Depressive symptoms predict incident stroke independently of memory impairments

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ABSTRACT

Background: We evaluated whether depressive symptoms predict the onset of first stroke independently of memory impairment. We conceptualized memory impairment as a marker of preexisting cerebrovascular disease. We hypothesized that if depressive symptoms are causally related to stroke through mechanisms unrelated to cerebrovascular disease, depressive symptoms should predict stroke independently of memory impairment.

Methods: Incidence of first stroke was assessed with self or proxy reports from 19,087 participants in the Health and Retirement Study cohort (1,864 events). Elevated depressive symptoms (3+ on an 8-item Centers for the Epidemiologic Study of Depression scale) and memory impairment (score of ≤6 on a combined immediate and delayed recall of a 10-word list) were used as predictors of incident stroke in Cox survival models with adjustment for sociodemographic and cardiovascular risk factors.

Results: After adjustment for sociodemographic and cardiovascular risk factors, elevated depressive symptoms (hazard ratio = 1.25; 95% confidence interval 1.12–1.39) and memory impairment (hazard ratio = 1.26; 95% confidence interval 1.13–1.41) each predicted stroke incidence in separate models. Hazard ratios were nearly unchanged and remained significant (1.23 for elevated depressive symptoms and 1.25 for memory impairment) when models were simultaneously adjusted for both elevated depressive symptoms and memory impairment. Elevated depressive symptoms also predicted stroke when restricting analyses to individuals with median memory score or better.

Conclusions: Memory impairments and depressive symptoms independently predict stroke incidence. Memory impairment may reflect undiagnosed cerebrovascular disease. These results suggest that depressive symptoms might be directly related to stroke rather than merely indicating preexisting cerebrovascular disease. *Neurology*® 2010;75:2063–2070

GLOSSARY

AF = atrial fibrillation; **BMI** = body mass index; **CES-D** = Centers for Epidemiologic Study of Depression; **CI** = confidence interval; **HPA** = hypothalamic-pituitary-adrenal; **HR** = hazard ratio; **HRS** = Health and Retirement Study; **IPW** = inverse probability weighting; **TICS** = Telephone Interview for Cognitive Status.

Stroke incidence is predicted by both cognitive impairment and depressive symptoms.[1-12] Associations are most consistent using measures of depressive symptoms,[7-12] but are also apparent with diagnostic measures of depression.[5,6]

Impaired cognitive performance correlates with indicators of subclinical cerebrovascular disease, such as white matter hyperintensities,[13-15] and is probably an early manifestation of vascular brain injury. However, it is uncertain whether depressive symptoms are markers of the same cerebrovascular pathologic process or represent independent physiologic mechanisms influencing stroke. Depressive symptoms are common sequelae of stroke[16] and subclinical cerebrovascular injuries are hypothesized to induce "vascular depression"; thus depressive

Supplemental data at www.neurology.org

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References e8, e9, e11, and e13 are listed in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

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symptoms may be merely markers for preexisting cerebrovascular disease.[17-19] This interpretation implies that depression does not cause stroke, so treating or reducing depressive symptoms would not reduce stroke risk.

In contrast to this hypothesis, depression may increase stroke risk, via vascular disease or acute stroke triggering mechanisms. Depression in healthy or patient samples is associated with adverse behavioral changes,[20] as well as physiologic disturbances affecting inflammatory pathways, the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and amygdalar regulation of the HPA, which may all influence stroke risk.[21-24]

This study aimed to evaluate competing models of the association between depressive symptoms and stroke: depression influences stroke vs depression is a marker of subclinical cerebrovascular disease. We hypothesized that if cognitive scores and depressive symptoms are markers of the same underlying physiologic pathway, adjustment for cognitive scores should substantially attenuate the association between depressive symptoms and stroke incidence.

METHODS

Study population. Data come from the Health and Retirement Study (HRS), a longitudinal national survey of US adults aged 50+ and their spouses. The HRS is sponsored by the National Institute on Aging (grant NIA U01AG009740) and is conducted by the University of Michigan. Study details and measurements are provided elsewhere.[25] Enrollment was staggered by birth cohort with enrollments in 1992, 1993, and 1998. The 1992 enrollment cohort first received standardized depression and memory assessments in 1996, so we consider 1996 interviews baseline for this cohort. Biennial interviews (or proxy interviews for decedents) were conducted through 2006. We included HRS participants age 50+ reporting themselves stroke-free at baseline interview. Original survey response rates varied across enrollment cohorts (70%–81%), and retention was high through 2006 (82%–86%).

