

# Stroke in women: Is it different?

Sydney Corbière<sup>1</sup> and Barbara Tettenborn<sup>1</sup> 

*Clinical & Translational Neuroscience*  
January-June 2021: 1–8  
© The Author(s) 2021  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/2514183X211014514  
journals.sagepub.com/home/ctn



## Abstract

In the last decades, there has been great progress in the field of stroke. With the introduction of acute therapies (intravenous thrombolysis and intra-arterial treatment), the outcome after stroke has improved significantly. Better prevention, improved acute therapy, and acute rehabilitation improved the morbidity and mortality rate after stroke. Gender differences in risk factors and epidemiology have been known for a long time, but lately attention to gender differences in stroke has increased. The aim of this mini-review is to demonstrate gender disparities in stroke with a focus on epidemiology, specific risk factors (gender-specific and unspecific), and outcomes. The influence of some risk factors for stroke is stronger in women (atrial fibrillation and hypertension) and there are risk factors exclusive to women such as pregnancy, pregnancy-associated hypertensive disorders, oral contraceptives, and hormonal replacement treatment. Data on the impact of other risk factors are inconsistent. The worse outcome after a stroke is mainly caused by demographic characteristics in women. Specific gender research is needed to better understand gender disparities in stroke to improve prevention strategies and treatment for women.

## Keywords

Stroke in women, gender difference

## Epidemiology

About 16,000 people suffer from stroke in Switzerland every year. Worldwide, there is a higher lifetime risk in females, mainly owed to the fact of higher life expectancy.<sup>1</sup>

The sex-specific incidence of all strokes between 1993 and 2010 declined significantly for males but not for females in a population-based study in the United States.<sup>2</sup> Newer data published in 2016 showed a decrease in incidence, prevalence, and stroke mortality in men and women even in people older than 80 years.<sup>3</sup> In Switzerland, the incidence of stroke is 164–236/100,000/year (varies on canton) for women and 227–358/100,000/year for men.<sup>4</sup>

The prevalence of stroke is age-dependant. It increases with advancing age in men and women.<sup>5</sup> Young women (<59 years) have a similar prevalence of stroke as men; in the higher age groups, there is a female dominance (>80 years), mainly due to the higher life expectancy of women.<sup>5</sup>

Worldwide, a narrative review in 2016 showed a higher incidence in men in post-socialist countries, Sub-Saharan, China, Latin America, urban India, Japan, Australia, New Zealand, United States, and Canada. A higher incidence in women occurred in Arab countries according to this review. But a population-based cohort study (2018) in Iran

showed a similar annual crude rate of first-ever stroke in women and men.<sup>6</sup> In Western Europe, the incidence is higher or similar in women compared to men.<sup>3</sup>

Stroke is the second leading cause of death worldwide.<sup>7</sup> It is the third leading cause of death after ischemic heart disease and cancer in Switzerland.<sup>8</sup> Six percent of all deaths in men and 8% in women are due to stroke in Switzerland.

Increasing age, high National Institutes of Health Stroke Scale, history of atrial fibrillation, and less than 12 years of education were associated with an increased 5 years risk of death for both genders.<sup>6</sup>

A meta-analysis of individual patient data from Europe, Australasia, South America, and the Caribbean between 1987 and 2013 showed greater long-term mortality after stroke in women. This is mostly because of age but also

<sup>1</sup> Department of Neurology, Kantonsspital St. Gallen, St. Gallen, Switzerland

## Corresponding author:

Barbara Tettenborn, Department of Neurology, Kantonsspital St. Gallen, Rorschacher Strasse, Sankt Gallen 9007, Switzerland.  
Email: barbara.tettenborn@kssg.ch



due to stroke severity, atrial fibrillation, and prestroke functional limitations. After adjustment for these factors, the sex differences were reversed.<sup>9</sup>

A population-based study supports these findings; after adjusting for age, the mortality rate in women and men was equal.<sup>10</sup>

## Outcome after stroke

Stroke is one of the leading causes of disability worldwide. In several studies, women tend to have worse outcomes than men after stroke. The following factors were identified as contributing to worse outcomes in women: low prestroke function, marital status, nursing home residence, stroke severity, history of stroke or transient ischemic attack, and body mass index (BMI). Prestroke function had the highest impact on outcomes in women after a stroke.<sup>10</sup>

These data suggest that sex-specific factors with high potential to reduce the difference in the outcome of a stroke exist, for example, physical activity in elderly women to improve prestroke dependency.

