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

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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; 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 confounders such as health behaviors or conditions. Persons with depression, for example, are at elevated risk of type 2 diabetes, and concurrently, those with type 2 diabetes are at greater risk of depression and stroke. 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.

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. If the causal mechanisms linking depression and
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. 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. 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%. 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. 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 scale 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/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. Depression 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<0.001) 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.
among women and non-Hispanic white participants. Recent onset of depressive symptoms did not predict incident stroke in any subgroup.

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 (8.7)                |
| 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.

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) and an overall adjusted relative risk of 1.34 (95% CI 1.17 to 1.54). 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.

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    | %  | 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  |
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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 then 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 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 misrepresented 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.

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.
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.

**Disclosures**

None.

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Appendix I. Baseline characteristics of HRS participants included vs excluded from our sample due to missing values at baseline, HRS 1998 (n= 18,766 participants)

| Characteristics          | Missing N (%) | Included N (%) | Significant difference |
|--------------------------|---------------|----------------|------------------------|
|                          | Mean (Std)    | Mean (Std)     |                        |
| Male                     | 1,388 (53.6)  | 6,712 (41.5)   | *                      |
| Race/Ethnicity           |               |                |                        |
| Non-Hispanic white       | 1,760 (68.1)  | 12,655 (78.2)  |                        |
| Non-Hispanic black       | 474 (18.4)    | 2,075 (12.9)   |                        |
| Hispanic                 | 280 (10.8)    | 1,151 (7.1)    |                        |
| “Other” race             | 69 (2.7)      | 293 (1.8)      |                        |
| Age (years)              | 68.1 (11.2)   | 65.9 (9.7)     | *                      |
| Married                  | 1,687 (65.7)  | 10,701 (66.1)  |                        |
| Income/household members |               |                |                        |
| >$42,988                 | 452 (1.76)    | 4061 (25.2)    |                        |
| $42,987 - $23,918        | 502 (19.6)    | 4050 (25.2)    |                        |
| $23,917 - $12,936        | 636 (24.8)    | 4048 (25.2)    |                        |
| <$12,935                 | 973 (38.0)    | 3932 (22.8)    |                        |
| Wealth/household members |               |                |                        |
| >$253,145                | 423 (21.7)    | 4050 (25.9)    |                        |
| $253,144 - $105,509      | 474 (24.3)    | 4055 (25.9)    |                        |
| $105,508 - $35,356       | 532 (27.3)    | 4059 (26.0)    |                        |
| <$35,355                 | 522 (26.8)    | 3474 (22.2)    |                        |
| Years of education       | 10.7 (3.9)    | 12.2 (3.2)     | *                      |
| CES-D score (continuous) | 2.2 (2.1)     | 1.5 (1.9)      | *                      |
| CES-D score >=3          | 382 (14.8)    | 3669 (22.7)    | *                      |
| Obese                    | 471 (18.2)    | 3790 (23.4)    | *                      |
| Smoker                   | 456 (17.6)    | 2636 (16.3)    |                        |
| Elevated blood pressure  | 1,289 (49.8)  | 7294 (45.1)    | *                      |
| Diabetes                 | 444 (17.2)    | 2117 (13.1)    | *                      |
| Heart disease            | 494 (22.7)    | 3076 (19.0)    | *                      |

*Significant difference at p<0.05
Appendix II. Hypothesized causal structure

Stroke\(_j\): Stroke reported at outcome wave \(j\)

\(E\(_{j-1}\): Second exposure wave depressive symptom category associated with outcome at wave \(j\)

\(E\(_{j-2}\): First exposure wave depressive symptom associated with outcome at wave \(j\)

\(UC\(_j\): Uncensored at outcome wave \(j\)

\(S\(_j\): Survival at outcome wave \(j-1\)

\(L\(_{j-2}\): Measured time-varying confounders/mediators at outcome wave \(j-2\)

\(L\(_{j-3}\): Measured time-varying confounders/mediators at outcome wave \(j-3\)
Appendix III. Details regarding inverse probability weight construction

The stabilized inverse probability weight SIPW_{ij} for individual i at outcome wave j (outcomes were assessed at waves 3 to 8) was the product of the inverse probability of survival weight (IPSW_{ij}), the inverse probability of exposure to depressive symptoms weight (IPEW_{ij}), and the inverse probability of remaining uncensored weight (IPUCW_{ij}). At each outcome wave strokes were recorded regardless of whether the participant was alive or dead as long as a proxy participated in the interview wave. Assessment of depressive symptoms, however, occurred only for living and participating respondents, so observations for outcome wave j required the participant to be alive at wave j-1 and to be in the study at wave j-1 to estimate the inverse probability of exposure. For a participant to be in our sample at outcome wave j, and therefore uncensored at outcome wave j, required the participant to be alive and in the study at wave j-1, provided depressive symptoms scores at waves j-1 and j-2, and had a stroke outcome assessment at wave j.

