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ORIGINAL ARTICLE

The association of bone mineral density measures with incident cardiovascular disease in older adults

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Abstract
Summary The associations of volumetric and areal bone mineral density (BMD) measures with incident cardiovascular disease (CVD) were studied in a biracial cohort of 2,310 older adults. BMD measures were inversely related to CVD in women and white men, independent of age and shared risk factors for osteoporosis and CVD.

Introduction We investigated the associations of volumetric (vBMD) and areal (aBMD) bone mineral density measures with incident cardiovascular disease (CVD) in older adults enrolled in the Health, Aging, and Body Composition study.
Methods The incidence of CVD was ascertained in 2,310 well-functioning white and black participants (42% black; 55% women), aged 68–80 years. aBMD measures of the hip were assessed using DXA. Spine trabecular, integral, and cortical vBMD measures were obtained using QCT.
Results During an average follow-up of 5.4 years, 23% of men and 14% of women had incident CVD. Spine vBMD measures were inversely associated with incident CVD in white men [HR(integral)=1.39, 95% CI 1.03–1.87; HR (cortical)=1.38, 95% CI 1.03–1.84], but not in black men. In women, aBMD measures of the total hip (HR=1.36, 95% CI 1.03–1.78), femoral neck (HR=1.44, 95% CI 1.10–1.90), and trochanter (HR=1.34, 95% CI 1.04–1.72) exhibited significant associations with CVD in blacks, but not in whites. All associations were independent of age and shared risk factors between osteoporosis and CVD, and were not explained by inflammatory cytokines or oxidized LDL.
Conclusion Our results provide support for an inverse association between BMD and incident CVD. Further research should elucidate possible pathophysiological mechanisms linking osteoporosis and CVD.

Keywords Areal BMD · Incident cardiovascular disease · Inflammatory cytokines · Oxidized LDL · Volumetric BMD

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Introduction

Cardiovascular disease (CVD) and osteoporosis are common age-related conditions. Mounting biological [1–5] and epidemiological evidence suggests a possible link

between the two diseases. In both cross-sectional and longitudinal epidemiologic studies, low bone mass has been related to increased cardiovascular mortality [6–10], cardiovascular morbidity [11–18], and subclinical measures of atherosclerosis [19–27].

Osteoporosis was found to be a strong predictor of future cardiovascular outcomes in postmenopausal women with low bone mass, independent of age and other traditional cardiovascular risk factors (adjusted HR=3.9, 95% CI 2.0–7.7) [12]. It was also associated with angiographically-determined coronary artery disease in a retrospective analysis of a population predominantly of women referred for angiography and BMD assessment [13]. Lower bone mass was related to higher incident coronary heart disease [15], incident stroke [17], and prevalent stroke in white postmenopausal women [16]. Associations between BMD and CVD were also reported in men. Previous myocardial infarction was associated with low BMD in a multiethnic population of men in the Third National Health and Nutrition Examination Survey (NHANES III) [14]. Lower bone mineral content was related to asymmetrical symptomatic peripheral arterial disease in a small study involving 18 men [18]. Recently, in a cross-sectional analysis in the Health, Aging, and Body Composition (Health ABC) study, we observed that volumetric BMD (vBMD) measures of the spine were significantly associated with prevalent CVD in women and men, and areal BMD (aBMD) of the trochanter was related to prevalent CVD in women. These inverse relationships were not age-related and were independent of shared risk factors between osteoporosis and CVD [11].

Although several lines of evidence support a link between CVD and osteoporosis, the nature of this association and the mechanisms involved are still not clearly elucidated. Most of the earlier work focused on white women [6–8, 12, 13, 17, 20, 21, 23]. Less is known about the presence of this relationship in men and in black populations. Additionally, previous studies relied on prevalent CVD or subclinical markers of atherosclerosis [13, 14, 16, 18–24, 26, 27], and areal assessments of BMD [6–10, 12–19, 21–27]. To our knowledge, no study assessed the association of volumetric BMD measures with incident CVD events. Furthermore, while inflammatory cytokines and oxidized LDL (oxLDL) were suggested as common denominators in the association between osteoporosis and CVD, their role requires further investigation.

The purpose of this analysis was to longitudinally examine the association of baseline volumetric and areal BMD measures with incident CVD in a biracial cohort of men and women with no history of CVD; and to determine whether such associations were a) independent of age, b) independent of shared risk factors between osteoporosis and CVD, or c) explained by common pathophysiological factors such as oxLDL or the inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).

