

## Volumetric and Areal Bone Mineral Density Measures Are Associated with Cardiovascular Disease in Older Men and Women: The Health, Aging, and Body Composition Study

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**Abstract.** The associations of volumetric (vBMD) and areal (aBMD) bone mineral density measures with prevalent cardiovascular disease (CVD) and subclinical peripheral arterial disease (PAD) were investigated in a cohort of older men and women enrolled in the Health, Aging, and Body Composition Study. Participants were 3,075 well-functioning white and black men and women (42% black, 51% women), aged 68–80 years. Total hip, femoral neck, and trochanter aBMD were measured using dual-energy X-ray absorptiometry. Quantitative computed tomography was used to evaluate spine trabecular, integral, and cortical vBMD measures in a subgroup ( $n = 1,489$ ). Logistic regression was performed to examine associations of BMD measures with CVD and PAD. The prevalence of CVD (defined by coronary heart disease, PAD, cerebrovascular disease, or congestive heart failure) was 29.8%. Among participants without CVD, 10% had subclinical PAD (defined as ankle-arm index  $< 0.9$ ). Spine vBMD measures were inversely associated with CVD in men (odds ratio of integral [OR<sub>integral</sub>] = 1.34, 95% confidence interval [CI] 1.10–1.63; OR<sub>trabecular</sub> = 1.25, 95% CI 1.02–1.53; OR<sub>cortical</sub> = 1.36, 95% CI 1.11–1.65). In women, for each standard deviation decrease in integral vBMD, cortical vBMD, or trochanter aBMD, the odds of CVD were significantly increased by 28%, 27%, and 22%, respectively. Total hip aBMD was associated with subclinical PAD in men (OR = 1.39, 95% CI 1.03–1.84) but not in women. All associations were independent of age and shared risk factors between BMD and CVD and were not influenced by inflammatory cytokines (interleukin-6 and tumor necrosis factors- $\alpha$ ). In conclusion, our results provide further evidence for an inverse association between BMD and CVD in men and women. Future research should investigate common pathophysiological links for osteoporosis and CVD.

**Key words:** Volumetric bone mineral density — Areal bone mineral density — Cardiovascular disease — Subclinical peripheral arterial disease — Inflammatory cytokine

Cardiovascular disease (CVD) and osteoporosis are common age-related conditions. Mounting biological [1–6] and epidemiological evidence supports a link between the two diseases. In both cross-sectional and longitudinal epidemiological studies, low bone mineral density (BMD) was related to higher cardiovascular mortality [7–11], cardiovascular morbidity [12–18], and subclinical measures of atherosclerosis [19–31].

An inverse association between bone density and cardiovascular mortality was reported in both women [7–9] and men [10, 11]. In white women, low bone mass was related to higher incidence [12, 15, 17] and prevalence [13, 16] of coronary artery disease and stroke. In men, previous myocardial infarction (MI) was associated with low BMD in a multiethnic population in the Third National Health and Nutrition Examination Survey (NHANES III) [14]. Consistent with these findings, several studies have reported inverse relationships between bone density and subclinical measures of atherosclerosis, including vascular calcification of the aorta [19–22] and coronary arteries [23], carotid plaque and intima-media thickness [24–26], pulse wave velocity [27], and endothelial dysfunction [28]. Similarly, ankle-arm index (AAI) was positively correlated with BMD in an elderly Chinese population [29] and in white postmenopausal women [30, 31].

Several hypotheses have been proposed to explain the link between CVD and osteoporosis, including (1) their age-related independent progression [32–34], (2) the

presence of shared risk factors (e.g., smoking and physical inactivity) [35, 36], (3) the presence of common pathophysiological mechanisms that could lead to the development of both conditions and may involve inflammatory cytokines or endogenous sex hormones [15, 27], and (4) a cause-effect relationship whereby one condition may lead to the other. For instance, atherosclerosis, by reducing blood flow to the lower extremities, could alter bone metabolism in the hip and result in osteoporosis [18, 31].

The nature of the putative link between CVD and osteoporosis is still controversial. Reports on this association have focused mostly on white postmenopausal women. Less is known about the presence of such a relationship in men and in other races. Additionally, the majority of previous studies have not utilized state-of-the-art assessments of bone mass involving quantitative computed tomography (QCT) and dual-energy X-ray absorptiometry (DXA) [8–10, 15, 17, 21, 22, 24, 27, 32]. Furthermore, while inflammatory cytokines have been suggested as a common denominator in the association between osteoporosis and CVD [15, 27], to our knowledge no study has actually examined their role.

The aim of the current study was to evaluate the association of volumetric and areal BMD measures (vBMD and aBMD, respectively) with prevalent CVD and subclinical peripheral arterial disease (PAD) in a biracial cohort of men and women and whether such associations were independent of age, independent of shared risk factors between osteoporosis and CVD, or explained by inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

## Materials and Methods

### Subjects

Participants were enrolled in the Health, Aging, and Body Composition (Health ABC) Study, a population-based prospective study investigating the association between changes in body composition and functional decline in the elderly. The cohort included 3,075 well-functioning, community-dwelling men and women aged 68–80 years. The demographic distribution of the population was as follows: 729 black women, 855 white women, 552 black men, and 939 white men. Participants were identified from a random sample of white Medicare beneficiaries and all age-eligible black community residents in designated zip code areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Subjects who reported difficulty walking one-quarter of a mile, climbing 10 steps, or performing basic activities of daily living; who had a life-threatening illness in the 3 years prior to the study; or who were planning to move in the next 3 years were excluded. Written informed consent was obtained from all participants. The study was approved by the institutional review boards of the University of Pittsburgh and the University of Tennessee.

