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Factors Influencing Sex Differences in Post-stroke Functional Outcome

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Abstract

Background and Purpose—Our objective was to identify factors that contribute to and/or modify the sex difference in post-stroke functional outcome.

Methods—Ischemic strokes (n=439) were identified from the BASIC Project (2008–2011). Data were ascertained from interviews (baseline and 90 days post-stroke) and medical records. Functional outcome was measured as an average of 22 ADL/IADL items (range 1–4, higher scores worse function). Tobit regression was used to estimate sex differences and to identify confounding and modifying factors.

Results—Fifty-one percent were women. Median age was 71 (IQR:59–80) in women and 64 (IQR:56–77) in men. Median ADL/IADL score at 90 days was 2.7 (IQR:1.8–3.6) in women and 2.0 (IQR:1·3–3·1) in men (P<0.01); this difference remained after age-adjustment (P<0.001). Factors contributing to higher ADL/IADL scores in women included pre-stroke function, marital status, pre-stroke cognition, nursing home residence, stroke severity, history of stroke/TIA, and BMI; pre-stroke function was the largest contributor. Stroke severity modified the sex difference in outcome such that differences were apparent for mild to moderate but not severe strokes. After adjustment, women still had significantly worse functional outcome than men.

Conclusions—These findings yield insight into possible strategies and subgroups to target to reduce the sex disparity in stroke outcome; demographics and pre-stroke and clinical factors explained only 41% of the sex difference in stroke outcome highlighting the need for future research to identify modifiable factors that contribute to sex differences.

Keywords

stroke; sex; outcomes

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Introduction

Causes of poorer functional outcomes following stroke in women compared with men are unknown.[1] Prior studies have simultaneously included all potential explanatory variables in multivariable models to measure "adjusted" sex differences in stroke outcome, precluding an understanding of which specific factors contribute to worse outcomes in women. This is crucially important as it is the identification of specific factors that could lead to interventions to reduce sex disparities in stroke outcomes. Further, studies have not considered whether certain factors modify sex differences in functional outcome which could identify subgroups that might be targeted to reduce sex disparities. Our objective was to identify specific factors that contribute to and/or modify sex differences in post-stroke 90-day functional outcome.

Methods

Data were from the BASIC Project (2008–2011), a population-based stroke surveillance study.[2] Stroke cases participated in baseline (~47% conducted during hospitalization) and outcome interviews (~90 days following stroke). Patients unable to answer orientation questions had a proxy interview. Data were collected from baseline interviews (demographics, pre-stroke modified Rankin scale (mRS), pre-stroke cognitive status (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)) and medical records (insurance, pre-stroke nursing home residence, BMI, risk factors, comorbidities, stroke severity, quality of care). First documented National Institutes of Health Stroke Scale (NIHSS) was abstracted or calculated using previously validated methods.[3] A pre-stroke comorbidity index was created by summing risk factors and comorbidities (range: 0–15). To measure quality of care, we created a binary defect-free score which indicated a patient received all stroke performance measures (n=6) he/she was eligible to receive. Functional outcome was assessed as the average of seven activities of daily living (ADL) and 15 instrumental activities of daily living (IADL); ADL/IADL score ranged from 1 (no difficulty) to 4 (can only do with help).

Statistical analysis

Tobit regression was used to assess the association between sex and ADL/IADL. We first generated a model that included sex and age. Each potential confounder was then added to this model and the estimated sex effects before and after inclusion of the variable were compared. If the sex coefficient changed by ≥5% the variable was considered a confounder. The final model included sex, age, race-ethnicity and confounders. Age and BMI were modeled linearly; initial NIHSS required a quadratic term. We investigated interactions between sex and all other variables and included them in the final model if significant ($P<0.10$). We conducted three sensitivity analyses: 1) we included a variable for proxy use in our final model; 2) we reran the final model considering ADL and IADL sub-scales as separate outcomes; 3) we considered the impact of loss to follow-up by modeling the probability of missing outcome as dependent on the outcome itself.

All patients or their surrogate provided written informed consent and the study was approved by the Institutional Review Boards at the University of Michigan and local hospitals.