From 24,372 age-eligible respondents, 1,834 (7.5%) were excluded due to reporting a stroke that occurred prior to baseline. From these 22,538 potentially eligible participants, 2,095 (8.6%) were excluded due to missing information on baseline depressive symptoms or baseline memory, 638 (2.6%) were excluded due to missing covariates, and 718 (2.9%) were excluded due to missing follow-up information, leaving 19,087 individuals contributing information to the primary analyses (154,751 person-years) and 1,864 events observed.

Standard protocol approvals, registrations, and patient consents. The HRS is approved by the University of Michigan Health Sciences Human Subjects Committee and written informed consent was obtained from all participants.

Stroke outcomes. Incident events were defined as first nonfatal or fatal stroke, based on self- or proxy-reported doctor's diagnosis ("Has a doctor ever told you that you had a stroke?"). Reports of temporary ischemic attacks were not systematically assessed and so were not coded as strokes. When participants were deceased or unavailable for direct interviews, proxy informants, typically spouses, were interviewed. It was not possible to verify self-reported strokes by clinical diagnosis or medical record review; our previous research on major risk factors and incident stroke in HRS suggests bias due to misclassification is modest.[26]

Respondents reported stroke month and year; events with unknown date within 2-year interview intervals (n = 302) were assigned the median month for events reported by others in the same interview wave.

Primary exposures and covariates. Elevated depressive symptoms were defined as scoring 3+ on an 8-item version of the Centers for Epidemiologic Study of Depression (CES-D) scale, following prior work.[27] Questions elicited yes/no answers: "Now think about the past week and the feelings you have experienced. Please tell me if each of the following was true for you much of the time this past week. Much of the time during the past week … I felt depressed/felt that everything I did was an effort/my sleep was restless/could not get going/felt lonely/enjoyed life/felt sad/was happy." Cronbach α (measuring internal consistency) for baseline CES-D was 0.80 (appendix e-1 on the *Neurology*® Web site at www.neurology.org). Memory impairment was assessed by summing immediate and delayed recall of 10-word lists of common nouns. Each word recalled was 1 point (total range 0–20). We classified anyone with a combined score of ≤6 as memory impaired.

Additional control variables were added in stages ordered by their life course timing and relationships with primary exposures. We first added core demographic covariates: age, age-squared, race (black or white), Hispanic ethnicity, Southern birth, father's and mother's education of 8+ years, and HRS enrollment year. These variables predict stroke and temporally precede participants' current depressive status.[26] We next incorporated adjustment for adult social risk factors likely to predict stroke but potentially influenced by life course depression experiences: years of education, household income and wealth at baseline (income and wealth were natural log-transformed to reduce skew), and marital status (divorced, widowed, never married, or currently married). The third set of covariates comprises well-established stroke risk factors that cannot properly be considered confounders because they are probably influenced by prior depressive symptoms: smoking status (current/past/never), overweight (body mass index [BMI] 25–<30) or obese (BMI 30+), moderate alcohol use (<3/day or <18/week), or heavy alcohol use (≥3/day or ≥18/week), and self-reported baseline diagnoses of hypertension, diabetes, or heart disease. Coefficients from models including these last covariates should not be interpreted as "causal," but we show them to assess whether depressive symptoms predict stroke independently of these other risk factors. In supplementary analyses, we controlled for an additional indicator of cognitive impairment, the Telephone Interview for Cognitive Status (TICS, range 0–13),[28,29] available for a subsample of HRS respondents (n = 17,798).

Methods of analysis. We show Kaplan-Meier survival curves adjusted for confounders using inverse probability weighting (IPW).[30] Hazard ratios (HR) for stroke associated with elevated depressive symptoms and impaired memory scores were estimated with Cox proportional hazard models. The dependent variable in these models was months from baseline interview to onset of first stroke (results presented in the metric of person-years). For those without stroke, person-time was censored at last

Table 1 Characteristics of Health and Retirement Study participants, stratified by baseline depressive symptoms[a]

