Stroke in women — from evidence to inequalities

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All authors helped research data for this Review and made substantial contribution to the discussion of the content. C.C., N.S., E.S., A.P., K.S., V.C. and H.C. wrote the article. C.C., N.S., E.S. and H.C. reviewed and/or edited the manuscript before submission.

Competing interests statement

The authors declare no competing interests.

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Abstract

Stroke is the second largest cause of disability-adjusted life-years worldwide. The prevalence of stroke in women is predicted to rise rapidly, owing to the present increase in the global elderly [aging rather than elderly?] female population. Vascular risk factors differ between women and men in terms of prevalence, but evidence also increasingly supports the clinical importance of sex differences in stroke. The influence of some risk factors for stroke — including diabetes mellitus and atrial fibrillation — are stronger in women, and hypertensive disorders of pregnancy also affect the risk of stroke decades after pregnancy. However, in an era of evidence-based medicine, women are notably underrepresented in clinical trials — despite governmental actions highlighting the need to include both men and women in clinical trials — resulting in reduced generalizability of study results to women. The aim of this Review is to highlight new insights into specificities of stroke in women, to plan future research priorities and to influence public health policies to decrease the worldwide burden of stroke in women.

Key points

- Hypertension and atrial fibrillation are more frequent in women than in men.
- The effect of some risk factors — including diabetes mellitus and atrial fibrillation — are stronger in women than in men
- Hypertensive disorders of pregnancy are important causes of stroke in pregnancy, with intracerebral haemorrhage being the leading cause of maternal death.
- Women are underrepresented in clinical trials despite governmental actions highlighting the need for inclusive and nondiscriminatory trials that include both men and women
- Women are more difficult to include in stroke trials than men, because they tend to be older at stroke onset have more comorbidities, and tend to live alone.
- Women living in societies with low access to education and hence to adequate healthcare have especially little awareness of stroke

Box 1 **| Areas for development:**

1. Data regarding stroke in women should be collected in all countries in order to develop specific actions tailored to each society structure and healthcare system.
2. Major sex differences in presentation and the effect of risk factors suggest a possible benefit from personalized medicine —including investigation and treatment — for women with stroke.
3. Early detection and treatment of hypertensive disorders of pregnancy (HDP) should be promoted. A clear understanding of the aetiology of HDP could lead to the development of preventative strategies.
4. Future studies assessing hormone replacement therapy early after menopause should focus on robust clinical endpoints to personalize stroke treatment based on women's individual risk of stroke.
5. More evidence is urgently required regarding the effects of treatment interventions in elderly women with stroke, particularly in stroke related to atrial fibrillation, and how these interventions influence cardiovascular outcomes in women.
6. Data are needed on the incidence of inherited thrombophilia and prevention of cerebral venous thrombosis in individuals at a high risk of these conditions. Randomized controlled trials or high quality registry data are needed to better assess therapeutic interventions.
7. Large-scale cohort studies into the risk factors for intracerebral haemorrhage in women are required to confirm whether women have worse outcome following intracerebral haemorrhage than do men, independent of age and premorbid functional status, and whether this association is related to a difference in care.
8. Educational campaigns for stroke awareness in women should include stroke symptoms and time-dependent therapeutic options, and should be tailored to different societal models worldwide.
9. Enrolment age limits for randomized controlled trials should be avoided, and enrolment should instead mirror the sex distribution of the disease being investigated.
10. Barriers to access to care and rehabilitation in women should be identified and addressed to provide equal access to both sexes.

In 2015, stroke became the second largest cause of disability-adjusted life-years worldwide, behind ischaemic heart disease[1]. With an anticipated increase in the average age of the female population worldwide , the prevalence of stroke in women is projected to rapidly increase, particularly among elderly women, leading to challenges for healthcare systems[2]. Stroke is not only a leading cause of disability, but is also a leading cause of death worldwide — particularly in women, in whom mortality due to stroke consistently exceeds that in men. The WHO reported an excess of total stroke-related deaths among women compared with men, of which 60% occurred in those aged over 75 years[3].

Women differ from men in a multitude of ways, including anatomy, vascular biology, immunity, neuroprotective factors, hormonal profiles, vascular risk factors, and lifestyle factors and societal roles. All of these factors might influence the risk of stroke and affect prognosis[4]. The aim of this Review is to highlight new insights into specificities of stroke in women, to plan future research priorities and to influence public health policies to decrease the burden of stroke on women worldwide.

