Sex difference in prevalence of depression after stroke

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Abstract

Objective

This study investigated the sex difference in prevalence of depression at 90 days after first-ever stroke.

Methods

Patients with first-ever stroke ($n = 786$) were identified from the population-based Brain Attack Surveillance in Corpus Christi project (2011–2016). Poststroke depressive symptoms were assessed by the 8-item Patient Health Questionnaire, and prestroke depression status (history and medication use) was self-reported. Logistic regression was used to examine the association between sex and depression after stroke, and effect modification by prestroke depression status, accounting for missing data.

Results

Women were more likely to have a history of and be on medication for depression at the time of stroke than men ($p < 0.001$). Prevalence of depression at 90 days was 28.2% for men (95% confidence interval [CI], 23.7%–32.8%) and 32.7% for women (95% CI, 27.8%–37.5%). The age-adjusted odds ratio (OR) of depression after stroke comparing women and men was 1.34 (95% CI, 0.97–1.85), and fully attenuated after adjustment for sociodemographic, stroke, and prestroke characteristics. Effect modification by prestroke depression status was present ($p = 0.038$). Among participants on medication for depression at the time of stroke, women were significantly less likely to have depression at 90 days compared with men (OR, 0.39; 95% CI, 0.16–0.96), whereas significant sex differences were not noted among those with and without a depression history.

Conclusion

The sex difference in prevalence of depression at 90 days after first-ever stroke was not significant overall, but varied by prestroke depression status. Interventions to address and prevent poststroke depression are needed, particularly among those with prestroke depression but not undergoing treatment for depression at stroke onset.

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Glossary

BASIC = Brain Attack Surveillance in Corpus Christi; **CI** = confidence interval; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; **OR** = odds ratio; **PHQ-8** = 8-item Patient Health Questionnaire.

Depression affects approximately one-third of stroke survivors, and is associated with morbidity and disability.¹ Women are at higher risk for poor stroke outcomes than men,² particularly poststroke disability,³ which increases risk for depression.⁴ Moreover, depression as a risk factor for stroke⁵ is more prevalent in women than men in the general population,⁶ thus female patients with stroke with a history of depression may experience prolonged or recurrent depressive episodes after stroke.

Existing evidence shows that women are more likely to have depression after stroke than men,^{2,7} but the vast majority of studies have been hospital-based and were not specifically designed to assess sex differences.² Studies have varied in terms of sample composition, inclusion criteria, and covariate adjustment.² Notably, patients with prestroke depression were excluded from many studies,^{2,7} which may have differentially excluded women and resulted in biased estimates. To better understand sex differences in poststroke depression, it is necessary to take prestroke depression into consideration.

The present study aimed to contribute to existing literature by (1) examining the sex difference in prevalence of depression at 90 days after first-ever stroke in a population-based stroke study; (2) investigating the moderating role of prestroke depression in this association; and (3) accounting for potential differential attrition to reduce selection bias.

Methods

Study design and participants

Data are from the Brain Attack Surveillance in Corpus Christi (BASIC) project, which is an ongoing population-based stroke surveillance study designed to capture all stroke cases among community residents aged ≥ 45 years of Nueces County in south Texas.⁸ The total population of Nueces County was approximately 340,223 in 2010, with a majority of the residents being nonimmigrant Mexican Americans and non-Hispanic whites.⁹ Stroke cases are identified by active and passive surveillance.¹⁰ Active surveillance is based on daily screening of hospital admission logs, and passive surveillance identifies cases from hospital and emergency department discharge diagnosis codes. Possible cases undergo blinded validation by stroke neurologists. Early in the study, ascertainment procedures also included out of hospital sources including a sample of primary care physicians and cardiology offices ($<1\%$ of strokes) and neurology offices (3.6%).¹¹ Given the very low number of cases identified, ascertainment from out of hospital sources was discontinued for efficiency before the start of the current study period. Even with removal of these sources, we obtain $>95\%$ of cases, a cutoff proposed by some for population-based studies.^{8,11} Further, we

demonstrated that the changes in surveillance had minimal effect on estimated trends in stroke rates.¹¹

Patients with validated stroke are invited to participate in structured interviews in person shortly after stroke onset (baseline interview) and approximately 90 days after the index stroke (outcome interview). Proxy interviews are conducted if patients with stroke are unconsentable, comatose, unresponsive, or unable to speak or communicate. Prestroke and poststroke depression assessment are not available in proxy interviews, hence data are missing for these participants.