	Baseline CES-D <3	Baseline CES-D ≥3
No.	15,245 (100)	3,842 (100)
Mean ± SD years of follow-up	8.3 ± 3.0	7.5 ± 3.4
Total person-years of follow-up	126,037	28,714
Incident strokes	1,352 (9)	512 (13)
Baseline memory impairment	2,505 (16)	1,109 (29)
Core demographic variables		
Mean ± SD age at enrollment, y	65.5 ± 9.5	66.8 ± 10.3
Male	6,588 (43)	1,234 (32)
Black	1,913 (13)	722 (19)
Hispanic	897 (6)	448 (12)
Southern birth state	5,144 (34)	1,562 (41)
Mother's education, y		
<8	6,171 (40)	1,972 (51)
8+	7,629 (50)	1,345 (35)
Unknown	1,445 (9)	525 (14)
Father's education, y		
<8	6,587 (43)	1,999 (52)
8+	6,731 (44)	1,159 (30)
Unknown	1,927 (13)	684 (18)
Adult social conditions		
Mean ± SD years of education	12.4 ± 3.1	10.7 ± 3.5
Median wealth (interquartile range)[b]	85,820 (165,260)	88,410 (98,140)
Median income (interquartile range)[b]	30,130 (26,070)	18,740 (16,320)
Marital status		
Married	11,122 (73)	2,063 (54)
Divorced or separated	1,320 (9)	565 (15)
Never married	436 (3)	142 (4)
Widowed	2,367 (16)	1,072 (28)
Cardiovascular risk factors		
Current smoker	2,464 (16)	855 (22)
Past smoker	6,340 (42)	1,404 (37)
Overweight	6,076 (40)	1,434 (37)
Obese	2,958 (19)	936 (24)
Alcohol use		
Never	6,918 (45)	2,288 (60)
Some	7,922 (52)	1,447 (38)
Heavy	405 (3)	107 (3)
Hypertension	5,825 (38)	1,862 (48)
Diabetes	1,514 (10)	673 (18)
Heart disease	2,353 (15)	969 (25)

Abbreviation: CES-D = Centers for Epidemiologic Study of Depression.
[a] Values are n (%) or mean ± SD (US dollars). Sample members were stroke-free aged 50+ at baseline (born 1900–1947).
[b] Income and wealth were standardized by dividing by the square root of household size.

interview, or proxy-reported death. We first modeled each primary exposure (memory impairment and elevated depressive symptoms) separately, and then simultaneously adjusted in a single model. To assess bias from exclusions due to missing data, we repeated primary analyses applying IPWs calculated as the inverse of the probability of observing each respondent, estimated with a logistic regression model including all covariates described above. This approach upweights those included sample members who were similar to others who were excluded. IPW avoids bias from missingness under the assumption that, conditional on observed covariates, data are missing at random.[31] In supplementary analyses, we examined whether associations differed by sex and age strata (≤65).

Primary analyses used baseline CES-D and memory values, but these variables evolved over time, so that by the 6th wave (after approximately 12 years), CES-D correlated only 0.41 with baseline CES-D, and memory score correlated only 0.43 with baseline word recall. To account for changes in our primary risk factors, we repeated the Cox models using time updated values of CES-D and memory, from successive biennial interviews.

We also repeated primary analyses using continuous (instead of dichotomized) word recall score (range 0–20) and adjusting for the TICS to improve control for cognitive impairment. To assess whether depressive symptoms predicted stroke among individuals with no evidence of memory impairment, we repeated analyses restricting to respondents with a median memory score of 10 or better at baseline (n = 10,685). In the supplementary models, we adjusted for all "adult social risk factors" described above.

