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LOW BONE MINERAL DENSITY AND MORTALITY IN MEN AND WOMEN: THE THIRD NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY LINKED MORTALITY FILE

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Abstract

Purpose—The aim of this study is to determine the association of bone mineral density and mortality over a median follow-up of 9 years.

Methods—The baseline data used are from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of non-institutionalized civilians. A cohort of 5,769 non-Hispanic whites, non-Hispanic blacks, and Mexican-Americans aged 50 years and older at baseline (1988–1994) was followed through 2000 for overall mortality using the restricted-use NHANES III Linked Mortality File (1,741 deaths). Total proximal femoral bone mineral density was measured by dual-energy x-ray absorptiometry and categorized into quartiles. Cox proportional hazards models were used to estimate the relative risk of death after adjusting for multiple risk factors.

Results—Compared to subjects in the highest quartile of bone mineral density, those in the lowest quartile had greater risk of death (relative risk, 1.53; 95% confidence interval 1.08, 2.18; $p=0.02$). There was no significant interaction of bone mineral density with race or ethnicity.

Conclusion—Low bone mineral density was associated with increased risk of death.

Keywords

Bone Density; Follow-up Studies; Longitudinal Studies; Mortality; Proportional Hazards Models; Men; Women

INTRODUCTION

Low bone mineral density (BMD) is a predictor of fractures (1). Low BMD has also been associated with increased mortality in prospective studies of the elderly (2–7), although a recent report on low BMD and risk of coronary heart disease and stroke mortality did not find any significant associations in men and women (8). The majority of studies have focused on white women; a lesser number have included white men. Only two reports included ethnic minorities (5,8). Data from the Third National Health and Nutrition Examination Survey (NHANES III)

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Linked Mortality File provide an opportunity to further assess the relationship of BMD and total mortality in non-Hispanic white, non-Hispanic black and Mexican American men and women.

METHODS

NHANES III is an extensive interview and examination study of a representative sample of noninstitutionalized Americans aged two months and older, conducted from 1988 to 1994. The study was approved by the appropriate institutional review authorities. Details of the survey methods have been described elsewhere (9). The National Center for Health Statistics has conducted a mortality linkage of NHANES III subjects with the National Death Index and created the restricted-use NHANES III Linked Mortality File (10).

Study Population

Mortality analyses were restricted to the 7,593 non-Hispanic white, non-Hispanic black, and Mexican-American men and women aged 50 years and older at baseline. Persons of “other” race-ethnicity groups (n=266) were omitted due to the small number of subjects. Of the 6,170 individuals who received the BMD measurement, 1 was ineligible for mortality follow-up and 1 had missing information on cause of death. Excluded from all analyses were 399 subjects with missing values on baseline covariates, leaving 5,769 persons in the analytic cohort.

Bone Mineral Density Measurement

Bone mineral density was measured by trained examiners in mobile examination centers. Total proximal femoral bone mineral density expressed in grams of bone mineral content per area of cm² was measured by dual energy x-ray absorptiometry (DXA). Scans were reviewed by consultants at the Mayo Clinic, Rochester, MN, for quality control (11).

Outcomes

Date of death and cause of death were determined from death certificates. The coverage period for mortality data collection was from the date of NHANES III baseline examination through December 31, 2000. There were 1,741 deaths (983 men, 758 women).

Risk Variables

Information on baseline age, race-ethnicity, smoking status (current, former, never), alcohol consumption (drinks per month), and physical activity level were obtained by interview. Physical activity was self-assessed and determined from the question, “Compared to most men/women your age, would you say that you are more active, less active, or about the same?” Subjects were categorized as having high, low, or moderate levels of physical activity, respectively. History of heart attack, congestive heart failure, stroke, and diabetes were based on self-reported doctors’ diagnoses. Body mass index (BMI) was calculated from measured height and weight. Hypertension was determined from elevated average blood pressure measurement at examination (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg) or history of recent blood pressure medication use.