[H1] Epidemiology

In 2009, a review of 56 population-based studies from high-income countries revealed a 42% decrease in worldwide stroke incidence rates from 163 per 100,000 person–years in 1970–1979 to 94 per 100,000 person–years in 2000–2008. A faster decline in incidence was observed in men than in women[5]. Data from the Framingham Heart Study also suggested that one in five women and one in six men who reach the age of 55 years free from stroke will develop a stroke event during their remaining lifetime[6].

A meta-analysis of individual participant data from high-quality stroke incidence studies confirmed that women consistently have greater long-term mortality than do men after stroke, regardless of study location and time period. In women, advanced age, more-severe strokes, worse prestroke function, and the presence of atrial fibrillation contributed to a greater mortality after stroke compared with men [7].

The quality and the availability of data regarding stroke in women is highly heterogeneous between countries. Rigorous evaluation of the epidemiology of stroke among women is difficult in some regions of the world[8]. The data on case fatality of stroke provide evidence for considerable variation among countries, even when studies with strict criteria for inclusion are focussed on[9]. Ethnicity could contribute to this variation, but little data exist on this topic, especially regarding the potential for sex differences to be influenced by ethnicity. Women

from some countries might be excluded from epidemiological data because they are not admitted to hospital, or because ascertainment and diagnosis patterns might be different in men compared with women[2]. Moreover, data from the GBD 2013 study highlighted that women are unequal to men when suffering from stroke throughout the world: in some regions of the world mortality due to stroke is higher in women than in men . This inequity is strongly associated with socioeconomic status: the majority of the countries where women had higher stroke mortality rates than men were developing countries and/or underwent negative historical events, such as natural disaster or war, within the past few years [2]. Consequently, data on incidence and case fatality of stroke in women should be collected in all countries to develop specific actions to address this issue that are tailored to each society structure and healthcare system.

[H1] Specific risk factors of ischemic stroke

Evidence increasingly shows that risk factors for stroke differ between men and women: frequencies of vascular disease vary between the sexes and some risk factors are specific to women. Stroke onset is later in women than in men, and rates of hypertension (60% versus 56%) and atrial fibrillation (24% versus 22%) are higher in women than in men. Conversely, rates of diabetes mellitus (16% versus 20%) and smoking (15% versus 16%) are higher in men than in women[10]. Differences in smoking rates are decreasing between sexes, but smoking still has a male preponderance[11].

Some female-specific characteristics increase the risk of stroke, including gestational hypertension (relative risk (RR) 1.51; 95% CI 1.27–1.80), oophorectomy (RR 1.42; 95% CI 1.34–1.50), preterm delivery (RR 1.62; 95% CI 1.46–1.79), and still birth (RR 1.86; 95% CI 1.15–3.03), whereas hysterectomy is possibly protective against stroke (RR 0.88; 95% CI 0.85–0.90)[12]. Furthermore, the effect of some individual risk factors seems to be stronger in women than in men. Atrial fibrillation is associated with double the risk of stroke in women compared with the risk in men (RR 1.99; 95% CI 1.46–2.71) [13]. In a study based on 12,701 patients with cardio-embolic strokes, women with atrial fibrillation underwent more-severe strokes than men (median NIH Stroke Scale 14 versus 8)[14]. The excess risk of stroke from diabetes mellitus is higher in women than in men: RR 2.28 (95% CI 1.93–2.69) versus 1.83 (95% CI 1.60–2.08)[15]. This result is in line with findings in metabolic syndrome in which women in a large scale meta-analysis had a larger risk of stroke (with an RR of 1.83; 95%CI:

1.31–2.56) than men (RR 1.47; 95%CI 1.22–1.78)[16]. Data on abdominal obesity also suggest a stronger effect on stroke risk among women than men[17].

Other risk factors have the same effect in men and women. A systematic review and meta-analysis based on 1.2 million individuals concluded that the effect of systolic hypertension [18] or increased total cholesterol[19] was equal in men and women. Evidence is inconclusive with regard to why certain risk factors have a stronger effect on women than men. Suggested explanations include the under-treatment of women, and physiological differences between the sexes[13, 20]. The different burden of risk factors in both sexes needs to be thoroughly explored to personalize prevention and treatment. In this regard, screening programs or interventions for type 2 diabetes mellitus or atrial fibrillation in women could carry considerably more benefit compared with those in men.

[H1] Three periods of stroke risk in women

Risk of stroke differs throughout the lifecourse. Here we will examine the factors associated with increased stroke risk in women at three stages of life: women of child-bearing age, postmenopause women and women over 80 years of age.

