Published Ahead of Print on March 22, 2023 as 10.1212/WNL.0000000000207220

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000207220

Association of Bone Mineral Density and Dementia: The Rotterdam Study

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Figure Count: 3

Table Count: 2

Search Terms:
[25] All Cognitive Disorders/Dementia, [26] Alzheimer's disease, [52] All epidemiology, [54] Cohort studies, [118] All Imaging

Acknowledgment:
We gratefully acknowledge the contribution of the participants of the Rotterdam Study, research assistants, the general practitioners, hospitals, and pharmacies in Rotterdam.

Study Funding:
The Rotterdam Study is sponsored by the Erasmus Medical Center and Erasmus University Rotterdam, The Netherlands Organization for Scientific Research (I), The Netherlands Organization for Health Research and Development (ZonMW), the Research Institute for Diseases in the Elderly (RIDE), The Netherlands Genomics Initiative, the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. Further support was obtained from the Netherlands Consortium for Healthy Ageing. This study was partly performed as part of the Netherlands Consortium of Dementia Cohorts (NCDC), which also receives funding in the context of Deltaplan Dementie from ZonMW Memorabel (projectnr 73305095005) and Alzheimer Nederland. Further funding was obtained through the Stichting Erasmus Trustfonds, grant number 97030.2021.101.430/057/RB. Moreover, LO is funded by an Erasmus MC fellowship grant. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosures:
The authors report no disclosures relevant to the manuscript.

Preprint DOI:

Received Date:
2022-10-03

Accepted Date:
2023-02-09

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Abstract

Background & Objective: Low bone mineral density and dementia commonly co-occur in the elderly, with bone loss accelerating in dementia patients due to physical inactivity and

poor nutrition. However, uncertainty persists over the extent to which bone loss already exists prior to the onset of dementia. Therefore, we investigated how dementia risk was affected by bone mineral density at various skeletal regions in community-dwelling older adults.

Methods: In a prospective population-based cohort study, bone mineral density at the femoral neck, lumbar spine, and total body and the trabecular bone score were obtained using dual-energy X-ray absorptiometry (DXA) in 3,651 participants free from dementia between 2002-2005. Persons at risk of dementia were followed up until 1 January 2020. For analyses of the association between bone mineral density 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 blood pressure, 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's disease. During the whole follow-up, participants with lower bone mineral density 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% Confidential interval [CI]: 1.02-1.23) and Alzheimer's disease (HR $_{\text{total follow-up}}$: 1.14, 95% CI: 1.02-1.28). Within the first ten years following baseline, the risk of dementia was greatest for groups with the lowest tertile of bone mineral density (femoral neck bone mineral density, $HR_{0\text{-}10\text{years}}$ 2.03; 95% CI, 1.39–2.96; total body bone mineral density, $HR_{0\text{-}10\text{years}}$ 1.42; 95% CI, 1.01–2.02; trabecular bone score, $HR_{0\text{-}10\text{years}}$ 1.59; 95% CI, 1.11–2.28).

Conclusions: In conclusion, participants with low femoral neck and total body bone mineral density and low trabecular bone score were more likely to develop dementia. Further studies should focus on the predictive ability of bone mineral density for dementia.

Keywords: Bone mineral density, femoral neck, lumbar spine, trabecular bone score, dementia, Alzheimer's disease.

INTRODUCTION

Over 45 million people worldwide suffer from dementia, and this figure is estimated to double in the next two 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 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 bone mineral density 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 dementia patients, including maintaining functional independence.

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

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

METHODS

Study population

This study was performed within the Rotterdam Study, a prospective ongoing cohort study that started in 1990, and all participants aged ≥ 45 years were invited for studying chronic diseases in the general population [17]. The Rotterdam cohort comprises one original cohort (RS-I, initiated in 1990, 7,983 participants aged ≥55 years) and other two cohorts (RS-II, starting from 2000, 3,011 participants aged ≥ 55 years; and RS-III, starting from 2006, 3,932 aged ≥ 45 years), respectively. Every four to five 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 Centre (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 a bone scans. A total of 3,651 persons with DXA scans and without prevalent dementia were finally included in this study (Figure1).

Measurements of bone mineral density

Bone mineral density 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 had completed at least one scan of bone mineral density, of whom 3,584 participants had data on the bone mineral density at the femoral neck, 3,608 at the lumbar spine, and 3,633 of the total body.

