.05 was considered statistically significant. The calcium scores were dichotomized, with a CAC score considered absent if it equaled 0, and present if it was > 0. Both BMD and T scores were presented as continuous variables. CAC was log transformed for linear regression analysis, where CAC=0 was log transformed as CAC+1. All analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Cary, North Carolina).

Multivariable linear regression analysis was used to examine the linear association between the CAC scores and thoracic spine BMD. Logistic regression analysis was used to evaluate the association between presence and absence of CAC and thoracic spine BMD. Our adjusted models controlled for the following variables, age, gender, race/ethnicity, BMI, diabetes mellitus, hypertension, lipid lowering agents, smoking history, family history of CAD, income level, physical activity, vitamin D supplementation and calcium supplementation.

We repeated the above analysis and modeling after stratifying the population based on gender. Hormone replacement therapy and menopause were also accounted for in females for the adjusted models.

3.0 Results:

3.1 Baseline characteristics:

Among the MESA cohort, it was possible to obtain thoracic BMD on 6,804 participants. The mean age was 62.2 (10.2) years and male subjects made up 47% of the total group. Of the subjects, 3,392 (50%) had a positive CAC score. The mean BMD in CAC zero group was 175 (45.8) and in CAC >0 was 151.6 (44.6). In groups CAC zero and CAC >0, the mean T-scores were −1.3 (1.3) and −1.9 (1.3), respectively. Clinical and demographic characteristics accordingly as per Table 1.

3.2 Association between reduced BMD and CAC score:

There was a significant linear association between BMD and CAC. One standard deviation decrease in BMD was associated with a 4% increase in CAC in all subjects after adjusting for relevant covariates in the model, p=0.011. Furthermore, participants were categorized based on CAC score category. Of the 6,804 participants, 64% of those with a zero CAC

score had normal T score, compared to 36% of those with a CAC score greater than zero ($p<0.05$). Conversely, 32% of the participants in the zero CAC group had osteoporosis compared to 68% in the group with a CAC score greater than zero ($p<0.05$) (Figure 2). When comparing those with a normal T score to those with osteoporosis, there exists a statistically significant inverse relationship between BMD and CAC severity, where CAC is categorized as, 0, 1–99, 100–399 and ≥400 (CAC categorized at clinically relevant levels).

Using logistic regression analysis, we calculated the odds ratio of having osteopenia and osteoporosis based on the presence of a CAC score (Table 2). Our unadjusted models found that the presence of a CAC score >0 was associated with a statistically significant increased odds of both osteopenia (OR:1.647, CI:1.468–1.848, p-value <0.0001) and osteoporosis (OR:3.65, CI:3.194–4.172, p-value <0.0001).

When we adjusted for potential confounding factors in model 1(age, gender, race/ethnicity, BMI, diabetes mellitus, hypertension, lipid-lowering agents, smoking history, family history CAD, income level, and moderate conditioning activity), the odds ratio for osteoporosis remained significant. (OR:1.573, CI:1.315–1.881, p-value <0.0001). Similar but weaker results were observed in osteopenia group after adjusting for confounding factors (OR:1.152, CI:1.001–1.327, p-value =0.048). In model 2, vitamin D and calcium supplementation were adjusted. The association between CAC >0 and osteoporosis were still statistically significant in model 2 (OR: 1.408, CI: 1.167–1.699, p-value <0.0004). However, the association between CAC >0 and osteopenia were no longer statistically significant after adjusting for confounders in model 2 (Table 2).

3.3 Gender-specific association between reduced BMD and CAC score

We then used logistic regression analysis and stratified the subjects by gender (Table 3). In addition to an overall significant relationship between reduced BMD and CAC, we also found this when the group was stratified by gender.

In our unadjusted models, women had a statistically significant increased odds of osteopenia (OR:1.735, CI:1.459–2.063, p-value:<0.0001) and osteoporosis (OR:4.393, CI:3.650–5.288, p-value:<0.0001) if they had a positive CAC score. Likewise, men with a positive CAC had a statistically significant increased odds of osteopenia (OR:1.596, CI:1.356–1.879, p-value:<0.0001) and osteoporosis (OR:3.806, CI:3.076–4.709, p-value:<0.0001) in our unadjusted model.