The IPSW_{ij} was estimated as the probability that individual i survived through wave j-1 given that individual i participated in wave j-1 and given individual i’s depressive symptoms and covariate values at time j-2 (Equation 1). The IPEW_{ij} was estimated as the probability that individual i had elevated depressive symptoms at wave j-1 given that individual i participated and survived up to wave j-1, and given individual i’s depressive symptoms and covariate values at time j-2 (Equation 2). The IPUCW_{ij} for each outcome wave j was estimated as the probability that individual i remained in the study (via self or proxy interviews) through wave j, given that individual i participated and survived up to wave j-1, provided depressive symptoms scores at waves j-1 and j-2, had a stroke outcome assessment at wave j, and given individual i’s depressive symptoms and covariate values at time j-1 and j-2 (Equation 3). Each weight was accumulated across all prior waves j.

Therefore SIPW_{ij} = IPSW_{ij} X IPEW_{ij} X IPUCW_{ij} with each component defined as below. Where S is survival, E is exposure status (i.e., elevated depressive symptoms or not), UC is being uncensored, k indexes the interview wave, V is a vector of time-constant baseline covariates, M is a vector of time-varying missing values status on depressive symptoms score or stroke, L is a vector of time-varying covariates from the first (j-2) or second (j-1) exposure waves.

\[
\text{IPSW}_{ij} = \prod_{i=3}^{j} \frac{Pr[S_{ik-1}|E_{ik-2},V_{i0},UC_{ik-1}=1,S_{ik-2}=1]}{Pr[S_{ik-1}|E_{ik-2},L_{ik-2},UC_{ik-1}=1,S_{ik-2}=1]}
\]

\[
\text{IPEW}_{ij} = \prod_{k=3}^{j} \frac{Pr[E_{ik-1}|E_{ik-2},V_{i0},UC_{ik-1}=1,S_{ik-1}=1]}{Pr[E_{ik-1}|E_{ik-2},L_{ik-2},UC_{ik-1}=1,S_{ik-1}=1]}
\]

\[
\text{IPUCW}_{ij} = \prod_{k=3}^{j} \frac{Pr[UC_{ik}|E_{ik-2},E_{ik-1},V_{i0},UC_{ik-1}=1,S_{ik-1}=1,M_{ik-1}=0,M_{ik-2}=0,M_{ik}=0]}{Pr[UC_{ik}|E_{ik-2},E_{ik-1},L_{ik-2},UC_{ik-1}=1,S_{ik-1}=1,M_{ik-1}=0,M_{ik-2}=0,M_{ik}=0]}
\]

We estimated the numerator and denominator of the weights with pooled logistic regressions. We considered incident strokes starting in 2000 and set the corresponding exposure wave 1 (i.e., 1996) values of depressive symptoms and covariates to zero. Since we required participants to be alive and participating up to that year, the corresponding weight participation and survival weights were set to 1; the estimation of these weights for future waves did not included data from 2000. Both sets of models adjusted for the following baseline covariates: sex, age at enrollment, race, ethnicity, and education. Additionally, models estimating the denominator included time-varying covariates. To avoid collinearity, a subset of covariates was selected from a large pool of plausible confounders by an automated forward stepwise selection process.
including all possible time-varying confounders using an entry and staying criteria of $p=0.2$ (Results shown in Appendix Table IV). Models were required to contain the previously described baseline covariates and depressive symptoms level from past exposure waves. Covariate values were obtained from exposure wave 1 ($j-2$) except when calculating the IPUCW, which also included values from exposure wave 2 ($j-1$). The analytic model estimates the hazard of stroke at outcome wave $j$ using only individuals who survived to time $j-1$ and participated until time $j$ and accounts for their history of confounders. Individuals who were included in the estimation of the person time specific IPSW but who passed away at that time point had missing values for their IPEW at that wave and their IPUCW the following wave. This resulted in missing values for final weights (SIPW*sample weights) and the exclusion of this observation in the MSM model sample.

