Depression and Hip Fracture Risk: The NHANES I Epidemiologic Follow-Up Study

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SYNOPSIS

Objective. Since hip fracture is the most devastating consequence of osteoporosis from a public health standpoint, addressing whether depression is predictive of fracture risk is important. The purpose of this study is to determine whether individuals with high depressive symptomatology are more likely to suffer an osteoporotic hip fracture than subjects with intermediate or low depressive symptomatology.

Methods. Data from the first National Health and Nutrition Examination Survey (NHANES I) were obtained from a nationally representative sample of noninstitutionalized civilians. A cohort aged 25 through 74 at baseline (1971–1975) was observed through 1992. Subjects were followed-up for a maximum of 22 years. Included in the analyses were 6,195 white and black subjects. Ninety-five percent of the original cohort completed the study. Hospital records and death certificates were used to identify a total of 122 hip fracture cases.

Results. In an unadjusted Cox proportional hazards regression model for all individuals, depression was predictive of hip fracture (hazard ratio [HR]=1.90; 95% confidence interval [CI]=1.13, 3.21; p=0.016). In a multivariate proportional hazards model controlling for (*1*) age at baseline, (*2*) gender, (*3*) race, (*4*) body mass index, (*5*) smoking status, (*6*) alcohol consumption, and (*7*) physical activity level, high depressive symptomatology remained predictive of hip fracture (HR=1.70; 95% CI=0.99, 2.91; p=0.055).

Conclusions. This study gives evidence of a prospective association between depression and hip fracture. Additional studies are needed to verify these findings and to elucidate the pathways for the effects of depression on hip fracture incidence.

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Osteoporosis is a disease characterized by low bone mineral density (BMD). Depression has been implicated as a possible risk factor for low BMD,[1] but the results to date have not been consistent. Among women, some studies have reported an association between depression and low BMD[2,3] or osteoporotic fractures,[4] while other studies found no such relationship.[5,6] Other research suggests that the relationship may vary depending on gender or race. For example, Schweiger et al.[7] and Halbreich et al.[8] reported that the relationship was more pronounced in men than in women, while Robbins et al.[9] found that the relationship occurred in white women, but were unable to show a statistically significant relationship in white men or black individuals of either gender.

The first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS), a large-scale national study, provides an opportunity to investigate whether depression is associated with hip fracture in a representative sample of men and women aged 25 to 74 at baseline. Unlike several previous studies that examined subjects in institutional settings,[1,7,8] our study allowed us to obtain a wider variation in the level of depressive symptomatology among subjects who met the full criteria for depression. Thus, our results may be more broadly generalizable than some of the previous studies.

METHODS

Study population

Data for these analyses were obtained from the NHEFS. In NHANES I, information was collected from a national probability sample of the civilian noninstitutionalized population aged 1 to 74 from 1971 through 1975. The survey consisted of a standardized medical examination and questionnaires on various topics[10–12] such as general medical history, 24-hour dietary intake recall, and a food frequency interview. Additional data were gathered from a sample of adults aged 25 to 74 who completed detailed medical examinations (n=6,913). The baseline cohort for the NHEFS consisted of the 14,407 individuals aged 25 to 74 who completed the standardized medical examinations in the original cross-sectional sample. Follow-up surveys were conducted from 1982 through 1984, as well as in 1986 (for those aged 55 years and older at baseline), 1987, and 1992.[13–16] Of the original NHEFS sample, only 5% were lost to follow-up at all four follow-up surveys.

The analysis presented here included individuals who were 25 to 74 years old at baseline and who underwent the detailed medical examination (n=6,913). Only white and black individuals were included because of the small numbers of individuals of other races (n=80). Of the 6,833 individuals eligible for study, 358 were unavailable for follow-up at all four periods, 116 had a history of hip fracture at baseline, and 164 had unknown values for one or more covariates associated with hip fracture. Thus, after all exclusions, 6,195 individuals were available for analysis.

