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Bone Mineral Density Measurements and Association With Brain Structure and Cognitive Function
The Framingham Offspring Cohort

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Background: Bone mineral density (BMD) is a potential surrogate marker of lifetime estrogen exposure previously linked to increased risk of Alzheimer dementia among elderly women. We examine the association between BMD in the "young old" with imaging biomarkers of brain aging and cognitive performance.

Methods: Offspring participants (N = 1905, mean age 66) of a population-based cohort who had BMD, brain imaging and detailed cognitive assessment were included in the study. Sex-stratified, linear, and logistic regression models were used for analysis.

Results: Higher femoral neck BMD was associated with lower white matter hyperintensity burden and better performance on Trails B-A in both sexes, even after adjustment for cerebrovascular risk factors. Among women, the positive association with Trails B-A performance was seen only in APOE4 allele carriers. Higher BMD measurements were linked to better visual reproductions test performance in men. Finally, among women, higher femoral trochanter BMD was associated with better logical memory and Hooper visual organization test performance.

Conclusion: Among the "young old," higher BMD is associated with less white matter hyperintensity burden and better, domain-specific, cognitive performance. This suggests that lifetime estrogen exposure may modulate the degree of cumulative vascular brain injury independent of cerebrovascular risk factors.

Osteoporosis and fragility fractures have a high prevalence among persons with dementia and greatly contribute to the morbidity and mortality of an aging population.[1–3] In addition to dietary and mobility factors that contribute to low bone mineral density (BMD) in older age,[1] there appears to be a common pathway underlying neurodegeneration and bone health as low BMD has been associated with more advanced normal age-related brain parenchyma atrophy,[4] prevalent Alzheimer disease (AD) and vascular dementia,[5,6] as well as an increased risk for developing AD.[7,8] One putative link between BMD and brain aging is cumulative exposure to estrogen supported by data showing that the length of the reproductive period in women was inversely related to their risk of cognitive impairment and protective against the development of AD.[9] Other factors that may shape this association include atherosclerosis,[10] physical activity,[11,12] and APOE4 allele status,[13] all of which have been linked to both bone and brain health. We now expand previous work done in the Framingham Heart Study (FHS) Original Cohort (mean age, 77 y)[7] to the offspring (mean age, 66 y) in order to assess the association between BMD and neuroimaging biomarkers of brain aging and performance in specific cognitive domains among younger, nondemented individuals. We hypothesize that low BMD—a surrogate marker of lifetime estrogen exposure—may be an indicator of poor brain health even among the "young old" independent of other risk factors.

METHODS

Study Design

The Framingham study is an ongoing longitudinal, community-based cohort study that began in 1948 with the enrollment of 5209 participants into the Original Cohort to prospectively investigate risk factors for cardiovascular disease (CVD).

Study population in 1971, the offspring of the Original Cohort and their spouses (n = 5124) were enrolled in the Framingham Offspring Study (Gen 2) and have attended clinic examinations approximately every 4 years since. Offspring participants who took part in examination cycles 7.5 and 8 (n = 2025) were invited to attend an osteoporosis examination and to undergo brain magnetic resonance imaging (MRI) and a neuropsychological (NP) battery.
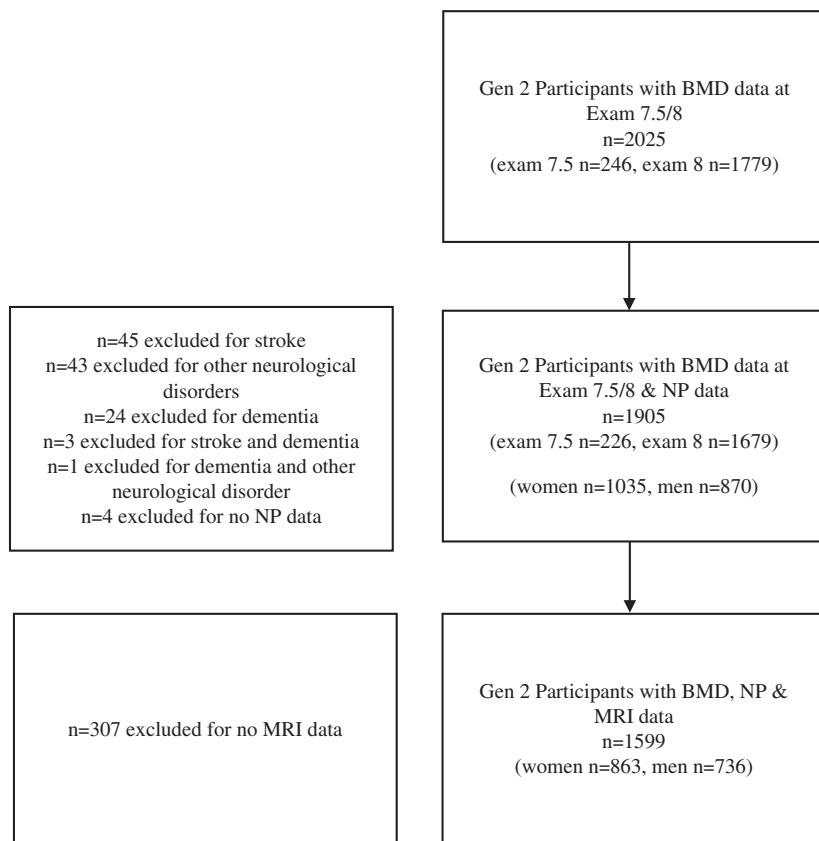
Gen 2 Participants with BMD data at
Exam 7.5/8
n=2025
(exam 7.5 n=246, exam 8 n=1779)

