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Sex differences in cerebrovascular diseases

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Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-83251-473-3
DOI 10.3389/978-2-83251-473-3

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Sex differences in cerebrovascular diseases

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Citation

Kremer, C., Lorenzano, S., Kruuse, C., eds. (2023). *Sex differences in cerebrovascular diseases*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-83251-473-3

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frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 10 January 2023
DOI 10.3389/fneur.2022.1128177

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

RECEIVED 20 December 2022
ACCEPTED 28 December 2022
PUBLISHED 10 January 2023

CITATION
Kremer C, Lorenzano S and Kruuse C (2023) Editorial: Sex differences in cerebrovascular diseases. *Front. Neurol.* 13:1128177. doi: 10.3389/fneur.2022.1128177

Editorial: Sex differences in cerebrovascular diseases

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KEYWORDS

stroke, prevention, treatment, outcome, sex differences

Editorial on the Research Topic
Sex differences in cerebrovascular diseases

Sex difference in the occurrence, detection, and treatment of cerebrovascular disease is being increasingly recognized. Indeed, recent studies have focused on how the etiology, course, and outcome of cerebrovascular disease may differ in men and women (1). Moreover, the effectiveness and safety of primary prevention, acute treatments, and secondary prevention of stroke may be affected by factors related to sex (2). Continued attention and focused research on these differences will allow us to have a better insight into the underlying pathophysiological, socioeconomic, and organizational aspects and improve stroke outcomes for men and women. Unfortunately, a significantly lower number of women over the years have been included in clinical stroke trials, leading to a limited amount of evidence for many stroke treatments in women.

In the Research Topic, "*Sex Differences in Cerebrovascular Diseases*," clinical research and reviews on different aspects of epidemiology, prevention, treatment, and outcome in men and women with cerebrovascular diseases during their lifespan are presented. Regarding the reproductive lifespan of women, it has been shown that early menarche is associated with a higher percentage of cerebrovascular events in later life (3). Additionally, during pregnancy and postpartum, the risk of stroke is increased. Contrary to the general decreasing trend of stroke incidence in the general population of western countries, stroke in pregnancy is increasing, as shown in a review of seven studies by Ijäs et al.. This is likely because of generally advancing maternal age, more prevalent comorbidities, and the presence of vascular risk factors, such as hypertension (Ijäs et al.). This stresses the importance of prospective studies and international registries, such as the Stroke in Pregnancy and Postpartum Study (SiPP) (4).

In another article in the collection by Norman et al. general sex differences in a younger age group and in trends in stroke incidence were analyzed using a large registry. Younger men appeared to have more conventional vascular risk factors and higher case fatality than younger women (Norman et al.).

Notwithstanding, others found that younger women taking oral contraceptives had a higher stroke risk, which was accentuated in women with a high BMI and increased 10-fold in women with migraines who also smoked (5).

Physical inactivity resulting in a higher BMI, a higher risk for metabolic syndrome, and higher blood pressure have become major challenges for stroke prevention, not only in the general population in western countries but also in relation to sex. Indeed, while on one side it could be concluded that physical inactivity has an impact on stroke severity in both sexes, stroke severity seems to be worse in women (Salmantabar et al.).

There are conflicting results regarding primary prevention with acetyl acetylic acid (ASA) in men and women. In the review by Gdovinova et al., ASA was effective in women with no increased risk of hemorrhagic stroke; however, they found an increase in general systemic bleeding risk. These data are indicative of a potential difference in antiplatelet treatment effect between sexes, which should be further investigated (Gdovinova et al.).

Stroke etiology was reported to differ between men and women, with more men showing large artery atherosclerosis and women having more cardiac embolic strokes due to an increased frequency of atrial fibrillation. In an analysis of systematic reviews, it was observed that there was a male preponderance in displaying cerebral small vessel disease-related ischemic stroke and that men tended to present more moderate-to-severe cerebral small vessel disease (Jiménez-Sánchez et al.).

Conflicting results were found in the study by Pavlovic et al., in which women with previous lacunar stroke had a more severe cerebral small vessel disease than men, particularly white matter hyperintensity, and seemed to develop cognitive impairment more frequently than their male counterparts. However, this association with sex was dependent on the occurrence of depression and the severity of white matter hyperintensities and could not be explained by differences in common vascular risk factors, which were not significantly different between women and men. This has implications for further clinical and translational research and organizational aspects of patient care (Pavlovic et al.).

Vascular risk factors seem to have a relevant impact, particularly in women during and after menopause. Women showed an increased stroke risk partly due to a change in arterial stiffness and a higher risk of hypertension (6). There are conflicting results regarding stroke risk and hormonal therapy. In the recently published guidelines of the European Stroke Organization, it was concluded that low to very low evidence on the subject was found, hence only a weak recommendation against the use of hormonal therapy during menopause could be given (7).

Additionally, in the acute treatment of stroke, sex may have an important role. Two articles focused on pre-hospital identification of stroke and possible delays in women. As shown by Walter et al., awareness of stroke symptoms and pre-notification patterns differ between men and women (Walter et al.). Women were well-informed about stroke symptoms but they showed less self-awareness when suffering a stroke. Women were more likely to live alone when older, which could lead *per se* to delays in reporting and notification. Additionally, once admitted, do not resuscitate orders were given more frequently for women than for men, a finding that needs to be explored further.

As reported with myocardial infarction, women who had a stroke reported more uncommon symptoms that could be misdiagnosed as stroke mimics (Eddelien et al.). The less identifiable stroke symptoms can make the timely and correct diagnosis of a stroke more difficult and challenging, which could delay acute treatment with intravenous thrombolysis and/or mechanical thrombectomy within the recommended therapeutic time windows.

Stroke outcomes following acute endovascular treatment with mechanical thrombectomy may be sex related. In stroke patients treated with mechanical thrombectomy, women show better collateral flow but at the same time worse outcomes (Lagebrant et al.). These discrepancies should be further investigated.

In the observational study on intracerebral hemorrhage, an analysis of outcomes after intracerebral bleeding while taking oral anticoagulants in 226 men and 176 women showed that women had lower odds of receiving reversal agents and a decision of do not resuscitate, but when surviving had a similar outcome as men at 3 months. Interestingly, stroke-associated risk factors, such as smoking and alcohol intake, were less frequent in women than men but women were older and more dependent according to the modified Rankin Scale (Grundtvig et al.).

A retrospective study on 287 women and men with subarachnoid hemorrhage by Cai et al. reported that women had worse outcomes after subarachnoid hemorrhage and more post-interventional ischemic complications than men (Cai et al.). The reasons for this difference in outcome between sexes are yet to be understood. A worse short-term outcome after stroke in women, in general, was also found by Eren et al. in a retrospective cross-sectional study of 611 female and 683 male stroke patients (Eren et al.). In summary, articles included in this Research Topic showed that numerous sex differences in cerebrovascular diseases exist and impact the diagnosis and treatment in both men and women.

Current evidence suggests that a more tailored and individualized approach to these diseases in both sexes is needed. Sex-specific analyses must be performed. In future randomized controlled trials, more women of all age groups must be included to provide more reliable evidence for stroke treatment in both men and women.

Author contributions

CKre wrote the draft. All authors contributed to review. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers in Neurology

SYSTEMATIC REVIEW
published: 28 October 2021
doi: 10.3389/fneur.2021.756887

Sex Differences in Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis

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Background: Cerebral small vessel disease (SVD) is a common cause of stroke, mild cognitive impairment, dementia and physical impairments. Differences in SVD incidence or severity between males and females are unknown. We assessed sex differences in SVD by assessing the male-to-female ratio (M:F) of recruited participants and incidence of SVD, risk factor presence, distribution, and severity of SVD features.

Methods: We assessed four recent systematic reviews on SVD and performed a supplementary search of MEDLINE to identify studies reporting M:F ratio in covert, stroke, or cognitive SVD presentations (registered protocol: CRD42020193995). We meta-analyzed differences in sex ratios across time, countries, SVD severity and presentations, age and risk factors for SVD.

Results: Amongst 123 relevant studies (n = 36,910 participants) including 53 community-based, 67 hospital-based and three mixed studies published between 1989 and 2020, more males were recruited in hospital-based than in community-based studies [M:F = 1.16 (0.70) vs. M:F = 0.79 (0.35), respectively; $p < 0.001$]. More males had moderate to severe SVD [M:F = 1.08 (0.81) vs. M:F = 0.82 (0.47) in healthy to mild SVD; $p < 0.001$], and stroke presentations where M:F was 1.67 (0.53). M:F did not differ for recent (2015–2020) vs. pre-2015 publications, by geographical region, or age. There were insufficient sex-stratified data to explore M:F and risk factors for SVD.

Conclusions: Our results highlight differences in male-to-female ratios in SVD severity and amongst those presenting with stroke that have important clinical and translational implications. Future SVD research should report participant demographics, risk factors and outcomes separately for males and females.

Systematic Review Registration: [PROSPERO], identifier [CRD42020193995].