Measurement of trabecular bone score

Trabecular bone score was calculated using the trabecular bone score iNsight software (Med-Imaps, Geneva, Switzerland) [15]. Briefly, the trabecular bone score 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], trabecular bone score was assessed using gray-level analysis of the DXA images and the methodology of the trabecular bone score has been described elsewhere [16]. Trabecular bone score was available for 3,573 participants at baseline.

Dementia assessment

The Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) were used for detecting dementia at baseline and subsequent visits [17]. Further investigation and interview, including the Cambridge Examination for Mental Disorders of the Elderly, were conducted on participants with a MMSE score < 26 or GRS score > 0. Additionally, 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 utilized 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: DSM-III-R) and Alzheimer's disease (AD) (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association: NINCDS–ADRDA). The follow-up were stopped until meeting any of following scenarios, including incident dementia diagnosis, death, loss to follow-up, or 1 January 2020, whichever came first.

Covariables

Potential covariables were selected according to literature evidence demonstrating an association with bone mineral density, 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 (mmHg), diastolic blood pressure (mmHg), 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 apolipoprotein E (*APOE*) genotype, a PCR was used in RS-I and a bi-allelic TaqMan assay (rs7412 and rs429358) was employed on labelled DNA samples in both RS-II and RS-III. This study included the first two sub-cohorts (RS-I and RS-II). *APOE*-ε4 allele represented carrier ship of at least one ε4 alleles. Participants were divided into three 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 ± standard deviation (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 bone mineral density 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 1 January 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 bone mineral density and trabecular bone score tertiles with respect to time to dementia. Cox proportional hazard models were adjusted for age, sex, *APOE* genotypes, education attainment, physical activity,

smoking status, body mass index, systolic blood pressure, diastolic blood pressure, cholesterol level, high-density lipoprotein cholesterol, and history of chronic disorders (stroke and diabetes mellitus). Age and sex are two strong risk factors for both low bone mineral density, as bone mineral loss is manifested after age 50 years or menopause [23, 24], therefore, the tertile categories of bone mineral density were derived by generating tertiles from the residuals of linear regression models adjusted for age (continuously) and sex. Effects of bone mineral density were also assessed when expressed as per one standard deviation (SD) decrease. Associations were determined by measuring the effects of each tertile or per one SD decrease of bone mineral density at the femoral neck, the lumbar spine, and total body, and trabecular bone score 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, baseline to over 10 years). In addition, we stratified analyses by sex and *APOE*-ε4 allele carrier ship (carrier versus non-carrier), which were suggested as possible effect modifiers [21, 25, 26].

A p-value of <0.05 was considered statistically significant. Data analyses were done using R version 3.6.0 (www.R-project.org.) (http://CRAN.R-project.org/package=lme4). 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

The Rotterdam Study is sponsored by the Erasmus Medical Center and Erasmus University Rotterdam, The Netherlands Organization for Scientific Research (I), The Netherlands

Organization for Health Research and Development (ZonMW), the Research Institute for Diseases in the Elderly (RIDE), The Netherlands Genomics Initiative, the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. Further support was obtained from the Netherlands Consortium for Healthy Ageing. This study was partly performed as part of the Netherlands Consortium of Dementia Cohorts (NCDC), which also receives funding in the context of Deltaplan Dementie from ZonMW Memorabel (projectnr 73305095005) and Alzheimer Nederland. Further funding was obtained through the Stichting Erasmus Trustfonds, grant number 97030.2021.101.430/057/RB. Moreover, LO is funded by an Erasmus MC fellowship grant. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. 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. We gratefully acknowledge the contribution of the participants of the Rotterdam Study, research assistants, the general practitioners, hospitals, and pharmacies in Rotterdam.

Data availability

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

RESULTS

Clinical characteristics

As shown in Table1, among 3,651 participants (median age 72.3±10.0 years), 2113 (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 Alzheimer's disease.

Bone mineral density and dementia risk over incremental epochs of follow-up duration

Throughout the whole follow-up, lower bone mineral density at the femoral neck (per SD decrease), not at other bone sites, was related to a higher risk of all-cause dementia (Hazard ratio $[HR]_{\text{total follow-up}}$: 1.12, 95% Confidential interval [CI]: 1.02-1.23) and Alzheimer's disease ($HR_{\text{total follow-up}}$: 1.14, 95% CI: 1.02-1.28) (Table 2). As presented in eTable 1 in the Supplement, results were similar when we categorized individuals by bone mineral density tertiles: the highest risks were observed for dementia and Alzheimer's disease in the lowest group.

