

2017

## Bone mineral density and risk of heart failure in older adults: The Cardiovascular Health Study

Raymond B. Fohtung  
*Washington University School of Medicine in St. Louis*

David L. Brown  
*Washington University School of Medicine in St. Louis*

William J.H. Koh  
*University of Washington - Seattle Campus*

Traci M. Bartz  
*University of Washington - Seattle Campus*

Laura D. Carbone  
*Medical College of Georgia at Augusta University*

*See next page for additional authors*

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### Recommended Citation

Fohtung, Raymond B.; Brown, David L.; Koh, William J.H.; Bartz, Traci M.; Carbone, Laura D.; Civitelli, Roberto; Stein, Phyllis K.; Chaves, Paulo H.M.; Kestenbaum, Bryan R.; and Kizer, Jorge R., "Bone mineral density and risk of heart failure in older adults: The Cardiovascular Health Study." *Journal of the American Heart Association*. 6, 3. e004344. (2017).  
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## Authors

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## Bone Mineral Density and Risk of Heart Failure in Older Adults: The Cardiovascular Health Study

Raymond B. Foftung, MD; David L. Brown, MD; William J. H. Koh, MS; Traci M. Bartz, MS; Laura D. Carbone, MD, MS; Roberto Civitelli, MD; Phyllis K. Stein, PhD; Paulo H. M. Chaves, MD, PhD; Bryan R. Kestenbaum, MD, MS; Jorge R. Kizer, MD, MSc

**Background**—Despite increasing evidence of a common link between bone and heart health, the relationship between bone mineral density (BMD) and heart failure (HF) risk remains insufficiently studied.

**Methods and Results**—We investigated whether BMD measured by dual-energy x-ray absorptiometry was associated with incident HF in an older cohort. Cox models were stratified by sex and interactions of BMD with race assessed. BMD was examined at the total hip and femoral neck separately, both continuously and by World Health Organization categories. Of 1250 participants, 442 (55% women) developed HF during the median follow-up of 10.5 years. In both black and nonblack women, neither total hip nor femoral neck BMD was significantly associated with HF; there was no significant interaction by race. In black and nonblack men, total hip, but not femoral neck, BMD was significantly associated with HF, with evidence of an interaction by race. In nonblack men, lower total hip BMD was associated with higher HF risk (hazard ratio, 1.13 [95% CI, 1.01–1.26] per 0.1 g/cm<sup>2</sup> decrement), whereas in black men, lower total hip BMD was associated with lower HF risk (hazard ratio, 0.74 [95% CI, 0.59–0.94]). There were no black men with total hip osteoporosis. Among nonblack men, total hip osteoporosis was associated with higher HF risk (hazard ratio, 2.83 [95% CI, 1.39–5.74]) compared with normal BMD.

**Conclusions**—Among older adults, lower total hip BMD was associated with higher HF risk in nonblack men but lower risk in black men, with no evidence of an association in women. Further research is needed to replicate these findings and to study potential underlying pathways. (*J Am Heart Assoc.* 2017;6:e004344. DOI: 10.1161/JAHA.116.004344.)

**Key Words:** bone mineral density • heart failure • osteoporosis • race

Heart failure (HF) and osteoporosis are highly prevalent aging-related diseases that exact an enormous toll on society. In the United States, where some 5.7 million adults are affected, HF ranks as the leading cause of hospitalization,

and carries a mortality rate of ≈50% within 5 years of diagnosis.<sup>1</sup> With the aging of the US population, the burden of HF is expected to significantly increase in the coming decades.<sup>2</sup> In the United States, osteoporosis and low bone mineral density (BMD) affect an estimated 53 million people, predominantly women and individuals of European descent.<sup>3</sup> As a result, an estimated 1 in 2 women, and 1 in 5 men, will experience an osteoporotic fracture during their lifetime.<sup>3</sup> Osteoporotic fractures, in particular, hip fractures, are associated with substantial costs and morbidity and carry a 1-year mortality rate of about 20%.<sup>4</sup>

Although HF and osteoporosis are generally thought of as separate diseases, the two have been linked. Epidemiological studies have found that having HF predisposes patients to low BMD and hip fracture, an association that is partly attributable to reduced physical activity and the effects of vasoactive and diuretic medications.<sup>5–7</sup> However, common mechanisms involving various biochemical pathways<sup>8–13</sup> may also be important in this link and could possibly drive this association in the opposite direction, with low BMD predisposing to HF. Such mechanisms may involve coronary atherosclerosis,<sup>14</sup> which has been associated with low BMD,<sup>15,16</sup> or affect the myocardium directly. A population-based European study

From the Department of Medicine, Washington University School of Medicine, Saint Louis, MO (R.B.F., D.L.B., R.C., P.K.S.); Department of Biostatistics, University of Washington School of Public Health, Seattle, WA (W.J.H.K., T.M.B.); Department of Medicine, Medical College of Georgia at Augusta University, Augusta, GA (L.D.C.); Charlie Norwood Veterans Affairs, Augusta, GA (L.D.C.); Benjamin Leon Center for Geriatric Research and Education, Department of Medicine, Family Medicine, and Community Health, Herbert Wertheim College of Medicine, Florida International University, Miami, FL (P.H.M.C.); Department of Medicine, University of Washington School of Medicine, Seattle, WA (B.R.K.); Departments of Medicine and Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (J.R.K.).

An accompanying Table S1 is available at <http://jaha.ahajournals.org/content/6/3/e004344/DC1/embed/inline-supplementary-material-1.pdf>

**Correspondence to:** Jorge R. Kizer, MD, MSc, Cardiovascular Clinical Research Unit, Albert Einstein College of Medicine, Bronx, NY 10461. E-mail: [jorge.kizer@einstein.yu.edu](mailto:jorge.kizer@einstein.yu.edu)

Received July 25, 2016; accepted January 17, 2017.

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examined this question using broadband ultrasound attenuation to measure BMD at the calcaneus and documented an inverse association of broadband ultrasound attenuation with incident HF risk, especially HF without antecedent myocardial infarction.<sup>17</sup>

No study to date has assessed low BMD as a risk factor for HF using dual-energy x-ray absorptiometry (DXA), which is the recommended method for determining BMD in clinical practice.<sup>3</sup> Nor has the impact of race on the relationship between BMD and HF been examined, particularly in blacks, who are at higher risk for incident HF compared with whites.<sup>18</sup> In addition, there are substantial differences in bone strength, density, and microarchitecture between blacks and whites, partly attributed to a significantly greater cortical thickness and trabecular volumetric BMD in blacks.<sup>19</sup> As a result, blacks have a lower fracture risk and prevalence of osteoporosis compared with whites.<sup>3</sup> To address these gaps, we investigated whether total hip and femoral neck BMD was associated with incident HF among older adults participating in the Cardiovascular Health Study (CHS) up to a maximum follow-up of 19 years.