Keywords: cerebral small vessel disease (SVD), sex differences, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), lacunar stroke, vascular dementia (VaD)

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *11 August 2021*
Accepted: *04 October 2021*
Published: *28 October 2021*

Citation:
Jiménez-Sánchez L, Hamilton OKL, Clancy U, Backhouse EV, Stewart CR, Stringer MS, Doubal FN and Wardlaw JM (2021) Sex Differences in Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis. Front. Neurol. 12:756887. doi: 10.3389/fneur.2021.756887

INTRODUCTION

Cerebral small-vessel disease (SVD) is a disorder of the brain small penetrating blood vessels leading to white and deep gray matter damage, and is a major cause of stroke (1) and dementia (2).

Sex differences occur in many vascular diseases (3), and they can also be expected in the context of SVD. SVD is most commonly sporadic, although there are rare familial types, like cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which although not sex-linked, seems to affect males more severely than females (4). Covert SVD is common in older persons, where differences in male:female incidence or severity have not been assessed. Several studies of stroke of any type have recruited more males than females and reported a higher age-adjusted incidence in males, but higher severity in females. However, as reviewed elsewhere, it is unclear whether these conclusions reflect underlying sex-specific biological differences, recruitment bias, or other factors (5). On average, females are older than males at stroke onset, more likely to live alone and have more severe baseline deficits (6), which could explain their increased pre-hospital delay, and their higher severity in first-ever acute stroke (7). These factors can affect females' eligibility for stroke research studies, with a bias toward recruitment of milder strokes, and for stroke treatment, as females are less likely to be treated with IV thrombolysis than males (8). Interestingly, females were more likely to refuse participation in stroke clinical trials than males independently of their age (9).

Globally, females tend to live longer than males but there is a lack of sex and gender-stratified data in aging research (10) that may impede more personalized care in older populations; especially when biological factors, treatments, or social disparities may differ between sexes (11). Understanding male:female differences in incidence or severity of disease, particularly of common diseases like SVD, is now a World Health Organization imperative.

We aimed to explore if there are sex differences in covert or clinical presentations of SVD by assessing the sex ratio of participants with clinical or radiological evidence of SVD recruited to a range of studies, and whether any difference could be explained by male:female differences in risk factors or the severity of SVD features.

METHODS

We followed the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and registered the protocol on PROSPERO on July 2, 2020 (CRD42020193995) (12).

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CMBs, cerebral microbleeds; MRI, magnetic resonance imaging; ICH, intracerebral hemorrhage; SVD, cerebral small vessel disease; VaD, vascular dementia; VaCI, vascular cognitive impairment; WMH, white matter hyperintensities.

Data Sources and Search Strategy

We identified relevant studies in two ways.

First, we examined studies that had been included in four recent published systematic reviews of different aspects of SVD, whose search terms were similar as for the current work, and identified studies that met our current inclusion criteria (see below). The four systematic reviews addressed (a) early life risk factors for SVD (13), (b) cognitive dysfunction in SVD (14), (c) neuropsychiatric and cognitive symptoms in SVD (15), and (d) cerebral blood flow in SVD (16). We used the four published systematic reviews as a highly efficient way to access a large relevant literature, a practice which is now endorsed as part of the drive toward reducing research waste, improving efficiency, and best practice in evidence synthesis (17, 18). These systematic reviews had already been thoroughly screened and quality assessed, had each been conducted according to PRISMA guidelines, used relevant search terms, performed study quality assessment, had undergone peer review, and been published (**Table 1**) (13–16). Each systematic review had assessed a very large literature on a different aspect of SVD, enabling us to assess a very large number of relevant studies as efficiently as possible.

Second, we designed an independent search to supplement all the studies collected from the four systematic reviews with recent publications. We used a search strategy modified from a published protocol (14) to identify studies including participants with clinical (stroke or cognitive presentations) or non-clinical presentations of sporadic or monogenic SVD (e.g., CADASIL). Stroke presentations included lacunar syndromes with corresponding small subcortical infarct on neuroimaging, or that excluded other causes of symptoms. Cognitive presentations included vascular cognitive impairment, either vascular mild cognitive impairment—VaMCI—or vascular dementia—VaD. Non-clinical presentations included radiological evidence of SVD—e.g., white matter hyperintensities (WMH), lacunes of presumed vascular origin, small subcortical infarcts or cerebral microbleeds (CMBs) on brain magnetic resonance imaging (MRI) (19)—in the absence of clinical diagnosis (generally in community-dwelling populations), i.e., "covert" SVD. We aimed to explore trends across time by comparing recent and previously published studies (see *Results, Trends across time*) and decided to use January, 1, 2015 as the starting publication date for recent studies. Thus, January, 1, 2015 was the first date used for the independent search. We searched MEDLINE through OVID for human studies published in English or Spanish from January, 1, 2015 to May, 26, 2020 as follows: Cerebral Small Vessel Diseases/ OR (small vessel disease or small vessel-disease or CSVD or SVD).ti.ab. OR stroke,Lacunar/ OR [(lesion* or hyperinten*) adj3 white matter].ti.ab. OR Leukoaraiosis/ OR lacune*.ti.ab. OR [(lacun* or subcort* or ischemi* or ischaemi* or silent or microscopic) adj3 lesion*).ti,ab.]. Since the used search strategy was modified from one of these systematic reviews' protocol, only the most recent 150 journal articles among the 4,871 filtered results were examined to avoid retrieving duplicated studies that were already present in the database. The electronic search was carried out on May, 26, 2020.

TABLE 1 | Systematic reviews.

Study (13–16) (primary author, year)	Title	Identified studies	Included studies	Total number of included participants in each review
Backhouse, 2017	Early life risk factors for cerebrovascular disease.	19,180	29	23,356
Clancy, 2020	Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis.	7,119	81	21,730
Hamilton, 2020	Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis.	8,562	69	6,908
Stewart, 2020	Associations between white matter hyperintensity burden, cerebral blood flow and transit time in small vessel disease: an updated meta-analysis.	783	30	3,396

Identified studies refer to those found by search after duplicates were removed. Included studies refer to those examined for data extraction. The number of included studies of each systematic review do not include duplicated studies or populations.

Study Selection

We included cross-sectional and longitudinal studies published in English or Spanish that considered clinical diagnosis of SVD, radiological markers for SVD or studies reporting on patients with stroke that provided data according to stroke subtype (cortical or lacunar stroke). We excluded studies that did not report proportions of males and females or stroke subtype in the case of studies in stroke, review papers other than the included systematic reviews, editorials, communications, case reports, case series and conference abstracts, studies about other neurodegenerative conditions (e.g., Parkinson's disease, Alzheimer's Disease, non-vascular, or mixed dementia), inflammatory disorders (e.g., encephalitis/meningitis/vasculitis), single-sex populations (e.g., pregnancy studies), and genetic-based studies that only recruited from families. To avoid possible confounding factors related to large vessel disease, studies that recruited participants based on cardiovascular events (e.g., heart failure) and diffuse cardiovascular disease (e.g., atherosclerosis) were also excluded. The population of interest was patients presenting with stroke-related SVD (lacunar stroke), cognitive impairment found to have radiological features of SVD on neuroimaging, or participants with no clinical presentation found to have radiological features of SVD on neuroimaging (covert SVD). SVD radiological features included WMH, lacunes, small subcortical infarcts, CMBs, silent brain infarcts, or prior hemorrhage.

Where more than one study presented data on the same population, the study considering the most information about SVD clinical diagnosis, radiological markers, or risk factors for SVD was selected.

Data Extraction

Screening, full-text review, study selection and data extraction were independently carried out by five authors (LJ-S, OKLH, EVB, UC, and CRS). Studies included in the published systematic reviews had already been assessed by two researchers. Studies identified in the new literature search were assessed by one researcher and cross-checked with another researcher in the case of uncertainty about inclusion.

We extracted data on the primary author, date of publication, country of recruited participants, study type (cross-sectional or longitudinal), clinical or non-clinical presentation of participants (including lacunar or subcortical stroke or hemorrhagic forms of SVD, subjective memory or cognitive complaints, VaMCI, VaD, or covert SVD), number of subjects, total sex ratio of participants, mean age of participants and sex-stratified mean age of participants, stratified sex ratio by clinical diagnosis of SVD, radiological features of SVD (presence and severity of WMH, lacunes, small subcortical infarcts, CMBs, silent brain infarcts or prior hemorrhage) or SVD score if provided. We calculated mean ages if not reported and data were available. Hypertension and current or ever-smoking data were recorded if available, since these are key modifiable risk factors known to worsen SVD (20), and calculated sex-stratified percentages of hypertension and smoking. An initial screening of papers indicated that there would be few sex-stratified data to explore other risk factors. We only extracted baseline data in longitudinal studies.

Statistical Analysis

We performed all analyses and generated plots using R (version 3.2.3) (21). We calculated sex ratios of study participants or SVD groups of all the included studies and compared sex ratio per type of SVD presentation. Our principal summary measure was the median sex ratio per study setting, SVD presentation and severity.

