Depressive Symptoms, Inflammation, and Ischemic Stroke in Older Adults: A Prospective Analysis in the Cardiovascular Health Study

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OBJECTIVES: To investigate the mediator role of inflammation in any relationship between depressive symptoms and ischemic stroke.

DESIGN: Longitudinal prospective study.

SETTING: Review of medical records, death certificates, and the Medicare healthcare utilization database for hospitalizations.

PARTICIPANTS: Total of 5,525 elderly men and women aged 65 and older who were prospectively followed from 1989 to 2000 as participants in the Cardiovascular Health Study.

MEASUREMENTS: Depression symptom scores, inflammatory markers.

RESULTS: Greater depressive symptoms were associated with risk of ischemic stroke (unadjusted hazard ratio (HR) = 1.32, 95% confidence interval (CI) = 1.09–1.59; HR = 1.26, 95% CI = 1.03–1.54, adjusted for traditional risk factors). When a term for inflammation (C-reactive protein (CRP)) was introduced in the model, the HRs were not appreciably altered (unadjusted HR = 1.31, 95% CI = 1.08–1.58; adjusted HR = 1.25, 95% CI = 1.02–1.53), indicating that CRP at baseline was not a mediator in this relationship. In analyses stratified according to CRP levels, a J-shaped relationship between depressive symptoms and stroke was evident in the unadjusted analyses; in the fully adjusted model, only CRP in the highest tertile was associated with a higher risk for stroke in the presence of higher depressive symptoms scores.

CONCLUSION: The analyses from this prospective study provide evidence of a positive association between depressive symptoms and risk of incident stroke. Inflammation, as measured according to CRP at baseline, did not appear to mediate the relationship between depressive symptoms and stroke. **J Am Geriatr Soc 55:1825–1830, 2007.**

Key words: stroke; depressive symptoms; inflammation; CHS; cohort

Several epidemiological studies indicate a positive association between depressive symptoms and stroke.[1–8] All of these have been longitudinal studies that have controlled for most of the commonly accepted stroke etiological factors. Although the relationship between depression and cerebrovascular disease events has been consistent, current understanding of the underlying mechanisms remains speculative. It has been hypothesized that inflammation could be one of the mechanisms by which depression increases risk for ischemic stroke. Inflammatory factors have been linked to stroke.[9–11] For example, one study found a relative risk of 1.2 (95% confidence interval (CI) = 1.01–1.54) in men and 1.3 (95% CI = 1.07–1.55) in women for stroke in subjects with high levels of C-reactive protein (CRP) after adjusting for common stroke risk factors. [9] Another study found that CRP was an independent risk factor for stroke and that carotid intima-media thickness did not appear to act as the mediator.[11] Recently, inflammation has also been linked to depression. A third study showed that elevated CRP, fibrinogen, and factor VIIc were associated with depression in older adults, although it found that exhaustion and fatigue had a stronger association with CRP than depression.[12] In young adult men included in the Third National Health and Nutrition Examination Survey sample, CRP was associated with current depression even after adjustment for body mass index (BMI), smoking, and health status. Men whose depression had resolved had almost the same prevalence of high CRP as those who had never experienced a major depressive episode.[13]

A systematic review and meta-analysis reported that CRP was associated with risk of stroke and cognitive impairment, but the relationship between CRP and depression was not consistent. Most of these studies have been cross-sectional, and the causal pathway between CRP and

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depression may be bidirectional. One conclusion was that future prospective studies designed to elucidate these associations are warranted.[14]

Current understanding of the underlying mechanisms by which depression increases the risk of stroke remains uncertain. This study examined prospectively the relationship between depressive symptoms and ischemic stroke using data from a large community-based cohort of older adults. The extent to which inflammation acts as a mediator for the relationship between depressive symptoms and stroke was assessed. Because depressive symptoms and inflammation may act synergistically to increase risk of stroke, whether the relationship between depressive symptoms and stroke differs according to level of inflammation was also examined. If inflammation was the primary pathway by which depression leads to stroke, preventive interventions could be targeted to normalizing inflammation.