Within the first ten years following baseline, associations were greatest between lower bone mineral density (per SD decrease) and a higher risk of all-cause dementia (femoral neck bone mineral density, $HR_{0\text{-}10\text{years}}$ 1.43; 95% CI, 1.19–1.72; total body bone mineral density, $HR_{0\text{-}10\text{years}}$ 1.22; 95% CI, 1.00–1.47), and Alzheimer's disease (femoral neck bone mineral density, $HR_{0\text{-}10\text{years}}$ 1.52; 95% CI, 1.20–1.92). The hazard ratios for incident all-cause dementia comparing the lowest tertile of the femoral neck bone mineral density, total body bone mineral density, and trabecular bone score 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 bone mineral density, trabecular bone score, and the risk of Alzheimer's disease, which were listed in eTable 1 in the Supplement.

As shown in Table 2 and eTable 1 in the Supplement, only bone mineral density at the femoral neck was related to all-cause dementia occurrence over the first five years of the follow-up ($HR_{0\text{-}5years}$ 2.13; 95% CI, 1.28–3.57, per SD decrease).

Kaplan-Meier curves of dementia-free survival by levels of bone mineral density

As presented in Figure 2 and eFigure 1 in the Supplement, within the first 5 years during the follow-up, the curves of dementia-free or Alzheimer's disease-free probability were nearly overlapped at all tertile levels of the bone mineral density, but the curve at the lowest tertile of the femoral neck bone mineral density 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 bone mineral density and trabecular bone score, but not for the lumbar spine bone mineral density.

Stratification

When stratified by sex and *APOE*-ε4 carriership, significant associations were found between lower femoral neck bone mineral density (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 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 inversed associations were also presented between low trabecular bone score and dementia risk (Figure 3). Stratification for the HR estimates of Alzheimer's disease was represented in eFigure 2 in the Supplement. Statistically significant interactions were observed between sex and low trabecular bone scores (P=0.02), and between *APOE*-ε4 carriership and low trabecular bone scores (P=0.01) (data not presented).

DISCUSSION

In this study, low femoral neck and total body bone mineral density and low trabecular bone score were associated with an increased risk of dementia. The associations were strongest in the first ten years of follow-up.

Participants with low bone mineral density at the femoral neck had an increased risk of dementia in both the current study and previous prospective studies [28, 29]. It has also been demonstrated that participants with low femoral neck bone mineral density 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 bone mineral density was common in the earliest clinical stages of Alzheimer's disease and was related to brain atrophy and memory decline [32], which was supported by the significant association between total body bone mineral density and dementia risk in this study. Potential pathophysiological mechanisms behind low bone mineral density being a prodrome of dementia might include the effect of amyloid-beta on suppressing osteoblast proliferation and enhancing osteoclast activity [33, 34], and/or impact of systemic Wnt/Beta-catenin signaling deficits on impeding osteoblast differentiation and bone formation [35, 36]. Apart from the above pathway, bone-derived proteins, such as osteopontin, osteocalcin, sclerostin might also impact both bone loss and dementia progression [37]. Moreover, the loss of cognition preceding dementia inevitably influences quality of life among elderly by modifying nutrition intake and self-care ability, which further accelerates the loss of bone mineral density 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 trabecular bone score and dementia risk. Low trabecular bone score 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 as an independent risk of dementia [42]. This suggests that low trabecular bone score might occur as a prodromal feature of dementia. Further evidence from prospective studies is warranted to demonstrate 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 bone mineral density at the lumbar spine was associated with cognitive decline over a 3-years 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 bone mineral density and increased risks of Alzheimer's disease and the conversion from mild cognitive impairment to the onset of dementia [44]. Different findings might result from relatively small sample size, short follow-up time, or cross-sectional design of previous studies.

Our study shows that femoral neck BMD is the most robustly associated 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. In contrast long bones, like 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, 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 to other skeletal sites[45, 46]. Risk factors, such as poor diet and physical activity, may impact these bones differentially, in terms of 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 bone mineral density and trabecular bone score 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 bone mineral density are at a high risk of falls and other mortalities, especially with longer follow-up duration, and thus death as a competing risk may also affect the associations. Additionally, the results in the first five years of follow-up would be unstable. The small number would primarily affect the power of these analyses, reflected in wider confidence intervals. The effect size itself would not necessarily be affected. Nevertheless, given the limited number of dementia cases, 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 bone mineral density increased the risk of dementia in males, but not in females. Tan ZS, et al [28] reported an increased risk of Alzheimer's disease only among women with low bone mineral density

at the femoral neck, which indicates 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 Alzheimer's disease 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 bone mineral density 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 multi-comorbidities and polypharmacy that are highly preventive 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. Additionally, 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, due to the fact that our participants were primarily of European origin, with a mean age over 70 years at baseline,

this might restrict the extrapolation of our findings to other populations/ethnicities and younger populations.

