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Bone mineral density and long-term progression of aortic valve and mitral annular calcification: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background and aims: Bone and mineral metabolism has been implicated in the pathophysiology of cardiac valve calcification. Whether bone demineralization, a common aging-related disorder, promotes calcific valve disease remains uncertain. We tested the hypothesis that

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Daniele Massera: Conceptualization, Methodology, Writing – original draft. **Petra Buzkova:** Methodology, Formal analysis, Writing – review & editing. **Anna E. Bortnick:** Conceptualization, Methodology, Investigation, Writing – review & editing. **David S. Owens:** Investigation, Writing – review & editing. **SongShou Mao:** Investigation, Writing – review & editing. **Dong Li:** Investigation, Writing – review & editing. **Ian H. De Boer:** Investigation, Writing – review & editing. **Bryan R. Kestenbaum:** Investigation, Writing – review & editing. **Matthew J. Budoff:** Methodology, Investigation, Writing – review & editing. **Jorge R. Kizer:** Conceptualization, Methodology, Writing – original draft, Resources, Supervision.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.08.031.

low bone mineral density (BMD) is associated with greater incidence/progression of cardiac valve calcification in the Multi-Ethnic Study of Atherosclerosis.

Methods: Using linear mixed-effects models, we related baseline measurement of BMD of the thoracic vertebrae by computed tomography (CT) in 6768 participants to serial CT assessments of aortic valve calcification (AVC) and mitral annular calcification (MAC) obtained over a >10-year period.

Results: After multivariable adjustment, lower BMD (per SD decrement) was associated with accelerated increase in AVC over time in women (0.76 [95% CI 0.42,1.09] Agatston -units [AU]/year) and men (1.41 [95% CI 0.48,2.33] AU/year), as well as for MAC in women (3.22 [95% CI 1.16,5.28] AU/year) and men (3.59 [95% CI 2.09,5.09] AU/year). Significant effect modification was observed, with more pronounced BMD-related acceleration of AVC and MAC progression in older or white participants of one or both sexes, as well as by estimated glomerular filtration rate, though the latter differed by sex for AVC and MAC.

Conclusions: In this multi-ethnic cohort, low thoracic BMD was significantly, but modestly, associated with increased AVC and MAC progression. This suggests that altered bone mineral metabolism does not have a major impact on calcific valve disease in the general population, but the possibility of a more meaningful influence in higher-risk individuals with osteoporosis will require further investigation.

Keywords

Bone mineral density; Aortic valve calcification; Mitral annular calcification; Epidemiology

1. Introduction

Calcification of the aortic valve and mitral annulus is a common-aging related disorder [1,2]. Aortic valve calcification (AVC) affects 25% of older individuals by echocardiography, and is associated with increased cardiovascular morbidity and mortality [3]. Progressive calcification restricts leaflet opening and, in ~4% of older adults [4], may eventuate in severe aortic stenosis, which becomes rapidly fatal once symptomatic [1]. Mitral annular calcification (MAC) is present in some 40% of older adults by echocardiography [2,3,5]. MAC can lead to mitral valve regurgitation or stenosis, endocarditis, and embolism, and has correspondingly been linked to increased risk of cardiovascular events [6,7]. To date, no medical therapies have been shown to prevent onset or progression of AVC or MAC, leaving costly procedural interventions as the only option once severe valvular disease occurs [1,2].

Development of effective medical treatments for calcific valve disease rests with improved understanding of its pathogenesis. Both AVC and MAC bear some of the pathophysiologic hallmarks of atherosclerosis and vascular calcification, although each exhibits distinctive features [2, 8]. One element common to both valvular/annular and arterial disease is ectopic bone formation, and these cardiovascular disorders have been linked to mineral metabolism and its regulation [9]. A reciprocal relationship between skeletal and cardiovascular health has been proposed, wherein bone demineralization and associated pathways promote heart and vascular calcification [8]. Epidemiological studies have documented such a link for osteoporotic bone loss and both arterial calcification [10] and cardiovascular disease (CVD)

events [11]. Corresponding evaluations of bone mineral density (BMD) and calcific valve disease are inconclusive, however, owing to limitations of modest sample size, partial adjustment for confounders, or cross-sectional design [12–15].

To address these gaps, we leveraged serial cardiac computed tomography (CT) scans obtained in a longitudinal population-based multi-ethnic study. Such cardiac CT scans were interpreted for BMD of the thoracic spine at baseline, as well as cardiac valve calcification at multiple time points. We tested the hypothesis that low BMD of the thoracic spine at study onset would be associated with higher incidence and progression of AVC and MAC over long-term follow-up.

2. Participants and methods

2.1. Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of subclinical CVD and its progression [16]. Briefly, a multi-ethnic sample of 6814 community-dwelling adults aged 45–84 years and free of CVD was recruited from six U.S. communities between 2000 and 2002 (Exam 1). Informed consent was obtained at enrollment, and the study was approved by all relevant institutional review boards.

All MESA participants received cardiac CT at Exam 1. A random half of returning participants underwent repeat cardiac CT in 2002–04 (Exam 2) and the second half did so in 2004–05 (Exam 3; combined n = 6058 in Exams 2 and 3) [17]. In 2010–12, 3410 participants completed an additional CT scan (Exam 5). Cardiac CTs at Exam 1, Exam 2/3 and Exam 5 were read for AVC (n = 6812 at baseline, n = 5884 at Exams 2/3, n = 3304 at Exam 5) and MAC (n = 6814 at baseline, n = 5882 at Exams 2/3, n = 3410 at Exam 5). Our analytic sample included all participants with CT-determined thoracic BMD at Exam 1 (n = 6768), all of whom had at least one measure of AVC or MAC during the study period.

