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Association of Bone Mineral Density and Dementia

The Rotterdam Study

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Abstract

Background and Objectives

Low bone mineral density (BMD) and dementia commonly co-occur in older individuals, with bone loss accelerating in patients with dementia due to physical inactivity and poor nutrition. However, uncertainty persists over the extent to which bone loss already exists before onset of dementia. Therefore, we investigated how dementia risk was affected by BMD at various skeletal regions in community-dwelling older adults.

Methods

In a prospective population-based cohort study, BMD at the femoral neck, lumbar spine, and total body and the trabecular bone score (TBS) were obtained using dual-energy X-ray absorptiometry in 3,651 participants free from dementia between 2002 and 2005. Persons at risk of dementia were followed up until January 1, 2020. For analyses of the association between BMD at baseline and the risk of incident dementia, we used Cox proportional hazards regression analyses, adjusting for age, sex, educational attainment, physical activity, smoking status, body mass index, systolic and diastolic blood pressure, cholesterol level, high-density lipoprotein cholesterol, history of comorbidities (stroke and diabetes mellitus), and *APOE* genotype.

Results

Among the 3,651 participants (median age 72.3 ± 10.0 years, 57.9% women), 688 (18.8%) developed incident dementia during a median of 11.1 years, of whom 528 (76.7%) developed Alzheimer disease (AD). During the whole follow-up period, participants with lower BMD at the femoral neck (per SD decrease) were more likely to develop all-cause dementia (hazard ratio [HR] $_{\text{total follow-up}}$ 1.12, 95% CI 1.02–1.23) and AD ($HR_{\text{total follow-up}}$ 1.14, 95% CI 1.02–1.28). Within the first 10 years after baseline, the risk of dementia was greatest for groups with the lowest tertile of BMD (femoral neck BMD, $HR_{0-10\ \text{years}}$ 2.03; 95% CI 1.39–2.96; total body BMD, $HR_{0-10\ \text{years}}$ 1.42; 95% CI 1.01–2.02; and TBS, $HR_{0-10\ \text{years}}$ 1.59; 95% CI 1.11–2.28).

Discussion

In conclusion, participants with low femoral neck and total body BMD and low TBS were more likely to develop dementia. Further studies should focus on the predictive ability of BMD for dementia.

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Glossary

AD = Alzheimer disease; **BMD** = bone mineral density; **DXA** = dual-energy X-ray absorptiometry; **GMS** = geriatric mental state schedule; **HR** = hazard ratio; **MMSE** = Mini-Mental State Examination; **RS** = Rotterdam Study; **TBS** = trabecular bone score.

More than 45 million people worldwide experience dementia, and this figure is estimated to double in the next 2 decades.[1,2] The initial step in mapping the health journey of persons developing dementia and understanding how systemic changes contribute to the pathogenesis and clinical manifestation of dementia is crucial to the development of efficacious preventive strategies. Numerous chronic conditions, including cardiac disorders, diabetes, lung function impairment, and kidney disease,[3,4] have been related to dementia. Several studies have also suggested a link between bone mineral density (BMD) and dementia or cognitive impairment,[5,6] most likely explained by shared risk factors, such as old age, subclinical hyperthyroidism,[7] sarcopenia,[8] sex steroids,[9] physical inactivity,[8] and vitamin D deficiency.[10] While it remains unclear whether bone health itself may be causally linked to dementia, it is an important predictor of fracture,[11,12] which is an important source of morbidity in dementia and can lead to loss of independence.[13] Therefore, temporally linking BMD to dementia can provide important insights into how comorbidities occur at the prodromal phase of dementia. This in turn can aid in preventive strategies aimed at optimizing the health and care of patients with dementia, including maintaining functional independence.

Previous studies focused solely on BMD, assessed through dual-energy X-ray absorptiometry (DXA) scanning of clinically relevant skeletal sites, that is, femoral neck and lumbar spine.[14] More recently, trabecular bone score (TBS) has been developed, which is a novel gray-level texture measurement connected to bone microarchitecture and other structural features.[15,16] The TBS offers further details, such as bone microarchitecture, which are not possible to infer from the areal BMD.

In this study, we aimed to investigate the association between BMD, measured across multiple skeletal sites, and dementia risk in community-dwelling older adults.