CONCLUSION

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

http://links.lww.com/WNL/C666

REFERENCES

1. Shah H, Albanese E, Duggan C, et al. Research priorities to reduce the global burden of dementia by 2025. Lancet Neurol 2016;15:1285-1294.
2. International AsD. World Alzheimer report 2015: the global impact of dementia.
3. Browne J, Edwards DA, Rhodes KM, Brimicombe DJ, Payne RA. Association of comorbidity and health service usage among patients with dementia in the UK: a population-based study. BMJ Open 2017;7:e012546.

4. Xu H, Garcia-Ptacek S, Trevisan M, et al. Kidney Function, Kidney Function Decline, and the Risk of Dementia in Older Adults: A Registry-Based Study. Neurology 2021;96:e2956-2965.
5. Frame G, Bretland KA, Dengler-Crish CM. Mechanistic complexities of bone loss in Alzheimer's disease: a review. Connect Tissue Res 2020;61:4-18.
6. Kostev K, Hadji P, Jacob L. Impact of Osteoporosis on the Risk of Dementia in Almost 60,000 Patients Followed in General Practices in Germany. J Alzheimers Dis 2018;65:401-407.
7. Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MM. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. Clin Endocrinol (Oxf) 2000;53:733-737.
8. Friedman SM, Menzies IB, Bukata SV, Mendelson DA, Kates SL. Dementia and hip fractures: development of a pathogenic framework for understanding and studying risk. Geriatr Orthop Surg Rehabil 2010;1:52-62.
9. Frenkel B, Hong A, Baniwal SK, et al. Regulation of adult bone turnover by sex steroids. J Cell Physiol 2010;224:305-310.
10. Kipen E, Helme RD, Wark JD, Flicker L. Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. J Am Geriatr Soc 1995;43:1088-1091.
11. Shevroja E, Cafarelli FP, Guglielmi G, Hans D. DXA parameters, Trabecular Bone Score (TBS) and Bone Mineral Density (BMD), in fracture risk prediction in endocrine-mediated secondary osteoporosis. Endocrine 2021;74:20-28.
12. Bruyere O, Varela AR, Adami S, et al. Loss of hip bone mineral density over time is associated with spine and hip fracture incidence in osteoporotic postmenopausal women. Eur J Epidemiol 2009;24:707-712.
13. Lary CW, Rosen CJ, Kiel DP. Osteoporosis and Dementia: Establishing a Link. J Bone Miner Res 2021;36:2103-2105.
14. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int 2014;25:2359-2381.
15. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res 2011;26:2762-2769.
16. Harvey NC, Glüer CC, Binkley N, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone 2015;78:216-224.

17. Ikram MA, Brusselle G, Ghanbari M, et al. Objectives, design and main findings until 2020 from the Rotterdam Study. Eur J Epidemiol 2020;35:483-517.
18. Burger H, de Laet CE, van Daele PL, et al. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. Am J Epidemiol 1998;147:871-879.
19. Pothuaud L, Barthe N, Krieg MA, Mehsen N, Carceller P, Hans D. Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. J Clin Densitom 2009;12:170-176.
20. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimers Dement 2015;11:718-726.
21. Rocca WA, Mielke MM, Vemuri P, Miller VM. Sex and gender differences in the causes of dementia: a narrative review. Maturitas 2014;79:196-201.
22. Licher S, Ahmad S, Karamujić-Čomić H, et al. Genetic predisposition, modifiable-risk-factor profile and long-term dementia risk in the general population. Nat Med 2019;25:1364-1369.
23. Wishart JM, Need AG, Horowitz M, Morris HA, Nordin BE. Effect of age on bone density and bone turnover in men. Clin Endocrinol (Oxf) 1995;42:141-146.
24. Greendale GA, Sowers M, Han W, et al. Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: results from the Study of Women's Health Across the Nation (SWAN). J Bone Miner Res 2012;27:111-118.
25. Peter I, Crosier MD, Yoshida M, et al. Associations of APOE gene polymorphisms with bone mineral density and fracture risk: a meta-analysis. Osteoporos Int 2011;22:1199-1209.
26. Bakulski KM, Vadari HS, Faul JD, et al. Cumulative Genetic Risk and APOE ε4 Are Independently Associated With Dementia Status in a Multiethnic, Population-Based Cohort. Neurol Genet 2021;7:e576.
27. Zhang Z. Multiple imputation with multivariate imputation by chained equation (MICE) package. Ann Transl Med 2016;4:30.
28. Tan ZS, Seshadri S, Beiser A, et al. Bone mineral density and the risk of Alzheimer disease. Arch Neurol 2005;62:107-111.
29. Zhou R, Deng J, Zhang M, Zhou HD, Wang YJ. Association between bone mineral density and the risk of Alzheimer's disease. J Alzheimers Dis 2011;24:101-108.