Since recruitment can be affected by different factors across different settings, we classified studies into community-based, hospital-based, or mixed (where participants were recruited from both community and hospitals). To investigate whether differences in sex ratios were influenced by study size, we calculated a new variable: Δ sex ratio = |a constant of the global population sex ratio (22) – sex ratio of each study|. We log-transformed sizes of recruited populations due to their skewed distribution and then assessed the correlation of Δ sex ratio with the log-transformed size of the recruited populations per study population type.

To explore trends across time and countries, we classified studies by year of publication and country of recruited participants, respectively. To explore trends across severity and

TABLE 2 | Study classification by SVD severity and presentation.

Group	Description
Healthy to mild SVD	According to the definitions used in the original articles from which data was extracted: those defined as neurologically, functionally or cognitively healthy, community-dwelling individuals or participants with mild covert SVD (no clinical presentation with radiological features of SVD originally described as "mild": deep or periventricular WMH, white matter lesions, vascular white matter disease, lacunes, leukoaraiosis, CMBs, silent brain infarcts, or ICH).
Moderate to severe SVD	According to the definitions used in the original articles from which data was extracted: those with moderate or severe clinical or non-clinical presentations of SVD. This group included stroke presentations, cognitive presentations, moderate to severe covert SVD and genetic SVD.
Stroke presentations	Those first presenting with a lacunar or subcortical stroke or lacunar syndrome. Since cerebrovascular events can precede cognitive impairment, participants with both stroke and cognitive presentations of SVD (e.g., participants with lacunar stroke who also presented with VaD) were considered part of the stroke presentations group rather than the cognitive presentations group.
Cognitive presentations	Those presenting with self-reported and/or diagnosed cognitive impairment (subjective cognitive/memory complaints, subjective cognitive decline, VaMCI, VaD, subcortical ischemic vascular dementia or multi-infarct dementia).
Moderate to severe covert SVD	Those with no clinical presentation found to have radiological features of SVD originally described as "moderate" or "severe" (deep or periventricular WMH, white matter lesions vascular white matter disease, lacunes, leukoaraiosis, CMBs, silent brain infarcts, or ICH).
Genetic SVD	CADASIL

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CMB, cerebral microbleeds; ICH, intracerebral hemorrhage; SVD, cerebral small vessel disease; VaD, vascular dementia; VaMCI, vascular mild cognitive impairment; WMH, white matter hyperintensities.

presentations of SVD, we then classified participants into healthy to mild SVD (mild covert SVD) vs. moderate to severe SVD (stroke presentations, cognitive presentations, moderate to severe covert SVD and genetic SVD; detailed in **Table 2**).

For quantitative analyses, we used Shapiro-Wilk tests to check for data normality. Sex ratio and sex-stratified data were not normally distributed, so we used non-parametric statistical tests. We used the Mann-Whitney-Wilcoxon test to explore comparisons between two groups and the Kruskal-Wallis test to explore comparisons between more than two groups. If the result of the Kruskal-Wallis test was significant, we further analyzed data by pairwise Mann-Whitney-Wilcoxon followed by Bonferroni *post-hoc* correction. We assessed correlations using Spearman's rank correlation coefficient. In text, we present data as median (interquartile range, IQR) with significance threshold set at $p < 0.05$.

Study Quality Assessment

We performed a quality assessment of all the studies identified through the systematic reviews and the supplementary search of the recent literature as previously (14), rated on a scale from 0 to 8 according to STROBE guidelines, and calculated the median and IQR of the quality score. To check sensitivity, we re-ran the meta-analyses excluding studies with quality scores lower than the median quality score of all included studies.

Risk of Bias Assessment

Bias refers to factors that can systematically affect the observations and conclusions of the study, making them differ from the truth (23). Relevant biases for this systematic review could be explored in studies that compared SVD incidence, severity, or risk factors in strata by sex. However, since very few studies have been published specifically on male-to-female ratios in SVD, and none (to our knowledge) aimed specifically to assess male:female differences in SVD, risk of bias was not assessed in this study.

RESULTS

We found 241 relevant journal articles in the four published systematic reviews and the independent search. After filtering by language, full texts of 228 publications were assessed against inclusion/exclusion criteria (**Figure 1**). We extracted data and meta-analyzed 123 studies that met the inclusion/exclusion criteria (n = 36,910 total participants) (24–146). Two studies included genetic SVD (CADASIL) (79, 83) and 121 studies included sporadic SVD (characteristics of the included studies are summarized in **Supplementary Table 1**). Studies were conducted from 1989 to 2020 in 23 countries across six continents (Europe 43; Asia 39; North America 35; South America 3; Australia 2; Africa 1).

None of the included studies reported data regarding non-binary participants. Hence, for simplicity and without prejudice, sex ratios are referred to as male:female ratios.

Trends Across Study Settings

Our literature search retrieved 53 community-based (n = 29,323 participants) (24–76), 67 hospital-based (n = 7,337 participants) (77–143), and three mixed studies (n = 250 participants) (144–146). The global sex ratio of all included studies was 0.92 (0.65). Sex ratios differed across study setting ($H = 24.35$, $df = 2$, $p < 0.001$), being greater in hospital-based studies (i.e., more males than females) than in community-based studies: 1.16 (0.70) vs. 0.79 (0.35), respectively ($p_{corrected} < 0.001$; **Figure 2A**). Considering that the mean age of the participants of the included studies was 67, the sex ratio of community-based studies was closer to the expected general population sex ratio (0.89 in a 70-year old population) (22) than that of the hospital-based studies.

Sex ratio varied with study size in community-based but not in hospital-based studies: in community-based studies, the sex ratio was closer to that of the general population when the sample size was larger ($rho_{Spearman} = -0.46$, $p < 0.001$; **Figure 2B**); there was no effect of sample size on sex ratio in hospital-based studies ($rho_{Spearman} = -0.10$; $p = 0.43$; **Figure 2B**).

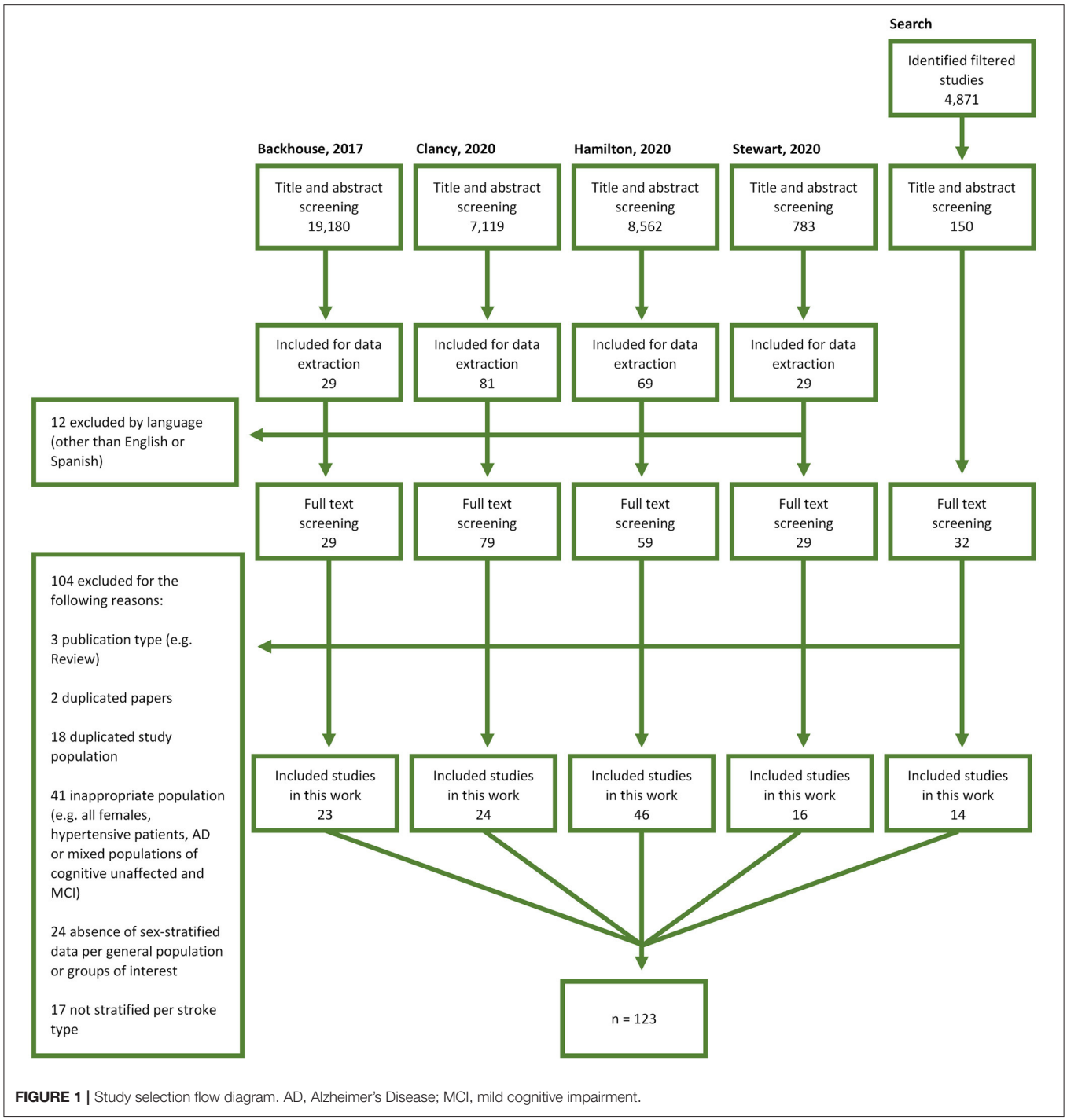


FIGURE 1 | Study selection flow diagram. AD, Alzheimer's Disease; MCI, mild cognitive impairment.

