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ORIGINAL RESEARCH

Poststroke Cognitive Outcomes: Sex Differences and Contributing Factors

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BACKGROUND: The study investigated sex differences in cognitive outcomes at 90 days after first-ever stroke using data from a population-based sample.

METHODS AND RESULTS: The study sample consisted of 1227 participants from the 2009–2016 Brain Attack Surveillance in Corpus Christi project (south Texas, United States) who had first-ever ischemic stroke or intracerebral hemorrhage and survived 90 days after stroke. Poststroke cognitive function was assessed by the Modified Mini-Mental State Examination (3MSE) (range: 0–100; dementia: <78). The associations of sex with dichotomized and continuous outcomes were examined using logistic regression and tobit regression, respectively. Inverse probability weighting and multiple imputation were used to deal with missing data. The study sample was evenly distributed by sex, and primarily composed of Mexican Americans (59.1%) and non-Hispanic whites (34.1%). Women scored 2.96 points worse on the 3MSE than men at 90 days poststroke (95% CI, –3.99 to –1.93). The prevalence of dementia was 27.6% for men (95% CI, 23.5%–31.6%) and 35.6% for women (95% CI, 31.5%–39.7%), and the unadjusted odds ratio (OR) of dementia comparing women with men was 1.45 (95% CI, 1.24–1.69). The association was attenuated after adjustment for sociodemographic, stroke, and prestroke characteristics (OR, 0.82; 95% CI, 0.61–1.09).

CONCLUSIONS: Women had worse cognitive outcomes than men at 90 days poststroke. The differences were attributable to sociodemographic and prestroke characteristics, especially widowhood status. Potential mechanisms linking widowhood to dementia in the acute poststroke stage warrant further investigation to inform interventions addressing the unique care needs of women stroke survivors with dementia and cognitive dysfunction.

Key Words: cognition ■ epidemiology ■ sex ■ stroke

Stroke is a major vascular contributor to cognitive impairment and dementia, which increases the risk for disability and poor quality of life.[1,2] Compared with men, women have worse poststroke functional and quality-of-life outcomes, because of their older age at stroke onset, greater stroke severity, worse prestroke functioning and higher prevalence of risk factors for cognitive impairment.[3] Sex differences in cognitive function and age-related cognitive decline exist as a result of biological and social factors throughout the life course,[4] and female sex is strongly associated with prestroke dementia.[5] However, sex differences in cognitive function and dementia after stroke remain unclear.

Existing studies on sex differences in poststroke cognitive outcomes are few and were heterogeneous in their designs and methods making comparisons across studies challenging.[3,5] In particular, there has been a lack of population-based studies, which limits the generalizability of the findings. Because previous studies were rarely designed to specifically investigate sex differences, residual confounding may exist because of inadequate covariate adjustment. Most importantly, older age and cognitive impairment, well-recognized risk factors for attrition,[6] are differentially distributed between men and women stroke survivors. Ignoring this informative missingness may have resulted in biased estimates of the sex difference in

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CLINICAL PERSPECTIVE

What Is New?

- The study provides contemporary, population-based data on sex differences in poststroke cognitive outcomes, and shows that the higher prevalence of being widowed among women may be a contributing factor to worse poststroke cognitive outcomes in women compared with men.

What Are the Clinical Implications?

- Women stroke survivors in special social circumstances, such as widowhood, may have greater unmet needs for social support, which is critical for postacute rehabilitation care and stroke recovery.

Nonstandard Abbreviations and Acronyms

3MSE	Modified Mini-Mental State Examination
BASIC	Brain Attack Surveillance in Corpus Christi
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
MMSE	Mini-Mental State Examination
NIHSS	National Institutes of Health Stroke Scale

poststroke cognitive function such that the sex difference was underestimated.

The present study aimed to contribute to existing literature by examining potential sex differences in cognitive outcomes at 90 days poststroke and contributing factors to the sex differences, using data from a population-based stroke study and methods to minimize selection bias caused by sex difference in attrition.

METHODS

Study Population

Data were obtained from the BASIC (Brain Attack Surveillance in Corpus Christi) project, a population-based stroke surveillance study that captures all stroke cases among residents aged 45 years and older in the nonimmigrant biethnic community of Nueces County in south Texas, United States.[7] Because of the sensitive nature of the data collected for this study, data will not be publicly available. Possible stroke cases are ascertained through active and passive surveillance methods, and then validated by stroke fellowship trained physicians.[8] Identified stroke patients are invited to participate in the baseline interview shortly after stroke onset, and those who complete the baseline interview are followed up at ≈ 90 days poststroke for an outcome interview. For participants who are unable to complete the interviews, proxy interviews are completed by informants on behalf of the patients. Details of the study have been described elsewhere.[7]

The present study drew participants from all stroke cases occurring between January 1, 2009, and December 31, 2016. Included participants were those who survived 90 days poststroke, had first-ever ischemic stroke or intracerebral hemorrhage, and completed both baseline and outcome interviews. During the specified period, 1708 of 2278 (75.0%) 90-day survivors of first-ever ischemic or hemorrhagic stroke completed the baseline interview, and 1227 of them (71.8%) subsequently completed the outcome interview, which constitutes the final sample for the primary analysis (Figure 1). Data for patients who did not participate in baseline or outcome interviews were used in the analysis to account for potential differential attrition and minimize selection bias.

The BASIC project was approved by the institutional review boards at the University of Michigan and the local hospital systems. Written informed consent was obtained from patients or their surrogate.

Measures

The outcome measure was cognitive function at 90 days poststroke, as measured by the Modified Mini-Mental State Examination (3MSE) among participants who were able to complete the outcome interview in-person.[9] The 3MSE has been widely used in research and clinical settings to detect decline in cognitive function, with good validity and reliability in the stroke population.[10] It measures a variety of cognitive domains across a range of difficulty levels, including orientation, memory, language, reasoning, and executive function.[9] The total score ranges from 0 to 100, with higher scores indicating better cognitive function. We classified participants scoring <78 as having dementia based on previous validation evidence.[11,12] Both continuous and dichotomized cognitive outcome measures were used in the analyses.

The 3MSE was administered in English or Spanish depending on participants' preference. Approximately 5.3% of the study sample (n=52) completed the assessment in Spanish. Participants with proxy outcome interviews did not have 3MSE assessment, and therefore had missing data on cognitive outcomes. A total of 249 of 1227 participants (20.3%) had missing cognitive outcome data, among which 213 (85.5%) were because of having proxy interviews and 36 did not compete the assessment because of other reasons such as refusal or telephone interviews.

