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The murky waters of sex differences in post-stroke cognitive impairment

Louise D. McCullough

McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA.

Abstract

A new study indicates that although men and women are equally likely to experience cognitive impairment after acute ischaemic stroke, there are sex differences in particular cognitive domains. Whether these differences are directly linked to biological sex is uncertain, as many factors, including age and pre-stroke factors, could contribute to cognitive outcomes.

Epidemiological studies have shown that biological sex influences outcomes after ischaemic stroke[1], with women tending to have poorer functional outcomes than men. A new study[2] has shown that women and men have an equal propensity to experience post-stroke cognitive impairment (PCSI), although sex differences were observed in specific cognitive domains. Attributing these differences to sex requires caution, as many factors, including age and pre-stroke function, contribute to morbidity and mortality after stroke and could also affect cognitive outcomes.

In the new paper[2], Exalto and colleagues examined individual data from nine cohorts of patients with ischaemic stroke (n = 2,343, 38% women). The data were harmonized and pooled in the Meta-VCI-Map Consortium. The inclusion criteria were a visible infarct on MRI or CT and cognitive assessments performed within 15 months of the acute ischaemic event. Logistic regression analyses were performed to compare men with women, adjusted for study cohort, to obtain odds ratios (ORs) for PSCI and to examine deficits in individual cognitive domains. The authors also examined sex differences in the sensitivity of commonly used cognitive screening tools, including the Mini-Mental State Examination (MMSE; four cohorts, n = 1,814) and the Montreal Cognitive Assessment (MoCA; three cohorts, n = 278) using supplementary information from three additional cohorts from the UK and the Netherlands.

A major strength of this study is that all of the participants in the main analysis underwent formal multidomain neuropsychological assessment to determine PSCI – an impressive achievement, as follow up rates in stroke cohorts are often poor. PSCI, defined as impairment in more than one cognitive domain on neuropsychological assessment, was

✉ louise.d.mccullough@uth.tmc.edu .

Competing interests

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equally common in men and women, affecting 51% of each group. A previous study found wide variations in the 5-year cumulative incidence of PSCI, ranging from 0% after transient ischaemic attack in patients younger than 65 years to over 80% in patients aged 75 years or older with major recurrent stroke[3], indicating that age and stroke severity are important factors in determining cognitive outcomes after stroke.

In the new study[2], impairments in specific cognitive domains differed between men and women. Of note, the neuropsychological test batteries that were used differed by cohort, but the authors harmonized the data into six specific cognitive domains. Regardless of age and educational status, men had higher rates of verbal memory impairment than women (OR 1.43). By contrast, women showed greater impairments in attention and executive function (OR 0.76 for men versus women) and had more language impairment (OR 0.67 for men versus women). The MMSE showed higher sensitivity but lower specificity for PSCI in women than in men. An MMSE score below 25, indicating cognitive impairment, was seen in 63% of women and 39% of men with PSCI. One surprising finding was the large number of women who scored below 25 on the MMSE but did not show PSCI on multidomain neuropsychological assessment (39%, compared with 9% of men).

The sensitivity and specificity of the MoCA for PSCI were comparable between women and men, suggesting that this tool could be more useful than the MMSE for screening patients with stroke. However, far fewer patients had documented MoCA scores, so the results should be interpreted with caution, and the screening tools that are used for PSCI clearly require further assessment.

As in most stroke studies, women were under-represented in this cohort, potentially introducing bias. Several factors could influence enrolment of women in stroke trials[4]. They could be less likely than men to volunteer, or they could be excluded on the basis of age. Alternatively, strokes could be more severe in women than in men, leading to higher mortality and resulting in survival bias. Consistent with almost all published studies, the women in the new study were significantly older and had higher stroke severity than the men. The women also had lower educational attainment (71% educated below high school level compared with 45% of men) – a variable that is known to contribute to cognitive resilience[5].