2.2. Cardiac CT

Participants underwent non-contrast cardiac CT scans for evaluation of coronary and extra-coronary calcification by the Agatston method [18]. Electron-beam CT (EBCT) or multi-detector CT (MDCT) was performed at Exam 1, with subsequent exams using only MDCT. CTs were performed in duplicate and scores were averaged [18]. There was good reproducibility of AVC and MAC Agatston scores, with variability of 4–13.2% between and within readers [19]. AVC was defined as =1 calcification foci with Agatston score >0 Agatston units (AU) within the aortic valve leaflets [19]. MAC was defined as ≥1 calcification foci with Agatston score >0 AU within the mitral annulus. Prevalent calcification was defined as a score >0 AU at Exam 1, and incident calcification as a score >0 on subsequent scans if baseline calcification was absent. All scans were centrally read at the Harbor-UCLA Research and Education Institute, Los Angeles, CA.

2.3. Thoracic BMD

BMD was measured in three consecutive thoracic vertebrae beginning at the level of the left main coronary artery (usually either T7 or T8) [20]. A region of interest was placed

at the center of each vertebra, with a 2–3 mm distance from the cortical shell, ensuring that BMD measurements within the vertebral body excluded cortical bone. Areas containing large vessels, bone island fractures or calcified herniated disks were excluded by manual free tracing. Mean BMD across the thoracic vertebrae was then calculated. Hounsfield units were converted to BMD (mg/cm^3) using a calibration phantom of known density or a scanner-specific mean calibration factor for the T7-T10 vertebrae from scans performed without the phantom. All BMD measurements were performed separately from the AVC and MAC determinations by one radiologist at Harbor-UCLA.

2.4. Covariates

Baseline demographic, lifestyle and clinical information was obtained by trained personnel [16]. Physical activity was measured using standardized questionnaires [21]. Blood samples were collected after a 12-h fast and analyzed centrally. Diabetes was defined as fasting glucose ≥126 mg/dL or anti-diabetic treatment. Smoking was defined as ≥1 cigarette smoked, and current if occurring in the preceding 30 days. Estimated glomerular filtration rate (eGFR) was calculated using cystatin-C. Lipoprotein (a) was measured using a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) [22]. Mineral metabolism markers were measured using standardized methods [23]. All covariates were missing at random in ≤5% of the cohort, with the exception of lipoprotein (a). The latter was measured in a subgroup of MESA participants, excluding those taking lipid-lowering medication (n = 1090) and another subset (n = 1000) whose stored samples had been depleted by the time of laboratory measurement.

2.5. Statistical analysis

Linear mixed-effects models (LMMs) were used to evaluate the association of thoracic BMD with AVC and MAC over time in participants without or with any calcification at baseline [23]. This approach permits assessment of relationships with both incidence and progression of the cardiac calcification outcomes in an integrated fashion [24]. LMMs enable inclusion of individuals with a variable number of observations in the analysis, even those with a single observation. They also allow adjustment for baseline levels of the outcome measure, circumventing the potential bias introduced in progression studies when controlling for measured baseline [24]. Further, the assumption that follow-up data are missing completely at random is not required, lessening concerns over selection bias. We used LMMs with random intercepts to test if lower volumetric BMD was associated with greater AVC and MAC scores per unit time while accounting for baseline levels of calcification, potential confounders, and, in exploratory models, putative intermediates. Although both AVC and MAC were heavily zero-weighted variables with skewed distributions, we relied on the premise that, in large samples, the mean of the outcome measure in generalized linear models is asymptotically normal [25]. The same LMM approach has been previously applied in MESA for coronary artery calcification [24] and valvular/annular calcification [23]. Our primary approach was to assess AVC and MAC in their original units for ease of interpretation, but given the skewness of these outcome measures, we also performed the analyses after logarithmic transformation (log2[AVC+1] and $\log_2$[MAC+1]). We assessed the functional form of exposure-outcome associations

using generalized additive model plots, which revealed no obvious departures from linearity. Robust standard errors were calculated using the parametric bootstrap method.

We stratified all analyses a priori by sex. Selection of potential confounding variables was based on known biology or prior associations. In Model 1, we adjusted for age, race/ethnicity, field center and scanner type. In Model 2 (main model), we additionally adjusted for education, body mass index (BMI), systolic blood pressure, antihypertensive treatment (excepting thiazide diuretic), thiazide diuretic treatment, diabetes, smoking, LDL, HDL, triglycerides, lipoprotein (a) (only for AVC), statin therapy, hormone replacement therapy, warfarin, oral glucocorticoid treatment, anti-resorptive therapy, and eGFR. In Model 3, we explored whether the association was independent of biochemical mineral markers, some partly in the causal pathway, by additionally adjusting for serum calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D and FGF-23. Moreover, we examined whether additional adjustment for physical activity or C-reactive protein (CRP) influenced the associations. Last, because a subset of participants, particularly those with high calcification values at baseline, exhibited negative valves for AVC or MAC progression, we assessed the impact of excluding those in the top 5% with the most negative progression values. $p < 0.05$ was the threshold for statistical significance.