The study sample was drawn from all first-ever stroke cases occurring between January 5, 2011, and December 31, 2016. Included participants were those who (1) had no history of stroke/TIA; (2) survived 90 days after stroke; (3) completed the nonproxy baseline interview; and (4) completed the depression assessment at the outcome interview. During the study period, 1,793 patients with first-ever stroke survived 90 days after stroke, among whom 1,367 (76.2%) participated in the baseline interview. We then sequentially excluded 301 with proxy baseline interview, 248 who did not participate in the outcome interview, 23 with proxy outcome interview, and 9 without depression assessment, which leads to a final sample of 786 participants (figure). Data from excluded patients were used in the analytical process to account for potential differential attrition. In the study sample, the median time of the baseline interview was 7 days poststroke (interquartile range, 13 days), and the median time of the outcome interview was 89 days poststroke (interquartile range, 13 days).

Measures

Outcome measure: depression at 90 days after stroke

The primary outcome measure was depression at 90 days after stroke, which included depression caused by stroke, poststroke, and/or prestroke factors. Depressive symptoms were assessed by the 8-item Patient Health Questionnaire (PHQ-8) during the outcome interview. PHQ-8 is an abbreviated version of the PHQ-9, which is a validated screening instrument for depression among stroke survivors.^{12,13} The PHQ-8/9 items match the diagnostic criteria for major depressive disorders in the DSM-5.¹⁴ Participants were asked to rate the frequency of having any of the following symptoms in the past 2 weeks: loss of interest, depressed mood, sleep disturbance, fatigue, appetite changes, low self-esteem, difficulty concentrating, and psychomotor changes. Responses for each item were recorded on a 4-point scale from “not at all” to “nearly every day.”¹² A total score ranging from 0 to 24 was calculated by summing the 8

p Values were from Pearson χ^2 tests for testing sex differences in each step.

items, with higher scores indicating more depressive symptoms. Participants scoring ≥ 10 were classified as having depression at 90 days after stroke.¹² The cutoff threshold demonstrates high sensitivity and specificity for identifying depression in stroke patients.¹³ We also generated a binary variable for each depressive symptom as a secondary outcome measure, with “nearly every day” coded as 1 and 0 otherwise.

Effect modifier: prestroke depression status

Self-reported prestroke depression status was ascertained from the nonproxy baseline interviews. Participants were asked whether they had ever been told by a doctor they had depression, and whether they were currently taking or had ever taken medications for depression. We generated 3 mutually exclusive categories, including no history of depression, history of depression and on medication for depression at the time of stroke. Participants not on medication for depression at the time of stroke were classified as having a history of depression if they reported having ever been diagnosed with depression or taken medications for depression; otherwise they were classified as no history of depression.

Sex and other covariates

Sex (male, female), the primary independent variable, and other covariates were ascertained at baseline from interviews or medical records. Covariates evaluated as potential confounders were sociodemographic, stroke, and prestroke characteristics. Sociodemographic characteristics included age (<65 , 65 – 79 , ≥ 80), race/ethnicity (non-Hispanic white, Mexican American, other race/ethnicity), education (less than high school, high school and above), marital status (married or partnered, single, widowed, separated or divorced), and health insurance status (insured, uninsured). Stroke characteristics included stroke type (ischemic stroke, intracerebral hemorrhage stroke) and initial stroke severity measured by the NIH Stroke Scale.¹⁵ Prestroke characteristics included cognitive function, functional disability, number of medical conditions, and health risk behaviors. Cognitive function was measured by the Informant Questionnaire on Cognitive Decline in the Elderly,¹⁶ and categorized as normal cognitive function (≤ 3), cognitive impairment no dementia (>3 and <3.44), or dementia (≥ 3.44).¹⁷ Functional disability was measured by the modified Rankin Scale,¹⁸ and categorized as no disability (0–1), slight or

moderate disability (2–3), or moderately severe or severe disability (4–5). Number of medical conditions was calculated by counting the following conditions: coronary artery disease, atrial fibrillation, congestive heart failure, diabetes, hypertension, high cholesterol, dementia, epilepsy, Parkinson disease, cancer, chronic obstructive pulmonary disease, and end-stage renal disease. Health risk behaviors included current smoking, excessive alcohol use, and obesity, defined as body mass index ≥ 30 .