Trends Across Time

We classified studies per year of publication into recent (from 2015 to 2020) and previously published (until and including 2014) studies.

Considering all the included studies, there were no significant differences between sex ratios of recent studies compared with earlier publications ($U = 1{,}814$, $p = 0.75$). This finding was consistent after classifying by study type ($U = 372$, $p = 0.58$ in community-based studies; $U = 551$, $p = 0.93$ in hospital-based studies; **Figures 2C,D**). Mixed studies (144–146) were not included in this analysis since only three were retrieved by our literature search, all published recently.

Trends Across Countries

We classified community-based and hospital-based studies by country of recruitment (**Figure 3**). For clarity, studies that

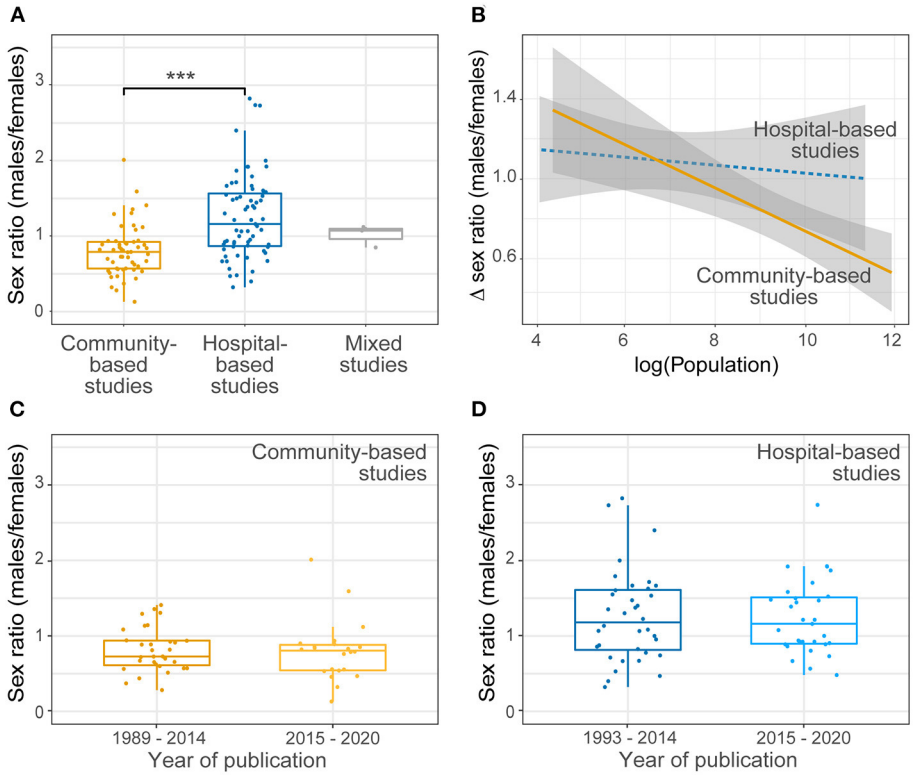


FIGURE 2 | Sex ratio of SVD studies across study setting and time. **(A)** Comparison of sex ratios per study type. Significant differences were found between sex ratios of community-based (CB) and hospital-based (HB) studies ($p_{corrected} < 0.001$). **(B)** Correlation between the sex ratio difference and the size of the recruited sample. Δ sex ratio = |sex ratio of general population – sex ratio of each study|. Given that the mean age of the participants of the included studies was 67, general population sex ratio corresponds to 70-year old population (89 males per 100 females) (22). There was a negative correlation between Δ sex ratio and the size of the population recruited in community studies (yellow, $rho_{Spearman} = -0.46$, $p < 0.001$) but not in hospital studies (blue, $rho_{Spearman} = -0.10$, $p = 0.43$). **(C,D)** Comparison of sex ratios across time. No significant differences were found between sex ratios of recent studies compared with those previously published considering all included studies ($n_{2015-2020} = 53$ vs. $n_{1989-2014} = 67$, $U = 1{,}814$, $p = 0.75$), **(C)** CB studies ($n_{2015-2020} = 22$ vs. $n_{1989-2014} = 31$, $U = 372$, $p = 0.58$) or **(D)** HB studies ($n_{2015-2020} = 31$ vs. $n_{1993-2014} = 36$, $U = 551$, $p = 0.93$). ***$p < 0.001$.

recruited participants from more than one country (37, 63, 83, 109, 127) and mixed studies (144–146) were excluded.

Amongst community-based studies, the highest sex ratio was found in participants recruited from the United Kingdom [1.36 (0.19), four studies, $n = 893$] and the lowest in participants recruited from the Republic of Ireland (0.37, one study, $n = 96$; **Figure 3A**). The largest recruited population came from the USA (21 studies, $n = 10{,}999$ participants), with a median sex ratio of 0.67 (0.36). Regarding hospital-based studies, the highest sex ratio was found in participants recruited from Singapore (2.73, one study, $n = 97$) and the lowest in participants recruited in Brazil (0.53, one study, $n = 26$; **Figure 3B**). The largest recruited population came from China (16 studies, $n = 2{,}274$ participants), with a median sex ratio of 1.08 (0.48).

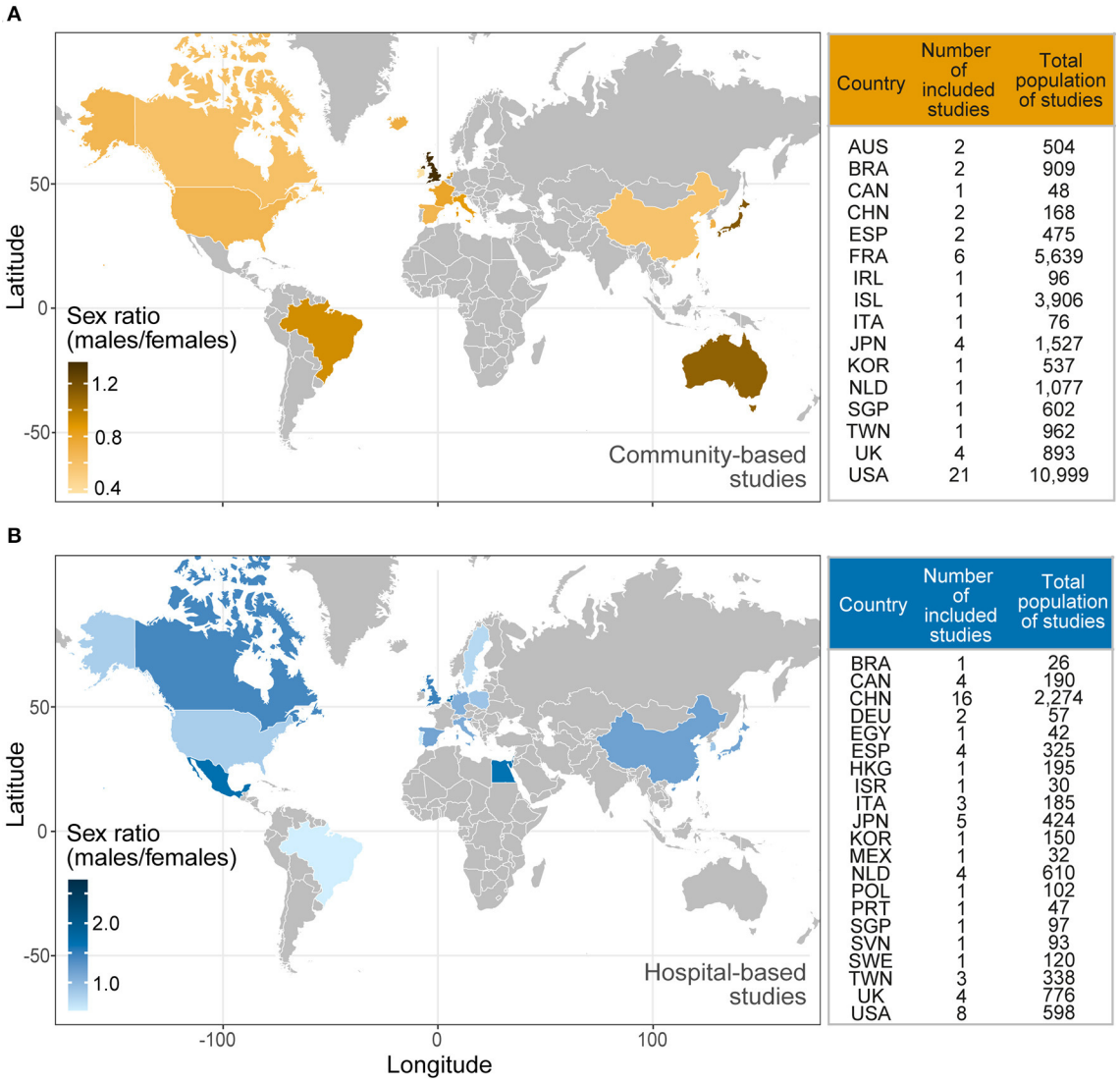
There were no obvious regional trends across countries for sex ratio vs. the total number of participants for either community-based or hospital-based studies.