For men, we found a significant relationship between osteoporosis and CAC scores after adjusting for the same aforementioned potential confounders, (OR:1.369, CI:1.042–1.799, p-value=0.024) in model 1. In model 2, after adjusting for vitamin D and calcium supplementation, the association between CAC and osteoporosis remained significant (OR:1.328, CI:1.006–1.754, p-value=0.045). In females, models were additionally adjusted for hormone replacement therapy and menopause which also resulted in a significant association with presence of CAC and osteoporosis, (OR:1.375, CI:1.052–1.797, p-value=0.020) in model 1. In model 2, for females while adjusting for vitamin D and calcium supplementation, the association between CAC and osteoporosis also remained significant (OR:1.407, CI:1.069–1.851, p-value=0.015). However, there was no significant relationship

between osteopenia and CAC scores in either the male or female groups in models 1 or 2. (Figure 3).

3.4 Association of baseline BMD with CAC progression

We further analysed the association between baseline BMD and the risk of CAC progression in the MESA cohort that has follow up data on CAC score. CAC progression defined based on previously published data(28, 29). Participants with osteoporosis at baseline had significantly increased risk of CAC progression. This analysis is reported in the supplementary material (Appendix 1).

4.0 Discussion:

In this study, we found an inverse relation between BMD and CAC score in both men and women. After adjusting for multiple confounding factors, we showed a statistically significant association between osteoporosis and increased CAC scores for both men and women independent of other atherosclerosis risk factors. However, we did not identify a significant link between osteopenia and CAC when stratified by gender.

Previous studies have shown conflicting results regarding the relationship between BMD and CAC,(11–16) Some studies have found no link between BMD and CAC.(13–15) Whereas other studies have found an inverse association between CAC and BMD in women only, but not in men.(11, 12)

Zhang et al. concluded from a meta-analysis of 11 studies and 4170 patients that there is no correlation between low BMD and the prevalence of CAD. The pooled odds ratio for the occurrence of CAD in patients with low BMD versus those with normal BMD was 1.58 (95% CI 0.99–2.52, P = 0.06), and no statistical difference was observed in men and women. Almost all the studies included in the meta-analysis evaluated BMD using dual energy x-ray absorptiometry (DXA), with the exception of one that utilized quantitative ultrasonography and almost all of the studies confirmed CAD using coronary angiography. (18) Subsequently, findings from another meta-analysis of 4156 participants from ten studies suggested a relationship between low BMD and CAD, with an OR of 1.65 (95% CI: 1.37–2.39, p = 0.01). However, subgroup examination of males and females separately revealed no statistical significance in either group. (OR 1.53, 95 % CI 0.62–3.77, p=0.35; OR 1.46, 95 % CI 0.91–2.34, p=0.13). All of the studies included in this meta- analysis utilized DXA except one study that utilized quantitative CT for BMD measurement. Two studies utilized coronary CT angiography and rest of the studies utilized coronary angiography to identify CAD. (17)

There are multiple possible reasons for the varying results between prior meta-analysis. A fundamental drawback of these prior meta-analyses is the substantial clinical and methodological heterogeneity among the studies considered. Furthermore, DXA is known to overestimate BMD due to spine degeneration, abdominal aortic calcification and other sclerotic lesions.(30) Whereas cross sectional studies have demonstrated that quantitative CT spine BMD allows for improved discrimination of individuals with fragility fractures. (31, 32) There is also significant ambiguity in defining CAD in these studies. Together,

these factors may have played a role resulting in mixed results. Our study aimed to limit this heterogeneity by using the MESA cohort and supports the findings of inverse relationship between BMD and CAD. Additionally, our results indicate a statistically significant association between BMD and CAD in both men and women.

In addition to the two meta-analyses previously mentioned, other previous studies have also aimed to examine the relationship between BMD and CAC. In 2019 Wiegandt et al. examined the relationship between volumetric thoracic bone mineral density and coronary calcification in men and women.(16) This study looked at 2,548 individuals within the general population in Copenhagen, Denmark. Wiegandt et al. found an inverse relationship between CAC scores and BMD in men and postmenopausal women (but not premenopausal women). Which, Wiegandt claimed, supported the hypothesis of a direct relationship between bone loss and the development of atherosclerosis, irrespective of gender. Wiegandt used a calibrated mass score (CMS) to assess CAC, whereas we have used Agatston scores. Agatston score is simple and is the most used scoring system across the body of literature.

