

Bone Mineral Density and the Risk of Alzheimer Disease

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Background: Some, but not all, studies have suggested that estrogen replacement therapy has a beneficial effect on cognition in postmenopausal women. Bone mineral density (BMD) is a potential surrogate marker for cumulative estrogen exposure and has been associated with cognitive performance and risk of cognitive deterioration.

Objective: To examine whether low BMD in elderly individuals is associated with an increased risk of developing Alzheimer disease (AD).

Design, Setting, and Participants: Community-based prospective cohort study of 987 subjects (610 women) who were cognitively intact and had baseline BMD measured at the femoral neck, the trochanter, and the radial shaft between 1988 and 1989.

Main Outcome Measures: Incidence of AD and all-cause dementia during an 8-year follow-up period.

Results: Women in the lowest quartile of femoral neck BMD had more than twice the incidence of AD (hazard

ratio, 2.04; 95% confidence interval, 1.11-3.75) and all-cause dementia (hazard ratio, 2.01; 95% confidence interval, 1.16-3.49) compared with those in higher quartiles after adjusting for age, sex, apolipoprotein E ϵ 4, baseline homocysteine level, education, estrogen use, smoking, and stroke. A similar but statistically nonsignificant relationship was observed between BMD of the femoral trochanter and AD, while no such relationship was seen between radial BMD and AD or all-cause dementia. In men, there was a trend toward an inverse relationship between BMD and the risk of AD, but the relationship was not statistically significant at any of the 3 sites.

Conclusions: Low femoral neck BMD was associated with approximately 2 times the risk of AD and all-cause dementia in women but not men, suggesting the possibility that cumulative estrogen exposure may influence the risk of developing AD. Additional studies are needed to confirm this correlation.

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ALZHEIMER DISEASE (AD) IS the most common form of dementia, accounting for 50% to 70% of all cases. The higher incidence in women¹ is only partly explained by a higher average life expectancy.

Postmenopausal estrogen replacement therapy (ERT) has been shown by several, but not all,^{2,3} studies to have a beneficial effect on cognition in nondemented perimenopausal and postmenopausal women.^{4,5} Observational studies of the association between ERT and the risk of dementia have suffered from biases, such as women who receive ERT being healthier, better educated, and more compliant with medical treatment in general than nonusers.^{6,7} In addition, many women take ERT for only a few years and may

not accurately recall the duration of intake. Women also have varying exposure to endogenous estrogen because of varying age at menarche, menopause, and oophorectomy, as well as other factors that make it difficult to estimate lifetime exposure to both exogenous and endogenous estrogen.

Bone mineral density (BMD) may be a surrogate marker for cumulative estrogen exposure. Bone mineral density has been correlated with early menarche, parity, late menopause,⁸ and cumulative exposure to endogenous and exogenous estrogens.^{9,10} Epidemiological studies have demonstrated that greater BMD is associated with an increased risk of breast cancer and a lower risk of colon cancer, further suggesting that bone density may capture cumulative estrogen exposure.¹¹⁻¹³

Table 1. Baseline Characteristics of Subjects at Examination Cycle 20 (1988-1989)*

Characteristic	Women (n = 610)	Men (n = 377)
Age, y	76.1 ± 5.0	75.5 ± 4.9
Follow-up, y	8.7 ± 3.2	7.7 ± 3.7
Apolipoprotein E ε4, %	20.6	21.1
Body mass index, kg/m ²	26.6 ± 5.0	27.1 ± 4.0
High school degree, %	69.0	67.8
Current estrogen use, %	4.6	0.3
Current cigarette smoking, %	10.7	9.4
Prevalent stroke, %	4.4	6.1
Plasma homocysteine level, mg/L (μmol/L)	1.68 ± 0.78 (12.4 ± 5.8)	1.76 ± 0.84 (13.0 ± 6.2)
Femoral neck bone mineral density, g/cm ²	0.72 ± 0.11	0.87 ± 0.15
Radius bone mineral density, g/cm ²	0.51 ± 0.09	0.72 ± 0.09
Trochanter bone mineral density, g/cm ²	0.62 ± 0.13	0.84 ± 0.15

*Data are presented as mean ± SD unless otherwise indicated.

Using prospectively collected data from the Framingham Study cohort, we examined the association between BMD measured at 3 skeletal regions and the risk of developing incident AD.

METHODS

STUDY POPULATION

The original Framingham Study is a population-based prospective cohort study of 5209 participants (2336 men, 2873 women) who have been evaluated at biennial examinations for cardiovascular risk factors since 1948. Between 1975 and 1978, 2611 of these subjects were determined to be free of dementia¹⁴⁻¹⁶ (1061 men, 1550 women; mean ± SD age, 66 ± 7.4 years; range, 54-85 years). At examination cycle 20 (1988-1989), 1237 subjects from this cohort were alive and remained free of dementia. Of these, 987 subjects (377 men, 610 women) had BMD measurements and constituted our study population.

