ORIGINAL INVESTIGATION

Depressive Symptoms and Increased Risk of Stroke Mortality Over a 29-Year Period

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Background: Several lines of evidence indicate that depression is importantly associated with cardiovascular disease end points. However, little is known about the role of depression in stroke mortality.

Methods: This study examined the association between depressive symptoms and stroke mortality in a prospective study of behavioral, social, and psychological factors related to health and mortality in a community sample of 6676 initially stroke-free adults (45.8% male; 79.1% white; mean age at baseline, 43.4 years) from Alameda County, California. Depressive symptoms were assessed by the 18-item Human Population Laboratory Depression Scale. Cox proportional hazards regression models were used to evaluate the impact of depressive symptoms after controlling for age, sex, race, and other confounders.

Results: A total of 169 stroke deaths occurred during 29 years of follow-up. Reporting 5 or more depressive symptoms at baseline was associated with increased risk of stroke mortality, after adjusting for age, sex, and race (hazard ratio, 1.66; 95% confidence interval, 1.16-2.39; $P<.006$). This association remained significant after additional adjustments for education, alcohol consumption, smoking, body mass index, hypertension, and diabetes (hazard ratio, 1.54; 95% confidence interval, 1.06-2.22; $P<.02$). Time-dependent covariate models, which allowed changes in reported depressive symptoms and risk factor levels during follow-up, revealed the same pattern of associations.

Conclusions: This population-based study provides the strongest epidemiological evidence to date for a significant relationship between depressive symptoms and stroke mortality. These results contribute to the growing literature on the adverse health effects of depression.

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RESEARCH HAS identified several important risk factors for stroke, including hypertension, diabetes mellitus, cigarette smoking, alcohol abuse, high cholesterol levels, and obesity[1,2]; however, little is known about the potential role of psychosocial factors in stroke incidence and mortality. This is surprising because psychosocial factors have been shown to be importantly related to all-cause mortality, cardiovascular disease (CVD) morbidity and mortality, prevalence and progression of carotid atherosclerosis, and acute myocardial infarction.[3-10] In particular, convincing evidence has accumulated in the past decade identifying depression as a significant factor in CVD.[5,7,11-17]

Depression could contribute to stroke risk or survival following a stroke through a variety of mechanisms. Depression has known neuroendocrine and immunological effects,[18,19] both of which could influence stroke risk. Moreover, depression may negatively impact stroke risk factors. For example, previous research has shown that high levels of depressive symptoms are associated with decreased physical activity, higher prevalence of smoking, and altered lipid metabolism.[13,20-23]

In addition, several recent studies are suggestive of this association. Among a sample of 103 patients with stroke, a diagnosis of major or minor depression was related to a 70% increased risk of mortality due to any cause over 10 years of follow-up.[24] Colantonio and colleagues[25] reported that higher scores on the Center for Epidemiological Studies Depression Scale (CES-D) were associated with increased risk of incident stroke over 7 years of follow-up among more than 2600 elderly men and women from the Yale Health and Aging Project, which was part of the Established Populations for Epidemiological Studies of the Elderly program. However, following multivariate adjustment for known stroke risk factors, CES-D scores were no longer significantly associated

METHODS

THE ALAMEDA COUNTY STUDY

The Alameda County Study is an ongoing longitudinal study of the role of various behavioral, psychological, social, and demographic factors in health and mortality among a community sample of men and women. The study began in 1965 and used a stratified random household sampling procedure to recruit a representative sample of the adult, noninstitutionalized population of Alameda County, California. A total of 6928 adults (86% of those eligible), ages 16 to 94 years, provided baseline information by written questionnaires on health history and status, health habits, psychological feelings and attitudes, marital history and status, childbearing practices, civic, social, and recreational activities, occupational history and status, life history during childhood and adolescence, and standard demographic variables. Subjects were tracked regardless of location or disability status and survivors were asked to complete questionnaires again in 1974, 1983 (50% sample), 1994, and 1995, with response rates between 85% and 97%. For the present study, only data from the 1965, 1974, and 1983 surveys were used. Questionnaires were similar in style and response format, and every effort was made to keep the wording of items and the length of the questionnaires consistent across all waves of data collection. Participants were requested to complete the questionnaires on their own, ie, "proxy" respondents were not used. After initial recruitment and determination of eligibility, questionnaires were sent to and returned from participants by mail. Detailed design and sampling procedures for this study have been reported previously.[28,29] The research protocol was approved by the California Health and Welfare Agency Committee for the Protection of Human Subjects and conducted in accordance with their guidelines regarding informed consent for participation in research in which the sole form of data collection is via mailed surveys.

