

Changes in Depressive Symptoms and Incidence of First Stroke Among Middle-Aged and Older US Adults

Paola Gilsanz, ScD; Stefan Walter, PhD; Eric J. Tchetgen Tchetgen, PhD; Kristen K. Patton, MD; J. Robin Moon, DPH; Benjamin D. Capistrant, ScD; Jessica R. Marden, MPH; Laura D. Kubzansky, PhD; Ichiro Kawachi, MD, PhD; M. Maria Glymour, ScD

Background—Although research has demonstrated that depressive symptoms predict stroke incidence, depressive symptoms are dynamic. It is unclear whether stroke risk persists if depressive symptoms remit.

Methods and Results—Health and Retirement Study participants ($n=16\ 178$, stroke free and noninstitutionalized at baseline) were interviewed biennially from 1998 to 2010. Stroke and depressive symptoms were assessed through self-report of doctors' diagnoses and a modified Center for Epidemiologic Studies - Depression scale (high was ≥ 3 symptoms), respectively. We examined whether depressive symptom patterns, characterized across 2 successive interviews (stable low/no, onset, remitted, or stable high depressive symptoms) predicted incident stroke (1192 events) during the subsequent 2 years. We used marginal structural Cox proportional hazards models adjusted for demographics, health behaviors, chronic conditions, and attrition. We also estimated effects stratified by age (≥ 65 years), race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), and sex. Stroke hazard was elevated among participants with stable high (adjusted hazard ratio 2.14, 95% CI 1.69 to 2.71) or remitted (adjusted hazard ratio 1.66, 95% CI 1.22 to 2.26) depressive symptoms compared with participants with stable low/no depressive symptoms. Stable high depressive symptom predicted stroke among all subgroups. Remitted depressive symptoms predicted increased stroke hazard among women (adjusted hazard ratio 1.86, 95% CI 1.30 to 2.66) and non-Hispanic white participants (adjusted hazard ratio 1.66, 95% CI 1.18 to 2.33) and was marginally associated among Hispanics (adjusted hazard ratio 2.36, 95% CI 0.98 to 5.67).

Conclusions—In this cohort, persistently high depressive symptoms were associated with increased stroke risk. Risk remained elevated even if depressive symptoms remitted over a 2-year period, suggesting cumulative etiologic mechanisms linking depression and stroke. (*J Am Heart Assoc.* 2015;4:e001923 doi: 10.1161/JAHA.115.001923)

Key Words: depression • epidemiology • longitudinal cohort study • marginal structural model • stroke

Depressive symptoms or diagnoses consistently predict elevated risk of stroke onset^{1,2}; however, it is unknown

whether stroke risk remains elevated if depressive symptoms remit or resolve. Assessing the persistence of the link between depression and stroke would provide insight into the causal nature of this relationship but is challenging because of possible time-varying confounders such as health behaviors or health conditions. Persons with depression, for example, are at elevated risk of type 2 diabetes,³ and concurrently, those with type 2 diabetes are at greater risk of depression^{3,4} and stroke.⁵ Consequently, adjusting for confounding effects of type 2 diabetes through direct inclusion in regression would block the mediated path between depression and stroke and, in general, underestimate the effect of depression. Statistical techniques, including marginal structural models (MSMs), have been developed to provide unbiased estimates in these scenarios.⁶

Previous research suggests several pathways through which depression or depressive symptoms might influence stroke. Mechanisms may involve long-term accumulation of biological damage, for example, hypertension and atherosclerosis.^{7,8} If the causal mechanisms linking depression and

From the Departments of Social and Behavioral Sciences (P.G., J.R. Marden, L.D.K., I.K., M.M.G.), Biostatistics, (E.J.T.T.) and Epidemiology (E.J.T.T.), Harvard T.H. Chan School of Public Health, Boston, MA; Department of Epidemiology and Biostatistics, University of California San Francisco School of Medicine, San Francisco, CA (S.W., M.M.G.); Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA (K.K.P.); Bronx Partners for Healthy Communities, Bronx, NY (J.R. Moon); Division of Epidemiology & Community Health, University of Minnesota School of Public Health, Minneapolis, MN (B.D.C.).