Additionally, women are reported to have poorer health-related quality of life (QoL). A study investigating the underlying reasons for this calculated the QoL using three different scales (European Quality of Life 5 Dimensions, Short Form 6-Dimension, and Assessment of Quality of Life) over a period of 1 year. Poorer health-related QoL was partly attributable to women's advanced age at onset of stroke, more severe strokes, prestroke dependency, and poststroke depression. After adjusting, there was still evidence of residual differences between men and women but too small to be clinically significant.<sup>11</sup>

A good outcome after stroke depends highly on the acute therapy. Intravenous thrombolysis (IVT) and intra-arterial thrombectomy are the only causal therapies for an ischemic stroke. Both therapies improve the outcome after a stroke and are strongly time-dependent.<sup>12,13</sup>

With special imaging (computed tomography (CT) perfusion and magnetic resonance imaging (MRI)), patients who would benefit from acute therapy (IVT or/and intra-arterial thrombectomy) can be identified beyond the classic time window.<sup>14,15</sup>

There are a few existing studies that have investigated sex differences regarding acute therapy.

In a registry-based study from Florida and Puerto Rico, women were significantly less likely to receive thrombolysis than men between the years of 2010 and 2014. Women had a longer door to needle time and were less likely to have a CT scan within 25 min after arrival than men.<sup>16</sup> A meta-analysis supports the finding that women are less likely to receive thrombolysis treatment when compared with men, despite the wide variation between the separate studies.<sup>17</sup> In contrast, a register-based study from Austria showed no differences in the acute care (onset-to-door times, door to CT or MRI, door-to-needle time, and rates of IVT).<sup>18</sup>

Newer data of a meta-analysis including recombinant tissue plasminogen activator (rtPA)-treated patients between 2008 and 2018 showed that women are still less likely to be treated with thrombolysis, but the sex difference has narrowed considerably.<sup>19</sup>

The improvement over a few years might be influenced by a selection bias. In the large studies about IVT, age above 80 years was an exclusion criterion.<sup>20</sup> Regarding stroke occurring in women at an older age than men and women having higher functional independence before the index stroke, thrombolysis was applied less common in everyday clinical practice in women. In randomized clinical trials (RCTs), which are the basis for therapy guidelines, women are usually underrepresented. A study showed stroke trials between 1990 and 2018 enrolled about 40% women, without an increasing rate in the past 10 years. Maybe this is another reason potentially leading to withholding acute therapies in women.<sup>21</sup>

The data about the functional outcome after IVT are inconsistent. In a multicentre European cohort trial (including data from Swiss Stroke Units and Centers), women had more often poor outcomes (odds ratio (OR), 1.15; 95% confidence interval (CI), 1.02–1.31) compared to men after IVT. These differences remained after adjusting for age, stroke severity, and functional independence before index stroke. In the same study, women had a longer stroke-to-needle time and atrial fibrillation and hypertension was more prevalent in women.<sup>22</sup> This is in contrast to what has been reported in a pooled analysis of RCTs.<sup>23</sup>

There is some evidence of sex differences in hemodynamic and temporal features. A sub-study from the DEFUSE trial showed that women had imaging evidence of better collateral circulation, smaller baseline core volumes, and slower ischemic core growth.<sup>24</sup>

Women are more likely to know symptoms of a stroke but less likely to call an ambulance for themselves.<sup>25</sup>

Data are limited in sex-related differences in quality of acute care on a stroke unit and further rehabilitation. A study showed that despite no differences in the acute care and comparable rehabilitation rate, women had a worse outcome than men at the 3-month follow-up but interestingly a lower mortality rate. Early postischemic start of secondary prevention and stroke unit care is also crucial for a good outcome.<sup>26,27</sup> Thus, the immediate recognition of stroke symptoms for a fast referral to a stroke center is essential.