METHODS

Description of Population

The Cardiovascular Health Study (CHS) is a longitudinal, observational study of men and women aged 65 and older designed to investigate risk factors for cardiovascular disease.[15] The main outcome measures in the CHS were coronary heart disease (CHD), peripheral vascular disease, and stroke. In the CHS, a total of 5,888 participants from a sample of Medicare-eligible individuals residing in one of four communities (Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Pittsburgh, Pennsylvania) were enrolled in two phases. In the initial recruiting phase, 5,201 participants were enrolled between 1989 and 1991. A second enrollment of 687 African-American participants was completed between 1992 and 1993. The exclusion criteria for the CHS included hospice treatment, being wheelchair bound in the home, and undergoing radiation or chemotherapy for cancer. Additionally, for this analysis, all participants in whom record review confirmed self-reported history of stroke were included. The institutional review boards at each participating institution approved the research protocols.

Data Collection

Depressive Symptoms

Information on depressive symptoms was based on questionnaire-derived data collected by trained interviewers in the CHS at baseline (1989–1991). Depressive symptoms were evaluated using the Center for Epidemiological Studies Depression Scale (CES-D).[16] A modified version of the CES-D with only 10-items was used in the CHS study.[17] The CES-D assesses frequency of depressive symptoms experienced in the previous week. The items are scored on a 4-point (0 = rarely to 3 = always) scale, and individual item scores are totaled to yield a summary score. Higher scores indicate more depressive symptoms. The traditional score (>8) on the 10-item CES-D, which has been considered to indicate "high likelihood of clinical depression," was used. This scale is reliable, and other investigators have validated it.[18] Its psychometric properties include a sensitivity of 90% and a specificity of 72% for major depression.[19]

Inflammatory Markers

Blood was drawn in the morning after an overnight fast. Samples were promptly centrifuged at 3,000 *g* for 10 minutes at -70°C. CRP was measured in 1997 on all stored baseline plasma samples using a high-sensitivity immunoassay with an interassay coefficient of variation of 6.25%. CRP levels at baseline were available as a continuous variable and were categorized into tertiles for the analyses.

Other Covariates

Information on sociodemographic characteristics (age, sex, race, education, income, occupation, marital status) and self-report of chronic diseases (hypertension, diabetes mellitus, and coronary heart disease) were collected at baseline. Anthropometric measurements and blood pressure were also recorded at baseline. BMI was calculated as weight (kg) per height (m) squared. Trained personnel measured blood pressure. The mean of two readings was used for this analysis. Hypertension was defined as a previous diagnosis of hypertension, taking antihypertensive medication, or having a current systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mm Hg or higher. Persons were considered diabetic if they had a medical diagnosis of diabetes mellitus or a fasting glucose of 126 mg/dL or higher. Information about smoking history was ascertained at baseline. Total cholesterol levels, high-density lipoprotein cholesterol (HDL-C) levels, and triglycerides were measured in blood samples at baseline, using well-established quality-assurance methods.[20] Low-density lipoprotein cholesterol (LDL-C) was estimated using Friedewald's formula.[21]

Diagnosis of Stroke

Methods for the classification of stroke status and subtype in the CHS have been reported elsewhere in detail.[22,23] Briefly, comprehensive protocols were conducted to identify cerebrovascular events or death during the course of the study. Participants were contacted every 6 months to establish vital status and to screen for the occurrence of events. Confirmation of events and deaths were conducted through review of medical records, death certificates and the Medicare healthcare utilization database for hospitalizations. Participants and contacts of participants unavailable for follow-up were interviewed about the event or death. When stroke was suspected, the study neurologist at the study site reviewed all sources of information (medical records and death certificates). Raters did not have access to participants' CES-D scores. The cerebrovascular adjudication committee, comprising study neurologists from each of four study sites, a neuroradiologist from the magnetic resonance imaging reading center, and an internist or neurologist representing the Coordinating Center reviewed all cerebrovascular events and all deaths. A neurologist in each center abstracted and reviewed hospital records for all reported strokes with *International Classification of Diseases, Ninth Revision*, codes 430 through 438 identifying cerebrovascular disease. Neuroimaging studies were completed for 86% of the participants. The committee considered all clinical and radiological information to decide whether a nonfatal stroke or fatal stroke had occurred and, if appropriate, assigned a stroke type: ischemic, hemorrhagic, or uncertain. The committee considered a death to be related