n=45 excluded for stroke
n=43 excluded for other neurological
disorders
n=24 excluded for dementia
n=3 excluded for stroke and dementia
n=1 excluded for dementia and other
neurological disorder
n=4 excluded for no NP data

Gen 2 Participants with BMD data at
Exam 7.5/8 & NP data
n=1905
(exam 7.5 n=226, exam 8 n=1679)

(women n=1035, men n=870)

n=307 excluded for no MRI data

Gen 2 Participants with BMD, NP &
MRI data
n=1599
(women n=863, men n=736)

FIGURE 1. Gen 2 study participants. BMD indicates bone mineral density; MRI, magnetic resonance imaging; NP, neuropsychological.

After exclusion for established clinical dementia, stroke, or other neurological conditions that could affect MRI measurements (tumor, multiple sclerosis, significant traumatic brain injury, etc.) 1905 participants in Gen 2 had both BMD measurements and NP testing available and of these 1599 participants also had MRI brain performed (Fig. 1).

BMD Measurements

BMD of the hip was measured using dual-energy X-ray absorptiometry (DXA) with a GE Lunar Prodigy fan-beam densitometer (GE Healthcare Inc., GE Healthcare, Piscataway, NJ), using standard positioning recommended by the manufacturer with BMD measured in g/cm^2. The right hip was scanned unless there was a history of previous fracture or hip replacement, in which case the left side was scanned. Measurements for femoral neck (FN), and femoral trochanter (FT) BMD were included. The coefficients of variation for FN and FT were 1.7% and 2.5%, respectively.

NP Testing

A battery of NP tests to measure aspects of cognitive function associated with brain aging were administered using standard administration protocols by trained examiners. Details of these tests administered in the FHS cohorts have been published previously.[14,15]

Executive function and processing speed were assessed based on time to complete Trail Making B-A (Trails B-A). Verbal and visual memory was assessed with the use of the delayed recall components of Logical Memory (LM-d) and Visual Reproductions (VR-d) tests, respectively. The test of

similarities from the Wechsler Adult Intelligence Scale (WAIS) involves asking participants to indicate in which way 2 items are alike to test abstraction, reasoning, verbal comprehension, and categorization. Finally, the Hooper Visual Organization Test (HVOT) measures visuoperceptual skills. Trails B-A and HVOT were natural log-transformed to normalize their skewed distributions. We reversed the sign of Trails B-A so that higher scores indicate superior performance for all cognitive measures.

Methodology for Volumetric Brain MRI

Details of brain MRI acquisition parameters, blinded analysis, definition of brain volumes, and normative data for the FHS Gen 2 cohort has been published previously.[16–20] Three MRI measures of subclinical brain aging were used as primary outcomes: total cerebral brain volume, a measure of overall (AD-type and vascular) brain aging, hippocampal volume (HV) which in older adults has been associated to AD-type pathology was manually defined as described earlier.[21] White matter hyperintensities volume (WMHV), a measure of vascular brain injury, was determined according to previously published methods[16,21] Each of these was analyzed as % of total cranial volume to correct for differences in head size.[17] WMHV was log-transformed to normalize its distribution. All analyses were performed using a custom-designed image analysis package, QUANTA 6.2, operating on a Sun Microsystems (Santa Clara, CA) Ultra 5 work station.