The American Heart Association/American Stroke Association describes common stroke symptoms such as numbness or weakness of the face, arm, or leg (especially on one side of the body), difficulty speaking and understanding, difficulty in seeing in one or both eyes, difficulty walking, dizziness, loss of balance or coordination, and severe headache with no known cause. Women tend to have more atypical stroke symptoms. A review of 23 articles addressing unique stroke symptoms demonstrated that women experience unique stroke symptoms like loss of

consciousness, fainting, general weakness, difficulty breathing, shortness of breath, confusion, unresponsiveness or disorientation, sudden behavioral change, agitation, hallucination, nausea or vomiting, pain, seizures, and hiccups more often than men.<sup>28</sup>

## Risk factors specific to women

Besides nonmodifiable risk factors for stroke (age, genetics, and race), there are several modifiable risk factors. Some of them are exclusive to women throughout the lifetime and occur at different ages. In young- and middle-aged women, these are oral contraceptives and pregnancy, in older women, menopause, and hormonal replacement therapy. Some risk factors are well-studied, while others show some inconsistent data.

## Pregnancy

The incidence rate of a stroke during pregnancy varies greatly. In a review from 2011, it varied from 9 to 34 per 100,000 deliveries worldwide.<sup>29</sup> In 2017, a systematic review and meta-analysis of 11 studies showed an incidence rate of 30 per 100,000 pregnancies. The rates for ischemic stroke, cerebral venous sinus thrombosis, and intracerebral hemorrhage are roughly the same.<sup>31</sup> Both reviews showed a three times higher risk for pregnant women compared to other young females with an incidence of stroke of 10/100,000.<sup>32</sup> A population-based study from England, which was published after the two systematic reviews, showed a slightly lower stroke rate of 24.7/100,000.<sup>33</sup>

There seems to be a trend to a higher incidence of stroke in women who have delivered after in vitro fertilization compared to those who delivered after natural conception.<sup>34</sup>

Pregnancy and its hypertensive associated disorders have long been identified as stroke risk factor. Hypertensive disorder in pregnancy includes gestation hypertension, preeclampsia, and eclampsia. Gestational hypertension is defined as a blood pressure of >140 mmHg systolic and/or 90 mmHg diastolic, resolving within 12 weeks after delivery). Preeclampsia is a combination of gestational hypertension and proteinuria >300 mg/24 h, and preeclampsia with seizure is called eclampsia.

The incidence of stroke in pregnancy has increased in recent years, maybe because of the increased number of hypertensive disorders in pregnancy.<sup>35</sup> Between 1994 and 2011, the rate of stroke and hypertensive disorders of pregnancy doubled (0.8–1.6). The rate of stroke in pregnancy without these disorders also increased but to a lesser extent. Women with hypertensive disorders of pregnancy were 5.2 times more likely to suffer from a stroke, had an increased risk of mechanical ventilation, and higher risk for discharge to a facility other than home.<sup>35</sup>

The most common etiologies associated with an ischemic stroke in pregnancy are cardioembolism, coagulopathy, preeclampsia, and eclampsia, while for hemorrhagic stroke, the most common etiologies are aneurysm, arteriovenous malformation, gestational hypertension, HELLP (hemolysis, elevated liver enzymes, low platelet count) Syndrom, and preeclampsia/eclampsia.<sup>30</sup> The mortality rate ranges from 2.7% to 20%.<sup>30</sup> Of all stroke types, intracerebral hemorrhage has the highest morbidity and mortality in pregnancy.<sup>29</sup> Women with hypertensive disorders of pregnancy and a stroke had a higher death rate during hospitalization compared to women without a hypertensive disorder (OR, 1.29; 95% CI, 1.02–1.64).<sup>35</sup>

Data about the recurrence rate of stroke in subsequent pregnancies are limited. A study including 441 women with history of stroke or cerebral venous thrombosis showed a low risk of recurrence during the following pregnancies. The relative risk of recurrence was significantly higher during the postpartum period than during pregnancy itself.<sup>36</sup> The risk increased with further risk factors (i.e. antiphospholipid syndrome)<sup>37</sup> and higher age of the mother (>35 years).<sup>38</sup>

## Acute therapy in pregnant women

Pregnant women are generally excluded in randomized controlled trials for safety reasons. There are just case reports or small series reporting the safety (for women and the baby) and benefit of using rtPA and intra-arterial thrombectomy in pregnancy.<sup>39,40</sup> A limitation of these data is a publication bias.