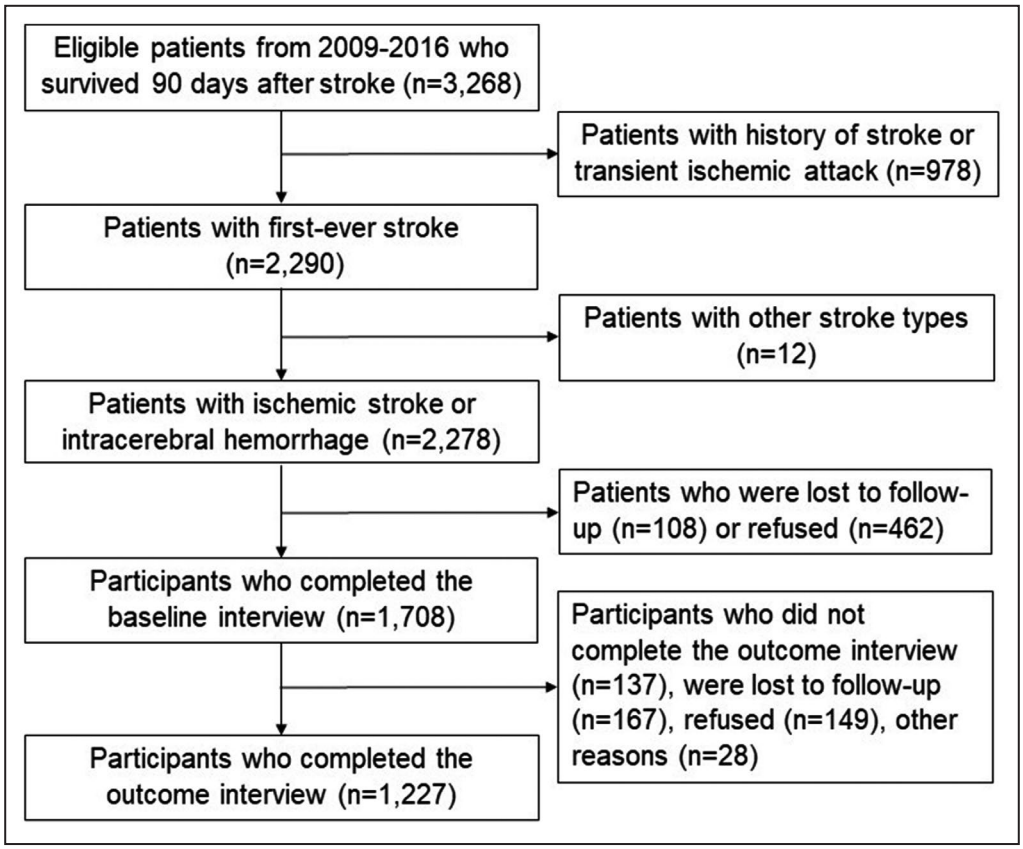

Figure 1. Flow diagram of the study sample, Brain Attack Surveillance in Corpus Christi project, United States, 2009–2016.

Sex (men, women), the primary independent variable, and other covariates were ascertained at baseline from interviews or medical records. Potential confounders were sociodemographic, stroke and prestroke characteristics. Sociodemographic characteristics included age, race/ethnicity (non-Hispanic white, Mexican American, other), education (below high school, high school, vocational/some college, college or more), marital status (married/partnered, single, widowed, separated/divorced), and health insurance status (insured, uninsured). Stroke characteristics included stroke type (ischemic stroke, intracerebral hemorrhage) and initial stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS).[13] Prestroke characteristics included prestroke cognitive function, prestroke disability, prestroke depression status, number of medical conditions, current smoking, and obesity. Prestroke cognitive function was measured by the Informant Questionnaire on Cognitive Decline in the Elderly,[14] a widely used screening tool for dementia based on proxy-report. Informants of the study participants were asked to rate changes in participants' cognitive functioning before stroke, upon which participants were classified as having normal cognitive function (≤3); cognitive impairment, no dementia (>3 and <3.44); or dementia (≥3.44) before stroke.[15] Prestroke disability was measured by the modified Rankin Scale, and categorized as no symptoms/disability (0 or 1), slight/moderate disability (2 or 3), and moderately severe/severe disability (4 or 5).[16] Prestroke depression status was based on self-report. Participants were asked whether they had ever been told they had depression by a doctor, and whether they were currently taking or had ever taken medications for depression. The 3 mutually exclusive categories included no history of depression, history of depression, and on medication for depression at stroke onset. The number of medical conditions was calculated as the total count of the following medical diagnoses ascertained from medical records: coronary artery disease, Alzheimer's disease or dementia, atrial fibrillation, cancer, chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, hypertension, high cholesterol, end-stage renal disease, epilepsy, and Parkinson's disease. Obesity was classified based on body mass index, which was calculated using measured height and weight ascertained from medical records (normal: <25; overweight: ≥25 and <30; obese: ≥30).

Statistical Analysis

We compared sample characteristics between men and women using Pearson chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. We examined missing data by comparing sample characteristics between included and excluded patients by baseline and outcome interview participation, respectively; and further compared sample characteristics by availability of the outcome measure in the study sample. We imputed missing values of cognitive outcomes and other covariates primarily attributable to having proxy interviews,[17] and then generated inverse probability weights to account for differential attrition due to nonparticipation.[18] Variables used in the imputation model included sociodemographic, stroke and prestroke characteristics obtained from the baseline interview and medical records, and poststroke outcomes obtained from the outcome interview, including neurological status assessed by the NIHSS, and disability assessed by a combined measure of activities of daily living and instrumental activities of daily living.

We estimated sex-specific prevalence of dementia at 90 days poststroke using weighted cross-tabulations for the dichotomized outcome measure. To examine the sex difference in the prevalence of poststroke dementia, we fit weighted logistic regression models. To examine the influence of each covariate on the sex association, we first fit an unadjusted model, and then fit a series of models by adding each covariate to the unadjusted model. Then, we fit a full model with adjustment for sociodemographic (age, race/ethnicity, education, marital status, and health insurance status), stroke (type and severity), and prestroke (prestroke cognitive function, prestroke depression status, prestroke disability, number of medical conditions, current smoking, and obesity) characteristics. In parallel with the logistic regression models, we fit a set of tobit regression models to examine the sex difference in cognitive scores, with the dependent variable being the continuous outcome measure. We examined collinearity between covariates by computing variance inflation factors.