[H2] Child-bearing age

[H3] Oral contraceptives. Hormonal contraception is common and its use is increasing: four of five sexually active women have taken the oral contraceptive pill in the USA[21]. Worldwide use of the oral contraceptive pill varies considerably between regions, from less than 10% of total anticonception use in developing countries to more than 25% in Europe [22]. A 2015 meta-analysis showed that combined hormonal contraception increased the risk of stroke 2.47-fold (95% CI 2.04–2.99). Low dose estrogen was associated with a reduced stroke risk, whereas the type of progesterone was not associated with stroke risk. No excess risk was observed in gestagen-only formulations[23]. A 1.7-fold (95% CI 1.5–1.9) increase in risk of stroke resulting from combined oral contraceptives was found in a systematic review[24]. Despite the fact that crude incidence of stroke in relation to hormonal contraceptives is very low (the crude incidence rate of ischaemic stroke was 21.4 per 100,000 person–years)[25], the observed increase in risk remains important as other modifiable risk factors might exist in healthy women. However, study findings underline that hormonal contraception is a very rare cause of ischaemic stroke and should be considered as such in clinical care.

[H3] Pregnancy. The increased risk of stroke in pregnancy is well recognized, particularly around the time of delivery. Reported rates of stroke incidence vary from 2.5–34 cases per 100,000 deliveries[26]. The rate of stroke increases ninefold at the time of delivery and threefold in the early postpartum period, with an increase in both ischaemic and haemorrhagic stroke.

Hypertensive disorders of pregnancy (HDP) (FIG. 1), a spectrum that includes gestational hypertension (blood pressure>140/90mmHg), pre-eclampsia (hypertension with proteinuria) and eclampsia (seizures) are a leading cause of maternal and perinatal morbidity and mortality worldwide[1]. The exact aetiology is unclear. Although only 1% of patients with pre-eclampsia undergo a stroke, pre-eclampsia is the most common cause of stroke in pregnancy[27] (FIG. 1). However, the effects of HDP persist beyond pregnancy, resulting in increased vascular disease[28] and mortality later in life[29]. Women with HDP are usually unaware of the long-term cardiovascular risks of this condition and long-term follow-up should be encouraged[30].

Intracranial haemorrhage is the leading cause of maternal death[31] and the majority of haemorrhages are due to HDP[32]. Management of pre-eclampsia and intracerebral haemorrhage (ICH) in pregnant women should focus on rapid, aggressive, blood pressure control in combination with delivery of the baby as soon as possible[33]. Notably, pregnant women with haemorrhagic stroke are younger, have fewer comorbidities and have a better outcome than nonpregnant women with haemorrhagic stroke[34]. Other neurological syndromes, such as reversible cerebral vasoconstriction syndrome — an important cause of pregnancy-associated stroke[36] —and posterior reversible encephalopathy can occur as a consequence of HDP[35] (FIG. 3).

Unenhanced CT remains the standard first-line imaging technique for the investigation of suspected stroke in pregnancy in many medical centres worldwide, but early use of MRI can distinguish between stroke and other neurological conditions[37]. In the context of HDP and neurological symptoms, MRI can help to differentiate permanent lesions (resulting from cytotoxic oedema) versus reversible lesions (resulting from vasogenic oedema) . Moreover, MRI enables assessment of intracranial vessels to diagnose reversible cerebral vasoconstriction syndrome.

Until the past few years, reports of use of thrombolysis and other reperfusion strategies had been limited to small case reviews, with uncertainty surrounding the use of thrombolysis in pregnancy. Although alteplase does not cross the placenta, some concerns surround the

use of this drug in pregnancy, particularly regarding the potential for placental haemorrhage. In the large US Stroke Registry 'Get with the Guidelines', pregnant women with ischaemic stroke, were less likely to receive thrombolysis with alteplase (4.4%) than were nonpregnant women (7.9%, *P* = 0.03) despite significantly greater stroke severity in pregnant women. In pregnant or postpartum patients who were treated with alteplase, no increase in systemic bleeding was detected, but a nonsignificant increase in the risk of symptomatic ICH was found[38]. Notably, the majority of stroke related to pregnancy occurred during the postpartum period[39]. Use of intra-arterial therapy for ischaemic stroke has been reported in a number of case series, and could be preferable to thrombolysis when the risk of maternal haemorrhage is high[40].

The presence of a patent foramen ovale in pregnancy is associated with increased risk of stroke in individuals with prothrombotic risk factors — including activated protein C resistance and reduced blood levels of protein S. However, in contrast to other stroke risk factors, risk of stroke owing to a patent foramen ovale peaks during the first and second trimesters of pregnancy. Pregnant women with hypercoagulable states should be considered for antithrombotic therapy with low-molecular-weight heparin, but patent foramen ovale is not a barrier to normal healthy delivery[41].