## Oral contraception

The risk of stroke under oral contraception is well-evaluated and the overall risk is low. A 2015 meta-analysis showed a 2.47-fold increase in the risk of stroke (95% CI, 2.04–2.99).<sup>41</sup> In another systematic review, the increased risk was 1.7 (95% CI, 1.5–1.9) taking a combined oral contraceptive.<sup>42</sup> The risk increases when oral contraceptives are described in women with an additional risk factor such as obesity, elevated cholesterol, or smoking<sup>43</sup> and with higher doses of estrogen.<sup>42</sup>

## Menopause

Menopause is defined as the point in time when menstrual cycles cease due to the natural depletion of ovarian oocytes from aging, corresponding to the absence of menstrual periods for at least 12 months. Exposure to endogenous estrogen was supposed to be protective for stroke in premenopausal women due to lower risk of ischemic stroke in this age group. The risk of stroke with early menopause is not clear. There are studies showing an association and others showing no association.

A meta-analysis from 32 studies showed similar results for the risk of stroke, thus in the same study, the stroke mortality was higher in patients with age at menopause younger than 45 years.<sup>44</sup> Lisbeth et al. described a doubled risk of stroke in women with onset of menopause before 42 years (rate ratio (RR), 2.03, 95% CI, 1.16–3.56) adjusted for age, stroke risk factors, and postmenopausal estrogen use.<sup>45</sup> There was a slight decrease of ischemic stroke risk in women after hysterectomy.<sup>31</sup> However, a population-based cohort study showed that hysterectomy in women aged 50 years or younger substantially increases the risk for cardiovascular disease later in life and oophorectomy further adds to the risk of both coronary heart disease and stroke.<sup>46</sup>

### Hormone replacement therapy

In a large case–control study, the risk of ischemic stroke was significantly increased with the use of oral estrogen plus progestin compared to placebo.<sup>47</sup> There are hints for the difference in risk using transdermal estrogen. In a large study, the rate of stroke in the cohort was 2.85 per 1000 per year. The adjusted RR of stroke associated with the current use of transdermal hormone replacement therapies was 0.95 (95% CI, 0.75–1.20) relative to no use. The risk of stroke was not increased with the use of low estrogen dose patches (RR, 0.81; 95% CI, 0.62–1.05) compared with no use, whereas the risk was increased with high-dose patches (RR, 1.89; 95% CI, 1.15–3.11). Current users of oral hormone replacement therapy had a higher rate of stroke than nonusers (RR, 1.28; 95% CI, 1.15–1.42), with both low dose and high dose.<sup>48</sup>

The risk of an ischemic stroke taking progestogens depends on the type of derivative. Progesterone, pregnane, and nortestoren derivatives are not associated with an increased risk of ischemic stroke, whereas nonpregnanes increased the risk of ischemic stroke (OR, 2.25; 95% CI 1.05–4.81).<sup>49</sup>

### Unspecific risk factors for stroke

A large case–control study identified 10 modifiable risk factors in men and women responsible for most strokes worldwide.<sup>50</sup> Prevention and therapy of these risk factors could lower the burden of stroke in both genders. Hypertension, abdominal obesity, and adverse lipid profiles are the most impactful causes of stroke in women.<sup>50</sup> It is known that a healthy lifestyle is supposed to have a positive effect on some of the risk factors for cerebrovascular diseases (arterial hypertension, cholesterol, and obesity).

There are some risk factors that are seen more frequently in women or have a greater impact on the risk for stroke in women.