We conducted 3 sensitivity analyses in relation to missing data. In the first, we repeated the analyses among participants with complete data, and compared them with the main analysis. In the second, we repeated the analyses among participants with normal cognitive function before stroke. In the third, we modeled the probability of missing cognitive outcome data as dependent on the cognitive score itself, because participants without cognitive assessments as a result of proxy interviews may have been more likely to have cognitive deficits.

Statistical analyses were completed with Stata version 14.2 (StataCorp LP) and SAS version 9.4 (SAS Institute Inc). SAS MI and MIANALYZE procedures were used for multiple imputation, and the MNAR statement in the MI procedure was used for the third sensitivity analysis.[17] The QLIM procedure was used for tobit regression.

RESULTS

There was no sex difference in baseline interview participation among 2278 patients who survived 90 days after first-ever ischemic stroke or intracerebral hemorrhage (Table S1). However, women were more likely to participate in the outcome interview than men (Table S2), and more likely to have missing data on the cognitive outcome measure (Table S3). Study participants with missing outcome data had significantly greater initial stroke severity, compared with those with complete outcome data. They were also significantly older, and more likely to be widowed and less educated and have intracerebral hemorrhage and prestroke functional deficits (Table S3). There was no sex difference in missing prestroke cognitive function data (P=0.917).

In the study sample, approximately three fifths were Mexican American, one third were non-Hispanic white, one third had educational attainment below high school, and nearly one fourth were widowed (Table 1). Men and women were approximately equally distributed; however, women were significantly more likely to be older, widowed, less educated, cognitively and functionally impaired before stroke, and to have greater stroke severity.

The prevalence of poststroke dementia was 27.6% in men (95% CI, 23.5%–31.6%) and 35.6% in women (95% CI, 31.5%–39.7%), after accounting for attrition and missing outcome data. In the unadjusted model, the odds of poststroke dementia were significantly greater in women, compared with men (odds ratio [OR], 1.45; 95% CI, 1.24–1.69). The association was attenuated toward the null after adjustment for marital status and age, respectively (Figure 2, Table S4), and remained nonsignificant after full adjustment for sociodemographic, stroke, and prestroke characteristics (OR, 0.82; 95% CI, 0.61–1.09) (Table 2). Concordantly, results from the unadjusted tobit regression model showed that women had lower 3MSE scores (estimate=–2.96; 95% CI, –3.99 to –1.93) (Table S4), but the difference diminished after covariate adjustment (estimate=0.76; 95% CI, –0.60 to 2.12) (Table 2). Variance inflation factors for testing collinearity (values <2) suggested that correlations among covariates did not have substantial impacts on the results.

Results of the first sensitivity analysis showed that complete case analysis yielded lower prevalence of dementia (men: 19.7% [95% CI, 16.3%–23.4%]; women:

Table 1. Sample Characteristics by Sex, Brain Attack Surveillance in Corpus Christi Project, United States, 2009–2016

	Total (N=1227)	Men (n=626)	Women (n=601)	*P* Value
Sociodemographic characteristics				
Age, y	67.6±12.3	65.7±11.3	69.5±13.0	<0.001
Race/ethnicity				0.908
Non-Hispanic white	418 (34.1)	215 (34.4)	203 (33.8)	
Mexican American	725 (59.1)	370 (59.1)	355 (59.1)	
Other	84 (6.9)	41 (6.6)	43 (7.2)	
Education*				0.002
Below high school	400 (32.8)	181 (29.1)	219 (36.6)	
High school	337 (27.6)	179 (28.8)	158 (26.4)	
Vocational/some college	304 (24.9)	150 (24.1)	154 (25.7)	
College or more	180 (14.7)	112 (18.0)	68 (11.4)	
Marital status*				<0.001
Married/partnered	594 (48.5)	377 (60.3)	217 (36.1)	
Single	103 (8.4)	55 (8.8)	48 (8.0)	
Widowed	282 (23.0)	64 (10.2)	218 (36.3)	
Separated/divorced	247 (20.2)	129 (20.6)	118 (19.6)	
Health insurance status*				0.096
Insured	1035 (86.2)	514 (84.5)	521 (87.9)	
Uninsured	166 (13.8)	94 (15.5)	72 (12.1)	
Stroke characteristics				
Stroke type				0.057
Ischemic stroke	1076 (87.7)	538 (85.9)	538 (89.5)	
Intracerebral hemorrhage	151 (12.3)	88 (14.1)	63 (10.5)	
Stroke severity (NIHSS)*	5.6±6.4	5.2±6.3	6.0±6.6	0.031
Prestroke characteristics				
Prestroke cognitive function (IQCODE)*				0.001
Normal	565 (46.1)	320 (51.1)	245 (40.8)	
Cognitive impairment no dementia	338 (27.6)	159 (25.4)	179 (29.8)	
Dementia	166 (13.5)	67 (10.7)	99 (16.5)	
Missing	158 (12.9)	80 (12.8)	78 (13.0)	
Prestroke depression status*				<0.001
No history of depression	640 (52.2)	383 (61.2)	257 (42.8)	
History of depression	153 (12.5)	67 (10.7)	86 (14.3)	
On medication for depression at stroke onset	166 (13.5)	55 (8.8)	111 (18.5)	
Missing	268 (21.8)	121 (19.3)	147 (24.5)	
Prestroke disability (mRS)*				<0.001
No symptoms/disability	590 (49.2)	337 (55.0)	253 (43.2)	
Slight/moderate disability	508 (42.4)	245 (40.0)	263 (44.9)	
Moderately severe/severe disability	101 (8.4)	31 (5.1)	70 (12.0)	
No. of medical conditions	2.5±1.5	2.5±1.5	2.5±1.5	0.536
Current smoking*				<0.001
No	947 (77.3)	448 (71.7)	499 (83.2)	
Yes	278 (22.7)	177 (28.3)	101 (16.8)	

(*Continued*)

Table 1. Continued

	Total (N=1227)	Men (n=626)	Women (n=601)	*P* Value
Obesity (body mass index)*				0.002
Normal	307 (25.0)	139 (22.2)	168 (28.0)	
Overweight	437 (35.6)	252 (40.3)	185 (30.8)	
Obese	482 (39.3)	235 (37.5)	247 (41.2)	

Values are expressed as mean±SD or number (percentage).
IQCODE indicates Informant Questionnaire on Cognitive Decline in the Elderly; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.
*Variables with missing data. The numbers of missing values are 6 for education, 1 for marital status, 26 for health insurance status, 158 for prestroke cognitive function, 268 for prestroke depression status, 28 for prestroke disability, 4 for stroke severity, 2 for current smoking, and 1 for obesity.