## Methods

### Study Population

CHS is a population-based longitudinal study of risk factors associated with development of cardiovascular disease (CVD) in older adults ( $\geq 65$  years).<sup>20</sup> Medicare-eligible individuals were recruited from four US communities, including Sacramento County, CA; Washington County, MD; Forsyth County, NC; and Allegheny County, PA. Eligible individuals had to be noninstitutionalized, expect to remain in the area for the following 3 years, receive no active cancer treatment, not be wheelchair-bound at home, and be capable of providing consent without requiring a proxy at entry. Household members of those sampled were recruited if eligible. The institutional review boards at all clinical centers and the coordinating center approved the study and all participants provided informed consent. Initially, 5201 mostly white participants were recruited in 1989–1990 (original cohort), followed by 687 predominantly black participants in 1992–1993 (supplemental cohort).

Of the 5888 participants recruited to CHS, 4842 participated in the 1994–1995 examination, which is the baseline for this study. In this examination, DXA scans were performed on participants in 2 of the 4 sites (Sacramento and Allegheny Counties) for determination of BMD. Scans were offered to participants in the order in which they came to the field centers for their visit until funding for these scans was exhausted. In total, 1576 participants (32.5%) underwent DXA scanning. Of these, we excluded 95 for prevalent HF, 37 for

current use of corticosteroids, and 9 for both prevalent HF and use of corticosteroids. An additional 185 participants were excluded because of missing covariates for multivariable analysis. Our analytic sample thus included 1250 participants.

### Measurement of BMD

DXA scans were performed with QDR 2000 densitometers (Hologic, Inc, Bedford, MA), using the array beam mode. Scans were read blindly at the University of California San Francisco Reading Center using Hologic software version 7.10, as previously described.<sup>21</sup> The primary measures of interest were BMD of the total hip and BMD of the femoral neck.

### Ascertainment and Adjudication of Incident HF Outcome

Follow-up consisted of annual in-person examinations alternating with semiannual telephone interviews between 1989 and 1999. Thereafter, telephone interviews continued semiannually, with one additional in-person examination in 2005–2006. Ascertainment and adjudication of incident HF events have been previously described.<sup>22</sup> Briefly, an expert panel reviewed all relevant data from hospitalizations or outpatient visits, including history, physical examination, report of chest radiography, and medication usage. Any self-report of a physician diagnosis of HF obtained during in-person visits and telephone contacts was confirmed by reviewing the medical record for documentation of a series of symptoms and physical signs (such as shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary rales, gallop rhythm, or displaced left ventricular apical impulse) or supporting clinical findings, such as those on chest radiography. For participants with a previous physician diagnosis of HF, the diagnosis was confirmed if the participant was receiving medical therapy for HF such as a current prescription for a diuretic and digitalis or a vasodilator (nitroglycerin, hydralazine, or angiotensin-converting enzyme inhibitor). The present report includes HF events adjudicated from baseline (year of BMD measurement) through June 30, 2013, for a maximum follow-up of 19 years.

### Assessment and Definition of Baseline Covariates

Participants received standardized health assessments involving questionnaires, anthropometry, physical examination, blood collection, electrocardiography, and spirometry during their study visits, as previously described.<sup>20</sup> Physical activity was determined using a validated questionnaire.<sup>23</sup> The Core Laboratory at the University of Vermont performed measurements on blood samples, as detailed elsewhere.<sup>24–26</sup>

Most variables including body weight, systolic blood pressure, smoking, systemic estrogen use, and treatment with antihypertensive medication were collected or measured in 1994–1995. For variables that were not assessed in 1994–1995, we used information from the closest prior examination where data were available, under the assumption that earlier values would be a reasonable proxy for current values. Physical activity, cystatin C, C-reactive protein (CRP), and height and waist circumference were measured in 1992–1993 and forced expiratory volume in 1 second was measured in 1993–1994. Body mass index was calculated using height measured in 1992–1993 and weight measured in 1994–1995. When not available at the 1992–1993 examination, height was carried forward from the CHS baseline examination in 1989–1990. Smoking was assessed in 1994–1995 and when missing was carried forward from the 1992–1993 visit.

Diabetes mellitus was defined as fasting glucose  $\geq 126$  mg/dL, nonfasting glucose  $\geq 200$  mg/dL, or treatment with oral hypoglycemic medications or insulin, based on the 1994–1995 visit or closest prior visit if missing. Cystatin C was used to calculate estimated glomerular filtration rate (eGFR) using standard methods.<sup>27,28</sup>

Prevalent CVD including coronary heart disease (CHD), stroke or transient ischemic attack, peripheral arterial disease, and HF were ascertained at the initiation of CHS and incident events adjudicated during follow-up from self-reported information obtained at semiannual contacts.<sup>29,30</sup> Atrial fibrillation was ascertained through a combination of annual ECGs and hospital or outpatient diagnostic codes.<sup>31</sup> Prevalent CVD and atrial fibrillation at baseline for the current study were determined through such ascertainment, and include events from the start of CHS to the 1994–1995 examination, while incident CHD was based on surveillance thereafter, comprising events after the 1994–1995 examination.

## Statistical Analysis

All analyses were stratified a priori by sex. Baseline characteristics were summarized using means (SDs) or medians (interquartile ranges) for continuous variables and counts (percentages) for categorical variables. Comparisons of baseline characteristics between blacks and nonblacks in each sex group were performed with *t* tests (allowing for unequal variances) and chi-square tests for continuous and categorical variables, respectively. Cross-sectional associations of BMD with covariates were examined using Pearson correlation coefficients for continuous variables, and linear regression for comparison of means across levels of categorical variables.

Total hip and neck BMD were evaluated both as continuous and categorical variables. Categories of BMD were based on

the World Health Organization classification of osteoporosis using T-scores. T-scores were obtained by calculating the number of SDs that the raw BMD values were from the average BMD in a population-based sample of non-Hispanic white women aged 20 to 29 years.<sup>32</sup> T-scores were categorized as normal BMD (T-score  $\geq -1.0$ ), osteopenia ( $-1.0 > \text{T-Score} > -2.5$ ) or osteoporosis (T-score  $\leq -2.5$ ). Of note, herein we refer to osteoporosis (or osteopenia) of the femoral neck or total hip to designate low BMD at those sites, recognizing that osteoporosis-level (osteopenia-level) BMD at either site is sufficient for a diagnosis of osteoporosis (osteopenia) for the affected individual.