Depression measurement

The General Well-Being Schedule (GWB-D)[17] was administered at baseline in mobile examination centers by trained interviewers (blind to study objectives and hypotheses) to the sample of adults aged 25 to 74 who had undergone the detailed medical examination. The GWB-D consists of four items, all of which ask subjects to rate the severity of symptoms experienced during the past month. The items are as follows: (*1*) "Have you felt downhearted and blue?" (six response categories scored from 0 to 5, with 0 indicating "in very low spirits" and 5 indicating "in excellent spirits"); (*2*) "How have you been feeling in general?" (six response categories scored from 0 to 5, with 0 indicating "in very low spirits" and 5 indicating "in excellent spirits"); (*3*) "Have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?" (six response categories scored from 0 to 5, with 0 indicating "extremely so—to the point that I have just about given up" and 5 indicating "not at all"); and (*4*) "How depressed or cheerful have you been?" (11 response categories scored from 0 to 10, with 0 indicating "very depressed" and 10 indicating "very cheerful"). The GWB-D score is the sum of these items, and the sum ranges from 0 to 25; lower scores indicate more depression, and higher scores indicate more cheerfulness. Based on the results of published studies, scores on the GWB-D were trichotomized for this analysis as follows: scores of 0 to 12 indicate a high level of depressive symptoms; scores of 13 to 18 indicate intermediate symptoms; and scores of 19 to 25 indicate low symptoms.[17,18]

Hip fracture outcome

Hospital records and death certificates were used to identify a total of 122 hip fracture cases. Information from hospital records was obtained by asking participants to report at each follow-up all hospital stays that had occurred since the previous interview. Hospitals named during the interviews were contacted, and discharge summaries were obtained for all hospital stays occurring during the period, including stays not mentioned during the interview (n=2). A case was defined as a hospital discharge with hip fracture (*International Classification of Diseases, 9th revision, Clinical Modification* [ICD-9-CM] code 820)[19] listed as a diagnosis. As many as 10 diagnoses could be listed on a single record. The hospital admission date was used as the date of the fracture. For participants with more than one record listing a hip fracture (n=8), the date of admission from the earliest record was used. All death certificates were searched for any mention of ICD-9 code 820—cited as either the underlying cause or as one of as many as 20 listed conditions. For cases identified by both a hospital record and a death certificate (n=7), the date of fracture was taken from the hospital record. Eight cases were identified from a death certificate only.

Statistical analysis

Our multivariate analyses include several variables previously identified as related to hip fracture risk, including self-reported data on age at baseline, gender, race, smoking status (current, former, never), alcohol consumption in the past year (none, any), and nonrecreational physical activity level (high, moderate, low). Body mass index (BMI, kg/m^2) was calculated from measured height and weight at baseline. Cumulative probabilities of surviving hip-fracture free were based on Kaplan-Meier statistics using the LIFETEST procedure in SAS.[20] Logrank, Wilcoxin, and −2 log likelihood ratio test results from the analysis were reported.

Rates of hip fracture incidence were calculated per 10,000 person-years of follow-up. The significance of differences in risk factor means or proportions between high and low depressive symptoms categories was tested by means of unadjusted least-squares estimates using the SAS general linear models procedure.[20] To control for all risk factors simultaneously and to account for unequal lengths of follow-up, Cox proportional hazards regression models (SAS procedure PHREG) were used to model time to the event and to calculate estimates of the hazard ratio (HR) of hip fracture and associated 95% confidence intervals (CIs).[21] PHREG performs regression analysis of survival data based on the Cox proportional hazards model. The Cox model is the preferred model for analyzing NHEFS data because it takes into account different lengths of follow-up and does not require assumptions about the distribution of survival time.[21] Length of follow-up was calculated as the time from the date of the baseline examination to the date of a hip fracture (cases) or to the date of the last follow-up interview or death (noncases). The length of follow-up for hip-fracture-free survivors ranged from 8.0 to 21.9 years (median 18.3 years). Among subjects with hip fractures, the length of follow-up ranged from 0.8 to 20.7 years (median 11.2 years). To assess the effect of complex survey design on the results, Cox proportional hazards regression analyses were confirmed using the Survival procedure in SUDAAN to incorporate the stratification, clustering, and sample weights.[22]

Table 1. Means and percentages of participants aged 25 to 74 at baseline (1971–1975) with risk factors for hip fracture by depressive symptoms category: NHEFS, 1971–1992

	Depression category		
Risk factors[a]	*High*	*Intermediate*	*Low*
n=6,195	569 (9.2%)	2,031 (32.8%)	3,595 (58.0%)
Age at baseline (years)	49.0	48.3	48.8
Female	68.4%	60.3%	48.3%[a]
Black	21.1%	12.8%	10.3%[a]
BMI (kg/m^2)	27.1	25.5	25.7[a]
Current smoker	45.0%	39.6%	35.5%[a]
Any alcohol consumption	70.3%	72.8%	75.3%[a]
Low nonrecreational physical activity	21.6%	10.9%	7.4%[a]

[a]Significant difference between high and low depressive symptoms categories ($p<0.05$).