Vascular Risk Factors

Systolic blood pressure was calculated as the average of 2 seated resting measurements performed by a physician. Diabetes mellitus was defined as a fasting blood glucose ≥ 126 mg/dL, a random blood glucose ≥ 200 mg/dL, previous diagnosis of diabetes mellitus or being on hypoglycemic medications or insulin. Fasting plasma TC and TG were measured enzymatically according to Centers for Disease Control and Prevention standards. Current cigarette smoking was defined as self-reported regular use in the year before the targeted examination cycle. In addition to the previously mentioned risk factors, history of CVD, as defined by history of prior coronary artery disease, congestive heart failure of peripheral vascular disease, as well as history of atrial fibrillation were also used in the analysis.

Other Variables

Physical activity index (PAI) is a composite score constructed for each participant by weighting each hour in a participant's typical day based on their activity level [sleep weighting factor (WF) = 1, sedentary WF = 1.1, slight activity WF = 1.5, moderate activity WF = 2.4, and heavy activity WF = 5] and summing up these weighted hours over a 24-hour period. PAI has been shown to have fair correlation to accelerometer-determined physical activity measures and lower PAI is linked to a higher risk of incident dementia.[12] BMI was calculated as weight divided by height^2 (kg/m^2). Osteoporosis medications was based on World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes and included reported active use of biphosphonates, calcium and its combinations with vitamin D and/or other drugs, parathyroid hormones and analogs, antiparathyroid agents, hormonal contraceptives for systemic use, and estrogen use. Participants who had BMD measured at exam 7.5 reported use of antidepressant medication as 0: no, 1: yes-now, 2: yes-not now, 3: maybe and 4: unknown. For our analysis, only code 1 was considered as active use of antidepressants. Antidepressant use in exam 8 was based on WHO ATC codes (current use of nonselective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, nonselective, monoamine oxidase a inhibitors, and other antidepressants).

Statistical Analysis

Sex and age are strong determinants of BMD. In the analysis, we used sex-stratified linear (for continuous variables) and logistic (for binary variables) regression models to examine the cross-sectional association between BMD measurements at each site and MRI phenotypes, as well as between BMD measurements and performance per cognitive domain.

In primary analysis (Model 1), for the MRI measurements we adjusted for age, age-squared and time between the participant exam and the time of MRI acquisition. For the cognitive analysis, we adjusted for age, educational status and time between the participant exam and the time of NP assessment. We also investigated potential effect modification by APOE genotype by including interaction terms in the model. Where evidence of effect modification was seen, we stratified by APOE. In secondary analysis (Model 2), we additionally adjusted for the vascular risk factors described above, which are strongly associated with both outcome measures in our study. In sensitivity analysis, we examined the individual effect of variables primarily affecting BMD, namely PAI,[22] BMI[23] and use of osteoporosis and antidepressant medications[24] on Model 2 in subgroups of participants with available data. We used log-transformations as necessary to normalize variables with skewed distributions.

