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 ε4, 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.

Arch Neurol. 2005;62:107-111
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 1973 and 1978, 2611 of these subjects were determined to be free of dementia.14-16 (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 measurements, 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 dementia in women in the lowest quartile of femoral neck BMD remained significant even after adjustment for education, homocysteine levels, cigarette smoking, and estrogen use.
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 statistically 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>
<thead>
<tr>
<th>BMD Measurement Site</th>
<th>BMD Quartile*</th>
<th>No. of Cases/No. of Subjects</th>
<th>Relative Risk, Unadjusted (95% Confidence Interval)</th>
<th>( P ) Value</th>
<th>Relative Risk, Adjusted for Age and Sex (95% Confidence Interval)</th>
<th>( P ) Value</th>
<th>Relative Risk, Adjusted for All Covariates (95% Confidence Interval)</th>
<th>( P ) Value</th>
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</thead>
<tbody>
<tr>
<td>Femoral neck</td>
<td>Q1</td>
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<td></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td></td>
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<tr>
<td></td>
<td>Q2</td>
<td>16/247</td>
<td>.53 (0.29-1.00)</td>
<td>.049</td>
<td>.53 (0.29-1.0)</td>
<td>.049</td>
<td>.57 (0.29-1.12)</td>
<td>.10</td>
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<td>Q3</td>
<td>12/251</td>
<td>.36 (0.18-0.72)</td>
<td>.004</td>
<td>.37 (0.18-0.73)</td>
<td>.004</td>
<td>.43 (0.21-0.88)</td>
<td>.02</td>
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<tr>
<td></td>
<td>Q4</td>
<td>17/246</td>
<td>.51 (0.28-0.96)</td>
<td>.049</td>
<td>.52 (0.28-0.96)</td>
<td>.049</td>
<td>.65 (0.34-1.27)</td>
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<td>Trochanter</td>
<td>Q1</td>
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<td>NA</td>
<td></td>
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<td></td>
<td>Q2</td>
<td>15/244</td>
<td>.69 (0.36-1.33)</td>
<td>.004</td>
<td>.70 (0.37-1.35)</td>
<td>.004</td>
<td>.83 (0.42-1.63)</td>
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<td>.64 (0.34-1.21)</td>
<td>.004</td>
<td>.65 (0.39-1.21)</td>
<td>.004</td>
<td>.66 (0.32-1.35)</td>
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<td></td>
<td>Q4</td>
<td>17/242</td>
<td>.70 (0.37-1.30)</td>
<td>.004</td>
<td>.70 (0.37-1.31)</td>
<td>.004</td>
<td>.90 (0.46-1.75)</td>
<td>.76</td>
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<td></td>
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<td></td>
<td>NA</td>
<td></td>
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<tr>
<td></td>
<td>Q2</td>
<td>19/245</td>
<td>.93 (0.48-1.79)</td>
<td>.004</td>
<td>.93 (0.48-1.79)</td>
<td>.004</td>
<td>1.21 (0.59-2.47)</td>
<td>.60</td>
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<td></td>
<td>Q3</td>
<td>20/251</td>
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<td>.004</td>
<td>.98 (0.51-1.88)</td>
<td>.004</td>
<td>1.19 (0.57-2.46)</td>
<td>.64</td>
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<tr>
<td></td>
<td>Q4</td>
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<td>.76 (0.37-1.54)</td>
<td>.004</td>
<td>.76 (0.37-1.54)</td>
<td>.004</td>
<td>1.25 (0.59-2.67)</td>
<td>.56</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

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

<table>
<thead>
<tr>
<th>Relative Risk, Unadjusted (95% Confidence Interval)</th>
<th>( P ) Value</th>
<th>Relative Risk, Adjusted for Age and Sex (95% Confidence Interval)</th>
<th>( P ) Value</th>
<th>Relative Risk, Adjusted for All Covariates (95% Confidence Interval)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>2.36 (1.34-4.16)</td>
<td>.003</td>
<td>2.37 (1.34-4.17)</td>
<td>.003</td>
<td>2.04 (1.11-3.75)</td>
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<tr>
<td>Men</td>
<td>1.72 (0.65-4.60)</td>
<td>.002</td>
<td>1.66 (0.62-4.43)</td>
<td>.002</td>
<td>1.83 (1.09-3.10)</td>
</tr>
<tr>
<td>Women and men</td>
<td>2.14 (1.31-3.48)</td>
<td>.002</td>
<td>2.13 (1.31-3.47)</td>
<td>.002</td>
<td>1.83 (1.09-3.10)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*Age- and sex-specific quartiles of bone mineral density, from Q1 (lowest) to Q4 (highest).
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. In vitro studies have shown a potential beneficial effect of estrogen on β-amyloid accumulation and neurotoxicity.

Previous studies of ERT and cognitive performance have found that ERT reduced the risk of dementia in cognitively intact individuals and improved cognitive function in those suffering from dementia. 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. Despite this finding, epidemiological studies examining the relationship between estrogen replacement and dementia have encountered substantial methodological problems and produced conflicting results. Differences in education, age, and health behaviors among women who are prescribed and choose to take estrogen made these studies inherently susceptible to bias. 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 and a decreased risk of colon cancer, both of which are influenced by estrogen. Using BMD as a marker of cumulative estrogen exposure, studies have shown a correlation between low BMD and poor cognitive performance. Additionally, non-demented older women with low BMD measurements have been found to be at greater risk for cognitive decline.

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. 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk, Unadjusted (95% Confidence Interval)</th>
<th>P Value</th>
<th>Relative Risk, Adjusted for Age and Sex (95% Confidence Interval)</th>
<th>P Value</th>
<th>Relative Risk, Adjusted for All Covariates (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>2.24 (1.34-3.74)</td>
<td>.002</td>
<td>2.24 (1.34-3.75)</td>
<td>.002</td>
<td>2.01 (1.16-3.49)</td>
<td>.01</td>
</tr>
<tr>
<td>Men</td>
<td>1.69 (0.79-3.62)</td>
<td>.17</td>
<td>1.66 (0.77-3.54)</td>
<td>.19</td>
<td>1.66 (0.71-3.58)</td>
<td>.24</td>
</tr>
<tr>
<td>Women and men</td>
<td>2.01 (1.32-3.07)</td>
<td>.001</td>
<td>2.01 (1.32-3.07)</td>
<td>.001</td>
<td>1.88 (1.19-2.97)</td>
<td>.007</td>
</tr>
</tbody>
</table>

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

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REFERENCES