NHEFS = the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study

BMI = body mass index

RESULTS

Table 1 shows the levels of hip fracture risk factors by depressive symptoms categories. Individuals reporting high as compared with low depressive symptoms were significantly more likely to be female, black, and have a high BMI. They were more likely to report a low level of nonrecreational physical activity and be current smokers. Any alcohol consumption in the past year was lower among individuals reporting high as compared with low depressive symptoms. Kaplan-Meier analysis indicates that the chances of surviving hip-fracture free was poorer for individuals with high depressive symptoms than for individuals with intermediate or low depressive symptoms. The logrank test for homogeneity over strata indicated statistically significant differences (chi-square=6.041; p=0.049), while the Wilcoxon test (chi-square=3.912; p=0.1414) and −2 log likelihood ratio test for homogeneity based on the exponential distribution (chi-square=4.879; p=0.087) did not reach significance.

Table 2 shows the incidence of hip fracture by depressive symptoms category. The incidence rates increased incrementally with depression category, i.e., participants reporting low depressive symptoms had the lowest hip fracture incidence rate, while those reporting high depressive symptoms had the highest incidence—about twice as high as the rate in the low category.

Table 3 shows the unadjusted and adjusted HRs of hip fracture associated with depression. The pattern of HR demonstrated a threshold effect (i.e., participants with high depressive symptoms had greater risk of fracture than those with intermediate or low symptoms). In the unadjusted model, a high level of depressive symptoms was associated with a significant increase in hip fracture risk. After controlling for known risk factors, the HR of hip fracture remained predictive for subjects with high levels of depressive symptoms compared with those with low depressive symptoms, but not significant at $p<0.05$. Results were not changed when history of previous fractures (other than the hip) or chronic conditions (coronary heart disease, stroke, kidney disease, diabetes, thyroid disease, bronchitis) were included in the model. Because these predictors were not significant in univariate models, they were not included in the main analysis. Depression was also assessed as a continuous variable. The Kolomogorov D statistic indicated that depression was not normally distributed ($p<0.01$); therefore, a logarithmic transformation of the depression variable was used. The unadjusted model for log-transformed depression indicated that subjects with fewer depressive symptoms had a lower risk of hip fracture (p=0.037). In the covariate adjusted model, however, this relationship was no longer statistically significant (p=0.194).

A test of the proportional hazards assumption did not indicate a significantly increasing or decreasing trend in the HR with time (p=0.188). No statistically significant ($p<0.05$) interactions were found after testing the following combinations of variables: depression and age at baseline, depression and gender, depression and race, depression and BMI, depression and alcohol consumption, depression and smoking status, and depression and physical activity.

DISCUSSION

We examined the prospective relationship between depressive symptomatology and hip fracture incidence among 6,195 white and black men and women aged 25 to 74 at baseline. The findings of this large, nationally representative study may lend additional support to an association between de-

Table 2. Incidence of hip fracture of participants aged 25 to 74 at baseline (1971–1975) by depressive symptoms category: NHEFS, 1971–1992, *n*=6,195

Depression category	*Hip fracture cases*	*Person-years at risk*	*Incidence per 10,000 person-years*
High	18	8,882	20.27
Intermediate	40	33,258	12.03
Low	64	59,105	10.83
Total	122	101,245	12.05

NHEFS = the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study

pressive symptoms and subsequent hip fracture incidence. After adjustment for established hip fracture risk factors (i.e., age, gender, race, BMI, smoking status, alcohol consumption, and physical activity level), individuals with a high level of depressive symptoms had an increased risk of hip fracture during the subsequent 22 years compared with subjects with low levels of depressive symptoms.