In conclusion, to promote early detection of HDP, patients should undergo aggressive treatment of high blood pressure and management of conventional risk factors before, during, and after pregnancy. A clearer understanding of the aetiology of HDP could lead to development of preventative strategies for this condition. Prospective registries are necessary to evaluate treatment strategies (such as thrombolysis and endovascular reperfusion) as randomized controlled trials are probably unfeasible.

[H3] Menopause and hormonal replacement therapy. The burden of risk factors for vascular dysfunction increases in woman after the menopause[42] — presumably owing to the postmenopausal decrease in estrogen, a hormone with vascular-protective properties. This assumption is consistent with the finding that early menopause increases the risk of stroke. According to a meta-analysis of 310,329 women from 32 observational studies, onset of the menopause before the age of 45 years increases the relative risks of overall coronary heart disease (RR 1.50; 95% CI: 1.28–1.76), overall stroke (RR 1.11; 95% CI 1.03–1.20), cardiovascular mortality (RR 1.19; 95% CI 1.08–1.31), and all-cause mortality (RR 1.12; 95% CI 1.03–1.21)[43].

Hormone replacement therapy (HRT) is thought to be vasoprotective, owing to the protective properties of estrogen; however, this hypothesis has not been confirmed . A pooled analysis of results from randomized controlled trials (RCTs) of stroke prevention from the past two decades has even suggested a 30% increase in the risk of stroke in women who receive HRT[44], in contrast to the apparent protection of HRT against cardiovascular disease that has been found in large observational trials[45]. A higher risk of stroke is associated with a longer duration of continuous use of HRT. After 3 years of HRT use, the risk of stroke increases from 6 per 1000 to 12 per 1000 treated women. After 7 years of HRT use, risk of stroke increased to 25–40 per 1000 women[46].

Results from observational and interventional studies of HRT differed considerably. In the observational studies, HRT was generally initiated in relation to the onset of menopause, whereas women in RCTs were often enrolled a decade or later after menopause. This discrepancy has led to the formation of the 'timing hypothesis', which proposes that HRT has differing effects on the cardiovascular system at different ages and stages of cardiovascular health. Potential vascular protective effects of estrogen include beneficial effects on the vascular endothelium and on cardiovascular disease risk factors[47]. Estrogen has been hypothesized to have a beneficial role in early atherogenesis and an adverse role later in the disease course[48]. This idea has led to studies investigating cardiovascular health in women early after menopause, with a focus on atherogenesis as an endpoint. However, a substantial effect of HRT on increase in carotid artery intima–media thickness (CIMT) was not documented: initiation of HRT 6–36 months after last menses did not affect CIMT compared with placebo during a 48-month follow-up[49].

In the ELITE (Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol) trial, HRT initiated within 6 years after menopause yielded a significantly smaller increase in CIMT after 5 years follow-up than did initiation of HRT 10 years or later after menopause, independent of progesterone treatment[50]. These data suggest that early initiation of HRT could have a lower risk of stroke than later initiation.

A nested case–control study undertaken in France also examined the risk of transdermal HRT in women aged 51–62 years. No association was found between ischaemic stroke and use of progesterone (OR 0.78; 95% CI 0.49–1.26), pregnanes (OR 1.00; 95% CI 0.60–1.67), or nortestosterones (OR 1.26; 95% CI 0.62–2.58), whereas norpregnanes increased the risk of ischaemic stroke (OR 2.25; 95%CI 1.05–4.81)[51]. These results are consistent with a previous case-nested control study that found no increased risk of stroke with transdermal

HRT[52]. Future studies assessing HRT early after menopause should focus on robust clinical endpoints to personalize treatment based on individual risk.

[H3] Women aged over 80 years. Elderly women represent a large proportion of the total stroke population and have more-severe strokes[53], poorer outcome [54-56], and more-limited access to care[57] than other demographics. Secondary prevention is far from optimal in this high-risk group: elderly women have a decreased likelihood of having adequate blood pressure control after stroke[58], being treated with antithrombotic drugs, and receiving anticoagulation treatment when found to have atrial fibrillation[56]. Management of atrial fibrillation is crucial if we are to decrease the burden of stroke among elderly women, but data on this issue remain insufficient and conflicting[59, 60]. One study found that women had an increased risk of stroke and a reduced quality of life compared with men, despite similar anticoagulation use.[61]. The paucity of data from RCT among elderly women could contribute to these findings; consequently, more research into stroke in elderly women is urgently required. Future studies should focus on how treatment and interventions affect quality of life and cardiovascular outcomes related to atrial fibrillation in women.