**SAS code:**

*time stable baseline covariates;*
%let demo_98=male b_ageyr b_ageyr_sq RAEDYRS HS PostHSyrs College nhblack Hispanic other; run;

/*******************************
Estimating numerator probabilities and sorting
*******************************/

*Survival at exposure wave 2 (i-1): Pr (SurvivedEW2|cesdDew1, demo_98, partEW2=1);*
proc genmod descending data=hrsipw;
where partEW2=1 and STKwave ne 3;
class STKwave HHIDPN ;
model SurvivedEW2=cesdDew1 &demo_98/dist=binomial link=logit;
repeated subject=hhidpn/ type=un;
output out=SurvivedEW2_num (keep= hhidpn stkwave p_SurvivedEW2_num)
p=p_SurvivedEW2_num;
run;

*Treatment at exposure wave 2 (i-1): Pr(treatedEW2|cesdDew1, demo_98, partEW2=1, SurvivedEW2=1);*
proc genmod descending data=hrsipw;
where partEW2=1 and survivedEW2=1;
class STKwave HHIDPN ;
model treatedEW2=cesdDew1 &demo_98 /dist=binomial link=logit;
repeated subject=hhidpn/ type=un;
output out=treatedEW2_num (keep= hhidpn stkwave p_treatedEW2_num)
p=p_treatedEW2_num;
run;

*Participation at outcome wave (i): Pr(partOW|cesdDew1, treatedEW2, demo_98, partEW2=1, SurvivedEW2=1, stkmiss=0, cesdCFew1=0, cesdCFew2=0);*
proc genmod descending data=hrsipw;
where partEW2=1 and survivedEW2=1 and stkmiss=0 and cesdCFew1=0 and cesdCFew2=0 and STKwave ne 3;
class STKwave HHIDPN;
model partOW=cesdDew1 treatedEW2 &demo_98/dist=binomial link=logit;
repeated subject=hhidpn type=un;
output out=partout_num (keep= hhidpn stkwave p_partout_num) p=p_partout_num;
run;

proc sort data=SurvivedEW2_num;   by hhidpn STKwave; run;
proc sort data=treatedEW2_num;       by hhidpn STKwave; run;
proc sort data=partout_num;       by hhidpn STKwave; run;

%let demo_98=male b_ageyr b_ageyr_sq RAEDYRS HS PostHSyrs College nhblack Hispanic other; run;

%let timevarallEW1=r_ageyrEW1 r_ageyrEW1_sq r_marriedEW1 incomecapEW1_qt
wlthcapEW1_qt r_antidepdEW1 r_drinkdEW1 r_smknowEW1 r_obeseEW1 r_heartdEW1
r_hibpdEW1 r_diabdEW1; run;

%let timevarallEW12=&timevarallEW1 r_ageyrEW2 r_ageyrEW2_sq r_marriedEW2
incomecapEW2_qt wlthcapEW2_qt r_antidepdEW2 r_drinkdEW2 r_smknowEW2 r_obeseEW2
r_heartdEW2 r_hibpdEW2 r_diabdEW2; run;

/**************************** Estimating denominator probabilities and sorting
***********************************************************************/
proc logistic data=hrsipw;
where partEW2=1 and STKwave ne 3;
class HHIDPN incomecapEW1_qt wlthcapEW1_qt;
model survivedEW2= cesdDew1 &demo_98 &timevarallEW1
/selection=stepwise slentry=.2 slstay = .2 include=11;
run;

*Survival at exposure wave 2 (i-1): Pr (SurvivedEW2=1|cesdDew1, demo_98, timecovariates,
partEW2=1);
proc genmod descending data=hrsipw;
where partEW2=1 and STKwave ne 3;
class STKwave hhidpn incomecapEW1_qt wlthcapEW1_qt;
model SurvivedEW2= cesdDew1 &demo_98 r_ageyrEW1_sq r_marriedEW1
incomecapEW1_qt wlthcapEW1_qt r_antidepdEW1 r_drinkdEW1 r_smknowEW1 r_obeseEW1
r_heartdEW1 r_hibpdEW1 r_diabdEW1/dist=binomial link=logit;
repeated subject=hhidpn type=un;
output out=SurvivedEW2_denom (keep= hhidpn stkwave p_SurvivedEW2_denom)
p=p_SurvivedEW2_denom;
Run;

proc logistic descending data=hrsipw;
where partEW2=1 and survivedEW2=1;
class HHIDPN incomecapEW1_qt wthcapEW1_qt;
model treatedEW2= cesdDew1 &demo_98 &timevarallEW1
/selection=stepwise slentry=.2 slstay = .2 include=11;
run;