Accompanying Appendices S1 through S6 are available at <http://jaha.aha-journals.org/content/4/4/e001923/suppl/DC1>

Correspondence to: Paola Gilsanz, ScD, Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, 667 Huntington Avenue, Boston, MA 02115. E-mail: pgilsanz@mail.harvard.edu

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stroke are exclusively long term, reductions in stroke risk would require years of successful symptom management. Alternatively, depression may influence stroke risk via short-term biological processes or stroke triggers, such as cerebrovascular reactivity or atrial fibrillation.⁹ If causal mechanisms exert their effects in the short term, via fast-acting pathways, reduced depressive symptoms might allow nearly immediate reductions in stroke risk. A combination of short- and long-acting pathways is plausible and would suggest that successful treatment of depressive symptoms may moderately reduce stroke risk.

This study used the Health and Retirement Study (HRS) cohort to assess how changes in depressive symptoms across 2 successive biennial assessments predicted stroke hazard in the subsequent 2-year interval. We examined the acute effect of depressive symptoms by controlling for baseline depressive symptoms, a proxy for depressive symptoms prior to the study period, and by implementing inverse probability weights to adjust depressive symptom history during the study. We hypothesized that, compared with participants with 2 consecutive assessments of low depressive symptoms, stroke hazard would be substantially elevated among those with recent-onset or stable high depressive symptoms and would remain modestly elevated among those with recently remitted depressive symptoms.

Methods

Study Population

The HRS is a longitudinal, nationally representative cohort of US adults aged >50 years and their spouses of any age, as described previously in detail.^{10,11} We used data from 1998 to 2010 for participants of the HRS enrolled during 1992, 1993, or 1998. These enrollment cohorts were merged in 1998 and had biennial interviews through 2010. Original survey response rates varied across enrollment cohorts from 70% to 82%, and retention rates through 2008 ranged from 86% to 91%.¹¹ The HRS is approved by the University of Michigan health sciences human subjects committee, and the Harvard School of Public Health human subjects committee determined the current analyses to be exempt.

We included noninstitutionalized HRS respondents who, in 1998, were aged at least 50 years and who reported no history of stroke. Of 18 766 eligible respondents, we excluded people missing values on baseline depression score (1482 respondents, 7.9%) or baseline covariates (1106 respondents, 5.9%). Missing data patterns are presented in Appendix S1. The remaining 16 178 respondents contributed 71 909 observations and 1192 incident strokes over the follow-up period (average follow-up of 8.88 years). Each time-updated stroke assessment wave between 2000 and 2010

was linked to a depressive symptom change pattern defined using a moving window of the 2 consecutive biennial interviews immediately preceding it; for example, for strokes reported during 2002 interviews (occurring after the 2000 assessment but before the 2002 assessment), 1998 was considered the first exposure wave and 2000 was the second exposure wave. For stroke outcomes reported in 2004, 2000 was the first exposure wave and 2002 was the second exposure wave.

Stroke Outcomes

Incident events were defined as first nonfatal or fatal stroke based on self- or proxy report of a doctor's diagnosis ("Has a doctor ever told you that you had a stroke?"). Neither stroke subtype nor transient ischemic attack information was available. For participants who were unavailable for direct interviews (eg, deceased), interviews were conducted with proxies, predominantly spouses. Self-reported strokes in the HRS corresponded with strokes coded according to the *International Classification of Diseases* in the Centers for Medicare and Medicaid Services records, with 74% sensitivity and 93% specificity (data not shown). We previously showed that major risk factors such as smoking and hypertension predict stroke in the HRS with incidence rates similar to those in studies with medical record verification, suggesting that bias due to misclassification is modest.¹² Participants were censored at time of first stroke.