Results

644 of 913 ischemic strokes patients (71%) agreed to an interview. There was no sex difference in age-adjusted 90-day mortality (*P*=0.50). After excluding deaths, 439 of 552 eligible patients (80%) completed the 90-day interview, with no sex difference in loss to follow-up (*P*=0.80). 399 (91%) had complete data. Women were more likely than men to have a proxy at baseline (*P*=0.001) and outcome (*P*=0.029). Table 1 includes sex differences in select baseline characteristics. Median ADL/IADL score at 90 days was 2.7 (IQR: 1.8–3.6) in women and 2.0 (IQR: 1.3–3.1) in men (Supplemental Table I, please see http://stroke.ahajournals.org). After age-adjustment women scored 0.40 points higher than men on the ADL/IADL score (95% CI: 0.19,0.61). Pre-stroke mRS, pre-stroke nursing home residence, history of stroke/TIA, stroke severity, marital status, BMI, and pre-stroke IQCODE contributed to poorer functional outcome in women (Figure 1). Demographics and confounders explained ~41% of the sex effect (Supplemental Table II, please see http://stroke.ahajournals.org). An interaction between sex and initial NIHSS was found (*P*=0.061; Supplemental Figure I, please see http://stroke.ahajournals.org); women scored 0.40 points higher on the ADL/IADL score than men (95% CI: 0.18,0.63) at the mean NIHSS (6). No other interactions were noted. Sensitivity analyses suggested minimal impact of proxy use and loss to follow-up (Supplemental Figure II, please see http://stroke.ahajournals.org) and that sex differences were more pronounced for IADLs than ADLs (data not shown).

Discussion

Women had significantly worse functional outcomes than men even after adjustment; but the most important factor attenuating the difference was pre-stroke function. Prevention efforts aimed at maintaining functional status in aging women could improve their stroke outcomes. Preexisting functional limitations may also impact effectiveness of post-stroke rehabilitation,[4] further substantiating the importance of maintaining physical well-being in elderly women.

Other factors that contributed to worse functional outcome in women included marital status, nursing home residence, pre-stroke IQCODE, history of stroke/TIA, BMI, and stroke severity, most of which are not amenable to intervention at stroke onset. Women were more likely to be widowed which was associated with poorer outcome; the negative effect of being widowed could be due to increased social isolation, a risk factor for poor post-stroke functional outcome.[5] The detrimental effects of social isolation could be amenable to intervention; however, interventions focused on increasing social support in stroke patients have largely been unsuccessful.[6, 7] Newer technologies, including social media, may provide a means of reaching socially isolated women with stroke but this requires additional research.[8]

Stroke severity modified the sex difference in functional outcome. The finding of no sex difference among those with severe strokes is intuitive as presumably severe stroke will result in poor outcome regardless of other factors. Causes of the sex difference in outcome in mild to moderately severe stroke population are unclear but given adjustment for demographics, pre-stroke and clinical factors explained only 41% of the sex difference in outcome, post-stroke factors, such as rehabilitation and depression, may be relevant and prove to be important intervention targets for reducing stroke disability in women.

There are limitations to this work. Differential reporting by sex may exist for some ADL/IADLs, although we used a composite measure which should minimize this effect. Pre-stroke factors were ascertained after stroke which could lead to measurement error. We did not have data on stroke subtype although we accounted for severity such that differences in severity by subtype were captured. Our results are model dependent. The study is focused on one predominantly Mexican American community in south Texas. Thus, results may not be generalizable.