Methods

Study Population

This study was performed within the Rotterdam Study (RS), a prospective ongoing cohort study that started in 1990, and all participants aged 45 years or older were invited for studying chronic diseases in the general population.[17] The Rotterdam cohort comprises 1 original cohort (RS-I, initiated in 1990, with 7,983 participants aged 55 years or older) and other 2 cohorts (RS-II, starting from 2000, with 3,011 participants aged 55 years or older; and RS-III, starting from 2006, with 3,932 participants aged 45 years or older). Every 4–5 years, participants participated in consecutive follow-up home interviews and diverse physical tests at the medical research center. The study has been approved by the medical ethics committee of the Erasmus Medical Center (Rotterdam, the Netherlands) and the review board of the Netherlands Ministry of Health, Welfare and Sports (1068889-159521-PG). At baseline, between 2002 and 2005, participants of RS-I and RS-II underwent bone scans. A total of 3,651 persons with DXA scans and without prevalent dementia were finally included in this study (Figure 1).

Measurements of BMD

BMD at the femoral neck, the lumbar spine, and the total body were measured using specific Prodigy DXA densitometer, as described elsewhere.[18] A trained technician performed and verified all bone scans and made adjustments when necessary. A total of 3,651 participants had completed at least 1 scan of BMD, of whom 3,584 participants had data on BMD at the femoral neck, 3,608 at the lumbar spine, and 3,633 of the total body.

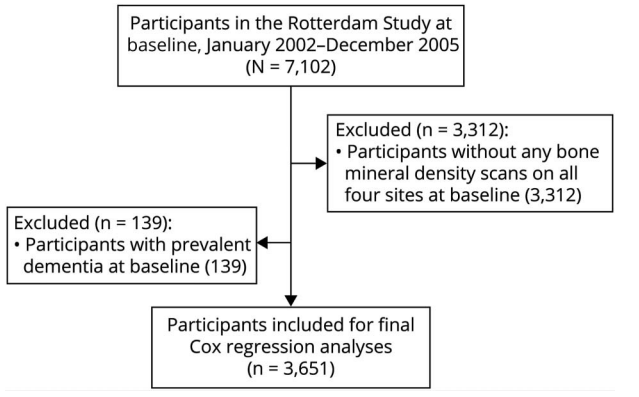
Measurement of TBS

TBS was calculated using the TBS iNsight software (MedImaps, Geneva, Switzerland).[15] In brief, the TBS is a novel gray-level texture measurement,[15,16] and a higher score indicates stronger and more fracture-resistant microarchitecture.[19] For each region of measurement (the L_2, L_3, and L_4 vertebrae),[19] TBS was assessed using gray-level analysis of the DXA images, and the methodology of the TBS has been described elsewhere.[16] TBS was available for 3,573 participants at baseline.

Dementia Assessment

The Mini-Mental State Examination (MMSE) and the geriatric mental state schedule (GMS) were used for detecting dementia at baseline and subsequent visits.[17] Further investigation and

Figure 1 Flowchart for Participants With Bone Mineral Density Scans Included in the Study



interview, including the Cambridge Examination for Mental Disorders of the Elderly, were conducted on participants with an MMSE score <26 or GMS score >0. In addition, the study database was electronically linked to medical records from general practitioners and the regional institute for outpatient mental health care, allowing for the ongoing monitoring of incident dementia. When necessary, cognition tests and clinical neuroimaging were used to confirm dementia subtypes.[17] An adjudication panel headed by a consultant neurologist established the final diagnosis in accordance with the accepted dementia diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorder, Third Edition-Revised*) and Alzheimer disease (AD) (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association). The follow-ups were stopped until meeting any of following scenarios, including incident dementia diagnosis, death, loss to follow-up, or January 1, 2020, whichever came first.

Covariables

Potential covariables were selected according to literature evidence, demonstrating an association with BMD, dementia, or both.[18,20,21] Baseline covariables included age, sex, education level (primary education, lower education, intermediate education, higher education), smoking status (never, former, current), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), total cholesterol level (mmol/L), high-density lipoprotein cholesterol (mmol/L), triglycerides (mmol/L), body mass index (kg/m^2, calculated by weight [kg] divided by height [m] squared), measurements of physical activity, and chronic disorders (diabetes and stroke). For determining *APOE* genotype, a PCR was used in RS-I and a biallelic TaqMan assay (rs7412 and rs429358) was used on labeled DNA samples in both RS-II and RS-III. This study included the first 2 subcohorts (RS-I and RS-II). *APOE*-ε4 allele represented carriership of at least 1 ε4 allele. Participants were divided into 3 different groups: high genetic risk (ε2ε4, ε3ε4, or ε4ε4), intermediate risk (ε3ε3) or low risk (ε2ε2 or ε2ε3) for dementia.[22]

Statistical Analysis

For baseline characteristics, normally distributed variables are described as mean ± SD and non-normally distributed continuous variables as median (interquartile range) among women and men.