In our primary analyses, we examined the association of BMD at baseline (1994–1995) with incidence of HF during follow-up. We report hazards ratios (HRs), Wald-based 95% CIs, and Wald-based *P* values based on Cox proportional hazards regression performed in men and women separately. Because we had a priori reasons to believe that the association of BMD with HF might differ between blacks and nonblacks (white [99.6%], American Indian, Alaskan native, Asian, Pacific Islander, and other), all analyses included a test for interaction by race using the Wald test, and the results were reported by race in both men and women regardless of significance. For analyses of the association of continuous BMD with incident HF, we assessed the functional forms of the associations using penalized cubic splines after including potential confounders from the fully adjusted model, as described below.

We fit models adjusting sequentially for covariates selected based on previously documented associations with HF. In our first model, the association of BMD with incident HF was adjusted for age at BMD measurement. In our second model, we additionally adjusted for body mass index, systolic blood pressure, antihypertensive medications, prevalent diabetes mellitus, smoking (none, current, or former smoker), alcohol consumption, estrogen replacement (in women), and physical activity (logarithm of kcal per week+1). In our final and fully adjusted model, we additionally adjusted for forced expiratory volume in 1 second, eGFR, and CRP and prevalent CHD, stroke/transient ischemic attack, peripheral arterial disease and atrial fibrillation. Last, in secondary analyses, we additionally adjusted for aspirin and/or digitalis use or waist circumference to assess their impact on the associations of interest.

Sensitivity analyses were conducted to exclude participants with possible subclinical HF at baseline. These sensitivity analyses examined the influence of excluding participants with N-terminal pro B-type natriuretic peptide (NT-proBNP)  $\geq 190$  pg/mL<sup>26</sup> or starting follow-up for incident HF 2 years after DXA scan. Sensitivity analyses were performed for continuous BMD only. In addition, we investigated the influence of time-dependent CHD on the association

of BMD with incident HF in our fully adjusted model for both continuous and categorical BMD. Statistical analyses were conducted using STATA version 14 (StataCorp, College Station, TX), excepting the functional form of the final Cox model, which was assessed in R3.1.1. A two-tailed  $P < 0.05$  was considered statistically significant.

W.J.H.K. had full access to all data in the study and takes responsibility for its integrity and the data analysis.

## Results

### Baseline Characteristics

Baseline characteristics of the cohort, stratified by sex, are summarized in Table 1. The study cohort comprised 1250 participants with a mean age of  $76 \pm 5$  years. Of these, 59% were women and 19% were black. Black women and men were younger; had higher prevalence of hypertension and diabetes mellitus; consumed less alcohol but engaged in less frequent exercise; had less prevalent use of lipid-lowering, estrogen (women), aspirin, and digitalis therapy; and had higher CRP and eGFR levels but lower triglycerides and forced expiratory volume in 1 second, as compared with their nonblack counterparts. Black women had higher waist circumference and low-density lipoprotein but lower high-density lipoprotein than white women, whereas the opposite was true in men. Black men had lower prevalent CHD than nonblack men, but black women had more prevalent stroke/transient ischemic attack than black women. BMD was lower in nonblacks than blacks for both sexes at both the total hip and femoral locations.

### Association of Baseline Covariates With BMD

Descriptive results for the association of baseline covariates with continuous total hip BMD in women and men are summarized in Table 2. In both sexes, total hip BMD was negatively correlated with age but positively associated with measures of adiposity, prevalent diabetes mellitus, and triglycerides. In women, antihypertensive medication and current estrogen use, along with higher forced expiratory volume in 1 second and CRP levels, were associated with higher total hip BMD, whereas prevalent atrial fibrillation was associated with lower total hip BMD. In men, total hip BMD was positively correlated with physical activity, alcohol consumption, and eGFR. Results for femoral neck BMD were similar (Table S1).

### Incident HF Events

Over a median follow-up of 10.5 years, there were 442 incident HF events. Of these, 245 (55%) occurred in women,

including 48 (11%) in black women and 197 (45%) in nonblack women. In addition, 197 (45%) incident HF events occurred in men, including 33 (7%) in black men and 164 (37%) in nonblack men. The number and incidence rates of HF events across BMD categories are summarized in Table 3. The highest event rates occurred for nonblack men with osteoporosis of the femoral neck and, especially, total hip. The marked differences in HF incidence by BMD category noted for nonblack men were not observed in women of either race. The incidence rate of HF for black men with osteopenia at the femoral neck was comparable to normal BMD, but lower at the total hip, although the subset with osteopenia at the total hip was especially small. There were no black men and few black women with total hip osteoporosis, and the numbers of black men and women with osteoporosis of the femoral neck were similarly scant. As a consequence, Cox regression analyses of the categories of total hip and femoral neck BMD were restricted to nonblacks.

### Results of the Primary Analyses

Results of the primary analyses are summarized in Table 4 and Figures 1 and 2. These findings are stratified by sex and reported separately for blacks and nonblacks. Assessment of the functional forms using penalized cubic smoothing splines showed that the associations of continuous total hip and femoral neck BMD with HF were consistent with linear trends. In summary, in women, there was no significant association of BMD with incident HF and no evidence of interaction of BMD with race. In men, there was a significant association of BMD with incident HF at the total hip only and significant interaction of BMD with race at the total hip and femoral neck. In men, this association of BMD with incident HF was positive in blacks and negative in nonblacks. The results of the primary analyses are presented in detail below.

### Lack of Association of Continuous or Categorical BMD With Incident HF in Both Black and Nonblack Women

Findings for the association of continuous total hip and femoral neck BMD with incident HF are summarized in Table 4. In both black and nonblack women, there was no significant association of continuous BMD with incident HF in the fully adjusted model (total hip: HR, 0.97 [95% CI, 0.85–1.10] for nonblacks; HR, 1.11 [95% CI, 0.89–1.39] for blacks). There was also no significant effect modification of continuous BMD by race (total hip BMD,  $P = 0.273$ ; femoral neck BMD,  $P = 0.466$ ).