DEMENTIA EVALUATION

The dementia evaluation procedures of the Framingham dementia study have previously been described.¹⁵ All subjects identified as having dementia satisfied the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria,¹⁷ had dementia of severity greater than or equal to 1 on the Clinical Dementia Rating scale, and had symptoms of dementia for a period of at least 6 months. All subjects identified as having AD dementia met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and

Related Disorders Association (NINCDS-ADRDA)¹⁸ criteria for probable or possible AD.

BMD MEASUREMENT

The BMDs of the femur (neck and trochanter) and the distal third of the radius were measured in members of the cohort who came for the 20th biennial examination in 1988 or 1989 using dual-photon absorptiometry for the hip (DP3; Lunar Corp, Madison, Wis) and single-photon absorptiometry for the distal third of the radius (LUNAR SP2; Lunar Corp). The coefficients of variation were 2.65% for the femoral neck and 2.80% for the trochanter. The coefficient of variation for the distal third of the radius was 3.94%.¹⁹

STATISTICAL ANALYSES

Age is a strong determinant of both dementia and BMD. Thus, we adjusted for age by stratifying subjects into 5-year age groups and assigning each subject to 1 of 4 quartiles of BMD according to the distribution for his or her sex and age group. Separate models were created for BMD at the femoral neck, trochanter, and radius. Kaplan-Meier survival curves were used to determine the cumulative incidence rate of AD for each quartile of BMD. We used Cox proportional hazards model, adjusting for (1) age and sex alone and (2) age, sex, education, baseline homocysteine levels, apolipoprotein E ε4 status, cigarette smoking, estrogen use, and stroke to determine the risk of AD for each age-specific quartile of BMD taken from the 3 different sites. Secondary analyses were performed that excluded all subjects with a history of stroke and controlled for degree of physical activity as measured by the physical activity index at examination cycle 20.

RESULTS

Baseline characteristics of subjects at the 1988-1989 examinations are presented in **Table 1**. Men and women were similar in most characteristics; as expected, men had greater BMD than women at all skeletal sites. Compared with subjects without BMD measures, subjects who had measurements were younger and more physically active and had higher body mass index, lower prevalent stroke cases, lower plasma homocysteine levels, and higher Mini-Mental State Examination scores.

During a mean ± SD follow-up period of 8.3 ± 3.4 years (range, 1-14 years), 384 of the 987 subjects died. A total of 95 subjects developed dementia, 75 of whom were classified as having AD. As shown in **Table 2** and **Table 3**, of the 243 subjects in the lowest quartile (Q1) of femoral neck BMD, 35 developed dementia (27 with AD), and among the 744 people in the other 3 quartiles (Q2-4), 60 developed dementia (45 with AD). There was no clear linear trend across increasing age-specific BMD quartiles.

As shown in **Table 4**, after adjusting for age, women in the lowest quartile of femoral neck BMD (Q1) had more than twice the risk of developing AD as women in the other 3 quartiles (Q2-4) (relative risk [RR], 2.37; 95% confidence interval [CI], 1.34-4.17; *P* = .003), and more than twice the risk for all-cause dementia (RR, 2.24; 95% CI, 1.34-3.75; *P* = .002) (**Table 5**). The increased risk for AD and all-cause

Table 2. Multivariable Cox Proportional Hazards Models Examining the Relationship Between Bone Mineral Density (BMD) and the Risk of Alzheimer Disease

BMD Measurement Site	BMD Quartile*	No. of Cases/No. of Subjects	Relative Risk, Unadjusted (95% Confidence Interval)	P Value	Relative Risk, Adjusted for Age and Sex (95% Confidence Interval)	P Value	Relative Risk, Adjusted for All Covariates (95% Confidence Interval)	P Value
Femoral neck	Q1	27/243	NA	NA	NA	NA	NA	NA
	Q2	16/247	.53 (0.29-1.00)	.049	.53 (0.29-1.0)	.049	.57 (0.29-1.12)	.10
	Q3	12/251	.36 (0.18-0.72)	.004	.37 (0.18-0.73)	.004	.43 (0.21-0.88)	.02
	Q4	17/246	.51 (0.28-0.95)	.04	.52 (0.28-0.96)	.04	.65 (0.34-1.27)	.21
Trochanter	Q1	23/241	NA	NA	NA	NA	NA	NA
	Q2	15/244	.69 (0.36-1.33)	.27	.70 (0.37-1.35)	.29	.83 (0.42-1.63)	.58
	Q3	17/247	.64 (0.34-1.21)	.17	.65 (0.39-1.21)	.17	.66 (0.32-1.35)	.25
	Q4	17/242	.70 (0.37-1.30)	.26	.70 (0.37-1.31)	.26	.90 (0.46-1.75)	.76
Radius	Q1	17/231	NA	NA	NA	NA	NA	NA
	Q2	19/245	.93 (0.48-1.79)	.82	.93 (0.48-1.79)	.82	1.21 (0.59-2.47)	.60
	Q3	20/251	.98 (0.51-1.89)	.96	.98 (0.51-1.88)	.94	1.19 (0.57-2.46)	.64
	Q4	14/239	.76 (0.37-1.54)	.44	.76 (0.37-1.54)	.44	1.25 (0.59-2.67)	.56

Abbreviation: NA, not applicable.