We checked functional forms of continuous covariates using locally weighted scatterplot smoothing, and applied appropriate terms respectively. The percentage of missing covariate data was the greatest for baseline cognitive function (17.1%), followed by current smoking (6.7%), and less than 2% for other covariates (table 1).

Statistical analysis

We compared sample characteristics between included and excluded patients for each main attrition step, and between study participants with and without missing data on baseline cognitive function. We dealt with missing data using an approach combining multiple imputation and inverse probability weighting.¹⁹ Multiple imputation was used to fill in missing values of covariates for the study sample, to avoid a decrease in statistical power and to minimize selection bias.²⁰ Inverse probability weighting was used to account for differential attrition and selection bias.²¹ We generated inverse probability weights to reflect the original patient population by upweighting study participants who were similar to those not in the study sample (e-Materials, doi.org/10.5061/dryad.07sc440).

We examined differences in sample characteristics by sex using Pearson χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables. We used weighted cross-tabulations to estimate sex-specific prevalence of depression and each depressive symptom at 90 days poststroke. We then used weighted logistic regression to examine the association between sex and depression after stroke, and estimated 3 sequential models. The base model (model 1) adjusted for age only; the intermediate model (model 2) additionally adjusted for prestroke depression status; and the full model (model 3) adjusted for model 2 covariates and sociodemographics (race/ethnicity, education, marital status, health insurance status), stroke (stroke type, stroke severity), and prestroke characteristics (functional disability, cognitive impairment, health risk behaviors). To examine potential effect modification by prestroke depression status, we introduced interaction terms between sex and prestroke depression status to model 3, calculated stratum-specific odds ratios (ORs), and tested the significance of the interaction using an *F* test (2 degrees of freedom). We further conducted a separate analysis among participants with no history of depression by fitting a model with adjustment for sociodemographic, stroke, and prestroke characteristics, to examine risk factors for first onset of depression after stroke.

We conducted 2 sensitivity analyses. To understand the possible influence of our missing data approach on the results, we conducted complete case analysis and analysis with multiple imputation only, and compared the results with our primary analysis. To consider potential violation of the missing at random assumption for multiple imputation of missing covariate data, we modeled the probability of missing baseline cognitive measures as dependent on the cognitive score itself.

Statistical analyses were completed with Stata version 14.2 (StataCorp) and SAS version 9.4 (SAS Institute, Cary, NC). The SAS procedures PROC MI with the FCS statement and PROC MIANALYZE were used for multiple imputation, and the MNAR statement in the MI procedure was used for the sensitivity analysis for the missing at random assumption.

Standard protocol approvals, registrations, and patient consents

The BASIC project was approved by the institutional review boards at the University of Michigan and the local hospital systems. Written informed consents were provided by patients or their surrogates.

Data availability

The data will not be made publicly available because of their restricted nature.

Results

Comparing sample characteristics between included and excluded participants, there was no statistically significant sex difference in study participation at baseline (table e-1, doi.org/10.5061/dryad.07sc440); however, women were more likely to have proxy baseline interview (table e-2, doi.org/10.5061/dryad.07sc440), and more likely to participate in the outcome interview (table e-3, doi.org/10.5061/dryad.07sc440). Compared with participants with nonproxy baseline interviews, those with proxy interviews were older, more likely to be widowed, more likely to be functionally and cognitively impaired, and more likely to have more medical conditions and cardiovascular risk factors (table e-2). However, such differences were not significant in outcome interview participation (table e-3). There was no statistically significant sex difference between participants with and without missing data on baseline cognitive function (table e-4, doi.org/10.5061/dryad.07sc440).