STUDY POPULATION

All participants who were interviewed in 1965, had complete data on the measure of depression and all covariates, and did not have a history of stroke were included in the present study. Of the 6867 persons eligible, 46 were excluded because of incomplete or missing data on the depression scale and 145 were excluded because of missing data on covariates, leaving a total of 6676 subjects for the present analyses. Nonparticipants were older, had fewer years of education, were more likely to have a history of diabetes or hypertension but were less likely to be current smokers and more likely to be nondrinkers than participants ($P<.01$).

HUMAN POPULATION LABORATORY DEPRESSION SCALE

Depressive symptoms were measured by the Human Population Laboratory (HPL) Depression Scale, an 18-item scale developed by Roberts and colleagues[30-32] that assesses mood disturbances, negative self-concept, loss of energy, problems with eating and sleeping, and psychomotor retardation or agitation. Scores are calculated by assigning 1 point for each "true" or "false" answer that corresponds to a depressed response. Item-total correlations for the depression scale range from 0.18 to 0.45 with Cronbach α of 0.77, indicating good internal consistency. A symptom score of 5 or higher is considered indicative of depression or mood disturbance, albeit not necessarily clinical depression. The symptoms do not fully operationalize *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* (*DSM-III-R*)[33] criteria for a major depressive episode. However, the cutoff of 5 or more symptoms to define caseness has been used in numerous analyses to indicate significant symptomatology, has demonstrated reliability and validity,[30-32] is conceptually similar to other brief symptom checklists such as the CES-D scale, and an earlier study found that it correlated well with the Beck Depression Inventory (r=0.66) in an outpatient clinical population.[31]

with stroke incidence. In addition, the majority of participants in that study had only a grade school education and many had very limited incomes, making the generalizability of the findings somewhat limited.

Simonsick and colleagues[26] used data from the 3 study sites from the Established Populations for Epidemiological Studies of the Elderly to assess the relationship between symptoms of depression and hypertension-related morbidity and mortality among a sample of older adults diagnosed as having hypertension. In general, they found that hypertensive men and women who reported high levels of depressive symptoms were more than twice as likely to experience a stroke during the subsequent 3 to 6 years than their hypertensive, nondepressed counterparts. However, results were not consistent across study sites, and because of the design of that study, there was no way of determining whether the depressive symptoms were a cause or a consequence of the complications of hypertension.

Also, it was recently reported that an increase in CES-D scores over a period of 4½ years was associated with excess risk of mortality, stroke, and myocardial infarction in more than 4300 participants from the Systolic Hypertension in the Elderly Program.[27] These findings were upheld after adjustments for age, race, sex, disease history, and smoking status, and the increase in depressive symptoms was a stronger risk factor for women than for men. Baseline levels of depressive symptoms were not related to cardiovascular events, however, and the authors noted that causal pathways could not be inferred from their data, in part because all participants had isolated systolic hypertension and it is plausible that premonitory symptoms of CVD contributed to increased depressive symptoms prior to a clinical event.

The present study examined the association between self-reported depressive symptoms and stroke mortality over a 29-year period in a community sample of 6676 men and women. The analyses reported are from

STROKE MORTALITY

Mortality tapes from California were searched annually for information on study participants. Out-of-state deaths were ascertained during follow-up contact, in which death certificates were requested from the state of residence. Death certificates were used to verify cause of death. Stroke mortality was based on *International Classification of Diseases, Ninth Revision (ICD-9)*[34] codes 400 to 436.

COVARIATES

Risk factors, assessed at each wave of data collection, included education, assessed as years of school completed; alcohol consumption, assessed as number of drinks per month and summed for individual report of beer, wine, and liquor consumption; body mass index, calculated as weight in kilograms divided by height in meters squared; smoking; and self-report of hypertension and diabetes.