The current cross-sectional analysis utilized data from the baseline Health ABC examination, performed between April 1997 and June 1998. aBMD data were missing for 32 participants. vBMD was performed at the Pittsburgh site only and

therefore available for only 1,489 participants (out of 1,527). AAI data were missing for 197 participants. Only subjects without CVD were included in the subclinical PAD analysis ( $n = 2,045$ ).

### Prevalent CVD Status

Prevalent disease algorithms were created by Health ABC investigators based on self-reported history and the use of selected drugs in the past 2 weeks. CVD was considered present if one or more of the following conditions were prevalent at the baseline examination: coronary heart disease (defined as self-report of surgical or percutaneous revascularization, self-report of MI or angina, use of antianginal medications, or electrocardiographic evidence of previous MI), cerebrovascular disease (defined as self-report of transient ischemic attack or stroke), PAD (defined as self-report of intermittent claudication or pain in legs or self-report of bypass or angioplasty in leg arteries), congestive heart failure (defined as self-report of congestive heart failure, use of diuretic, and use of vasodilator or cardiac glycoside), or the presence of positive results on the Rose questionnaire for angina or claudication. Overall, 915 participants (29.8%) were identified in this group.

### Subclinical PAD Status

Among participants who did not have CVD, subclinical PAD status was defined using the AAI, which was defined as the ratio of either the right or the left ankle artery systolic blood pressure to the right upper arm systolic blood pressure, measured by a hand-held, 6 MHz Doppler probe placed directly over the artery and a conventional mercury sphygmomanometer. First, two AAI averages were calculated based on two ratios with the right leg and two ratios with the left leg. The lower AAI of the two averages was used. Participants were categorized as having subclinical PAD if they had low AAI, i.e., a ratio of  $<0.9$  [37]. Overall, 206 participants (10.1%) without CVD had subclinical PAD.

### aBMD

aBMD ( $\text{g}/\text{cm}^2$ ) measures of the total hip and hip subregions (femoral neck and trochanter) were assessed using DXA (Hologic 4500A, version 9.03; Hologic, Waltham, MA). DXA quality-assurance measures were performed at both study sites, and identical scan protocols were used for all participants.

### vBMD

QCT was used to obtain vBMD measures ( $\text{mg}/\text{cc}$ ) of the spine (General Electric 9800 Advantage, 80 kVp/140 mAs, 10 mm slice thickness; GE Medical Systems, Milwaukee, WI). QCT images were acquired at the level of the L3 vertebra to obtain trabecular and integral BMD. Cortical BMD, which includes the cortical shell of the vertebral body and the posterior elements, was estimated by taking the difference in BMC between the integral and trabecular regions and dividing it by the difference in the volumes of these two regions. CT numbers were converted to equivalent tissue concentration of hydroxyapatite using a reference calibration phantom placed under the lower back of the participant. Osteophytes were edited out of the external bone contour during image analysis. Scans were performed by certified technicians and analyzed with a standardized protocol at the University of California, San Francisco.

### Inflammatory Cytokines

Concentrations of IL-6 and TNF- $\alpha$  were obtained from frozen stored serum samples collected via venipuncture after an

overnight fast. Cytokines were measured in duplicate using commercial enzyme-linked immunofluorescent assays from R&D Systems (Minneapolis, MN). The lower detectable limit was 0.10 pg/mL for IL-6 and 0.18 pg/mL for TNF- $\alpha$ , the detection range was 0.156–17.0 pg/mL for IL-6 and 0.5–32 pg/mL for TNF- $\alpha$ , and the interassay coefficient of variation was 10.3% for IL-6 and 15.8% for TNF- $\alpha$ . IL-6 and TNF- $\alpha$  were available for 2,913 and 2,872 participants, respectively.

### Potential Confounders

Sociodemographic factors (age, gender, race, study site, education), smoking history, alcohol consumption, weekly physical activity from walking and exercise (kcal/kg/hour), medication use (including hormone therapy, statins, osteoporosis drugs, thiazide diuretics, systemic corticosteroids, calcium supplements, vitamin D supplements), and time since menopause were determined by an interview-administered questionnaire.

Medication use in the previous 2 weeks was coded using the Iowa Drug Information System (IDIS) ingredient codes [38]. Prevalent diabetes was defined as self-report of diabetes previously diagnosed by a physician, use of hypoglycemic medications, or fasting glucose  $\geq 126$  mg/dL. Prevalent hypertension was defined as self-report of hypertension and use of antihypertensive medications. Prevalent osteoporosis (total hip BMD 2.5 standard deviations [SDs] or more below the young adult mean) was defined using gender- and race-specific T scores determined from the NHANES III study population [39].

Lower extremity physical function was assessed by the Health ABC performance battery, a supplemented version of the lower extremity performance test used in the Established Populations for Epidemiologic Studies of the Elderly (EPSE); chair stands, standing balance, 6 m walk for gait speed) with increased test duration, a single foot stand, and a narrow walk test of balance as previously described (score range 0–12) [40]. Height and weight were obtained using a Harpenden stadiometer (Holtain, Crymmych, UK) and a standard balance beam, respectively, and body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). Seated systolic and diastolic blood pressures were measured by a manual mercury sphygmomanometer using a standardized protocol.

Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were measured by a colorimetric technique (Vitros 950 analyzer; Johnson & Johnson New Brunswick, NJ). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Plasma glucose was measured using an automated glucose oxidase reaction (YSI 2300 STAT Plus Glucose & Lactate Analyzer; YSI Life Sciences, Yellow Springs, OH). Serum insulin was assessed using a commercially available radioimmunoassay kit (Pharmacia, Uppsala, Sweden).

### Data Analysis

All analyses were stratified by gender. Baseline characteristics and BMD measures of groups with or without prevalent CVD were compared using the chi-squared test for categorical variables and either the two-sample *t*-test or Wilcoxon's rank-sum test for continuous data. Logistic regression was used to determine the associations of BMD measures with CVD. Separate logistic regression models were fitted for each BMD variable using gender-specific SD scores (calculated as the deviation from the mean BMD divided by the SD of the BMD measure in each gender) instead of raw values. Unadjusted, age-adjusted, and risk factor-adjusted models were fitted. Variables were selected for entry into the multiple regression models if they were associated with CVD and any of the BMD variables at the 0.15 level of significance in univariate analyses.

The effect of IL-6 and TNF- $\alpha$  on statistically significant associations between BMD measures and CVD was tested by

introducing these variables, separately, into multiple regression models. Because of the skewed distribution of IL-6 and TNF- $\alpha$ , their log-transformed values were used in analyses.

Potential racial differences in the relationship of BMD with CVD were tested by entering product terms for race and BMD measures in the multiple logistic regression models. Associations between BMD measures and CVD were presented as unadjusted, age-adjusted, and risk factor-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) per 1 SD decrease in BMD. The Hosmer and Lemeshow test was used to evaluate the goodness of fit of logistic regression models. The level of significance was considered to be  $< 0.05$  except for the initial identification of shared risk factors between CVD and BMD as described above. The same analytical approach was followed for subclinical PAD. In both the CVD and PAD models, no significant interactions between race and BMD measures were observed; therefore, no race-specific analyses were performed. Data were analyzed using SAS version 8.01 (SAS Institute, Cary, NC).

## Results

### Prevalent CVD

Overall, 29.8% ( $n = 915$  out of 3,075) of the study population had CVD. Gender-specific rates were 25.1% in women and 34.7% in men. In both women and men, participants with CVD had higher triglyceride, glucose, insulin, IL-6, and TNF- $\alpha$  levels; had lower HDL and Health ABC performance battery scores; and were more likely to be hypertensive, diabetic, and on statins (Table 1).

In women, none of the BMD variables was related to prevalent CVD in unadjusted or age-adjusted analyses. However, after controlling for shared risk factors between CVD and BMD, cortical vBMD, integral vBMD, and trochanter aBMD became significantly associated with CVD. For every SD decrease in each of these BMD measures, the odds of CVD were increased by 28%, 27%, and 22%, respectively (Table 2). No associations were observed between CVD and trabecular vBMD of the spine, total hip aBMD, or femoral neck aBMD (Table 2).

In men, all vBMD measures (integral, trabecular, and cortical) of the spine were significantly associated with CVD in unadjusted, age-adjusted (except for trabecular), and risk factor-adjusted models. A 1 SD decrease in cortical, integral, or trabecular BMD increased the odds of CVD by 36%, 34%, and 25%, respectively. However, none of the aBMD measures showed an association with CVD (total hip, adjusted OR = 1.14, 95% CI 0.96–1.36; femoral neck, adjusted OR = 1.00, 95% CI 0.87–1.15; trochanter, adjusted OR = 1.02, 95% CI 0.91–1.22) (Table 2).

We tested the effect of IL-6 and TNF- $\alpha$  on the associations that were statistically significant in fully adjusted models. In women, IL-6 and TNF- $\alpha$  levels were significantly higher among participants with CVD compared to those who did not have CVD (Table 1). IL-6 was positively correlated with BMD measures (integral

**Table 1.** Comparison of baseline characteristics (% , mean  $\pm$  SD, or median [interquartile range]) in women and men by prevalent cardiovascular disease status, Health ABC Study

