Symptoms of Depression as a Prospective Risk Factor for Stroke

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Objective: The objective of this study was to assess baseline levels of depression as a risk factor for stroke among white and black men and women. **Methods:** A population-based cohort of 6095 stroke-free white and black men and women aged 25 to 74 years in the NHANES I Epidemiologic Followup Study were followed for an average of 16 years to a maximum of 22 years. The association between stroke and baseline self-reported depressive symptomatology was analyzed using Cox proportional hazards models adjusting for baseline age, race, sex, education, smoking status, body mass index, alcohol use, nonrecreational physical activity, serum cholesterol level, history of diabetes, history of heart disease, and systolic blood pressure. Hospital records and death certificates were used to identify stroke cases; a total of 483 cases were identified. **Results:** In age-adjusted models for all persons, white men, white women, and black persons of both sexes, depression was predictive of stroke. In risk-adjusted models for all persons (relative risk (RR) = 1.73, 95% confidence interval (CI) = 1.30–2.31) and for white men (RR = 1.68, 95% CI = 1.02–2.75), depression remained predictive of stroke. For white women, depression (RR = 1.52, 95% CI = 0.97–2.38) reached borderline significance (p = .07). For black persons, depression (RR = 2.60, 95% CI = 1.40–4.80) demonstrated a higher risk of stroke. A series of supplemental analyses also supported the association between depression and stroke. **Conclusions:** Depression is predictive of stroke across all strata. This nationally representative study gives evidence of a prospective association between depression and stroke. **Key words:** depression, stroke, prospective studies, longitudinal studies, incidence, risk factors.

BMI = body mass index; CI = confidence interval; GWB-D = General Well-Being Schedule, Cheerful vs. Depressed Mood Scale; ICD-9 = *International Classification of Diseases*, ninth revision; NHANES I = first National Health and Nutrition Examination Survey; NHEFS = NHANES I Epidemiologic Followup Study; RR = relative risk; SBP = systolic blood pressure.

INTRODUCTION

Epidemiologic studies have identified important risk factors for stroke, including low levels of physical activity, high serum cholesterol levels, obesity, alcohol use, cigarette smoking, diabetes mellitus, and hypertension (1–3). Depression commonly occurs after a stroke, with a prevalence as high as 30% in the first year after the event (4). However, there has been relatively little research on depression as a potential precursor of stroke even though depression has been identified as a significant risk factor for hypertension (5) and coronary heart disease (6–11). Depression may also affect other stroke risk factors. Previous studies have shown that depressive symptomatology is associated with a higher prevalence of smoking (12) and lower levels of physical activity (13, 14).

Several recent prospective studies provide evidence of an association between depression and risk of stroke. Everson et al. (15) found an elevated risk of mortality due to stroke among depressed individuals in a community sample of initially stroke-free adults from Alameda County, California. Data on morbidity due to stroke were not available. Simonsick et al. (16) found an elevated risk of stroke among elderly hypertensive men and women who reported high levels of depressive symptoms. Wassertheil-Smoller et al. (17) also studied stroke risk among elderly hypertensive men and women. Although these investigators did not find an elevated stroke risk related to baseline depressive symptoms, they did find that an increase in depression over time was prognostic. However, it was not possible to determine in either study whether symptoms of depression preceded or followed the onset of hypertension. Furthermore, Colantonio et al. (18) did not find an elevated risk of stroke among depressed elderly men and women after adjusting for known stroke risk factors. Together, the results of these prospective studies show an inconsistent relationship between depression and stroke.

We examined the role of depressive symptomatology in the subsequent development of stroke in the NHEFS, a study of a representative sample of the US population that used standardized assessments of depressive symptoms at baseline and followed participants for up to 22 years. Separate analyses were performed for white men and women. Black men and women were combined to obtain an adequate number of stroke cases (19). We hypothesized that after adjusting for possible confounders, depressive symptomatol-

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ogy in white men, white women, and all blacks would be associated with an increased risk of stroke.