Depression could lower BMD through several direct pathways. For example, persistently elevated plasma cortisol levels have been associated with clinical depression.[2] Michelson et al. reported that increases in cortisol secretion in women were in the range that may lead to decreased BMD.[2] Elevated plasma cortisol levels in depression have been associated with hypothalamic-pituitary-adrenocortical axis disturbances.[3,23] Lower BMD and osteoporotic fractures involve complex mechanisms associated with hypothalamic dysfunction that are not fully elucidated, including hypercortisolism and hypogonadism.[3] Thus, through these hypothalamic disturbances, bone metabolism may be altered in depressed patients.

Depression may also operate indirectly in that its presence may affect behaviors that may in turn increase the risk of lowered proximal femoral BMD. For example, depression has been found to be associated with increases in smoking and alcohol use and with decreases in physical activity.[24–27] In addition, both depression and lowered BMD or osteoporosis have been linked to deficits of n–3 fatty acids, so that the relationship between BMD, osteoporosis, and depression could be jointly explained, at least in part, by reduced intake and/or metabolism of these fatty acids.[28,29]

The data show that other behavioral factors, considered as potential confounders, did not drastically attenuate the association between depression and hip fracture incidence. For example, although individuals with a high level of depressive symptoms in the study were more likely to have low levels of nonrecreational physical activity, adjusting for this factor, as well as other risk factors, did not drastically change the association. These covariates, however, may not have been sufficiently modeled. In particular, alcohol consumption in the past year was modeled dichotomously (none vs. any use) and thus may lack the sensitivity to fully detect variation in hip fracture incidence. Another concern is whether depression might operate through BMI. Additional analyses including running a reduced model without BMI to test the net effect of confounding did not change the relationship between hip fracture and depression.

Confounding by variables not measured cannot be excluded. Of particular concern is history of antidepressant medication use. Liu et al. reported an association between the use of antidepressant medication and hip fracture risk.[30] The association, however, that they observed may have been related to underlying depression, not the use of antidepressant medications. This hypothesis was not tested by the authors. Results have been mixed in other studies. For example, Michaelson et al. reported no association between lifetime antidepressant drug treatment and bone density.[2] Other studies also support the theory that antidepressant medication use may not be an important confounder of the bone density and depression relationship.[31,32] In addition, the mechanisms by which antidepressant drugs may increase hip fracture risk have not been established.[30]

Other limitations of this study include possible bias due to cohort exclusions based on loss to follow-up (5.2%) or missing data on baseline risk factors (2.4%). Because these exclusions were relatively small, however, it may be concluded that they should result in only minimal bias. Individuals who

Table 3. Hazard ratios for hip fracture according to depressive symptoms category: NHEFS, 1971–1992, *n*=6,195

	HR (95% CI)			
Depression category	*Unadjusted*	p-*value*	*Multivariate*[a]	p-*value*
High	1.90 (1.13, 3.21)	0.0160	1.70 (0.99, 2.91)	0.0550
Intermediate	1.11 (0.75, 1.65)	0.5988	1.01 (0.68, 1.51)	0.9563
Low	Reference		Reference	

[a]HRs adjusted for the following: age at baseline, gender, race, body mass index (BMI), smoking status, alcohol consumption, and nonrecreational physical activity level.

CI = confidence interval

HR = hazard ratio

NHEFS = the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study

were excluded from the analysis due to missing values on covariates or unavailability for follow-up were slightly younger (mean age 46.0 years compared with 48.7 years) and more likely to be female (56.0% compared with 54.1%). Individuals with missing values on covariates were about as likely to have had a hip fracture during follow-up as individuals included in the study (1.9% compared with 2.0%). Another potential source of bias, incorrect diagnosis of hip fracture, is unlikely on medical records,[33] but may be of more concern for death certificates.[34]

In conclusion, an association between high depressive symptomatology and hip fracture risk was observed. This study has the advantage of being based on a representative sample that included a relatively large number of subjects with depression compared to other studies; thus, the results may be more generalizable than those of previous studies. Addressing whether depression is predictive of fracture is important, since hip fracture is the most devastating consequence of osteoporosis from a public health standpoint. Additional large-scale studies of the depression and osteoporotic fracture relationship are warranted, particularly to clarify the biological and behavioral pathways involved in the association

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