We next examined three-way interactions by the prespecified covariates age, sex, race/ethnicity, and eGFR. To account for multiple comparisons, we used $p < 0.01$ to define statistical significance for interactions.

In secondary analyses of participants with follow-up calcification measures, we assessed relationships of thoracic BMD with onset of AVC and MAC in the subset without baseline calcification, and progression of AVC and MAC in the subset with baseline calcification. We focused on Exam 5 measures of AVC and MAC when available, given the more informative nature of long-term follow-up, and used Exam 2/3 measures otherwise. We also repeated the analyses only among participants with available Exam 5 calcification measures. For incident AVC and MAC, we applied quasi-Poisson regression with an offset for different time intervals between baseline and follow-up outcome measures. For AVC and MAC progression, we used linear regression of change in calcification measures divided by time interval between scans to yield annualized change as the outcome measure. All analyses were performed with R 3.3.1 (Vienna, Austria) and GraphPad Prism 7 (La Jolla, CA).

3. Results

3.1. Baseline characteristics

A total of 6768 participants were included. Mean (SD) BMD was 62.1 (10.3) mg/cm^3 in women and 62.2 (10.2) mg/cm^3 in men. The distributions of baseline covariates overall and by quartiles of BMD are shown in Table 1. BMD was inversely associated with age, systolic blood pressure, 25-hydroxyvitamin D, osteoporosis medication, oral glucocorticoid use, AVC and MAC, and positively with BMI, education, hormone replacement therapy, eGFR and CRP. A larger proportion of White and Chinese participants had low BMD compared with Black and Hispanic participants.

3.2. Incidence/Progression of cardiac calcification

Follow-up times for the 5943 participants with ≥1 repeat AVC determination, wherein the Exam 5 measure was used primarily when available, and the Exam 2 or 3 measure used otherwise, are plotted in Supplemental Fig. 1 (the virtually identical plot for MAC is not shown.) The median (IQR) interval between exams was 8.9 (2.1,9.4) years. Sex-stratified incidence rates and annual changes of AVC and MAC are shown in Table 2. Incidence and annual change of both calcification measures increased from the fourth quartile of thoracic BMD to the first quartile. Box plots of overall annualized changes in AVC and MAC are presented in Supplemental Fig. 2. Altogether, 274 (5.3%) and 153 (2.8%) participants of either sex had negative values for AVC and MAC progression, respectively, all with prevalent calcification (AVC>0 or MAC>0) at baseline. The top 5th percentile of such negative annualized progression values was —107.3 AU/year for AVC and —346.8 AU/year for MAC.

3.3. BMD and incidence/progression of cardiac calcification

The beta coefficients for the cross-product term of BMD by time, corresponding to the slope of increase in AVC and MAC, are presented in Fig. 1. Lower thoracic BMD was associated with a faster rate of increase in AVC and MAC over time in both sexes at all levels of adjustment. This was the case for the main model (Model 2), as well as for the model additionally adjusting for mineral metabolism factors (Model 3). These associations were more pronounced in men than women, significantly so for AVC in the main model ($p_{\text{interaction}}<0.001$), but marginally nonsignificantly for MAC ($p_{\text{interaction}} = 0.017$). For AVC,after adjustmntn for covariates in the main model, the annual increase was accelerated by 0.76 (95% CI 0.42,1.09) AU for every SD decrement of BMD in women, and by 1.41 (95% CI 0.48,2.33) AU in men. For MAC, after similar adjustment, the annual increase was accelerated by 3.22 (95% CI 1.16,5.28) AU for every SD decrement in women, and by 3.59 (95% CI 2.09,5.09) AU in men. Removal of lipoprotein (a), a covariate with substantial missingness, from Model 2 did not meaningfully influence the risk estimates for AVC in either sex. Further adjustment for physical activity or CRP also had no material impact. Exclusion of participants with extreme negative values (top 5%) for AVC or MAC progression did not meaningfully alter the results. Similar associations were detected when AVC and MAC were logarithmically transformed (Supplemental Table 1).

To place in context the magnitude of annual AVC and MAC increases associated with a SD decrement in BMD in context, we provide the corresponding increases (main effects) associated with a 1-year increment in participant age after adjustment for Model 2 covariates. Specifically, these were 1.89 (95% CI 1.40,2.39) AU for women and 3.54 (2.32,4.76) AU for men in the case of AVC, and 9.74 (95% CI 6.92,12.55) AU for women and 4.06 (2.05,6.07) AU for men in the case of MAC.

3.4. Effect modification

Analyses of three-way interactions for thoracic BMD with time and pre-specified covariates are presented in Table 3. There was significant effect modification by age of the association of thoracic BMD with accelerated incidence/progression of AVC and MAC. Participants of either sex aged ≥65 years had more pronounced acceleration of AVC than those <65

years. This was also the case for men with regard to acceleration of MAC, but was not seen for women. Significant effect modification was likewise observed for race/ethnicity, where acceleration of AVC and MAC for Whites was more pronounced than for other race/ethnic groups. There was also evidence of effect modification by eGFR. For AVC, the interaction was significant for continuous eGFR but not dichotomized eGFR (at 60 ml/min/1.73 m^2) in women, whereas the opposite was true in men (significant interaction for dichotomized, but not continuous eGFR). For MAC, interactions with both continuous and categorized eGFR were significant. Directions of effect modification also differed in men and women for AVC and MAC, wherein the acceleration of AVC incidence/progression by thoracic BMD was more pronounced with low eGFR in women, but high eGFR in men. By contrast, BMD-related acceleration of MAC incidence/progression was more pronounced at high eGFR in women, but low eGFR in men.