These findings yield insight into possible strategies and subgroups to target to reduce the sex disparity in stroke outcome; because demographics and pre-stroke and clinical factors explained less than half of the sex disparity it highlights the need for future research to identify modifiable factors that contribute to sex differences in stroke outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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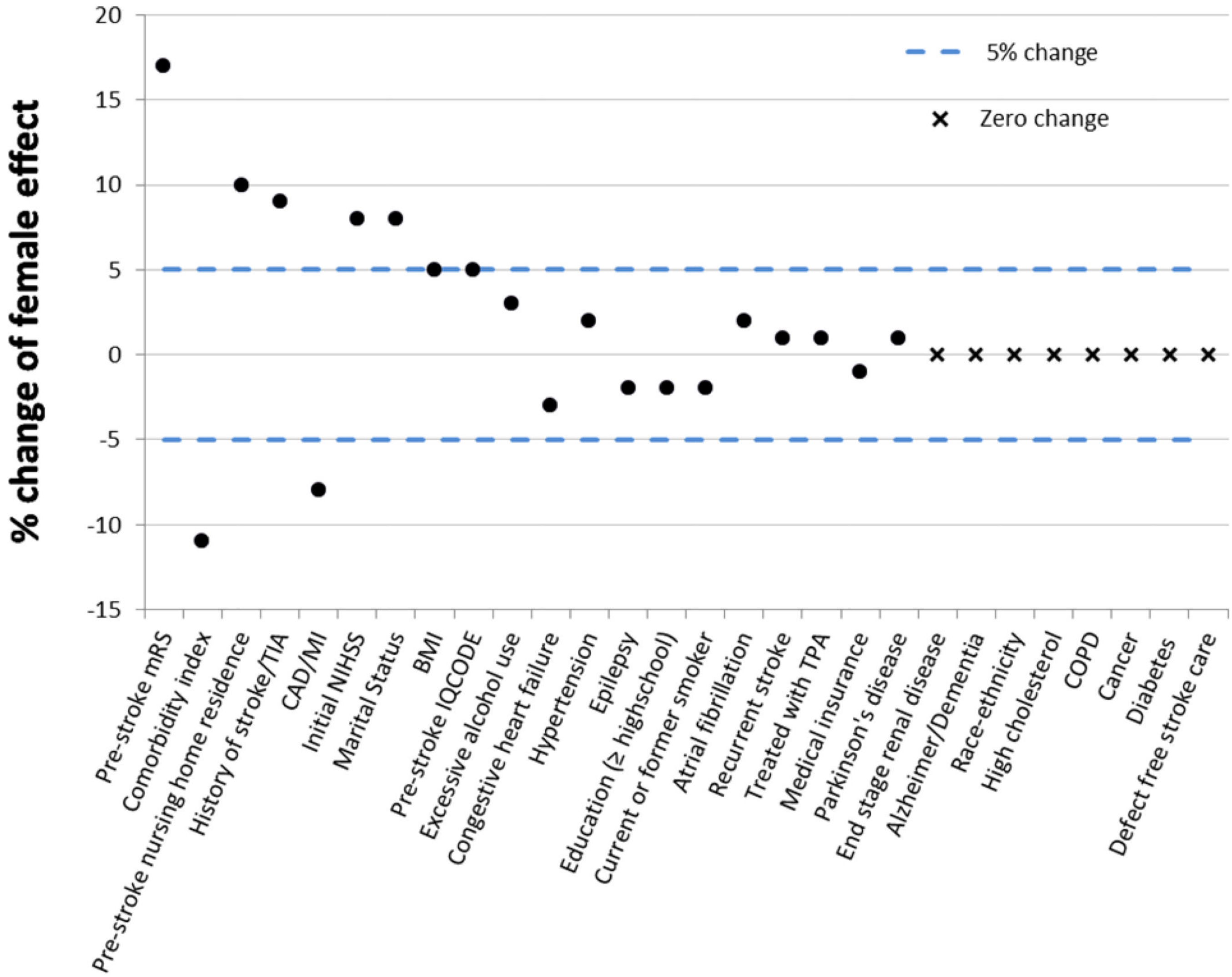

Figure 1.

Impact of Variables on Age-Adjusted Sex-Functional Outcome Association.
mRS=modified Rankin scale, IQCODE=Informant Questionnaire for Cognitive Decline in the Elderly, CAD=coronary artery disease, MI=myocardial infarction, COPD=chronic obstructive pulmonary disease, TIA=transient ischemic attack, BMI=body mass index, NIHSS=National Institute for Health Stroke Scale, tPA=tissue plasminogen activator.

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Table 1

Select Baseline Characteristics by Sex.

Variable	Male (N=268) N or Median	Male (N=268) % or (Q1,Q3)	Female (N=284) N or Median	Female (N=284) % or (Q1,Q3)	*P*
Age	64	(56,77)	71	(59,80)	0.001
Race-ethnicity					
White	81	30.7	99	35.2	0.430
Mexican American	162	61.4	157	55.9	
African American	13	4.9	19	6.8	
Other	8	3.0	6	2.1	
Marital status					
Married/living with someone	157	58.8	108	38.0	<.0001
Single	22	8.2	21	7.4	
Widowed	32	12.0	111	39.1	
Divorced/separated	56	21.0	44	15.5	
High school education	92	34.1	102	36.0	0.630
Insurance	205	76.5	245	86.3	0.003
Pre-stroke nursing home residence	3	1.1	18	6.3	0.001
Pre-stroke mRS					
0–1	149	55.8	122	43.0	0.005
2–3	98	36.7	125	44.0	
4+	20	7.5	37	13.0	
Pre-stroke IQCODE	3.1	(3,3.4)	3.1	(3,3.6)	0.011
Comorbidity index	3	(2,5)	3	(2,5)	0.459
Initial NIHSS	4	(2,7)	4	(2,8)	0.220
Treated with TPA	18	6.7	30	10.6	0.109
Recurrent stroke	8	3.0	12	4.2	0.436
Defect free stroke care	160	64.8	155	58.9	0.175

mRS=modified Rankin scale; IQCODE=Informant Questionnaire for Cognitive Decline in the Elderly; NIHSS=National Institutes for Health Stroke Scale; tPA=tissue plasminogen activator.