As with Wiegandt's study, we have found evidence for an inverse relationship between CAC scores and BMD in both men and women. Unlike Wiegandt, we have not stratified our female group into pre and postmenopausal women. Our study adds nicely to the current body of evidence available on the subject of BMD and CAC score correlation. Moreover, given our large numbers and wide demographic range within our cohort, our results are generalizable and do demonstrate a significant association between increasing CAC scores and diminishing BMD.

There are several possible mechanisms to account for a link between osteoporosis and atherosclerosis. Inflammation is present in both atherosclerosis and osteoporosis. Additionally, the inflammatory cytokines, TNF-alpha and IL-6, are both associated with atherosclerosis and osteoperosis.(33) Atherogenic inflammatory cytokines play a key role in pathogenesis and progression of coronary atherosclerosis and osteocyte related cytokines regulate osteoclast activity and bone resorption.(34, 35) The involvement of inflammatory cytokines in both of these processes suggests a complex interplay in calcium and bone metabolism. The association between coronary atherosclerosis and bone mineral density in relation to inflammatory markers needs to be explored.

Vitamin K2 (VitK2), a collection of several naturally occurring isoforms, often referred to as menaquinones, has recently gained considerable attention for its role in calcium homeostasis and may impact the interplay between osteoporosis and CAC. A meta-analysis of 19 clinical studies involving 6759 people established the efficacy of VitK2 supplementation in improving bone mineral density and reducing the incidence of fractures in osteoporotic adults(36) Furthermore, a higher VitK2 intake was related with a lower risk of CAD, according to data from the Prospect-EPIC (European Prospective Investigation into Cancer and Nutrition) cohort research.(37) VitK2 seems to modulate several molecular pathways at vascular level and in bone tissue. VitK2 insufficiency could be the reason of the so-called "calcium paradox" phenomenon, which is characterized by low bone calcium deposition and calcium accumulation in the artery wall.

Dyslipidaemia may also play a role in both osteoporosis and atherosclerosis.(33, 38) Both osteoporosis and cardiac disease lead to an increased amount of lipid oxidation products.(38) These oxidized lipids increase vascular calcification by causing differentiation of calcifying vascular cells. In contrast, oxidized lipids can lead to a decrease in bone mineralization by inhibiting osteoblast differentiation.(33) Additionally, statins have been implicated in alterations in bone mineral density and osteoporosis. The research addressing the role of statin therapy in osteoporosis is equivocal. A nationwide population study in Taiwan demonstrated a protective role of statin in osteoporosis incidence in both men and women.(39) However, another European population study suggested that osteoporosis is underrepresented in low-dose statin treatment and overrepresented in high-dose statin treatment, implying a dose dependent effect.(40)

Cardiac disease remains the leading cause of death within the United States. In 2017, nearly 18 million deaths worldwide were attributed to cardiovascular disease.(41) In addition, osteoporosis is increasingly becoming a cause of poor health outcomes globally, with approximately 1.6 million hip fractures occurring annually and a projected annual incidence of 4.5 million by 2050.(42)

Given how prevalent cardiac disease is within our society, thoracic BMD measured by utilizing CAC scans may allow us to detect osteopenia and osteoporosis before the development of a significant bone fracture. We have demonstrated that there is an inverse relationship between CAC severity and osteoporosis. Performing a single scan to identify both BMD and CAC is significantly cheaper, more convenient for patients and has the benefit of decreasing unnecessary exposure to radiation.(43) Furthermore, intervening early, and preventing a hip fracture from occurring, has proven to be a cost-effective health strategy.(44, 45)

One limitation of our study is that the data availability is limited to calcium progression but not the follow up BMD data. Therefore, we were only able to evaluate whether baseline BMD predicts CAC progression and do not have information about the progression of osteopenia or osteoporosis. BMD measurements over time are unavailable at this time to investigate the temporal relation between outcome and predictor. We selected a sample of subjects from a large and heterogeneous study population. Thus, they are susceptible to selection bias. In addition, we have not stratified our female cohort into pre and postmenopausal. This may be significant as at least one prior study has shown that lower estradiol levels impact BMD(11). Another limitation is, we did not account for serum vitamin D levels and bisphosphonate use due to lack of data availability at this time. Finally, despite our comprehensive adjustment for multiple established CVD risk variables, residual confounding should be considered when interpreting our findings given the study's observational design.