MATERIALS AND METHODS

Study Population and Data Collection

Data for these analyses were obtained from the NHANES I and NHEFS. In NHANES I, information was collected from a national probability sample of the civilian noninstitutionalized population aged 1 to 74 years from 1971 through 1975. The survey consisted of a standardized medical examination and questionnaires on various topics (20–22), such as general medical history, 24-hour dietary intake recall, and a food frequency interview. Additional data were gathered from the detailed sample of adults aged 25 to 74 years (N = 6913). These subjects provided supplemental information about their medical history and healthcare needs, completed a general well-being questionnaire, and underwent a more detailed medical examination. The baseline cohort for the NHEFS consisted of the 14,407 persons aged 25 to 74 years who completed the physical examinations in the cross-sectional NHANES I survey (70% of the original cross-sectional sample). Follow-up surveys were conducted from 1982 through 1984, in 1986 (for those aged 55 years and older at baseline), and in 1987 and 1992 (23–26). 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 = 6913). Only white and black persons were included because of the small numbers of persons of other races. Of the 6833 individuals eligible for study, 358 were unavailable for follow-up at all four periods, 116 had a history of stroke at baseline, and 264 had unknown values for one or more variables assessed in the study. Thus, after all exclusions, 6095 persons were available for analysis.

Psychological Measures

The GWB-D (27) 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 years 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?" (this item has 6 response categories scored from 0 to 5, with 0 = "all of the time" and 5 = "none of the time"); 2) "How have you been feeling in general?" (6 response categories scored from 0 to 5, with 0 = "in very low spirits" and 5 = "in excellent spirits"); 3) "Have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?" (6 response categories scored from 0 to 5, with 0 = "extremely so—to the point that I have just about given up" and 5 = "not at all"); and 4) "How DEPRESSED or CHEERFUL have you been?" (11 response categories scored from 0 to 10, with 0 = "very depressed" and 10 = "very cheerful"). The GWB-D score is the sum of these items and ranges from 0 to 25; lower scores indicate more depression and higher scores indicate more cheerfulness. For these analyses, scores on the GWB-D were trichotomized as follows: scores of 0 to 12 indicated a high level of depressive symptoms; scores of 13 to 18, intermediate symptoms; and scores of 19 to 25, low symptoms. A score of 0 to 12 has been shown to give a good approximation of high depressive symptoms (28). High scores reflect responses indicating few or no depressive symptoms (27). The intermediate group was constructed as the balance between the high and low symptoms groups, and scores in this range reflect responses indicating moderate levels of depressive symptoms (27).

The GWB-D measures *self-reported* symptoms of depression; thus, a score indicating high depressive symptoms is not synonymous with a clinical diagnosis of depression. However, the GWB-D has been shown to predict clinically trained interviewers' ratings of depression (27). GWB-D scores have also been correlated with scores on other instruments designed to assess clinical depression, including the Zung Depression Scale (r = 0.62), the Personal Feelings Inventory-Depression (r = 0.67), and the Psychiatric Symptoms Scale-Depression (r = 0.70) (27) In the NHANES I sample that underwent detailed medical examination, the internal consistency of the GWB-D scale was 0.77 (29). Furthermore, in a 9-year longitudinal study, Costa et al. (30) demonstrated that the level of negative affect was relatively stable over time among NHEFS participants aged 25 to 74 years. Given the size and representativeness of the sample, this is strong evidence of the stability of mean levels of negative affect in adulthood.

Stroke Outcome

Hospital records and death certificates were used to identify stroke cases; a total of 483 cases were identified. At each follow-up survey, participants were asked to report all hospital stays since the previous interview. Hospitals named during an interview were contacted, with permission from the subject, and discharge summaries were obtained for all hospital stays occurring during the period, including stays not mentioned during the interview. A discharge diagnosis of stroke (ICD-9 codes 431 to 434.9, 436, and 437.0 to 437.1) identified a case (31, 32). Up to 10 diagnoses could be listed on a single record. The hospital admission date was used as the date of stroke occurrence. For persons with more than one record listing a stroke, the earliest admission date was used. All death certificates were also searched for any mention of these ICD-9 codes (ie, underlying cause or up to 20 ancillary conditions). For cases identified by both a hospital record and death certificate, the date of stroke occurrence was taken from the hospital record. Seventy-six cases were identified only from death certificates.