Covariates were modeled as follows: education was coded as less than vs equal to or greater than 12 years of education; alcohol consumption was categorized as heavy (>45 drinks per month) or none, with moderate consumption (1-45 drinks per month) as the reference category; body mass index was modeled continuously; smoking was coded as pack-years of smoking; hypertension and diabetes history were dichotomized in response to the question, "Have you ever seen a medical doctor for (condition)?"

DATA ANALYSES

The relationship between self-reported depressive symptoms and mortality due to stroke was examined using Cox proportional hazards models,[35] with and without time-dependent covariates. All assumptions for the Cox models were tested and met. Deaths were included through 1994. Subjects known to have died of stroke and not lost to follow-up were kept in the analysis until the year of their death. Subjects not known to have died and who were available for follow-up were given a survival time of 29 years. Subjects unavailable for follow-up in either the 1974 or 1983 surveys were censored on the survey date when unavailability for follow-up occurred. Subjects who died of causes other than stroke were censored in the year of their death. Statistical analyses were performed using commercially available software (PROC PHREG in SAS, version 6.09[36]) installed on a Sun SPARCstation 20 (Sun Microsystems Computer Corporation, Mountain View, Calif).

Two types of models were calculated. In the first type, the initial model examined the crude relationship between depressive symptoms reported at baseline and subsequent stroke mortality. Initial analyses modeled depression continuously. However, because our prior use of the HPL Depression Scale indicated that a cutoff of 5 symptoms was indicative of significant symptomatology,[30-32] subsequent analyses contrasted subjects with 5 or more depressive symptoms and those with fewer than 5 symptoms. Covariate adjustments for age, sex, and race (white or nonwhite) were then added. A third Cox model was then calculated that also included covariates representing the 1965 values of education, alcohol consumption, smoking, body mass index, and history of hypertension and diabetes.

The second type of model used consisted of time-dependent covariate models, which were calculated to determine if changes in depressive symptoms and changes in risk factor levels during follow-up influenced the association between depression and stroke mortality. In these analyses, all variables except age, sex, and race were allowed to change based on data from the additional survey periods. For example, a participant who reported that he or she drank 20 drinks per month in 1965 but whose alcohol consumption had increased to more than 50 drinks per month in 1974 would be scored as a "moderate drinker" from 1965 to 1973, and as a "heavy drinker" from 1974 until date of censor or death or until his or her reported average alcohol consumption changed in a subsequent survey. Our 1983 survey was conducted on a 50% sample and thus we did not obtain information on depressive symptoms or covariates for a large number of participants for whom we had data in 1965 and 1974. Consequently, 68 stroke deaths were counted as "censored" observations owing to missing data in the time-dependent covariate models, leaving a total of 101 fatal stroke cases in these analyses.

the Alameda County Study in which data on depressive symptoms and other risk factors were obtained on multiple occasions between 1965 and 1994. Using information from repeated assessments of these variables enabled us to more rigorously examine the relationship between depression and stroke mortality, which could be expected to vary with changes in risk factors over time.

RESULTS

SUBJECT CHARACTERISTICS

At baseline, participants ranged in age from 17 to 94 years (mean, 43.4; SD, 15.9), 45.8% were male, and 79.1% were white. Most (65%) participants had completed 12 or more years of school, although nearly 18% reported less than 9 years of formal education. Approximately 14.5% of participants reported consuming more than 45 alcoholic drinks per month (coded by the quantity and frequency of beer, wine, and liquor intake), 63.5% reported more moderate alcohol consumption (<45 drinks in a month), and 22% were abstainers. At baseline, 39.7% of subjects were never smokers, 15.7% were former smokers, and 44.6% were current smokers. A total of 677 (10.1%) participants reported a history of hypertension, and 143 (2.1%) reported a history of diabetes. Mean body mass index was 23.8 kg/m^2.

