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Bone Mineral Density and Verbal Memory Impairment

Third National Health and Nutrition Examination Survey

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Previous studies have examined the relation of endogenous estrogen levels or estrogen replacement therapy to the risk of poor cognitive function, but results have been inconclusive. Bone mineral density has been proposed as a marker for cumulative estrogen exposure. The authors studied the relation of bone mineral density to the prevalence of verbal memory impairment among 4,304 elderly subjects in the Third National Health and Nutrition Examination Survey (1988–1994). Bone mineral density was measured in five regions of the proximal femur with dual-energy x-ray absorptiometry. Verbal memory was assessed using delayed recall of a three-item word list and a six-item story. Verbal memory impairment was defined as a combined score of <4. The prevalence of verbal memory impairment for each increasing bone mineral density quintile at the femoral neck was 8.35, 5.74, 5.22, 5.00, and 3.38% in women and 11.54, 7.27, 8.47, 6.29, and 5.89% in men, respectively. With adjustment for age, sex, and other covariates, the prevalence ratios of verbal memory impairment for each increased bone mineral density quintile were 1.00, 0.64, 0.65, 0.55, and 0.44, respectively (p for trend < 0.001). These results suggest that bone mineral density in the elderly is associated with verbal memory impairment. The mechanisms underlying this relation are not understood, but cumulative exposure to estrogen may play a role. *Am J Epidemiol* 2001;154:795–802.

bone density; estrogens; memory

Over the past decades, evidence from animal studies indicates that estrogen affects neuronal survival and physiology in brain areas vital to memory function (1). However, studies relating estrogen to memory and various other measures of cognitive performance in human populations have been equivocal. Some investigators have reported that low levels of serum endogenous estrogen assessed from a single measurement were associated with an increased risk of poor verbal memory (2, 3), while others have failed to confirm this (4). Estrogen replacement therapy administered to postmenopausal women has been associated with improved verbal memory in some studies (5–9) but not in all (10, 11).

If estrogen does improve memory, one would expect that women with a greater cumulative estrogen exposure during their lifetime would experience a lower prevalence of memory impairment. However, because of methodological and logistic problems, adequate assessment of cumulative estrogen exposure has been difficult. Several investigators have proposed that bone mineral density may serve as a marker of cumulative estrogen exposure in women (12, 13). We and other investigators have shown that high bone mass and bone mineral density are strongly associated with an increased risk of breast cancer among women (14, 15). Studies have shown that estradiol, the major circulating form of estrogen, plays an important role in bone metabolism not only in women but also in elderly men (16–19). A case-control study conducted among Japanese women suggested that dementia was associated with low bone mineral density (20). Recently, Yaffe et al. (21) reported that high bone mineral density in women was associated with improved cognitive function; their study evaluated a global index of cognition and tests of attention, executive function, and psychomotor speed rather than focusing on verbal memory.

Verbal memory impairment is one of the strongest predictors for the future development of dementia or Alzheimer's disease (22, 23) and is the single cognitive index most often related to estrogen deficiency in human studies (7, 23, 24). To our knowledge, previous studies have not examined the relation of cumulative estrogen exposure assessed by bone mineral density to the risk of memory impairment in either women or men. We used data from the Third National Health and Nutrition Examination Survey (NHANES III) (25) to examine the relation of bone mineral density to the prevalence of verbal memory impairment among elderly men and women.

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Abbreviations: CI, confidence interval; NHANES III, Third National Health and Nutrition Examination Survey.

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MATERIALS AND METHODS

NHANES III was a cross-sectional survey to obtain nationally representative information on the health and nutritional status of the civilian, noninstitutionalized, US population. The survey began in the fall of 1988 and was completed in the fall of 1994, with oversampling of the elderly, children under age 5 years, African Americans, and Mexican Americans. NHANES III consisted of two separate components, that is, the survey and the medical examination. The survey was conducted at the participant's home by interviewers using the Household Adult Questionnaire and Family Questionnaire, followed shortly thereafter by a standardized medical examination performed at either the Mobile Examination Center or the subject's home by physicians and health technicians. A total of 6,596 persons aged 60 years or over completed the Household Adult Questionnaire, and 5,302 of these persons had a health examination at the Mobile Examination Center.