As shown in table 1, women and men were approximately equally distributed in the study sample, with a mean age of 65.4 years. Nearly three-fifths were Mexican American and two-fifths were non-Hispanic white. Compared with men, women were older, had lower educational attainment and greater stroke severity, and were more likely to be widowed and to have more prestroke functional limitations and cognitive impairment. Women were less likely than men to report history of coronary artery disease, excessive alcohol use, and smoking. Notably, approximately one-fourth of women were on

Table 1 Baseline sample characteristics by sex, Brain Attack Surveillance in Corpus Christi project, United States, 2011–2016

	Total (n = 786)	Men (n = 403)	Women (n = 383)	p Value
Sociodemographic characteristics				
Age, y	65.4 ± 11.1	64.3 ± 10.2	66.5 ± 11.9	0.012
Age, y				0.007
<65	391 (49.8)	218 (54.1)	173 (45.2)	
65–79	294 (37.4)	146 (36.2)	148 (38.6)	
≥80	101 (12.9)	39 (9.7)	62 (16.2)	
Race/ethnicity				0.394
Non-Hispanic white	285 (36.3)	155 (38.5)	130 (33.9)	
Mexican American	448 (57.0)	223 (55.3)	225 (58.8)	
Other	53 (6.7)	25 (6.2)	28 (7.3)	
Education ^a				0.037
Less than high school	227 (28.9)	103 (25.6)	124 (32.4)	
High school and above	558 (71.1)	299 (74.4)	259 (67.6)	
Marital status ^a				<0.001
Married/partnered	380 (48.4)	240 (59.7)	140 (36.6)	
Single	75 (9.6)	39 (9.7)	36 (9.4)	
Widowed	154 (19.6)	35 (8.7)	119 (31.1)	
Separated/divorced	176 (22.4)	88 (21.9)	88 (23.0)	
Health insurance status				0.075
Insured	698 (88.8)	350 (86.9)	348 (90.9)	
Uninsured	88 (11.2)	53 (13.2)	35 (9.1)	
Stroke characteristics				
Stroke type ^a				0.034
Ischemic stroke	721 (91.9)	362 (89.8)	359 (94.0)	
Intracerebral hemorrhage stroke	64 (8.2)	41 (10.2)	23 (6.0)	
Stroke severity (NIHSS) ^a	3.9 ± 4.6	3.6 ± 4.0	4.3 ± 5.1	0.040
Prestroke characteristics				
Depression status ^a				<0.001
No history of depression	511 (65.9)	299 (75.7)	212 (55.6)	
History of depression ^b	125 (16.1)	51 (12.9)	74 (19.4)	
On medication for depression at the time of stroke	140 (18.0)	45 (11.4)	95 (24.9)	
Disability (mRS) ^a				0.027
No disability (0–1)	402 (52.1)	223 (56.5)	179 (47.6)	
Slight/moderate disability (2–3)	330 (42.8)	157 (39.8)	173 (46.0)	
Moderately severe/severe disability (4–5)	39 (5.1)	15 (3.8)	24 (6.4)	
Cognitive function (IQCODE) ^a	3.1 ± 0.3	3.1 ± 0.3	3.1 ± 0.2	0.097
Cognitive function (IQCODE) ^a				0.039

Continued

Table 1 Baseline sample characteristics by sex, Brain Attack Surveillance in Corpus Christi project, United States, 2011–2016 (continued)

	Total (n = 786)	Men (n = 403)	Women (n = 383)	p Value
Normal (0–3)	398 (61.0)	220 (64.9)	178 (56.9)	
CIND (3.01–3.43)	196 (30.1)	87 (25.7)	109 (34.8)	
Dementia (≥3.44)	58 (8.9)	32 (9.4)	26 (8.3)	
No. of medical conditions	2.4 ± 1.5	2.5 ± 1.5	2.4 ± 1.6	0.407
Cardiovascular risk factors				
Coronary artery disease	192 (24.4)	121 (30.0)	71 (18.5)	<0.001
Atrial fibrillation	86 (10.9)	42 (10.4)	44 (11.5)	0.632
Congestive heart failure	42 (5.3)	17 (4.2)	25 (6.5)	0.150
Hypertension	618 (78.6)	318 (78.9)	300 (78.3)	0.843
Diabetes	359 (45.7)	184 (45.7)	175 (45.7)	0.992
High cholesterol	381 (48.5)	194 (48.1)	187 (48.8)	0.847
Health risk behaviors				
Current smoking^a	194 (26.5)	121 (33.1)	73 (19.9)	<0.001
Excessive alcohol use	59 (7.5)	41 (10.2)	18 (4.7)	0.004
Obesity (body mass index ≥30)	333 (42.5)	158 (39.3)	175 (45.9)	0.061

