Focused Update of Sex Differences in Patient Reported Outcome Measures After Stroke

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Women experience worse outcomes after stroke than men[1] despite their lower age-adjusted incidence of stroke.[2] Previous reviews of sex differences in select stroke outcomes, including activity limitations,[3–5] participation restriction,[4] poststroke depression (PSD),[3] and health-related quality of life (HRQoL),[3,4] demonstrated that women had worse outcomes than men across many of these measures. Women's greater age and stroke severity, as well as poorer prestroke function, seem to contribute to the sex difference in outcomes, but data on other contributing factors are limited.[4] Existing reviews included studies published >5 years ago, and given the rapid increase in the number of studies addressing sex differences in stroke outcomes, an updated review is warranted.

Methods

Full details of our methods are provided in the online-only Data Supplement. A previous review included studies up to 2007,[3] so we reviewed studies from 2007 onwards that examined sex differences in patient reported outcome measures (PROMs) at ≤12 months after stroke, including activity limitations, HRQoL, participation restriction, impaired cognition, and mood.[6] Full results tables are shown in the online-only Data Supplement.

Results

Activity Limitations

Of 1875 articles identified, 22 studies (3 population based) that were designed to examine sex differences (Results and Table I in the online-only Data Supplement) met criteria for inclusion. The most common instrument to assess activity limitations was the modified Rankin Scale, followed by the Barthel Index.

In 8 studies including ischemic and hemorrhagic strokes, unadjusted estimates showed that women had more activity limitations than men through significantly lower odds of good outcome (odds ratio [OR] range: 0.44–0.61)[7–9] or greater odds of poor outcome (OR range: 1.29–1.62).[10–14] In multivariable adjusted analyses, women had worse outcome than men with significantly lower odds of good outcome (OR range: 0.37–0.75) or greater odds of poor outcome (OR range: 1.17–1.74).[7,8,10,12,13] In 2 studies, there was no statistically significant difference between women and men.[11,14] Adjustment for covariates, most commonly age, stroke severity, comorbidities, and prestroke function, reduced the associations between 9% and 20%, suggesting these factors partly explain the greater activity limitations for women after stroke.

In 11 studies of ischemic stroke (Table I in the online-only Data Supplement), women generally had worse outcome than men demonstrated by greater odds of poor outcome (mostly modified Rankin Scale ≥3 versus <3; range in ORs: 1.13–2.40) or lower odds of good outcome (eg, modified Rankin Scale ≤1 versus >1 or independent walking).[15–25] Among 13 multivariable adjusted comparisons between men and women (some studies had >1 comparison), women's significantly worse outcome compared with men persisted in 7 comparisons with a greater odds of poor outcome (range, 1.30–3.40) or a higher activities of daily living score.[17–19,22–24] Common covariates included age, stroke severity, and comorbidities. There were 6 comparisons rendered nonsignificant by adjustment for covariates,[15,16,20,21,25] which were most commonly age, stroke severity, comorbidities, and health behaviors. Adjustment for covariates reduced the sex differences by between 2% and 47%. In several studies, prestroke modified Rankin Scale was the largest contributor to sex differences in activity limitations.[15,18]

In the 3 studies of intracerebral hemorrhage,[26–28] women had more activity limitations than men demonstrated by significantly higher odds of poor outcome (range, 1.77–2.00),[28] a higher proportion with poor outcome (58.4% versus 45.3%),[27] or a lower proportion with good outcome (33.4% versus 41%).[26] In adjusted analyses, some studies showed no statistically significant sex difference at 90 days[27] and 12 months.[28] Other studies showed worse outcomes in women at 3 [26,28] and

Received October 9, 2017; final revision received December 3, 2017; accepted December 20, 2017.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.018417/-/DC1.

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(*Stroke*. 2018;49:531-535. DOI: 10.1161/STROKEAHA.117.018417.)

6 months after multivariable adjustment.[28] Notably, studies of intracerebral hemorrhage tended to include more clinical covariates, such as intracerebral hemorrhage volume or location and admission delays, in adjusted analyses.

There were also 17 studies that were not designed to examine sex differences in outcome but reported sex-specific results. These studies were of all strokes and ischemic stroke only. They showed similar results to those above and are reported in the online-only Data Supplement (Results and Table II in the online-only Data Supplement).

Health-Related Quality of Life

The search identified 1674 articles of which 13 met our criteria (2 population based) with 2 being specifically designed to examine sex differences (Results and Table III in the online-only Data Supplement).[7,18,29–39] Outcomes included generic instruments, such as the EuroQol-5D, 36-Item Short Form Health Survey, or 12-Item Short Form Health Survey, as well as stroke-specific instruments, including the Stroke-Specific Quality of Life and Stroke Impact Scale.