Severity and Presentation of SVD

The included studies enrolled $n = 25{,}972$ healthy to mild SVD participants (no SVD presentation or mild covert SVD, **Table 2**) and $n = 10{,}938$ moderate to severe SVD participants (clinical presentation and/or high radiological burden of SVD, **Table 2**). The sex ratio was higher in healthy to mild SVD [1.08 (0.81)] than in moderate to severe SVD [0.82 (0.47)], $U = 3{,}031$, $p < 0.001$ (**Figure 4A**).

We further classified moderate to severe SVD participants into cognitive or stroke presentations or moderate to severe covert SVD (**Table 2**, **Figure 4B**). We excluded CADASIL studies due to insufficient data (79, 83). Sex ratios differed significantly between SVD presentations ($H = 36.58$, $df = 3$, $p < 0.001$). Participants with stroke showed the highest sex ratio, 1.67 (0.53), compared with healthy to mild covert SVD [0.82 (0.47), $p_{corrected} < 0.001$], cognitive SVD [1.03 (0.91), $p_{corrected} = 0.003$], and moderate to severe covert SVD [0.96 (0.44), $p_{corrected} < 0.001$].

Since community-based studies recruited mostly healthy participants and presented lower sex ratios, we repeated the severity analysis restricted to hospital-based studies (77–143), and found similar trends. Across SVD severity, the sex ratio was higher in moderate to severe SVD [1.26 (0.87)] than in healthy to mild SVD [0.90 (0.58)], $U = 1{,}240$, $p < 0.001$. Across SVD presentations, the sex ratio was higher in stroke presentations



Country	Number of included studies	Total population of studies
AUS	2	504
BRA	2	909
CAN	1	48
CHN	2	168
ESP	2	475
FRA	6	5,639
IRL	1	96
ISL	1	3,906
ITA	1	76
JPN	4	1,527
KOR	1	537
NLD	1	1,077
SGP	1	602
TWN	1	962
UK	4	893
USA	21	10,999

Country	Number of included studies	Total population of studies
BRA	1	26
CAN	4	190
CHN	16	2,274
DEU	2	57
EGY	1	42
ESP	4	325
HKG	1	195
ISR	1	30
ITA	3	185
JPN	5	424
KOR	1	150
MEX	1	32
NLD	4	610
POL	1	102
PRT	1	47
SGP	1	97
SVN	1	93
SWE	1	120
TWN	3	338
UK	4	776
USA	8	598

FIGURE 3 | Sex ratio of SVD studies across the world. Colored world maps representing the mean sex ratio of the total number of participants of **(A)** community-based and **(B)** hospital-based studies. Darker shades in the color gradient correspond to higher sex ratios (i.e., more males than females). The tables on the right specify the country of recruited participants, the number of included studies and the total population of included studies per study type. Neither multicentre nor mixed studies were represented in these maps. AUS, Australia; BRA, Brazil; CAN, Canada; CHN, China; DEU, Germany; EGY, Egypt; ESP, Spain; FRA, France; HKG, Hong Kong; IRL, Ireland; ISR, Israel; ITA, Italy; JPN, Japan; KOR, Korea; MEX, Mexico; NLD, The Netherlands; POL, Poland; PRT, Portugal; SGP, Singapore; SVN, Slovenia; SWE, Sweden; TWN, Taiwan; UK, United Kingdom; USA, The United States of America.

[1.67 (0.55)] than in healthy to mild covert SVD [0.90 (0.58), $p_{corrected} < 0.001$], cognitive SVD [1.11 (0.81), $p_{corrected} = 0.037$], and moderate to severe covert SVD [1.13 (0.87) $p_{corrected} = 0.02$], $H = 21.82$, $df = 3$, $p < 0.001$.

Only two studies (73, 81) provided data to calculate sex-stratified SVD risk factors (hypertension and smoking), which were insufficient to perform further analyses.

Age and Risk Factors for SVD

Only 10 studies (38, 64, 65, 69, 73, 81, 102, 111, 136, 143) (2,953 participants) provided sufficient data to calculate the sex-stratified participants' age. There was no significant difference in median age between total recruited males [63.78 (9.71)] and females [64.45 (13.71), $U = 49.5$, $p > 0.99$].

Quality Assessment

The median study quality score was 5.5 (1). As a sensitivity analysis, quantitative analyses were re-run excluding all studies with a quality score < 5.5/8. All the trends observed in the total included studies were consistent in the subset of higher-quality studies (score ≥ 5.5/8; **Supplementary Table 2**).

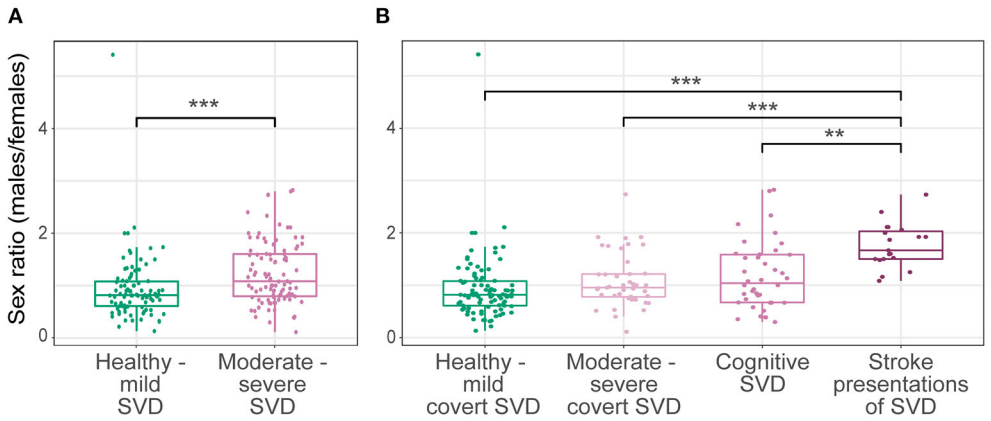


FIGURE 4 | Sex ratio across SVD severity and presentation. Sex ratio of healthy to mild SVD compared with **(A)** moderate to severe SVD and **(B)** stratified moderate to severe SVD. Significant differences were found between SVD severity groups i.e., sex ratios of healthy to mild SVD and moderate to severe SVD (A; $U = 3{,}031$, $p < 0.001$). Significant differences were also found between SVD presentation groups ($H = 36.58$, $df = 3$, $p < 0.001$) i.e., stroke presentations of SVD compared with healthy to mild covert SVD, moderate to severe covert SVD or cognitive SVD (B; $p_{corrected} < 0.001$, $p_{corrected} < 0.001$, $p_{corrected} = 0.003$, respectively). $^{**}p < 0.01$, $^{***}p < 0.001$.

DISCUSSION

This meta-analysis of 123 studies (24–146) including 36,910 participants demonstrates sex differences in SVD across study settings, by SVD severity and presentation. A greater male-to-female ratio was found in hospital-based (77–143) compared to community-based studies (24–76) (**Figure 2**), and in moderate to severe SVD, particularly in stroke presentations (**Figure 4**). The pattern was consistent across recent (2015–2020) and previous (1989–2014) studies (**Figures 2C,D**), and world regions (**Figure 3**). To the best of our knowledge, this is the first systematic review and meta-analysis to explore sex differences in SVD and has important implications. The apparent presence of more severe SVD in males, particularly amongst those presenting with stroke, may indicate differences in risk factor exposures, susceptibility to SVD, adherence to risk factor interventions, or differences in study recruitment. Awareness of these differences, which were robust to study location and population, may help inform approaches to mitigate the long-term effects of covert SVD and for secondary prevention of SVD-related stroke. Unfortunately, very few studies reported risk factor differences between males and females and even age was not commonly reported. Furthermore, future studies should report male and female demographics, risk factors and outcomes, not just total sample data.

The different sex ratios between community-based and hospital-based studies may reflect differences in recruitment in these settings. Typically, females are older and have more disability at stroke onset (7), which may affect study eligibility. For example, ischemic stroke patients older than 80 years have higher rates of disability following thrombolysis treatment (147) and are less likely to be recruited into stroke trials (148). Furthermore, women with stroke may present with non-traditional symptoms like altered mental status (149), which could be overlooked or misdiagnosed (150, 151), and are important since atypical and neuropsychiatric symptoms are increasingly recognized to associate with SVD (15). Sex differences in clinical presentations are also present in dementia (152) but none of the included studies reported these in VaCI or VaD. Moreover, informal carers of dependent persons in the UK are more likely to be middle-aged women with multiple roles until later life (70+) (153). Thus, females may be reluctant to participate in studies due to care responsibilities or may normalize their early symptoms while providing care. Caregiving roles vary by country (154), socioeconomic status and culture of care (155), which might explain why more females seemed to participate in Chinese hospital-based studies compared with the UK or Canada (**Figure 3B**) since Chinese males are traditionally the predominant caregivers for older parents (156). Some of the aforementioned factors that may alter female recruitment to SVD studies have recently been highlighted as contributors to lower enrolment of women in stroke clinical trials more generally (157).