Abbreviations: CIND = cognitive impairment no dementia; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

Values are mean ± SD or n (%).

^a Variables with missing data. The numbers of missing values were 134 for prestroke cognitive function (17.1%), 53 for current smoking (6.7%), 15 for prestroke disability (1.9%), 10 for prestroke depression status (1.3%), 3 for stroke severity (<1.0%), 3 for obesity (<1.0%), 1 for stroke type (<1.0%), 1 for education level (<1.0%), and 1 for marital status (<1.0%).

^b A participant was classified as having a history of depression if he or she reported having ever been diagnosed with depression or taken medication for depression, but not on medication for depression at the time of stroke.

medication for depression at the time of stroke, and one-fifth of women were not on medication for depression but reported history of depression, which were significantly higher than estimates in men.

The mean PHQ-8 score at 90 days poststroke was 6.4 (SD, 6.4) for men and 7.5 (SD, 6.8) for women ($p = 0.012$). After adjustment for attrition, the prevalence of depression (as defined by a PHQ-8 score of 10 or higher) at 90 days after first-ever stroke was 28.2% for men (95% confidence interval [CI], 23.7%–32.8%) and 32.7% for women (95% CI, 27.8%–37.5%) ($p = 0.187$). Fatigue and sleep disturbance were the most common depressive symptoms in both men and women. The prevalence of fatigue and appetite changes was higher in women than in men whereas the prevalence of psychomotor changes was higher in men than in women (table 2).

As presented in table 3, the age-adjusted OR of depression after stroke comparing women with men (OR, 1.34; 95% CI, 0.97–1.85) was attenuated towards the null after additional adjustment for prestroke depression status. In the fully adjusted model, factors associated with depression after stroke included prestroke depression status, age, education, number of medical comorbidities, and current smoking at

baseline (table 3). Effect modification of the association between sex and depression after stroke by prestroke depression status was significant after adjustment for all covariates (table 4). There was no statistically significant sex difference in depression after stroke among participants with no history of depression before stroke (OR, 1.11; 95% CI, 0.66–1.86). Among participants with a history of depression before stroke, women tended to have higher odds than men (OR, 1.92; 95% CI, 0.80–4.61). However, among participants on medication for depression at the time of stroke, women were significantly less likely to have depression at 90 days after stroke than men (OR, 0.39; 95% CI, 0.16–0.96).

Among participants with no history of depression, approximately two-fifths were women (table e-5, doi.org/10.5061/dryad.07sc440). Compared with men, women in this subset were older, were more likely to be widowed, and had greater stroke severity and more medical conditions. However, there were no statistically significant sex differences in prestroke disability and cognitive impairment. Factors associated with first-onset depression after first-ever stroke included being uninsured, number of medical conditions, and current smoking at the time of stroke onset (table e-6, doi.org/10.5061/dryad.07sc440).

Table 2 Sex differences in prevalence of depression and individual depressive symptoms at 90 days poststroke, Brain Attack Surveillance in Corpus Christi project, United States, 2011–2016

	Men, % (95% CI)	Women, % (95% CI)	p Value
Depression (PHQ-8 ≥ 10)	28.2 (23.7–32.8)	32.7 (27.8–37.5)	0.187
Individual depressive symptoms			
Loss of interest	19.1 (15.2–23.0)	21.4 (17.2–25.6)	0.425
Depressed mood	18.3 (14.4–22.2)	21.9 (17.6–26.1)	0.215
Sleep disturbance	27.4 (22.9–31.9)	31.2 (26.3–36.0)	0.259
Fatigue	29.9 (25.3–34.4)	39.5 (34.4–44.6)	0.005
Appetite changes	13.9 (10.4–17.3)	20.2 (15.9–24.5)	0.021
Low self-esteem	16.6 (12.8–20.4)	19.5 (15.2–23.8)	0.297
Difficulty concentrating	17.6 (13.7–21.4)	15.8 (12.0–19.7)	0.513
Psychomotor changes	19.1 (15.1–23.2)	14.4 (10.6–18.1)	0.082

Abbreviations: CI = confidence interval; PHQ-8 = 8-item Patient Health Questionnaire. The sample size was 786.