TABLE 1. Baseline Demographic and Clinical Characteristics

	Gen 2		
	Men (n = 870)	**Women (n = 1035)**	**Significance**
Age, years	66.28 (8.85)	65.64 (9.17)	NS
Time interval between exam to NP/MRI evaluation, years	0.51 (0.71)	0.56 (0.78)	NS
Systolic blood pressure, mg/dL	129.06 (16.68)	127.51 (17.56)	NS
BMI, kg/m^2	28.33 [25.81, 31.31]	26.83 [23.65, 31.07]	*
Physical activity index	35.57 (6.17)	34.98 (5.10)	*
Total cholesterol, mg/dL	175.70 (34.75)	199.61 (35.96)	*
Triglycerides, mg/dL	104 [75, 143]	102 [73, 142]	NS
Education, n (%)			*
Up to high school degree	242 (27.82)	321 (31.01)	
Some college	220 (25.29)	365 (35.27)	
≥ College graduate	408 (46.90)	349 (33.72)	
Smoking, n (%)	66 (7.59)	101 (9.76)	NS
APOE4, n (%)	192 (22.59)	212 (20.99)	NS
Osteoporosis drug, n (%)	44 (5.33)	260 (25.92)	*
Antidepressant drug, n (%)	69 (8.36)	180 (17.93)	*
Lipid lowering drug, n (%)	432 (49.66)	406 (39.23)	*
Antihypertension drug, n (%)	456 (52.47)	433 (41.84)	*
Diabetes mellitus, n (%)	160 (18.63)	106 (10.44)	*
Prevalent CVD, n (%)	139 (15.98)	94 (9.08)	*
Prevalent AF, n (%)	65 (7.47)	39 (3.77)	*
Bone mineral density			
Femoral neck BMD, g/cm^2	0.96 (0.14)	0.87 (0.13)	*
Femoral trochanter BMD, g/cm^2	0.88 (0.14)	0.71 (0.13)	*
Cognitive tests			
LM-d recall score	10.63 (3.81)	11.65 (3.72)	*
VR-d recall score	8.09 (3.33)	8.1 (3.31)	NS
Trail making B-A, minutes	0.36 [0.31, 0.39]	0.36 [0.32, 0.40]	*
Similarities test score	17.08 (3.80)	16.79 (3.50)	NS
HVOT score	25.0 [23.5, 27.0]	26.0 [24.0, 27.0]	*
Brain MRI measures			
TCBV, % of TCV	75.97 (2.68)	76.35 (2.50)	*
HPV, % of TCV	0.53 (0.05)	0.55 (0.05)	*
WMHV, % of TCV	0.07 [0.04, 0.14]	0.07 [0.04, 0.14]	NS

AF indicates atrial fibrillation; APOE4, apolipoprotein E4 allele; BMD, bone mineral density; BMI, body mass index; CVD, cardiovascular disease; HPV, hippocampal volume; HVOT, Hooper Visual Organization test score; LM-d, logical memory delayed recall; MRI, magnetic resonance imaging; TCBV, total cerebral brain volume; TCV, total intracranial volume; VR-d, visual reproduction delayed; WMHV, white matter hyperintensity volume.

Data are mean (SD) or median [quartile 1 to quartile 3], unless stated otherwise.

*Significant difference in characteristic between sexes (*P* < 0.05). Nonsignificant (*P* ≥ 0.05).

All protocols were approved by the Boston University Medical Center Institutional Review Board, and participants provided written informed consent. All data collected

TABLE 2. MRI Outcomes

BMD Measure	Total Cerebral Brain Volume*		Hippocampal Volume*		White Matter Hyperintensity Volume* (log)	
	β [95% CI]	P	β [95% CI]	P	β [95% CI]	P
Men (M1 n = 736, M2 n = 724)						
Femoral neck M1	−0.23 [−1.26; 0.80]	0.657	−0.02 [−0.05; 0.004]	0.098	**−0.70 [−1.23; −0.16]**	**0.011**
Femoral neck M2	−0.19 [−1.22; 0.84]	0.715	−0.02 [−0.05; 0.005]	0.104	**−0.68 [−1.22; −0.13]**	**0.015**
Femoral trochanter M1	−0.08 [−1.07; 0.91]	0.877	−0.01 [−0.04; 0.01]	0.277	−0.49 [−1.01; 0.03]	0.065
Femoral trochanter M2	−0.01 [−1.01; 0.99]	0.988	−0.02 [−0.04; 0.01]	0.244	−0.46 [−0.99; 0.07]	0.091
Women (M1 n = 863, M2 n = 847)						
Femoral neck M1	−0.43 [−1.50; 0.65]	0.435	0.004 [−0.02; 0.03]	0.748	**−0.59 [−1.16; −0.02]**	**0.042**
Femoral neck M2	−0.33 [−1.45; 0.79]	0.562	0.01 [−0.02; 0.03]	0.710	**−0.64 [−1.23; −0.04]**	**0.035**
Femoral trochanter M1	0.52 [−0.51; 1.54]	0.326	0.02 [−0.002; 0.05]	0.076	−0.49 [−1.04; 0.05]	0.077
Femoral trochanter M2	0.71 [−0.38; 1.80]	0.200	0.02 [−0.004; 0.05]	0.088	**−0.61 [−1.18; −0.03]**	**0.040**

M1: model 1 adjusted for age, age-squared, and time interval between exam and MRI assessment.
M2: model 2 adjusted for age, age-squared, time interval between exam and MRI assessment, systolic blood pressure, antihypertensive medication use, smoking, diabetes, prevalent CVD, atrial fibrillation, total cholesterol, and triglycerides.
Bold values indicate statistical significance ($P < 0.05$).
*% of total intracranial volume. β corresponds to the change in MRI assessment associated with a 1 unit-increase in BMD.
CI indicates confidence interval; CVD, cardiovascular disease; MRI, magnetic resonance imaging.

on Framingham Study participants, including those used in our analysis, are available to qualified scientific investigators outside FHS who complete a research application, in accordance to FHS data sharing policies.