Results for the association of categories of total hip and femoral BMD with incident HF in nonblacks are summarized in



**Table 1.** Baseline Characteristics of the Study Cohort Stratified by Sex and Race

Characteristics	Women			Men		
	Black (n=145)	Nonblack (n=589)	P Value	Black (n=91)	Nonblack (n=425)	P Value
Age, y	74.2±4.9	76.3±4.2	<0.001	74.8±4.6	77.1±4.7	<0.001
Body mass index, kg/m <sup>2</sup>	29.3±4.6	26.3±4.8	<0.001	26.7±3.8	26.6±3.6	<0.001
Waist circumference, cm	101.2±14.2	93.6±14.3	<0.001	95.9±10.9	98.4±9.3	<0.001
Systolic blood pressure, mm Hg	136±19	134±21	<0.001	134±22	131±19	<0.001
Antihypertensive medication,* No. (%)	104 (72)	263 (45)	<0.001	48 (53)	216 (51)	0.739
Diabetes mellitus, No. (%)	37 (26)	51 (9)	<0.001	24 (26)	66 (16)	0.013
Smoking, No. (%)			0.328			<0.001
Never smoker	65 (45)	302 (51)		22 (24)	114 (27)	
Former smoker	67 (46)	233 (40)		52 (57)	287 (68)	
Current smoker	13 (9)	54 (9)		17 (19)	24 (6)	
Alcohol, drinks per wk	0 (0–0)	0 (0–1)	<0.001	0 (0–3)	1 (0–7)	<0.001
Physical activity, kcal per wk	490 (180–1255)	930 (322.5–2017.5)	<0.001	867 (315–1843)	1413 (540–3175)	<0.001
Low-density lipoprotein, mg/dL	134±38	132±32	<0.001	120±31	122±29	<0.001
High-density lipoprotein, mg/dL	58±14	59±15	<0.001	52±11	46±11	<0.001
Triglycerides, mg/dL	103 (79–142)	124 (90–170)	<0.001	91 (73–130)	112 (83–158)	<0.001
Lipid-lowering medication, No. (%)	14 (10)	69 (12)	<0.001	5 (5)	35 (8)	<0.001
Aspirin, No. (%)	40 (28)	237 (40)	<0.001	29 (32)	183 (43)	<0.001
Digitalis, No. (%)	8 (6)	35 (6)	<0.001	7 (8)	40 (9)	<0.001
Estrogen use, No. (%)	15 (10)	122 (21)	0.004	...	...	
Prevalent coronary heart disease, No. (%)	29 (20)	82 (14)	0.067	17 (19)	128 (30)	0.028
Prevalent stroke/transient ischemic attack, No. (%)	10 (7)	17 (3)	0.022	10 (11)	37 (9)	0.492
Prevalent peripheral arterial disease, No. (%)	3 (2)	7 (1)	0.413	5 (5)	24 (6)	0.954
Prevalent atrial fibrillation, No. (%)	8 (6)	30 (5)	0.837	3 (3)	35 (8)	0.102
Serum creatinine, mg/dL	0.9±0.3	0.9±0.2	<0.001	1.2±0.3	1.2±0.2	<0.001
Estimated glomerular filtration rate (cystatin-based), mL/min per 1.73 m <sup>2</sup>	85±23	77±18	<0.001	82±17	71±15	<0.001
Forced expiratory volume in 1 s, L	1.6±0.4	1.8±0.4	<0.001	2.1±0.6	2.5±0.6	<0.001
C-reactive protein, mg/L	4.9 (2.0–9.3)	2.4 (1.1–5.6)	<0.001	2.2 (1.0–4.2)	1.9 (1.0–4.0)	<0.001
Total hip BMD, g/cm <sup>2</sup>	0.9±0.1	0.7±0.1	<0.001	1.0±0.2	0.9±0.2	<0.001
Femoral neck BMD, g/cm <sup>2</sup>	0.8±0.1	0.6±0.1	<0.001	0.9±0.2	0.8±0.1	<0.001
Total hip, WHO categories, No. (%)			<0.001			0.004
Normal	73 (50)	83 (14)		75 (82)	283 (67)	
Osteopenia	53 (37)	282 (48)		16 (18)	120 (28)	
Osteoporosis	19 (13)	224 (38)		0 (0)	22 (5)	
Femoral neck, WHO categories, No. (%)			<0.001			<0.001
Normal	58 (40)	53 (9)		64 (70)	181 (43)	
Osteopenia	69 (48)	271 (46)		24 (26)	205 (48)	
Osteoporosis	18 (12)	265 (45)		3 (3)	39 (9)	

Data for continuous variables are presented as mean±SD or median (interquartile range). BMD indicates bone mineral density; WHO, World Health Organization. \*Antihypertensive medication defined as the use of β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, vasodilators, or diuretics.

**Table 2.** Cross-Sectional Association of Continuous Total Hip BMD With Baseline Characteristics of the Study Cohort

Characteristics	Total Hip BMD							
	Women (n=734)				Men (n=516)			
	No.	Correlation Coefficient	Mean±SD	P Value	No.	Correlation Coefficient	Mean±SD	P Value
Age, y	734	−0.32		<0.001	516	−0.21		<0.001
Body mass index, kg/m <sup>2</sup>	734	0.51		<0.001	516	0.36		<0.001
Waist circumference, cm	731	0.41		<0.001	516	0.22		<0.001
Systolic blood pressure, mm Hg	734	0.03		0.505	516	0.03		0.510
Antihypertensive medication								
No	367		0.74±0.14	0.003	252		0.95±0.16	0.784
Yes	367		0.77±0.15		264		0.95±0.17	
Diabetes mellitus								
No	646		0.74±0.14	<0.001	426		0.94±0.16	0.011
Yes	88		0.84±0.16		90		0.99±0.17	
Smoking status								
Never smoker	367		0.75±0.14	0.345	136		0.94±0.17	0.677
Former smoker	300		0.76±0.15		339		0.95±0.16	
Current smoker	67		0.73±0.13		41		0.94±0.16	
Alcohol, drinks per wk	734	−0.001		0.981	516	0.01		0.026
Physical activity, kcal per wk*	734	−0.003		0.935	516	0.10		0.022
Low-density lipoprotein, mg/dL	726	0.001		0.981	509	0.03		0.556
High-density lipoprotein, mg/dL	733	−0.05		0.148	516	0.01		0.899
Triglycerides, mg/dL	734	0.12		0.004	516	0.09		0.044
Lipid-lowering medication								
No	651		0.75±0.14	0.313	476		0.95±0.16	0.333
Yes	83		0.77±0.15		40		0.92±0.19	
Aspirin								
No	454		0.75±0.14	0.483	302		0.95±0.16	0.732
Yes	277		0.75±0.14		212		0.95±0.17	
Digitalis								
No	691		0.75±0.14	0.972	469		0.95±0.16	0.586
Yes	43		0.75±0.15		47		0.96±0.20	
Estrogen use								
No	597		0.75±0.14	0.034				
Yes	137		0.77±0.14					
Prevalent coronary heart disease								
No	623		0.75±0.14	0.776	371		0.95±0.16	0.449
Yes	111		0.75±0.16		145		0.94±0.18	
Prevalent stroke/transient ischemic attack								
No	707		0.75±0.14	0.926	469		0.95±0.16	0.204
Yes	27		0.75±0.15		47		0.92±0.18	
Prevalent peripheral arterial disease								
No	109		0.74±0.15	0.955	95		0.91±0.19	0.167

Continued



**Table 2.** Continued

Characteristics	Total Hip BMD							
	Women (n=734)				Men (n=516)			
	No.	Correlation Coefficient	Mean±SD	P Value	No.	Correlation Coefficient	Mean±SD	P Value
Yes	625		0.75±0.14		421		0.96±0.16	
<b>Prevalent atrial fibrillation</b>								
No	696		0.75±0.14	0.011	478		0.95±0.16	0.814
Yes	38		0.69±0.15		38		0.95±0.19	
Creatinine, mg/dL	725	0.07		0.062	512	-0.01		0.918
Estimated glomerular filtration rate (cystatin-based), mL/min per 1.73 m <sup>2</sup>	734	0.06		0.085	516	0.09		0.033
Forced expiratory volume in 1 s, L	734	0.11		0.003	516	0.07		0.110
C-reactive protein, mg/L	734	0.11		0.004	516	0.02		0.723

BMD indicates bone mineral density.