*Age- and sex-specific quartiles of BMD, from Q1 (lowest) to Q4 (highest).

Table 3. Multivariable Cox Proportional Hazards Models Examining the Relationship Between Bone Mineral Density (BMD) and the Risk of Dementia

BMD Measurement Site	BMD Quartile*	No. of Cases/No. of Subjects	Relative Risk, Unadjusted (95% Confidence Interval)	P Value	Relative Risk, Adjusted for Age and Sex (95% Confidence Interval)	P Value	Relative Risk, Adjusted for All Covariates (95% Confidence Interval)	P Value
Femoral Neck	Q1	35/243	NA	NA	NA	NA	NA	NA
	Q2	23/247	.61 (0.36-1.04)	.07	.61 (0.36-1.04)	.07	.58 (0.32-1.04)	.02
	Q3	15/251	.36 (0.20-0.67)	.001	.36 (0.20-0.67)	.001	.42 (0.23-0.80)	.008
	Q4	22/246	.53 (0.31-0.91)	.02	.53 (0.31-0.91)	.02	.61 (0.34-1.09)	.09
Trochanter	Q1	33/241	NA	NA	NA	NA	NA	NA
	Q2	20/244	.64 (0.37-1.13)	.11	.64 (0.37-1.11)	.11	.77 (0.43-1.37)	.37
	Q3	21/247	.57 (0.33-0.98)	.04	.57 (0.33-0.98)	.04	.56 (0.29-1.02)	.07
	Q4	21/242	.61 (0.35-1.05)	.07	.61 (0.35-1.05)	.08	.77 (0.43-1.38)	.38
Radius	Q1	23/231	NA	NA	NA	NA	NA	NA
	Q2	26/245	.97 (0.55-1.70)	.91	.97 (0.55-1.70)	.91	1.34 (0.72-2.49)	.35
	Q3	24/251	.90 (0.51-1.61)	.72	.90 (0.51-1.61)	.73	1.05 (0.54-2.03)	.89
	Q4	19/239	.77 (0.42-1.42)	.40	.77 (0.42-1.42)	.41	1.24 (0.64-2.40)	.53

Abbreviation: NA, not applicable.

*Age- and sex-specific quartiles of BMD, from Q1 (lowest) to Q4 (highest).

Table 4. Relationship of Femoral Neck Bone Mineral Density to the Risk of Alzheimer Disease (Q1 vs Q2-4)*

	Relative Risk, Unadjusted (95% Confidence Interval)	P Value	Relative Risk, Adjusted for Age and Sex (95% Confidence Interval)	P Value	Relative Risk, Adjusted for All Covariates (95% Confidence Interval)	P Value
Women	2.36 (1.34-4.16)	.003	2.37 (1.34-4.17)	.003	2.04 (1.11-3.75)	.02
Men	1.72 (0.65-4.60)	.28	1.66 (0.62-4.43)	.31	1.33 (0.46-3.86)	.60
Women and men	2.14 (1.31-3.48)	.002	2.13 (1.31-3.47)	.002	1.83 (1.09-3.10)	.02

*Age- and sex-specific quartiles of bone mineral density, from Q1 (lowest) to Q4 (highest).

dementia persisted after adjusting for smoking, ERT, stroke, education, apolipoprotein E ε4, baseline homocysteine levels, and age (RR, 2.04; 95% CI, 1.11-3.75; $P=.02$; and RR, 2.01; 95% CI, 1.16-3.49; $P=.01$, respectively). This inverse relationship was also observed for trochanteric BMD and AD risk (RR, 1.77; 95% CI, 1.00-3.11; $P=.049$), although the results were no longer sta-

tistically significant after adjustment for covariates ($P=.14$). A similar relationship was found between trochanteric BMD and all-cause dementia. We found no relationship between BMD measured at the radial shaft and the risk of AD (RR, 1.13; 95% CI, 0.58-2.18; $P=.72$) and all-cause dementia, and no statistically significant relationships between BMD measured at the

Table 5. Relationship of Femoral Neck Bone Mineral Density to the Risk of All Dementias (Q1 vs Q2-4)*