### Atrial fibrillation

The prevalence of atrial fibrillation is higher in men, but the risk of stroke due to atrial fibrillation is higher in women.<sup>51</sup> A meta-analysis of 30 cohort studies with more than 4 million patients showed a higher relative risk of cardiovascular and all-cause mortality stroke and heart failure in women with atrial fibrillation than men (for stroke RR, 1.9; 95% CI, 1.46–2.71).<sup>52</sup> In a prospective population-based study, atrial fibrillation was associated with a considerably greater risk of hemorrhagic stroke in women.<sup>53</sup>

The usual therapy for atrial fibrillation is anticoagulation. There are some data, which demonstrate, that women are less likely to be treated with anticoagulation<sup>54</sup> and that women have a higher risk for stroke despite anticoagulation with warfarin.<sup>55</sup> The difference between men and women was not seen in women treated with novel anticoagulants.<sup>56</sup>

### Hypertension

High systolic blood pressure is a known risk factor for ischemic and hemorrhagic stroke in men and women with no difference in the impact on stroke risk.<sup>57</sup> New data from a prospective, population-based cohort study showed a significant sex difference with stroke incidence for hypertension (defined as systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg), although sex differences in incremental blood pressure increases were not significant. Women with hypertension had a 30% excess stroke risk.<sup>53</sup> Men tend to have better control of their blood pressure than women (33.6 vs. 30.6%).<sup>58</sup> Blood pressure control was especially poor in high-risk elderly women.<sup>59</sup> In a large study in 26 countries, only 29% of the women aged 70–79 years had well-controlled blood pressure<sup>60</sup> and this despite the higher treatment rate according to another study.<sup>61</sup> The reasons are unclear; there may be poorer compliance or an unknown physiological mechanism in women.

### Obesity, metabolic syndrome, and lifestyle factors

General obesity, abdominal adiposity, and metabolic syndrome are independent risk factor for stroke besides hypertension and type 2 diabetes.<sup>62</sup> A pooled analysis of 97 prospective cohorts with 1.8 million participants showed that after reducing high blood pressure, cholesterol, and glucose the risk of stroke could be decreased by 75%, but it remains an increased stroke risk due to obesity.<sup>62</sup> The risk of total stroke and ischemic stroke increases with increasing BMI to a similar extent in women and men.<sup>53,62</sup> Data regarding the gender-specific impacts of obesity on the risk of stroke are inconsistent. Some data suggest that BMI influences the risk of stroke in men but not in women; other data show the opposite results.<sup>63,64</sup>

Besides medical treatment of risk factors, physical activity and a healthy lifestyle are essential in stroke prevention. A prospective cohort study divided women without a prior stroke into different groups according to their lifestyle. The “healthy lifestyle score” was composed of smoking, physical activity, BMI, alcohol consumption, and diet. It ranges from 0 to 20 (20 is the healthiest range). A healthy lifestyle is associated with better functional outcomes after all types of stroke (ischemic and overall stroke; mild, moderate, and severe stroke). A healthy lifestyle and some lifestyle modifications could decrease the risk of disabling stroke in women.<sup>65</sup>

## Diabetes

In a systematic review and meta-analysis of 64 cohorts, the excess risk of stroke associated with diabetes is higher in women than men.<sup>66</sup> These findings are not consistent with another study showing no sex disparities in the association between diabetes and stroke risk.<sup>67</sup>

## Migraine with aura

Migraine with aura is more common in women than men and increases the risk of an ischemic stroke. The risk increases with additional risk factors such as oral contraceptives and smoking and is higher with increasing frequency of migraine.<sup>68</sup>

## Conclusion

The lifetime stroke risk is higher in women than in men and the presentation of stroke might be atypical. The demographic baseline characteristics in women compared to men are different. Women tend to be older at the time of onset of stroke, suffer from more severe strokes, have a higher pre-stroke disability, and have a worse outcome. This worse outcome is partly due to the disparities in demographic characteristics.

Additionally, some risk factors are exclusive to women and have a known increased stroke risk, such as pregnancy, pregnancy-related hypertensive disorders, oral contraceptives, hormonal replacement treatment, and oophorectomy. Some of the general known risk factors, like hypertension and atrial fibrillation, have a higher impact in women than men. Data on gender differences and the impact of other risk factors are inconsistent. This especially applies to data about the benefits of acute stroke therapies, which are limited in general and partly conflicting between different studies.

Identifying gender differences in risk factors, demographic characteristics, efficacy of acute therapies, and rehabilitation will lead to better treatment and leads the way to gender-specific prevention to lower the burden of stroke in women worldwide. Additionally, women are

underrepresented in clinical trials, potentially leading to mistreatment or withholding therapy in women.