*Treatment at exposure wave 2 (i-1): Pr(treatedEW2|cesdDew1, demo_98, timecovariates,
partEW2=1, SurvivedEW2=1);
proc genmod descending data=hrsipw;
where partEW2=1 and survivedEW2=1;
class STKwave hhidpn incomecapEW1_qt wthcapEW1_qt;
model treatedEW2= cesdDew1 &demo_98 r_ageyrew1 r_ageyrew1_sq r_marriedEW1
incomecapEW1_qt wthcapEW1_qt r_antidepdEW1 r_drinkdEW1 r_smknowEW1 r_obeseEW1
r_heartdEW1 r_hibpdEW1 r_diabdEW1/dist=binomial link=logit;
repeated subject=hhidpn/ type=EXCH;
output out=treatedEW2_denom (keep= hhidpn stkwave p_treatedEW2_denom)
p=p_treatedEW2_denom;
run;

proc logistic descending data=hrsipw;
where partEW2=1 and survivedEW2=1 and stkmiss=0 and cesdCFew1=0 and cesdCFew2=0 and
STKwave ne 3;
class HHIDPN incomecapEW1_qt wthcapEW1_qt incomecapEW2_qt wthcapEW2_qt;
model partOW= cesdDew1 treatedEW2 &demo_98 &timevarallEW12
/selection=stepwise slentry=.2 slstay = .2 include=11;
run;

*Participation at outcome wave (i): Pr(partOW|cesdDew1, demo_98, timecovariates,
partEW2=1, SurvivedEW2=1, strokemissing=0, CESDCFew1=0, CESDCRew2=0, treatedEW2);
proc genmod descending data=hrsipw;
where partEW2=1 and survivedEW2=1 and stkmiss=0 and cesdCFew1=0 and cesdCFew2=0 and
STKwave ne 3;
class STKwave hhidpn incomecapEW1_qt wthcapEW1_qt incomecapEW2_qt wthcapEW2_qt;
model partOW= cesdDew1 treatedEW2 &demo_98 r_marriedEW1 incomecapEW1_qt
wthcapEW1_qt r_smknowEW1 r_diabdEW1 r_ageyrew1 r_ageyrew1_sq incomecapEW2_qt
wthcapEW2_qt r_obeseEW2 /dist=binomial link=logit;
repeated subject=hhidpn/ type=un;
output out=partout_denom (keep= hhidpn stkwave p_partout_denom) p=p_partout_denom;
run;

proc sort data=survivedEW2_denom;  by hhidpn STKwave; run;
proc sort data=treatedEW2_denom;    by hhidpn STKwave; run;