Compared with the main analysis, the age-adjusted OR was stronger and significant among cases with complete data (OR, 1.39; 95% CI, 1.01–1.90), whereas the moderating effect by prestroke depression status on the association between sex and depression after stroke was weaker in the complete case analysis and the analysis with imputation only (table e-7, doi.org/10.5061/dryad.07sc440). Results from the sensitivity analysis for the potentially not missing at random covariate data were consistent with the main findings (table e-8, doi.org/10.5061/dryad.07sc440).

Discussion

This study investigated the sex difference in prevalence of depression at 90 days after first-ever stroke in a population-based sample. We found that there was no statistically significant sex difference in prevalence of depression after accounting for attrition. However, we identified significant effect modification of the association between sex and depression after stroke by prestroke depression status such that compared with men, women on medication for depression at the time of stroke were significantly protected against depression after stroke, whereas women with depression history but not on medication showed a tendency for elevated risk compared with men. The non-significant overall association was therefore attributable to the heterogeneity according to prestroke depression status. It is also worth mentioning that women were significantly more likely to have a history of depression before stroke and to use medication for depression at the time of stroke, and prestroke depression status was strongly associated with depression after stroke, consistent with previous research.²²

Our findings showed that among stroke survivors on medication for depression at the time of stroke, women had

significantly lower risk for depression at 90 days poststroke compared with men, which may be explained by differential drug response due to sex differences in depression characteristics. Among individuals prone to stroke, vascular risk factors may lead to late-onset depression through neural disconnectivity, hypoperfusion, and inflammation.^{23,24} Men with late-onset depression have increased inflammation and cognitive deficits,^{25,26} which are associated with dysregulation of the hypothalamic-pituitary-adrenal axis,^{22,27} and poor response to antidepressant treatment.^{23,27,28} Furthermore, women's higher likelihood of seeking treatment for depression than men may cause differences in symptom severity at treatment,²⁹ and therefore lead to sex differences in antidepressant response and symptom persistence after stroke.³⁰ Different antidepressants generate sex-specific pathophysiologic changes that may or may not have beneficial effects on mood in certain subgroups,²⁵ however, data on types of antidepressants used at the time of stroke onset were not available in the present study. Future research on treatment for poststroke depression may need to consider potential sex-specific treatment response, given the sex differences in etiologies, pathophysiology and severity of depression. Because depression is a risk factor for stroke and is more prevalent in women,^{5,6} adequately treating women with depression may serve as a prevention strategy to both reduce risk of stroke and lessen poststroke depression in this high-risk group.

We found that women with prestroke depression but not on medication for depression at the time of stroke tended to have higher risk for depression after stroke than men. Although the sex difference did not reach statistical significance in the present sample, possibly due to low power, there is biological plausibility for this finding. A sex difference in depression is found in the general population, with women at higher risk compared with men due to a variety of biological and psychosocial factors.³¹ For

Table 3 Results from weighted logistic regression models of the association between sex and depression after stroke, Brain Attack Surveillance in Corpus Christi project, United States, 2011–2016