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 3075 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 recruited between April 1997 and June 1998 and were identified from a random sample of white Medicare beneficiaries and all age-eligible black community residents in designated zip code areas surrounding Pittsburgh, PA, and Memphis, TN. 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 protocol was approved by the Institutional Review Boards of the University of Pittsburgh and the University of Tennessee.

The current analyses included 2310 participants. We excluded participants who had one or more cardiovascular diseases (N=765) at the baseline visit including coronary heart disease (CHD) (N=559), cerebrovascular disease (N=223), or peripheral arterial disease (PAD) (N=158). Areal BMD data was missing for 25 participants. Volumetric BMD was collected at the Pittsburgh site only and was therefore available for 1,095 participants (out of 1,124).

Incident cardiovascular disease

Incident CVD was defined as the onset of one or more of the following conditions between study entry and June 30, 2004: coronary heart disease (CHD) (defined as coronary death or any overnight hospitalization in an acute care hospital due to myocardial infarction, angina pectoris, symptomatic coronary insufficiency, or other ischemic heart disease, N=277); cerebrovascular disease (defined as cerebrovascular death or any overnight hospitalization due to stroke or transient ischemic attacks, N=150), PAD (defined as overnight hospitalization due to lower extremity claudication, atherosclerosis, or thrombosis/ embolism, N=32), or carotid artery disease (defined by vascular or surgical procedure to improve flow to the ipsilateral brain,

symptomatic disease with abnormal findings (>50% stenosis on carotid angiogram or Doppler), or symptomatic disease with carotid artery disease listed on discharge summary, N=33).

Participants were contacted every 6 months, alternating clinic visits and telephone interviews, to elicit information about events. For each reported event, hospital records were collected and abstracted. Cardiovascular events were reviewed locally by a study physician, and verified using standard criteria. Dates and causes of death were verified by a committee made up of 4–6 Health ABC physicians, using death certificates, hospital records, and proxy interviews. Adjudicated events occurring through June 30, 2004 were available. Follow-up time was calculated from the date of the first study visit to the date of the first cardiovascular event, or last contact with the patient (for participants who did not develop CVD or were lost to follow-up), or death (for participants who died from non-CVD causes). The average follow-up time was 5.4 years (range of follow-up=0.02–7.17 years, median=6.02 years).

Areal bone mineral density (aBMD)

Baseline areal BMD (g/cm2) measures of the total hip and hip subregions (femoral neck and trochanter) were determined using dual-energy X-ray absorptiometry (DXA) (Hologic 4500A, version 9.03; Hologic, Inc., Waltham, MA, USA). DXA quality assurance measures were performed at both study sites and identical scan protocols were used for all participants.

Volumetric bone mineral density (vBMD)

Baseline volumetric BMD measures (mg/cc) of the spine were determined using quantitative computed tomography (QCT) (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. Scans were performed by certified technicians and analyzed with a standardized protocol at the University of California, San Francisco.

Inflammatory markers and oxidized LDL

The concentrations of IL-6, TNF-α, and oxLDL were obtained from frozen stored serum samples collected via venipuncture after an overnight fast at baseline. IL-6 and TNF-α were measured in duplicate using commercial ELISA 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-α, the detection range was 0.156–17.0 pg/ml for IL-6 and 0.5–32 pg/ml for TNF-α, and the interassay coefficient of variation was 10.3% for IL-6 and 15.8% for TNF-α. Plasma levels of oxLDL were measured using a monoclonal antibody (4E6)-based competition enzyme-linked immunosorbent assay. The interassay coefficient of variation of oxLDL is 12%. IL-6, TNF-α, and oxLDL were available for 2,197, 2,152, and 2,282 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 [28].

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 the Epidemiologic Studies of the Elderly (EPESE; 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) [29]. Height and weight were obtained using a Harpenden stadiometer (Holtain, Wales, UK) and a standard balance beam, respectively. Body mass index (BMI) was calculated as weight divided by height squared (Kg/m^2). Seated systolic and diastolic blood pressures were measured by a manual mercury sphygmomanometer using a standardized protocol.

Prevalent diabetes was defined as self-report of diabetes previously diagnosed by a physician, use of hypoglycemic medications, or a fasting glucose ≥126 mg/dl. Prevalent hypertension was defined as self-report of hypertension and use of anti-hypertensive medications. Prevalent osteoporosis (total hip BMD 2.5 SD or more below the young adult mean) and low bone mass (total hip BMD between 1.0 and 2.5 SD below the young adult mean) were defined using gender and race-specific T-scores determined from the NHANES III study population [30].

Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were measured by a colorimetric technique (Johnson & Johnson Vitros 950 analyzer, New Brunswick, New Jersey). 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, Inc., Yellow Springs, Ohio). 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 incident CVD were compared using chi-square test for categorical variables and either 2-sample t-test or Wilcoxon rank-sum test for continuous data. Cox proportional hazards regression was used to estimate the hazard ratio (HR) of incident CVD per SD decrease in BMD (calculated as the deviation from the mean BMD divided by the standard deviation of the BMD measure in each gender). Unadjusted, age-adjusted, and risk factors adjusted models were fitted. Variables were selected for entry into the multiple Cox models if they were associated with incident CVD and any of the BMD variables at the 0.15 level of significance in univariate analyses. Separate regression models were fitted for each BMD variable. The proportional hazards assumption was checked by testing the significance of interaction terms of BMD variables with time. Racial differences in the relationship of BMD with incident CVD were tested by entering product terms for race and BMD measures in the adjusted Cox regression models. In cases where significant race interactions were observed at the 0.1 level of significance, the analyses were further stratified by race. In women, interactions between race and aBMD measures of the total hip (p-value for BMD x race=0.05), femoral neck (p-value=0.04), and trochanter (p-value=0.05) were observed. In men, interactions between race and integral (p-value=0.07), cortical (p-value=0.08), and trabecular (p-value=0.10) vBMD measures of the spine were observed. Therefore, the Cox models specific for these BMD measures were further stratified by race.

The effects of IL-6, TNF-α, and oxLDL on statistically significant associations between BMD measures and CVD were tested by introducing these variables, separately, into adjusted Cox models. Because of the skewed distribution of IL-6, TNF-α, and oxLDL, their log-transformed values were used in analyses. Data were analyzed using SAS version 8.01 (SAS Institute Inc., Cary, NC, USA).

Results

Participants characteristics

During an average follow-up of 5.4 years, 23% (241 out of 1040) of men and 14% (182 out of 1270) of women had an incident CVD event. Compared to men who did not develop CVD, those who did were older, less educated, more likely to have diabetes, had lower HDL and Health ABC physical performance score, and had higher levels of glucose, systolic blood pressure, and inflammatory markers. In women, participants who had incident CVD were more likely to be hypertensive or diabetic, had higher BMI, glucose level, systolic blood pressure, and inflammatory markers, had a lower Health ABC physical performance score, and were less likely to be calcium users (Table 1).

BMD and incident CVD in women

In women, none of the areal or volumetric BMD variables were significantly associated with incident CVD in unadjusted or age-adjusted analyses. However, after controlling for shared risk factors between CVD and BMD, femoral neck aBMD was found to be significantly associated with CVD. A decrease in femoral neck aBMD by 1 SD below the mean was related to a 24% increased risk for incident CVD (Table 2).

In race-specific adjusted models, we observed that aBMD measures of the total hip and hip subregions were significantly associated with CVD in black women. A 1 SD decrease in aBMD of the total hip, femoral neck, and trochanter was related to an increased CVD risk in the order of 36%, 44%, and 34%, respectively. On the other hand, none of these measures showed associations with CVD in white women (Table 3).

We looked at the effects of IL-6, TNF-α, and oxLDL on the associations of BMD with CVD in black women. IL-6 level was significantly higher among black women who had CVD (median IL-6=1.97 pg/ml) compared to those who did not (median IL-6=1.82 pg/ml, p=0.003). However, IL-6 was positively correlated with aBMD measures of the hip (total hip: r=0.17, p<.0001; femoral neck: r=0.19, p<.0001; trochanter: r=0.14, p=.0009). Adding IL-6 to the adjusted models did not affect the strength or significance of the association between BMD measures and CVD (Table 4). For instance, the adjusted HR for incident CVD per 1 SD decrease in femoral neck aBMD was similar before (HR=1.51, 95% CI 1.14–1.99) and after adjusting for IL-6 (HR=1.49, 95% CI 1.13–1.96). Similarly, adjusting for TNF-α or oxLDL had no effect on the associations of aBMD measures with incident CVD (Table 4).