Statistical Methods

The significance of differences in baseline risk factor means or proportions between BMD quartiles was tested by the REGRESS procedure in SUDAAN and the SAS general linear models procedure (weighted) controlling for age at interview (SAS, Cary, NC, 2003) (12,13). To control for all risk factors simultaneously and to account for unequal lengths of follow-up, Cox proportional hazards regression models (SURVIVAL procedure in SUDAAN) were used to model time to the event and to calculate estimates of the relative risk of death and associated

95 percent confidence intervals (13). Sample weights were used when calculating point estimates, so estimates are representative of the civilian, noninstitutionalized US population at the time of NHANES III. Length of follow-up was calculated as the time from the date of examination to (1) the date of death (cases), or (2) the end of follow-up on December 31, 2000 for surviving subjects (noncases). The length of follow-up for survivors ranged from 6.2 to 12.1 years (median 9.0 years). A test of nonlinearity using a quadratic term (BMD-squared) was significant ($p<0.01$). Consequently, BMD was categorized into quartiles (≤ 0.741 , $0.742-0.865$, $0.866-0.982$, and ≥ 0.983) with cutoff values based on the sample distribution ($n=5,769$).

RESULTS

Baseline characteristics of persons are shown in Table 1. Compared with persons in the fourth BMD quartile (highest BMD), those in the first quartile (lowest BMD) were more likely to be older, female, non-Hispanic white, have low body mass index, low consumption of alcohol, and to be current smokers. Persons in the first quartile of BMD were less likely to have high levels of physical activity and were less likely to have hypertension, a history of heart disease or diabetes.

Relative risks from the Cox proportional hazards regression models with BMD quartiles are shown in Table 2. Compared with subjects in the fourth quartile (reference group), risk of death was highest in the first quartile after adjusting for age, gender, race-ethnicity and multiple risk factors. There was some evidence of a dose-response relationship in BMD for mortality.

A test of the proportional hazards assumption did not indicate a significantly increasing or decreasing trend in the relative risk with time ($p=0.85$). Test of the interaction of BMD quartiles and gender was not significant. In additional testing, the interaction of BMD quartiles and race/ethnicity was not significant suggesting the effect of BMD is the same in all three race/ethnicity groups, although the relationship was somewhat stronger for non-Hispanic whites than for the other two groups. Results did not change when physical functioning (difficulty walking $\frac{1}{4}$ mile) was added to the Cox proportional hazards model. Nor did the addition of self-assessed health status alter the results. Results remained unchanged with the addition of ever use of estrogen to the risk-adjusted model.

Additional analyses were performed for cardiovascular and non-cardiovascular mortality. Results for coronary heart disease and stroke mortality have been previously reported (8). Looking at the entire range of cardiovascular deaths (ICD-9 390-459 and ICD-10 I00-I99) ($n=813$), individuals in the first quartile did not have a higher risk of cardiovascular death. Persons in the first quartile had nearly twice the risk of non-cardiovascular death compared to persons in the fourth quartile. To further assess non-cardiovascular mortality, this group was subdivided into 1) deaths with an underlying cause of cancer ($n=408$) and 2) all other non-cardiovascular deaths ($n=520$). In separate models, BMD was strongly associated with non-cardiovascular mortality other than cancer (first quartile, risk-adjusted relative risk 2.04, 95% confidence interval 1.24, 3.35) while no statistically significant association between BMD and cancer mortality was observed.

DISCUSSION

This is one of the few large-scale longitudinal studies of BMD and mortality in a multi-ethnic cohort of men and women. Low proximal femoral BMD was found to be associated with increased subsequent risk of death from all causes after controlling for age and other potential confounding factors. In contrast to the earlier NHANES I Epidemiologic Follow-up Study (NHEFS) report where BMD was assessed with radiographic absorptiometry measured at the

phalanges (5) the current study utilized the superior and widely used DXA measured at the proximal femur – an axial site.