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proc sort data=partout_denom; by hhidpn STKwave; run;
/
Merging probabilities and creating weights
proc sort data=hrsipw; by hhidpn STKwave; run;
data hrs_ipw_wtspart1;
merge hrsipw
SurvivedEW2_num  survivedEW2_denom
treatedEW2_num  treatedEW2_denom
partout_num   partout_denom;
by hhidpn STKwave;
if first.hhidpn=1 then firstobs=1;
if firstobs=1 then do; p_SurvEW2_num=1;
p_SurvEW2_denom=1;
survEW2prb_s=1;
survEW2prb_us=1;
depEW2prb_s=1;
depEW2prb_us=1;
p_partout_num=1;
p_partout_denom=1;
partoutprb_s=1;
partoutprb_us=1;
end;
/*Estimate stabilized (s) and unstablized (us) weights for current wave (T) and multiple with prior waves;*/
treatment/depression at wave 2 (i-1);
if depsxEW2=1 then depEW2prb_sT=(p_depsxEW2_num/p_depsxEW2_denom);
if depsxEW2=0 then depEW2prb_sT=((1-p_depsxEW2_num)/(1-p_depsxEW2_denom));
if depsxEW2=1 then depEW2prb_usT=(1/(p_depsxEW2_denom));
if depsxEW2=0 then depEW2prb_usT=(1/(1-p_depsxEW2_denom));
depEW2prb_s= depEW2prb_s* depEW2prb_sT;
depEW2prb_us= depEW2prb_us* depEW2prb_usT;
if firstobs ne 1 then do;
*survival at exposure wave 2 (i-1);
if survivedEW2=1 then
survEW2prb_sT=(p_survivedEW2_num/p_survivedEW2_denom);*stabilized;
if survivedEW2=0 then survEW2prb_sT=((1-p_survivedEW2_num)/(1-p_survivedEW2_denom));
if survivedEW2=1 then survEW2prb_usT=(1/(p_survivedEW2_denom));
if survivedEW2=0 then survEW2prb_usT=(1/(1-p_survivedEW2_denom));*unstablized;
if survivedEW2=0 then survEW2prb_usT=(1/(1-p_survivedEW2_denom));
survEW2prb_s=        survEW2prb_s*        survEW2prb_sT;
survEW2prb_us=        survEW2prb_us*        survEW2prb_usT;
retain survEW2prb_s survEW2prb_us;
end;
*participation in outcome wave (i);
if partOW=1    then partoutprb_sT=(p_partout_num/p_partout_denom);
if partOW=0    then partoutprb_sT=((1-p_partout_num)/(1-p_partout_denom));
if partOW=1    then partoutprb_usT=(1/p_partout_denom);
if partOW=0    then partoutprb_usT=(1/(1-p_partout_denom));
partoutprb_s=     partoutprb_s*     partoutprb_sT;
partoutprb_us=     partoutprb_us*     partoutprb_usT;

retain partoutprb_s partoutprb_us;
end;
run;

data hrs_ipw_wts;
set hrs_ipw_wtspart1;
wt_combine_s= survEW2prb_s *depEW2prb_s* partoutprb_s;
wt_combine_us= survEW2prb_us *depEW2prb_us* partoutprb_us;
run;
Appendix IV. Results from pooled logistic regression models for estimating the denominators of the inverse probability of survival (IPSW), the inverse probability of exposure weights (IPEW), and the inverse probability of participation weights (IPUCW)*