BMD and incident CVD in men

In men, none of the BMD measures showed statistically significant associations with CVD in unadjusted or adjusted analyses. However, there was a trend for higher CVD incidence with decreased integral (HR=1.17, 95% CI 0.93–1.48), cortical (HR=1.18, 95% CI 0.94–1.48), and trabec-

Table 1 Comparison of baseline characteristics (%, mean ± SD, or median (IQR)) in women and men by incident cardiovascular disease status, the Health ABC Study

	Women			Men		
	No cardiovascular disease (N=1088)	Incident cardiovascular disease (N=182)	P-value	No cardiovascular disease (N=799)	Incident cardiovascular disease (N=241)	P-value
Demographics						
Age (yrs)	73.4±2.8	73.3±2.8	.68	73.4±2.8	74.1±3.1	.001
% Black	43.4	50.0	.10	40.0	34.4	.12
% Post-secondary education	38.8	35.4	.61	48.1	38.9	.04
Lifestyle/Diet						
% Smoking	8.6	11.0	.27	11.4	11.2	.95
% Alcohol drinking	43.8	40.1	.35	58.9	55.4	.34
Physical activity (Kcal/week)*	365.8 (47.2–959.7)	215.1 (18.5–938.1)	.06	635.8 (170.6–1737.5)	701.1 (129.1–1969.1)	.98
Calcium supplements	31.6	24.2	.04	8.8	6.7	.30
Vitamin D supplement	14.9	11.0	.16	4.1	2.5	.24
Anthropometric Measures						
BMI (kg/ms)	27.5±5.6	28.6±5.3	.02	27.0±4.0	27.2±4.0	.36
Weight (Kg)	70.2±15.0	72.2±13.4	.08	81.5±13.5	82.0±13.3	.62
Height (cm)	159.6±6.1	159.1±6.3	.29	173.7±6.7	173.4±6.2	.54
HABC performance score	6.8±1.6	6.5±1.6	.03	7.6±1.6	7.2±1.7	.0004
Lipids						
Total cholesterol (mg/dl)	213.0±37.4	217.2±39.9	.16	192.9±35.4	196.2±31.4	.18
LDL (mg/dl)	124.9±35.7	128.8±38.7	.21	118.5±32.7	122.7±28.9	.06
HDL (mg/dl)	61.0±16.8	60.3±18.9	.62	48.9±14.8	46.3±12.8	.01
Triglyceride (mg/dl)*	118.5 (90.0–162.5)	127.0 (92.0–166.0)	.17	112.0 (83.0–151.0)	119.0 (89.0–165.0)	.11
Inflammatory Markers and oxLDL						
IL-6 (pg/ml)*	1.7 (1.1–2.5)	2.2 (1.3–3.2)	<.0001	1.7 (1.2–2.5)	2.0 (1.4–3.0)	.0004
TNF-α (pg/ml)*	3.0 (2.3–3.8)	3.1 (2.6–4.3)	.007	3.1 (2.4–3.9)	3.4 (2.6–4.3)	.002
oxLDL (mg/dl)	1.1 (0.8–1.6)	1.3 (0.9–1.7)	.09	1.1 (0.8–1.5)	1.2 (0.9–1.6)	.10
Blood pressure (mmHg)						
Systolic	135.3±20.4	138.6±21.2	.04	134.5±19.9	137.7±21.5	.03
Diastolic	70.0±11.6	71.2±11.7	.19	73.3±11.4	73.8±11.5	.56
Glucose level (mg/dl)*	91.0 (85.0–101.0)	94.0 (87.0–104.0)	.007	95.0 (90.0–120.0)	97.0 (90.0–119.5)	.004
Insulin level (uIU/ml)*	6.8 (4.8–10.0)	7.6 (5.0–10.8)	.05	6.6 (4.8–10.0)	7.0 (4.8–10.0)	.49
Time since menopause (yrs)	27.4±7.4	27.9±8.8	.46	–	–	–
Medical history						
% Hypertension	43.3	53.8	.008	31.3	36.7	.12
% Diabetes	12.8	23.3	.0002	18.2	28.8	.0004
% Osteoporosis	14.0	15.5	.61	3.0	4.6	.23
Medication use						
% Oral estrogen	23.9	22.0	.56			
% Osteoporosis drugs	8.3	7.1	.59	0.6	0.8	.73 [a]
% Statins	10.9	13.7	.26	7.2	5.4	.35
% Thiazide	21.3	30.2	.008	12.7	15.9	.20
% Oral steroid	2.8	5.0	.12	1.2	0.8	.74 [a]
% Diabetes drugs	8.9	15.9	.003	10.5	17.6	.004
BMD measures						
Volumetric (mg/cc)						
Spine integral	237.6±51.5	241.5±49.2	.49	265.6±56.5	254.3±54.9	.07
Spine trabecular	110.9±41.2	114.1±36.6	.48	134.9±43.9	128.4±45.7	.19
Spine cortical	277.9±54.3	280.6±51.7	.65	311.5±59.8	299.2±58.2	.06
Areal (g/cm^2)						
Total hip	0.81±0.15	0.81±0.14	.84	0.97±0.15	0.96±0.16	.40
Trochanter	0.62±0.12	0.61±0.11	.81	0.76±0.14	0.75±0.14	.30
Femoral neck	0.70±0.13	0.69±0.12	.76	0.80±0.14	0.79±0.14	.43