Cox proportional hazards models were used for investigating the association between BMD and dementia risk. Follow-up time started on the baseline date of bone scan and ended until the date of diagnosis of dementia, death, loss to follow-up, or January 1, 2020. Schoenfeld residuals were calculated for checking the proportional hazards assumption. And the proportional hazards assumptions were not violated if p values were above 0.05. We used Kaplan-Meier survival curves to map group differences in BMD and TBS tertiles for dementia. Cox proportional hazard models were adjusted for age, sex, *APOE* genotypes, education attainment, physical activity, smoking status, body mass index, systolic and diastolic blood pressure, cholesterol level, high-density lipoprotein cholesterol, and history of chronic disorders (stroke and diabetes mellitus). Age and sex are 2 strong risk factors of low BMD because bone mineral loss is manifested after the age of 50 years or menopause[23,24]; therefore, the tertile categories of BMD and TBS were derived by generating tertiles from the residuals of linear regression models adjusted for age (continuously) and sex. Effects of BMD were also assessed when expressed as per 1 SD decrease. Associations were determined by measuring the effects of each tertile or per 1 SD decrease of BMD at the femoral neck, the lumbar spine, and total body and TBS on the dementia risk.

As a consequence of the proportionality assumption of the Cox model being violated in some analyses, stratified Cox models by incremental epochs of follow-up time were used to examine how the aforementioned risk of incident dementia changed over follow-up duration (extending epochs, e.g., baseline to 5 years, baseline to 10 years, and baseline to more than 10 years). In addition, we stratified analyses by sex and *APOE*-ε4 allele carriership (carrier vs noncarrier), which were suggested as possible effect modifiers.[21,25,26]

A p value of <0.05 was considered statistically significant. Data analyses were performed using R version 3.6.0. Missing covariates were computed using predictive mean matching for numeric variables and logistic regression for binary variables using the MICE package.[27]

Standard Protocol Approvals, Registrations, and Patient Consents

A written informed consent was provided before participants participated in the study and agreed to have their information acquired given by treating physicians. All authors could get access to the study data and are responsible for the data, analyses, and interpretation of results.

Data Availability

Data can be obtained by sending request toward the management team of the RS (datamanagement.ergo@erasmusmc.nl), which follows the protocol for approving data requests. To meet the requirements of privacy regulations and informed consent of the participants, data cannot be publicly available.

Results

Clinical Characteristics

As summarized in Table1, among 3,651 participants (median age 72.3 ± 10.0 years), 2,113 (57.9%) are women. During a median follow-up duration of 11.1 years, 688 (18.8%) developed incident dementia, of whom 528 (76.7%) developed AD.

BMD and Dementia Risk Over Incremental Epochs of Follow-up Duration

Throughout the whole follow-up period, lower BMD at the femoral neck (per SD decrease), not at other bone sites, was related to a higher risk of all-cause dementia (hazard ratio $[HR]_{total\ follow\text{-}up}$ 1.12, 95% CI 1.02–1.23) and AD ($HR_{total\ follow\text{-}up}$ 1.14,