30. Minn YK, Suk SH, Do SY. Osteoporosis as an independent risk factor for silent brain infarction and white matter changes in men and women: the PRESENT project. Osteoporos Int 2014;25:2465-2469.
31. Bae IS, Kim JM, Cheong JH, Ryu JI, Han MH. Association between bone mineral density and brain parenchymal atrophy and ventricular enlargement in healthy individuals. Aging (Albany NY) 2019;11:8217-8238.
32. Loskutova N, Honea RA, Vidoni ED, Brooks WM, Burns JM. Bone density and brain atrophy in early Alzheimer's disease. J Alzheimers Dis 2009;18:777-785.
33. Xia WF, Jung JU, Shun C, et al. Swedish mutant APP suppresses osteoblast differentiation and causes osteoporotic deficit, which are ameliorated by N-acetyl-L-cysteine. J Bone Miner Res 2013;28:2122-2135.
34. Li S, Liu B, Zhang L, Rong L. Amyloid beta peptide is elevated in osteoporotic bone tissues and enhances osteoclast function. Bone 2014;61:164-175.
35. Sen B, Styner M, Xie Z, Case N, Rubin CT, Rubin J. Mechanical loading regulates NFATc1 and beta-catenin signaling through a GSK3beta control node. J Biol Chem 2009;284:34607-34617.
36. Krishnan V, Bryant HU, Macdougald OA. Regulation of bone mass by Wnt signaling. J Clin Invest 2006;116:1202-1209.
37. Yuan J, Meloni BP, Shi T, et al. The Potential Influence of Bone-Derived Modulators on the Progression of Alzheimer's Disease. J Alzheimers Dis 2019;69:59-70.
38. Teng E, Tassniyom K, Lu PH. Reduced quality-of-life ratings in mild cognitive impairment: analyses of subject and informant responses. Am J Geriatr Psychiatry 2012;20:1016-1025.
39. Bliuc D, Tran T, Adachi JD, et al. Cognitive decline is associated with an accelerated rate of bone loss and increased fracture risk in women: a prospective study from the Canadian Multicentre Osteoporosis Study. J Bone Miner Res 2021;36:2106-2115.
40. Murata S, Ono R, Sugimoto T, Toba K, Sakurai T. Functional Decline and Body Composition Change in Older Adults With Alzheimer Disease: A Retrospective Cohort Study at a Japanese Memory Clinic. Alzheimer Dis Assoc Disord 2021;35:36-43.
41. Zhao Y, Shen L, Ji HF. Alzheimer's disease and risk of hip fracture: a meta-analysis study. ScientificWorldJournal 2012;2012:872173.
42. Tsai CH, Chuang CS, Hung CH, et al. Fracture as an independent risk factor of dementia: a nationwide population-based cohort study. Medicine (Baltimore) 2014;93:e188.

43. Kang HG, Park HY, Ryu HU, Suk SH. Bone mineral loss and cognitive impairment: The PRESENT project. Medicine (Baltimore) 2018;97:e12755.
44. Zhou R, Zhou H, Rui L, Xu J. Bone loss and osteoporosis are associated with conversion from mild cognitive impairment to Alzheimer's disease. Curr Alzheimer Res 2014;11:706-713.
45. Berger C, Langsetmo L, Joseph L, et al. Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. Cmaj 2008;178:1660-1668.
46. Boyanov MA. Whole Body and Regional Bone Mineral Content and Density in Women Aged 20-75 Years. Acta Endocrinol (Buchar) 2016;12:191-196.
47. Jilka RL, Hangoc G, Girasole G, et al. Increased osteoclast development after estrogen loss: mediation by interleukin-6. Science 1992;257:88-91.
48. Fox M, Berzuini C, Knapp LA. Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. Psychoneuroendocrinology 2013;38:2973-2982.
49. LeBlanc ES, Janowsky J, Chan BK, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis. Jama 2001;285:1489-1499.
50. Seshadri S, Zornberg GL, Derby LE, Myers MW, Jick H, Drachman DA. Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. Arch Neurol 2001;58:435-440.