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Sex			
Men	Reference	Reference	Reference
Women	1.34 (0.97–1.85)	0.96 (0.68–1.36)	1.00 (0.67–1.49)
Age, y			
<65	Reference	Reference	Reference
65–79	0.36 (0.25–0.52)	0.35 (0.24–0.51)	0.38 (0.24–0.60)
≥80	0.48 (0.28–0.81)	0.58 (0.33–1.01)	0.61 (0.30–1.25)
Prestroke depression status			
No history of depression		Reference	Reference
History of depression		3.17 (2.04–4.93)	2.75 (1.67–4.53)
On medication for depression at the time of stroke		5.42 (3.49–8.43)	4.94 (3.01–8.10)
Race/ethnicity			
Non-Hispanic white			Reference
Mexican American			1.22 (0.78–1.93)
Other			1.49 (0.69–3.20)
Education			
Less than high school			1.71 (1.10–2.65)
High school and above			Reference
Marital status			
Married/partnered			Reference
Single			0.98 (0.51–1.91)
Widowed			1.09 (0.62–1.91)
Separated/divorced			1.45 (0.92–2.30)
Health insurance status			
Insured			Reference
Uninsured			1.73 (0.98–3.05)
Stroke type			
Ischemic stroke			Reference
Intracerebral hemorrhage stroke			1.07 (0.57–2.00)
Stroke severity (NIHSS)			1.03 (1.00–1.06)
Prestroke disability (mRS)			
No disability			Reference
Slight/moderate disability			1.39 (0.93–2.10)
Moderately severe/severe disability			2.00 (0.86–4.63)
Prestroke cognitive function (IQCODE)			
Normal			Reference
CIND			1.09 (0.68–1.76)

Continued

Table 3 Results from weighted logistic regression models of the association between sex and depression after stroke, Brain Attack Surveillance in Corpus Christi project, United States, 2011–2016 (continued)

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Dementia			0.80 (0.42–1.54)
No. of medical conditions			1.20 (1.03–1.40)
Coronary heart disease			
No			Reference
Yes			1.00 (0.59–1.67)
Current smoking			
No			Reference
Yes			1.94 (1.25–3.01)
Excessive alcohol use			
No			Reference
Yes			0.97 (0.48–1.96)
Obesity			
No			Reference
Yes			1.24 (0.84–1.82)

Abbreviations: CI = confidence interval; CIND = cognitive impairment no dementia; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio. The sample size of all 3 models was 786.

instance, women have greater proinflammatory response in the face of inflammatory challenges and stress,^{32,33} thus greater impairments in mood and behaviors.³³ Elevated inflammation levels from prestroke depression may differentially exacerbate deficits in hemodynamics and cerebral perfusion between men and women,²³ cause sex-specific vascular risk profiles,^{34,35} and therefore lead to sex differences in stroke severity, which is a risk factor for poststroke depression.²² From the perspective of psychopathology, participants with prestroke depression due to

predisposed vulnerabilities such as personality, interpersonal, and cognitive risk factors may be prone to depressive recurrence according to the kindling hypothesis.³⁶ Prospective studies indicated that women had significantly higher rates of depression recurrence than men.^{37,38} Thus, prestroke depression as a risk factor for stroke and poststroke depression^{5,22} may play a significant role in sex differences in depression after stroke.

We did not find a sex difference in first onset of depression after first-ever stroke. Existing findings from studies excluding patients with a history of depression are mixed,^{2,7} with some evidence suggesting higher risk in women at 3 months post-stroke.³⁹ In our study sample, women with no history of depression did not show worse functional status at baseline, despite their older age, widowhood, and greater stroke severity. This indicates they might have higher levels of beneficial characteristics than men that protected them from depression after stroke, such as social support.⁴⁰ Alternatively, because having a known history of depression is influenced by treatment-seeking behaviors, there may be differential misclassification between sexes given the fact that men are less likely to seek help for depression than women.²⁹ Men in this subgroup might therefore have higher than average susceptibility to depression, which masked the true sex difference in depression among stroke survivors with no history of depression.

Our study also suggests potential sex differences in the prevalence of individual depressive symptoms among participants

Table 4 Stratum-specific odds ratios (OR) of depression at 90 days poststroke comparing women with men by prestroke depression status, Brain Attack Surveillance in Corpus Christi project, United States, 2011–2016

	OR (95% CI)	<i>p</i> Value for interaction ^a
No history of depression	1.11 (0.66–1.86)	0.038
History of depression	1.92 (0.80–4.61)	
On medication for depression at the time of stroke	0.39 (0.16–0.96)	

Abbreviation: CI = confidence interval. The model included the interaction between sex and prestroke depression status, and covariates of model 3. The sample size was 786.