In the 2 studies designed to examine sex differences, women had lower mean HRQoL than men in unadjusted and adjusted analyses.[7,30] In the one study with both unadjusted and adjusted results, the magnitude of the sex difference was reduced by 20% at 3 months and 45% at 12 months with adjustment for age, sociodemographics, stroke severity, and function at 3 months.[30]

The remaining 11 studies were not designed to examine sex differences but reported sex-specific results. In multivariable adjusted estimates, most commonly including age, stroke severity, and functional outcomes, only 1 study reported that women had better HRQoL than men.[32] By contrast, significantly poorer HRQoL in women was found in 5 studies.[31,33,35,37,38] The remaining 5 studies reported no association between sex and HRQoL after accounting for covariates.[18,29,34,36,39] These studies tended to adjust for PSD and functional outcomes.

Poststroke Depression

We identified 590 studies with 10 meeting our inclusion criteria (none were population based).[40–49] None were designed to examine sex differences in PSD. The most common instruments to assess PSD were the Hamilton Depression Rating Scale, the Centre for Epidemiological Studies Depression Scale, or clinical diagnoses. Unadjusted associations between sex and PSD were reported for 8 studies, generally showing more PSD in women through a higher likelihood of PSD (OR range: 1.27–3.15 and hazard ratio, 3.52)[43,47,49] or higher mean PSD symptoms[41,45] (Results and Table IV in the online-only Data Supplement). Multivariable adjustment, most commonly for age, stroke severity, and activity limitations, did not appreciably change these results, with women still significantly being more likely to have higher prevalence, incidence, or symptoms of depression than men.[40,42,43,45–49] Notably, studies of PSD include a wider range of covariates than other outcomes, such as work status,[41] social factors,[42,46] and cognition.[40,43,46]

Cognitive Impairment

Our search identified 523 articles, of which 5 met the inclusion criteria (none were population based[50–54]; Results and Table V in the online-only Data Supplement). A variety of cognitive tests were used. There were 2 studies designed to examine sex differences in cognitive impairment with one showing men had a 3-fold higher risk than women (OR: 3.07; 95% confidence interval, 1.12–8.42) and the other showing a higher prevalence among women (OR: 1.60; 95% confidence interval, 1.01–2.57) in adjusted analyses.[51,54] Among the 3 remaining studies, results were inconsistent with 1 observing a higher risk of cognitive impairment among men[53] and 1 study observing a higher risk of cognitive impairment among women.[52] In 1 other study, women had a higher risk of cognitive impairment in unadjusted analyses but not after adjustment for a wide range of covariates, including sociodemographics, prestroke health behaviors, and clinical stroke factors.[50]

Participation

There were 665 articles identified with 5 meeting our inclusion criteria (1 population based; Results and Table VI in the online-only Data Supplement). Outcome measures included the London Handicap Scale, the Work and Social Adjustment Scale, and the participation domain of the Stroke Impact Scale. In the one study designed to examine sex differences,[55] the authors reported no significant sex difference, but the study was small and possibly underpowered. Women and men had similar participation restriction in the 4 remaining studies,[56–59] but there was a trend toward women having significantly worse participation restriction than men in one of the studies[58] (OR for less participation restriction: 0.65; 95% confidence interval, 0.20, 1.09) after accounting for a range of covariates, including age, stroke type, and PSD.

Discussion

This updated review of sex differences in PROMs found consistent evidence that women have more activity limitations, worse HRQoL, and a higher prevalence of PSD than men after accounting for a range of covariates. There was less evidence for sex differences in cognitive impairment or participation restrictions. With the exception of studies of activity limitations, there have been few studies specifically designed to examine sex differences in PROMs after stroke. In addition, little data on sex differences from population-based studies exist.

Studies generally considered a wide range of potential confounders of the associations between sex and stroke outcomes. Most studies with multivariable adjusted analyses included age, stroke type, stroke severity, and some measure(s) of cardiovascular comorbidities as potential confounders. Few studies considered aspects of clinical care, social factors, or mental health that may drive poor outcomes in women. In addition, many investigators failed to report unadjusted estimates of the sex association making it difficult to understand the contribution of specific covariates to sex differences. For these reasons, studies that identify modifiable factors contributing to sex differences in stroke outcomes remain a priority. Studies that quantify the effect of adjusting for individual factors on sex differences, rather than simply adjusting for a list of covariates, are needed because they could suggest potential targets for intervention and provide a means for prioritizing these interventions.[18] Of particular interest are studies that consider less well-studied potential confounding factors, including prestroke health, social isolation and loneliness, socioeconomic status (SES), and mental health, because of their unique patterning in women with stroke compared with men.