\*The logarithm of physical activity+1 was used to compute the correlation.

Figures 1 and 2, respectively. Compared with normal BMD, there was no evidence of significant association of osteoporosis (or osteopenia) at the total hip (HR, 0.83; 95% CI, 0.54–1.28) or femoral neck (HR, 1.03; 95% CI, 0.64–1.64) with incident HF in the fully adjusted model among nonblack women.

### Significant Associations of Continuous and Categorical BMD With Incident HF in Men

Results for the association of continuous total hip and femoral neck BMD with incident HF in men are also summarized in

**Table 3.** HF Events During Follow-Up in Participants With Normal BMD, Osteopenia, and Osteoporosis Stratified by Sex and Race

	Women		Men	
	Black	Nonblack	Black	Nonblack
Median follow-up, y	12.0	12.1	8.9	8.7
<b>HF events</b>				
Total hip, No. (incidence rate*)				
Normal BMD	25 (30.2)	36 (34.9)	29 (41.5)	103 (37.7)
Osteopenia	16 (23.9)	99 (28.8)	4 (23.6)	51 (48.7)
Osteoporosis	7 (39.9)	62 (26.3)	...	10 (96.6)
Femoral neck, No. (incidence rate*)				
Normal BMD	19 (28.1)	22 (34.4)	25 (38.7)	58 (35.4)
Osteopenia	24 (29.1)	97 (29.1)	8 (41.3)	91 (46.5)
Osteoporosis	5 (28.9)	78 (27.3)	0 (0)	15 (53.3)

BMD indicates bone mineral density; HF, heart failure.

\*Per 1000 person-years.

Table 4. There was a significant interaction of BMD and race in men (total hip BMD,  $P=0.001$ ; femoral neck BMD,  $P=0.009$ ). In nonblack men, lower total hip BMD was associated with a significantly higher HF risk in the fully adjusted model (HR, 1.13 [95% CI, 1.01–1.26] for every 0.1 g/cm<sup>2</sup> decrement in BMD). In contrast, among black men, lower total hip BMD was associated with a significantly lower risk of HF in the fully adjusted model (HR, 0.74 [95% CI, 0.59–0.94] for every 0.1 g/cm<sup>2</sup> decrement in BMD). The race-specific associations of femoral neck BMD with incident HF were in the same direction as for total hip BMD but were not statistically significant (nonblack men: HR, 1.14 [95% CI, 0.99–1.30]; black men: HR, 0.79 [95% CI, 0.62–1.01]).

Findings for the association of categories of total hip and femoral neck BMD with incident HF in nonblack men are also summarized in Figures 1 and 2, respectively. Nonblack men with osteoporosis at the total hip had a nearly 3-fold higher risk of HF (HR, 2.83; 95% CI, 1.39–5.74 [ $P=0.004$ ]) and nonblack men with osteoporosis of the femoral neck had an almost 2-fold risk of HF (HR, 1.88; 95% CI, 1.02–3.47 [ $P=0.043$ ]) as compared with normal BMD at these sites. Higher risk of HF was observed for osteopenia of the total hip (HR, 1.35; 95% CI, 0.94–1.93 [ $P=0.104$ ]) and of the femoral neck (HR, 1.37; 95% CI, 0.96–1.95 [ $P=0.081$ ]) relative to normal BMD but these were not significant (Figure 2).

### Secondary and Sensitivity Analyses

The results in men and women for continuous and categorical total hip and femoral neck BMD were similar after additionally adjusting for aspirin, digitalis use, or waist circumference.

In sensitivity analyses excluding participants with NT-proBNP  $\geq 190$  pg/mL or starting follow-up 2 years after

**Table 4.** Association Between BMD of the Total Hip or Femoral Neck and Incident Heart Failure Stratified by Sex

Group	Women (n=734)		Men (n=516)	
	Age-Adjusted HR* (95% CI)	Fully Adjusted <sup>†</sup> HR* (95% CI)	Age-Adjusted HR* (95% CI)	Fully Adjusted <sup>†</sup> HR* (95% CI)
<b>Total hip BMD</b>				
Nonblack	0.88 (0.79–0.99) <i>P</i> =0.036	0.97 (0.85–1.10) <i>P</i> =0.647	1.09 (0.98–1.21) <i>P</i> =0.096	1.13 (1.01–1.26) <i>P</i> =0.034
Black	0.99 (0.80–1.22) <i>P</i> =0.915	1.11 (0.89–1.39) <i>P</i> =0.358	0.74 (0.59–0.93) <i>P</i> =0.011	0.74 (0.59–0.94) <i>P</i> =0.014
Interaction of BMD with race <sup>‡</sup>	1.12 (0.88–1.42) <i>P</i> =0.354	1.14 (0.90–1.46) <i>P</i> =0.273	0.68 (0.53–0.87) <i>P</i> =0.003	0.66 (0.51–0.85) <i>P</i> =0.001
<b>Femoral neck BMD</b>				
Nonblack	0.88 (0.77–1.01) <i>P</i> =0.060	0.97 (0.84–1.12) <i>P</i> =0.692	1.08 (0.96–1.22) <i>P</i> =0.204	1.14 (0.99–1.30) <i>P</i> =0.062
Black	0.94 (0.74–1.20) <i>P</i> =0.635	1.08 (0.84–1.38) <i>P</i> =0.533	0.79 (0.63–1.00) <i>P</i> =0.051	0.79 (0.62–1.01) <i>P</i> =0.057
Interaction of BMD with race <sup>‡</sup>	1.07 (0.82–1.41) <i>P</i> =0.613	1.11 (0.84–1.46) <i>P</i> =0.466	0.74 (0.57–0.95) <i>P</i> =0.020	0.70 (0.53–0.91) <i>P</i> =0.009

\*Per 0.1 g/cm<sup>2</sup> decrement in bone mineral density (BMD).