3.5. Secondary analyses

Among participants without baseline calcification, there was no association of thoracic BMD with incident AVC and MAC in either sex (Supplemental Table 2). When restricting the analyses to participants with available Exam 5 calcification measures, however, there was a significant association of BMD with incident MAC in men (HR 1.28 per SD decrement, 95% CI 1.04,1.54; $p = 0.012$), but not in women (Supplemental Table 2). Last, in analyses of AVC or MAC progression among those with calcification at baseline, there were no significant associations of thoracic BMD with these measures (Supplemental Table 3).

4. Discussion

4.1. Main findings

In this study, we demonstrate modest inverse associations of thoracic BMD with incidence/progression of AVC and MAC in men and women from a multi-ethnic population-based cohort without known CVD. Lower BMD was significantly associated with greater incidence/progression of AVC and MAC by cardiac CT at repeated time points over ~10 years. These associations persisted despite adjustment for lipids, kidney function, bone-influencing medications, and even biomarkers of bone mineral metabolism, many of which are shared risk factors for valve calcification and osteoporosis. In secondary analyses, these associations were more pronounced in those ≥65 years, as well as Whites. In the case of eGFR, however, there was a suggestion of discordant effect modification. Namely, BMD-related acceleration of AVC incidence/ progression was more pronounced for low eGFR in women and high eGFR in men, whereas the opposite was apparent for MAC incidence/progression, where high eGFR in women but low eGFR in men were associated with more marked acceleration.

4.2. Prior literature

Various clinical studies have investigated the relationship between bone demineralization and calcific valve disease. In different referral-based cross-sectional studies of modest size, BMD of the lumbar spine or hip measured by dual-energy x-ray absorptiometry (DXA) was found to be inversely associated with prevalent echocardiographic AVC [26, 27] or MAC [28] in men and women. By contrast, in a small sample with calcific aortic valve disease,

no association was detected between CT-determined thoracic BMD and either AVC or MAC, nor was 18F-sodium fluoride bone activity related to valvular/annular calcification [29,30].

Larger cross-sectional studies of population samples, in the main, have also been null. Among 1497 older adults in the Cardiovascular Health Study who received DXA, we found no associations between hip BMD and echocardiographic AVC or MAC, though men with BMD in the osteoporotic range had increased prevalence of AVC [14]. Likewise, in the Framingham Offspring Study, in which vertebral BMD and cardiac calcification were determined by CT in 1318 men and women, no association was detected between lumbar BMD and prevalent AVC or MAC [13]. Yet in a prospective evaluation of 15,651 EPIC-Norfolk participants, ultrasound-derived calcaneal BMD was found to be inversely associated in men and women with hospitalization for incident aortic stenosis (122 cases), determined by billing codes [12]. The relationship was marginally significant, however, and no adjustment for kidney function was undertaken. Meanwhile, in a longitudinal study of 162 men and women with aortic stenosis who underwent DXA of the femoral neck and repeat echocardiograms, sex-specific tertiles of BMD were not associated with rate of aortic stenosis progression, but osteoporosis was [15].

To our knowledge, the present study of CT-determined thoracic BMD and repeated CT measures of AVC and MAC over ~10 years of follow-up in a multi-ethnic population initially free of clinical CVD is the first of its kind. Among the study's strengths are the high accuracy and precision of CT-based measures of volumetric BMD and valvular/annular calcification. These strengths also include the use of LMMs to account for prevalent cardiac calcification while incorporating all available data points to evaluate incidence/progression of AVC or MAC during the course of long-term follow-up – as highlighted by failure of the secondary analyses assessing incidence and progression separately to detect similar associations. Against the lack of previous compelling data, the prospective associations documented here for thoracic BMD and both AVC and MAC in men and women alike therefore represent the best evidence to date of the link between osseous demineralization and calcification of the fibrous skeleton of the heart.

4.3. Potential mechanisms

Several mechanisms could account for the observed relationships. First, bone demineralization releases calcium and phosphate into the circulation, and elevated extracellular phosphate promotes trans-differentiation of valvular interstitial cells to an osteogenic phenotype [31]. Furthermore, high plasma phosphate stimulates osteocyte release of FGF-23, a phosphaturic hormone that we previously linked to accelerated progression of MAC in this cohort, which could engage cardiac FGF receptors to stimulate calcification-inducing pathways [23]. Adjustment for circulating phosphate and FGF-23, however, had no discernible impact on the associations. Second, the bone regulatory system composed of receptor activator of nuclear factor kappa B (RANK) – found on osteoclasts and osteoblasts – its ligand (RANKL), and its inhibitor, osteoprotegerin, may be a factor [32]. Whereas high extracellular RANKL levels stimulate resorption in osteoclast-rich bone, they have the opposite effect in valvular/annular tissue, where cells of osteoblastic phenotype predominate, to promote bone formation [8]. Whether perturbations in circulating RANKL

and osteoprotegerin levels could account for the reciprocal relationship of mineralization in heart and bone remains uncertain, however.