[H2] Psychosocial factors and depression

An increased risk of stroke risk has inconsistently been reported in individuals exposed to various psychosocial stressors. Psychosocial factors can include psychological, behavioural, vocational, and interpersonal processes that may be associated with social disruption, social status and integration. A meta-analysis of 10,130 incidences of stroke found that people with perceived psychosocial stress (defined as self-reported sensation of tension, irritability, nervousness, anxiety or sleeplessness)**]** , exposure to general or work stress or who experienced stressful life events (such as loosing a job) had an increased risk of stroke (1.33; 95% CI 1.17–1.50), and this increase in risk was higher in women than in men[62]. The Chicago Health and Aging Project assessed psychosocial distress as a composite measure of depressive symptoms, perceived stress, neuroticism, and life dissatisfaction, and reported that a high distress score in elderly individuals was associated with an increased risk of death resulting from stroke, after adjustment for age, race and sex. In this population, women reported higher distress scores than did men[63].

Depression is a documented risk factor for stroke and research has suggested a 'dose-dependent' association between higher stroke risk and higher severity of depression [64]. An

analysis based on a nationwide sample from Denmak reported that depression was predictive of stroke (OR 1.22, 95% CI 1.08–1.38), and that the effect of depression on stroke was higher in men than in women (the difference in OR between men and women was 1.30; 95% CI 1.01–1.68)[65]. Depression could be associated with an increased risk of stroke through a variety of mechanisms. Depression has known neuroendocrine effects (such as dysregulation of the hypothalamic–pituitary–adrenocortical axis and dysfunction of platelet aggregation)[66], and immunological or inflammatory effects[67]. Moreover, depression can be associated with poor health behaviours that might increase stroke risk: in a cohort of more than 80,000 nurses in the USA, women with depression were more likely to be single, had a higher body mass index, were more likely to smoke cigarettes, and were less likely to be physically active[44]. Whatever the mechanisms are, the idea that women with depression could have an increased risk of stroke deserves more recognition. Further research is necessary to determine whether the risk associated with depression can be reduced by specific interventions. The role of negative historical events (such as war or tsunami) on the risk of stroke and the mechanisms of these effects among women should be further documented.

A meta-analysis of prospective cohort studies showed that women with high strain jobs had higher risk of stroke than women with low strain (RR 1.33, 95% CI 1.04–1.69); however, this difference was not observed in men[68]. High psychological demands, low job control, and job strain were all associated with an increased risk of stroke among working women[69]. However, the data are scarce and conflicting, and the influence of cultural habits (for example on whether there is a share of daily responsablities at home) has not been explored[70].

Socioeconomic status has also been associated with stroke risk. In a nation-wide study from Denmark, the lowest-income group had double the risk of stroke compared with the highest-income group[71]. No sex differences were reported in this study, despite the fact that the women more often had low income, only basic education and were older than the men studied[72]. Moreover, low education, consistently low income and consistent financial strain predicted increasing carotid intima–media thickness in a cohort of women, even after adjustment for standard cardiovascular risk factors[73].

Living alone increases the risk of dying from stroke in men (HR 3.47; 95% CI 2.13–5.65), but not in women before the age of 70 years[74]. Men also seem to be more vulnerable to unemployment as a stressor, compared with women[75]. With regards to ambient stressors,

pollution has been reported only to affect the risk of stroke in women, but not in men, and has an increased effect on women with obesity[76].

[H1] Cerebral venous thrombosis

Cerebral venous thrombosis (CVT) has a female preponderance of 75%[77], with a 68% preponderance of female patients reported in isolated cortical vein thrombosis[78]. The sex distribution of CVT has shifted over time towards a larger proportion of affected women[79], possibly owing to increased use of hormonal contraception by women. The 65% of women with stroke who have sex-specific risk factors (such as use of hormonal contraception, pregnancy, postpartum risk factors, and use of hormone replacement therapy) have much better prognosis after CVT than other women and men [77], although differences in recanalization rates have not been observed[80]. Women more often have headache at the onset of CVT, and less often a head or neck infection[81]. Hormonal contraception remains the most frequent single risk factor for CVT, and doubles the risk of any venous thromboembolism (that is, CVT, deep vein thrombosis or pulmonary embolism)[82]. The risk of CVT increases in pregnancy, with most cases occurring during the postpartum period, and risk factors include caesarean section, dehydration and dural puncture after anaesthesia**.** CVT occurring early in pregnancy is often due to inherited thrombophilias. Treatment with low–molecular-weight heparin is recommended as the safest option during pregnancy and the puerperium[83]. In women with previous CVT, the absolute risk of pregnancy-related CVT was one of 217 pregnancies together with a risk of noncerebral venous thromboembolism (VTE) of one of 37 pregnancies[83]. The risk of CVT is acceptably low in the case of a subsequent pregnancy with access to good care; however, the risk of other VTE is high and prophylaxis should be considered. Data are needed on the incidence of inherited thrombophilia and prevention of CVT in high-risk patients. RCTs or high-quality registry data are needed to better assess interventions. Similarly to many other rare conditions, guidelines are key for homogenizing the management of CVT in women worldwide.