	Relative Risk, Unadjusted (95% Confidence Interval)	P Value	Relative Risk, Adjusted for Age and Sex (95% Confidence Interval)	P Value	Relative Risk, Adjusted for All Covariates (95% Confidence Interval)	P Value
Women	2.24 (1.34-3.74)	.002	2.24 (1.34-3.75)	.002	2.01 (1.16-3.49)	.01
Men	1.69 (0.79-3.62)	.17	1.66 (0.77-3.54)	.19	1.66 (0.71-3.88)	.24
Women and men	2.01 (1.32-3.07)	.001	2.01 (1.32-3.07)	.001	1.88 (1.19-2.97)	.007

*Age- and sex-specific quartiles of bone mineral density, from Q1 (lowest) to Q4 (highest).

femoral neck, trochanter, or radius and risk of AD or all-cause dementia in male subjects. The exclusion of all subjects with a history of stroke and additionally controlling for the degree of physical activity did not significantly alter the elevated risk of AD and dementia in women in the lowest quartile of femoral neck BMD.

COMMENT

The results of this prospective, observational study indicate an association between low femoral neck BMD and risk of subsequent AD dementia in women that may be attributed to a protective role of cumulative estrogen exposure. Plausible biological mechanisms support the protective role of estrogen in cognitive function and dementia. Estrogen receptors are found in several brain regions, including the CA1 region of the hippocampus, a region associated with memory and learning.²⁰ In vitro studies have shown a potential beneficial effect of estrogen on β -amyloid accumulation and neurotoxicity.²¹

Previous studies of ERT and cognitive performance have found that ERT reduced the risk of dementia in cognitively intact individuals²²⁻²⁴ and improved cognitive function in those suffering from dementia.²⁵ A meta-analysis of 29 studies showed a significant reduction (RR, 0.66) in the relative risk of AD in women taking postmenopausal estrogen replacement.²⁶ Despite this finding, epidemiological studies examining the relationship between estrogen replacement and dementia have encountered substantial methodological problems and produced conflicting results.^{4,27} Differences in education, age, and health behaviors among women who are prescribed and choose to take estrogen made these studies inherently susceptible to bias.²⁸ In addition, such potentially important variables as the type of estrogen preparation and the length of estrogen use are difficult to control and ascertain.

Bone mineral density may be a reliable surrogate marker for cumulative endogenous estrogen exposure. As a surrogate marker of lifetime estrogen exposure, BMD has been shown to be significantly associated with an increased risk of postmenopausal breast cancer^{11,12} and a decreased risk of colon cancer, both of which are influenced by estrogen.¹³ Using BMD as a marker of cumulative estrogen exposure, studies have shown a correlation between low BMD and poor cognitive performance.^{29,30} Additionally, nondemented older women with low BMD measurements have been found to be at greater risk for cognitive decline.³¹

In this study, lower femoral neck BMD increased the risk of developing AD and all-cause dementia. This relation was modestly attenuated at the trochanter site and became statistically nonsignificant after adjustment for covariates. Further, the relation between BMD and incidence of AD was not observed at all for the radius site. The lack of consistency between sites of BMD measurement and the risk of AD is difficult to explain, but it may be due to the fact that the metabolically more active trabecular bone makes up a greater percentage of bone in the hip compared with the radius. Although studies have reported significant correlations between BMD measurement sites, the degree of correlation decreases with age, as rates of bone loss vary between sites. For example, it has been shown that while the correlation between BMD measured at the femoral neck and spine at age 65 to 69 years was 0.65, the correlation was only 0.49 at age 85 years or older.³¹ Metabolically more active trabecular bone, which is minimal at the radial shaft, has a higher turnover rate compared with cortical bone, which is more abundant in the radius. These observations may partly explain the observed lack of consistency of the relationship between radial BMD and the risk of AD and all-cause dementia. Nevertheless, these inconsistencies between bone sites require that our findings be confirmed in other populations. In addition, the primarily white American population in this study limits the applicability of the conclusions drawn from this study to other populations.

The recent discontinuation of the estrogen and progesterone arm of the Women's Health Initiative trial due to the increased risk of breast cancer and cardiovascular complications and the discontinuation of the estrogen-only arm due to an increased risk of stroke in women receiving these medications will make it more difficult to draw conclusions regarding the role of ERT in the prevention or treatment of AD and other forms of dementia. The Women's Health Initiative has shown that postmenopausal estrogen replacement actually increases the risk of dementia, but lifelong estrogen exposure has not been addressed with that study design. To our knowledge, this is the first study to report an increase in the risk of AD in women with the lowest BMD at the femoral neck. This finding suggests that women with a low BMD are at highest risk for dementia and may benefit from ERT despite the increased risk of nonneurologic complications. Controlled trials of prophylactic ERT may be justified in this high-risk subgroup if additional studies confirm our finding of a strong association between a lower BMD and the risk of dementia in women.

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