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

[a] Fisher's exact test

Table 2 Results of Cox regression models for incident CVD: unadjusted, age-adjusted, and risk factors-adjusted hazard ratios (95% CI) per 1 SD decrease in baseline BMD measures for women and men in the Health ABC study

BMD[3]	Women[1]		Men[2]	
	N at risk (events)	Hazard ratio (95% CI)	N at risk (events)	Hazard ratio (95% CI)
Total hip aBMD				
Unadjusted	1257 (181)	0.98 (0.85–1.14)	1028 (237)	1.06 (0.93–1.20)
Adjusted for age	1257 (181)	0.99 (0.85–1.14)	1028 (237)	1.04 (0.91–1.18)
Adjusted for shared risk factors between osteoporosis and CVD	1208 (176)	1.18 (0.97–1.43)	976 (217)	1.04 (0.89–1.22)
Femoral neck aBMD				
Unadjusted	1257 (181)	1.02 (0.88–1.18)	1028 (237)	1.05 (0.92–1.19)
Adjusted for age	1257 (181)	1.02 (0.88–1.18)	1028 (237)	1.02 (0.90–1.16)
Adjusted for shared risk factors between osteoporosis and CVD	1208 (176)	1.24 (1.02–1.52) [a]	976 (217)	1.04 (0.89–1.21)
Trochanter aBMD				
Unadjusted	1257 (181)	1.01 (0.88–1.17)	1028 (237)	1.08 (0.94–1.22)
Adjusted for age	1257 (181)	1.02 (0.88–1.18)	1028 (237)	1.06 (0.93–1.20)
Adjusted for shared risk factors between osteoporosis and CVD	1208 (176)	1.16 (0.97–1.39)	976 (217)	1.07 (0.92–1.25)
Spine integral vBMD				
Unadjusted	599 (94)	0.92 (0.76–1.13)	496 (103)	1.20 (0.98–1.47)
Adjusted for age	599 (94)	0.94 (0.76–1.15)	496 (103)	1.18 (0.96–1.44)
Adjusted for shared risk factors between osteoporosis and CVD	574 (93)	1.02 (0.80–1.28)	475 (95)	1.17 (0.93–1.48)
Spine trabecular vBMD				
Unadjusted	599 (94)	0.93 (0.76–1.13)	496 (103)	1.14 (0.93–1.40)
Adjusted for age	599 (94)	0.94 (0.77–1.15)	496 (103)	1.11 (0.91–1.37)
Adjusted for shared risk factors between osteoporosis and CVD	574 (93)	0.99 (0.79–1.24)	475 (95)	1.10 (0.87–1.39)
Spine cortical vBMD				
Unadjusted	599 (94)	0.95 (0.77–1.16)	496 (103)	1.20 (0.98–1.48)
Adjusted for age	599 (94)	0.96 (0.78–1.18)	496 (103)	1.19 (0.97–1.46)
Adjusted for shared risk factors between osteoporosis and CVD	574 (93)	1.04 (0.83–1.31)	475 (95)	1.18 (0.94–1.48)

[1] Models in women were adjusted for: age, race, study site, physical activity, Health ABC physical performance score, BMI, cholesterol, systolic blood pressure, glucose level, history of hypertension, and use of diabetes drugs, calcium supplements, and oral estrogen

[2] Models in men were adjusted for: age, race, study site, education, physical activity, Health ABC physical performance score, BMI, HDL, LDL, systolic blood pressure, glucose level, history of hypertension, and use of diabetes drugs

[3] BMD SDs: Women: total hip aBMD=0.15 g/cm2, trochanter aBMD=0.12 g/cm2, femoral neck aBMD=0.13 g/cm2, integral vBMD=51.14 mg/cc, trabecular vBMD=40.53 mg/cc, cortical vBMD=53.87 mg/cc. Men: total hip aBMD=0.16 g/cm2, trochanter aBMD=0.14 g/cm2, femoral neck aBMD=0.14 g/cm2, integral vBMD=56.3 mg/cc, trabecular vBMD=44.3 mg/cc, cortical BMD=59.7 mg/cc

[a] $p<0.05$

ular (HR=1.10, 95% CI 0.87–1.39) vBMD measures of the spine (Table 2).