[H1] Haemorrhagic strokes

Data are limited regarding sex differences in spontaneous ICH. Available data are based mostly on single centre hospital registries, and differences across the populations — such as age, ethnicity and location — might contribute to the inconsistent results that are observed. Independent of age and stroke severity, women with ICH are treated less aggressively than

men. Do-not-resuscitate orders are more common for women[84] and women are less-likely to be admitted to intensive care units[85].

Although data are inconsistent, women seem to have a worse prognosis than men overall. Studies have found that women have an increased risk of dependency as an end-point[86], and an increased risk of the combined end-point of death or dependency[85]. However, a meta-analysis from 2010 that was based on 4,658 patients with ICH recruited before the year 2000 found no difference in mortality between men and women [87]. Case fatality ranged from 16–52% in women and 19–48% in men. Similar results have also been seen in subsequent studies[85]. Nevertheless, other studies have reported an overall lower[88, 89] or of higher risk of death in women than in men[90].

ICH outcome in women versus men is influenced by age[91], prestroke functional status and stroke severity[86]. Evidence increasingly suggests that sex-specific effects of genetic polymorphisms could play a part in sex differences in both the risk and outcome of ICH[92].

Hematoma location might also differ across sexes. In a prospective hospital registry of 515 patients with ICH in Spain, lobar hematoma location was more common in women (age-adjusted OR 1.75, 95% CI 1.18–2.58)[85]. No sex differences in cerebral amyloid angiopathy or hypertension were detected at baseline, suggesting explanations other than aetiology[85]. Despite the association with outcome, no sex differences in haematoma volume or expansion have been identified; however, women might have less perihaematomal oedema than men have [93].

No efficient acute treatment currently exists for ICH[94]. Trials have been neutral, male-dominated and most have not reported subgroup analysis according to sex. The most promising treatment has been acute and intensive lowering of blood pressure [95]. A small trial suggested an association between a faster rate of blood pressure decline and mortality in men, but not in women[96]; however, large-scale clinical trials have not shown differential effects of blood-pressure-lowering treatment in subgroups according to sex[95, 97]. Large-scale cohort studies are required to identify specific risk factors for ICH in women. Data are also needed to confirm whether women have a worse outcome following ICH than men — independent of age and premorbid functional status — and whether this difference is related to difference in care.

[H1] Long-term consequences

Research has indicated that intravenous thrombolysis is less-effective on functional outcome after stroke in women than in men, even after adjustment for age[98]. Consequently, women are more likely to be discharged with more severe neurological deficits than men. In a Dutch study of young patients with ischaemic stroke (aged 18–50 years), women had a twofold to threefold higher risk of a poor functional outcome than men during 13 years of follow up[99]. Other studies have shown no such difference[100], and extrapolation of results is difficult as confounding factors such as access to acute care or rehabilitation should also be taken into account.

Return to work after stroke is an important factor for overall life satisfaction in younger men and women [101]. Nevertheless, in Sweden, men are more likely to be unhappy than women if they cannot return to work[102], and data from Australia[103] and Denmark[104], suggest that women are less likely to return to work than men. Stroke severity is not the only factor that predicts the return to work after stroke: work characteristics (such as manual work, demands of flexibility at work) and national healthcare policies, which differ drastically across countries, are also important. The duration of official sick-leave is one example.

Suicide after stroke might reflect the effect of the stroke on the life situation of the individual. A study from Sweden indicated that young men were more likely to attempt suicide than were women[105], in contrast to an earlier Danish study in which women had a higher risk of suicide[106]. However, in both these studies, people aged below 50 were more at risk than older individuals.