It could also be that SVD is more prevalent and/or severe in males than in females, increasing the likelihood of males becoming participants in studies investigating severe SVD. In support of this, male-sex was an independent predictor of severity of SVD in an adjusted analysis, albeit in a 62% male population (20). Similarly, a greater prevalence of stroke, higher cognitive impairment and cerebral atrophy have been reported in men with CADASIL (158). Sex differences can be driven by sex-specific biological factors e.g., sexual dimorphism in endothelial function (159). In premenopausal females, oestrogens enhance endothelial production of vasodilator factors (160). This may explain young males having greater vasoconstrictor tone compared to pre-menopausal females (159) and male endothelial function becoming suboptimal under certain insults. We found no differences in age between recruited males and females, although fewer data were available for this analysis. Different lifestyle-related risk factors could also contribute to the sex-specific severity of SVD, e.g., utilization of preventative health

care services, smoking, or hypertension. Interestingly, the prevalence of smoking and hypertension is higher among males in most countries (161, 162), varying with ethnicity (163). Unfortunately, there were insufficient data to determine if sex-specific risk factor effects were driving the sex ratio difference in SVD severity and presentation.

The unequal sex ratios found here may be explained by factors with different contributions across different settings, evidenced by the different effect of study size on sex ratio within community-based and hospital-based studies (**Figure 2B**), or in the context of higher SVD severity and stroke presentations. The lack of difference between sex ratios of recent and earlier studies (**Figures 2C,D**) suggests that the same factors may have operated long term.

The implications for future research and clinical practice are varied and important. The lack of sex-stratified data, previously reported in brain structural studies (164) and aging research (10), hampers translational research and personalized care. Results should be reported and analyzed by sex, especially when biological factors, treatments or social disparities may differ between sexes (11). This was addressed recently (165, 166) in support of the Sex and Gender Equity in Research (SAGER) guidelines (167) and the European Commission second report on Gendered Innovations (168), which provides guidance for researchers to incorporate sex, gender and intersectional analysis across several research topics. Future studies should also identify and try to avoid recruitment bias, explore whether SVD is more frequently underestimated or misdiagnosed in females and investigate reasons why males may be more severely affected. Larger sample sizes may help to reduce sampling variability at least within community-based studies with a majority of functionally healthy individuals (**Figure 2B**). If the disease in females is going unrecognized, doctors and the public could be educated to better recognize atypical symptoms in females. If males are more severely affected or exposed to certain lifestyle factors, trials may need to target drivers of males' vulnerability and health promotion campaigns could be designed to have more impact on males.

This study had limitations. First, it was not possible to explore common risk factors of SVD due to the scarcity of sex-stratified data. Also, other risk factors and their differences between sexes were not explored (e.g., lower educational attainment, associated with increased risk of SVD in later life) (13). Most studies are from industrialized countries (**Figure 3**), so our results might not fully represent other populations. Since this study relied on studies' own criteria for SVD severity, future explorations could investigate heterogeneity in study criteria and attempt further standardization efforts. Future work could also explore the sex-stratified functional status of participants, which may affect eligibility criteria and result in exclusion of females who are more functionally disabled (6, 8, 169).

The study also has strengths. We included studies from four recent systematic reviews, which covered different aspects of SVD (and therefore likely different literatures), each had assessed a large literature, and the source files were immediately available to us. We did not use our older systematic reviews as the included literature would not have been so up to date or comprehensive. We hope that our approach might encourage other groups to evaluate their high-quality systematic reviews in the same way. A broad approach was taken to capture changes across time, study settings, different cultural or ethnic groups, SVD severity and presentation. The included studies were conducted from 1989 to 2020, recruited 36,910 participants from the community and/or hospitals in 23 countries across six continents, and explored a wide range of SVD radiological features and presentations. Our results highlight sex-specific variability in study participation, SVD severity, and presentation. These findings are relevant for future research and clinical practice, but much more work is needed to unmask sex-specific biological and social disparities and disentangle their contributions to sex differences in SVD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LJ-S carried out the independent literature search, extracted the data, performed the meta-analyses, and drafted the manuscript. OKLH, EVB, UC, and CRS carried out the literature search of their corresponding systematic reviews and provided their databases and reviewed and edited the manuscript. MSS co-supervised one of the systematic reviews (conducted by CRS) and checked and edited the manuscript. FND co-supervised one of the systematic reviews (conducted by UC) and checked and edited the manuscript. JMW conceived and managed the project, designed the protocol, checked the search strategy, supervised the contributing meta-analyses, reviewed uncertain articles, advised on the meta-analysis and interpretation of data, and reviewed and edited the manuscript. The final draft of the manuscript was approved by all authors.

FUNDING

This research was funded, in part, by the Wellcome Trust [Grant No. 108890/Z/15/Z]. For the purpose of open access, the author has applied a CC BY public copyright license to any Author Accepted manuscript version arising from this submission. LJ-S is a Translational Neuroscience PhD student funded by Wellcome (108890/Z/15/Z). OKLH was a Translational Neuroscience PhD student funded by the College of Medicine and Veterinary Medicine at the University of Edinburgh. OKLH was supported by a Translational Neuroscience PhD student funded by the College of Medicine and Veterinary Medicine at the University of Edinburgh. UC was funded by a Chief Scientist Office of Scotland Clinical Academic Fellowship (CAF/18/08) and Stroke Association Princess Margaret Research Development Fellowship (2018). EVB was funded by the Sackler Foundation, the Stroke Association, British Heart Foundation and Alzheimer's Society through the R4VaD Study. MSS was funded by the

Fondation Leducq (ref no. 16 CVD 05) and EU Horizon 2020 (PHC-03-15, project No 666881, SVDs@Target) and the MRC UK Dementia Research Institute at the University of Edinburgh (UK DRI LTD, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK). FND was funded by a Stroke Association Garfield Weston Foundation (TSALECT 2015/04) Senior Clinical Lectureship and NHS Research Scotland. JMW was funded by the Stroke Association, British Hearth Foundation, Row Fogo Charitable Trust, Fondation Leducq (Perivascular Spaces Transatlantic Network of Excellence), and EU Horizon 2020 (SVDs@Target) and the MRC UK Dementia Research Institute at the University of Edinburgh (UK DRI LTD, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK). All authors hold grants from government/charitable agencies. The funding sources had no role in the study design, execution, analysis, interpretation of the data, decision to publish, or preparation of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.756887/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CC declared a past co-authorship with one of the authors JMW to the handling editor.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 14 February 2022
doi: 10.3389/fneur.2022.793181

Sex Differences in Ischemic Stroke Within the Younger Age Group: A Register-Based Study

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Background: Stroke incidence is decreasing in most developing countries. However, worrisome trends of an increase in the younger population have been described.

Aim: To investigate sex differences and longitudinal changes in ischemic stroke regarding incidence, cardiovascular risk factors, and outcome, in the young.

Methods: This is an observational study based on the data from the Swedish national stroke registry, Riksstroke. Patients, 18–54 years of age, having ischemic stroke between 2005 and 2018 were included, resulting in a study population of 16,210 patients.

Results: The incidence was higher in men than in women (30.6 vs. 19.1 per 100,000, $P < 0.001$). After an initial increase, the incidence stabilized and then decreased, resulting in a similar level in 2018 as in 2005. Atrial fibrillation, diabetes, and usage of anti-hypertensives at stroke onset were more common among men and did not change over time. Smoking was common and slightly more so in women, but with a reduced prevalence in both men and women during the study period. Dependency in Activities of Daily Living (ADL) and case fatality showed no clear trends or sex differences.

Conclusions: The results show that there are sex differences in ischemic stroke in the younger age group regarding incidence and vascular risk factors, particularly smoking. Temporal trends in stroke incidence are difficult to interpret as fluctuations are substantial, largely due to stroke being quite uncommon in the younger population.

Keywords: ischemic stroke, register, sex differences, younger population, cerebrovascular disease

OPEN ACCESS

Edited by:
Christine Kremer, Lund University, Sweden

Reviewed by:
Maurice Giroud, Centre Hospitalier Regional Universitaire De Dijon, France
Seana Gall, University of Tasmania, Australia

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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *11 October 2021*
Accepted: *11 January 2022*
Published: *14 February 2022*

Citation:
Norman K, Eriksson M and von Euler M (2022) Sex Differences in Ischemic Stroke Within the Younger Age Group: A Register-Based Study. Front. Neurol. 13:793181. doi: 10.3389/fneur.2022.793181

INTRODUCTION

Age and sex are important non-modifiable risk factors for stroke. Women are older at the time of stroke onset but have a longer life expectancy (1). Thus, the absolute number of strokes is lower for women before the age of 75 years but more than twice as high as in men after the age of 75 (2). Protective effects of physiological estrogen until menopause (3), and more men having stroke risk factors such as smoking and untreated vascular risk factors have been suggested as explanations (4, 5). The incidence is higher among men than women below the age of 60. In a study of 411 patients between 18 and 50 years of age from China, 67% were male and 88% of the male patients had at least one risk factor, compared to 54% of the women (4). Some of the risk factors observed more often in men were hypertension, diabetes mellitus, and smoking (4).