Bone mineral density measurement

Bone mineral density measurements were made with dual-energy x-ray absorptiometry among subjects aged 20 years or over. Areal bone mineral density was measured in five regions in the proximal femur: femoral neck, trochanter, intertrochanter, Ward's triangle, and total region (25). Bone mineral density was assessed in 4,818 subjects over 60 years of age; of these, 4,697 subjects had valid measurements.

Cognitive function assessment

Among subjects 60 years of age or over, cognitive function was assessed at the home examination and at the Mobile Examination Center. No specific attempt was made to exclude the subjects with cognitive impairment from the memory test. In one section of the Household Adult Questionnaire, the interviewer recited a list of three items: "apple," "table," and "penny." Subjects were then asked to repeat the three items until they had learned all three. About 7.6 percent of the subjects were unable to learn all three items (i.e., they learned two, one, or none of the items) after the interviewer repeated these three words three times. After performing an unrelated task, all subjects (regardless of whether or not they could repeat the three items immediately) were asked to recall the three items. This is referred to as a delayed item recall. One point was awarded for the recall of each item with a total score ranging from 0 to 3.

During the health examination, subjects were read the following story. "Three children were alone at home and the house caught on fire. A brave fireman managed to climb in a back window and carry them to safety. Aside from minor cuts and bruises, all were well." Subjects were asked to repeat the story immediately after it was read to them. After a few minutes of answering unrelated questions, the subjects were again asked to repeat the story. This was referred to as a delayed story recall. One point was scored for each of the following ideas, if present in the answer: three children, house on fire, fireman climbed in the house, children rescued, minor injuries, and everyone was well. Therefore, a total score for the recall of the story ranged from 0 to 6.

We combined scores from the "delayed item recall" and the "delayed story recall" to yield a summary score for verbal memory ranging from 0 to 9. In the current analysis, we adopted the same definition as that proposed by Pekins et al. (26) to classify verbal memory impairment among the participants in NHANES III. In that analysis, a subject was considered to have verbal memory impairment if his or her summary score was less than 4 (26).

Other risk factors

Information on other potential risk factors associated with impairment of verbal memory was also collected. Such factors included age, gender, racial/ethnic origin, number of years of education, income, smoking history (never, former, current), lifetime abstention from alcohol, and history of stroke. For women, information on hormone replacement therapy was also collected. Subjects were defined as having hypertension if their systolic blood pressure was greater than or equal to 140 mmHg, or if their diastolic blood pressure was greater than or equal to 90 mmHg, or if they answered positively to the question: "Have you ever been told by a doctor or other health professional that you have hypertension, also called high blood pressure?"

Statistical analysis

In this analysis, we include non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans; the number of subjects of other racial/ethnic origin was too small to generate valid estimates.

Because age, sex, and race/ethnicity are important determinants of memory and because subjects in older age groups, females, and non-Hispanic Whites had lower bone mineral density than those at a younger age, males, and non-Hispanic Blacks, we created age-, gender-, and race/ethnicity-specific categories based on femoral neck bone mineral density. Specifically, we stratified all subjects into 96 strata according to gender (two groups: male and female), age (16 groups: 2-year age intervals), and ethnicity (three groups: non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans). Within each stratum we assigned each subject to a quintile of bone mineral density.

We calculated the prevalence of verbal memory impairment across different categories of potential confounding factors for men and women separately. We estimated the prevalence of verbal memory impairment according to the quintile of bone mineral density and fitted a logistic regression model to examine the relation of bone mineral density to the prevalence of verbal memory impairment. In a multiple logistic regression model, we adjusted for education, alcohol consumption, smoking status, income, history of stroke, and hypertension. Because the association between bone mineral density and the prevalence of verbal memory impairment was similar among men and women, we also estimated the effect for both genders combined.