Apart from these mechanisms that place dysregulated bone metabolism in a causal role, the link between osseus demineralization and cardiac calcification could relate to common underlying processes. In particular, aging-related inflammation has been implicated in both osteoporosis and heart calcification [33,34]. We did not, however, find any appreciable effect of additional adjustment for CRP on our findings. Moreover, oxidized LDL has been shown to contribute to both osteoporosis and calcific valve disease [35]. Although oxidized LDL measures were not available in our cohort, the associations persisted after adjustment for LDL and, in the case of AVC, lipoprotein (a). In addition, shared modifiable risk factors such as physical activity or dietary factors such as vitamin K deficiency, through the latter's effects on key regulators of mineral metabolism – matrix γ-carboxyglutamic acid protein or osteocalcin [8] – could account for the observed relationships. Additional adjustment for physical activity had no material impact on the associations, but measures of vitamin K status were not widely obtained in MESA, precluding assessment of their contributions herein.

We found that effect modification by sex was such that the associations of BMD with AVC and, less clearly, MAC were stronger for men than women. Because the pathogenesis of osteoporotic bone loss differs between men and women, being predominantly related to postmenopausal estrogen withdrawal in the latter [36], this finding suggests that osteoporosis mechanisms in men may bear a closer relationship to cardiac calcification, particularly involving the aortic valve. The presence of effect modification by age is consistent with the age dependence of osteoporosis and cardiac calcification processes. In turn, the associations of BMD with AVC and MAC were most pronounced in non-Hispanic White participants, findings consistent with the higher susceptibility to osteoporosis and cardiovascular calcification previously documented in this race/ethnic group [37]. Last, there was evidence of effect-modification by eGFR that followed sex-specific lines, such that chronic kidney disease (CKD) accentuated the inverse association of BMD with AVC in women and MAC in men, with the converse true for AVC in men and MAC in women. But only ~12% of women and ~8% of men in our cohort had CKD (eGFR<60 ml/min/1.73 m^2), predominantly of mild severity. Hence, these results based on relatively limited observations lack rigor and must be interpreted with caution. As with all interactions documented in our secondary analyses, such findings will require replication, especially in cohorts with more prevalent or advanced CKD. Yet, because AVC has a male predilection, while MAC exhibits a female predominance, these results could indicate that the roles of CKD and associated mineral bone disease as determinants of heart mineralization may assume greater importance for the kind of cardiac calcification to which each sex exhibits a lower inherent predisposition.

4.4. Clinical implications

With rising age of the population, the public health impact of osteoporosis and calcific valve disease is bound to rise. Given the potential link between the two disorders, SALTIRE 2 recently evaluated whether anti-osteoporosis medications prevent AVC progression in

patients with mild-moderate aortic stenosis not receiving osteoporosis treatment [38]. This clinical trial of White and predominantly male patients did not, however, find benefit for either alendronate or denosumab in reducing AVC progression in this context.

Although we document statistically significant associations of BMD with AVC and MAC in our study, these associations are modest in magnitude, with a SD change in BMD associated with 33–88% of the valvular calcification differences seen for a 1-year change in age. Such modest associations may relate to the study population being substantially middle-aged and generally healthy, with no cardiovascular and little CKD. In fact, the baseline and annual increases in AVC levels were quite mild in reference to prior cohort studies that included participants with clinical CVD [13], as well as to cutpoints for severe aortic stenosis, namely, ≥1200 AU in women and ≥2000 AU in men [1]. There was also variability in AVC and MAC determinations, such that negative progression values were observed in a minority of participants, mostly with high baseline values for calcification. Such negative progression values are primarily explainable by measurement variability or error, which likely biased the associations toward the null hypothesis. Additionally, a single measurement of BMD, and one limited to one body region, is unlikely to fully capture the systemic and dynamic processes of bone remodeling over time. This may also have resulted in underestimation of the true strength of the associations. Hence, that these modest prospective associations with AVC and MAC were observed for a one-time measure of thoracic BMD in the early stages of valvular/annular calcification occurring in our cohort supports the premise that biological mechanisms underlie the relationship between bone demineralization and calcific valve disease. The modest association observed is consistent with the SALTIRE 2 findings in indicating that demineralization is not a dominant risk factor for valvular calcification progression. But our findings do point to the possibility that targeting individuals that were not the focus of SALTIRE 2, such as those with osteoporosis, women, or with only mild AVC; or other bone demineralization pathways that might bear more direct linkage to valvular/annular calcification, could still yield clinical benefit.

4.5. Limitations

As noted, BMD was analyzed at baseline only, but may have changed during follow-up, suggesting that the observed risk estimates could be strengthened by repeated BMD measures over time. Furthermore, the burden of AVC and MAC was relatively low in this cohort, which may have limited power to detect associations in subgroups. In addition, while our use of LMM allowed us to include all available observations and reduce biases stemming from loss to follow-up, it should be noted that much of the data on incidence and progression of AVC and MAC was predicated on completing the Exam 5 cardiac CT scan. Hence, the current findings must be interpreted as applying to generally healthier participants in our cohort. Last, Lp (a) measurement was available in a non-random subset of the cohort, such that we could not definitively evaluate its influence on the BMD-AVC relationship. Lp (a) measures were obtained in a majority of participants, however, such that complete measurement is unlikely to have had a different impact on the associations observed.