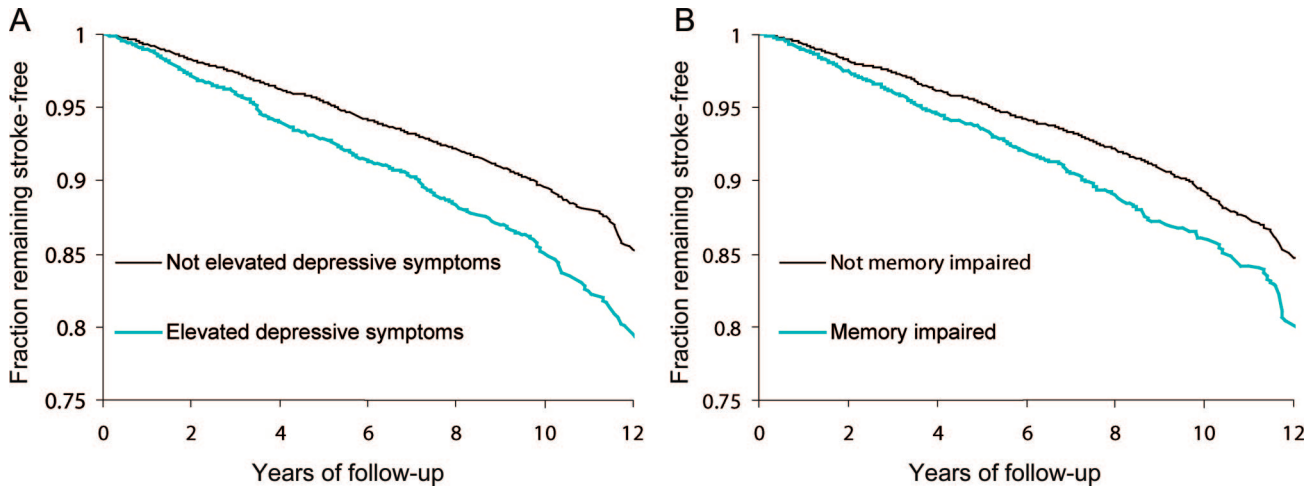
Because vascular depression is hypothesized to have stronger associations with some symptoms of depression (e.g., apathy) than others,[17,32] we conducted exploratory analyses examining relationships between each CES-D symptom and incident stroke. We considered each of the 8 CES-D items one by one (without adjustment for the other 7 items), then in combination, and finally in combination when restricted to those with elevated CES-D score.

Analyses were conducted using SAS 9.1.

RESULTS The crude stroke rate was higher among subjects with elevated baseline depressive symptoms (17.8 vs 10.7 per 1,000 person-years), but these individuals also had worse profiles for several potential confounders (table 1). At baseline, memory impairment was more common among those with elevated depressive symptoms (29% vs 16%, $p < 0.01$). The Spearman correlation between the 8-item CES-D and continuous memory score was −0.19 (95% confidence interval [CI] −0.21 to −0.18).

Kaplan-Meier curves suggest a survival advantage of those without elevated depressive symptoms over those with symptoms, and a survival advantage for those without memory impairment over participants with memory impairment (figure 1). Table 2 shows the results of covariate adjusted Cox proportional hazards models. In separate models adjusting only for demographics (top 2 rows of table 2), both baseline depressive symptom elevation (HR = 1.51) and memory impairment (HR = 1.40) were associated with elevated stroke hazard. HRs changed little when including both depressive symptom elevation and memory impairment in the same model (bottom 2 rows in table 2); for example, in the demographic-adjusted model, the HR for elevated depressive

Figure 1 Adjusted survival curves by baseline elevated depressive symptoms (A) and memory impairment (B)



Survival curves calculated after inverse probability weighting for age at baseline (linear and quadratic), Hispanic ethnicity, race, southern birth, mother's and father's education >8 years, and year of Health and Retirement Study enrollment. Curves for elevated depressive symptoms (left) also weighted by baseline memory impairment; curves for memory impairment (right) also weighted by baseline elevated depressive symptoms.

symptoms declined from 1.51 to 1.47 when memory impairment was included as a covariate. The pattern was similar in models additionally adjusted for adult social and cardiovascular risk factors. Applying IPWs to account for missing observations changed the coefficient for elevated depressive symptoms from 1.47 to 1.50 (results not shown). HRs for depressive symptoms and memory impairment were substantially lower after adjusting for adult social, behavioral, and clinical risk factors. However, effect estimates for depressive symptoms were similar regardless of whether memory impairment was included or excluded from the models. Even in models restricted to individuals with at least the median memory score of 10, elevated depressive symptoms predicted a 55% increased risk of incident stroke (95% CI 1.29 to 1.85; results not shown in tables).

Elevated depressive symptoms were associated with increased risk of incident stroke for men and women above and below age 65 (table 3). Across each age- and sex-stratified model examined, simultaneous adjustment for elevated depressive symptoms and impaired memory scores resulted in little change in their respective HRs compared to models in which their effects were estimated separately.

We conducted supplementary analyses to assess whether results were sensitive to alternative modeling decisions. Because depressive symptoms and memory scores changed over successive interviews, we repeated the primary analyses using time-updated values of depression and memory. Adjusting for time-constant demographic covariates (as in the first column of table 1), the separate coefficients were 1.60 (1.45 to 1.76) for elevated depressive symptoms and 1.63 (1.47 to 1.81) for memory impairment. Coefficients declined only slightly when simultaneously adjusted for elevated depressive symptoms (HR 1.53; 1.39 to 1.69) and memory impairment (HR 1.56; 1.40 to 1.73).