Primary Exposures

Depressive symptoms were measured by an 8-item version of the Center for Epidemiologic Studies - Depression scale¹³ querying symptoms experienced in the prior week (yes or no): 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. For each exposure wave, participants were classified as having elevated depressive symptoms if they reported ≥ 3 symptoms (positive items were reverse coded). Prior studies have found this threshold to have high sensitivity and specificity for depression, as defined by the Composite International Diagnostic Interview-Short Form.¹³

Depressive symptoms were classified into 4 exposure categories, with a score of ≥ 3 indicating elevated depressive symptoms: (1) *Stable high* indicated elevated depressive symptoms at both exposure waves prior to stroke assessment wave, (2) *recently remitted* indicated elevated depressive symptoms at the first exposure wave but with < 3 depressive symptoms at the second exposure wave, (3) *recent onset* indicated no elevated depressive symptoms at the first exposure wave but elevated depressive symptoms at the

second exposure wave, and (4) *stable low/no* indicated no elevated depressive symptoms at either exposure wave. Respondents with stable low/no depressive symptoms were the reference group for most analyses. Depressive symptoms at baseline (1998) also served as a proxy for depressive symptoms prior to study start.

Covariates

We examined possible confounding by both time-constant and time-varying covariates. Time-constant variables were from baseline (1998) and included sex, age at baseline (linear and quadratic), race or ethnicity (non-Hispanic white, non-Hispanic black, or Hispanic), and education (continuous years of education with discontinuities at completion of high school and college).^{14,15}

Time-varying confounders of the relationship between depressive symptoms and stroke were lagged 2 interview waves prior to stroke assessment (ie, first exposure wave). Time-varying confounders included self-reports of age at interview; number of days per week respondent consumed alcohol (continuous); current smoking (yes or no); current psychiatric medication use (yes or no); obesity (body mass index >30); history of diagnoses of heart disease, hypertension, or diabetes (yes or no for each); and household income and wealth (both divided by the square root of household size).^{14,16–18} We used the most recent prior report for missing time-updated covariates.

Methods of Analysis

We examined the distributions of depressive symptoms and covariates at each wave. In primary analyses, we modeled the incident stroke hazard ratio (HR) associated with the 4 depressive symptom change patterns using marginal structural Cox proportional hazards models. MSMs were estimated with pooled logistic regressions to accommodate the discrete time data structure, using sampling weights to account for the complex sampling design. Each observation corresponded to an outcome wave when stroke status was reported, linked to the 2 preceding interview waves, when depressive symptoms were assessed. Time-constant demographic variables and 1998 depressive symptoms were included as covariates in the MSM regression predicting hazard of stroke.

Because time-varying factors can be both confounders and mediators, we applied stabilized inverse probability weights truncated to the 99th percentile to account for time-varying confounders while avoiding conditioning on mediating pathways.^{6,19,20} These time- and person-specific weights were the product of the inverse probability of survival weight, the inverse probability of exposure weight, and the inverse probability of remaining uncensored weight. Assuming no

unobserved confounding, the weighting adjusted for differential dropout, survival, and depressive symptom history. MSMs were weighted by stabilized inverse probability weights multiplied by the survey sampling weights. We excluded participants who were missing combined weight values. Appendices S2 through S6 include visual representations of hypothesized relationships, details of the stabilized inverse probability weight formula, estimation, and distribution.

In MSM analyses, we used interaction terms and their global tests of significance as well as stratified models to assess multiplicative effect modification by age (50 to 64 versus ≥ 65 years), sex, and race or ethnicity. Given their small sample size, respondents with self-reported other race were excluded from our race or ethnicity effect modification analyses. We also conducted a sensitivity analysis that required at least a 2-point change in depressive symptom levels for participants to be classified as recent onset or remitted. All analyses were conducted using SAS 9.3 (SAS Institute Inc).

Results

Average age of sample members at baseline was 65.7 years (Table 1). Stable low/no depressive symptoms was the most commonly reported symptom pattern (71.7%) across consecutive interview waves (Table 2).