We tested the significance of the trend in the prevalence of verbal memory impairment by including a single variable of quintile of bone mineral density in the multivariable model. To determine whether the association between bone mineral density and prevalence of verbal memory impairment was modified by other risk factors, we examined the effect of bone mineral density at the femur neck within strata of other risk factors. We tested for statistical significance of effect modification by including an interaction term in the multivariable regression model. To evaluate whether the association between bone mineral density and prevalence of verbal memory impairment observed at the femoral neck would also hold true at other bony sites, we also assessed the effect of bone mineral density in other proximal femur sites: trochanter, intertrochanter, Ward's triangle, and total proximal region.

To examine whether the association between bone mineral density and prevalence of verbal memory impairment may vary depending on the cutpoint of the combined verbal memory score, we tested our results using two other cutpoints for verbal memory impairment, that is, summary score of <3 or summary score of <5.

Because NHANES III data were collected using a complex sampling design, we used sample weights in all analyses to account for unequal probability of selection and nonresponse and to produce an estimate of prevalence that was representative of the noninstitutionalized, civilian, US population. We used SUDAAN statistical software (27) to incorporate sample weights and to account for the complex survey design in the variance estimates.

RESULTS

Of the 6,596 subjects aged 60 years or over in NHANES III, 872 did not have a health examination, 422 received only a home examination, 159 were of other racial and ethnic groups, 337 had missing information on memory testing (54 subjects had missing information on both tests, 112 subjects had missing information on a delayed item recall only, and 171 subjects had missing information on a delayed story recall), 480 had missing or unacceptable bone mineral density data (30 subjects did not have bone mineral density measured, and in 450 subjects bone mineral density measurements were excluded because the values were considered outliers), and 22 had missing data on other potential risk factors. These subjects ($n = 2,292$) were excluded from the analysis. The characteristics of the excluded subjects were similar to those of the remaining subjects with regard to distribution by gender, smoking status, and history of hypertension. However, compared with excluded subjects, those remaining in the analysis were younger ($p < 0.001$), more likely to be non-Hispanic Whites ($p < 0.001$), and better educated; they also had a lower percentage of lifetime abstention from alcohol ($p = 0.015$), higher annual income ($p < 0.001$), and a lower prevalence of self-reported prior stroke ($p = 0.001$). Of the remaining 4,304 subjects, the average score on testing verbal memory was 6.65 (standard error, 0.04), with 1.15 percent of subjects scoring 0, 0.82 percent scoring 1, 1.64 percent scoring 2, 2.94 percent scoring 3, and 5.13 percent scoring 4.

Table 1 presents the prevalence of verbal memory impairment according to potential confounding factors in men and women, respectively. A higher prevalence of verbal memory impairment was associated with older age, non-Hispanic Black ethnicity, fewer years of education, lower annual family income, and lifetime alcohol abstinence among men and women. Men with a history of stroke and nonsmoking women showed a higher prevalence of verbal memory impairment.

The prevalence of verbal memory impairment decreased as bone mineral density at the femur neck increased in both men and women (table 2). Compared with those in the lowest quintile of bone mineral density, the multivariable-adjusted prevalence odds ratios of verbal memory impairment for men and women combined in each increased quintile of bone mineral density were 0.64 (95 percent confidence interval (CI): 0.43, 0.95), 0.65 (95 percent CI: 0.45, 0.92), 0.55 (95 percent CI: 0.35, 0.87), and 0.44 (95 percent CI: 0.28, 0.69), respectively (p for trend < 0.001). A similar association was also found when the different cutpoints of combined score (<3 and <5) were used to define verbal memory impairment (data not presented). Significant associations were also observed between bone mineral density at other proximal femoral sites and the prevalence of verbal memory impairment (data not presented). In light of the possibility that smoking and alcohol consumption could have a direct effect on estrogen levels, so that adjusting for these factors might diminish the association between bone mineral density and verbal memory impairment, we removed these two risk factors from the regression model; the results did not change materially.

An association between higher bone mineral density and a lower prevalence of verbal memory impairment was consistent across various strata of other risk factors, with the exceptions being for Mexican Americans and current smokers (table 3). No statistically significant interaction was found between bone mineral density and verbal memory impairment according to other risk factors.