	Women			Men		
	No cardiovascular disease ( <i>n</i> = 1,186)	Cardiovascular disease ( <i>n</i> = 398)	<i>P</i>	No cardiovascular disease ( <i>n</i> = 974)	Cardiovascular disease ( <i>n</i> = 517)	<i>P</i>
<b>Demographics</b>						
Age (years)	73.4 $\pm$ 2.8	73.7 $\pm$ 2.9	0.116	73.6 $\pm$ 2.9	74.0 $\pm$ 2.8	0.032
% Black	43.3	54.0	0.002	38.4	34.4	0.131
<b>Lifestyle/diet</b>						
%Current smoking	8.7	13.6	0.005	11.4	9.7	0.307
%Current alcohol drinking	43.2	38.9	0.133	58.1	56.1	0.468
Physical activity (kcal/week)*	351.2 (42.0–970.4)	182.9 (7.0–644.5)	<0.0001	660.3 (163.8–1839.9)	702.8 (165.1–1738.5)	0.737
% Calcium supplements	30.7	21.6	0.0005	8.1	5.6	0.073
% Vitamin D supplements	14.2	10.3	0.049	3.6	3.7	0.948
<b>Anthropometric measures</b>						
BMI (kg/m <sup>2</sup> )	27.7 $\pm$ 5.6	27.8 $\pm$ 5.2	0.726	27.0 $\pm$ 4.0	27.2 $\pm$ 3.9	0.228
Weight (kg)	70.5 $\pm$ 14.8	70.8 $\pm$ 14.4	0.701	81.5 $\pm$ 13.5	81.2 $\pm$ 12.9	0.658
Height (cm)	159.6 $\pm$ 61.2	159.5 $\pm$ 61.6	0.822	173.7 $\pm$ 66.4	172.6 $\pm$ 65.4	0.003
Health ABC performance score	6.7 $\pm$ 1.6	6.4 $\pm$ 1.7	0.0003	7.6 $\pm$ 1.6	7.2 $\pm$ 1.6	<0.0001
<b>Lipids</b>						
Total cholesterol (mg/dL)	214.0 $\pm$ 38.1	210.1 $\pm$ 42.3	0.110	193.4 $\pm$ 34.6	189.2 $\pm$ 35.0	0.028
LDL (mg/dL)	125.7 $\pm$ 36.4	123.1 $\pm$ 37.0	0.213	119.3 $\pm$ 31.9	114.8 $\pm$ 32.1	0.011
HDL (mg/dL)	61.1 $\pm$ 17.3	57.5 $\pm$ 17.5	0.0004	48.3 $\pm$ 14.4	46.3 $\pm$ 13.1	0.009
Triglyceride (mg/dL)*	119.0 (90.0–163.0)	125.0 (92.0–177.0)	0.045	112.0 (84.0–154.0)	121.0 (87.0–173.0)	0.004
<b>Inflammatory markers</b>						
IL-6 (pg/mL)*	1.7 (1.1–2.7)	1.9 (1.4–3.0)	0.003	1.8 (1.3–2.6)	2.2 (1.5–3.2)	<0.0001
TNF- $\alpha$ (pg/mL)*	3.0 (2.3–3.9)	3.4 (2.5–4.4)	<0.0001	3.1 (2.4–4.0)	3.5 (2.7–4.5)	<0.0001
<b>Blood pressure (mm Hg)</b>						
Systolic	135.8 $\pm$ 20.4	138.6 $\pm$ 23.2	0.030	135.4 $\pm$ 20.3	135.0 $\pm$ 21.8	0.734
Diastolic	70.1 $\pm$ 11.7	70.4 $\pm$ 12.5	0.684	73.5 $\pm$ 11.3	71.3 $\pm$ 11.7	0.0004
Glucose level (mg/dL)*	92.0 (85.0–101.0)	95.0 (87.0–109.0)	<0.0001	95.0 (89.0–107.0)	98.0 (90.0–115.0)	0.009
Insulin level (IU/mL)*	6.9 (4.8–10.2)	7.8 (5.1–11.2)	0.003	6.6 (4.8–9.8)	7.1 (5.1–10.5)	0.009
Time since menopause (years)	27.4 $\pm$ 7.6	28.8 $\pm$ 8.2	0.004	—	—	—
<b>Medical history</b>						
% Hypertension	44.2	63.9	<0.0001	32.2	53.5	<0.0001
% Diabetes	13.9	24.0	<0.0001	20.3	25.9	0.014
% Osteoporosis	13.8	16.4	0.20	3.4	3.4	0.95
<b>Medication use</b>						
% Oral estrogen	23.6	18.6	0.040	—	—	—
%Osteoporosis medication	8.2	5.0	0.035	0.6	1.4	0.147
% Statins	10.8	20.4	<0.0001	6.9	23.2	<0.0001
<b>BMD measures</b>						
Volumetric (mg/cc)						
Spine integral	238.1 $\pm$ 51.0	237.8 $\pm$ 50.4	0.95	264.3 $\pm$ 56.7	253.6 $\pm$ 51.1	0.012
Spine trabecular	111.6 $\pm$ 40.1	111.6 $\pm$ 39.7	0.99	134.2 $\pm$ 44.6	127.0 $\pm$ 41.5	0.032
Spine cortical	278.2 $\pm$ 53.8	277.1 $\pm$ 53.8	0.80	310.2 $\pm$ 60.0	297.9 $\pm$ 55.2	0.006
Areal (g/cm <sup>2</sup> )						
Total hip	0.81 $\pm$ 0.14	0.80 $\pm$ 0.15	0.55	0.97 $\pm$ 0.15	0.97 $\pm$ 0.15	0.94
Trochanter	0.62 $\pm$ 0.12	0.60 $\pm$ 0.12	0.08	0.76 $\pm$ 0.13	0.76 $\pm$ 0.13	0.60
Femoral neck	0.70 $\pm$ 0.13	0.70 $\pm$ 0.13	0.65	0.80 $\pm$ 0.14	0.79 $\pm$ 0.14	0.93

\* *P* value obtained using Wilcoxon's rank-sum test since variables were not normally distributed

vBMD, correlation coefficient [*r*] = 0.12, *P* < 0.01; cortical vBMD, *r* = 0.12, *P* < 0.01; trochanter aBMD, *r* = 0.12, *P* < 0.0001). However, no associations between TNF- $\alpha$  and any of the BMD measures were noted.