A trend of increasing incidence of stroke in the younger age group in Sweden has previously been described. One such report by Rosengren et al. in 2013 based on Swedish Hospital Discharge and Cause of Death (CDR) registries researched cases of ischemic stroke from 1987 to 2010. The study showed that there was a continuous increase in the incidence of ischemic stroke for both men and women in the age group 18 to 44 years, although slightly larger among women (+1.3 in men, +1.6 in women) (6). Factors that were hypothesized to contribute were increasing obesity rates but also increased detection of smaller strokes. Nevertheless, the report describes this worrisome trend and its possibility to be carried forward as this younger population grows older. An increase in incidence in a slightly older age group, 35–64 years, in the Netherlands has also been found in the years 1997 to 2005 (7). As the number of strokes in younger age groups is small, a lesser change in the number of cases results in a large change in proportions. Both the number of strokes and the case fatality (CF) have continued to decrease in men and women in the older age groups and thus, it is interesting to follow the incidence over time in the younger age groups. We aimed to investigate sex differences in ischemic stroke regarding incidence, risk factors, and case fatality in the younger populations.

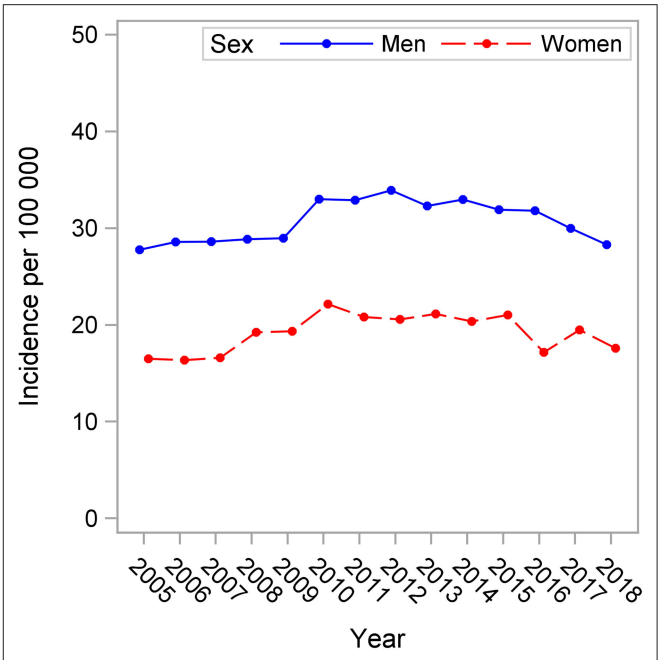

FIGURE 1 | Estimated stroke incidence per 100,000 in 18–54 years old men and women, 2005–2018.

MATERIALS AND METHODS

This is an observational register-based study based on prospectively collected data from the Swedish national quality registry for stroke, Riksstroke. The registry's coverage of stroke incidence is high, calculated to 89% when compared to the patient registry (PAR) (8). The study population consisted of men and women between the ages of 18 and 54 and is a subset of a data set that has been published previously (9). Both first-ever and recurrent ischemic strokes (ICD-10 code I63) were included.

The risk factors diabetes, high blood pressure (assessed as using anti-hypertensive medication), previous history of stroke (yes or no), smoking, and atrial fibrillation are recorded in Riksstroke. Smoking is defined as the consumption of one cigarette or more per day, or if the patient had quit during the 3 months leading up to the stroke attack. The date of death was retrieved from the Cause of Death Register (managed by the National Board of Health and Welfare), giving statistics of 90 days-CF. Dependency in ADL was based on the patient's reported outcome (mobility, toileting, and dressing) 3 months after stroke.

Statistical Analysis

Age (years) was non-normally distributed and described with medians and quartiles (Q1 and Q3). Binary variables were presented by proportions with approximately 95% CIs. Group comparisons were made with the Mann-Whitney test for age and Pearson's chi-squared test for categorical variables.

The stroke incidence was analyzed by Poisson regression, with an offset equal to the natural logarithm of the size of the general population (using population statistics from Statistics Sweden, Central Bureau of Statistics). The model included the independent variables year, sex, and sex-by-year interaction. Risk factors and outcomes were analyzed by binary logistic regression. The models included the independent variables sex, year of stroke, age, and age^2. In addition, the sex-by-year interaction was included to test if the time trend differed between men and women.

A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS® statistics version 26.0 for Windows (IBM Corp., Armonk, NY, USA), and SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Ethical Considerations

This study was approved by the Swedish Ethical Review Authority (reference no. 2018-02777). In accordance with the Personal Data Act (Swedish law No. SFS 1998:204), no informed consent is needed to collect data from medical charts and inpatient records for quality registers but there is information and an opt-out possibility.

RESULTS

In all, 16,210 persons were included (6,073 women, 10,137 men). Throughout 2005–2018, the estimated stroke incidence was higher in men than in women (30.6 per 100,000 in men and 19.1 per 100,000 in women, $P < 0.001$, **Figure 1**). The incidence changed significantly over the years ($P < 0.001$) similarly in men and women (P for sex-by-year interaction = 0.278). There was a slight increase between 2005 and 2010 the trend levels off after this, and in 2018 the incidence rates for both men and women were almost at the same level as in 2005.

Smoking decreased during the study period ($P < 0.001$), from 38.3% in 2005 to 25.8% in 2018 (**Figure 2**). This was

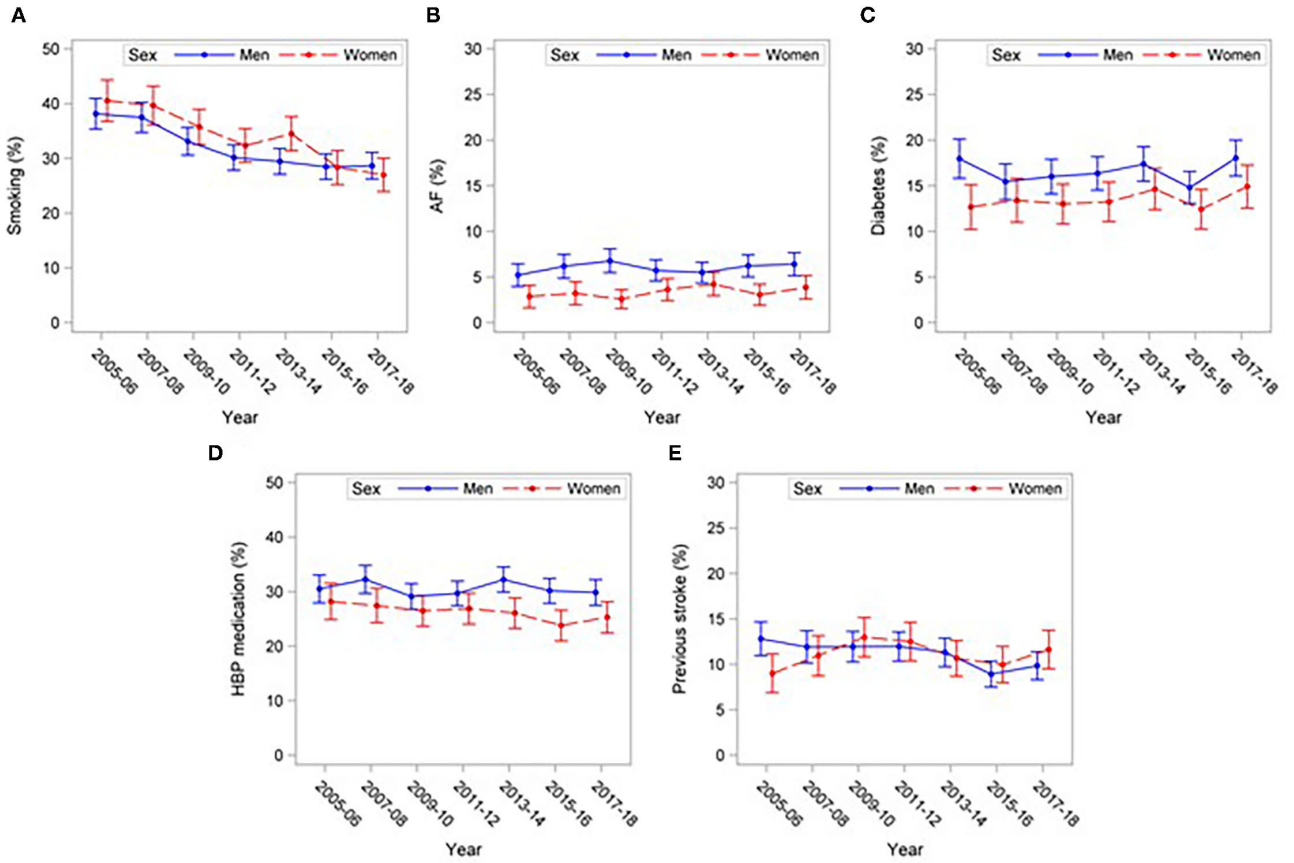

FIGURE 2 | Prevalence of cardiovascular risk factors (%) with 95% CIs in 18–54-year-old patients with stroke 2005–2018. **(A)** Smoking, **(B)** Atrial fibrillation (AF), **(C)** Diabetes, **(D)** High Blood Pressure (HBP) medication, **(E)** Previous stroke.