Strengths of this study include the large sample size and the use of cardiac CT to calculate both CAC and quantitative thoracic spine BMD. This cohort, as well as being large population-based sample of both men and women, encompasses multiple different ethnic communities, increasing the generalisability of our results. Unlike previous studies, the use of CAC as an imaging marker of atherosclerosis, provides a better assessment of

subclinical atherosclerosis compared to invasive coronary angiography. CAD using invasive angiography was defined in previous studies based on >50 stenosis in one vessel wherein people without >50% stenosis may have been classified as not having CAD although they may have had subclinical atherosclerosis.(17) Additionally, we found a statistically significant inverse correlation between osteoporosis and CAC score after adjustment for multiple confounders in both men and women.

5.0 Conclusion:

Within the largest known cohort to date, we have shown a statistically significant association between osteoporosis and CAC score in both men and women. Our findings support the hypothesis that thoracic spine BMD is inversely related to CAC scores independent of other cardiovascular risk factors. Further research should focus on assessing for causal relationships between these two entities and elucidating the underlying pathophysiological processes common to both conditions. This in turn may help determine future therapeutic strategies targeting both atherosclerosis and osteoporosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of interest/Funding Support:

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Highlights

- CAC is associated with thoracic spine BMD independent of age and other cardiovascular risk factors.
- In a large ethnically diverse population, as CAC increases the BMD decreases.
- The presence of CAC is associated with increased prevalence of osteoporosis in both men and women.
- CAC and thoracic spine BMD can be obtained from a same non-contrast chest CT scan.

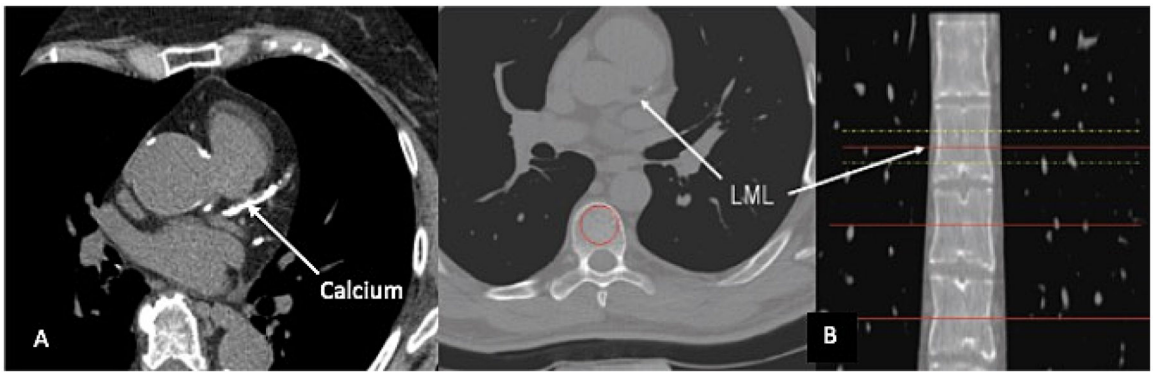

Figure 1:

Illustration of CAC and BMD measurements on thoracic CT scan.

A. Coronary artery calcium in left anterior descending artery. **B.** Measurements are outlined by circle on axial image (left) and indicated by horizontal lines on sagittal image (right). Measurement started at level of section containing left main coronary artery caudally. LML: left main level.