DEPRESSIVE SYMPTOMS, RISK FACTORS, AND STROKE MORTALITY

A total of 969 subjects (14.5%) reported 5 or more depressive symptoms at baseline. As shown in **Table 1**, these subjects were older, less likely to be male or white, less likely to have at least 12 years of education, more likely to be abstainers and current smokers, and more likely to have prevalent hypertension and prevalent diabetes than those who were not depressed at baseline

Table 1. Subject Characteristics and Risk Factors by Level of Depressive Symptoms Among 6676 Adults, Alameda County, California, 1965-1994*

Characteristic	Nondepressed (n = 5707)	Depressed (≥5 Depressive Symptoms) (n = 969)	P†
Age, y	43.0 (15.6)	45.6 (17.5)	.001
BMI, kg/m^2	23.9 (3.6)	23.9 (4.4)	.69
Male	2702 (47.3)	358 (36.9)	.001
White	4542 (79.6)	740 (76.4)	.02
Education			
<12 y	1886 (33.0)	456 (47.1)	.001
≥12 y	3821 (67.0)	513 (52.9)	.001
Alcohol consumption			
Abstainers	1188 (20.8)	273 (28.2)	.001
Heavy drinkers	837 (14.7)	134 (13.8)	.49
Smoking			
Never	2295 (40.2)	355 (36.6)	.04
Former	926 (16.2)	124 (12.8)	.007
Pack-years	16.0 (17.6)	14.3 (14.8)	.25
Current	2486 (43.6)	490 (50.6)	.001
Pack-years	19.3 (16.4)	21.0 (17.4)	.03
Prevalent disease			
Hypertension	504 (8.8)	173 (17.9)	.001
Diabetes	114 (2.0)	29 (3.0)	.05

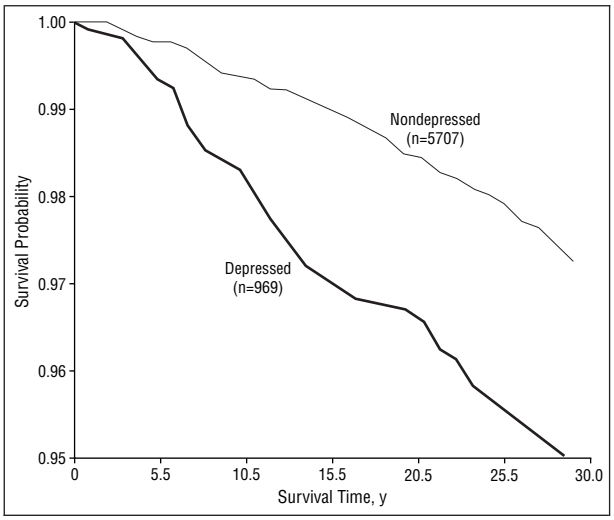
**Values are given as number (percentage) except for age, body mass index (BMI), and pack-years, which are mean (SD).*
† P values are from χ^2 or paired t *tests.*

($P<.05$). In addition, among those who were current smokers at the time of the baseline survey, the depressed group had more pack-years of smoking than the nondepressed group ($P<.03$). Depressed and nondepressed groups did not differ in body mass index or prevalence of heavy drinking.

One hundred sixty-nine stroke deaths occurred during follow-up, 39 of which occurred among participants reporting 5 or more symptoms of depression (4.0%) and 130 of which occurred among the nondepressed group (2.3%). The **Figure** illustrates the Kaplan-Meier cumulative survival curves for the depressed and nondepressed groups. The unadjusted Cox model hazard ratio associated with having 5 or more depressive symptoms was 1.94 (95% confidence interval [CI], 1.36-2.78; $P<.001$).

Table 2, top, presents the unadjusted results from the analysis with depressive symptoms modeled continuously and the findings from the models with depression modeled categorically, with added covariates. Each 1-point increase on the HPL Depression Scale was associated with more than an 8% increase in risk of death from stroke ($P<.003$). With depressive symptoms modeled categorically, the risk associated with reporting 5 or more depressive symptoms was 1.66 ($P<.006$), after adjustments for age, sex, and race. In the model that included additional adjustments for baseline values of education, alcohol consumption, smoking, hypertension, diabetes, and body mass index, having 5 or more depressive symptoms was associated with a 54% increased risk of stroke mortality ($P<.02$).