Adding IL-6 and TNF- $\alpha$  separately to the adjusted logistic regression model did not affect the associations between BMD measures and CVD. For instance, the adjusted OR for CVD per 1 SD decrease in integral

**Table 2.** Results of logistic regression models for prevalent CVD: unadjusted, age-adjusted, and risk factor-adjusted OR (95% CI) per 1 SD decrease in BMD measures for women and men in the Health ABC Study

BMD <sup>c</sup>	Women <sup>a</sup>		Men <sup>b</sup>	
	Cases (n)	OR (95% CI)	Cases (n)	OR (95% CI)
<b>Spine integral vBMD</b>				
Unadjusted	764 (216)	1.01 (0.86–1.18)	725 (261)	1.22 (1.04–1.43)*
Adjusted for age	764 (216)	0.99 (1.00–1.54)	725 (261)	1.20 (1.03–1.41)*
Adjusted for shared risk factors between osteoporosis and CVD	649 (178)	1.27 (1.01–1.58)*	634 (224)	1.34 (1.10–1.63)**
<b>Spine trabecular vBMD</b>				
Unadjusted	764 (216)	1.00 (0.85–1.18)	725 (261)	1.19 (1.01–1.39)*
Adjusted for age	764 (216)	0.98 (0.83–1.15)	725 (261)	1.17 (1.00–1.37)
Adjusted for shared risk factors between osteoporosis and CVD	649 (178)	1.20 (0.96–1.49)	634 (224)	1.25 (1.02–1.53)*
<b>Spine cortical vBMD</b>				
Unadjusted	764 (216)	1.02 (0.87–1.19)	725 (261)	1.24 (1.06–1.45)**
Adjusted for age	764 (216)	1.00 (0.85–1.18)	725 (261)	1.22 (1.05–1.43)**
Adjusted for shared risk factors between osteoporosis and CVD	649 (178)	1.28 (1.02–1.59)*	634 (224)	1.36 (1.11–1.65)**
<b>Total hip aBMD</b>				
Unadjusted	1,570 (396)	1.04 (0.92–1.16)	1,473 (507)	1.00 (0.89–1.11)
Adjusted for age	1,570 (396)	1.02 (0.91–1.14)	1,473 (507)	0.98 (0.88–1.10)
Adjusted for shared risk factors between osteoporosis and CVD	1,300 (323)	1.14 (0.96–1.36)	1,289 (436)	1.05 (0.91–1.22)
<b>Trochanter aBMD</b>				
Unadjusted	1,570 (396)	1.11 (0.99–1.24)	1,473 (507)	1.02 (0.92–1.15)
Adjusted for age	1,570 (396)	1.10 (0.98–1.23)	1,473 (507)	1.02 (0.92–1.14)
Adjusted for shared risk factors between osteoporosis and CVD	1,300 (323)	1.22 (1.03–1.43)*	1,289 (436)	1.05 (0.91–1.22)
<b>Femoral neck aBMD</b>				
Unadjusted	1,570 (396)	0.97 (0.87–1.09)	1,473 (507)	1.01 (0.90–1.12)
Adjusted for age	1,570 (396)	0.96 (0.86–1.08)	1,473 (507)	0.99 (0.89–1.11)
Adjusted for shared risk factors between osteoporosis and CVD	1,300 (323)	1.04 (0.87–1.23)	1,289 (436)	1.00 (0.87–1.15)

<sup>a</sup> Models in women were adjusted for age, ethnicity, study site (aBMD models), educational level, time since menopause, BMI, physical activity, Health ABC physical performance score, smoking status, drinking status, systolic blood pressure, total cholesterol, HDL, triglyceride, plasma glucose level, serum insulin level, history of hypertension, history of diabetes, use of calcium and vitamin D supplements, statins, osteoporosis medications, and oral hormones

<sup>b</sup> Models in men were adjusted for age, ethnicity, study site (aBMD models), BMI, physical activity, diastolic blood pressure, total cholesterol, HDL, triglyceride, plasma glucose level, serum insulin level, history of hypertension, history of diabetes, and use of statins

<sup>c</sup> BMD SD scores for women: total hip aBMD (SD = 0.15 g/cm<sup>2</sup>), femoral neck aBMD (SD = 0.13 g/cm<sup>2</sup>), trochanter aBMD (SD = 0.12 g/cm<sup>2</sup>), integral vBMD (SD = 50.82 mg/cc), trabecular vBMD (SD = 39.98 mg/cc), cortical BMD (SD = 53.80 mg/cc). BMD SD scores for men: total hip aBMD (SD = 0.15 g/cm<sup>2</sup>), femoral neck aBMD (SD = 0.14 g/cm<sup>2</sup>), trochanter aBMD (SD = 0.13 g/cm<sup>2</sup>), integral vBMD (SD = 54.94 mg/cc), trabecular vBMD (SD = 43.59 mg/cc), cortical BMD (SD = 58.61 mg/cc)

\*  $P < 0.05$

\*\*  $P < 0.01$

BMD changed from 1.28 (95% CI 1.02–1.62, based on 616 women with nonmissing IL-6 values) to 1.30 (95% CI 1.03–1.64,  $n = 616$ ) after adjusting for IL-6. The same was observed for TNF- $\alpha$ .

In men, participants with CVD had significantly higher IL-6 and TNF- $\alpha$  levels compared to those who did not have CVD. On the other hand, these cytokines showed no associations with vBMD measures and adding them separately to the adjusted models had no effect on the strength or statistical significance of the associations of vBMD measures with CVD. For example, the adjusted OR related to integral vBMD

remained the same before (OR = 1.30, 95% CI 1.06–1.59, based on 614 men with nonmissing IL-6) and after (OR = 1.30, 95% CI 1.06–1.60,  $n = 616$ ) IL-6 was added to the logistic regression model. Similar results were observed for TNF- $\alpha$ .