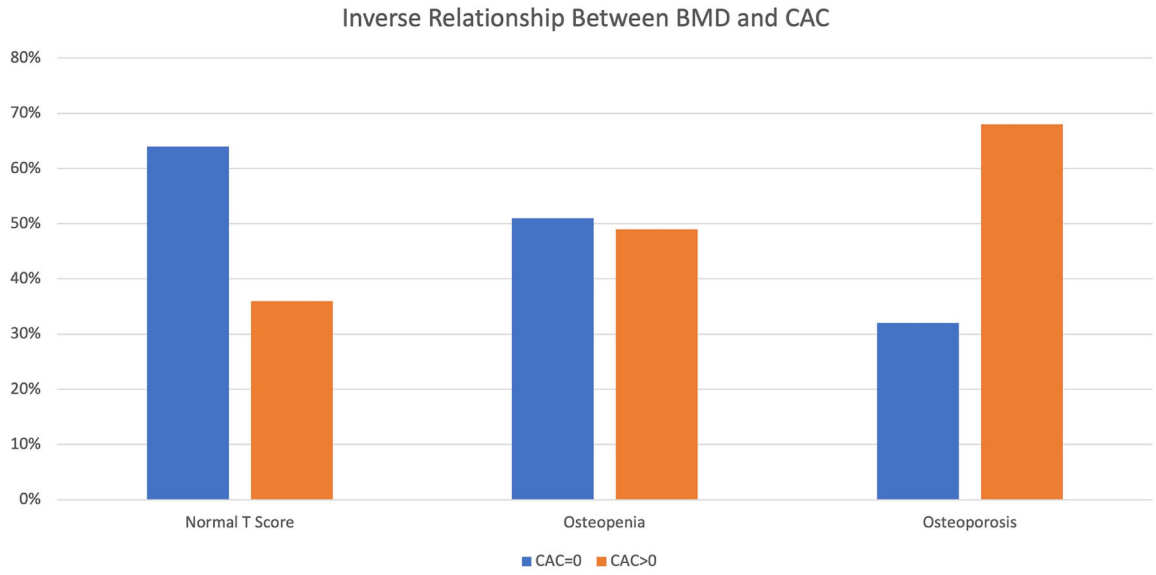

Figure 2:
Prevalence of CAC in participants with normal T-scores, osteopenia and osteoporosis.

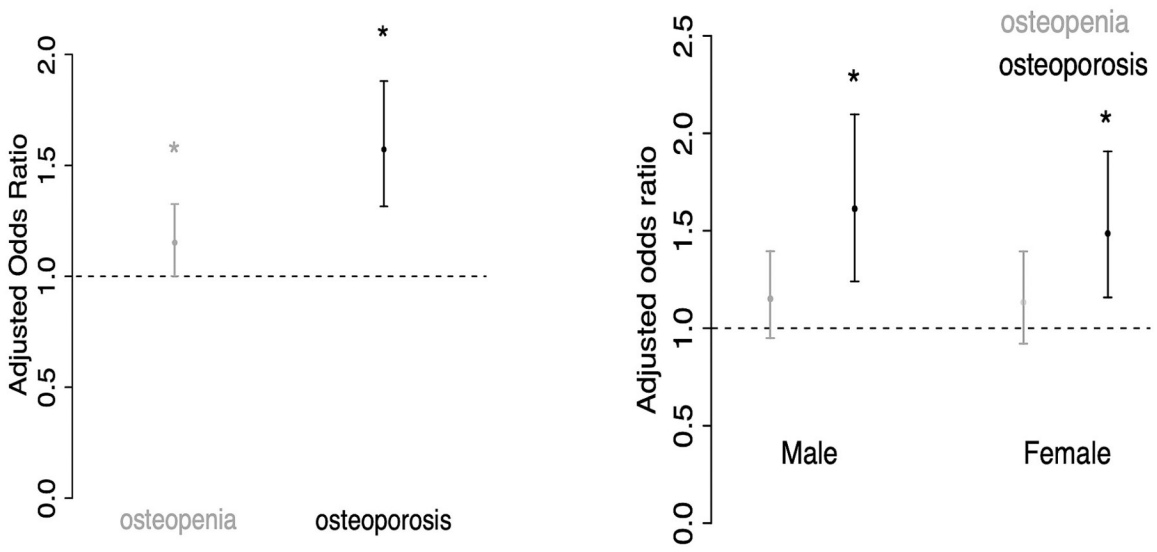

Figure 3:
Graphical representation of measure of association between BMD and CAC score in men and women.

Table 1:

Baseline characteristics of the study population according to CAC score.