Although no evidence currently supports sex disparities in cognition after stroke (ref), women are at an increased risk of neurodegenerative dementia[107] because stroke onset occurs at an older age in women than in men. The occurrence of stroke has a substantial effect on the absolute risk of dementia in the general population; therefore, the prevention of stroke could reduce the rate of dementia[108]. However, the older age at stroke and higher prevalence of mood symptoms after stroke in women could affect cognitive performances directly[109]. Studies have reported a lower quality of life in women after stroke, but despite the fact that rates of fatigue after stroke seem higher in women than in men, this trend disappears when age is adjusted for in a population-based setting[110-112]. More knowledge of the so-called invisible handicaps (cognitive impairment, lack of initiative, extreme fatigue) after stroke is needed, particularly regarding the possible sex disparities that are not explained by age .

[H1] Stroke symptoms and risks

Prompt recognition of stroke symptoms is crucial for timely treatment. Women have a longer delay to treatment[113], arrive later to hospitals, and receive less frequently acute stroke treatment and diagnostic investigation than men[114, 115]. Reasons for these delays are unclear, although they might be due in part to sex-related differences in clinical presentation and differences in patients' knowledge of stroke and response to symptoms[55].

Several studies have sought to evaluate knowledge of stroke symptoms and risk factors by the general population, but few have focused on sex differences. Women have been reported to possess a better knowledge of major stroke symptoms and stroke risk factors than men[116]. Moreover, women tend to learn from health behaviour and stroke campaigns independently of their educational background. One hypothesis may be that women have greater interests in health topics than men.

Despite a better awareness of stroke, women are less likely to call an ambulance for themselves and are more likely to have an unknown time of stroke onset than are men[117]. These differences remain after adjustment for age, residence or socioeconomic level — factors known to be associated with a more appropriate response to stroke[118]. This gap between knowledge and health behaviour is possibly due to societal factors. Specifically, women with stroke in low-income countries tend not to be admitted to hospitals[8]. Absence of universal health-care systems — as well as a lack of stroke units, stroke care pathways and stroke guidelines — makes treatment more difficult to deliver in women . Moreover, obstacles to access of education and therein to adequate healthcare created by some societies lead to inequities of care independently from the knowledge of stroke symptoms. [8].

Improved control of risk factors for stroke, better treatment, and implementation of specific stroke guidelines for women are needed to reduce stroke incidence in women; these initiatives will be complimented by stroke awareness programs, such as the "I am woman" campaign by the World Stroke Organisation. This campaign focussed on the burden of stroke among women and the responsibility of being the primary caregiver for a family member recovering from a stroke. [44, 119]. Specific campaigns regarding stroke in women are needed that include instructions on stroke symptoms and information on time-dependent therapeutic options. These campaigns need to be tailored to different societal models worldwide.

[H1] Inclusion in clinical trials

To date, most RCTs and meta-analyses on the use of antithrombotic agents in cerebrovascular disease have neither performed subanalyses on sex-related differences nor adequately represented women in their samples. One exception was the Women's Health Study, which showed that aspirin was effective in the primary prevention of ischaemic stroke among women, without a substantial increase in ICH[120]. On the other hand, the Men's Health Study reported that aspirin was effective among men in the primary prevention of myocardial infarct, but with a slight increase in the risk of ICH[121].

Healthcare authorities sought to rectify the low representation of women in clinical trials with the introduction of the NIH Revitalization Act in 1993, which urged for the inclusion of women in RCTs[122]. In 2005, the European Society of Cardiology and the European Medicines Agency recommended that there should be a meaningful representation of women in clinical trials[123]. In 2016, the Motion for a European Parliament Resolution on promoting sex equality in mental health and clinical research (2016/2096 (INI)) underlined the fact that clinical trials of pharmaceutical products on both men and women are necessary, and that these should be inclusive, nondiscriminatory and performed under conditions of equality and inclusion[124]. Unfortunately, the male:female ratio in stroke trials still does not reflect the real world demographics of stroke.

Trials from the past few years that focussed on non-vitamin K oral anticoagulants (NOACs) illustrate the current situation. NOACs were evaluated in seven RCTs, in which less than 40% of the people enrolled were women[125]. To correspond with epidemiological data, more than 50% of the patients in these RCTs should have been women: firstly, because female sex is recognized as a risk factor in the CHA2DS2-VASc-score for systemic embolism[126], and secondly because cardioembolic strokes have a higher fatality rate at 1 month poststroke in women than in men[127]. These seven RCTs did not report any sex differences concerning the safety and efficacy of the NOACs. However, the overall mean age of the included patients was 71.5 years, almost 4 years lower than the average age of women admitted for cardioembolic strokes[128].