Baseline Variables

Our multivariate analyses included several variables previously identified as related to stroke risk, including age at baseline, educational attainment ($<$12, $\geq$12 years), smoking status (current, not current), alcohol consumption in the past year (none, any), nonrecreational physical activity (three categories: much, moderate, or none), history of diabetes, and history of heart disease. At the beginning of the baseline physical examination, the physician measured blood pressure once with the subject seated (33). BMI (measured in kg/m^2) was calculated from the height and weight recorded at baseline. Baseline blood samples were obtained, and frozen sera were sent to the then Centers for Disease Control for determination of serum cholesterol level (20, 34).

Statistical Analyses

Incidence rates for stroke are calculated per 1000 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 (35). 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 relative risk of stroke and associated 95% confidence intervals (36, 37). 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 (38). Length of follow-up was calculated as the time from the date of examination to the date of a stroke (cases) or to the date of the last follow-up interview or death (noncases). Participants were followed up for a mean length of 16.0 years (maximum length = 21.8 years). The SAS-callable SUDAAN survival procedure was used to check for changes in stroke risk after using sampling weights (39). Because the weights and complex survey design variances did not change the overall conclusions of the study, only unweighted results are presented.

RESULTS

Table 1 shows the levels of stroke risk factors by depressive symptoms category. For all race and sex groups, persons reporting high as compared with low depressive symptoms were significantly more likely to report a low level of nonrecreational physical activity, less than high school education, and a history of diabetes. White men and white women in the high depressive symptoms category were more likely to be current smokers. White women in the high depressive symptom category were more likely to have a higher BMI and a history of heart disease. Depressed blacks more often reported a history of heart disease. All other risk factors were comparable across depressive symptoms categories.

Table 2 shows the number and percentage of respondents and the number of stroke cases by race, sex, and depressive symptoms category. Blacks had the largest percentage of subjects reporting high depressive symptoms (15.7%), followed by white women (10.4%) and white men (5.6%). Blacks and white women also had higher percentages of subjects reporting an intermediate level of depressive symptoms compared with white men. Age-adjusted incidence rates are shown in Figure 1. For white men, white women, and all black persons, the incidence rate for stroke was highest for persons with high depressive symptoms, followed by persons with intermediate and then low depressive symptoms.

Table 3 shows the relative risks for stroke incidence associated with each risk factor among all persons aged 25 to 74 years. Among the continuous measures,

TABLE 1. Levels of Stroke Risk Factors by Depressive Symptoms Category[a]

Risk Factor	High	Intermediate	Low
White men			
Age (y)	50.6	49.0	48.9
SBP (mm Hg)	133.0	132.9	133.3
BMI (kg/m^2)	25.6	25.4	25.9
Current smoker (%)	55.4	44.5	41.1*
Any alcohol intake (%)	80.6	81.3	81.6
Low nonrecreational physical activity (%)	19.4	12.0	8.0*
Less than high school graduate (%)	59.7	45.4	37.8*
History of diabetes (%)	7.2	5.7	3.4*
History of heart disease (%)	10.8	10.6	6.8
Serum cholesterol level (mg/dl)	220.6	220.5	218.3
White women			
Age (y)	48.0	48.1	48.3
SBP (mm Hg)	131.2	129.9	130.5
BMI (kg/m^2)	27.0	25.1	25.0*
Current smoker (%)	40.1	35.8	27.7*
Any alcohol intake (%)	67.7	68.4	70.4
Low nonrecreational physical activity (%)	20.9	9.6	6.5*
Less than high school graduate (%)	55.6	41.2	31.0*
History of diabetes (%)	8.4	4.8	2.8*
History of heart disease (%)	8.4	7.4	4.3*
Serum cholesterol level (mg/dl)	223.7	226.1	225.7
Blacks			
Age (y)	50.6	47.4	51.3
SBP (mm Hg)	140.6	140.5	145.2
BMI (kg/m^2)	28.4	27.2	27.1
Current smoker (%)	47.4	46.4	47.4
Any alcohol intake (%)	63.8	71.5	68.5
Low nonrecreational physical activity (%)	26.7	11.8	6.7*
Less than high school graduate (%)	80.2	65.4	63.0*
History of diabetes (%)	12.9	5.7	7.2*
History of heart disease (%)	17.2	11.0	7.2*
Serum cholesterol level (mg/dl)	225.3	220.8	223.3

[a] Values are means or percentages.
* Significant difference between high and low depressive symptoms categories ($p < .05$).