24.7% [95% CI, 20.9%–28.9%]), a weaker unadjusted association between sex and poststroke dementia (OR, 1.34; 95% CI, 0.99–1.81), and a similar adjusted association (OR, 0.75; 95% CI, 0.45–1.27). In the second sensitivity analysis, the prevalence of poststroke dementia among participants with normal cognitive function before stroke was lower than that in the full sample (men: 22.4% [95% CI, 17.8%–27.0%]; women: 27.4% [95% CI, 21.6%–33.3%]), after accounting for attrition and missing outcome data. The unadjusted and adjusted associations between sex and poststroke cognitive outcomes and the most influential factors were consistent with the results of the main analysis (Table S5). The third sensitivity analysis assuming a series of hypothesized relationships between missing values of the cognitive outcomes and the probability of missingness yielded generally consistent results (Table S6).

DISCUSSION

This study examined sex differences in cognitive outcomes at 90 days after stroke among first-ever stroke patients using data from a population-based study. We found that women had significantly lower levels of cognition function and a higher unadjusted prevalence of dementia than men; however, the differences were fully attenuated after adjustment for sociodemographic, stroke, and prestroke characteristics. The major contributing

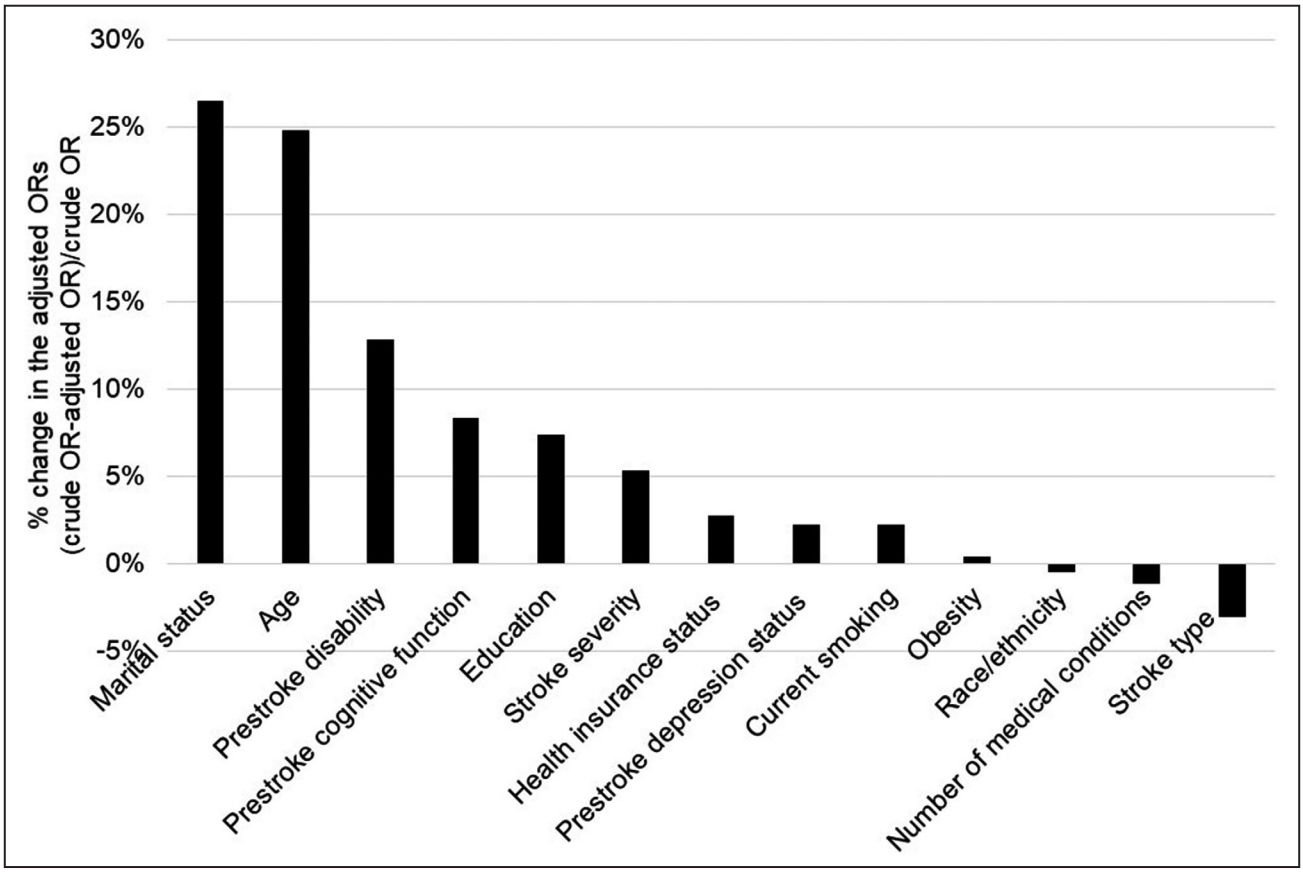

Figure 2. Influence of individual covariates on the association between sex and poststroke dementia, Brain Attack Surveillance in Corpus Christi project, United States, 2009–2016.

factors to the worse poststroke cognitive outcomes in women compared with men were a higher prevalence of being widowed, older age at stroke onset, having worse prestroke functional and cognitive status, and lower educational attainment. The finding that the sex association was influenced by missing outcome data as a result of having a proxy interview, which closely relates to cognitive deficits that were more prevalent in women, highlights the importance of accounting for selection bias in studies of sex disparities in stroke outcomes. Because women have poorer poststroke outcomes than men, the common practice of restricting study participants to only those who are capable of completing cognitive assessment differentially excludes women and may therefore lead to biased estimates.

This study contributes to existing literature by providing contemporary, population-based data on sex differences in poststroke cognitive outcomes. There has been relatively less research in this area compared with other stroke outcomes, such as function and quality of life, and none of the studies published since 2007 were population-based.[3] Existing findings have been mixed, partially attributable to variations in study design.[3] Our results are consistent with the Cognitive Function After Stroke Nigeria Study that the greater odds of poststroke dementia at 90 days in women was reduced after covariate adjustment.[3,19] Although age and stroke characteristics were typically adjusted for in previous studies, some important confounders, such as education and prestroke cognitive and functional status, were often not accounted for,[3] which might have resulted in residual confounding as demonstrated in the current study. Consistent with established risk factors for dementia, women stroke survivors in the study sample presented a high-risk profile compared with men, including older age, lower educational attainment, greater stroke severity and worse prestroke cognitive function. Notably, the proportion of widowed participants among women was over one third, which was more than triple that in men; and marital status showed the greatest influence on the association between sex and poststroke cognitive outcomes, especially among those with normal cognitive function before stroke.