Women might be more difficult to include in RCTs than men because they tend to be older at stroke onset, have more comorbidities, and are more likely to have pre-existing functional impairment. Moreover, they are more likely to live alone than are men. These factors might affect the availability of a representative who can give consent for treatment if they lack the capacity to give consent themselves. Social aspects also need to be considered: women

tend to be the caregivers in families, and in many societies decisions regarding women's health still depend on men. To foster the inclusion of women in clinical trials, age exclusions should be considered only in light of safety considerations and not as an arbitrary age cut-off. Indeed, trials often do not need to have an age restriction: instead, designs should include comorbidities or other health conditions to mirror the sex distribution of the disease investigated; therefore, trials must be adequately powered or use stratified randomization by sex to enable the investigation of sex differences in treatment efficacy.

[H1] Access to care

Across the globe, access to stroke care seems to be more difficult for women than men. Key treatments such as intravenous thrombolysis are less likely to be offered to elderly women than other demographics. Despite the fact that evidence indicates that older women benefit from thrombolysis as much as older men[129], women are more likely to be excluded from thrombolysis treatment (38%) than men (19%) if they are over 80 years of age[130].

Secondary prevention of stroke also seems to vary between men and women. Data come from different settings in a worldwide perspective. In a community setting in South America, men were more likely to receive adequate cardiovascular prevention than were women[131]. This finding was also reported in a primary care setting in northern Sweden, where women were less likely to receive statins than were men[132]. Whether secondary prevention of stroke in patients with atrial fibrillation differs between men and women remains unclear, and varies geographically. In Germany[133], women were less likely to receive adequate antithrombotic treatment than were men, whereas in Sweden[134], sex was not observed to have an effect on secondary treatment, but other socioeconomic factors did .

Data are lacking regarding access to rehabilitation after stroke, and a huge variability in access is observed across different countries and healthcare systems. For example, a comparison between specialized rehabilitation in Latvia and Sweden, showed that Latvian men were more likely to be admitted to rehabilitation than were Latvian women while in Sweden there was an equal access to rehabilitation among men and women [135]. This finding is in contrast to the UN Convention on the Rights of Persons with Disabilities, which highlights the vulnerability of women to disabilities[136]. Besides access to rehabilitation, women tend to be discharged from specialized rehabilitation units despite having a remaining need for support[137]. In developing countries, the situation regarding access to rehabilitation is

even more difficult: for example in sub-saharian Africa there is only one stroke unit. [138]. In summary, barriers for access to care and rehabilitation for women should be identified and equal access provided.

[H1] Conclusions

Stroke is the leading cause of death and disability in women, who have worse outcomes after stroke than do men. Risk factors differ between men and women and across age groups, and specific stroke subtypes are more common in women than in men.

Personalized medicine is needed to improve prevention and treatment of stroke in women. Little is known about the treatment and prognosis of stroke subtypes that are specific to women. Stroke is very prevalent in older women; however, women and especially older women are considerably underrepresented in clinical trials, resulting in a paucity of evidence in this group. Further research is needed to establish why outcomes are worse in women than in men, and to identify effective interventions to reduce the inequitable burden of stroke in women. In many countries, the position of women in society might influence their access to care, which could contribute to the poor outcome of women undergoing a stroke worldwide.

Figure 1 | **Hypertensive disorders of pregnancy**

Figure 2 | **Causes of stroke in pregnancy**

Figure 3 | **Hypertensive disorders of pregnancy are associated with a high risk of stroke.** A 38 years old woman was admitted for a first-ever generalized seizure with eclampsia at 27 weeks of gestation. The eclampsia was associated with a reversible posterior encephalopathy. **a** | An axial MRI fluid attenuation inversion recovery (FLAIR) sequence and apparent diffusion coefficient (ADC) cartography showing bilateral symmetrical posterior hyperintense lesions with increased ADC suggesting vasogenic oedema (arrows). No vessel irregularity was present at that time (image not shown). The patient underwent a caesarean section, and was treated with intravenous magnesium, enalapril, nicardipine and furosemide. On day 11, the patient presented with a left middle cerebral artery stroke. **b** | An axial MRI diffusion-weighted imaging sequence performed 2 hours after symptom onset with a large left hemispheric ischaemic stroke. NIH Stroke Scale Score was 7 and intravenous thrombolysis was not administered owing to the prior caesarean. Mechanical thrombectomy was performed but failed to achieve recanalization. **c** | A middle cerebral artery occlusion is visible on an axial view of the angiogram at the end of the endovascular procedure (arrow). The hypothesis of a paradoxal embolism was excluded, owing to the absence of patent foramen ovale and the absence of deep vein thrombosis. **d** | Severe vasoconstriction syndrome was present at the time of stroke, as illustrated by this coronal plane, CT angiogram, which shows a segmental and focal stenosis on the anterior circulation (arrow).

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