TABLE 2. Number of Incident Cases of Stroke[a] by Race, Sex, and Depressive Symptoms Category in the NHEFS Cohort

Race, Sex, and Depression Category	Respondents at Baseline		Stroke[a] Cases (*N*)
	N	(%)	
White men			
Total	2497	(100.0)	208
High	139	(5.6)	19
Intermediate	699	(28.0)	60
Low	1659	(66.4)	129
White women			
Total	2860	(100.0)	192
High	297	(10.4)	27
Intermediate	1034	(36.1)	77
Low	1529	(53.5)	88
Blacks			
Total	738	(100.0)	83
High	116	(15.7)	20
Intermediate	263	(35.6)	25
Low	359	(48.7)	38

[a] Persons through the 1992 follow-up with a diagnosis of stroke from a healthcare facility or stroke listed as an underlying or contributing cause of death for decedents.

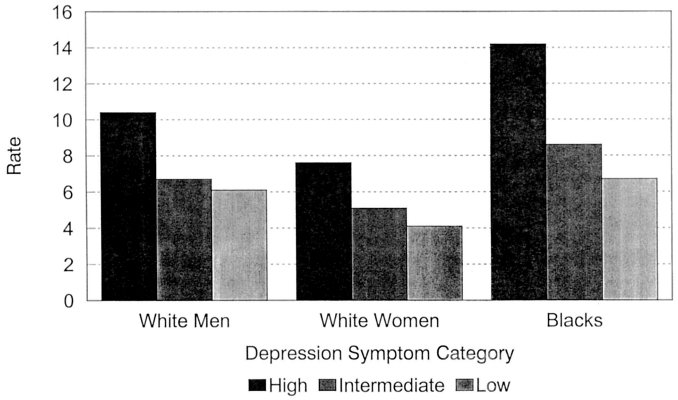

Fig. 1. Age-adjusted incidence rates for stroke (per 1000 person-years) by race and sex groups and depressive symptoms categories (based on data from NHEFS, 1971–1992).

TABLE 3. Relative Risks for Stroke Associated With All Risk Factors in the NHEFS Cohort Among Persons Aged 25 to 74 Years

Risk Factor	Stroke[a]	
	RR	(95% CI)
Age (5-y increase)	1.59	(1.50–1.67)
Race (black)	1.20	(0.94–1.54)
Sex (men)	1.74	(1.44–2.12)
Smoking (current)	1.54	(1.25–1.90)
History of diabetes (yes)	1.56	(1.15–2.12)
History of heart disease (yes)	1.51	(1.18–1.93)
Education (<12 y)	1.12	(0.92–1.37)
SBP (10-unit increase)	1.14	(1.10–1.18)
Serum cholesterol level (10-unit increase)	1.03	(1.01–1.05)
BMI (1-SD increase, SD = 4.8)	0.99	(0.90–1.09)
Alcohol consumption in past year (any)	0.84	(0.69–1.02)
Nonrecreational physical activity (low)	1.13	(0.83–1.55)
Nonrecreational physical activity (moderate)	1.14	(0.93–1.39)
Depressive symptomatology (high)	1.73	(1.30–2.31)
Depressive symptomatology (intermediate)	1.25	(1.02–1.52)

[a] Persons through the 1992 follow-up with a diagnosis of stroke from a healthcare facility or stroke listed as an underlying or contributing cause of death for decedents.

increases in age, SBP, or serum cholesterol level were associated with increased stroke risk. Among the categorical measures, men, current smokers, persons with a history of diabetes or heart disease, and persons reporting a high (RR = 1.73, CI = 1.30–2.31, p = .00) or intermediate level (RR = 1.25, CI = 1.02–1.52, p = .03) of depressive symptoms had an increased risk of stroke.