We also considered depressive symptoms as a continuous variable ranging from 0 to 8. Each 1-point increase in baseline depressive symptoms was associated with an 8% increase in hazard of stroke incidence (95% CI 1.05 to 1.11), in models adjusted for core demographics and adult social conditions. After adding continuous memory score and continuous TICS score to this model to improve control of cog-

Table 2 Elevated depressive symptoms and memory impairment as independent predictors of first stroke incidence[a]

	Adjusted only for demographics[b]	Additionally adjusted for adult social risk factors[c]	Additionally adjusted for cardiovascular risk factors[d]
Separate models			
Elevated depressive symptoms	1.51 (1.36 to 1.68)	1.39 (1.25 to 1.55)	1.25 (1.12 to 1.39)
Memory impairment	1.40 (1.26 to 1.56)	1.30 (1.16 to 1.45)	1.26 (1.13 to 1.41)
Simultaneously adjusted models			
Elevated depressive symptoms	1.47 (1.32 to 1.63)	1.38 (1.24 to 1.53)	1.23 (1.11 to 1.38)
Memory impairment	1.35 (1.21 to 1.50)	1.28 (1.14 to 1.43)	1.25 (1.12 to 1.40)

[a] Values are hazard ratio (95% confidence interval).
[b] Adjusted for age at baseline (linear and quadratic), Hispanic ethnicity, black race, southern birth, mother's and father's education >8 years, and year of Health and Retirement Study enrollment.
[c] Adjusted for all demographic variables plus own years of education, income, wealth and marital status.
[d] Adjusted for all demographic and adult socioeconomic status variables, plus indicators for overweight, obese, level of alcohol use, smoking status, and self-reported diagnoses of hypertension, diabetes, or heart disease.

Table 3 Elevated depressive symptoms and memory impairment as independent predictors of first stroke incidence, stratified by sex and age[a]

	Men	Women
All ages		
Separate models		
Elevated depressive symptoms	1.34 (1.10 to 1.62)	1.44 (1.26 to 1.64)
Memory impairment	1.16 (0.97 to 1.39)	1.39 (1.20 to 1.60)
Simultaneously adjusted models		
Elevated depressive symptoms	1.33 (1.10 to 1.61)	1.42 (1.24 to 1.61)
Memory impairment	1.15 (0.96 to 1.37)	1.36 (1.18 to 1.57)
Baseline age <65		
Separate models		
Elevated depressive symptoms	1.37 (0.97 to 1.92)	1.71 (1.33 to 2.21)
Memory impairment	1.09 (0.73 to 1.60)	1.47 (1.03 to 2.12)
Simultaneously adjusted models		
Elevated depressive symptoms	1.36 (0.97 to 1.92)	1.69 (1.31 to 2.19)
Memory impairment	1.07 (0.72 to 1.58)	1.42 (0.99 to 2.05)
Baseline age 65+		
Separate models		
Elevated depressive symptoms	1.33 (1.05 to 1.68)	1.34 (1.15 to 1.56)
Memory impairment	1.20 (0.98 to 1.46)	1.39 (1.19 to 1.63)
Simultaneously adjusted models		
Elevated depressive symptoms	1.31 (1.04 to 1.66)	1.32 (1.13 to 1.53)
Memory impairment	1.18 (0.97 to 1.44)	1.37 (1.17 to 1.60)

[a] Values are hazard ratio (95% confidence interval). All models are adjusted for age at baseline (linear and quadratic), Hispanic ethnicity, black race, southern birth, mother's and father's education, year of Health and Retirement Study enrollment, years of education, income, wealth, and marital status.

nitive impairment, the HR associated with each additional point on the CES-D was nearly unchanged: 1.07 (1.05 to 1.10).

When adjusted only for demographic and adult social risk factors, each of the 8 CES-D symptom items individually predicted incident stroke (figure 2, dark, left-hand columns for each symptom). Adjusting for baseline memory impairment attenuated the effect estimates very little (figure 2, gray, middle columns). After adding all 8 items simultaneously to the model, only 2 were significantly associated with stroke: "everything was an effort" and "sleep was restless" (figure 2, light right-hand columns). When this analysis (including all 8 items) was repeated restricting to individuals with elevated baseline depressive symptoms, "everything was an effort" (HR 1.26; 1.02 to 1.56) and "couldn't get going" (HR 1.22; 1.05 to 1.47) remained significant, but "sleep was restless" did not predict incident stroke (HR 0.96; 0.79 to 1.16) (results not shown).