Several studies have found that baseline BMD is inversely related to subsequent mortality in women and men (2–7). Further, in a large cohort of white women 65 years of age and older, a rapid decrease in BMD was associated with increased mortality from all causes and cardiovascular disease regardless of initial BMD (14). However, the mechanism of this association is unknown. Some investigators have suggested that low BMD serves as a nonspecific indicator of frailty, ill health or other comorbidities (2,3). However, adding a variable on inability to walk ¼ mile or poor self-assessed health, measures likely associated with frailty at baseline, did not change the results. Osteoprotegerin, a cytokine that regulates osteoclastogenesis and may regulate vascular calcification, was directly associated with all-cause and cardiovascular mortality in a prospective cohort of older white women (15). However, osteoprotegerin was not associated with baseline BMD, subsequent strokes or fractures. Thus, further *in vitro* and *in vivo* research is needed to determine whether a biological mechanism exists for an independent association of BMD with mortality or whether BMD is merely a marker of frailty.

Limitations of the study include possible selection bias arising from missing data on baseline risk variables or other exclusions. Errors in measurement of bone density could be a source of information bias. However, this is unlikely given the excellent precision and accuracy of DXA. Such errors should be random producing bias towards the null. Errors in measurement of other baseline variables could result in confounding but this would be minimized given the standardized nature of the NHANES III examination. Confounding by variables not measured cannot be excluded. This study has the advantage of being based on a nationally representative sample that included a large number of deaths; thus, the results may be more generalizable than those of some previous studies. In conclusion, low bone mineral density was significantly related to increased total mortality.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Abbreviations

BMD, bone mineral density; NHANES III, Third National Health and Nutrition Examination Survey; RR, relative risk; CI, confidence interval.

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Table 1Baseline characteristics of persons by bone mineral density quartile, NHANES III.[†]

Variable	Bone mineral density quartile			
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
Age at interview, mean years	70.0	65.1	62.5	61.3 [*]
Body mass index, mean (kg/m ²)	24.5	26.7	28.1	29.9 [*]
Alcohol, mean (drinks/month)	6.0	7.3	9.1	10.1 [*]
Smoking status, %				
Current	23.9	18.4	13.6	10.8 [*]
Former	29.4	37.1	43.8	50.4 [*]
Never	46.7	44.5	42.6	38.8
Gender, %				
Male (n=2,801)	13.9	35.8	56.7	77.5 [*]
Female (n=2,968)	86.1	64.2	43.3	22.5 [*]
Race-ethnicity, %				
Non-Hispanic White (n=3,404)	92.9	90.7	89.2	82.9 [*]
Non-Hispanic Black (n=1,247)	5.2	6.7	8.3	13.9 [*]
Hispanic Mexican-American (1,118)	1.9	2.6	2.5	3.2 [*]
Physical activity level, %				
Low	15.8	14.7	14.2	15.8
Moderate	44.2	43.2	43.3	36.1 [*]
High	40.0	42.1	42.5	48.1 [*]
Hypertension, %	49.3	51.5	55.0	61.3 [*]
History of heart disease, %	10.2	11.0	12.6	13.2 [*]
History of stroke, %	4.9	6.3	4.8	5.3
History of diabetes, %	7.6	9.4	11.8	15.8 [*]

Cutoff values for quartiles of bone mineral density: 0.741 or less, 0.742 to 0.865, 0.866 to 0.982, and 0.983 or greater g/cm².^{*} $p < 0.05$, t-test comparing first and fourth quartile of bone mineral density.[†] Controlling for age at interview. NHANES III, Third National Health and Nutrition Examination Survey

Table 2

Relative risks for bone mineral density quartile associated with mortality, NHANES III.

BMD Quartile	Age, Gender, and Race-Ethnicity Adjusted		Risk-Adjusted [†]	
	RR	95% CI	RR	95% CI
1	1.82	1.36, 2.43 [*]	1.53	1.08, 2.18 [*]
2	1.38	1.08, 1.75 [*]	1.27	0.98, 1.64
3	1.13	0.91, 1.40	1.06	0.86, 1.32
4	1.00		1.00	

Cutoff values for quartiles of bone mineral density: 0.741 or less, 0.742 to 0.865, 0.866 to 0.982, and 0.983 or greater g/cm².

^{*} $p < 0.05$.

[†] Model was adjusted for age at interview, gender, race-ethnicity, body mass index, alcohol consumption, smoking status, physical activity, hypertension, history of heart disease, history of stroke, and history of diabetes. NHANES III, Third National Health and Nutrition Examination Survey