In adjusted models stratified by race, we observed that spine integral and cortical vBMD measures were significantly associated with CVD in white men. The risk of incident CVD was increased by 39% and 38%, respectively, with every SD decrease in integral and cortical vBMD measures. On the other hand, none of these measures showed associations with CVD in black men (Table 3).

We looked at the effects of IL-6, TNF-α, and oxLDL on the associations of BMD with CVD in white men. White men with CVD had higher IL-6 and TNF-α levels than those who did not have CVD, whereas no significant difference in oxLDL was observed between the two groups. IL-6, TNF-α, and oxLDL were not correlated with integral or cortical BMD measures in white men, and adding them, separately, to adjusted Cox models did not affect the associations of BMD with CVD (Table 5).

Discussion

This prospective analysis examined the association of BMD measures with incident CVD in a biracial cohort of older

Table 3 Adjusted hazard ratios (95% CI) for incident CVD per 1 SD decrease in baseline BMD measures for black and white women and men in the Health ABC Study

	Black women[1]		White women[1]	
BMD	N at risk (events)	Hazard ratio (95% CI)	N at risk (events)	Hazard ratio (95% CI)
Total hip aBMD	526 (86)	1.36 (1.03–1.78) [a]	682 (90)	1.02 (0.76–1.37)
Femoral neck aBMD	526 (86)	1.44 (1.10–1.90) [b]	682 (90)	1.05 (0.78–1.41)
Trochanter aBMD	526 (86)	1.34 (1.04–1.72) [a]	682 (90)	1.00 (0.77–1.32)
	Black Men[2]		White Men[2]	
Spine integral vBMD	187 (30)	0.86 (0.58–1.28)	288 (65)	1.39 (1.03–1.87) [a]
Spine trabecular vBMD	187 (30)	0.84 (0.57–1.24)	288 (65)	1.27 (0.94–1.72)
Spine cortical vBMD	187 (30)	0.87 (0.59–1.28)	288 (65)	1.38 (1.03–1.84) [a]

[a] $p<0.05$
[b] $p<0.01$
[1] Models in women were adjusted for the following: age, study site, physical activity, Health ABC physical performance score, BMI, cholesterol, systolic blood pressure, glucose level, history of hypertension, and use of diabetes drugs, calcium supplements, and oral estrogen
[2] Models in men were adjusted for the following: age, race, study site, education, physical activity, Health ABC physical performance score, BMI, HDL, LDL, systolic blood pressure, glucose level, history of hypertension, and use of diabetes drugs

men and women who had no evidence of cardiovascular disease at baseline. Volumetric BMD measures of the spine were significantly associated with incident CVD in white men. Areal BMD of the femoral neck was related to CVD in women, and in race-specific analyses, aBMD measures of the total hip, trochanter, and femoral neck were associated with CVD in black women. These inverse relationships were independent of age and shared risk factors between BMD and CVD and were not explained by ox-LDL, IL-6, or TNF-α.

Table 4 Effect of controlling for IL-6, TNF-α, or oxLDL on the adjusted associations of aBMD measures with incident CVD in black women

BMD	N at risk (events)	Adjusted for risk factors[1] Hazard ratio (95% CI)	Adjusted for risk factors + IL-6, TNF-α, or oxLDL[2] Hazard ratio (95% CI)
Total hip aBMD			
IL-6	502 (84)	1.39 (1.06–1.83) [a]	1.39 (1.06–1.82) [a]
TNF-α	486 (77)	1.32 (0.99–1.76)	1.33 (1.00–1.77)
oxLDL	524 (86)	1.32 (1.02–1.72) [a]	1.35 (1.03–1.77) [a]
Femoral neck aBMD			
IL-6	502 (84)	1.51 (1.14–1.99) [b]	1.49 (1.13–1.96) [b]
TNF-α	486 (77)	1.46 (1.09–1.96) [a]	1.48 (1.10–1.98) [b]
oxLDL	524 (86)	1.42 (1.09–1.86) [b]	1.44 (1.09–1.89) [b]
Trochanter aBMD			
IL-6	502 (84)	1.36 (1.05–1.77) [a]	1.35 (1.05–1.74) [a]
TNF-α	486 (77)	1.32 (1.01–1.73) [a]	1.31 (1.01–1.72) [a]
oxLDL	524 (86)	1.32 (1.02–1.69) [a]	1.34 (1.03–1.72) [a]