Besides governmental actions, like the National Institutes of Health Revitalization Act in 1993<sup>69</sup> or specified guidelines for women and stroke in development from the European Stroke Organization, articles highlight the importance of increased enrolment of women in RCTs to reflect real-life conditions.<sup>70</sup>

## Acknowledgments

We would like to thank Anna Müller for reading the manuscript regarding the English.

## Author contributions

SC and BT researched literature and took care of data analysis. SC wrote the first draft of the manuscript. Both authors reviewed and edited the manuscript and approved the final version of the manuscript.


## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## ORCID iD

Barbara Tettenborn  <https://orcid.org/0000-0002-2072-7923>

## References

1. GBD 2016 Lifetime Risk of Stroke Collaborators. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N Engl J Med* 2018; 379(25): 2429–2437. DOI: 10.1056/NEJMoa1804492. PMID: 30575491; PMCID: PMC6247346.
2. Madsen TE, Khoury J, Alwell K, et al. Sex-specific stroke incidence over time in the Greater Cincinnati/Northern Kentucky Stroke Study. *Neurology* 2017; 89(10): 990–996.
3. Arnao V, Acciarresi M, Cittadini E, et al. Stroke incidence, prevalence and mortality in women worldwide. *Int J Stroke* 2016; 11(3): 287–301.
4. Schweizerisches Gesundheitsobservatorium. Hirnschlag. <https://www.obsan.admin.ch/de/indikatoren/hirnschlag> (zuletzt abgerufen am. 09 November 2020)
5. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation* 2020; 141(9): e139–e596.
6. Amiri A, Kapral MK, Thrift AG, et al. The incidence and characteristics of stroke in urban-dwelling Iranian women. *J Stroke Cerebrovasc Dis* 2018; 27(3): 547–554.
7. Institute for Health Metrics and Evaluation. GBD compare data visualization. 2019. <https://vizhub.healthdata.org/gbd-compare/> (zuletzt abgerufen am. 21 November 2020)
8. Bundesamt für Statistik. Spezifische Todesursachen. <https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheits>