4.6. Conclusions

We found that a one-time CT measure of BMD bears significant, but modest, inverse associations with development of AVC and MAC over long-term follow-up in both men and women from a multi-ethnic study. These prospective associations appeared stronger in men, older participants, and those of White race/ethnicity, and to be differentially influenced by CKD in men and women. Our findings align with a recent clinical trial of osteoporotic drug therapies indicating that bone loss may not be a dominant risk factor for AVC progression generally. The present results do suggest, however, that mechanisms linking demineralization and calcific valve disease could be of relevance in certain groups with more severe bone loss. As such, they provide impetus for further investigation into underlying pathways and whether these could be manipulated to lessen the impact of these disorders in such high-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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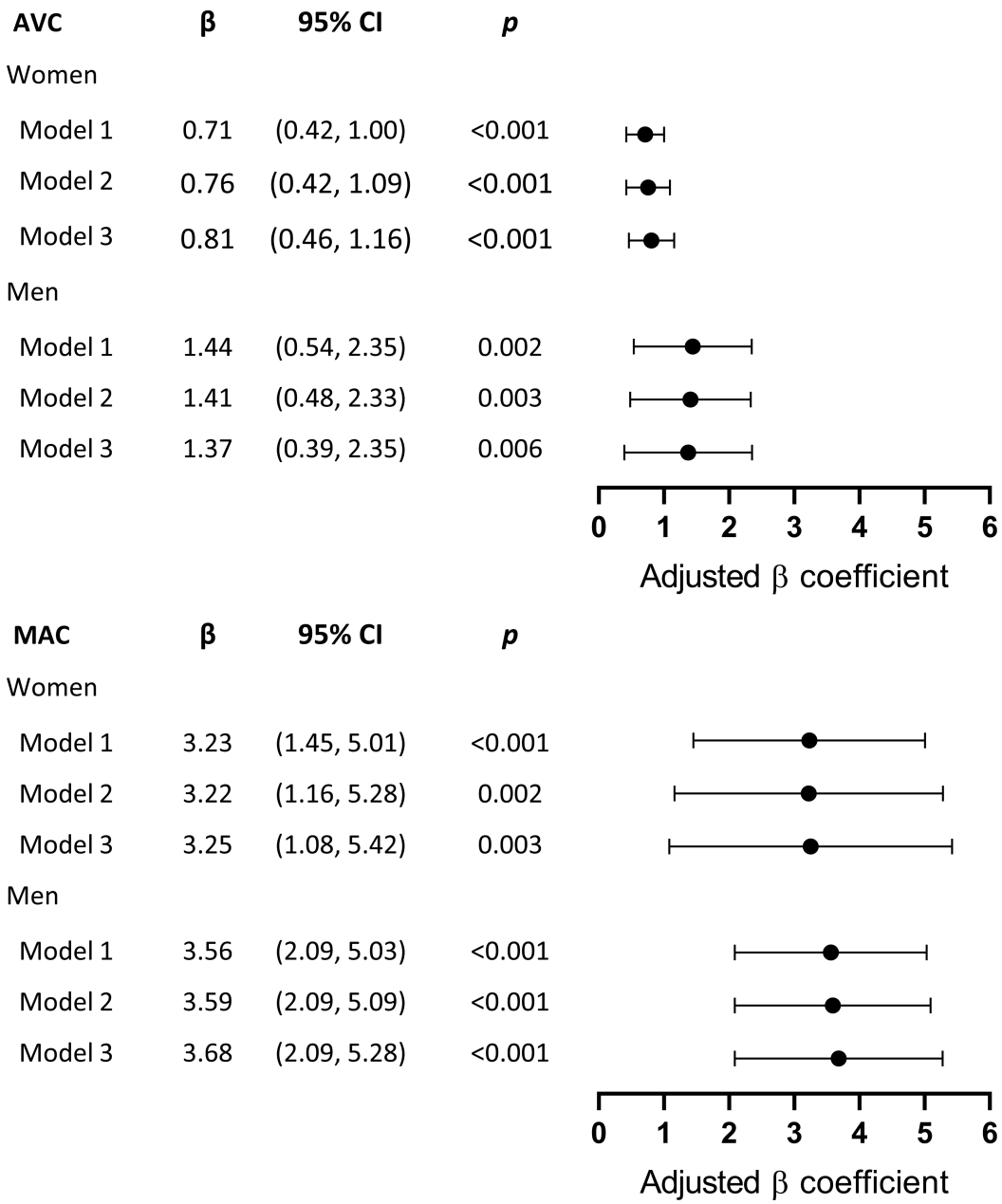

Fig. 1.

Associations of thoracic BMD with AVC and MAC incidence/progression stratified by sex. β coefficients represent the change in AVC or MAC in AU/year associated with a standard deviation [46.84 mg/cm^3] decrement in BMD. Models 1–3 are as described in the Participants and methods section.

Table 1

Baseline characteristics overall and by quartiles of BMD.