#### Subclinical PAD

Among participants who did not have CVD, 10% ( $n = 206$ ) had evidence of subclinical PAD. A low AAI was observed in 10.4% ( $n = 117$ ) of women and 9.7% ( $n = 89$ ) of men.

**Table 3.** Results of logistic regression models for subclinical PAD: unadjusted, age-adjusted, and risk factor-adjusted OR (95% CI) per 1 SD decrease in BMD measures for women and men in the Health ABC Study

BMD <sup>c</sup>	Women <sup>a</sup>		Men <sup>b</sup>	
	<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)
<b>Integral vBMD</b>				
Unadjusted	528 (48)	1.07 (0.79–1.44)	441 (38)	0.91 (0.66–1.25)
Adjusted for age	528 (48)	1.05 (0.78–1.42)	441 (38)	0.85 (0.62–1.16)
Adjusted for shared risk factors between osteoporosis and PAD	493 (42)	1.04 (0.70–1.53)	423 (37)	1.07 (0.74–1.56)
<b>Spine trabecular vBMD</b>				
Unadjusted	528 (48)	0.97 (0.72–1.30)	441 (38)	0.83 (0.62–1.14)
Adjusted for age	528 (48)	0.95 (0.71–1.28)	441 (38)	0.77 (0.57–1.05)
Adjusted for shared risk factors between osteoporosis and PAD	493 (42)	0.94 (0.66–1.35)	423 (37)	0.96 (0.67–1.38)
<b>Spine cortical vBMD</b>				
Unadjusted	528 (48)	1.10 (0.81–1.49)	441 (38)	0.95 (0.69–1.32)
Adjusted for age	528 (48)	1.08 (0.80–1.47)	441 (38)	0.89 (0.65–1.23)
Adjusted for shared risk factors between osteoporosis and PAD	493 (42)	1.05 (0.71–1.54)	423 (37)	1.13 (0.77–1.65)
<b>Total hip aBMD</b>				
Unadjusted	1,115 (116)	1.19 (0.98–1.45)	913 (89)	1.28 (1.02–1.60)*
Adjusted for age	1,115 (116)	1.15 (0.94–1.41)	913 (89)	1.23 (0.98–1.54)
Adjusted for shared risk factors between osteoporosis and PAD	1,011 (101)	1.26 (0.94–1.68)	881 (87)	1.39 (1.03–1.84)*
<b>Trochanter aBMD</b>				
Unadjusted	1,115 (116)	1.26 (1.03–1.54)*	913 (89)	1.24 (0.99–1.56)
Adjusted for age	1,115 (116)	1.22 (1.00–1.50)	913 (89)	1.20 (0.96–1.51)
Adjusted for shared risk factors between osteoporosis and PAD	1,011 (101)	1.28 (0.97–1.69)	881 (87)	1.27 (0.97–1.66)
<b>Femoral neck aBMD</b>				
Unadjusted	1,115 (116)	1.01 (0.83–1.23)	913 (89)	1.07 (0.86–1.34)
Adjusted for age	1,115 (116)	0.98 (0.80–1.19)	913 (89)	1.03 (0.82–1.29)
Adjusted for shared risk factors between osteoporosis and PAD	1,011 (101)	1.18 (0.88–1.58)	881 (87)	1.11 (0.84–1.46)

<sup>a</sup> Models in women were adjusted for age, ethnicity, study site (aBMD models), educational level, time since menopause, BMI, physical activity, Health ABC physical performance score, smoking status, drinking status, systolic blood pressure, total cholesterol, plasma glucose level, history of hypertension, history of diabetes, use of calcium and vitamin D supplements, osteoporosis medications, and oral hormones

<sup>b</sup> Models in men were adjusted for age, ethnicity, study site (areal BMD models), educational level, systolic blood pressure, physical activity, smoking status, BMI, history of hypertension, and history of diabetes

<sup>c</sup> BMD SD scores for women: total hip aBMD (SD = 0.15 g/cm<sup>2</sup>), femoral neck aBMD (SD = 0.13 g/cm<sup>2</sup>), trochanter aBMD (SD = 0.12 g/cm<sup>2</sup>), integral vBMD (SD = 50.82 mg/cc), trabecular vBMD (SD = 39.98 mg/cc), cortical BMD (SD = 53.80 mg/cc). BMD SD scores for men: total hip aBMD (SD = 0.15 g/cm<sup>2</sup>), femoral neck aBMD (SD = 0.14 g/cm<sup>2</sup>), trochanter aBMD (SD = 0.13 g/cm<sup>2</sup>), integral vBMD (SD = 54.94 mg/cc), trabecular vBMD (SD = 43.59 mg/cc), cortical BMD (SD = 58.61 mg/cc)

\*  $P < 0.05$

In women, no unadjusted differences in aBMD or vBMD measures existed between participants with and without subclinical PAD, except for trochanter aBMD being significantly and inversely associated with subclinical PAD (OR = 1.26, 95% CI 1.03–1.54). However, this association became nonsignificant after controlling for age. In adjusted models, all aBMD measures of the hip showed inverse associations with PAD; however, these did not reach statistical significance. None of the spine vBMD measures exhibited a significant relationship with subclinical PAD (Table 3).