to a stroke when a majority opinion was that, more likely than not, the death would not have occurred in the absence of stroke. Stroke was defined as a neurological deficit of rapid onset lasting more than 24 hours or, if less than 24 hours, an appropriate lesion to explain the deficit seen on brain imaging. Time of stroke was established according to the first diagnosis, if recorded in medical records, or on the death certificate.

Statistical Analysis

The chi-square (χ^2) test was used to assess associations between categorical variables. Differences in means of risk factors levels between the depressed group and the nondepressed group were tested using a *t*-test. Because of skewed distribution, CRP was log transformed for analyses when indicated. Incidence rates of stroke were calculated according to depressive symptoms category. Cox proportional hazards models were used to compute HRs as estimates of relative risk of stroke for high depressive scores, with adjustment for sociodemographic (age, sex, race, occupation, income, education level, marital status) and classic stroke risk factors (hypertension status, diabetes mellitus status, smoking, CHD status, cholesterol, HDL-C, LDL-C, triglycerides, and BMI) (Figure 1).

The interaction between depressive symptoms and CRP as continuous variables and as categorical variables was tested. To determine the extent to which inflammation mediates the relationship between depressive symptoms and stroke, Cox regression was used to compare the analyses with and without CRP in the unadjusted and adjusted models. All statistical analyses were performed using Stata version 7.0 (Stata Corp., College Station, TX). All tests were two sided, and statistical significance was considered at an alpha level of 0.05.

RESULTS

Of the 5,888 participants in the study, 249 were excluded because of the presence of baseline stroke. Thus, 5,639 were considered for this analysis. Because there was no relationship between depressive symptoms and hemorrhagic strokes (n = 114), hemorrhagic strokes were also excluded from the remaining analyses, leaving 5,525 participants.

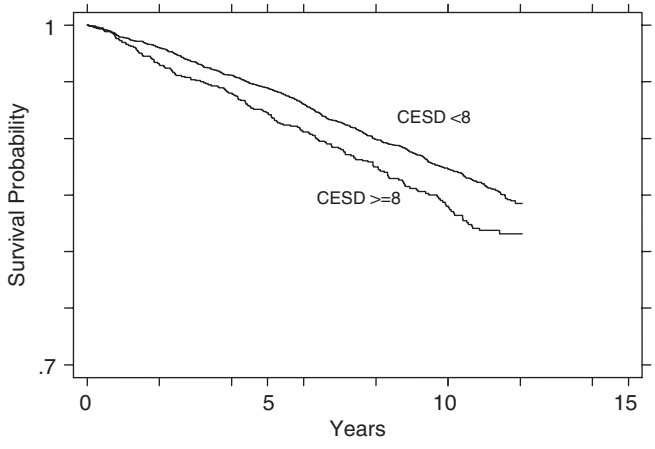

Figure 1. Time to first ischemic stroke according to depressive scores, Cardiovascular Health Study 1989–2000.

The Kaplan–Meier curve shows that subjects with high depressive scores ($\geq$8 points) had greater risk of stroke than subjects with low depressive scores ($<$8 points), with no stabilization of risk. The difference in the risk of stroke between the two categories of depressive symptoms was highly statistically significant (log rank value = 8.33, P = .004).