Widowhood has been considered as an older women's issue because of women's higher life expectancy in late life and lower likelihood of remarriage after becoming widowed compared with men.[20] Loss of a spouse ranks among the most stressful life events in one's life,[21] and can cause acute stress from bereavement and chronic stress as a result of reduction in emotional, financial and social support.[22] Widowhood-related stress adversely affects mental, physical and cognitive health, as well as health behaviors, through psychosocial and physiological pathways.[22] Consistent with existing findings that widowhood is associated with increased risk for dementia,[23,24] widowed participants in our study sample had a significantly higher prevalence of dementia history and risk factors for dementia before stroke, compared with those in other marital status categories. Stroke may cause additional brain pathology and functional impairments that require substantial informal care and impose difficulties for widowed patients.[25] Because widowhood is highly prevalent in women stroke survivors, who have greater cognitive impairment and higher prevalence of dementia, women may have greater unmet needs for social support including emotional, instrumental and informational support, which is critical for intensive rehabilitation care and stroke recovery. Given the high burden of dementia in women and their special social circumstances, there is a need for better understanding of the role of widowhood in postacute care and its outcomes, which could lead to tailored interventions to meet their unique care needs and improve cognitive outcomes.

Depression affects men and women differently,[26] and is linked to dementia through biological mechanisms including vascular disease.[27] In the study sample, the prevalence of self-reported history of depression and medication use for depression before stroke tended to be higher in women than in men. However, we did not find a significant association between prestroke depression and poststroke cognitive outcomes, nor an influence of prestroke depression status on the association between sex and poststroke cognitive outcomes (Table S4). This may be because all participants in the study were stroke patients, which is a form of conditioning on stroke, a mediator or confounder of the association between depression and dementia.[27]

The study has several limitations. First, cognitive function at 90 days poststroke was assessed using the 3MSE, which is a dementia screening tool rather than a comprehensive diagnostic examination according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) or the National Institute on Aging-Alzheimer's Association guidelines.[28,29] Despite its good sensitivity and specificity for identification of dementia in the stroke population,[10] the cognitive scores are subject to measurement errors influenced by noncognitive factors such as cultural differences,[30] and the use of a single cutoff score may result in misclassification. Our findings on the prevalence of poststroke dementia are similar to previous population-based studies that used the Mini-Mental State Examination (MMSE) to examine the prevalence of dementia within 1 year after stroke including those with prestroke dementia, but higher than estimates using *DSM*-based diagnostic criteria.[5] Additionally, the cutoff score obtained from existing literature has not been validated in this biethnic population, which may have different optimal cutoff points given their specific sociodemographic

Table 2. Results From Fully Adjusted Regression Models of the Association Between Sex and Poststroke Cognitive Outcomes, Brain Attack Surveillance in Corpus Christi Project, United States, 2009–2016

	Dichotomized Outcome	Continuous Outcome
	Odds Ratio (95% CI)	Estimate (95% CI)
Sex		
Men	Reference	Reference
Women	0.82 (0.61–1.09)	0.76 (–0.60 to 2.12)
Age	1.08 (1.07–1.09)	–0.44 (–0.48 to –0.40)
Race/ethnicity		
Non-Hispanic white	Reference	Reference
Mexican American	1.85 (1.49–2.30)	–4.07 (–5.33 to –2.80)
Other	2.30 (1.70–3.10)	–4.49 (–5.97 to –3.01)
Education		
Below high school	Reference	Reference
High school	0.35 (0.30–0.41)	7.91 (7.05–8.76)
Vocational/some college	0.22 (0.16–0.31)	10.34 (9.09–11.59)
College or more	0.18 (0.14–0.23)	12.52 (10.93–14.12)
Marital status		
Married/partnered	Reference	Reference
Single	1.47 (1.19–1.81)	–2.84 (–4.16 to –1.51)
Widowed	1.36 (1.07–1.74)	–1.22 (–2.38 to –0.07)
Separated/divorced	0.86 (0.67–1.12)	–0.37 (–1.43 to 0.68)
Health insurance status		
Insured	Reference	Reference
Uninsured	0.81 (0.62–1.06)	–0.21 (–1.13 to 0.72)
Stroke type		
Ischemic stroke	Reference	Reference
Intracerebral hemorrhage	2.00 (1.56–2.58)	–3.78 (–4.73 to –2.83)
Stroke severity (NIHSS)		
Linear term	1.16 (1.12–1.19)	–3.70 (–4.64 to –2.76)
Quadratic term	1.00 (1.00–1.00)	Not applicable
Prestroke cognitive function (IQCODE)		
Normal	Reference	Reference
Cognitive impairment no dementia	1.19 (0.92–1.55)	–0.62 (–1.66 to 0.43)
Dementia	2.86 (1.83–4.46)	–5.95 (–9.05 to –2.86)
Prestroke depression status		
No history of depression	Reference	Reference
History of depression	1.08 (0.75–1.54)	0.01 (–2.33 to 2.35)
On medication for depression at stroke onset	1.02 (0.63–1.66)	–0.39 (–3.21 to 2.42)
Prestroke disability (mRS)		
No symptoms/ disability	Reference	Reference
Slight/moderate disability	1.24 (1.01–1.51)	–0.97 (–1.84 to –0.11)
Moderately severe/severe disability	1.85 (1.10–3.12)	–3.87 (–6.68 to –1.07)
No. of medical conditions	1.02 (0.95–1.10)	–0.16 (–0.56 to 0.24)
Current smoking		
No	Reference	Reference
Yes	1.46 (1.19–1.81)	–1.14 (–1.86 to –0.43)
Obesity		
Normal	Reference	Reference
Overweight	0.96 (0.71–1.29)	–0.21 (–1.87 to 1.44)
Obese	0.80 (0.60–1.05)	0.91 (–0.85 to 2.67)

The sample size for all models was 1227.