Table 4 shows the age-adjusted and risk-adjusted relative risks of stroke associated with depression for white men, white women, and all blacks. For all three groups, the pattern of relative risks demonstrated a gradient from high to low symptomatology. In the age-adjusted models, a high level of depressive symptoms

TABLE 4. Relative Risks for Stroke Associated With Depressive Symptoms by Race and Sex Groups Adjusted for Age and Selected Risk Factors in Persons Aged 25 to 74 Years

Race, Sex, and Depression Category	Stroke[a]			
	Age-Adjusted		Risk-Adjusted[b]	
	RR	(95% CI)	RR	(95% CI)
White men				
High	1.88	(1.16–3.05)	1.68	(1.02–2.75)
Intermediate	1.26	(0.92–1.71)	1.20	(0.88–1.64)
Low	1.00		1.00	
White women				
High	1.86	(1.21–2.87)	1.52	(0.97–2.38)
Intermediate	1.35	(0.99–1.83)	1.24	(0.90–1.70)
Low	1.00		1.00	
Blacks				
High	2.18	(1.27–3.75)	2.60	(1.40–4.80)
Intermediate	1.32	(0.79–2.21)	1.41	(0.84–2.38)
Low	1.00		1.00	

[a] Persons through the 1992 follow-up with a diagnosis of stroke from a healthcare facility or stroke listed as an underlying or contributing cause of death for decedents.
[b] Adjusted for baseline age, SBP, education, smoking status, BMI, alcohol use, nonrecreational physical activity, serum cholesterol level, history of diabetes, and history of heart disease.

was associated with a significant increase in stroke risk for all three groups. After controlling for known risk factors, the relative risk of stroke remained significantly elevated for white men with high levels of depressive symptoms (RR = 1.68, CI =1.02–2.75, p = .04) compared with those with low depressive symptoms. Stroke risk for white women with high depressive symptoms also remained marginally significant (RR = 1.52, CI =0.97–2.38, p = .07). Adjustment for additional risk factors did not reduce the excess risk associated with high depressive symptoms among blacks (RR = 2.60, CI = 1.40–4.80, p = .00).

Exclusion of Early Stroke Events

Because depressive symptomatology may be associated with occult cerebrovascular disease, we excluded individuals who may have had an undiagnosed stroke at the beginning of the study by excluding stroke cases that occurred within 3 years after the baseline examination (N = 43). After these exclusions, the age-adjusted relative risks of stroke associated with high depressive symptomatology were little changed (white men: RR = 1.73, CI = 1.02–2.91, p = .04; white women: RR = 1.90, CI = 1.21–2.97, p = .01; and blacks: RR = 2.12, CI = 1.20–3.74, p = .01). The fully adjusted relative risks were slightly reduced but still elevated among white men (RR = 1.59, CI = 0.93–2.72, p = .09), virtually unchanged for white women (RR = 1.53, CI =

0.96–2.44, $p = .07$), and slightly higher for blacks (RR = 2.70, CI = 1.41–5.14, $p = .00$). Similar results were found when stroke cases that occurred within the first 5 and 10 years after the baseline examination were excluded.

Exclusion of Baseline Chronic Diseases

Because depressive symptomatology is known to be elevated among persons with heart disease or diabetes (40, 41), we reexamined the relationship between baseline levels of depression and subsequent stroke after excluding individuals who reported a history of heart disease or diabetes ($N = 651$). The age-adjusted relative risks of stroke associated with high depressive symptomatology were relatively unchanged for all strata (white men: RR = 1.75, CI = 0.96–3.19, $p = .07$; white women: RR = 1.73, CI = 1.02–2.94, $p = .04$; and blacks: RR = 2.33, CI = 1.22–4.46, $p = .01$). These exclusions resulted in a somewhat stronger risk-adjusted relative risk of stroke associated with high depressive symptoms for white men (RR = 1.89, CI = 1.02–3.47, $p = .04$) and for blacks (RR = 2.70, CI = 1.33–5.49, $p = .01$), but there was little difference in the point estimate for white women (RR = 1.45, CI = 0.83–2.51, $p = .19$) (see Table 4).