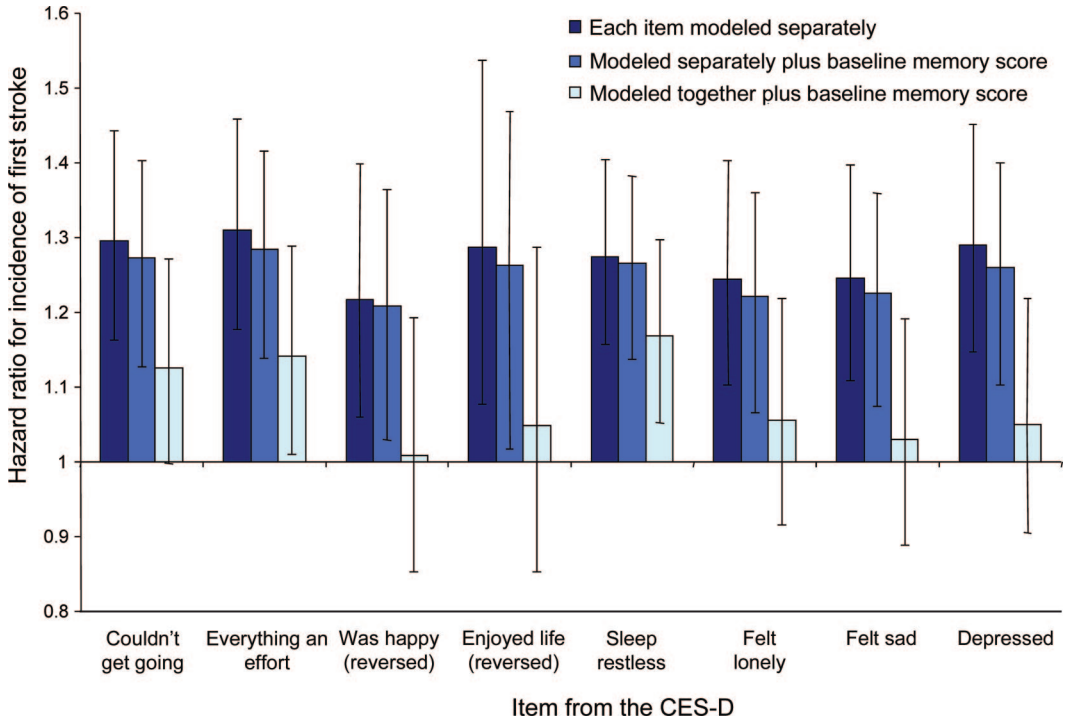
DISCUSSION In a large national study with over 8 years of average follow-up, we found that elevated depressive symptoms predicted stroke incidence independently of memory impairment. This result was robust to several alternative model specifications and evident in all population subsamples examined. This suggests that depression is independently associated with stroke rather than being only a sign of early cerebrovascular disease.

These results are consistent with prior findings from several studies showing that depressive symptoms or related affective phenotypes are important risk factors for stroke incidence.[7-10] Prior research suggests that depressive symptoms as a continuous phenotype may be more relevant for stroke, while diagnosable depressive disorder may have a threshold effect more strongly related to ischemic heart disease.[7,33,34] Our data are not ideal to address this debate because we have no direct diagnostic measures. Our findings do suggest a continuous dose-response relationship between level of depressive symptoms and stroke risk.

Our analyses extend earlier results by examining whether memory impairment and depressive symptoms predict stroke independently. We hypothesized that if both risk factors were markers for a single shared pathway to stroke, simultaneous adjustment for both risk factors should substantially attenuate their effects on the risk of stroke. In contrast, if depressive symptoms influence stroke risk at least in part via a pathway independent of cerebrovascular disease, depressive symptoms should predict stroke independently of memory impairment. We found only a moderate correlation between depressive symptoms and cognitive impairment. Thus, adjustment for memory scores only slightly attenuated the hazard ratio associated with elevated depressive symptoms. The very small attenuation suggests that the observed association between depressive symptoms and stroke might operate at least partially through pathways that are independent of those accounting for the association between memory impairment and stroke. Future analyses including direct neuroimaging indicators of cerebrovascular disease and evaluating the relationship between new onset of depressive symptoms or remission of depressive symptoms and subsequent stroke would help assess this hypothesis.