Table 1 Baseline Characteristics of Participants in Longitudinal Analyses

	Men	Women	Total
N (%)	1,538 (42.1)	2,113 (57.9)	3,651 (100)
Follow-up, y	10.9 (4.3)	11.2 (2.2)	11.1 (2.9)
Age, y	72.3 (9.5)	72.3 (10.4)	72.3 (10.0)
Body mass index, kg/m^2, n (%)			
Normal 18.5–24.9	389 (25.3)	588 (27.8)	977 (26.8)
Underweight <18.5	4 (0.3)	19 (0.9)	23 (0.6)
Overweight 25–30	863 (56.1)	948 (44.9)	1,811 (49.6)
Obesity >30	282 (18.3)	558 (26.4)	840 (23.0)
Alcohol, g/d	12.1 (21.5)	2.9 (12.0)	7.1 (19.3)
Smoking, n (%)			
Never	237 (15.4)	916 (43.4)	1,153 (31.6)
Former	1,100 (71.5)	921 (43.6)	2,021 (55.4)
Current	201 (13.1)	276 (13.1)	477 (13.1)
Educational level, n (%)			
Primary	122 (7.9)	293 (13.9)	415 (11.4)
Low	472 (30.7)	1,162 (55.0)	1,634 (44.8)
Intermediate	602 (39.1)	528 (25.0)	1,130 (31.0)
High	342 (22.2)	130 (6.2)	472 (12.9)
Physical activity, h/mo	68.7 (53.3)	90.0 (56.7)	81.1 (55.4)
Systolic blood pressure, mm/Hg	147.0 (27.5)	150.0 (28.0)	148.5 (28.0)
Diastolic blood pressure, mm/Hg	80.5 (15.0)	79.0 (14.0)	80.0 (14.5)
Cholesterol, mmol/L	5.28 (1.23)	5.84 (1.24)	5.60 (1.28)
High-density lipoprotein cholesterol, mmol/L	1.24 (0.41)	1.51 (0.54)	1.39 (0.52)
Diabetes, n (%)	133 (8.6)	142 (6.7)	275 (7.5)
Stroke, n (%)	25 (1.6)	17 (0.8)	42 (1.2)
***APOE*-ε4, n (%)**	390 (26.5)	527 (26.7)	917 (26.6)
Total body BMD, g/cm^2	1.20 (0.13)	1.06 (0.14)	1.12 (0.17)
Femoral neck BMD, g/cm^2	0.92 (0.18)	0.82 (0.17)	0.86 (0.19)
Lumbar spine BMD, g/cm^2	1.21 (0.27)	1.04 (0.24)	1.10 (0.28)
TBS, mm^{-1}	1.33 (0.12)	1.25 (0.14)	1.28 (0.14)

Abbreviations: BMD = bone mineral density; TBS = trabecular bone score. Data presented as mean (SD) or median (interquartile range). Proportions of missing data: alcohol intake (2.1%), *APOE* genotype (5.6%), body mass index (1.5%), diabetes (5.1%), education attainment (1.6%), high-density lipoprotein (1.8%), physical activity (3.8%), serum total cholesterol (1.8%), and systolic and diastolic blood pressure (0.2%). Missing data were imputed using Bayesian linear regression for continuous variables, logistic regression for binary variables, and polytomous logistic regression for categorical variables with more than 2 subgroups.

95% CI 1.02–1.28) (Table 2). As summarized in eTable 1 (links.lww.com/WNL/C666), results were similar when we categorized individuals by BMD tertiles: the highest risks were observed for dementia and AD in the lowest group.

Within the first 10 years after baseline, associations were greatest between lower BMD (per SD decrease) and a higher risk of all-cause dementia (femoral neck BMD, $HR_{0–10\ years}$ 1.43; 95% CI 1.19–1.72; total body BMD, $HR_{0–10\ years}$ 1.22; 95% CI 1.00–1.47) and AD (femoral neck BMD, $HR_{0–10\ years}$ 1.52; 95% CI 1.20–1.92). The HRs for incident all-cause dementia comparing the lowest tertile of the femoral neck BMD, total body BMD, and TBS with the highest tertile were 2.03 (95% CI 1.39–2.96), 1.42 (95% CI 1.01–2.02), and 1.59 (95% CI 1.11–2.28) separately (Table 2). Similar results remained only between femoral neck BMD, TBS, and the risk of AD, which are listed in eTable 1 (links.lww.com/WNL/C666).

As summarized in Table 2 and eTable 1 (links.lww.com/WNL/C666), only BMD at the femoral neck was related to all-cause dementia occurrence over the first 5 years of the follow-up ($HR_{0–5\ years}$ 2.13; 95% CI 1.28–3.57, per SD decrease).

Kaplan-Meier Curves of Dementia-Free Survival by Levels of BMD

As presented in Figure 2 and eFigure 1 (links.lww.com/WNL/C666), within the first 5 years during the follow-up, the curves of dementia-free or AD-free probability were nearly overlapped at all tertile levels of the BMD, but the curve at the lowest tertile of the femoral neck BMD started to fall faster than that at the highest tertile later on. Similar temporal curve trends for dementia-free probability were also observed for the total body BMD and TBS, but not for the lumbar spine BMD.