FIGURE 1 Flow chart for participants with bone mineral density scans included in the study

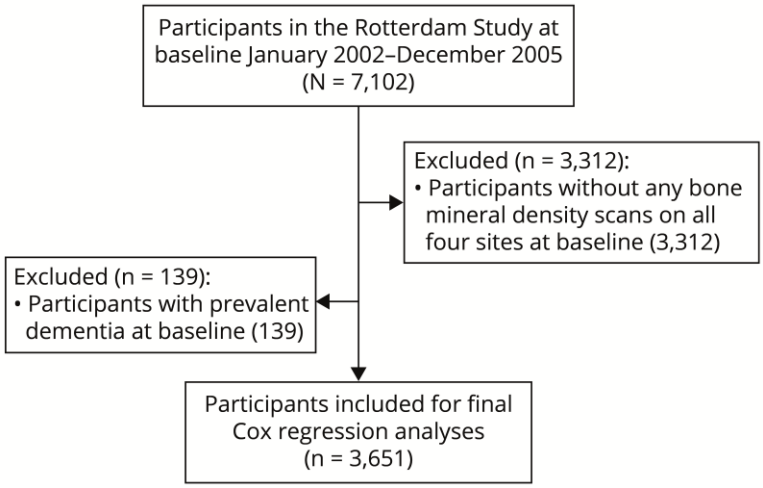

FIGURE 2 Kaplan-Meier curves of dementia-free survival at different levels of bone mineral density at each site.

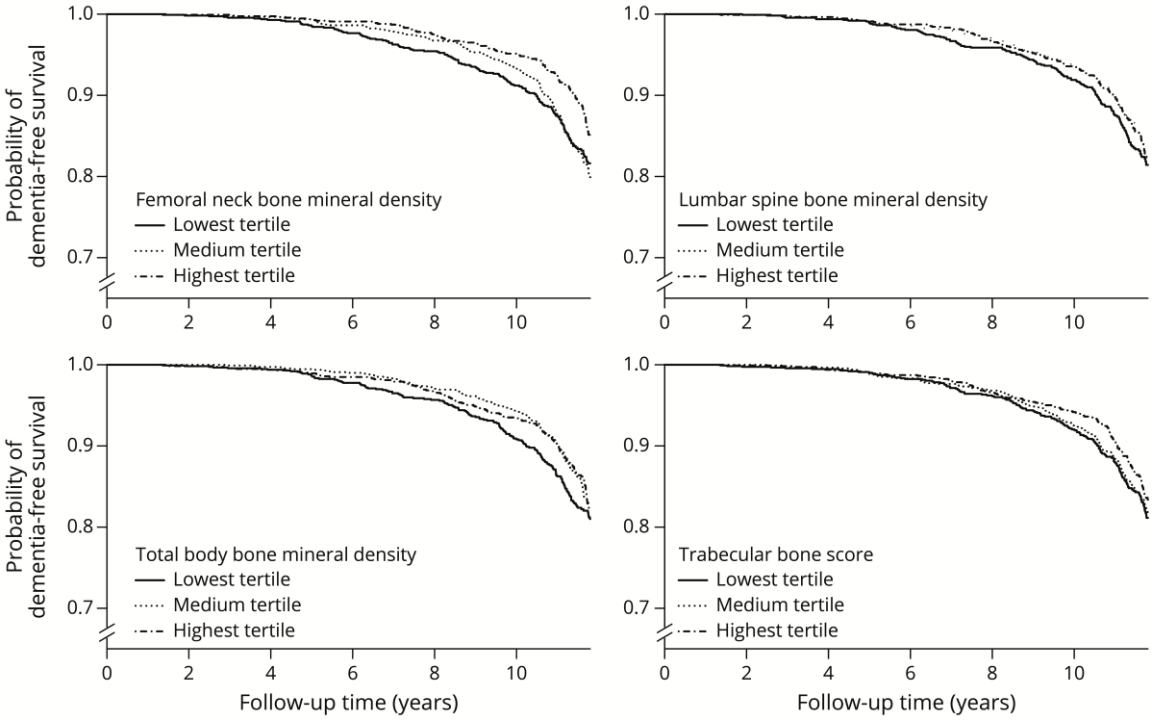

FIGURE 3 Associations of low bone mineral density of the total body (A), the femoral neck (B), the lumbar spine (C), and trabecular bone scores with the risk of all-cause dementia, stratified by sex and *APOE*-ε4 allele carriership.

APOE = Apolipoprotein E; BMD = Bone Mineral Density; HR = Hazard Ratio. Participants in the highest tertile of bone mineral density 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 bone mineral density were derived by generating tertiles from the residuals of linear regression models adjusted for age (continuously) and sex. The highest tertile as the reference group.