In men, total hip aBMD was significantly associated with outcome in unadjusted (OR = 1.28, 95% CI 1.02–1.60) and risk factor-adjusted models. In the full

model, a 1 SD decrease in total hip aBMD was related to a 39% increase in the odds for subclinical PAD. Trochanter and femoral neck aBMD were also inversely related with PAD, but these associations did not achieve statistical significance. Spine vBMD variables were not related to subclinical PAD (Table 3).

We tested the effect of IL-6 and TNF- $\alpha$  on the association of total hip aBMD with subclinical PAD in men. IL-6 level was significantly higher among men who had subclinical PAD (median IL-6 = 2.11 pg/mL) compared to those who did not (median IL-6 = 1.72 pg/mL,  $P = 0.0002$ ). However, no association between TNF- $\alpha$  and PAD was noted. On the other hand, no correlations between both inflammatory cytokines and

total hip aBMD were observed. Adjusting for IL-6 minimally reduced the strength of the association between total hip aBMD and subclinical PAD. The adjusted OR was reduced from 1.38 (95% CI 1.02–1.87,  $P = 0.04$ , based on 844 men with nonmissing IL-6 values) to 1.34 (95% CI 0.98–1.82,  $P = 0.07$ ,  $n = 844$ ) after controlling for IL-6. TNF- $\alpha$  had no effect on the magnitude and significance of the association.

## Discussion

In this cross-sectional analysis performed in an older biracial cohort, vBMD measures of the spine were significantly associated with CVD in men and women and aBMD of the trochanter was related to CVD in women. Additionally, aBMD of the total hip was related to subclinical PAD in men. These inverse relationships were not age-related, were independent of shared risk factors between BMD and CVD, and were not influenced by the inflammatory cytokines IL-6 and TNF- $\alpha$ .

Our results in men, regarding both CVD and subclinical PAD, make an important addition to the existing literature as previous reports failed to demonstrate strong evidence for the presence of such associations in men. The majority of studies investigating the relation of BMD with CVD and subclinical atherosclerosis in men [10, 11, 14–16, 18, 21, 27, 29, 30] have reported no associations [15, 16, 21, 29, 30]. Moreover, most of the reports that found significant relationships in women failed to observe the same associations in men [15, 16, 21, 30]. In our study, trabecular, integral, and cortical vBMD measures of the spine were significantly associated with prevalent CVD in men. Results from NHANES III showed a significant association, of comparable magnitude to ours, between MI and low BMD (OR = 1.39, 95% CI 1.03–1.87) in a multiethnic cohort of 2,281 men aged 50–79 years [14]. Additionally, BMD was inversely related to CVD mortality in white men in the NHANES I study and in a British population [10, 11].

The associations of BMD measures with CVD in women confirm prior findings and extend them by including a cohort of black and white women and by using vBMD. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, osteoporosis was found to be a strong predictor of future cardiovascular outcomes in white postmenopausal women with low bone mass, independent of age and other traditional cardiovascular risk factors (adjusted hazard ratio = 3.9, 95% CI 2.0–7.7). In a 30-year follow-up to the Framingham Study, metacarpal cortical area predicted coronary heart disease in white women free from CVD at baseline (hazard ratio for highest vs. lowest metacarpal cortical area quartile = 0.73, 95% CI 0.53–1.00). Additionally, low bone mass was associated with stroke incidence, prevalence, and mortality in older white women [16, 17].

Notably, the associations between BMD and CVD in women were observed only after adjusting for risk factors. These associations seemed to be masked by negative confounders such as BMI, race, diabetes, glucose level, and statin use, which were associated with higher BMD and increased risk for CVD.

We observed a significant association between total hip aBMD and subclinical PAD in men. The hip subregions showed a trend for an inverse association with PAD; however, these relationships did not reach statistical significance. Spine vBMD measures were not associated with PAD. Results from other large studies did not indicate significant relationships between BMD and PAD in men [29, 30]. However, in a small study of men with asymmetrical symptomatic PAD, hip bone mineral content (BMC) was lower in the affected leg compared to the unaffected one [18].

Similarly, in women, aBMD measures of the total hip and hip subregions tended to be inversely associated with PAD, but these relationships did not achieve statistical significance. On the other hand, spine vBMD measures did not exhibit a relationship with PAD. In the Rotterdam Study, which included a cohort of white women of similar age to our population, femoral neck aBMD was found to be associated with PAD. In line with our findings, no associations with spine BMD were reported. The lack of significant associations in women in our study may be explained by the lower prevalence of PAD (10%) compared to that in the Rotterdam Study (16%). Also, due to the smaller sample size available for PAD analysis ( $n = 1,011$  vs.  $n = 2,984$  in the Rotterdam cohort), we had lower power to detect similar associations [30].

A biological basis for the inverse association between hip BMD and PAD has been sought in the reduced blood flow hypothesis. It was suggested that atherosclerosis, by reducing blood flow to the lower extremities, could alter bone metabolism in the hip and result in decreased bone density [20, 31]. This hypothesis is supported by studies that observed site-specific associations between AAI and BMD of the hip but not other areas [29–31]. In a Chinese cohort of older men and women, an increase in AAI of 1 SD was related to a 0.5% increase in BMD of the total hip but not the spine [29]. In the Study of Osteoporotic Fractures, decreased AAI was associated with increased bone loss at the hip and calcaneus [31]. In line with this notion, men with asymmetrical PAD had lower hip BMC in the affected leg compared to the unaffected one [18]. Our study lends support to the reduced blood flow hypothesis as there was evidence for an association between BMD and PAD at the total hip but not the spine.