RESULTS

Baseline demographic and clinical characteristics are presented by sex in Table 1.

BMD and Brain MRI Measures

Higher BMD measurement at the FN was associated with lower white matter hyperintensity (WMH) burden in both men and women. This association remained significant even after adjustment for vascular risk factors (Model 2) (Table 2). This association was not present when BMD was measured at the FT, except among women in Model 2 of the analysis. Among women, after adjustments in Model 2 for PAI, BMI, osteoporosis and antidepressant medications, the effect size remained largely the same, but the association lost significance (Supplemental Table B, Supplemental Digital Content 1, http://links.lww.com/WAD/A335). BMD measurements were not significantly associated with total cerebral brain volume or HV (Table 2).

Effect of BMD on Cognitive Function

The effect of BMD on cognitive function differed among specific cognitive domains, BMD measurement site and between the sexes. Higher BMD measured at the FN was significantly associated with better performance on Trails B-A in both women and men and this association persisted after adjustment for vascular risk factors. In men, FN BMD was also positively associated with VR-d performance. In women, this association was seen with FT BMD, but the association was attenuated after adjusting for vascular risk factors. Finally, only among women, higher FT BMD was associated with better performance on LM-d and HVOT (model 1 only) (Table 3).

Further analysis adjusting for PAI, osteoporosis and antidepressant medications did not greatly change effect sizes, even though significance was lost in certain cases. Adjustment for BMI in women led to a loss of association between trochanter BMD and logical memory, indicating that BMI is a potential confounder (Supplemental Table C, Supplemental Digital Content 2, http://links.lww.com/WAD/A336). When we stratified by high/low BMI category (cut off 30 kg/cm²), we saw no difference in the specific association between those with high versus low BMI (data not shown).

Effect Modification by APOE4 Status

BMD was associated with better Trails B-A performance among women with positive APOE4 status compared with APOE4 negative participants, showing potential protective effect of lifetime estrogen exposure on executive function and processing speed among women with increased risk for neurodegeneration. In men, BMD was linked to better Trails B-A performance irrespective of APOE status (Table 4). Conversely, APOE4 status had no effect on the association between BMD and structural brain changes (data not shown).

DISCUSSION

Our study addresses the association between BMD and structural and cognitive markers of brain aging among nondemented Gen 2 participants of the FHS. Our results show sex-dependent associations, some of them new, that are mostly in accordance with the accepted theory that BMD is linked to cerebral function and structure, most likely, through its role as a biomarker of cumulative estrogen exposure.

Estrogen is a plausible common denominator protecting both bone and brain health; it inhibits bone resorption through receptors found on bone tissue;[25] serum estrogen is related to BMD in both premenopausal and postmenopausal women and the MrOs study underscored its role in bone health even among men.[26,27] At the same time, estrogen reduces neuronal apoptosis and atherosclerosis, inhibits amyloid-b formation and tau hyperphosphorylation and reduces oxidative stress in the brain.[9,28] Despite these neuroprotective observations, administration of estrogen in postmenopausal women has not demonstrated neuroprotective effects[29] and does not decrease the risk for incident AD.[30] Instead, it has been associated with increased WMHV in the absence of significant cardiovascular risk factors,[31] gray matter volume loss,[32] lower HVs.[33] The negative effects of exogenous estrogen suggest that rather

