

# Stroke in young women: the need for targeted prevention and treatment strategies

Stroke is a devastating disease, leaving survivors with physical and cognitive impairments, and emotional and psychological instability. In 2021, the most current year available, the coronavirus disease 2019 (COVID-19) pandemic shifted the rankings of the *Global Burden of Disease Study*, bringing stroke down to the third leading cause of death worldwide,<sup>1</sup> and fourth leading cause of disability-adjusted life years.<sup>2</sup> In Australia, in 2022, cerebrovascular disease (mostly stroke) was the third leading cause of death in women compared with fifth in men.<sup>3</sup>

Women have a lower age-adjusted incidence of stroke than men.<sup>4</sup> However, on age group breakdowns, authors of a recent meta-analysis of 16 studies (33 775 women and 36 018 men) found that sex difference in ischaemic stroke incidence was the greatest in adults younger than 35 years of age, with an estimated 44% more women than men.<sup>5</sup> These findings, showing that young women may be disproportionately at risk of ischaemic stroke, represent a significant shift from our current understanding, with important implications regarding causes and potential management of ischaemic strokes in young adults.

We acknowledge that the studies referenced herein use mostly sex data. However, in this perspective article, we use the term “women” in a binary manner to denote females.

## Traditional and sex-specific risk factors

There are key modifiable risk factors that are more strongly associated with stroke risk in women than in men. In the *UK Biobank Study* of 471 971 individuals (56% women),<sup>6</sup> in women, hypertension and obesity were associated with a 30% greater risk of stroke, and smoking and type 2 diabetes a 20–25% greater risk of stroke, compared with men.

In young women, non-atherosclerotic factors that increase the risk of stroke may be important. These include female-specific risk factors such as exogenous hormones and pregnancy-related exposures. Hormonal contraceptives are very effective, reliable and provide women with multiple health benefits. Combined oral contraceptives (COCs) containing oestrogen and progestogen carry an increased risk of arterial thrombosis, with a Cochrane systematic review noting a 1.7-fold increased risk of ischaemic stroke compared with non-users (relative risk [RR], 1.7; 95% confidence interval [CI], 1.5–1.9). The risk increased the higher the dose of oestrogen.<sup>7</sup> In a separate meta-analysis (six case–control studies), progestogen-only contraceptives were not associated with stroke when compared with individuals that had never used or formerly used this type of contraceptive.<sup>8</sup> Although overall COC-use ischaemic stroke risk is low for individuals, women with migraine who also use COCs have a further increased risk (RR, 7.02 [95% CI, 1.51–32.68]) while

women experiencing a migraine with aura, COC use, and who are active smokers have a tenfold increase (RR, 10 [95% CI, 1.4–73.7]).<sup>9</sup>

Pregnancy-related complications, including preeclampsia (one in 30 pregnancies) and gestational diabetes mellitus (GDM, one in seven pregnancies), increase the risk of stroke during pregnancy and later life. During pregnancy, stroke affects 30/100 000 pregnancies, with preeclampsia further increasing the risk of haemorrhagic stroke (RR, about tenfold) and ischaemic stroke (RR, 40-fold), secondary to preeclamptic endotheliopathy and hypertension from oestrogen-related hypercoagulability in pregnancy.<sup>10</sup> Following pregnancy, GDM and hypertensive pregnancy disorders increase a young women’s risk of stroke. A recent meta-analysis of cardiovascular and cerebrovascular disease risk after GDM found a 40% increased risk of stroke (95% CI, 1.29–1.51), and ten-year post-gestational diabetes mellitus RR of 1.46 (95% CI, 1.32–1.61) for cardiovascular/cerebrovascular events.<sup>11</sup> Following hypertensive pregnancy, a meta-analysis of 12 studies found that stroke risk more than doubled in the first ten years postpartum (RR, 2.64, 95% CI, 2.15–3.35).<sup>12</sup> Although not incorporated into cardiovascular disease risk calculators or recommended as a formal risk reclassification in the 2023 *Australian guideline for assessing and managing cardiovascular disease risk*, the guidelines do note pregnancy complications of GDM and hypertensive disorders of pregnancy as important risk considerations.<sup>13</sup> These guidelines recommend taking a thorough pregnancy history during cardiovascular risk assessment as well as emphasising the importance of follow-up appointments for women experiencing GDM and/or hypertensive disorders of pregnancy. Other reproductive metabolic disorders, such as polycystic ovarian syndrome, are also associated with an increased risk of stroke, likely due to elevated traditional and non-traditional cardiovascular risk factors in polycystic ovarian syndrome including insulin resistance, obesity, hypertension, chronic inflammation and oxidative stress.<sup>14</sup>

## Recognition and diagnoses

Existing disparities in diagnosis and recognition of stroke exacerbate poor outcomes for women who are more likely to have a poorer quality of life after a stroke.<sup>15</sup> Compared with men, younger women are less likely to be recognised as having a stroke in the pre-hospital<sup>16</sup> and emergency department setting, possibly due to atypical presentations such as generalised weakness, confusion or fatigue,<sup>17</sup> which are less commonly recognised as stroke symptoms. It is possible that women, who are often primary caregivers for children and/or ageing parents, may de-prioritise their own health care needs (eg, stroke symptoms) to continue caring for others. This is poorly understood and requires further research. Biases in health

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care contribute to diagnostic delays, with women's symptoms often misattributed to non-neurological causes.<sup>18</sup> Timely recognition and diagnosis of stroke is necessary for initiating reperfusion therapies, which greatly improve functional outcome.<sup>19</sup>

### Tailored prevention and treatment

Addressing these disparities in recognition and diagnoses requires multifaceted solutions. For prevention, a postpartum follow-up after a hypertensive pregnancy and GDM to screen for, reduce and manage stroke risk factors, such as chronic hypertension and type 2 diabetes, is key.<sup>20</sup> Appropriate COC use, including consideration of alternatives such as long-acting reversible contraception for higher-risk women (eg, women experiencing migraines or women who smoke) is also important.

Enhancing pre-hospital stroke recognition is critical. Improving public awareness campaigns focusing on women's stroke symptoms can ensure timely medical intervention. Advanced stroke training for paramedics on sex-specific symptoms and early detection could facilitate diagnosis and treatment.

The five-year stroke recurrence risk in young patients can be as high as 12%.<sup>21</sup> Young stroke clinics can address sex-specific risk factors to provide optimal stroke prevention and prevent recurrence. These clinics diagnose, treat, provide ongoing management, prevention and recovery with a multidisciplinary team including, but not limited to, neurologists, stroke nurses, neurosurgeons, cardiologists, obstetricians, other specialists, nutritionists and social workers. Personalised education and prevention strategies can be tailored to a young women's unique risk factors, such as return to work activities, caregiving responsibilities and contraceptive use.

Improving the participation of women in clinical trials is essential for generating robust evidence on the efficacy and safety of stroke interventions. Efforts should focus on designing inclusive clinical trials that adequately represent women across various socio-demographic profiles. Regulatory agencies and funding bodies can incentivise women's inclusion through policy mandates and as part of funding requirements. Implementing sex-specific analyses (efficacy and safety) in clinical trials will provide valuable insights into differential treatment effects between men and women.

In summary, women have worse outcomes after a stroke.<sup>15</sup> Addressing these challenges through targeted interventions, improved pre-hospital recognition, and increased participation in clinical trials is essential for closing the gender gap in stroke outcomes and ensuring equitable health care.

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