IQCODE indicates Informant Questionnaire on Cognitive Decline in the Elderly; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

and cultural characteristics. Furthermore, the broad measure of cognition used in the present study does not cover the full spectrum of cognitive function and may result in floor and ceiling effects, which was dealt with using tobit regression in the analysis. Evidence suggests differential item functioning by sex in certain items of the MMSE,[31] based upon which the 3MSE was developed. However, little is known about differential item functioning by sex of the 3MSE in stroke patients. Because the 3MSE measure was not available for baseline assessment, we cannot eliminate potential item-response bias by using a difference-in-differences approach. Nevertheless, we used the total score of the 3MSE to assess overall cognitive function, which may be less sensitive to item bias than domain-specific cognitive function. Future research should investigate the metric equivalence of stroke outcome measures across sociodemographic subgroups to enhance accuracy of epidemiological inferences in health disparities research. Second, we examined all-cause dementia and cognitive impairment, which may be caused by stroke or prestroke neurological disorders, such as Alzheimer's disease, epilepsy, and Parkinson's disease. Sex differences in these preexisting conditions may contribute to the overall sex differences in poststroke cognitive outcomes. However, it may have limited influence on the findings because of their low prevalence in the study sample and nonsignificant sex differences after age adjustment. Consistent results with and without participants with prestroke cognitive impairment or dementia support the robustness of the findings. Third, prestroke depression status and disability were self-reported and therefore subject to recall

bias and measurement errors. Self-reported medication use for depression may have been influenced by help-seeking behaviors and social desirability. Fourth, because the study population was mainly composed of nonimmigrant Mexican Americans and non-Hispanic whites, the results may not be generalized to other racial/ethnic subgroups and recent Mexican immigrants.

CONCLUSIONS

The unadjusted prevalence of dementia at 90 days after first-ever stroke was high, with women having significantly worse cognitive outcomes compared with men. The sex differences were attributable to sociodemographic and prestroke characteristics, especially widowhood status. Potential mechanisms linking widowhood to cognitive impairment and dementia in the acute poststroke stage warrant further investigation. Future research should develop interventions to promote cognitive reserve and resilience of women at high risk for stroke and to address their unique care needs poststroke.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S6

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Supplemental Material

Table S1. Sample characteristics by baseline interview participation among 2278 eligible participants, Brain Attack Surveillance in Corpus Christi project, United States, 2009-2016

Sample characteristics	Total (n=2278)	Baseline Interview Participation		*P* Value
		Yes (n= 1708)	No (n=570)	
Sociodemographic characteristics				
Sex				0.715
Men	1198 (52.6)	902 (52.8)	296 (51.9)	
Women	1080 (47.4)	806 (47.2)	274 (48.1)	
Age, y	67.7 ± 12.5	67.3 ± 12.3	69.0 ± 13.0	0.008
Race/ethnicity*				<0.001
Non-Hispanic white	839 (36.9)	587 (34.4)	252 (44.4)	
Mexican American	1274 (56.0)	995 (58.3)	279 (49.1)	
Other	163 (7.2)	126 (7.4)	37 (6.5)	
Stroke characteristics				
Stroke type				0.270
Ischemic stroke	2013 (88.4)	1502 (87.9)	511 (89.7)	
Intracerebral hemorrhage	265 (11.6)	206 (12.1)	59 (10.4)	
Stroke severity (NIHSS)*	5.6 ± 6.5	5.6 ± 6.5	5.4 ± 6.7	0.044
Prestroke characteristics				
Number of medical conditions	2.5 ± 1.5	2.5 ± 1.5	2.4 ± 1.6	0.424
Current smoking*				0.221
No	1733 (76.3)	1312 (76.9)	421 (74.4)	
Yes	539 (23.7)	394 (23.1)	145 (25.6)	
Obesity*				0.008
Normal	603 (26.5)	426 (25.0)	177 (31.3)	
Overweight	819 (36.1)	621 (36.4)	198 (35.0)	
Obese	850 (37.4)	660 (38.7)	190 (33.6)	

Values are expressed as mean ± standard deviation or number (percentage).
NIHSS, National Institutes of Health Stroke Scale.
*Variables with missing values. The number of missing values was 2 for race/ethnicity, 5 for stroke severity, 6 for current smoking, and 6 for obesity.

Table S2. Sample characteristics by outcome interview participation among 1708 participants who completed the baseline interview, Brain Attack Surveillance in Corpus Christi project, United States, 2009-2016

		Outcome Interview participation		
Sample characteristics	Total (n=1708)	Yes (n= 1227)	No (n=481)	*P* value
Sociodemographic characteristics				
Sex				0.018
Men	902 (52.8)	626 (51.0)	276 (57.4)	
Women	806 (47.2)	601 (49.0)	205 (42.6)	
Age, y	67.3 ± 12.3	67.6 ± 12.3	66.5 ± 12.2	0.110
Race/ethnicity				0.317
Non-Hispanic white	587 (34.4)	418 (34.1)	169 (35.1)	
Mexican American	995 (58.3)	725 (59.1)	270 (56.1)	
Other	126 (7.4)	84 (6.9)	42 (8.7)	
Education*				0.287
Below high school	576 (33.9)	400 (32.8)	176 (36.9)	
High school	466 (27.4)	337 (27.6)	129 (27.0)	
Vocational/some college	419 (24.7)	304 (24.9)	115 (24.1)	
College or more	237 (14.0)	180 (14.7)	57 (12.0)	
Marital status*				0.381
Married/partnered	821 (48.2)	594 (48.5)	227 (47.4)	
Single	151 (8.9)	103 (8.4)	48 (10.0)	
Widowed	379 (22.2)	282 (23.0)	97 (20.3)	
Separated/divorced	354 (20.8)	247 (20.2)	107 (22.3)	
Health insurance status*				0.008
Insured	1419 (84.7)	1035 (86.2)	384 (81.0)	
Uninsured	256 (15.3)	166 (13.8)	90 (19.0)	
Stroke characteristics				
Stroke type				0.619
Ischemic stroke	1502 (87.9)	1076 (87.7)	426 (88.6)	
Intracerebral hemorrhage	206 (12.1)	151 (12.3)	55 (11.4)	
Stroke severity (NIHSS)*	5.6 ± 6.5	5.6 ± 6.4	5.7 ± 6.5	0.951
Prestroke characteristics				
Prestorke cognitive function (IQCODE)*				<0.001
Normal	806 (47.2)	565 (46.1)	241 (50.1)	
Cognitive impairment no dementia	448 (26.2)	338 (27.6)	110 (22.9)	
Dementia	206 (12.1)	166 (13.5)	40 (8.3)	
Missing	248 (14.5)	158 (12.9)	90 (18.7)	
Prestroke depression status*				0.123
No history of depression	903 (52.9)	640 (52.2)	263 (54.7)	
History of depression	209 (12.2)	153 (12.5)	56 (11.6)	
On medication for depression at stroke onset	212 (12.4)	166 (13.5)	46 (9.6)	
Missing	384 (22.5)	268 (21.8)	116 (24.1)	
Prestroke disability (mRS)*				0.750