DISCUSSION

Our results suggest that there is an association between bone mineral density and the prevalence of verbal memory impairment among the elderly: The prevalence of verbal memory impairment decreased with increasing bone mineral density. This relation was consistent across almost all strata of potential confounding factors and was robust when different cutpoints were used to define verbal memory impairment. Although the biologic mechanisms that link high bone mineral density to a low prevalence of verbal memory impairment are not fully understood, a high cumulative estrogen exposure is one compelling explanation. Thus, our results suggest that high levels of long-term estrogen exposure may be a critical element in the preservation of verbal memory with aging.

To date, evidence for the beneficial effect of estrogen on cognitive function in human subjects comes mainly from studies of estrogen replacement therapy in postmenopausal women. A few studies have indicated that estrogen replacement therapy may improve verbal memory in healthy women

TABLE 1. Prevalence of verbal memory impairment according to characteristics of subjects, Third National Health and Nutrition Examination Survey, 1988–1994

Characteristics	Men (n = 2,115)		Women (n = 2,189)	
	Prevalence (%)	p value	Prevalence (%)	p value
Age (years)				
60–64	2.7		2.5	
65–69	5.2		2.0	
70–74	6.4		3.5	
75–79	13.9		7.1	
80–84	20.2		15.2	
≥85	27.4	<0.001	19.6	<0.001
Race/ethnicity				
Non-Hispanic Whites	6.3		4.4	
Non-Hispanic Blacks	24.3		15.2	
Mexican Americans	14.8	<0.001	16.5	<0.001
Education (years)				
0–8	18.6		13.6	
9–11	7.7		6.1	
12	4.1		3.1	
>12	3.0	<0.001	2.1	<0.001
Income (dollars/year)				
<20,000	14.7		8.5	
≥20,000	3.3	<0.001	2.4	<0.001
Alcohol consumption				
Abstainer	14.6		12.3	
Ever-drinker	7.2	0.022	3.0	<0.001
Smoking				
Nonsmoker	9.5		7.3	
Past smoker	6.9		2.7	
Current smoker	8.4	0.266	4.3	<0.001
History of stroke				
No	7.3		5.3	
Yes	17.8	0.023	9.3	0.072
Hypertension				
No	8.0		5.9	
Yes	7.7	0.897	5.4	0.457

(6–8). Administration of estrogen to postmenopausal women has been reported to induce significant modifications in brain activation patterns as assessed by functional magnetic resonance imaging or by a positron emission tomography scan done while women perform verbal memory tasks (28, 29). Results from epidemiologic studies, however, often suggest that women who take estrogen replacement therapy tend to be healthier, better educated, and more physically active (30, 31). Thus, the positive impact of estrogen replacement therapy on memory function may be partly attributed to residual confounding effects.

Only a few studies have examined the endogenous estrogen level in relation to verbal memory. Phillips and Sherwin (2, 5) found that verbal memory was positively correlated with estradiol levels through the menstrual cycle and declined after surgical oophorectomy. Drake et al. (32) measured circulating sex hormone levels in 39 elderly, White, nondemented subjects and found that high estradiol levels were correlated with better performance on simultaneous tests of verbal memory. However, Yaffe et al. (4) did not find a consistent association between serum estrogen levels and subsequent cognitive decline among elderly women. The inconsistency among studies is probably due to measurement error in the assessment of serum estrogen levels, including fluctuation of endogenous estrogen levels over time and different assay methods in different studies. Furthermore, it is unlikely that a single measurement of serum estrogen indicates a woman's cumulative exposure to estrogen. Smith et al. (11) found that an index of lifetime estrogen exposure computed from menstrual and reproductive histories was associated with verbal abilities in elderly women. This index, however, is based on a retrospectively

TABLE 2. Relation of age-, sex-, and race-specific quintile of femur neck bone mineral density to prevalence of verbal memory impairment, Third National Health and Nutrition Examination Survey, 1988–1994