The time-dependent covariate models, shown in Table 2, bottom, revealed a similar, albeit slightly weaker,



Cumulative survival without fatal stroke by depression status among residents of Alameda County, California, 1965-1994.

Table 2. Relation Between Depressive Symptoms and Stroke Mortality With Baseline and Time-Dependent Covariates in 6676 Adults, Alameda County, California, 1965-1994*

Model	Covariates Included	RH (95% CI)	P
	Baseline Covariates		
I	Unadjusted, depressive symptoms modeled continuously	1.09 (1.03-1.15)	.003
II	Age, sex, and ethnicity, depressive symptoms modeled categorically	1.66 (1.16-2.39)	.006
III	Model II plus risk factors	1.54 (1.06-2.22)	.02
	Time-Dependent Covariates		
I	Unadjusted, depressive symptoms modeled continuously	1.06 (0.99-1.14)	.10
II	Age, sex, and ethnicity, depressive symptoms modeled categorically	1.56 (0.98-2.47)	.06
III	Model II plus risk factors	1.55 (0.97-2.47)	.07

**RH indicates relative hazard ratio; CI, confidence interval. Models II and III contrasted persons with 5 or more depressive symptoms to those with less than 5 depressive symptoms. Baseline covariates model: number of stroke deaths, 169. Time-dependent covariates model: number of stroke deaths, 101. Risk factors in model III were allowed to vary according to information obtained in each of 3 waves of data collection (1965, 1974, and 1983) and included education, smoking, alcohol consumption, body mass index, hypertension, and diabetes.*

pattern of associations. The initial model, with scores on the measure of depression modeled continuously and allowed to vary with each wave of data collection and age, sex, and race held constant, revealed a 6% increase in risk of stroke mortality with each 1-point increase in depression ($P<.10$). In the categorical model, with age, sex, and race held constant and number of times 5 or more depressive symptoms were reported in the successive waves of data collection allowed to change, self-report of 5 or more depressive symptoms was associated with a 56% increased risk of stroke mortality ($P<.06$). The elevation in risk associated with a high level of depressive symptoms was essentially unchanged in the fully adjusted model in which covariates for all risk factors were allowed to vary according to participants' reported values

in 1965, 1974, and 1983. Clearly, the point estimates for these models were similar to those with the baseline covariates, although the statistical significance was diminished slightly because of the fewer number of fatal strokes included in the analyses.

EFFECT OF PREVALENT CVD

Because rates of depressive syndromes are known to be elevated among individuals with CVD,[11,13-15] we recalculated the Cox model examining the relationship between baseline level of depressive symptoms and subsequent stroke mortality, excluding 259 participants (including 11 cases of fatal stroke) who reported a history of heart disease in 1965. Results were unchanged from the original model. Each 1-point increase in depression was associated with an 8% increase in risk of stroke mortality (hazard ratio, 1.08; 95% CI, 1.02-1.15; $P<.006$); and persons reporting 5 or more depressive symptoms at baseline had 70% excess risk of stroke mortality, after adjustment for age, sex, and race (hazard ratio, 1.70; 95% CI, 1.15-2.50; $P<.007$). Additional adjustments for education, alcohol consumption, body mass index, smoking status, diabetes, and hypertension had little effect on this relationship (hazard ratio, 1.57; 95% CI, 1.06-2.32; $P<.03$).

EFFECT OF EARLY DEATHS

Because symptoms of depression may be a response to illness and we wanted to exclude individuals who may have been sick at the beginning of the study, baseline covariate analyses were then repeated eliminating the participants who died during the first 3 years of the study of stroke (n=14) or any other cause (n=231). Again, each 1-point increase on the measure of depression was associated with nearly an 8% increase in risk of stroke mortality in the initial model (hazard ratio, 1.08; 95% CI, 1.02-1.14; $P<.01$). Similarly, the categorical models showed that individuals with 5 or more depressive symptoms at baseline were at 1.67-fold increased risk of subsequent mortality due to stroke (95% CI, 1.14-2.45; $P<.008$), which remained significantly elevated after adjustment for all risk factors (hazard ratio, 1.53; 95%CI, 1.04-2.26; $P<.03$).