	All subjects (n=6,804)	CAC=0 (n=3,412)	CAC>0 (n=3,392)	p value
Age	62.2 (10.2)	58 (9.1)	66.4 (9.5)	<0.0001
Male	3,209 (47%)	1,249 (37%)	1,960 (58%)	<0.0001
Caucasian	2,615 (38%)	1,125 (33%)	1,490 (44%)	<0.0001
Chinese American	804 (11%)	400 (12%)	404 (12%)	<0.0001
African American	1,892 (27%)	1,072 (31%)	820 (24%)	<0.0001
Hispanic	1,493 (21%)	815 (24%)	678 (20%)	<0.0001
Income Level <40,000	3,574 (53%)	1,689 (50%)	1,885 (56%)	<0.0001
Ever smoker	3,370 (50%)	1,496 (44%)	1,874 (55%)	<0.0001
Family history CAD	2,728 (43%)	1,202 (37%)	1,526 (48%)	<0.0001
Menopause[+]	2,943 (82%)	1,625 (75%)	1,318 (92%)	<0.0001
Hypertension	3,054 (45%)	1,199 (35%)	1,855 (55%)	<0.0001
Diabetes Mellitus	1,796 (27%)	721 (21%)	1075 (32%)	<0.0001
BMI	28.3 (5.5)	28.3 (5.7)	28.4 (5.3)	0.63
T-score	−1.6 (1.3)	−1.3 (1.3)	−1.9 (1.3)	<0.0001
BMD	163.4 (46.7)	175 (45.8)	151.6 (44.6)	<0.0001
LDL Chol. (mg/dl)	117.2 (31.4)	116 (30.6)	118.3 (32.1)	0.0025
Triglycerides (mg/dl)	131.6 (88.8)	126.8 (85)	136.4 (92.2)	<0.0001
Lipid lowering medications	1,100 (16%)	364 (11%)	736 (22%)	<0.0001
HRT, Ever Use[+]	1,028 (32%)	625 (34%)	403 (29%)	0.0111

Abbreviations: CAC: coronary artery calcium; BMD: bone mineral density; BMI: body mass index; Chol.: cholesterol; CAD: coronary artery disease; HRT: Hormone replacement therapy. Data are presented as mean (SD) or number (%).

[+]: Indicates applicable to female participants only.

Table 2:

Association between CAC score and reduced thoracic spine BMD

	Osteopenia			Osteoporosis		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Unadjusted	1.657	1.468–1.848	<0.0001	3.650	3.194–4.172	<0.0001
Model 1	1.152	1.001–1.327	0.048	1.573	1.315–1.881	<0.0001
Model 2	1.057	0.913–1.224	0.457	1.408	1.167–1.699	0.0004

Abbreviations: OR: odds ratio; CI: confidence interval.

Model 1: Adjusted for age, gender; BMI, race/ethnicity, diabetes mellitus, hypertension, lipid lowering medications, smoking history, family history CAD, income level and moderate conditioning activity. Model 2: model 1 plus vitamin D and calcium supplementation.

Table 3:

Association between CAC score and reduced thoracic spine BMD stratified by gender

	Females					
	Osteopenia			**Osteoporosis**		
	OR	**CI**	**p value**	**OR**	**CI**	**p value**
Unadjusted	1.735	1.459–2.063	<0.0001	4.393	3.650–5.288	<0.0001
Model 1	1.084	0.868–1.352	0.478	1.375	1.052–1.797	0.020
Model 2	1.089	0.868–1.366	0.461	1.407	1.069–1.851	0.014
	Males					
	Osteopenia			**Osteoporosis**		
	OR	**CI**	**p value**	**OR**	**CI**	**p value**
Unadjusted	1.596	1.356–1.879	<0.0001	3.806	3.076–4.709	<0.0001
Model 1	1.037	0.851–1.263	0.719	1.369	1.042–1.799	0.0242
Model 2	1.003	0.819–1.288	0.977	1.328	1.006–1.754	0.045

Abbreviations: OR: odds ratio; CI: confidence interval.

Model 1 in males: Adjusted for age, BMI, race/ethnicity, diabetes mellitus, hypertension, lipid lowering medications, smoking history, family history CAD, income level and moderate conditioning activity. Model 1 in females: Adjusted for age, BMI, race/ethnicity, diabetes mellitus, hypertension, lipid lowering medications, smoking history, family history CAD, income level, moderate conditioning activity, menopause and ever use of hormone replacement therapy. Model 2: model 1 plus vitamin D and calcium supplementation.