TABLE 3. Neuropsychological Outcomes

BMD Measure	Logical Memory Delayed Recall		Visual Reproduction Delayed Recall		Trail Making B-A (Log)		Similarities Test		HVOT(Log)	
	β [95% CI]	P	β [95% CI]	P	β [95% CI]	P	β [95% CI]	P	β [95% CI]	P
Men (M1 n = 870, M2 n = 857)										
Femoral neck M1	1.31 [−0.43; 3.04]	0.140	**1.70 [0.23; 3.16]**	**0.023**	**0.16 [0.05; 0.27]**	**0.003**	0.67 [−0.95; 2.30]	0.417	−0.01 [−0.24; 0.22]	0.937
Femoral neck M2	1.32 [−0.46; 3.09]	0.145	**1.64 [0.15; 3.12]**	**0.031**	**0.16 [0.05; 0.27]**	**0.004**	0.89 [−0.77; 2.55]	0.291	−0.001 [−0.24; 0.24]	0.996
Femoral trochanter M1	0.71 [−0.98; 2.41]	0.410	1.24 [−0.20; 2.68]	0.091	**0.15 [0.05; 0.26]**	**0.004**	0.10 [−1.49; 1.69]	0.899	−0.05 [−0.28; 0.17]	0.645
Femoral trochanter M2	0.69 [−1.07; 2.44]	0.442	1.19 [−0.28; 2.67]	0.112	**0.14 [0.04; 0.25]**	**0.008**	0.24 [−1.4; 1.88]	0.774	−0.04 [−0.27; 0.20]	0.747
Women (M1 n = 1035, M2 n = 1015)										
Femoral Neck M1	1.03 [−0.87; 2.93]	0.289	0.79 [−0.78; 2.36]	0.324	**0.16 [0.04; 0.28]**	**0.010**	0.30 [−1.38; 1.97]	0.727	0.20 [−0.05; 0.46]	0.117
Femoral Neck M2	1.08 [−0.89; 3.05]	0.283	0.47 [−1.15; 2.09]	0.569	**0.16 [0.03; 0.29]**	**0.013**	0.49 [−1.24; 2.23]	0.577	0.18 [−0.08; 0.44]	0.176
Femoral trochanter M1	**2.32 [0.50; 4.14]**	**0.012**	**1.71 [0.20; 3.21]**	**0.026**	0.07 [−0.05; 0.19]	0.254	−0.34 [−1.95; 1.26]	0.674	**0.25 [0.004; 0.49]**	**0.046**
Femoral trochanter M2	**2.72 [0.8; 4.64]**	**0.006**	1.53 [−0.05; 3.11]	0.058	0.08 [−0.04; 0.21]	0.182	−0.17 [−1.87; 1.52]	0.841	0.22 [−0.04; 0.48]	0.094

M1: model 1 adjusted for age, education, and time interval between exam and NP assessment.
M2: model 2 adjusted for age, education, time interval between exam and NP assessment, systolic blood pressure, antihypertensive medication use, smoking, diabetes, prevalent CVD, atrial fibrillation, total cholesterol, and triglycerides.
Bold values indicate statistical significance ($P < 0.05$).
β corresponds to the change in cognitive test outcome associated with a 1 unit-increase in BMD.
CI indicates confidence interval; CVD, cardiovascular disease; HVOT, Hooper Visual Organization test; NP, neuropsychological.

than estrogen alone, factors such as the hormonal and/or neurotrophic milieu, age at exposure and genetic predisposition, may all be important in driving the neuroprotective effects of intrinsic estrogen.

In our study of the "young old" participants (Gen 2, mean age 66) high BMD is linked to less WMHV and better performance on the Trails B-A test, suggesting less cumulative vascular injury to the brain. This association is seen in both sexes and persists even after adjusting for the presence of known cerebrovascular risk factors studied at FHS. Similar observations with WMHV have been described among older individuals (mean age 78) in the Cardiovascular Health Study[34] which included both Caucasians and African Americans, as well as in an Asian, community-based cohort of nondemented and stroke-free individuals aged 50 to 75.[35] These findings suggest that low BMD may be a surrogate marker of increased risk of cerebrovascular disease even in the absence of known vascular risk factors . The lack of an association between BMD and HV in our study is likely because of our sample of nondemented participants; in a prior study by Luskotova et al[36] low BMD was linked to hippocampal atrophy only among participants with early AD, and not among nondemented controls.