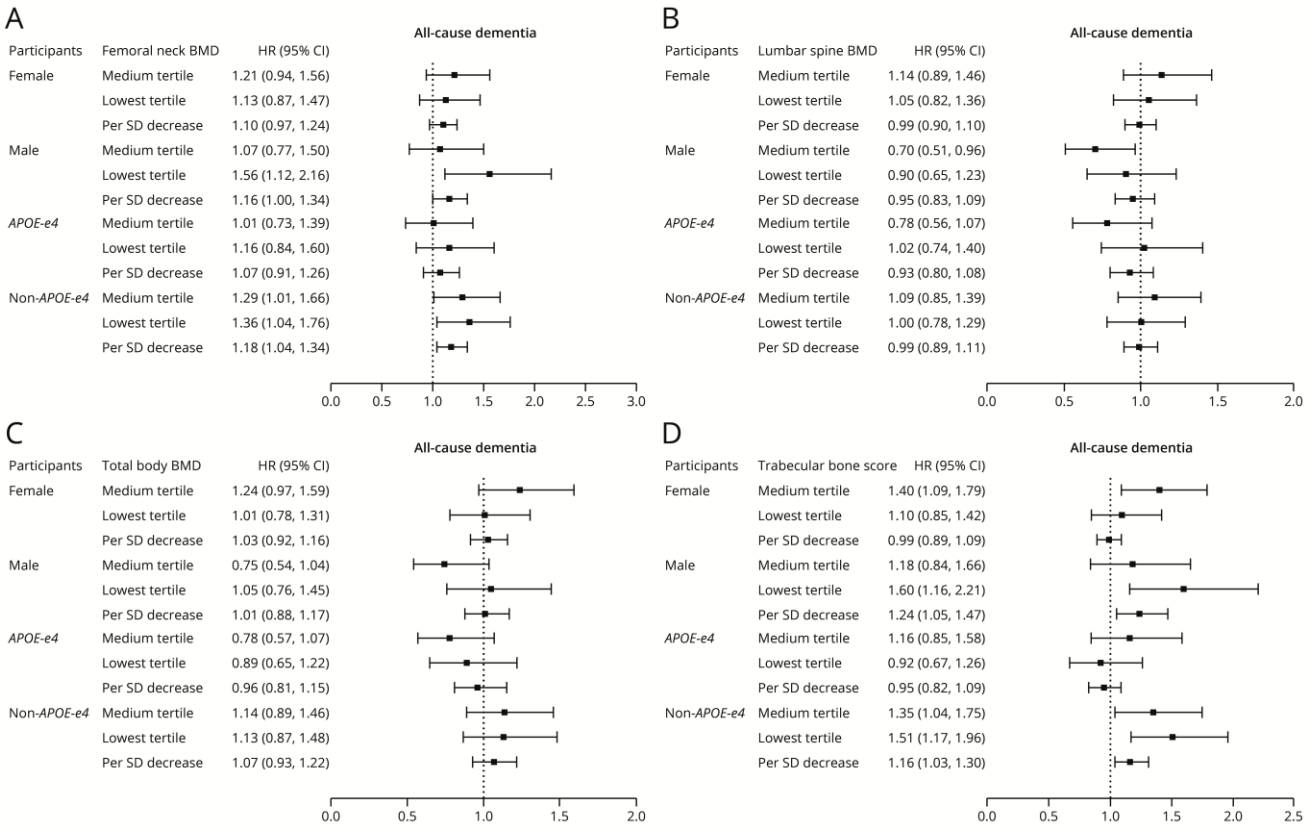

TABLE 1 Baseline characteristics of participants in longitudinal analyses

	Men	Women	Total
N, (%)	1538 (42.1)	2113 (57.9)	3651 (100)
Follow-up, years	10.9 (4.3)	11.2 (2.2)	11.1 (2.9)
Age, years	72.3 (9.5)	72.3 (10.4)	72.3 (10.0)
Body mass index, Kg/m^2, (%)			
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)	1811 (49.6)
Obesity > 30	282 (18.3)	558 (26.4)	840 (23.0)
Alcohol, g/day	12.1 (21.5)	2.9 (12.0)	7.1 (19.3)
Smoking, (%)			
Never	237 (15.4)	916 (43.4)	1153 (31.6)
Former	1100 (71.5)	921 (43.6)	2021 (55.4)
Current	201 (13.1)	276 (13.1)	477 (13.1)
Educational level, (%)			
Primary	122 (7.9)	293 (13.9)	415 (11.4)
Low	472 (30.7)	1162 (55.0)	1634 (44.8)
Intermediate	602 (39.1)	528 (25.0)	1130 (31.0)
High	342 (22.2)	130 (6.2)	472 (12.9)
Physical activity, hours/month	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, (%)	133 (8.6)	142 (6.7)	275 (7.5)
Stroke, (%)	25 (1.6)	17 (0.8)	42 (1.2)
APOE-ε4, (%)	390 (26.5)	527 (26.7)	917 (26.6)
Total body bone mineral density , g/cm^2	1.20 (0.13)	1.06 (0.14)	1.12 (0.17)
Femoral neck bone mineral density, g/cm^2	0.92 (0.18)	0.82 (0.17)	0.86 (0.19)
Lumbar spine bone mineral density, g/cm^2	1.21 (0.27)	1.04 (0.24)	1.10 (0.28)
Trabecular bone score, mm^{-1}	1.33 (0.12)	1.25 (0.14)	1.28 (0.14)

Definition of abbreviations: *APOE* = Apolipoprotein E. 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%), HDL (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 two subgroups.

TABLE 2 Bone mineral density and the risk of incident dementia stratified by incremental epochs of follow-up time

	0~5 years		0~10 years		Total follow-up	
	n/N	HR (95%CI)	n/N	HR (95%CI)	n/N	HR (95%CI)
Femoral neck bone mineral density						
Highest tertile	8/1195	1	49/1195	1	201/1195	1
Medium tertile	7/1194	0.85 (0.26, 2.73)	67/1194	1.34 (0.91, 1.98)	236/1194	1.16 (0.96, 1.42)
Lowest tertile	16/1195	2.32 (0.84, 6.44)	86/1195	**2.03 (1.39, 2.96)**	229/1195	**1.26 (1.03, 1.54)**