Bone density quintile	No. of cases	Prevalence (%)	Age-, sex-, race-adjusted OR*	Multivariable adjusted	
				OR	95% CI*
Men†					
1 (low)	67	11.54	1.0	1.0	
2	71	7.27	0.60	0.60	0.36, 1.01
3	64	8.47	0.71	0.71	0.43, 1.16
4	57	6.29	0.51	0.51	0.30, 0.86
5 (high)	46	5.89	0.48	0.53	0.31, 0.90
p for trend			$p = 0.012$		
Women†					
1 (low)	54	8.35	1.0	1.0	
2	44	5.74	0.67	0.65	0.37, 1.15
3	44	5.22	0.61	0.58	0.35, 0.97
4	52	5.00	0.58	0.59	0.35, 1.00
5 (high)	37	3.38	0.38	0.35	0.20, 0.61
p for trend			$p = 0.003$		
Men and women‡					
1 (low)	121	9.70	1.0	1.0	
2	115	6.40	0.63	0.64	0.43, 0.95
3	108	6.62	0.66	0.65	0.45, 0.92
4	109	5.55	0.55	0.55	0.35, 0.87
5 (high)	83	4.47	0.43	0.44	0.28, 0.69
p for trend			$p < 0.001$		

* OR, odds ratio; CI, confidence interval.
† Adjusted for age, race/ethnicity, education, alcohol consumption, smoking, income, history of stroke, and hypertension.
‡ Adjusted for age, sex, race/ethnicity, alcohol consumption, smoking, income, history of stroke, and hypertension.

ascertained history and may suffer from the biases inherent in such a method.

Estrogens may affect cognitive function through various mechanisms. Estradiol may decrease oxidative stress, inhibit neuronal apoptosis, and promote synaptogenesis and synaptic plasticity (33, 34). Estrogens also raise high density lipoprotein cholesterol levels, reduce atherosclerosis, inhibit endothelin-mediated vasoconstriction, promote vasodilatation, and by all these means improve cerebral blood flow (35–38).

The relation of estrogen level to bone mineral density has been recognized for decades. Numerous studies have shown that serum or urine estrogen levels are strongly associated with bone mineral density in pre- and postmenopausal women, and skeletal effects of low levels of estrogens are clearly seen after menopause or removal of the ovaries (39–44). In addition, women who have been receiving estrogen replacement therapy, especially long-term estrogen users, have significantly higher bone mineral density than do women who have never used estrogens (45, 46). These findings, in conjunction with our and other investigators' reports of an association between bone mass or bone mineral density and breast cancer risk (14, 15), suggest that skeletal status may serve as a proxy for cumulative estrogen exposure. Recently, Yaffe et al. (21) reported in a longitudinal study that women with lower baseline levels of bone mineral density and reductions in bone mineral density during the follow-up, or vertebral fractures, had poorer cognitive function and greater risk of cognitive deterioration. In their study, subjects on estrogen replacement therapy were excluded. In our main analysis we did not exclude subjects who were receiving estrogen replacement therapy, because we hypothesize that bone mineral density may serve as a marker of cumulative estrogen exposure, including exposure to exogenously administered estrogens. Nevertheless, when we excluded 628 women who had hormone replacement therapy from the analysis, a strong inverse relation between bone mineral density and prevalence of verbal memory impairment still exists.

Our findings of an association between bone mineral density and the prevalence of verbal memory impairment in men are intriguing. Animal studies have shown that high levels of endogenous androgens are associated with improved memory in mice (47). Administration of testosterone to hypogonadal men, however, failed to improve verbal memory (48). Instead, Kampen and Sherwin (49) found that circulating levels of estradiol, but not testosterone, were associated with better performance on tests of visual memory. To our knowledge, no prior study has examined the relation of bone mineral density to the risk of verbal memory impairment in men. Studies have shown that testosterone, the predominant circulating androgen in men, is positively correlated with bone mineral density in young adult men (50–52). Such an association, however, has been weak and inconsistent in elderly men (52–56). More recently, evidence has been accumulated that estradiol levels are strongly associated with bone mineral density in men (16–19). Thus, high levels of cumulative estrogen exposure may be one of the explanations for an inverse relation between bone mineral density and verbal memory impairment in men. Nevertheless, there may be other, as yet unknown, mechanisms that result in both an increased prevalence of verbal memory impairment and a decreased bone mineral density.