Pathways leading from depression to stroke might involve mechanisms that "trigger" stroke (i.e., precipitate ischemic events), or exacerbate underlying cerebrovascular disease. The inflammatory, hypercoagulable, and platelet-activating effects of depression may all increase cardioembolic stroke risk.[35-37] Less is known about stroke triggers than about factors that influence accumulating cerebrovascular pathology.[38] Stroke triggers may include cardiovascular auto-

Figure 2 Hazard ratios for incidence of first stroke associated with each item on the 8-item Centers for Epidemiologic Study of Depression (CES-D) Scale



All models were adjusted for age at baseline (linear and quadratic), Hispanic ethnicity, black race, southern birth, mother's and father's education >8 years, year of Health and Retirement Study enrollment, years of education, baseline income, wealth, and marital status. Separate models included only a single CES-D item. Separate plus baseline memory impairment models included that CES-D item plus an indicator for baseline memory impairment. The third set of models "modeled together" included all 8 items from the CES-D in the same model, as well as baseline memory impairment.

nomic dysregulation, manifested by elevated basal catecholamine levels, hypertension, increased heart rate responses to stressors, reduced heart rate variability, and baroreceptor sensitivity. Depression may influence stroke risk via HPA axis disturbances or amygdala modifications that compromise amygdalar regulation of the HPA axis. However, whether these HPA and amygdala disturbances are caused by depression remains uncertain, with some evidence indicating that HPA and amygdala functioning are indicators of vulnerability to depression.[21] For example, feedback inhibition triggered by circulating glucocorticoids appears reduced in depressed patients,[21] but chronic stress and early life adversity have also been linked to increased amygdala volume, possibly leading to exaggerated anxiety responses and HPA upregulation. HPA axis disturbances predict increased circulating catecholamines, platelet activation, endothelial dysfunction, and reduced heart rate variability, all of which may increase stroke risk.[21-24] Autonomic dysfunction is associated with the development and maintenance of atrial fibrillation (AF), a major stroke risk factor.[e8] Although depressive states are clearly linked to ventricular arrhythmias and sudden cardiac death,[e11] there has been little research on the relationship between affective states and AF. The limited available evidence suggests an association; for example, depression predicts AF recurrence after cardioversion.[e9] Tension and anger, emotional states closely related to depression, predict AF incidence among Framingham Heart Study men. We do not have sufficient data to directly evaluate these hypotheses, but such pathways are promising avenues for future research.

In exploratory analyses, we found that the "restless sleep" and "everything was an effort" symptoms from the CES-D scale independently predicted incident stroke. When restricting to individuals with elevated depressive symptoms, "restless sleep" was no longer predictive, but "everything was an effort" and "couldn't get going" both predicted stroke. These findings should be interpreted with caution, because endorsement of a single-item assessment of a specific symptom may reflect other physiologic or behavioral issues besides manifestations of depression. Sleep may influence stroke risk independently of other depressive symptoms,[39,40] but this association was not observed among those with elevated depressive symptoms.

The HRS oversampled black and Hispanic subjects in the original design, so the sample is quite diverse compared to many community-based studies. Little is known about potentially heterogeneous effects of stroke risk factors in minority populations.[e13] However, this dataset has several limitations; most importantly, we have only brief assessments of depressive symptoms and memory impairments which probably imperfectly capture the underlying physiologic process. The measurement challenge is potentially exacerbated in socioeconomically and ethnically diverse samples. Measurement error in memory scores is a particular concern. Extensive measurement error in memory could result in the spurious appearance of an independent relationship between depressive symptoms and stroke even after adjusting for memory. Reliance on past-week measures of depressive symptoms is another limitation; findings may differ with longer-term symptom assessments or lifetime diagnoses measures. Use of self- or proxy-reported strokes is a limitation, although our previous findings indicate that stroke assessments in HRS perform well compared to data sets with medical record verification.[26] Approximately 15% of the eligible sample was excluded from primary analyses due to missing data on predictors, outcomes, or key covariates. Although IPW analyses indicated results did not differ when analyzed accounting for missing observations, this approach is only valid if data are missing at random, conditional on measured covariates.

Despite these limitations, these findings provide evidence that depressive symptoms are associated with an increased risk of stroke independently of memory scores, possibly via mechanisms that trigger or precipitate acute stroke.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. M. Maria Glymour.

DISCLOSURE

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