The baseline characteristics of the study cohort according to stroke status are presented in Table 1. Participants with incident ischemic stroke were more likely to be older and nonprofessional; have an income less than $25,000; have a lower educational level; and be widowed, divorced, or separated. No differences were found according to sex or race. Participants with stroke were more likely to have a history of hypertension, diabetes mellitus, impaired fasting glucose, and coronary heart disease and higher systolic and diastolic blood pressure, cholesterol, triglycerides, and depressive scores than their counterparts without stroke. No differences were found according to BMI, HDL-C, or LDL-C. Mean and median baseline CRP was significantly higher in the stroke group than in the control group ($P<.01$). Participants with higher depressive scores were more likely to be older, female, African American, and nonprofessional; have an income less than $25,000; have a lower educational level; and be widowed, divorced, or separated. Compared to those with lower depressive scores participants with higher depressive symptoms scores were also more likely to have a history of hypertension, diabetes mellitus, and coronary heart disease; to be a current smoker; and to have higher BMI, HDL-C, and CRP levels than those with lower depressive symptoms scores.

During a median follow-up of 11 years, 607 incident ischemic strokes occurred: an incidence rate of 12.1 strokes per 1,000 person-years. Incidence rates were 14.9 and 11.4 strokes per 1,000 person-years for individuals with and without depression, respectively ($P<.01$). When subjects without depression were stratified according to CRP levels, stroke incidence rates were lowest in the lowest CRP tertile (9.6 per 1,000 person-years) and highest in the highest CRP tertile (13.2 per 1,000 person-years). For participants with higher depressive scores, a higher incidence rate was detected in the third tertile of CRP, with a range from 12.3 to 18.3 per 1,000 person-years.

Multivariate Survival Analysis

The unadjusted HR of ischemic stroke was 1.32 (95% CI = 1.09–1.59) for higher depressive symptoms. After adding the CRP term (as a continuous variable), the HR was not attenuated and was equal to 1.31 (95% CI = 1.08–1.58). After adjustment for sociodemographic characteristics (age, sex, race, occupation, income, education, and marital status) and traditional stroke risk factors (cholesterol, HDL-C, LDL-C, triglycerides, BMI, high blood pressure, diabetes status, and CHD status), depressed individuals had a 26% greater HR of ischemic stroke. Adding the CRP term as a continuous variable instead of a categorical variable to the fully adjusted model, the association between depressive mood and stroke remained of similar magnitude, and CRP contributed significantly to stroke risk.

Table 1. Baseline Characteristics of Participants According to Ischemic Stroke Status