Stratification

When stratified by sex and *APOE*-ε4 carriership, significant associations were found between lower femoral neck BMD (the lowest tertile vs the highest tertile) and a higher risk of all-cause dementia in men (HR 1.56; 95% CI 1.12–2.16), but not in women (HR 1.13; 95% CI 0.87–1.47); and in non-*APOE*-ε4 carriers (HR 1.36; 95% CI 1.04–1.76), but not in *APOE*-ε4 carriers (HR 1.16; 95% CI 0.84–1.60). Significant associations were also observed between low TBS and increased risk of dementia (Figure 3). Stratification for the HR estimates of AD was represented in eFigure 2 (links.lww.com/WNL/C666). Statistically significant interactions were observed between sex and low TBSs ($p = 0.02$) and between *APOE*-ε4 carriership and low TBSs ($p = 0.01$) (data not presented).

Discussion

In this study, low femoral neck and total body BMD and low TBS were associated with an increased risk of dementia. The associations were strongest in the first 10 years of follow-up.

Table 2 BMD and the Risk of Incident Dementia Stratified by Incremental Epochs of Follow-up Time[a]

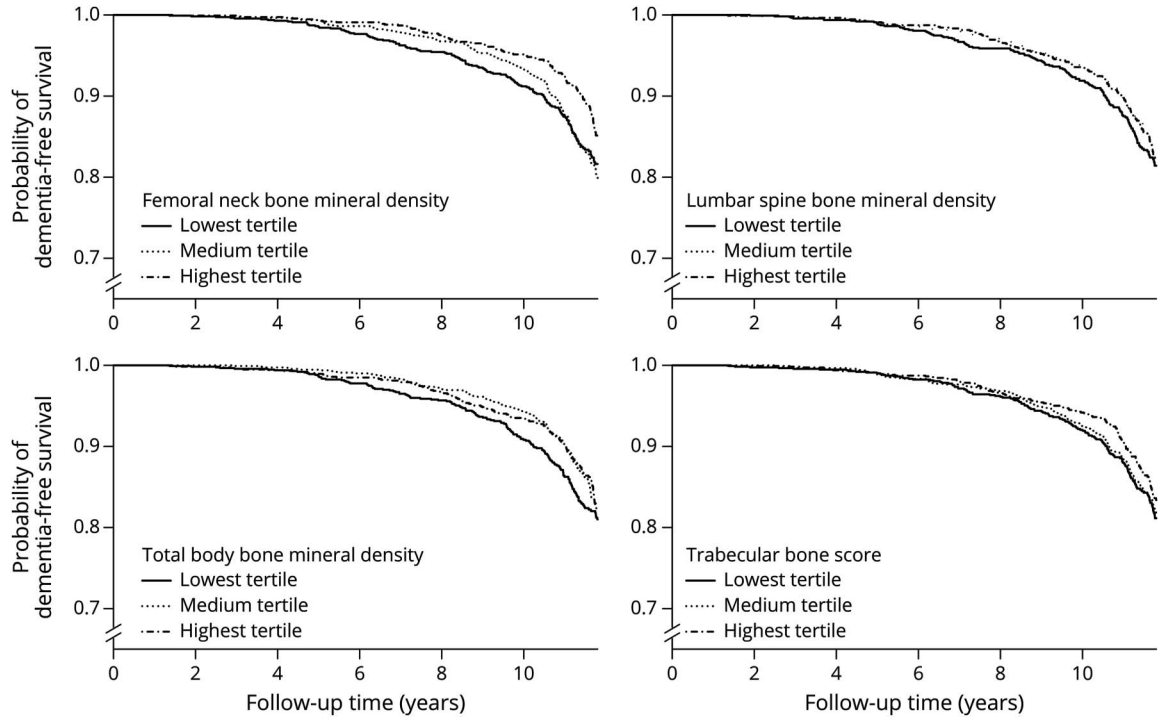
	0–5 y		0–10 y		Total follow-up	
	n/N	HR (95% CI)	n/N	HR (95% CI)	n/N	HR (95% CI)
Femoral neck BMD[b]						
Highest tertile	8/1,195	1	49/1,195	1	201/1,195	1
Medium tertile	7/1,194	0.85 (0.26–2.73)	67/1,194	1.34 (0.91–1.98)	236/1,194	1.16 (0.96–1.42)
Lowest tertile	16/1,195	2.32 (0.84–6.44)	86/1,195	**2.03 (1.39–2.96)**	229/1,195	**1.26 (1.03–1.54)**
Per SD decrease	31/3,584	**2.13 (1.28–3.57)**	202/3,584	**1.43 (1.19–1.72)**	666/3,584	**1.12 (1.02–1.23)**
Lumbar spine BMD[b]						
Highest tertile	10/1,203	1	64/1,203	1	224/1,203	1
Medium tertile	11/1,202	1.09 (0.41–2.91)	67/1,202	1.07 (0.74–1.54)	224/1,202	0.96 (0.79–1.17)
Lowest tertile	12/1,203	1.23 (0.47–3.20)	80/1,203	1.27 (0.89–1.80)	233/1,203	1.00 (0.82–1.21)
Per SD decrease	33/3,608	1.04 (0.69–1.56)	211/3,608	1.08 (0.93–1.27)	681/3,608	0.97 (0.89–1.05)
Total body BMD[b]						
Highest tertile	12/1,211	1	68/1,211	1	227/1,211	1
Medium tertile	6/1,211	0.49 (0.16–1.46)	57/1,211	0.85 (0.58–1.24)	227/1,211	1.00 (0.83–1.22)
Lowest tertile	15/1,211	1.00 (0.39–2.56)	90/1,211	**1.42 (1.01–2.02)**	232/1,211	1.00 (0.82–1.22)
Per SD decrease	33/3,633	1.27 (0.77–2.08)	215/3,633	**1.22 (1.00–1.47)**	686/3,633	1.02 (0.92–1.14)
TBS[b]						
Highest tertile	10/1,191	1	59/1,191	1	210/1,191	1
Medium tertile	12/1,191	2.47 (0.94–6.52)	74/1,191	**1.55 (1.08–2.21)**	226/1,191	1.21 (0.99–1.47)
Lowest tertile	11/1,191	2.04 (0.73–5.68)	77/1,191	**1.59 (1.11–2.28)**	236/1,191	1.19 (0.98–1.45)
Per SD decrease	33/3,573	1.37 (0.92–2.04)	210/3,573	1.16 (1.00–1.35)	672/3,573	1.04 (0.95–1.14)