COMMENT

This population-based study provides, to our knowledge, the best epidemiological evidence to date for a significant, positive relationship between depressive symptoms and stroke mortality. After adjustment for established stroke risk factors, individuals reporting 5 or more symptoms of depression at baseline experienced more than 50% excess risk of mortality due to stroke during the subsequent 29 years. This level of risk was unchanged after taking into account changes in reported depressive symptoms and risk factor levels during follow-up. Moreover, these relationships were upheld in models that excluded early deaths and individuals with prevalent CVD at baseline. The consistency of the association between depressive symptoms and stroke mortality is highlighted by the relatively unchanged effect sizes we observed in our various statistical models.

The mechanisms by which depression may increase stroke risk remain to be determined. Our data show that behavioral factors do not explain the association between depression and stroke mortality. For example, although participants with 5 or more symptoms of depression were more likely to smoke and to have more pack-years of smoking than those who were not depressed (Table 1), smoking did not significantly affect the observed association. Similarly, preexisting hypertension or diabetes accounted only for a small portion of the relationship. Our measures of hypertension and diabetes were by self-report only, which may not be as sensitive as other measures of disease, eg, medication review or physician report; however, these risk factors were significant or marginally significant ($P<.20$) covariates in our models. Thus, although our self-report measures were not ideal, they were reliable indicators of these risk factors and important covariates in our models.

Other risk factors, unavailable to us, also should be considered. For example, associations between depression or other affective states and lipid levels or metabolism, while somewhat conflicting, have been reported[13,37-39] and it will be important for future research to examine these potential pathways. New evidence indicates that platelet calcium (Ca++) responsivity to serotonin is heightened in depressed patients,[40] suggesting that platelet activation could also be an important factor in the relationship between depression and stroke mortality. In addition, depression may increase stroke mortality through immunological or neuroendocrine mechanisms. The present study did not have the data to examine these hypotheses, although other studies are suggestive.[18,19,41,42]

Nearly 15% of participants in this study reported 5 or more symptoms of depression at baseline. Our measure of depression estimates the point prevalence of depressive symptoms but our rates do not reflect the prevalence of clinical depression. This measure includes many (but not all) symptom criteria for major depression from the *DSM-III-R*. Because our data are self-report, we were not able to use *DSM-III-R* exclusionary criteria; therefore, our prevalence rates are higher than would be the case if clinical diagnoses had been made on the basis of structured psychiatric interviews. However, available data (not shown) from our 1994 survey, which included a measure with full coverage of *DSM-III-R* symptom criteria as well as the HPL Depression Scale, indicate that 65% of those with 5 or more symptoms on the HPL Depression Scale also met the criteria for major depressive episode according to *DSM-III-R* criteria. Also, as noted elsewhere,[32,43,44] the 2 different measurement strategies assess somewhat different domains of depressive experience. Clinical depression can be a serious, debilitating chronic disease; however, the presence of many symptoms of depression can also involve considerable impairment and negative sequelae. Thus, our symptom-based measure may underestimate the effect of depression on risk of stroke.

Some limitations to our study should be noted. We did not have access to data on nonfatal strokes and thus

were unable to examine the relation between depression and incident stroke among our participants. Such data would provide valuable information and greater understanding of the role of depression in stroke risk. We also did not have data on the types of stroke participants suffered. It would be interesting to determine if depression had more or less impact on hemorrhagic vs ischemic stroke. Such information may provide clues to the mechanisms underlying the association. Also, we had too few stroke deaths among women to reliably investigate sex differences in the association between depression and stroke mortality. Given that women have higher rates of depression,[45] and that stroke accounts for a greater proportion of overall deaths among women than among men,[46] it is critical that this issue be addressed.

In sum, the present study provides compelling evidence that depressive symptoms are a significant factor in subsequent stroke mortality in a representative adult sample. These results contribute to the growing literature on the adverse health effects of depression. Given the high lifetime prevalence rates of depression in the United States for men (2.8/100) and women (7.4/100),[47] and the convincing evidence that depression has a strong negative impact on physical health, in addition to its devastating mental health consequences, it is imperative that symptoms of depression be recognized and appropriately treated.

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