- gesundheitszustand/sterblichkeit-todesursachen/spezifische.html (zuletzt abgerufen am. 09 November 2020)
9. Phan HT, Blizzard CL, Reeves MJ, et al. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational STROke oUtComes sTudy): a meta-analysis of individual participant data. *Circ Cardiovasc Qual Outcomes* 2017; 10(2): e003436. DOI: 10.1161/CIRCOUTCOMES.116.003436. Epub 22 February 2017. PMID: 28228454.
  10. Lisabeth LD, Reeves MJ, Baek J, et al. Factors influencing sex differences in poststroke functional outcome. *Stroke* 2015; 46(3): 860–863.
  11. Phan HT, Blizzard CL, Reeves MJ, et al. Sex differences in long-term quality of life among survivors after stroke in the INSTRUCT. *Stroke* 2019; 50(9): 2299–2306.
  12. Berkhemer OA, Fransen PS, Beumer D, et al. MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372(1): 11–20.
  13. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359(13): 1317–1329. DOI: 10.1056/NEJMoa0804656.
  14. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; 378(1): 11–21.
  15. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging (DEFUSE-3). *N Engl J Med* 2018; 378: 708–718.
  16. Asdaghi N, Romano JG, Wang K, et al. Sex disparities in ischemic stroke care: FL-PR CReSD study (Florida-Puerto Rico collaboration to reduce stroke disparities). *Stroke* 2016; 47(10): 2618–2626.
  17. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol* 2008; 7(10): 915–926.
  18. Gatttringer T, Ferrari J, Knoflach M, et al. Sex-related differences of acute stroke unit care: results from the Austrian stroke unit registry. *Stroke* 2014; 45(6): 1632–1638. DOI: 10.1161/STROKEAHA.114.004897.
  19. Strong B, Lisabeth LD and Reeves M. Sex differences in IV thrombolysis treatment for acute ischemic stroke: a systematic review and meta-analysis. *Neurology* 2020; 95(1): e11–e22.
  20. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; 274(13): 1017–1025.
  21. Carcel C, Woodward M, Balicki G, et al. Trends in recruitment of women and reporting of sex differences in large-scale published randomized controlled trials in stroke. *Int J Stroke* 2019; 14(9): 931–938.
  22. Spaander FH, Zinkstok SM, Baharoglu IM, et al. Sex differences and functional outcome after intravenous thrombolysis [published correction appears in *Stroke*. 2017 Mar;48(3): e97]. *Stroke* 2017; 48(3): 699–703.
  23. Kent DM, Price LL, Ringleb P, et al. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. *Stroke* 2005; 36(1): 62–65.
  24. Dula AN, Mlynash M, Zuck ND, et al. Neuroimaging in ischemic stroke is different between men and women in the DEFUSE 3 cohort. *Stroke* 2020; 51(2): 481–488.
  25. Stroebele N, Müller-Riemenschneider F, Nolte CH, et al. Knowledge of risk factors, and warning signs of stroke: a systematic review from a gender perspective. *Int J Stroke* 2011; 6(1): 60–66.
  26. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013; 369(1): 11–19.
  27. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2013; 2013(9): CD000197. Published 11 September 2013.
  28. Colsch R and Lindseth G. Unique stroke symptoms in women: a review. *J Neurosci Nurs* 2018; 50(6): 336–342. DOI: 10.1097/JNN.0000000000000402. PMID: 30334864.
  29. Tate J and Bushnell C. Pregnancy and stroke risk in women. *Womens Health (Lond)* 2011; 7(3): 363–374.
  30. Swartz RH, Cayley ML, Foley N, et al. The incidence of pregnancy-related stroke: a systematic review and meta-analysis. *Int J Stroke* 2017; 12(7): 687–697.
  31. Poorthuis MH, Algra AM, Algra A, et al. Female- and male-specific risk factors for stroke: a systematic review and meta-analysis. *JAMA Neurol* 2017; 74(1): 75–81.
  32. Petitti DB, Sidney S, Quesenberry CP Jr, et al. Incidence of stroke and myocardial infarction in women of reproductive age. *Stroke* 1997; 28(2): 280–283. DOI: 10.1161/01.str.28.2.280.
  33. Ban L, Sprigg N, Abdul Sultan A, et al. Incidence of first stroke in pregnant and nonpregnant women of childbearing age: a population-based cohort study from England. *J Am Heart Assoc* 2017; 6(4): e004601. Published 27 April 2017.
  34. Westerlund E, Brandt L, Hovatta O, et al. Incidence of hypertension, stroke, coronary heart disease, and diabetes in women who have delivered after in vitro fertilization: a population-based cohort study from Sweden. *Fertil Steril* 2014; 102(4): 1096–1102. DOI: 10.1016/j.fertnstert.2014.06.024.
  35. Leffert LR, Clancy CR, Bateman BT, et al. Hypertensive disorders and pregnancy-related stroke: frequency, trends, risk factors, and outcomes. *Obstet Gynecol* 2015; 125(1): 124–131.
  36. Lamy C, Hamon JB, Coste J, et al. Ischemic stroke in young women: risk of recurrence during subsequent pregnancies. French Study Group on Stroke in Pregnancy. *Neurology* 2000; 55(2): 269–274.
  37. Fischer-Betz R, Specker C, et al. Pregnancy outcome in patients with antiphospholipid syndrome after cerebral ischaemic events: an observational study. *Lupus* 2012; 21(11): 1183–1189.
  38. James AH, Bushnell CD, Jamison MG, et al. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol* 2005; 106(3): 509–516.