<sup>†</sup>Adjusted for age, body mass index, systolic blood pressure, antihypertensive medication, diabetes mellitus, smoking, alcohol consumption, physical activity, estrogen replacement (women), prevalent coronary heart disease, prevalent stroke or transient ischemic attack, prevalent peripheral arterial disease, prevalent atrial fibrillation, estimated glomerular filtration rate, forced expiratory volume in 1 second, and C-reactive protein.

<sup>‡</sup>Ratio of hazard ratio (HR) between black and nonblack groups.

DXA scan, findings were similar in women. After exclusion of individuals with NT-proBNP  $\geq$ 190 pg/mL in nonblack men, lower total hip BMD remained significantly associated with higher HF risk (HR, 1.20; 95% CI, 1.03–1.40 [*P*=0.020]), and lower femoral neck BMD was stronger and significantly associated with higher HF risk (HR, 1.22 per 0.1 g/cm<sup>2</sup>; 95% CI, 1.02–1.46 [*P*=0.030]). In black men, the association of total hip BMD with incident HF became weaker and no longer statistically significant (HR, 0.81; 95% CI, 0.61–1.07 [*P*=0.142]), although evidence of an interaction of BMD with race remained (*P*=0.013). The association between femoral neck BMD with HF in black men was similar in the fully adjusted model (HR, 0.81; 95% CI, 0.61–1.08 [*P*=0.147]).

The sensitivity analysis starting follow-up 2 years after DXA scan showed similar findings. In nonblack men, lower total hip BMD remained significantly associated with higher HF risk (HR, 1.14; 95% CI, 1.01–1.28 [*P*=0.032]) and lower femoral neck BMD again was significantly associated with higher HF risk (HR, 1.17; 95% CI, 1.02–1.34 [*P*=0.030]). In black men, the association of total hip BMD with HF was attenuated (HR, 0.82; 95% CI, 0.63–1.07 [*P*=0.149]). For femoral neck BMD, the results were similar (HR, 0.82; 95% CI, 0.62–1.07 [*P*=0.144]).

Additional adjustment for CHD as a time-dependent covariate had similar results for continuous BMD of both total hip and femoral neck (both black and nonblack men), and categorical BMD at the total hip among nonblack men. Among nonblack men, the risk estimate for osteoporosis of

the femoral neck was similar (HR, 1.85; 95% CI, 1.001–3.41 [*P*=0.0497]), while osteopenia of the femoral neck with HF was substantially strengthened (HR, 1.50; 95% CI, 1.05–2.14 [*P*=0.026]).

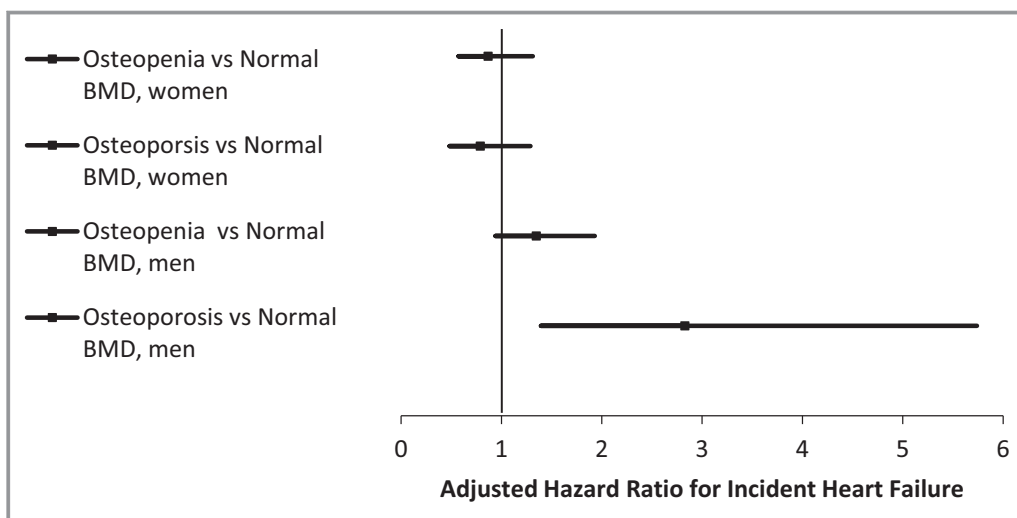
## Discussion

### Main Findings

In this population-based study of older adults, we did not find a significant association between total hip or femoral neck BMD and incident HF in women. Among men, however, there was evidence of a significant association and also effect modification by race. Lower total hip BMD was independently associated with higher HF risk in nonblack men, but lower risk in black men. Findings were similar for femoral neck BMD, although these fell short of statistical significance, possibly reflecting DXA's higher precision errors for BMD at the femoral neck than the total hip.<sup>33</sup> The statistically significantly higher risk of HF with lower BMD of the hip in nonblack men persisted after exclusion of subclinical HF (NT-proBNP  $\geq$ 190 pg/mL), although the lower risk of HF with lower BMD in black men was attenuated and no longer significant.

### Prior Studies

To our knowledge, only one previous study has examined the association of BMD with incident HF risk. This study assessed

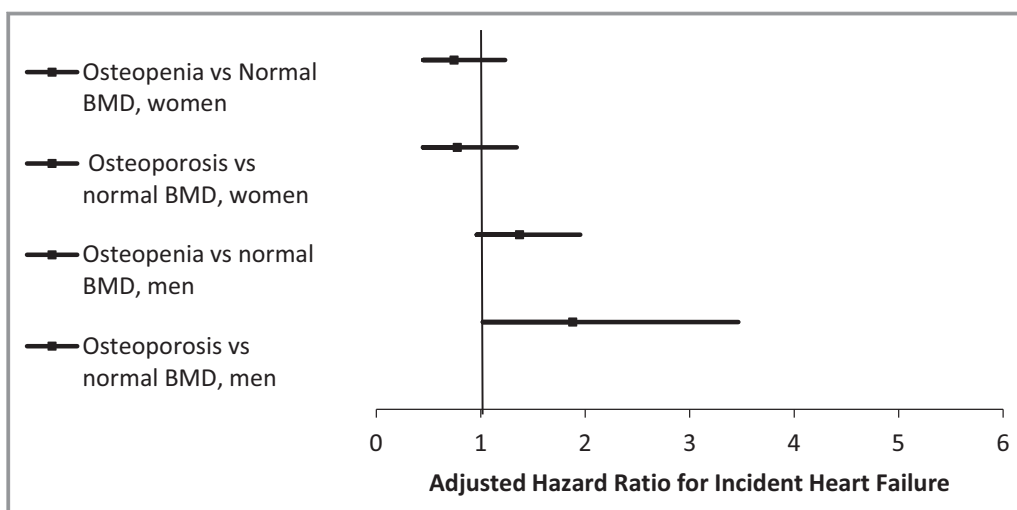


**Figure 1.** Adjusted hazard ratio for incident heart failure by World Health Organization classification of osteoporosis or osteopenia compared with normal bone mineral density (BMD) at the total hip in nonblacks. Models are fully adjusted.

a cohort of 13 666 British adults, aged 42 to 82 years, who participated in the EPIC-Norfolk (European Prospective Investigation into Cancer and Nutrition-Norfolk) study.<sup>17</sup> Participants were followed for a mean of 9.3 years, similar to the median follow-up of 10.5 years in our study.<sup>17</sup> The EPIC-Norfolk study found that lower BMD at the calcaneus was associated with higher HF risk. The study found no evidence of effect modification by sex, and risk estimates were similar in men and women although the association was not significant in women. The EPIC-Norfolk study did not report testing of effect modification by race.