Traditionally, osteoporosis and CVD have been regarded as independent processes that occur with aging. Therefore, the association between them was attributed to their age-related independent progression [32–34].

Mounting biological observations [1–6] and epidemiological evidence from this study and others [7–17, 19–31] suggest a link between the two conditions that is independent of age. Laboratory studies indicate that atherosclerotic calcification and bone calcification share a number of features. It is now understood that the arterial tissue is calcified in a highly regulated and organized process by mechanisms similar to those involved in bone mineralization [1]. Hydroxyapatite, a mineral that is present in bones, is also found in calcium deposits of atherosclerotic plaques [4]. In addition, calcified plaques express several bone matrix proteins such as GLA protein, bone morphogenetic protein-2, osteopontin, osteocalcin, and collagen I [2, 3, 5, 6].

Other hypotheses proposed to explain the link between osteoporosis and CVD include (1) shared etiological factors (e.g., menopause, smoking, physical activity, hypertension, etc.), which may simultaneously promote or inhibit atherogenesis and bone demineralization [11, 20, 35, 36], and (2) common pathophysiological mechanisms that could lead to the development of both conditions and may involve inflammatory cytokines.

In our analysis, the inverse associations observed between BMD and CVD were present after controlling for age and other common etiological factors for osteoporosis and CVD, including ethnicity, weight, physical activity, blood pressure, and lipids. Common pathophysiological factors may therefore be at play in the progression of the two conditions. Inflammatory cytokines, for instance, have been implicated in both atherogenesis and bone resorption [15, 27]. Aging is associated with increased levels of circulating inflammatory markers such as IL-6 and TNF- $\alpha$  [41]. These cytokines stimulate osteoclast formation, thereby increasing the rate of bone resorption [42]. IL-6 was shown to be a marker of subclinical CVD [43] and a predictor of CVD mortality in elderly people [44]. Previous analyses in the Health ABC cohort showed that IL-6 and TNF- $\alpha$  were significantly associated with prevalent clinical and subclinical disease [45] as well as incident cardiovascular events [46]. In our analyses, IL-6 and TNF- $\alpha$  did not affect the associations of BMD with CVD. To our knowledge, no other study has investigated the role of IL-6 and TNF- $\alpha$  in these relationships. Other cytokines, such as the osteoprotegerin/receptor activator of nuclear factor  $\kappa$ B (RANK)/RANK ligand triad seem to play a dual role in bone physiology and vascular calcification and may therefore be implicated in the pathogenesis of CVD and osteoporosis [47]. Other factors that could be involved include endogenous sex hormones, oxidized lipids [48], imbalances in the calciferol endocrine system [49], vitamin K status [50], and genetic factors [47, 51].

Notably, all the associations we observed were consistently stronger in men. While this suggests that the

potential pathophysiological mechanisms involved in the association between osteoporosis and CVD have an impact that may vary by gender, it can also point to the presence of other shared risk factors for the two conditions in men which we could not account for.

Bone density was measured in body regions containing different proportions of trabecular and cortical bone. In women, there was no apparent relationship between the type of bone and CVD as the associations were observed at both spine and hip sites. In men, however, associations seemed to be specific to BMD of the spine, which is composed primarily of trabecular bone. This may reflect gender differences in the patterns of trabecular and cortical bone loss with age. In women, a period of accelerated trabecular bone loss begins at the time of menopause and plateaus 5–10 years later [52]. In men, a greater magnitude of trabecular bone loss compared to cortical bone loss occurs after the age of 70 years [53].

Our study has several advantages. The associations were investigated in a large and well-characterized biracial cohort of older men and women and adjusted for a comprehensive set of shared risk factors for osteoporosis and CVD. Our study also had the benefit of utilizing QCT for vBMD determination at the spine. In a large number of studies, bone mass was determined using radiographic techniques, single-photon or single X-ray absorptiometry, or dual-photon absorptiometry [8–10, 15, 17, 21, 22, 24, 27, 32]. Some studies have employed DXA in bone determination [7, 11–14, 16, 18, 20, 23, 25, 26, 28–31, 33]; however, this technique is limited by its two-dimensional areal assessment of BMD, which does not adjust for bone size. This is especially important in studies of different ethnic and gender groups since there are established differences in bone size by race and gender [54, 55]. DXA is also affected by the presence of extraosseous calcium, such as aortic calcification and degenerative osteoarthritic changes, which are incorporated in the region of interest and lead to a falsely increased bone density at the spine [56]. This is an important drawback, particularly in the elderly who have an increased prevalence of such degenerative conditions [57]. QCT, which allows for three-dimensional volumetric determination of bone density, adjustment for bone size, and assessment of purely trabecular bone, was used only in one study [19].

The main limitation of our analysis is its cross-sectional nature, which does not allow evaluation of a causal association between CVD and osteoporosis or elucidation of common mechanisms involved in the pathogenesis of both conditions. Additionally, our cohort included well-functioning, community-dwelling older adults, which may limit the generalizability of the results to other populations.

In conclusion, our results provide further evidence for the inverse association between BMD and CVD in

both men and women. However, establishment of a link between osteoporosis and atherogenesis requires more longitudinal evidence, which will remain far from conclusive until further investigations into common pathophysiological mechanisms for the two conditions become available.

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