Abbreviations: BMD = bone mineral density; HR = hazard ratio; TBS = trabecular bone score.
Cox regressions were adjusted for age, sex, *APOE* genotype, education attainment, physical activity, smoking status, body mass index, systolic and diastolic blood pressure, total cholesterol levels, high-density lipoprotein cholesterol levels, and history of comorbidities (stroke and diabetes mellitus).
Bold font corresponds to significant *p* value threshold.
[a] Follow-up time started after BMD scans at baseline.
[b] The tertile categories of BMD and TBS were derived by generating tertiles from the residuals of linear regression models adjusted for age (continuously) and sex. The highest tertile was considered as the reference group.

Participants with low BMD at the femoral neck had an increased risk of dementia in both this study and previous prospective studies.[28,29] It has also been demonstrated that participants with low femoral neck BMD may also experience structural brain changes, including declined white matter volume, increased white matter hyperintensity volume, occurrence of silent brain infarction, and progression of parenchymal atrophy.[30,31] A small cross-sectional study found that low total body BMD was common in the earliest clinical stages of AD and was related to brain atrophy and memory decline,[32] which was supported by the significant association between total body BMD and dementia risk in this study. Potential pathophysiologic mechanisms behind low BMD being a prodrome of dementia might include the effect of β-amyloid on suppressing osteoblast proliferation and enhancing osteoclast activity[33,34] and/or impact of systemic Wnt/β-catenin signaling deficits on impeding osteoblast differentiation and bone formation.[35,36] Apart from the abovementioned pathway, bone-derived proteins, such as osteopontin, osteocalcin, and sclerostin, might also affect both bone loss and dementia progression.[37] Moreover, the loss of cognition preceding dementia inevitably influences quality of life among older individuals by modifying nutrition intake and self-care ability, which further accelerates the loss of BMD and increases fracture risk with aging.[38,39]

Concerning scarcity of evidence on the association between bone microarchitecture and dementia, an inverse association was observed between TBS and dementia risk. Low TBS was associated with a weak and less fracture-resistant microarchitecture[19] and, consequently, also with fractures.[11] As the disease progresses, participants with subclinical dementia could experience changes in body composition[40] and confront with an increased risk of fracture,[41] which was reported

Figure 2 Kaplan-Meier Curves of Dementia-Free Survival at Different Levels of Bone Mineral Density at Each Site



as an independent risk of dementia.[42] This suggests that low TBS might occur as a prodromal feature of dementia. Further evidence from prospective studies is warranted to demonstrate the causality of the association.