Women's prestroke health clearly impacts their recovery. Studies of activity limitations demonstrated that prestroke function was an important contributor to the sex difference in this outcome.[15,18] Although many authors considered prestroke function or cardiovascular comorbidities as confounders, few considered musculoskeletal (eg, osteoporosis or arthritis) or mental disorders that are more prevalent in women compared with men.[60] Associated with prestroke health is women's older age than men at the time of stroke.[5] Both age and prestroke health may contribute to women's worse outcome by limiting their physical and cognitive reserve[61,62] or contraindicating interventions and medications.[63] Even though sex differences exist in the quality of and access to stroke care,[2,5] few authors considered these as potential drivers of worse outcomes in women. Studies examining aspects of care may highlight avenues for interventions to reduce sex disparities in stroke outcome.

We found a higher prevalence of PSD in women, which can effect recovery and HRQoL after stroke.[64] Few studies we reviewed included PSD as a covariate, so its impact on sex differences in other stroke outcomes is unclear. There is a need for high-quality longitudinal studies designed to disentangle the potential bidirectional nature of the sex difference in PSD and other PROMs, such as activity limitations and HRQOL after stroke. More efforts to identify and manage PSD in both women and men are needed because it remains a major barrier to improving stroke outcomes.[64]

Older women, who carry much of the burden of stroke, may be vulnerable to loneliness, social isolation, low social support, and limited social networks. Older women are at least twice as likely to live alone than older men (46% of women versus 23% of men >75 years).[65] Living alone before stroke is associated with delays in arrival to hospital[66] and lower use of tissue-type plasminogen activator therapy, which likely affects PROMs.[67] Despite this, few of the studies reviewed here included social factors as potential confounders of sex differences with the exception of a small number of studies that adjusted for marital status or living alone.[18,42] A prospective study of ischemic stroke survivors found that social isolation, but not living alone, was associated with a 40% increase in the risk of cardiovascular events or death.[68] Others reported harmful effects of living alone on mortality in younger but not older people.[69,70] Because living alone measures both normative behavior and functional independence, it can act as a marker of stressful psychosocial situations in younger people but a marker of independence and better health in older people.[71] They are likely to be important, but as yet undiscovered, effects of these social factors on stroke outcomes in women with further research warranted.

Elderly women may be exposed to greater socioeconomic disadvantage than men.[72] This could increase stroke burden in women because people exposed to lower SES have worse outcomes than those with higher SES.[73] Men and women with strokes seem to have similar area-level[74] and individual-level SES, measured using educational attainment.[1] However, others have noted the difficulties in defining exposure to SES in women.[72] In studies we reviewed, analyses of HRQoL commonly adjusted for SES, but few analyses of other outcomes considered it as a covariate. One study showed SES did not influence the sex difference in activity limitations[18] whereas others showed that lower education was associated with greater activity limitations in men but not women[75] or that area-level SES was associated with greater activity limitations in women but not men.[74] Although it is plausible that women's SES relative to men may adversely affect their stroke outcomes, this is not supported by current evidence. Investigators should measure several SES markers reflecting access to material and social resources to better understand the impact on sex differences in outcomes.

A few methodologic considerations warrant discussion. There was a clear lack of population-based studies of sex differences in PROMs identified in our review. Population-based studies have less selection bias and better reflect the broader stroke population, providing the best estimates of sex differences from a public health perspective. Existing population-based studies could contribute to these efforts by ensuring that PROMs are included in future data collection efforts and that sex differences are considered. PROMs are ascertained directly from patients, so many studies exclude people with language or cognitive dysfunction that are more prevalent in women than men.[5] It is, therefore, possible that existing literature misestimates the magnitude of sex differences in PROMs. Advanced statistical methods, such as inverse probability weighting techniques, can account for selection issues but are not common in stroke research. There were few studies of intracerebral hemorrhage, with 3 studies of activity limitations in this group but no studies for other outcomes. We only considered quantitative studies, and there might be qualitative studies that could aid our understanding of sex differences in outcome after stroke. Addressing these issues will improve our understanding of the magnitude of sex disparities and allow us to better identify contributors to sex differences.

Conclusions

This review confirmed that after stroke women experience more activity limitations, worse HRQoL, and more PSD, but not worse cognitive impairment or participation restriction, than men. These differences in outcomes are at least partially explained by women's advanced age, greater stroke severity, and poorer health at the time of stroke. There is a pressing need for high-quality population-based studies of sex differences in PROMs after stroke. Studies exploring potential modifiable contributors to these differences are needed, so effective interventions to reduce sex disparities in outcome can be designed.

Sources of Funding

Dr Gall is funded by a National Heart Foundation of Australia Future Leader Fellowship (FLF100446). Dr Phan is funded by a Merle Weaver PhD Scholarship. P. Rist is funded by K01 HL128791. Dr Lisabeth is funded by R01HL123379, R01HL126700, R01 NS38916, and R01 MD008879.

Disclosures

None.

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KEY WORDS: comorbidity ■ intracranial hemorrhages ■ quality of life ■ sex characteristics ■ stroke