[a] $p<0.05$
[b] $p\leq0.01$
[1] Adjusted for same risk factors listed in Tables 2 and 3
[2] oxLDL models did not include cholesterol level due to the high correlation between the two measures

Our findings in men make an important addition to the existing literature as this is the first longitudinal study to report an association between BMD and cardiovascular events in men with no history of CVD. These associations were consistent with previous findings. In a cross-sectional analysis in this cohort, we observed significant inverse associations between spine vBMD measures and prevalent CVD in men. A one SD decrease in cortical, integral, or trabecular vBMD was associated with 36%, 34%, and 25% increased odds for CVD, respectively [11]. In NHANES III, men with a history of MI had a significantly higher prevalence of low BMD (OR=1.39, 95% CI 1.03–1.87) [14]. In a study involving 18 men with asymmetrical symptomatic peripheral arterial disease, bone mineral

Table 5 Effect of controlling for IL-6, TNF-α, or oxLDL on the adjusted associations of vBMD measures with incident in white men

BMD	N at risk (events)	Adjusted for risk factors[1] hazard ratio (95% CI)	Adjusted for risk factors + IL-6, TNF-α, or oxLDL[2] Hazard Ratio (95% CI)
Integral vBMD			
IL-6	280 (62)	1.37 (1.01–1.86) [a]	1.38 (1.02–1.88) [a]
TNF-α	276 (63)	1.40 (1.04–1.89) [a]	1.40 (1.04–1.89) [a]
oxLDL	292 (66)	1.39 (1.04–1.87) [a]	1.41 (1.05–1.89) [a]
Cortical vBMD			
IL-6	280 (62)	1.37 (1.02–1.85) [a]	1.38 (1.02–1.86) [a]
TNF-α	276 (63)	1.39 (1.03–1.86) [a]	1.38 (1.03–1.85) [a]
oxLDL	292 (66)	1.39 (1.04–1.85) [a]	1.41 (1.05–1.88) [a]

[a] $p<0.05$
[b] $p<0.01$
[1] Adjusted for same risk factors listed in Tables 2 and 3
[2] oxLDL models did not include LDL level due to the high correlation between the two measures

content was shown to be significantly lower in the affected compared to the unaffected leg [18]. Additionally, BMD was inversely related to CVD mortality in white men in the NHANES I study and in a British population [9, 10].

Interestingly, the associations of BMD measures with CVD were observed in white men, but not in blacks. This might be explained by the lower BMD and the higher incidence of CVD in white men compared to blacks. In this cohort, the incidence of CVD was 23% in white men and 16% in black men. Spine vBMD measures were significantly lower in whites than blacks (mean integral vBMD= 248.6 mg/cc in whites vs. 285.2 mg/cc in blacks, p<.0001; mean cortical vBMD=294.8 mg/cc in whites vs 330.0 mg/cc in blacks, p<.0001). Also, due to the smaller sample size available for analysis in black men, we had limited power to detect associations similar to those observed in whites.

In women, we observed that a decrease in femoral neck aBMD by 1 SD below the mean was related to a 24% increased risk for incident CVD. Notably, this association was observed only after adjusting for risk factors and it seemed to be masked by negative confounders such as BMI and glucose level, which were associated with higher BMD and increased risk for cardiovascular disease. In race-specific analyses, lower aBMD measures of the total hip, femoral neck, and trochanter were associated with higher CVD risk in black women, but not in white women. To our knowledge, none of the previous reports have explored associations between BMD and CVD in black women separately. Studies have focused on white women [6–8, 12, 13, 17, 20, 21, 23], and blacks have been excluded from analyses due to their reduced risk for osteoporosis and fractures [6, 7, 17]. A higher than expected prevalence of low BMD was observed among black women in our cohort: 13% were osteoporotic, and 44.5% had low bone mass. Estimates from NHANES III indicate that the prevalence of osteoporosis and osteopenia in black women aged 50 years and older are 8% and 28%, respectively [31]. The high prevalence of osteoporosis and low bone mass in this group of black women may have lead to more pronounced associations between BMD and CVD.