Stratification by Age

To investigate whether age modified the associations between depression and stroke, we reexamined the data by baseline age group (25–59 and 60–74 years). Among the 4475 subjects aged 25 to 59 years and the 1620 subjects aged 60 to 74 years, the crude incidence rates for stroke were 3.9% and 19.0%, respectively. Of the 483 stroke cases identified, 307 (63.6%) were among persons aged 60 to 74 years and 176 (36.4%) were among persons aged 25 to 59 years at baseline. Because of sample size constraints (ie, number of stroke events), it was not possible to further stratify by age within defined race and sex groups, nor was it possible to stratify into three age groups to specify a younger group (eg, 25–44 years). In models adjusting for age (continuous), sex, and race, high and intermediate levels of depressive symptoms were associated with stroke in both age groups. Similar results were found in models adjusting for all risk factors. For subjects aged 25 to 59 years, stroke risk was associated with high depressive symptoms (RR = 2.01, CI = 1.27–3.18, $p = .00$); the association did not reach significance for intermediate depressive symptoms (RR = 1.32, CI = 0.95–1.85, $p = .10$). For subjects aged 60 to 74 years, stroke risk was increased for those with high levels of depressive symptoms (RR = 1.62, CI = 1.12–2.34, $p = .01$) and was marginally significant for those with intermediate levels of depressive symptoms (RR = 1.25, CI = 0.97–1.61, $p = .09$).

Controlling for Anxiety

Depression and anxiety are correlated ($r = 0.75$) in this cohort. To determine whether controlling for anxiety would attenuate results for depression and stroke, we reexamined the data, including the score on the Anxiety Scale of the General Well-Being Schedule as an additional covariate (5). For all subjects in models adjusting for age, sex, and race, the relative risks of stroke associated with depressive symptomatology were relatively unchanged for high (RR = 1.86, CI = 1.31–2.65, $p = .00$) and intermediate levels (RR = 1.27, CI = 1.02–1.60, $p = .04$). In models adjusting for all risk factors, relative risks were similarly unaffected for high (RR = 1.80, CI = 1.26–2.57, $p = .00$) and intermediate levels (RR = 1.23, CI = 0.98–1.54, $p = .08$). In all models, neither high nor intermediate levels of anxiety were significantly related to stroke.

Assessment of Cheerfulness

If depression is associated with an increased risk of stroke, one might ask whether cheerfulness protects against stroke. One might also ask whether cheerfulness, if simultaneously assessed, would attenuate the relationship between depression and stroke. To address these questions, we looked at the high end of the GWB-D score distribution (scores of 23–25); 20.3% of subjects had scores in this range, indicating high levels of cheerfulness. This variable was then entered into models along with high and intermediate depressive symptoms. For all subjects in models adjusting for all risk factors, high levels of cheerfulness were not significantly protective against stroke. In these models, the relative risks of stroke associated with high and intermediate depressive symptoms were virtually unchanged. Similar results were found when high cheerfulness was redefined as scores of 24 to 25 (top 11.2%) and scores of 25 (top 4.6%).

Assessment of Hopelessness

The GWB-D includes hopelessness as one of its component items. Anda et al. (6), using NHEFS data through 1987, found that hopelessness, in addition to the entire GWB-D, was predictive of ischemic heart disease. To assess whether hopelessness was related to stroke incidence, we similarly defined hopelessness using the same grouping and response categories: severe (scores of 0 and 1), moderate (2 and 3), and none/

low (4 and 5). Among all 6095 subjects, 221 (3.6%) reported severe levels and 718 (11.8%) reported moderate levels of hopelessness. For all subjects in models adjusting for age, sex, and race, stroke was associated with severe (RR = 1.66, CI = 1.13–2.44, $p = .01$) and moderate levels of hopelessness (RR = 1.44, CI = 1.11–1.87, $p = .01$). In models adjusting for all risk factors, stroke was associated with severe levels of hopelessness (RR = 1.52, CI = 1.02–2.25, $p = .04$); the association between stroke and moderate levels of hopelessness was marginally significant (RR = 1.27, CI = 0.98–1.66, $p = .08$).