Participants with recent-onset depressive symptoms were not at elevated stroke hazard compared with those with stable low/no depressive symptoms (adjusted HR 1.08, 95% CI 0.81 to 1.44; $P=0.60$); however, participants with stable high (adjusted HR 2.14, 95% CI 1.69 to 2.71; $P<0.0001$) or remitted (adjusted HR 1.66, 95% CI 1.22 to 2.26; $P<0.01$) depressive symptoms had significantly elevated incident stroke hazard compared with those with stable low/no depressive symptoms (Table 3). The hazard associated with stable high depressive symptoms did not differ significantly from that of remitted depressive symptoms ($P=0.11$). We found a similar pattern in analyses requiring a difference of at least 2 points for depressive symptoms to be considered remitted or onset (Table 4).

The global tests for interactions showed evidence of differences in the relative effect of depressive symptoms on stroke by age (Wald chi-square 24.49; $P<0.001$) but not by sex (Wald chi-square 7.96; $P=0.05$) or race or ethnicity (Wald chi-square 0.26; $P=0.97$). Stable high depressive symptoms were associated with increased stroke hazard compared with stable low/no depressive symptoms across age, race or ethnicity, and sex categories, although the association was only marginally significant among older participants ($P=0.06$) (Table 5). Recently remitted depressive symptoms were significantly associated with increased stroke hazard only

Table 1. Baseline Characteristics of Sample Population, Health and Retirement Study 1998 (n=16 178)

Characteristics	Results
Male, n (%)	6712 (41.5)
Race/ethnicity, n (%)	
Non-Hispanic white	12 655 (78.2)
Non-Hispanic black	2079 (12.9)
Hispanic	1151 (7.1)
Other race	293 (1.8)
Age, y, mean (SD)	65.7 (9.7)
Married, n (%)	10 701 (66.2)
Income/household members, n (%)	
>\$43 219	3818 (23.6)
\$43 218 to \$24 102	3912 (24.2)
\$24 101 to \$13 093	4105 (25.4)
<\$13 092	4343 (26.9)
Wealth/household members, n (%)	
>\$255 267	3873 (23.9)
\$255 266 to \$107 128	3927 (24.3)
\$107 127 to \$36 210	4101 (25.4)
<\$36 209	4277 (26.4)
Years of education, mean (SD)	12.2 (3.2)
CES-D score (continuous), mean (SD)	1.5 (1.9)
CES-D score ≥ 3 , n (%)	3669 (22.7)
Obese, n (%)	3790 (23.4)
Current smoking, n (%)	2636 (16.3)
Hypertension, n (%)	7294 (45.1)
Diabetes, n (%)	2117 (13.1)
Heart disease, n (%)	3076 (19.0)

CES-D indicates Center for Epidemiologic Studies Depression Scale.

among women and non-Hispanic white participants. Recent onset of depressive symptoms did not predict incident stroke in any subgroup.

Table 2. Frequency of Depressive Symptom Categories Across Successive Interview Waves (71 909 Outcome Wave Observations)

Year	Stable Low/No		Recent Onset		Recently Remitted		Stable High	
	n	%	n	%	n	%	n	%
1998–2000	9615	68.0	1472	10.4	1404	9.9	1656	11.7
2000–2002	8452	68.9	1250	10.2	1174	9.6	1385	11.3
2002–2004	7680	70.4	1009	9.3	1037	9.5	1188	10.9
2004–2006	7023	72.1	901	9.2	780	8.0	1042	10.7
2006–2008	6310	72.8	741	8.6	772	8.9	840	9.7

Discussion

In this nationally representative cohort, we found that participants with persistently elevated depressive symptoms over a 4-year exposure period experienced double the hazard of incident stroke in the 2-year period after exposure assessment compared with participants with consistently low depressive symptoms. Stroke risk remained elevated even among participants whose depressive symptoms remitted over the exposure period, and differences between the a HRs of participants with remitted depressive symptoms and those with persistently high depressive symptoms were not statistically significant. The estimated relative effect of depressive symptoms on stroke did not vary by race. Though not significantly different, a stronger effect of recently remitted depressive symptoms on stroke risk was observed among women compared with men. We also observed differences in effect by age, with stable high and remitted depressive symptoms having stronger effects among younger participants than among those aged ≥ 65 years. Contrary to our hypothesis, the recent onset of depressive symptoms was not associated with higher stroke risk, at least within the subsequent 2-year interval. Our findings suggest that changes in depressive symptoms over a 2-year period (whether onset or remission) do not alter stroke risk associated with depressive symptoms reported during the first exposure wave. These findings suggest that the stroke risk associated with depressive symptoms is unlikely to be completely eliminated in the short term, even with successful treatment of depression.