This study has several limitations. First, the findings were based on a cross-sectional survey; thus, we were unable to establish the temporal relation between bone mineral density and verbal memory impairment. For instance, it is possible that subjects with severe verbal memory impairment would be unable to maintain their previous levels of physical activity, resulting in loss of bone mineral density. If that were the case, adjusting for physical activity level would diminish an association between bone mineral density and verbal memory impairment. Despite the fact that subjects with a low physical activity level had a higher prevalence of verbal memory impairment in NHANES III, adding physical activity level into the model had little, if any, effect on the association. Similarly, subjects with a low verbal memory score may not practice other lifestyle measures that are associated with a high bone mineral density. Second, we

TABLE 3. Multivariable-adjusted odds ratios* of femur neck bone mineral density to prevalence of verbal memory impairment according to other risk factors, Third National Health and Nutrition Examination Survey, 1988–1994

Risk factor	Bone mineral density quintiles (low to high)					*p* for trend
	1†	2	3	4	5	
Race/ethnicity						
Non-Hispanic Whites	1.0	0.59	0.56	0.46	0.38	<0.001
Non-Hispanic Blacks	1.0	0.73	0.99	0.75	0.46	0.106
Mexican Americans	1.0	1.33	0.77	1.43	1.11	0.673
Education (years)						
<12	1.0	0.67	0.78	0.68	0.44	0.004
≥12	1.0	0.47	0.43	0.32	0.40	0.026
Income of <$20,000/year						
Yes	1.0	0.49	0.82	0.73	0.46	0.267
No	1.0	0.64	0.59	0.49	0.42	0.001
Alcohol consumption						
Abstainer	1.0	1.78	1.34	0.89	0.59	0.214
Ever-drinker	1.0	0.37	0.45	0.38	0.46	0.002
Smoking history						
Nonsmokers	1.0	0.57	0.64	0.57	0.36	0.003
Past smokers	1.0	0.35	0.61	0.28	0.37	0.016
Current smokers	1.0	1.29	0.65	1.29	0.98	0.970
History of stroke						
Yes	1.0	0.70	2.04	0.59	0.17	0.144
No	1.0	0.54	0.53	0.49	0.43	0.002
Hypertension						
Yes	1.0	0.79	0.92	0.74	0.54	0.013
No	1.0	0.37	0.33	0.31	0.34	0.007

* Adjusted for age, sex, race/ethnicity, education, alcohol consumption, smoking, income, history of stroke, and hypertension.
† Reference group.

were unable to adjust for some other potential confounding factors, such as nutrition factors and general health status; the residual confounding effects due to these factors may account for such an association. Studies have shown that depression in women is associated with a decreased bone mineral density, and depression has also been related to verbal memory impairment (57). We were unable to control for the effect of depression because mood was not assessed among subjects aged over 60 years in NHANES III; nevertheless, the effect of depression on memory impairment is modest and unlikely to explain these findings (58). Third, subjects with severe verbal memory impairment may have been less likely to participate in NHANES III; this nonresponse bias would lead to an underestimation of the prevalence of verbal memory impairment. However, there is no reason to speculate that the nonrespondents, who were older and had lower incomes than did the respondents, would have a higher bone mineral density when compared with the respondents who had memory impairment. Finally, this analysis focuses on the prevalence of significant memory impairment and does not address the association between bone mineral density and milder degrees of memory loss.

The current study has several strengths as well. Numerous studies have shown that, among cognitive functions, verbal memory impairment is one of the strongest predictors of the risk of dementia (22, 23); thus, the current findings are clearly of clinical relevance. Second, the verbal memory test used in this analysis consists of a simple three-item recall test and a more challenging six-component story recall test; the three-item test helps to reduce the chances of a "floor effect." Finally, the combined score allowed us to use different cutpoints to define verbal memory impairment so that we were able to perform sensitivity analyses. The method used to assess bone mineral density is state-of-the-art, so misclassification of exposure is unlikely to account for our findings. In addition, the participants of the NHANES III were randomly selected from the US population; therefore, our results should be fairly generalizable to the elderly in the United States.

In conclusion, results from the NHANES III suggest that bone mineral density in elderly women and men is associated with performance on tests of verbal memory. Further studies should extend this observation to examine the association between bone mineral density and clinical dementia.

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