Depression as a Continuous Measure

To determine the graded risk associated with a one-point change in the continuum of depressive symptoms, the GWB-D was analyzed as a continuous measure. For all subjects in models adjusting for age, sex, and race, the relative risk of stroke associated with a one-point increase in the depression score was 1.04 (CI = 1.02–1.06, $p = .00$). In models adjusting for all risk factors, the relative risk was unchanged (RR = 1.04, CI = 1.01–1.06, $p = .00$).

DISCUSSION

We examined the prospective relationship between depressive symptomatology and stroke incidence among 6095 white and black men and women aged 25 to 74 years. The findings of this large, nationally representative study lend additional support to a significant association between depressive symptoms and subsequent stroke incidence. After adjustment for established stroke risk factors (ie, age, sex, race, SBP, education, smoking status, BMI, alcohol use, nonrecreational physical activity, serum cholesterol level, history of diabetes, and history of heart disease), individuals with a high level of depressive symptoms had a 50% to 160% increased risk of stroke during the subsequent 22 years compared with subjects with low levels of depressive symptoms. The consistency of the significance of these associations was observed across the race-sex strata of white men, white women, and all blacks. Blacks had an increased risk of stroke associated with high depressive symptomatology in comparison with whites. In general, the risk-adjusted models did not substantially attenuate risks in comparison with age-adjusted models.

This does not imply that other covariates considered here were not predictive of stroke. The overall analysis presented in Table 3 showed that, in addition to high and intermediate levels of depressive symptoms, age, sex, smoking status, SBP, serum cholesterol level, history of diabetes, and history of heart disease were all predictive of stroke incidence. Among the categorical variables, a high level of depressive symptoms seems to be a strong predictor, with a relative risk of 1.73 (about the same as that for sex, 1.74). Among the continuous variables modeled, age is clearly the strongest predictor; SBP and serum cholesterol level were also prognostic. To place the relative risk of high depressive symptomatology into context, the effect of the relative risk of depression was roughly comparable to a 40-point increase in baseline SBP.

In addition, consistent associations between depression and stroke were observed in a variety of supplemental models. In models that excluded early stroke events, depression continued to be prognostic of stroke. In models that excluded individuals with heart disease or diabetes at baseline, the depression-stroke connection was similarly unaffected. Wassertheil-Smoller et al. (17) and Penninx et al. (42) showed that only change in depression over time, rather than baseline depression, was predictive of future cardiovascular events. This finding implies that vascular disease could be a potential cause of both subsequent depression and stroke. Because baseline depression was predictive of stroke in the analyses reported here, and because the impact of excluding early stroke cases (up to 10 years after the NHANES I examination) or subjects with baseline heart disease or diabetes on these analyses was minimal, we conclude that baseline vascular disease leading first to depression and subsequently to stroke is not a likely explanation for the observed associations. Baseline age was a strong predictor of stroke incidence, with incidence rates rising sharply with increasing age. However, analyses stratified by age showed that depression was consistently associated with stroke incidence in both the younger (25–59 years) and older (60–74 years) age groups. Thus, age did not seem to modify the effects of depression on stroke.

Anxiety is a correlate of depression. However, anxiety was not associated with stroke, nor did its inclusion in models attenuate the association between depression and stroke. Although we cannot rule out the possibility that the depression measure overlaps with other psychological domains, the results of this analysis support the argument that depression, rather than some other psychological dimension related to depression, is related to stroke. Cheerfulness, defined as the extreme low level of depressive symptoms, was not protective against stroke. We therefore conclude that a depressed mood places one at increased risk for stroke rather than that extreme cheerfulness places one at decreased risk. We also conclude that hopelessness, a component assessed by the GWB-D, places one at in-

creased risk for stroke. Finally, the analysis of the GWB-D as a continuous scale demonstrated that increasing depressive symptomatology along a continuum was associated with increasing stroke incidence, not just at defined cutoffs.