Recent meta-analyses examining the effects of depression and depressive symptoms on stroke risk, both including HRS data, estimated an adjusted HR of 1.45 (95% CI 1.29 to 1.63)¹ and an overall adjusted relative risk of 1.34 (95% CI 1.17 to 1.54).² Our finding of no significant difference in the relative effect by sex is consistent with findings from both meta-analyses. Similarly, our findings regarding differences in the relative effect by age is consistent with prior research reporting that depressive symptoms were associated with incident stroke or transient ischemic attack among participants aged <65 years but not among those older.²¹

Table 3. Adjusted Hazard Ratios for Incident Stroke by Depressive Symptom Category Among HRS Participants (71 909 Outcome Wave Observations)

Depressive Symptom Category	aHR (95% CI)
Stable low/no	Reference
Recent onset	1.08 (0.81 to 1.44)
Recently remitted	1.66 (1.22 to 2.26)*
Stable high	2.14 (1.69 to 2.71)†

Model controls for sex, race or ethnicity, education, and baseline age and depressive symptoms through direct inclusion in the MSM. All models were weighted to adjust for sampling, survival, participation, and prior depressive symptoms. aHR indicates adjusted hazard ratio; HRS, Health and Retirement Study; MSM, marginal structural models.

* $P < 0.01$.

† $P < 0.0001$.

Past studies have reported a significant association between baseline or time-updated values of depressive symptoms and stroke, but none have explicitly examined changes in depressive symptoms.^{1,2,22,23} Pan et al have examined the effect of prior and/or current depression diagnosis or antidepressant use and found that women with prior depression had marginally elevated risk of stroke, although not significantly different than women without current or past depression, whereas those with current depression had significantly elevated risk.²³ An important next step to build on these compelling earlier results is to explicitly examine the effect of change in depressive symptoms; we were able to do so by classifying depressive symptoms into categories reflecting change in depressive symptoms (ie, onset and remitted symptoms) and stable depressive symptoms (ie, stable high and stable low symptoms). Furthermore, by using a narrow time frame, we were able to identify possible shorter term effects of depressive symptoms on stroke risk. Consequently, our effect estimate

Table 4. Adjusted Hazard Ratio of Incident Stroke by Depressive Symptom Category for HRS Participants Requiring at Least a 2-Unit Change for Symptom Onset or Remission (71 909 Outcome Waves)

Depressive Symptom Category	2-Unit Change aHR (95% CI)
Stable low/no	Reference
Recent onset	0.99 (0.73 to 1.34)
Recently remitted	1.51 (1.10 to 2.07)*
Stable high	2.10 (1.70 to 2.60)†

Model controls for sex, race or ethnicity, education, baseline age, and depressive symptoms through direct inclusion in the MSM. All models were weighted to adjust for sampling, survival, participation, and prior depressive symptoms. aHR indicates adjusted hazard ratio; HRS, Health and Retirement Study; MSM, marginal structural models.

* $P < 0.05$.

† $P < 0.0001$.

of remitted symptoms more closely approximated the effect that an intervention focused on alleviating depressive symptoms would have on stroke risk. We also built on prior literature by implementing inverse probability weights to appropriately control for confounders that may simultaneously act as mediators and to mitigate the effects of selective attrition. Limitations of our study include self- and proxy-reported measures of stroke without medical verification. Our results could have been biased if particular subgroups systematically misreported health exposures or outcomes; however, a prior study found this would result in only modest bias.¹² Although depressive symptoms were inversely associated with survival in the study, the effects of selective attrition were mitigated by weighting our sample by the inverse of the probability of survival. Additional information regarding stroke type or psychiatric medication was not available. Given that more than twice as many participants with recent-onset depressive symptoms had initiated psychiatric medication compared with those with remitted symptoms (8.7% versus 3.6%), it is unlikely that medication mediates the relationship between remitted depressive symptoms and stroke. The MSM assumes that the effects of depressive symptoms that occurred >4 years prior to outcome assessment are completely mediated through the 2 measured exposure waves. If this was not the case, our models overestimated the effects of depressive symptoms included in our model (ie, the 2 most recent exposure waves). Despite the large sample, our stratified analyses had wide CIs; conclusive findings about age, sex, and race differences will most likely require meta-analyses. Finally, despite adjustment for many potential confounders, the possibility of unmeasured confounding remains in this observational study.