39. Bhogal P, Aguilar M, AlMatter M, et al. Mechanical thrombectomy in pregnancy: report of 2 cases and review of the literature. *Interv Neurol* 2017; 6(1–2): 49–56.
40. Watanabe TT, Ichijo M and Kamata T. Uneventful pregnancy and delivery after thrombolysis plus thrombectomy for acute ischemic stroke: case study and literature review. *J Stroke Cerebrovasc Dis* 2019; 28(1): 70–75.
41. Gillum LA, Mamidipudi SK and Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA* 2000; 284(1): 72–78.
42. Roach RE, Helmerhorst FM, Lijfering WM, et al. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev* 2015; 2015(8): CD011054. Published 27 August 2015.
43. Ryan KA, Cole JW, Saslow K, et al. Prevention opportunities for oral contraceptive-associated ischemic stroke. *Stroke* 2014; 45(3): 893–895.
44. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol* 2016; 1(7): 767–776.
45. Lisabeth LD, Beiser AS, Brown DL, et al. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. *Stroke* 2009; 40(4): 1044–1049.
46. Ingelsson E, Lundholm C, Johansson AL, et al. Hysterectomy and risk of cardiovascular disease: a population-based cohort study. *Eur Heart J* 2011; 32(6): 745–750.
47. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288(3): 321–333.
48. Renoux C, Dell'aniello S, Garbe E, et al. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010; 340: c2519.
49. Canonico M, Carcaillon L, Plu-Bureau G, et al. Postmenopausal hormone therapy and risk of stroke: impact of the route of estrogen administration and type of progestogen. *Stroke* 2016; 47(7): 1734–1741.
50. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; 376(9735): 112–123.
51. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998; 98(10): 946–952.
52. Emdin CA, Wong CX, Hsiao AJ, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016; 532: h7013.
53. Peters SAE, Carcel C, Millett ERC, et al. Sex differences in the association between major risk factors and the risk of stroke in the UK Biobank cohort study. *Neurology* 2020; 95(20): e2715–e2726.
54. Thompson LE, Maddox TM, Lei L, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the national cardiovascular data registry (NCDR®) PINNACLE registry. *J Am Heart Assoc* 2017; 6(7): e005801.
55. Sullivan RM, Zhang J, Zamba G, et al. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). *Am J Cardiol* 2012; 110(12): 1799–1802.
56. Pancholy SB, Sharma PS, Pancholy DS, et al. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am J Cardiol* 2014; 113(3): 485–490.
57. Peters SA, Huxley RR and Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke* 2013; 44(9): 2394–2401.
58. Thoenes M, Neuberger HR, Volpe M, et al. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. *J Hum Hypertens* 2010; 24(5): 336–344.
59. Lloyd-Jones DM, Evans JC and Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005; 294(4): 466–472.
60. Wassertheil-Smoller S, Anderson G, Psaty BM, et al. Hypertension and its treatment in postmenopausal women: baseline data from the Women's Health Initiative. *Hypertension* 2000; 36(5): 780–789.
61. Gu Q, Burt VL, Paulose-Ram R, et al. Gender differences in hypertension treatment, drug utilization patterns, and blood pressure control among US adults with hypertension: data from the National Health and Nutrition Examination Survey 1999–2004. *Am J Hypertens* 2008; 21: 789–798.
62. Strazzullo P, D'Elia L, Cairella G, et al. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. *Stroke* 2010; 41(5): e418–e426.
63. Saito I, Iso H, Kokubo Y, et al. Body mass index, weight change and risk of stroke and stroke subtypes: the Japan Public Health Center-based prospective (JPHC) study. *Int J Obes (Lond)* 2011; 35(2): 283–291.
64. Asplund K, Karvanen J, Giampaoli S, et al. Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. *Stroke* 2009; 40(7): 2319–2326.
65. Rist PM, Buring JE, Kase CS, et al. Healthy lifestyle and functional outcomes from stroke in women. *Am J Med* 2016; 129(7): 715–724.e2.
66. Peters SA, Huxley RR and Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 2014; 383(9933): 1973–1980.

67. Dinesh Shah A, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of a wide range of cardiovascular diseases: a cohort study in 1·9 million people. *Lancet* 2015; 385(suppl 1): S86.
68. Schürks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009; 339: b3914.
69. US Congress. *National Institutes of Health Revitalization Act of 1993: Act to Amend the Public Health Service Act to Revise and Extend the Programs of the National Institutes of Health, and for other Purposes*. Public Law 103-43. Washington: US Congress, 1993.
70. Cordonnier C, Sprigg N, Sandset EC, et al. Stroke in women—from evidence to inequalities. *Nat Rev Neurol* 2017; 13(9): 521–532. DOI: 10.1038/nrneurol.2017.95.