Characteristic	Total Sample (N = 5,525)	Ischemic Stroke		*P*-value
		No (n = 4,914)	Yes (n = 611)	
	n (%)			
Age, mean ± SD	72.7 ± 5.6	72.5 ± 5.5	74.3 ± 5.7	<.001
Male, n (%)	2,312 (41.8)	2,059 (41.9)	253 (41.4)	.82
African American, n (%)	842 (15.3)	764 (15.7)	78 (12.8)	.07
Professional or technician, n (%)	1,939 (35.1)	1,742 (35.5)	197 (32.4)	.13
Income <$25,000, n (%)	3,184 (61.5)	2,799 (60.9)	385 (66.4)	.01
Education, n (%)				
High school or general equivalency degree	1,540 (28.0)	1,359 (27.7)	181 (29.8)	
Some college	1,807 (32.8)	1,619 (33.0)	188 (30.9)	
Graduate or professional	557 (10.1)	516 (10.5)	41 (6.7)	.007
Marital status, n (%)				
Widowed, divorced, or separated	1,634 (29.6)	1,433 (29.2)	201 (32.9)	
Never married	225 (4.1)	211 (4.3)	14 (2.3)	.02
Hypertension, n (%)				
Borderline	794 (14.4)	698 (14.2)	96 (15.7)	
Hypertensive	2,397 (43.4)	2,045 (41.7)	352 (57.7)	<.001
Diabetes mellitus, n (%)				
Impaired fasting glucose or glucose intolerance	741 (13.5)	640 (13.2)	101 (16.7)	
Diabetes mellitus	878 (16.1)	749 (15.4)	129 (21.4)	<.001
Smoking, n (%)				
Former smoker	2,283 (41.4)	2,043 (41.6)	240 (39.3)	
Current smoker	661 (12.0)	594 (12.1)	67 (11.0)	.26
Coronary heart disease, n (%)	1,052 (19.0)	893 (18.2)	159 (26.0)	<.001
Medication, n (%)				
Antidepressant	193 (3.5)	168 (3.4)	25 (4.1)	.40
Estrogen	385 (7.0)	348 (7.1)	37 (6.1)	.34
Aspirin	2,523 (46.1)	2,226 (45.7)	297 (48.8)	.16
Statins	124 (2.3)	113 (2.3)	11 (1.8)	.43
Body mass index, kg/m^2, mean ± SD	26.7 (4.7)	26.7 (4.8)	26.6 (4.5)	.55
Systolic blood pressure, mmHg, mean ± SD	136.2 ± 21.6	135.3 ± 21.2	143.5 ± 23.7	<.001
Diastolic blood pressure, mmHg, mean ± SD	70.7 ± 11.4	70.5 ± 11.3	72.2 ± 12.0	<.001
Cholesterol, mg/dL, mean ± SD	211.3 ± 39.2	210.9 ± 39.0	214.6 ± 40.3	.03
High-density lipoprotein cholesterol, mg/dL, mean ± SD	54.3 ± 15.6	54.4 ± 15.5	53.8 ± 17.0	.37
Low-density lipoprotein cholesterol, mg/dL, mean ± SD	129.9 ± 35.6	129.7 ± 35.5	132.0 ± 36.1	.13
Triglycerides, mg/dL, mean ± SD	139.2 ± 74.7	138.1 ± 74.4	147.8 ± 76.6	.003
Depression score, mean ± SD	4.66 ± 4.58	4.60 ± 4.56	5.14 ± 4.69	.006
C-reactive protein, mg/L, mean ± SD	3.57 ± 6.04	3.49 ± 5.71	4.21 ± 8.22	.005

SD = standard deviation.

Stratified Analyses

Whether depressive symptoms and inflammation might act synergistically to increase risk of stroke was analyzed (Table 2). Both variables (depressive symptoms and CRP) were first modeled as continuous variables at baseline. In these analyses, the interaction term did not meet criteria for statistical significance ($P = .85$), although the main effect terms for depressive symptoms and CRP remained statistically significant. When the data were analyzed according to tertiles of CRP, there appeared to be a J-shaped relationship, with the highest risk for participants with the highest CRP levels. Adjustment for multiple factors did not appreciably change the relationships.

DISCUSSION

These analyses demonstrated a positive relationship between baseline higher depressive symptoms and risk of ischemic stroke. Older adults with a depressive symptom score in the range of clinical depression at baseline had, on average, a 32% greater HR for ischemic stroke. This HR was minimally lower after adjustment for sociodemographic

Table 2. Baseline Depressive Scores and Risk of Ischemic Stroke Stratified According to C-Reactive Protein (CRP) Level

Center for Epidemiologic Studies Depression Scale Score	Hazard Ratio (95% Confidence Interval) *P*-Value	
	Unadjusted	Adjusted*
CRP tertile 1		
<8	1.00 (Reference)	1.00 (Reference)
≥8	1.45 (1.03–2.06) .03	1.30 (0.90–1.88) .16
CRP tertile 2		
<8	1.00 (Reference)	1.00 (Reference)
≥8	1.05 (0.74–1.49) .80	1.02 (0.69–1.51) .92
CRP tertile 3		
<8	1.00 (Reference)	1.00 (Reference)
≥8	1.39 (1.04–1.86) .03	1.43 (1.04–1.97) .03
Mantel-Haenszel hazard ratio	1.29 (1.07–1.56) .007	1.25 (1.02–1.53) .03