Potential mechanisms linking depressive symptoms and stroke may occur during a short or long time frame. Depressive symptoms may influence stroke risk through physiological changes involving accumulation of vascular damage over the long term. Depressive phenotypes have been linked with various physiological risk factors for stroke that develop slowly over time, such as hypertension,⁷ dysregulation of the autonomic nervous system,²⁴ and increased inflammatory responses,^{25,26} which can promote vascular disease and create a substrate for thrombotic or embolic events. Damage can also be incurred by indirect effects of depression on health behaviors, whereby depressed individuals are more likely to engage in deleterious behavior such as smoking and physical inactivity.²⁷ Alternatively, depressive symptoms might induce acute effects on risk, such as initiating stroke triggers. Triggers can spur stroke regardless of a person's underlying vascular pathology²⁸ and may include infection²⁹ or atrial fibrillation.^{27,30} Acute infection, for example, can increase platelet reactivity and platelet-leukocyte interactions, increasing platelet aggregation.²⁸ Our

Table 5. Adjusted Hazard Ratio for Incident Stroke by Depressive Symptom Category Stratified by Sex, Race or Ethnicity, and Age

Variables (n observed)	Recently Remitted	Recent Onset	Stable High
Sex			
Male (n=28 632)	1.26 (0.79 to 2.02)	1.18 (0.75 to 1.85)	2.59 (1.80 to 3.72)*
Female (n=43 277)	1.86 (1.30 to 2.66) [†]	1.02 (0.72 to 1.45)	1.96 (1.48 to 2.59)*
Race or ethnicity			
Non-Hispanic white (n=57 027)	1.66 (1.18 to 2.33) [†]	1.13 (0.84 to 1.53)	2.00 (1.53 to 2.63)*
Non-Hispanic black (n=8688)	1.67 (0.83 to 3.33)	1.08 (0.59 to 2.00)	2.53 (1.64 to 3.88) *
Hispanic (n=4952)	2.36 (0.98 to 5.67)	0.80 (0.28 to 2.26)	4.14 (1.56 to 10.95) [†]
Age			
50 to 64 years (n=38 812)	1.55 (0.91 to 2.64)	1.13 (0.61 to 2.07)	1.87 (1.10 to 3.16) [†]
≥65 years (n=33 097)	1.08 (0.75 to 1.56)	1.13 (0.87 to 1.46)	1.32 (0.99 to 1.77)

Data are shown as adjusted hazard ratio (95% CI). Reference was stable low/no depressive symptoms. All models were weighted to adjust for sampling, survival, participation, and exposure to depressive symptoms. The following time-constant variables (baseline age and depressive symptoms, sex, and race or ethnicity) were controlled for through direct inclusion in the regression unless they were the stratifying variable.

* $P < 0.0001$.

[†] $P < 0.05$.

study did not directly evaluate possible mediators of the relationship between depressive symptoms and stroke but rather focused on evaluating evidence that might suggest short- versus long-term mechanisms of action.

Our findings suggest that effects occur over the longer term through accumulated damage, given that we saw little differential in stroke risk prediction by short-term increases or decreases in depressive symptoms. Future research should continue to examine possible mediators of the relationship between depressive symptoms and stroke. This study, in conjunction with other work confirming that depressive symptoms are causally related to stroke risk, suggests that clinicians should seek to identify and treat depressive symptoms as early as possible relative to their onset, before adverse consequences begin to accumulate.

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Disclosures

None.

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