We show novel, sex-specific associations between BMD and certain cognitive domains; in particular, women with higher BMD performed better on a verbal memory test and men with higher BMD performed better on a visual memory test. A positive link between femoral BMD and verbal memory has been shown independently in elderly men[37] and postmenopausal women.[38] In studies that, similar to ours, included both sexes[28,39] a sex-specific association was not seen. The link between BMD and visual memory is novel. In cohorts focusing on healthy older individuals, a baseline advantage in verbal memory tasks has been reported in women compared with men[40–44] and it has been argued that estrogen may have domain-specific cognitive effects in nondemented women.[45] In regards to visuospatial performance, some studies show a male over female advantage[42,43] while others show no sex-specific differences.[44] Its potential link to estrogen warrants further studies. Understanding the factors underlying verbal and visuospatial memory impairments is very important as they are potential markers of neurodegeneration and may predict the development of dementia and AD.[28,46,47] Our results suggest that cumulative estrogen exposure may be protective against vascular damage, regardless of the presence of vascular risk factors. With regards to neuronal degeneration, its effect may differ between the sexes and specific cognitive domains.

We investigated the effect of APOE4 status on the association between BMD and cognition and observed that BMD is linked to better Trails B-A performance in men regardless of their status, but among women the positive association is seen only among those with APOE4 positive. This finding may indicate a protective role for cumulative estrogen exposure against vascular degeneration among women with a genetic predisposition to neurodegeneration.[48] It also underscores a probable underestimation of the role of estrogen on cognition among men. Of note, previous studies have not shown a significant effect of APOE4 status on the association between BMD and cognition.[39]

Discrepancies in the literature compared with our results may be attributable to differences in the studies' participant age groups, race,[4] BMD measurements sites (hip, spine, whole body, etc.), and cognitive performance tests, some of which are considered more crude measures of

TABLE 4. Stratified Analysis by APOE4 Status in the Association Between BMD Measures and NP Test Performance (Where the Interaction was Significant)

| | Trail Making B-A (Log) | | | | HVOT (Log) | | | |
| | APOE4 | | No APOE4 | | APOE4 | | No APOE4 | |
BMD Measure	β [95% CI]	P	β [95% CI]	P	β [95% CI]	P	β [95% CI]	P
Men (n = 847)								
Femoral neck	**0.20 [0.01; 0.39]**	**0.043**	**0.15 [0.02; 0.28]**	**0.020**	−0.36 [−0.85; 0.13]	0.150	0.14 [−0.13; 0.42]	0.308
Women (n = 1005)								
Femoral neck	**0.40 [0.09; 0.71]**	**0.012**	0.10 [−0.03; 0.24]	0.144	0.32 [−0.25; 0.89]	0.271	0.18 [−0.11; 0.47]	0.221

Adjusted for age, education, and time interval between exam and NP assessment.
Bold values indicate statistical significance ($P < 0.05$).
β corresponds to the change in cognitive test outcome associated with a 1 unit-increase in BMD.
BMD indicates bone mineral density; CI, confidence interval; HVOT, Hooper Visual Organization test; NP, neuropsychological.

cognitive function (mini-mental state examination).[13,38,49,50] In our study, the majority of associations are noted when BMD is measured at the FN and not at the level of the trochanter with the exception of verbal memory in women where the link is seen when BMD is measured at the trochanter, but not at the FN. The etiology for this discrepancy is unclear. Studies focusing on osteoporosis pattern have shown bone mass loss at both sites with increasing age which is maximal in the early post-enopausal phase.[51] However, it has been reported that between sites of BMD measurement the rate of bone loss may vary, and the correlation decreases with increasing age[7,52] and with degree of bone loss. Higher between-site correlations were seen in individuals with normal BMD and those with osteopenia compared with those with osteoporosis.[53] Another limitation of our study is the primarily Caucasian population of the FHS which limits applicability of the results to other populations. In addition, participants who were included in the analysis, when compared with participants who had BMD, but did not present for NP testing, represent a healthier subgroup with lower prevalence of vascular risk factors and CVD (Supplemental Table A, Supplemental Digital Content 3, http://links.lww.com/WAD/A337). Healthier individuals are more likely to come for multiple ancillary studies in cohort studies.[34] Finally, diet which is known to affect both BMD and brain health volumes[54] was not considered in our analysis.

Overall, our study expands on previously described associations between BMD and WMH burden in the "young old" independent of known cerebrovascular risk factors. Screening for low BMD in healthy subjects may offer an opportunity for an intervention to decrease the risk of cerebral vascular injury. Our study provides further evidence that the link between BMD and cognition may differ between the sexes and for different cognitive domains, and that this link may be further modulated by the presence of a genetic predisposition towards neurodegeneration. Further studies to address molecular interactions on how estrogen affects bone and brain health may help create more effective interventions for those at higher risk for developing neurodegenerative diseases.

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