Cohort-specific inclusion and exclusion criteria are also important to consider. Most of the cohorts excluded patients with severe aphasia or dysarthria, and some excluded mortality within 2 weeks and individuals with a modified Rankin Scale score >4, which could have led to differential exclusion of women. Importantly, of the 2,343 patients examined in the main analysis, 58% of the cohort were from patients enrolled in two Korean studies, the Budang Vascular Cognitive Impairment (VCI) cohort (n = 753) and the Hallym VCI cohort (n = 641). Neither of these cohorts excluded patients with pre-existing cognitive deficits or dementia, which was an exclusion criterion in six of the nine cohorts examined. Of note, these were the two cohorts that showed statistical differences in PSCI in women, suggesting a potential interaction of PSCI with pre-stroke cognitive function. Several of the cohorts attempted to assess pre-stroke cognitive function using the Informant Reported Assessment

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of Pre-Stroke Cognitive Decline (IQCODE), which confirmed higher baseline cognitive deficits in women.

Overall, there is little doubt that women face a disproportionate burden from stroke. In the most recent Centers for Disease Control and Prevention data, the crude mortality rate from stroke was 54.9 in 100,000 for women and 43.1 in 100,000 for men[6]. Women tend to be older when they have their first stroke, often resulting in increased rates of pre-existing disability, which makes post-stroke assessments difficult if baseline function is unknown. This caveat is important, and should be considered in the interpretation of all studies examining ‘sex differences’ in stroke.

Among stroke survivors, poorer health-related quality of life is seen in women than in men[7]. However, in studies that adjusted for factors such as age, pre-stroke disability, stroke severity and post-stroke depression, all of which are more common in women than in men, the sex differences in outcomes and health-related quality of life became small or non-existent[7,8], suggesting that factors such as depression or initial stroke severity could be targeted to improve outcomes.

In a recent study of patients with acute ischaemic stroke who were eligible for endovascular therapy, female sex, Black race and Hispanic ethnicity were associated with significantly higher door-in-door-out times for patients transferred for intervention, leading to potential delays in reperfusion[9]. Women were also less likely to be transferred to a comprehensive stroke centre for further management, even within an integrated system[9]. These findings suggest that stroke severity represents a modifiable risk factor for PSCI, particularly in women and minoritized groups.

In conclusion, improvements in acute stroke care to enhance reperfusion and decrease stroke severity, treatment of post-stroke depression, and improvements in secondary prevention to reduce the risk of recurrent stroke could all pave the way to reducing the long-term risk of PCSI and dementia in both men and women.

References

1. Rexrode KM et al. The impact of sex and gender on stroke. Circ. Res 130, 512–528 (2022). [PubMed: 35175851]
2. Exalto LG et al. Sex differences in poststroke cognitive impairment: a multicenter study in 2343 patients with acute ischemic stroke. Stroke 54, 2296–2303 (2023). [PubMed: 37551589]
3. Pendlebury ST & Rothwell PM Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. Lancet Neurol. 18, 248–258 (2019). [PubMed: 30784556]
4. Strong B et al. Sex disparities in enrollment in recent randomized clinical trials of acute stroke: a meta-analysis. JAMA Neurol. 78, 666–677 (2021). [PubMed: 33900363]
5. Centers for Disease Control and Prevention. Underlying cause of death by single race 2018–2021. CDC WONDER https://wonder.cdc.gov/wonder/help/ucd-expanded.html (2023).
6. Phan HT et al. Factors contributing to sex differences in health-related quality of life after ischemic stroke: BASIC (Brain Attack Surveillance in Corpus Christi) project. J. Am. Heart Assoc 11, e026123 (2022). [PubMed: 36056724]
7. Stamm B et al. Door-in-door-out times for interhospital transfer of patients with stroke. J. Am. Med. Assoc 330, 636–649 (2023).

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8. Phan HT et al. Sex differences in long-term quality of life among survivors after stroke in the INSTRUCT. Stroke 50, 2299–2306 (2019). [PubMed: 31412754]
9. Tariq MB et al. Women with large vessel occlusion acute ischemic stroke are less likely to be routed to comprehensive stroke centers. J. Am. Heart Assoc 12, e029830 (2023). [PubMed: 37462071]