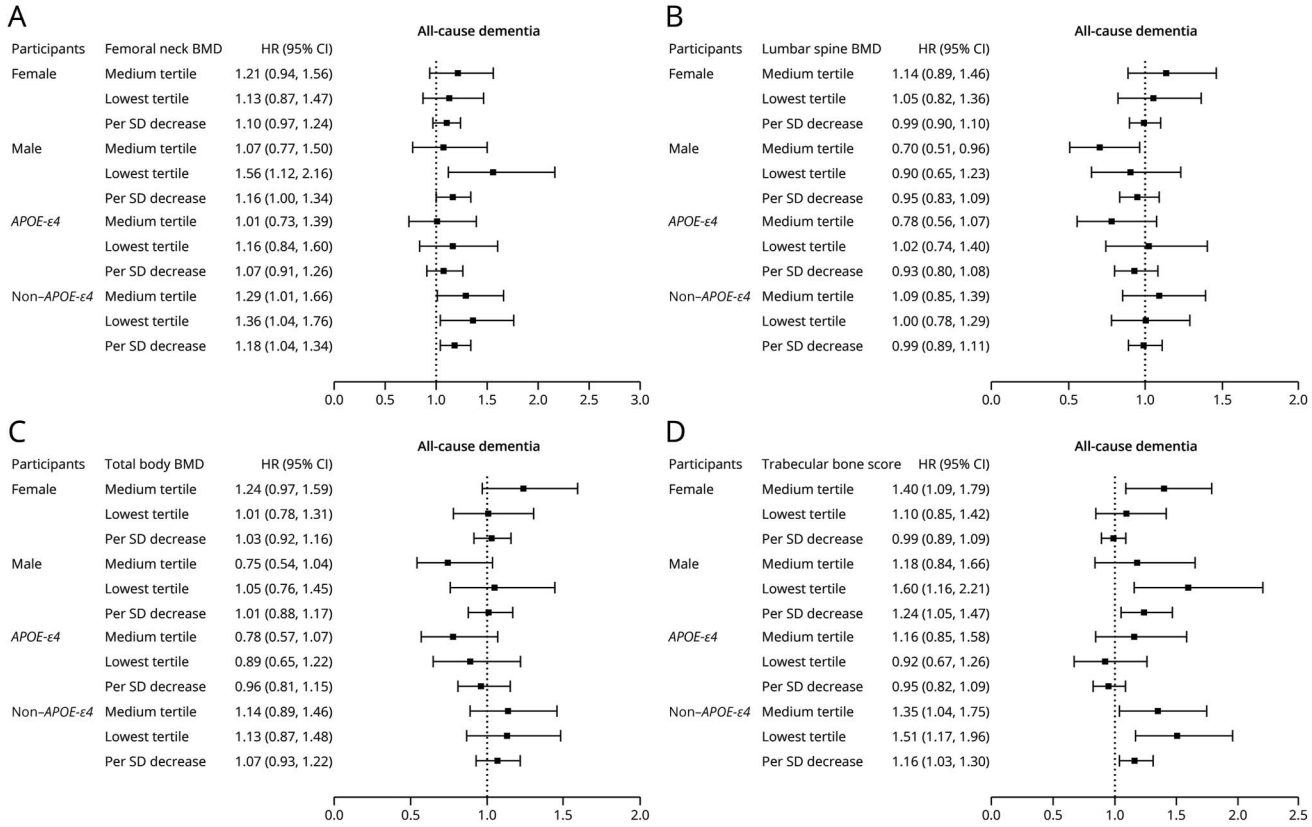
Our findings did not support a link between lumbar spine bone density and dementia risk, which contrasts with findings of prior studies.[43,44] Low BMD at the lumbar spine was associated with cognitive decline over a 3-year follow-up period in a Korean middle-aged community-dwelling population.[43] Moreover, a Chinese cohort study (n = 946) reported an association between low lumbar spine BMD and increased risks of AD and the conversion from mild cognitive impairment to the onset of dementia.[44] Different findings might result from relatively small sample size, a short follow-up time, or cross-sectional design of previous studies.