Among other notable differences between the EPIC-Norfolk study and the present investigation, participants in

the British study were younger (mean age 62±9 versus 76±5 years), which likely accounts for the lower incidence of HF events (2.8%) compared with that reported here (35.4%). Also, while the EPIC-Norfolk investigation used broadband ultrasound attenuation of the calcaneus to measure BMD, our study used DXA scans of the total hip and femoral neck. In addition, the British study based incident HF events on inpatient International Classification of Disease, 9th and 10th revision codes only, whereas our study used adjudicated incident HF events. Last, like the EPIC-Norfolk report, we accounted for a series of potential confounders in our analyses. We additionally included measures of chronic kidney disease (cystatin C-based eGFR)



**Figure 2.** Adjusted hazard ratio for incident heart failure by World Health Organization classification of osteoporosis or osteopenia compared with normal bone mineral density (BMD) at the femoral neck in nonblacks. Models are fully adjusted.

and inflammation (CRP), however, which allowed for more extensive assessment for potential confounding.

### Potential Explanation of Findings in Nonblack Men

The association between low BMD and increased risk of HF documented here among nonblack men has several potential explanations, some of which have been previously discussed.<sup>17</sup> One possibility is that the association may be driven by shared risk factors of osteoporosis and HF, including advancing age, sedentary lifestyle, and kidney disease. In our analyses, however, the observed association persisted after adjustment for these factors, making this potential explanation unlikely.

Given evidence that HF is a risk factor for osteoporosis and fractures,<sup>5–7,34</sup> another potential explanation is that the inverse association in nonblack men could reflect subclinical HF at the time of BMD measurement. To address this possibility, we performed sensitivity analyses excluding participants with NT-proBNP  $\geq 190$  pg/mL at the time of DXA scan, and moving the start of the HF follow-up to 2 years after DXA scans. Neither analysis showed a noticeable change in the inverse association of BMD with incident HF in nonblack men, arguing against reverse causation.

Hence, the inverse association documented here among nonblack men is consistent with the premise that aging-related processes leading to osteoporosis in this group may relate, and possibly contribute, to mechanisms involved in the pathogenesis of HF. In this regard, various experimental and clinical studies have identified molecular pathways that provide a link between low BMD and increased HF risk. Some of these pathways involve the parathyroid hormone–vitamin D axis. Notably, elevated parathyroid hormone and low vitamin D levels, which can be associated with bone catabolism, have been shown to predict HF hospitalization and death, respectively.<sup>8,9</sup> Also, vitamin D has been documented to be a negative endocrine regulator of the renin-angiotensin system, which is an important system in the pathophysiology of HF.<sup>9</sup> Other pathways involve receptor activator of nuclear factor  $\kappa$ -B ligand, a protein known to stimulate bone resorption. For example, neurohormonal activation and higher levels of adrenergic agonists in HF have been shown to stimulate or increase levels of receptor activator of nuclear factor  $\kappa$ -B ligand.<sup>11,12</sup> Receptor activator of nuclear factor  $\kappa$ -B ligand has also been shown to upregulate metalloproteinase activity in fibroblasts that could potentially contribute to adverse left ventricular remodeling.<sup>13</sup> Although these mechanisms are plausible, further research is needed to elucidate their role.

In addition to these direct myocardial pathways, low BMD is associated with vascular calcification through a number of

mechanisms.<sup>14</sup> Although the relationship between osteoporosis and atherosclerotic CVD has been documented,<sup>15,16</sup> we found the association to persist despite adjustment for CHD at baseline and during follow-up, suggesting that the explanation goes beyond ischemic heart disease. Apart from coronary atherosclerosis, calcification of the aorta is another potentially important mechanism, which, by fostering arterial stiffness and central blood pressure augmentation, could promote cardiac hypertrophy and lead to the development of HF.<sup>35,36</sup> Measures of vascular stiffness were not available in CHS, and their impact could not be evaluated here, although it bears noting that adjusting for systolic blood pressure as a surrogate of aortic stiffness did not materially influence the association in question.

### Potential Explanation of Findings in Black Men

The association of lower BMD with lower HF risk in black men has, to our knowledge, not been previously reported. The reason for this positive association in black men is unclear. It is well established that blacks have a lower prevalence of low BMD<sup>3,19</sup> but a higher overall risk of HF<sup>18</sup> compared with whites. In our study, there were no black men who met the criterion for osteoporosis at the total hip, with less than one fifth having osteopenia. Hence, any adverse relationship of truly low BMD with HF risk may not have been observable in this sample. In this context, the positive association of higher BMDs could reflect their association with other HF risk factors, such as increased adiposity, although the relationship persisted after adjustment for body mass index and waist circumference. An additional possibility is that black men in our study had more vascular calcifications in the field of the DXA scan, which could falsely elevate BMD while also increasing HF risk. The original DXA scan images were not available for review, however, and this possibility could not be explored. Nevertheless, vascular calcification has been reported to be less common in blacks than whites.<sup>37</sup> Last, the finding that the association did not hold up after sensitivity analyses excluding participants with elevated NT-proBNP or early HF events suggests that the association in black men could have been biased by subclinical HF. Regardless, the race interaction observed will require further study in adequately powered samples.

### Potential Explanations for Sex-Based Differences

In women, the basis for the lack of association of BMD and HF risk is uncertain. It could relate to the fact that the prevalence of osteoporosis in women is higher than in men and fostered by the postmenopausal state.<sup>38</sup> In this regard, the lack of association could pertain to menopause being such a dominant risk factor for osteoporosis that—given that all

the women in our sample were postmenopausal—it could overshadow other potentially weaker factors linking osteoporosis and incident HF. Indeed, sex hormones play an important role in bone homeostasis and may affect cardiac health, yet we were not able to assess the influence of endogenous sex hormones in our study. Finally, although stronger correlations of CVD risk factors with low BMD in nonblack men could account for the observed sex differences, there was no evidence that this was the case in our sample.