Per SD decrease	31/3584	**2.13 (1.28, 3.57)**	202/3584	**1.43 (1.19, 1.72)**	666/3584	**1.12 (1.02;1.23)**
Lumbar spine bone mineral density						
Highest tertile	10/1203	1	64/1203	1	224/1203	1
Medium tertile	11/1202	1.09 (0.41, 2.91)	67/1202	1.07 (0.74, 1.54)	224/1202	0.96 (0.79, 1.17)
Lowest tertile	12/1203	1.23 (0.47, 3.20)	80/1203	1.27 (0.89, 1.80)	233/1203	1.00 (0.82, 1.21)
Per SD decrease	33/3608	1.04 (0.69, 1.56)	211/3608	1.08 (0.93, 1.27)	681/3608	0.97 (0.89;1.05)
Total body bone mineral density						
Highest tertile	12/1211	1	68/1211	1	227/1211	1
Medium tertile	6/1211	0.49 (0.16, 1.46)	57/1211	0.85 (0.58, 1.24)	227/1211	1.00 (0.83, 1.22)
Lowest tertile	15/1211	1.00 (0.39, 2.56)	90/1211	**1.42 (1.01, 2.02)**	232/1211	1.00 (0.82, 1.22)
Per SD decrease	33/3633	1.27 (0.77, 2.08)	215/3633	**1.22 (1.00, 1.47)**	686/3633	1.02 (0.92, 1.14)
Trabecular bone score						
Highest tertile	10/1191	1	59/1191	1	210/1191	1
Medium tertile	12/1191	2.47 (0.94, 6.52)	74/1191	**1.55 (1.08, 2.21)**	226/1191	1.21 (0.99, 1.47)
Lowest tertile	11/1191	2.04 (0.73, 5.68)	77/1191	**1.59 (1.11, 2.28)**	236/1191	1.19 (0.98, 1.45)
Per SD decrease	33/3573	1.37 (0.92, 2.04)	210/3573	1.16 (1.00, 1.35)	672/3573	1.04 (0.95;1.14)

Definition of abbreviations: n = Cases, N = Total participants, *APOE* = Apolipoprotein E; CI = Confidence Interval; HR = Hazard Ratio; SD = Standard Deviation. 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).

* follow-up time started after bone mineral density scans at baseline.

* The tertile categories of bone mineral density were derived by generating tertiles from the residuals of linear regression models adjusted for age (continuously) and sex. The highest tertile as the reference group.

Bold font corresponds to significant P-value threshold

Association of Bone Mineral Density and Dementia: The Rotterdam Study

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Neurology published online March 22, 2023
DOI 10.1212/WNL.0000000000207220