No symptoms/disability	817 (48.8)	590 (49.2)	227 (47.9)	
Slight/moderate disability	718 (42.9)	508 (42.4)	210 (44.3)	
Moderately severe/severe disability	138 (8.3)	101 (8.4)	37 (7.8)	
Number of medical conditions	2.5 ± 1.5	2.5 ± 1.5	2.4 ± 1.6	0.134
Current smoking*				0.530
No	1312 (76.9)	947 (77.3)	365 (75.9)	
Yes	394 (23.1)	278 (22.7)	116 (24.1)	
Obesity*				0.567
Normal	426 (25.0)	307 (25.0)	119 (24.7)	
Overweight	621 (36.4)	437 (35.6)	184 (38.3)	
Obese	660 (38.7)	482 (39.3)	178 (37.0)	

Values are expressed as mean ± standard deviation or number (percentage).
IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
*Variables with missing data. The numbers of missing values are 10 for education, 3 for marital status, 33 for health insurance status, 5 for stroke severity, 248 for prestroke cognitive function, 384 for prestroke depression status, 35 for prestroke disability, 2 for current smoking and 1 for obesity.

Table S3. Comparison by data availability of the cognitive outcome measure among 1227 participants included in the final sample, Brain Attack Surveillance in Corpus Christi project, United States, 2009-2016

	Cognitive outcome measure			
Sample characteristics	Total (n=1227)	Complete (n= 978)	Missing (n=249)	*P* value
Sociodemographic characteristics				
Sex				0.046
Men	626 (51.0)	513 (52.5)	113 (45.4)	
Women	601 (49.0)	465 (47.6)	136 (54.6)	
Age, y	67.6 ± 12.3	65.6 ± 11.5	75.4 ± 12.2	<0.001
Race/ethnicity				0.071
Non-Hispanic white	418 (34.1)	347 (35.5)	71 (28.5)	
Mexican American	725 (59.1)	562 (57.5)	163 (65.5)	
Other	84 (6.9)	69 (7.1)	15 (6.0)	
Education*				<0.001
Below high school	400 (32.8)	288 (29.5)	112 (45.7)	
High school	337 (27.6)	280 (28.7)	57 (23.3)	
Vocational/some college	304 (24.9)	262 (26.8)	42 (17.1)	
College or more	180 (14.7)	146 (15.0)	34 (13.9)	
Marital status*				<0.001
Married/partnered	594 (48.5)	485 (49.6)	109 (43.8)	
Single	103 (8.4)	92 (9.4)	11 (4.4)	
Widowed	282 (23.0)	194 (19.9)	88 (35.3)	
Separated/divorced	247 (20.2)	206 (21.1)	41 (16.5)	
Health insurance status*				0.001
Insured	1035 (86.2)	809 (84.5)	226 (92.6)	
Uninsured	166 (13.8)	148 (15.5)	18 (7.4)	
Stroke characteristics				
Stroke type*				0.008
Ischemic stroke	1076 (87.7)	870 (89.0)	206 (82.7)	
Intracerebral hemorrhage	151 (12.3)	108 (11.0)	43 (17.3)	
Stroke severity (NIHSS)*	5.6 ± 6.4	4.3 ± 5.0	10.5 ± 8.8	<0.001
Prestroke characteristics				
Prestroke cognitive function (IQCODE)*				<0.001
Normal	565 (46.1)	469 (48.0)	96 (38.6)	
Cognitive impairment no dementia	338 (27.6)	263 (26.9)	75 (30.1)	
Dementia	166 (13.5)	94 (9.6)	72 (28.9)	
Missing	158 (12.9)	152 (15.5)	6 (2.4)	
Prestroke depression status*				<0.001
No history of depression	640 (52.2)	604 (61.8)	36 (14.5)	
History of depression	153 (12.5)	144 (14.7)	9 (3.6)	
On medication for depression at stroke onset	166 (13.5)	157 (16.1)	9 (3.6)	
Missing	268 (21.8)	73 (7.5)	195 (78.3)	
Prestroke disability (mRS)*				<0.001

No symptoms/disability	590 (49.2)	515 (53.8)	75 (31.1)	
Slight/moderate disability	508 (42.4)	395 (41.2)	113 (46.9)	
Moderately severe/severe disability	101 (8.4)	48 (5.0)	53 (22.0)	
Number of medical conditions	2.5 ± 1.5	2.4 ± 1.5	2.7 ± 1.6	0.016
Current smoking*				0.014
No	947 (77.3)	740 (75.8)	207 (83.1)	
Yes	278 (22.7)	236 (24.2)	42 (16.9)	
Obesity (body mass index)*				<0.001
Normal	307 (25.0)	210 (21.5)	97 (39.0)	
Overweight	437 (35.6)	349 (35.7)	88 (35.3)	
Obese	482 (39.3)	418 (42.8)	64 (25.7)	

Values are expressed as mean ± standard deviation or number (percentage).
IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
*Variables with missing data. The numbers of missing values are 6 for education, 1 for marital status, 26 for health insurance status, 4 for stroke severity, 158 for prestroke cognitive function, 268 for prestroke depression status, 28 for prestroke disability, 2 for current smoking and 1 for obesity.

Table S4. Influence of individual covariates on the association between sex and poststroke cognitive outcomes, Brain Attack Surveillance in Corpus Christi project, United States, 2009-2016