*Adjusted for age, sex, race, occupation, income, education level, marital status, hypertension status, diabetes status, smoking, coronary heart disease status, cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and body mass index.

characteristics and other traditional stroke risk factors, including smoking and existing clinical cardiovascular disease. There was essentially no association between depressive symptoms and hemorrhagic stroke. These results confirm those reported in other prospective studies.[1–3,5,7,8]

Even though there was a positive association between level of CRP and baseline depressive symptoms, it was not found that CRP acted as an important mediator in the relationship between depressive symptoms and stroke. It is possible that the relationship between depressive symptoms and stroke was too weak to allow an adequate test of inflammation as a mediator. Another aspect of the analysis that should be kept in mind is that CRP was measured at baseline. Although little is known about the temporal relationship between depressive symptoms and CRP, it is possible that the results would have been different if CRP had been measured months or years after the depressive symptoms were measured. This would be a more-definitive test of inflammation as a mediator between depressive symptoms and stroke. Because it has been suggested that the association between CRP and stroke might be stronger in men than in women,[11] a stratified analysis was conducted based on sex. The results for men and women were similar, with no suggestion that inflammation was an important mediator for the relationship between depressive symptoms and stroke. CRP was an inflammatory indicator in our analyses. Interleukin-6 and other inflammatory markers could be mediators in the relationship between depression and stroke.[24] The data from the current study suggest that there may be pathways other than inflammation by which depressive symptoms act as a risk for stroke. Possibilities include platelet dysfunction, abnormalities in blood coagulation, endothelial dysfunction, autonomic dysfunction, and abnormalities in heart rate variability.[25–28]

A pattern was identified in unadjusted and fully adjusted models, indicating that depressed individuals in the highest tertile of CRP had a greater risk of stroke than those in the other two tertiles. Although this relationship needs to be confirmed before changing any clinical practice guidelines, it is possible that the combination of depressive symptoms and elevated CRP may be useful for targeting interventions to a high-risk group.

LIMITATIONS

These analyses have some limitations. First, no diagnostic confirmation of depression was completed. Depressive symptoms as the exposure variable was considered to be a proxy for a clinical diagnosis of major depression. The CES-D has been found to be a good screening instrument for major depression with good to excellent sensitivity and specificity.[18] The results might have been different if there had been a measure of clinical depression. For example, a previous study reported findings indicating a dose–response relationship between diagnostically defined depression and stroke.[7] Second, there is the possibility of residual confounding, although the maximum information available for the reported statistical models was used, and it was possible to include information on a number of potential confounding factors. In addition, depressive symptoms were assessed as a continuous and a categorical variable. The consistency of findings was preserved. Third, the possibility cannot be excluded that higher depressive symptoms scores are not a consequence of subclinical strokes. The clinical evidence of stroke at baseline was used as an exclusion criterion. Subclinical cases could have been identified using MRI. Although the CHS investigators conducted an MRI evaluation, it was done in the third year of the study and not at baseline. Consequently, it was decided not to use this information. Fourth, the CHS participants might differ with respect to some characteristics from the general older adult population, although the rate of higher depressive symptom scores in this study was comparable with what has been found in other studies of older adults in the general population. There is no evidence to support a selection differential according to depression status, and the internal validity necessary for comparisons should be preserved.

Notwithstanding these limitations, the current report improves understanding of the relationships between depressive symptoms and inflammation with the subsequent development of ischemic stroke. Future analyses will need to explore in more detail the temporal relationships between depressive symptoms and inflammatory markers and to examine other mechanisms that may mediate the effect of depression on cerebrovascular disease. Depression has been found to be a risk factor for a wide range of cardiovascular diseases and has been associated with some measures of subclinical atherosclerosis,[29] suggesting that platelet aggregation is not the sole mechanism. Multiple pathways leading to atherosclerosis will need to be considered.

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