Our study shows that femoral neck BMD is the most robustly associated factor with incident dementia. There are biological differences between skeletal sites, which may explain these differences in effect. Bones within the lumbar spine consist predominantly of trabecular bone with a thin sheet of cortical bone surrounding them. By contrast, long bones, similar to those of the femur, are comprised predominantly of a thicker sheet of cortical bone and a thin inner layer of trabecular bone. Cortical and trabecular bone differ in their material and mechanical and functional properties. Thus, changes to cortical BMD could affect dementia risk more strongly than trabecular BMD, and this could be reflected in the differences in associations between sites. Furthermore, BMD of the femoral neck and total hip has been shown to decrease more rapidly with age in comparison with other skeletal sites.[45,46] Risk factors, such as poor diet and physical activity, may affect these bones differentially, regarding their composition and rate of decline, which in turn may explain the differential associations with dementia. However, the exact mechanism remains unclear and should be the focus of future study.

Our study added extra knowledge to previous findings that associations change with time, with the strength of the effect decreasing with increasing follow-up time. This suggests that total BMD and TBS might occur as prodromal features instead of causes of dementia and related toxic protein accumulation in the brain. In other words, persons with subclinical incipient dementia may have poor bone health due to the dementia process instead of vice versa. Alternatively, participants with a low level of BMD are at a high risk of falls and other mortalities, especially with a longer follow-up duration, and thus, death as a competing risk may also affect the associations. In addition, the results in the first 5 years of follow-up would be unstable. The small number would primarily affect the power of these analyses, reflected in wider CIs. The effect size itself would not necessarily be affected. Nevertheless, given the limited number of cases with dementia, the interpretation of this part result should be taken with caution.

In contrast to the finding of a prior study,[28] our study suggested that low BMD increased the risk of dementia in male,

Figure 3 Associations of Low BMD of the Total Body (A), the Femoral Neck (B), the Lumbar Spine (C), and Trabecular Bone (D) Scores With the Risk of All-Cause Dementia, Stratified by Sex and *APOE-ε4* Allele Carriership



Participants in the highest tertile of BMD were regarded as the reference group (hidden). Estimated HRs were obtained after adjustment of (if applicable) age, sex, *APOE* genotype, education attainment, physical activity, smoking status, body mass index, systolic and diastolic blood pressure, total cholesterol levels, high-density lipoprotein cholesterol levels, and history of comorbidities (stroke and diabetes mellitus). *The tertile categories of BMD and trabecular bone score were derived by generating tertiles from the residuals of linear regression models adjusted for age (continuously) and sex. The highest tertile was considered as the reference group. BMD = bone mineral density; HR = hazard ratio.

but not in female individuals. A previous study[28] reported an increased risk of AD only among women with low BMD at the femoral neck, which indicates the potentially protective effect of estrogen on mediating the negative association through inhibiting bone resorption and deterring neuronal apoptosis, atherosclerosis, and oxidative stress.[47,48] Although the risk of AD decreased after taking estrogen replacement,[49] this was contradicted by another study.[50] In addition, little evidence supports sex differences in the associations of low BMD with brain atrophy.[30] Future research is therefore needed to explore these hypotheses further.

The aim of our study was not necessarily etiologic, but instead to demonstrate the pattern of association. Indeed, we do not feel that BMD per se is causally related to dementia. Unraveling such etiologic link could, for instance, be a topic of study in Mendelian Randomization studies. Nevertheless, as an indicator of dementia risk, intervening in BMD may improve clinical care of these persons, especially considering the multicomorbidities and polypharmacy that are highly prevalent in this group.

The major important strength of our study is the relatively long follow-up time (mean 11.1 ± 2.9 years) and sufficient incident cases of dementia (n = 688). One limitation of this study lies in the weakness in determining the causality of associations concerning inherent restraints of observational study, including unmeasured confounders such as vitamin D and K and osteoporosis medications, although a large number of covariables were adjusted for in models. Future studies are warranted to assess the effect of these factors on the association. In addition, another weakness of this study is the violation of the proportionality assumption in some cox models. However, we performed stratification by incremental epochs of follow-up duration extending from the baseline. Finally, because our participants were primarily of European origin, with a mean age older than 70 years at baseline, this might restrict the extrapolation of our findings to other populations/ethnicities and younger populations.

In conclusion, participants with low femoral neck and total body BMD and low TBS were more likely to develop dementia. Further studies should focus on the predictive ability of BMD for dementia.

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Disclosure

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