	Total (n = 6768)	Q1 (n = 1692)	Q2 (n = 1693)	Q3 (n = 1691)	Q4 (n = 1692)
BMD, mg/cm^3	162.57 (46.84)	106.45 (17.75)	145.06 (8.65)	174.51 (9.11)	224.27 (29.93)
Age, years	62.2 (10.2)	69.6 (8.3)	63.3 (9.3)	59.6 (9.4)	56.1 (8.8)
Men, n (%)	3195 (47.2)	701 (41.4)	854 (50.4)	894 (52.9)	746 (44.1)
Race/ethnicity, n (%)					
White	2606 (38.5)	932 (55.1)	727 (42.9)	570 (33.7)	377 (22.3)
Chinese	802 (11.8)	222 (13.1)	220 (13)	209 (12.4)	151 (8.9)
Black	1884 (27.8)	224 (13.2)	372 (22)	503 (29.7)	785 (46.4)
Hispanic	1476 (21.8)	314 (18.6)	374 (22.1)	409 (24.2)	379 (22.4)
EBCT scanner type, n (%)	3570 (52.7)	873 (51.6)	903 (53.3)	933 (55.2)	861 (50.9)
>High school education, n (%)	4304 (63.8)	995 (59.2)	1068 (63.2)	1127 (66.8)	1114 (66.1)
Body mass index, kg/m^2	28.3 (5.5)	26.6 (4.7)	27.9 (5.2)	28.5 (5.1)	30.3 (6.2)
Physical activity, MET-min/wk	5751 (5906)	4654 (4829)	5368 (5155)	6170 (6573)	6812 (6621)
Systolic blood pressure, mmHg	127 (22)	130 (23)	127 (21)	125 (21)	124 (20)
Diastolic blood pressure, mmHg	72 (10)	70 (10)	72 (10)	73 (10)	73 (10)
Antihypertensive treatment,[a] n (%)	2280 (33.7)	622 (36.8)	564 (33.3)	549 (32.5)	545 (32.2)
Thiazide diuretic, n (%)	755 (11.2)	193 (11.4)	184 (10.9)	160 (9.5)	218 (12.9)
Diabetes, n (%)	854 (12.7)	179 (10.6)	219 (13)	209 (12.4)	247 (14.7)
Ever smoking, n (%)	3348 (49.6)	830 (49.3)	887 (52.5)	824 (48.8)	807 (47.9)
LDL-cholesterol, mg/dL	117 (31)	118 (32)	117 (32)	118 (31)	115 (31)
HDL-cholesterol, mg/dL	51 (15)	53 (15)	51 (15)	50 (15)	50 (14)
Triglycerides, mg/ dL	132 (89)	130 (91)	131 (75)	134 (95)	132 (93)
Lipoprotein (a), mg/dL	30 (32)	28 (32)	28 (31)	29 (31)	34 (35)
Cholesterol lowering therapy, n (%)	1098 (16.2)	340 (20.1)	305 (18)	244 (14.4)	209 (12.4)
Hormone replacement therapy, n (%)	1024 (31.8)	206 (21.3)	263 (33.1)	267 (37.9)	288 (38.1)
Warfarin, n (%)	24 (0.4)	11 (0.7)	6 (0.4)	4 (0.2)	3 (0.2)
Oral gluococorticoid therapy, n (%)	105 (1.6)	46 (2.7)	24 (1.4)	19 (1.1)	16 (0.9)
Osteoporosis medication, n (%)	311 (4.6)	180 (10.6)	80 (4.7)	34 (2)	17 (1)
eGFR, ml/min/1.73m^2	81 (18)	77 (17)	802 (17)	83 (21)	84 (18)
C-reactive protein, mg/L	1.9 (0.8,4.3)	1.6 (0.7,3.6)	1.8 (0.9,4.1)	1.9 (0.8,4.2)	2.3 (1.0,5.7)
Calcium, mg/dL	9.7 (0.4)	9.7 (0.4)	9.7 (0.4)	9.7 (0.4)	9.6 (0.4)
Phosphate, mg/dL	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)	3.6 (0.5)	3.7 (0.5)
25-hydroxyvitamin D, ng/mL	25.4 (11.5)	27.6 (11.2)	26.2 (11.3)	24.9 (11.7)	23.0 (11.5)
Parathyroid hormone, pg/mL	44.7 (21.8)	44.3 (20.6)	44.3 (21.3)	44.6 (21.8)	45.8 (23.5)
Fibroblast growth factor-23, pg/mL	40.3 (18.5)	40.3 (18.4)	40.5 (16.9)	40.1 (15.8)	40.4 (22.1)
AVC>0 AU, n (%)	908 (13.4)	360 (21.3)	260 (15.4)	181 (10.7)	107 (6.3)
MAC>0 AU, n (%)	640 (9.5)	307 (18.1)	157 (9.3)	114 (6.7)	62 (3.7)

AU = Agatston units; AVC = aortic valve calcification; EBCT = electron beam computed tomography; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAC = mitral annular calcification.

[a]Excluding thiazide diuretics.

Table 2

Incidence rates and annual change of AVC and MAC overall and by quartiles of BMD.