^a *p* Value from an *F* test to test the statistical significance of the interaction between sex and prestroke depression status.

with depression at 90 days after stroke. The most prevalent symptoms in both sexes were fatigue and sleep disturbance, which could be depressive symptoms, direct complications of stroke, or both. We found psychomotor changes occurred more frequently in men, whereas somatic symptoms occurred more frequently in women, which is consistent with existing findings of sex differences in depression symptomatology.^{31,41} This could be a reflection of different clinical manifestations of poststroke depression between men and women. Future studies with clinical examinations and biomedical tests could further investigate sex differences in the depressive phenotype and genotype among patients with stroke, which might aid in the development of better screening tools for poststroke depression.

These results should be considered as hypothesis generating. Larger studies should seek to replicate these findings, particularly our finding of effect modification, with consideration for potential selection bias. Our investigation of the influence of missing data suggests that the estimates of the sex difference would have been biased without accounting for differential attrition due to women's worse stroke outcomes and higher propensity for depression. Using complete cases alone may cause selection bias in the presence of unmeasured factors that influence both the probability of remaining in the study and poststroke depression.²¹

Our study has several limitations. First, prestroke depression status was based on self-report of prior diagnoses and treatment rather than direct depression assessment, and therefore subject to misclassification due to recall bias and social desirability bias, and influenced by sex-specific help-seeking behaviors. Second, depression classification after stroke was based on self-reported symptoms assessed by the PHQ-8 rather than DSM-based diagnostic interviews. Although the PHQ-9 has been identified as one of the potentially optimal instruments for assessing poststroke depression,⁴² it does not have requirements for depressed mood or loss of interest as in the DSM-5, and may be subject to misclassification due to the complexity of stroke.⁴² There may also be measurement error due to differential reporting patterns between sexes.⁴³ However, recent evidence from the European older adult population suggests the observed sex difference in late-life depression is not attributable to sex-specific reporting of symptoms.⁴³ Third, both measures of prestroke depression status and the PHQ-8 did not include items related to manic episodes, therefore participants with bipolar disorder could not be differentiated. Fourth, despite the high response rate of the BASIC project for studies of this kind (approximately 77%), a proportion of patients did not have depression assessment due to the lack of appropriate tools in proxy interviews. Although the inverse probability weighting approach was used to upweight study participants who were similar to those not included, it may not be able to account for extremely severe cases of aphasia and cognitive impairment that cannot be presented by the study participants.²¹ Fifth, because our study sample was

drawn from a biethnic population in south Texas, the results may not be generalizable to populations with different racial and ethnic composition. However, the results are generalizable to the broader nonimmigrant Mexican American population in the United States that bears higher risk for poor poststroke outcomes.⁴⁴

Results from this population-based stroke study, using statistical approaches to reduce selection bias, suggest that depression among stroke survivors is multifactorial and heterogeneous with substantial sex differences throughout the disease course before and after stroke. Interventions to address and prevent poststroke depression are needed, particularly among those with prestroke depression but not undergoing treatment for depression at stroke onset.

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Disclosure

L. Dong, B. Sánchez, L. Skolarus, E. Stulberg, L. Morgenstern, and L. Lisabeth report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Liming Dong, PhD	University of Michigan, Ann Arbor	Conceptualized the study, analyzed the data, interpreted the data, drafted the manuscript
Brisa N. Sánchez, PhD	University of Michigan, Ann Arbor	Contributed to statistical analysis, interpreted the data, revised the manuscript, provided final approval
Lesli E. Skolarus, MD	University of Michigan, Ann Arbor	Interpreted the data, revised the manuscript, provided final approval
Eric Stulberg, BS	University of Michigan, Ann Arbor	Interpreted the data, revised the manuscript, provided final approval
Lewis B. Morgenstern, MD	University of Michigan, Ann Arbor	Provided the data, revised the manuscript, provided final approval
Lynda D. Lisabeth, PhD	University of Michigan, Ann Arbor	Provided the data, conceptualized the study, interpreted the data, revised the manuscript, provided final approval, supervised the study

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