Well-validated self-reported depression scales such as the GWB-D have the advantage that an intermediate level of depression symptomatology can be established. Individuals in the present study with an intermediate level of depressive symptoms had a 20% to 40% increased risk of stroke, which was suggestive of a risk gradient. Dimsdale (43) observed that subsyndromal depression can have significant health consequences. The high prevalence of intermediate depression cases coupled with even marginally significant elevated relative risks suggests that even modest increases in risk for stroke in this group may have important public health implications.

The direct mechanisms underlying a depression-stroke connection are not well understood. Depression has been shown to result directly in acute autonomic arousal. Siever and Davis (44) hypothesized that affective disorders are syndromes of neurotransmitter dysregulation. They cite evidence that regulatory failure of the noradrenergic and related systems results in a loss of selectivity of responsiveness to environmental stimuli and in a delayed return to basal activity when stressful stimuli are withdrawn. Results of other studies suggest that depression may increase stroke through increased adrenergic activity (44, 45) or through neuroendocrine and immunological effects (46–48). It has also been suggested that platelet activation may be a factor explaining the depression-stroke connection (49, 50).

It is also possible that depression operates indirectly by increasing the risk of other diseases that may in turn increase the risk of stroke. For example, Jonas et al. (5) found that persons with high depressive symptomatology had elevated risks for hypertension and that the pattern of elevated risks was higher for blacks. Other studies (51, 52) have demonstrated higher relative risks for hypertension among African Americans compared with whites. In the present study, race by itself was not significantly associated with increased stroke incidence in the overall risk-adjusted model; however, the pattern of elevated risks for depression and stroke were higher in the stratified models for blacks. Thus, intervening hypertension might explain, at least in part, the pathway from depression to stroke as well as the higher risk of stroke among depressed black persons. Anda et al. (6) also found an increased risk of ischemic heart disease among persons with high depressive symptomatology. Future research should address the potential pathway of depression, intervening hypertension, and cardiovascular disease and stroke.

Our data show that other behavioral factors, considered as potential confounders, do not attenuate the association between depression and stroke incidence. For example, although persons with a high level of depressive symptoms in our study were more likely to have low levels of nonrecreational physical activity, adjusting for this factor as well as other risk factors did not significantly change the observed association. However, these covariates 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 stroke incidence. Similarly, adjusting for preexisting heart disease or diabetes did not substantially alter the depression-stroke association. These conditions were generally significant covariates in our models. However, these baseline measures were self-reported and thus may not be as accurate as other measures, such as medical records from healthcare facilities. Furthermore, although the GWB-D is well validated, a score indicating a high level of depressive symptoms is not synonymous with a clinical diagnosis of depression. The prospective association between a clinical diagnosis of depression and stroke also needs to be studied. Confounding by variables not measured cannot be excluded.

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 (3.9%). However, because these exclusions were relatively small, we conclude that they should result in only minimal bias. In addition, inaccuracy of the baseline history of stroke could result in cases being identified during follow-up that were actually diagnosed before baseline. Another possible source of bias is misclassification due to the inaccurate diagnoses coded on medical records and death certificates. Finally, the stroke identification approach taken in this study, which required that a self-report of hospitalization for stroke be confirmed by a medical record listing stroke as a discharge diagnosis, could lead to incomplete case ascertainment. Self-reported stroke cases may exist without a matching medical record because no medical record was obtained or because the medical record contains a discharge diagnosis other than stroke. However, we found that the results were not affected by treating the unconfirmed stroke cases as true cases.

Despite these limitations, this study provides additional evidence that, among white men, white women, and all blacks aged 25 to 74 years, there is an association between self-reported depressive symptomatology and stroke incidence. An extended set of supple-

mental analyses supported the robustness of the prospective association between depression and stroke. These analyses also demonstrated the consistency of this association across age groups and provided evidence that depression itself, along with hopelessness as a component of depression, was the operating psychological dimension prospectively associated with stroke incidence. The suggestion of a graduated relationship between level of depressive symptoms and stroke indicates that reducing depression may be important for everyone, not just those whose high symptomatology may have clinical implications. Additional studies are needed to verify these findings and to elucidate the pathways for the effects of depression on stroke incidence.

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