Unlike other cross-sectional and longitudinal studies, we did not observe an association between BMD and incident CVD in white women. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, osteoporosis was found to be a strong predictor of future cardiovascular outcomes in postmenopausal women with low bone mass, independent of age and other traditional cardiovascular risk factors (adjusted HR=3.9, 95% CI 2.0–7.7) [12]. In the MORE study, 53% of the women were osteoporotic and the remaining 47% had low bone mass. In another study of white postmenopausal women, the presence of aortic calcification (AC) was associated with lower BMD and higher prevalence of vertebral and hip fractures. The progression of AC was also linked to increased trabecular BMD loss at the spine. In this study, 70% of the women had osteoporosis [20]. In our cohort, the prevalence of osteoporosis in white women was 15%, consistent with estimates from NHANES III [31]. However, the incidence of CHD (15/1,000 person-years) was lower than that reported in the Cardiovascular Health Study (CHS) for white women of similar age (18.6/1,000 person-years) [32]. This suggests that the relationship between BMD and CVD may be more evident in populations at high risk.

The lack of association of BMD with CVD in white women may also be explained, in part, by selective survival bias. We observed that white women who died from non-CVD causes had lower baseline aBMD of the total hip, compared to the rest of the group (mean aBMD=0.77 vs. 0.72, respectively, p-value=.03). This suggests that white women with low BMD were at higher risk of death from non-CVD causes, and were therefore eliminated from the CVD risk group.

Traditionally, osteoporosis and CVD have been regarded as independent processes that occur with aging. However, mounting biological observations and epidemiological evidence from this study and others suggest a link between the two conditions that is independent of age. Several hypotheses have been proposed to explain the link between CVD and osteoporosis including shared etiological factors (such as menopause, smoking, physical inactivity, etc.) which may simultaneously promote atherosclerosis and bone demineralization. In our analysis, the observed inverse associations between BMD and incident CVD were present after controlling for age and other common etiological factors for osteoporosis and CVD including weight, physical activity, blood pressure, and lipids. Common pathophysiological mechanisms involving inflammatory cytokines and oxidized lipids have been implicated in the link between osteoporosis and CVD. Aging is associated with increased levels of circulating inflammatory markers such as IL-6 and TNF-α [33]. IL-6 was shown to stimulate osteoclasts, thereby increasing the rates of bone remodeling and bone loss [34]. Previous analyses in the Health ABC cohort have shown that IL-6 and TNF-α were significantly associated with prevalent clinical and subclinical disease [35], as well as incident cardiovascular events [36]. The role of oxidized lipids in atherogenesis is well established [37]. In vitro, Parhami et al. observed that lipid oxidation products including minimally oxidized LDL have opposite effects on bone and vascular cells; they were found to inhibit osteoblast differentiation in bone cells and stimulate it in calcifying vascular cells [38]. In our analysis, oxLDL and the inflammatory markers IL-6 and TNF-α did not explain the associations of BMD measures with CVD. It is possible that other cytokines are involved. The osteoprotegerin (OPG)/ receptor activator of nuclear factor kappa B

(NF-κB) (RANK)/RANK ligand (RANKL) triad seems to play a role in bone physiology and vascular calcification [39]. Other mechanisms involving elevated homocysteine levels [40], low endogenous sex hormones, imbalances in the calciferol endocrine system [41], vitamin K status [42], and genetic factors [39, 43] may also have a role in the link between low BMD and CVD. Additionally, it has been suggested that atherosclerosis, by reducing blood flow to the lower extremities, could alter bone metabolism in the hip and result in decreased bone density [18, 44].

Our study extends previous findings by longitudinally examining the association of BMD with CVD in a healthy cohort with no history of CVD, in separate gender and race groups, and across a wider range of BMD values, not just the lower range. This study also had the benefit of utilizing QCT for volumetric determination of BMD at the spine. This technique adjusts for differences in bone size, an important confounder in studies that involve multiethnic groups and different genders. The additional advantage of QCT is that, in contrast to DXA, it is not affected by the presence of extra-osseous calcification such as aortic calcification and degenarative osteoarthritic changes, which get incorporated in the region of interest and lead to a falsely increased areal bone density of the spine. The main limitation of this study is the generalizability of its findings to other populations because of its inclusion of a well-functioning cohort of older adults. Another limitation is that inflammatory cytokines were measured at a single time point. Owing to their circadian variability, more than one assay may be needed to adequately classify an individual's level.

In summary, we observed a longitudinal inverse association between BMD measures and incident CVD in older women and white men with no prior history of cardiovascular disease. These findings provide further support for a relationship between osteoporosis and CVD that is independent of age and shared risk factors. Further research should assess this association in separate race groups and investigate common pathophysiological mechanisms between the two conditions. Once confirmed, a link between low BMD and CVD may lead to the early identification of subjects at higher risk for CVD, and to the potential for common preventive and therapeutic interventions that target both osteoporosis and CVD.

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