	Total	Q1	Q2	Q3	Q4
AVC					
Women					
Number of events/sample	169/2830	56/684	36/649	41/680	36/817
Incidence rate[a] (95% CI)	0.95 (0.80,1.13)	1.45 (1.05,1.99)	0.88 (0.63,1.23)	0.95 (0.65,1.38)	0.65 (0.46,0.91)
Annualized change, mean (SD)	1.23 (22.35)	2.32 (34.17)	1.04 (18.17)	1.14 (14.99)	0.42 (15.26)
Annualized change among participants with prevalent AVC at baseline (n = 287), mean (SD)	6.22 (60.48)	5.14 (60.09)	6.92 (55.01)	11.77 (57.69)	1.44 (78.30)
Men					
Number of events/sample	223/2369	63/459	59/621	53/690	48/599
Incidence rate[a] (95% CI)	1.51 (1.31,1.73)	2.36 (1.83,3.04)	1.50 (1.12,2.01)	1.21 (0.90,1.63)	1.25 (0.94,1.64)
Annualized change, mean (SD)	3.55 (44.22)	5.80 (76.69)	3.88 (34.88)	3.46 (32.64)	1.10 (11.86)
Annualized change among participants with prevalent AVC at baseline (n = 457), mean (SD)	16.09 (107.69)	15.86 (147.57)	17.31 (80.97)	18.90 (85.09)	7.49 (40.56)
MAC					
Women					
Number of events/sample	312/2803	108/654	88/655	66/676	50/818
Incidence rate[a] (95% CI)	1.76 (1.57,1.98)	2.86 (2.35,3.47)	2.15 (1.70,2.70)	1.55 (1.23,1.95)	0.90 (0.68,1.20)
Annualized change, mean (SD)	10.82 (94.14)	21.83 (145.83)	10.25 (69.23)	7.93 (77.66)	3.14 (51.26)
Annualized change among participants with prevalent MAC at baseline (n = 314), mean (SD)	86.28 (277.25)	93.81 (307.27)	77.68 (194.79)	88.41 (285.83)	62.37 (263.60)
Men					
Number of events/sample	256/2610	76/536	73/698	61/747	46/629
Incidence rate[a] (95% CI)	1.57 (1.38,1.78)	2.47 (1.99,3.06)	1.65 (1.29,2.11)	1.29 (1.01,1.64)	1.13 (0.82,1.55)
Annualized change, mean (SD)	7.01 (62.44)	17.88 (109.20)	5.04 (43.01)	3.24 (44.08)	3.44 (28.83)
Annualized change among participants with prevalent MAC at baseline (n = 217), mean (SD)	70.01 (210.41)	105.64 (269.10)	38.60 (143.54)	38.50 (168.54)	81.25 (142.50)

CI = confidence interval; SD = standard deviation.

[a]Per 100 person-years.

Table 3

Assessment of interactions of thoracic BMD, time and pre-specified subgroups in relation to incidence/progression of AVC or MAC.

	Women				Men			
	n	***p* interaction**	**β[a] (95% CI)**	***p***	**n**	***p* interaction**	**β[a] (95% CI)**	***p***
AVC								
Age		<.001[b]				<.001[b]		
≥65 years	1497		1.15 (0.30,1.00)	0.008	1391		1.10 (−1.21,3.42)	0.351
<65 years	1660		0.17 (−0.12,0.46)	0.245	1734		0.69 (0.09,1.30)	0.025
Race/ethnicity		0.017[c]				<.001[c]		
White	1210		1.65 (0.96,2.34)	<.001	1223		3.05 (1.05,5.06)	0.003
Chinese	353		0.27 (−0.09,0.62)	0.145	381		0.12 (−1.25,1.49)	0.863
Black	929		0.07 (−0.39,0.52)	0.777	824		0.86 (0.19,1.53)	0.012
Hispanic	665		0.74 (−0.16,1.64)	0.106	697		−1.85 (−4.36,0.67)	0.150
eGFR		0.320[d]				<.001[e]		
≥60 ml/min/1.73m^2	2783		0.65 (0.31,0.99)	<.001	2881		1.90 (1.01,2.78)	<.001
<60 ml/min/1.73m^2	374		1.63 (−0.27,2.98)	0.019	244		−6.19 (−12.98,0.61)	0.074
MAC								
Age		<.001[b]				<.001[b]		
≥65 years	1497		−2.14 (−7.97,3.68)	0.471	1391		5.56 (1.96,9.15)	0.002
<65 years	1660		−0.01 (−0.74,0.72)	0.972	1734		0.89 (−0.24,2.01)	0.123
Race/ethnicity		<.001[c]				<.001[c]		
White	1210		6.58 (3.62,9.54)	<.001	1223		3.50 (1.15,5.86)	0.004
Chinese	353		1.38 (−0.98,3.73)	0.253	381		1.70 (−2.32,5.72)	0.407
Black	929		3.09 (0.45,5.73)	0.022	824		0.36 (−0.22,1.48)	0.145
Hispanic	665		0.31 (−7.14,7.76)	0.935	697		7.47 (1.96,12.98)	0.008
eGFR		<.001[f]				<.001[d]		
≥60 ml/min/1.73m^2	2783		4.08 (2.40,5.76)	<.001	2881		2.43 (1.14,3.71)	<.001
<60 ml/min/1.73m^2	374		−14.69 (−29.49,0.12)	0.052	244		23.48 (8.11,38.85)	0.003

[a] β coefficient (annual acceleration in AU per SD decrement in BMD).

[b] For continuous age, corresponding $p_{interaction}<.001$.

[c] Model with interaction terms for all race-ethnic groups as compared with no such terms.

[d] For continuous eGFR, corresponding $p_{interaction}<.001$.

[e] For continuous eGFR, corresponding $p_{interaction} = 0.160$.

[f] For continuous eGFR, corresponding $p_{interaction} = 0.003$.