## Study Limitations

There are a number of limitations to this study. BMD measures were only available for a subset of the CHS cohort attending the 1994–1995 visit obtained mainly at 2 sites. The analysis included only 91 black men with 33 incident HF events and 144 black women with 48 incident HF events. There were no black men with osteoporosis and consequently, given the race interaction found in men, our analysis of BMD as a categorical variable included only nonblack men. Also, the subset of CHS participants who survived and attended the 1994–1995 visit to undergo DXA scanning was healthier than the subset who did not.<sup>39</sup> Hence, our findings apply to healthier older adults and are not necessarily generalizable to the broader older population. In addition, we were not able to investigate the association of BMD with HF with preserved ejection fraction versus HF with reduced ejection fraction separately because of insufficient sample size. Nor were we able to explore the potential influence of vitamin D, parathyroid hormone, FGF23, phosphate, or calcium, which were only available in a small subset of the study sample.

## Potential Clinical Implications

Despite the previously described limitations, our study has notable strengths, including use of DXA-based measures of BMD, adjudicated HF end points, extensive adjustment for potential confounders, and the ability to exclude subclinical HF. Our findings therefore add to previous evidence linking low BMD with higher incident HF risk specifically for (mostly) white men, while calling into question a similar association for (mostly) white women, but also suggest that shared pathways may be at least partly involved in the pathogenesis of osteoporosis and HF.

## Conclusions

Our results provide impetus for additional research into the molecular pathways linking osteoporosis and HF, which could identify novel therapeutic targets for prevention of both conditions. Moreover, these findings suggest that screening

for osteoporosis in whites may potentially offer opportunities for earlier detection and prevention of HF, at least in men. Further studies are needed to assess the sex- and race-based differences documented here.

## Acknowledgments

A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

## Sources of Funding

This research was supported by contracts HHSN 268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, and N01HC85086, and grant U01HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by R01AG023629 from the National Institute on Aging. Analysis for this study was supported by the Mentors in Medicine Program, Division of Medical Education, Department of Internal Medicine, Washington University School of Medicine.

## Disclosures

Dr Kizer reports consultant fees/honoraria from ClearView Healthcare Partners and ownership interest (stock ownership) in Gilead Sciences Inc. and Pfizer, Inc. Dr Civitelli reports ownership interest (stock ownership) in Amgen, Eli Lilly & Company, and Merck. There are no disclosures to report for the other coauthors.

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# SUPPLEMENTAL MATERIAL

**Table S1. Cross-sectional Association of Continuous Femoral Neck BMD with Baseline Characteristics of Study Cohort**

Characteristics	Femoral Neck BMD							
	Women (n=734)				Men (n=516)			
	n	Correlation coefficient	mean $\pm$ SD	p value	n	Correlation coefficient	mean $\pm$ SD	p value
Age, years	734	-0.29		<0.001	516	-0.20		<0.001
Body mass index, kg/m <sup>2</sup>	734	0.47		<0.001	516	0.31		<0.001
Waist circumference, cm	731	0.41		<0.001	516	0.19		<0.001
Systolic blood pressure, mmHg	734	0.02		0.632	516	0.02		0.661
Anti-hypertensive medication								
No	367		0.63 $\pm$ 0.12	<0.001	252		0.79 $\pm$ 0.14	0.749
Yes	367		0.66 $\pm$ 0.13		264		0.78 $\pm$ 0.15	
Diabetes								
No	646		0.64 $\pm$ 0.12	<0.001	426		0.77 $\pm$ 0.14	0.006

Yes	88		0.72 ± 0.14		90		0.82 ± 0.16	
Smoker								
Never Smoker	367		0.64 ± 0.12	0.269	136		0.78 ± 0.15	0.732
Former Smoker	300		0.66 ± 0.13		339		0.78 ± 0.14	
Current Smoker	67		0.64 ± 0.11		41		0.79 ± 0.13	
Alcohol, drinks/week	734	0.02		0.638	516	0.12		0.015
Physical Activity (kcal/week)*	734	0.004		0.921	516	0.07		0.105
Low-density lipoprotein (LDL), mg/dl	726	-0.01		0.769	509	0.02		0.642
High-density lipoprotein (HDL), mg/dl	733	-0.03		0.494	516	0.01		0.836
Triglycerides, mg/dl	734	0.07		0.062	516	0.05		0.238
Lipid-lowering medication								
No	651		0.65 ± 0.12	0.765	476		0.78 ± 0.15	0.587

Yes	83		0.64 ± 0.12		40		0.77 ± 0.16	
Aspirin								
No	454		0.65 ± 0.12	0.465	302		0.79 ± 0.14	0.588
Yes	277		0.64 ± 0.12		212		0.78 ± 0.15	
Digitalis								
No	691		0.65 ± 0.12	0.838	469		0.78 ± 0.14	0.266
Yes	43		0.65 ± 0.15		47		0.81 ± 0.17	
Estrogen Use								
None	597		0.64 ± 0.13	0.087				
Yes	137		0.66 ± 0.12					
Prevalent coronary heart disease								
No	623		0.65 ± 0.12	0.936	371		0.78 ± 0.14	0.624
Yes	111		0.65 ± 0.13		145		0.78 ± 0.15	

Prevalent stroke/transient ischemic attack								
No	707		0.65 ± 0.12	0.897	469		0.79 ± 0.14	0.194
Yes	27		0.64 ± 0.11		47		0.76 ± 0.16	
Prevalent peripheral arterial disease								
No	109		0.65 ± 0.14	0.896	95		0.76 ± 0.17	0.540
Yes	625		0.65 ± 0.12		421		0.79 ± 0.14	
Prevalent atrial fibrillation								
No	696		0.65 ± 0.12	0.015	478		0.78 ± 0.15	0.475
Yes	38		0.60 ± 0.13		38		0.80 ± 0.14	
Creatinine, mg/dl	725	0.07		0.065	512	0.004		0.923
Estimated glomerular filtration rate (eGFR,	734	0.05		0.143	516	0.07		0.112

cystatin-based), ml/min/1.73 m <sup>2</sup>								
Forced expiratory volume in 1 second, l	734	0.10		0.010	516	0.07		0.125
C-reactive protein, mg/l	734	0.13		<0.001	516	0.05		0.272

\*The logarithm of physical activity + 1 was used to compute the correlation

BMD: bone mineral density





## **Bone Mineral Density and Risk of Heart Failure in Older Adults: The Cardiovascular Health Study**

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*J Am Heart Assoc.* 2017;6:e004344; originally published March 13, 2017;

doi: 10.1161/JAHA.116.004344

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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