| Variable                                      | Model predicting survival at the second exposure wave (for IPSW estimate) | Model predicting exposure by elevated depressive symptoms at the second exposure wave (for IPEW estimates) | Model predicting remaining uncensored at the outcome wave (for IPUCW estimates) |
|-----------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
|                                               | OR  95% CI  P-value                                           | OR  95% CI  P-value                                           | OR  95% CI  P-value |
| Elevated depression score at exposure wave 1 | 0.58  0.53  0.63  <.0001                                           | 1.84  1.74  1.95  <.0001                                           | 1.02  0.90  1.15  0.80 |
| Elevated depression score at exposure wave 2 | -- -- -- -- --                                                      | -- -- -- -- -- --                                                  | 0.93  0.82  1.05  0.23 |
| Time-constant covariates: Baseline           |                                                                         |                                                                  | 0.99  0.90  1.09  0.86 |
| Male                                          | 0.49  0.44  0.53  <.0001                                           | 0.69  0.65  0.73  <.0001                                           | 0.82  0.71  0.94  <0.01 |
| Baseline age                                  | 1.00  0.95  1.05  0.96                                           | 0.90  0.87  0.93  <.0001                                           | 1.00  1.00  1.00  0.03 |
| Baseline age squared                          | 1.00  1.00  1.00  0.79                                           | 1.00  1.00  1.00  <.0001                                           | 0.95  0.92  0.99  0.01 |
| Years of education                            | 0.96  0.94  0.99  0.01                                           | 0.94  0.93  0.96  <.0001                                           | 1.22  1.04  1.44  0.02 |
| High school degree                            | 1.15  1.01  1.32  0.04                                           | 0.81  0.75  0.88  <.0001                                           | 1.10  1.03  1.18  <0.01 |
| Years of higher education                     | 1.00  0.94  1.06  0.98                                           | 0.97  0.93  1.00  0.06                                           | 1.00  0.80  1.25  0.99 |
| College degree                                | 1.16  0.94  1.42  0.16                                           | 0.92  0.80  1.05  0.23                                           | 0.78  0.67  0.90  <0.01 |
| Non-Hispanic white                            | ref  ref  ref  ref                                                  | ref  ref  ref  ref                                                  | ref  ref  ref  ref |
| Non-Hispanic black                            | 1.23  1.07  1.41  0.01                                           | 1.30  1.17  1.45  <.0001                                           | 0.78  0.67  0.90  <0.01 |
| Hispanic                                      | 1.35  1.11  1.65  0.01                                           | 1.34  1.10  1.62  <.0001                                           | 0.81  0.66  0.99  0.04 |
| Self-identified "Other" race                  | 1.45  1.03  2.05  0.03                                           | 1.84  1.74  1.95  <0.01                                           | 0.58  0.43  0.78  <0.01 |
| Exposure wave 1                               |                                                                         |                                                                  | 0.99  0.90  1.09  0.86 |
| Age (linear)                                  | -- -- -- -- --                                                      | 0.99  0.99  1.00  <.0001                                           | -- -- -- -- -- |
| Age (squared)                                 | 1.00  1.00  1.00  <.0001                                           | 1.00  1.00  1.00  <.0001                                           | -- -- -- -- -- |
| Marital Status                                | 1.21  1.10  1.33  <.0001                                           | 1.04  0.98  1.10  0.23                                           | 1.14  1.03  1.28  0.02 |
| Income per capita                             |                                                                         |                                                                  | 0.81  0.63  1.05  0.11 |
| 1st quartile                                  | 0.67  0.54  0.83  <.0001                                           | 1.16  1.04  1.28  0.01                                           | -- -- -- -- -- |
| Exposure wave 2 | 2nd quartile | 3rd quartile | 4th quartile | Wealth per capita | Psychiatric medication | Smoking | Obesity | Heart disease | High blood pressure | Diabetes |
|----------------|-------------|-------------|-------------|------------------|-----------------------|---------|---------|--------------|-------------------|---------|
| Age (linear)   | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| Age (squared)  | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| Income per capita | --      | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| 1st quartile   | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| 2nd quartile   | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| 3rd quartile   | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| 4th quartile   | --          | --          | --          | --               | --                    | ref     | ref     | ref           | ref               | ref     |
| Wealth per capita | --      | --          | --          | --               | --                    | ref     | ref     | ref           | ref               | ref     |
| 1st quartile   | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| 2nd quartile   | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| 3rd quartile   | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |
| 4th quartile   | --          | --          | --          | --               | --                    | ref     | ref     | ref           | ref               | ref     |
| Obesity        | --          | --          | --          | --               | --                    | --      | --      | --            | --                | --      |

* Pool of possible confounders included the following time-updated variables for exposure wave 1 for all models and exposure wave 2 for IPUCW models: age at interview (yrs), income per capita quartile, wealth per capita quartile, number of days/week respondent
drinks alcohol (0-7 days), current smoking status (yes/no), current psychiatric medication use (yes/no), obesity (BMI>30), and self-report of ever being diagnosed with heart disease, high blood pressure, or diabetes (yes/no for each condition).
Appendix V. Descriptive statistics of the stabilized combined inverse probability weight trimmed at the 99% percentile stratified by wave and overall

| Outcome wave | N    | Mean | Std Dev | Minimum | Maximum |
|--------------|------|------|---------|---------|---------|
| 3            | 16,178 | 1.00 | 0.05    | 0.78    | 1.08    |
| 4            | 14,147 | 0.97 | 0.16    | 0.29    | 1.74    |
| 5            | 12,261 | 0.96 | 0.20    | 0.12    | 1.74    |
| 6            | 10,914 | 0.95 | 0.25    | 0.06    | 1.74    |
| 7            | 9,746  | 0.94 | 0.28    | 0.02    | 1.74    |
| 8            | 8,663  | 0.93 | 0.31    | 0.01    | 1.74    |
| Overall      | 71,909 | 0.96 | 0.21    | 0.01    | 1.74    |
Appendix VI. Histogram of the stabilized combined inverse probability weight trimmed at the 99% percentile
Changes in Depressive Symptoms and Incidence of First Stroke Among Middle-Aged and Older US Adults
Paola Gilsanz, Stefan Walter, Eric J. Tchetgen Tchetgen, Kristen K. Patton, J. Robin Moon, Benjamin D. Capistrant, Jessica R. Marden, Laura D. Kubzansky, Ichiro Kawachi and M. Maria Glymour

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