	Dichotomized outcome		Continuous outcome	
	Female sex OR (95% CI)	Covariate OR (95% CI)	Female sex Estimate (95% CI)	Covariate Estimate (95% CI)
Unadjusted	1.45 (1.24, 1.69)	-	-2.96 (-3.99, -1.93)	-
Adjusted for covariate individually				
Age	1.09 (0.92, 1.30)	1.08 (1.07, 1.09)	-0.83 (-1.83, 0.18)	-0.54 (-0.60, -0.48)
Race/ethnicity	1.46 (1.25, 1.70)		-2.92 (-3.94, -1.89)	
Non-Hispanic white		Reference		Reference
Mexican American		2.12 (1.80, 2.50)		-7.01 (-8.23, -5.79)
Other		2.24 (1.81, 2.78)		-6.69 (-8.30, -5.09)
Education	1.34 (1.12, 1.61)		-1.90 (-2.97, -0.84)	
Below high school		Reference		Reference
High school		0.25 (0.23, 0.28)		12.50 (11.37, 13.64)
Vocational/some college		0.16 (0.13, 0.20)		15.97 (14.41, 17.52)
College or more		0.19 (0.14, 0.25)		15.62 (13.7, 17.55)
Marital status	1.07 (0.90, 1.26)		-0.62 (-1.58, 0.34)	
Married/partnered		Reference		Reference
Single		0.87 (0.76, 1.00)		0.64 (-0.51, 1.79)
Widowed		2.95 (2.55, 3.41)		-8.81 (-10.22, -7.39)
Separated/divorced		0.73 (0.61, 0.87)		1.36 (0.40, 2.32)
Health insurance status	1.41 (1.20, 1.65)		-2.73 (-3.76, -1.69)	
Insured		Reference		Reference
Uninsured		0.30 (0.24, 0.38)		6.16 (5.25, 7.06)
Stroke type				
Ischemic stroke	1.49 (1.28, 1.74)	Reference	-3.13 (-4.17, -2.10)	Reference
Intracerebral hemorrhage		1.96 (1.66, 2.32)		-4.97 (-5.92, -4.02)
Stroke severity (NIHSS)	1.37 (1.16, 1.63)		-2.41 (-3.44, -1.38)	
Linear term		1.16 (1.13, 1.19)		-5.00 (-5.94, -4.07)
Quadratic term		1.00 (1.00, 1.00)		-
Prestroke cognitive function (IQCODE)	1.33 (1.12, 1.58)		-2.17 (-3.25, -1.09)	
Normal		Reference		Reference
Cognitive impairment no dementia		1.43 (1.21, 1.69)		-2.38 (-3.65, -1.11)
Dementia		4.08 (3.20, 5.20)		-11.83 (-14.77, -8.90)
Prestroke disability (mRS)	1.26 (1.09, 1.47)		-1.71 (-2.60, -0.81)	
No symptoms/disability		Reference		Reference
Slight/moderate disability		2.13 (1.88, 2.40)		-5.54 (-6.40, -4.67)
Moderately severe/severe disability		5.47 (4.04, 7.40)		-14.93 (-17.37, -12.49)

Prestroke depression status	1.42 (1.17, 1.72)		-2.76 (-4.34, -1.18)	
No history of depression		Reference		Reference
History of depression		1.23 (0.91, 1.66)		-1.21 (-3.77, 1.35)
On medication for depression at stroke onset		1.07 (0.66, 1.73)		-0.88 (-5.17, 3.41)
Number of medical conditions	1.47 (1.25, 1.72)	1.19 (1.14, 1.25)	-3.00 (-4.03, -1.97)	-1.50 (-1.84, -1.16)
Current smoking	1.42 (1.21, 1.66)		-2.77 (-3.78, -1.75)	
No		Reference		Reference
Yes		0.82 (0.76, 0.88)		1.70 (1.14, 2.26)
Obesity	1.45 (1.24, 1.68)		-2.93 (-3.93, -1.92)	
Normal		Reference		Reference
Overweight		0.71 (0.58, 0.88)		2.16 (0.47, 3.86)
Obese		0.48 (0.40, 0.59)		5.22 (3.26, 7.19)

CI, confidence interval; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Table S5. Results of the association between sex and poststroke cognitive outcomes among participants with normal cognitive function before stroke, Brain Attack Surveillance in Corpus Christi project, United States, 2009-2016

	Dichotomized outcome Odds Ratio (95% CI)	Continuous outcome Estimates (95% CI)
Unadjusted	1.31 (1.10, 1.55)	-2.22 (-3.40, -1.04)
Fully adjusted	0.87 (0.60, 1.27)	0.18 (-1.42, 1.79)
Adjusted for covariate individually		
Age	1.14 (0.96, 1.36)	-1.38 (-2.52, -0.24)
Race/ethnicity	1.28 (1.07, 1.53)	-1.96 (-3.23, -0.68)
Education	1.22 (1.01, 1.49)	-1.48 (-2.72, -0.23)
Marital status	1.02 (0.81, 1.29)	-0.59 (-2.05, 0.88)
Health insurance status	1.29 (1.09, 1.53)	-2.13 (-3.29, -0.97)
Stroke type	1.36 (1.16, 1.59)	-2.44 (-3.61, -1.27)
Stroke severity (NIHSS)	1.22 (1.00, 1.47)	-1.58 (-2.84, -0.32)
Prestroke disability (mRS)	1.23 (1.01, 1.49)	-1.76 (-3.02, -0.50)
Prestroke depression status	1.28 (1.08, 1.53)	-2.15 (-3.36, -0.95)
Number of medical conditions	1.34 (1.11, 1.62)	-2.41 (-3.67, -1.15)
Current smoking	1.29 (1.09, 1.54)	-2.13 (-3.31, -0.95)
Obesity	1.35 (1.15, 1.59)	-2.49 (-3.55, -1.43)

CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table S6. Results of the association between sex and poststroke cognitive outcomes from sensitivity analyses for missing not at random, Brain Attack Surveillance in Corpus Christi project, United States, 2009-2016

Scale parameter		Dichotomized outcome Odds Ratio (95% Confidence Interval)		Continuous outcome Estimate (95% Confidence Interval)	
Men	Women	Unadjusted model	Fully adjusted model	Unadjusted model	Fully adjusted model
1.00	1.00	1.45 (1.24, 1.69)	0.82 (0.61, 1.09)	-2.96 (-3.99, -1.93)	0.76 (-0.60, 2.12)
0.90	0.90	1.41 (1.10, 1.81)	0.78 (0.68, 0.89)	-3.04 (-4.04, -2.05)	1.16 (-0.06, 2.39)
0.85	0.85	1.41 (1.10, 1.81)	0.80 (0.67, 0.97)	-3.28 (-4.92, -1.65)	1.02 (-1.16, 3.19)
0.80	0.80	1.39 (1.10, 1.76)	0.79 (0.73, 0.85)	-3.07 (-4.30, -1.85)	1.21 (0.02, 2.40)
0.95	0.90	1.49 (1.16, 1.92)	0.86 (0.72, 1.02)	-3.66 (-4.44, -2.88)	0.52 (-0.81, 1.85)
0.90	0.85	1.50 (1.18, 1.92)	0.90 (0.81, 0.99)	-3.76 (-5.24, -2.29)	0.48 (-1.14, 2.09)
0.85	0.80	1.46 (1.15, 1.85)	0.86 (0.78, 0.94)	-3.93 (-4.93, -2.92)	0.32 (-0.88, 1.52)