TABLE 1 | Baseline characteristics of the cohort.

	All	Men	Women	*P*-value
Demographics, Frequency, *N* (%)	16,210 (100)	10,137 (62.5)	6,073 (37.5)	
Age, median (Q25 and Q75), years	49 (43 and 52)	49 (44 and 52)	48 (42 and 52)	<0.001*
Risk factors				
Atrial fibrillation, *N* (%) [95% CI]	810 (5.0)	606 (6.0) [5.6–6.5]	204 (3.4) [2.9–3.8]	<0.001*
Diabetes *N* (%) [95% CI]	2,487 (15.4)	1,670 (16.6) [15.8–17.3]	817 (13.5) [12.7–14.4]	<0.001*
Hypertensive blood pressure (HBP) medication, *N* (%) [95% CI]	4,656 (28.9)	3,071 (30.5) [29.6–31.4]	1,585 (26.2) [25.1–27.4]	<0.001*
Smoking[#], *N* (%) [95% CI]	4,924 (30.4)	3,012 (29.7) [28.8–30.1]	1,912 (31.5) [30.3–32.7]	0.060
Previous stroke, *N* (%) [95% CI]	1,805 (11.2)	1,129 (11.2) [10.6–11.8]	676 (11.2) [10.4–12.0]	0.986
None of the above, *N* (%) [95% CI]	6,039 (37.3)	3,672 (36.2) [35.3–37.2]	2,367 (39.0) [37.8–40.2]	0.007*

**Statistically significant p-value [#] in 6.9% of cases (6.8% and 7.0% in men and women, respectively) data on smoking were missing.*
N, number of subjects or events; CI, confidence interval.
All percentages (%) refer to the proportion of that column, except the top row which refers to the proportion of total subjects.

the only studied risk factor that changed significantly during the study (**Figure 2**). Atrial fibrillation, diabetes, and use of antihypertensive medication were all significantly more common among men than women (**Table 1**), and as for previous stroke, they did not change over time (**Figure 2**). The prevalence of all risk factors increased with age for both men and women (**Supplementary Table 1**). After adjustment for age, smoking was significantly more common in women than in men ($P = 0.018$).

No clear sex differences could be seen for ADL-dependency at 3 months after stroke (**Figure 3**). Similarly, there was no consistent difference in case fatality between the sexes as some years, men have higher case fatality and other years, women

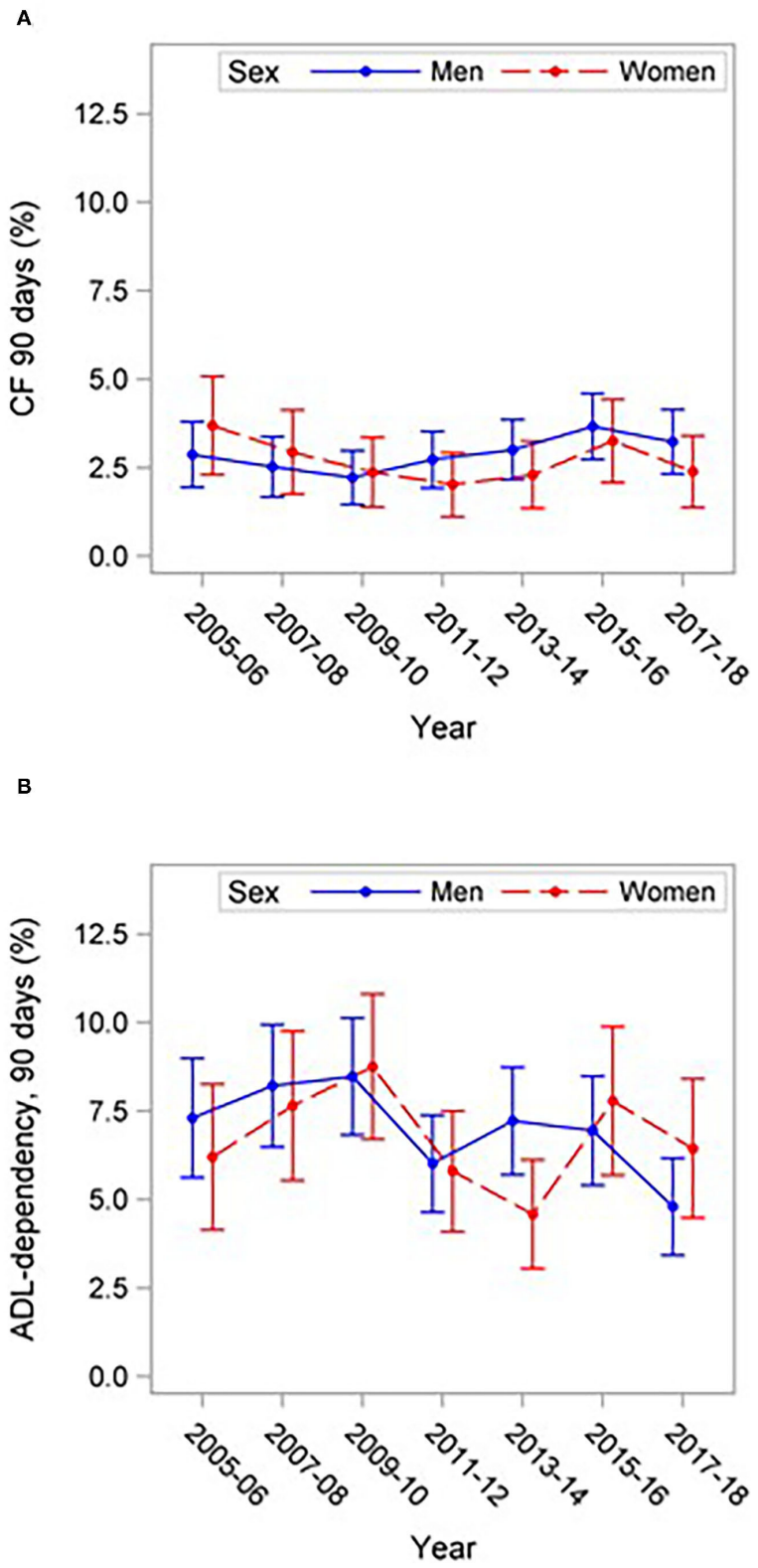

FIGURE 3 | Outcome 90 days after stroke (%) with 95% CIs in 18–54-year-old patients with stroke 2005–2018. **(A)** 90 days case fatality, **(B)** ADL-dependency in patients who were independent before the stroke.

(**Figure 3**). Overall, ADL-dependency in patients who were independent before a stroke and case fatality at 3 months after stroke did not differ significantly between men and women and did not change significantly during 2005–2018.

DISCUSSION

In contrast to the declining stroke incidence among the entire stroke population seen in Sweden and most other affluent countries (6, 10, 11), we observed an initial increase in incidence that was later reversed, resulting in similar levels in 2005 and 2018 in the younger population (18–54 years) in Sweden. Men had higher stroke incidence and more often atrial fibrillation, diabetes, and hypertension than women at stroke onset. Smoke prevalence in patients with stroke decreased substantially over the study period. The outcome was similar in men and women and did not change significantly over time.

The incidence was a bit lower than what has been described from an American cohort where the stroke incidence (both ischemic and hemorrhagic) was 28/100, 000 in adults 20–44 years of age (12). A recent analysis of Riksstroke data for all adults from our group shows a declining incidence of 24% in men and 31% in women during the last 15 years (9). Stroke etiology in younger people is less due to the traditional risk factors and improvements in control of these may thus have a greater impact in the older age groups. An important risk factor for ischemic stroke where treatment has improved immensely over the last decade is atrial fibrillation, which increases in prevalence with age (13, 14). In our cohort, atrial fibrillation was approximately three times as common in 42–54-year-olds compared to 18–29-year-olds. Swedish data estimate that around 10% of the reduction in ischemic stroke incidence can be related to increased oral anticoagulants treatment, especially non-vitamin K antagonist oral anticoagulants (11). Assumably, as atrial fibrillation is less common in younger people, this reduction is not as apparent in the younger age group.

Smoking became less common in the studied stroke population over the studied period. At the time of the study start, around 40% of the patient were smoking compared to 30% at the study end. Compared to the overall Swedish population, this is still a high number. From 2006 to 2020, daily smoking in Sweden has decreased from 14 to 7%, and in the youngest group (16–29 years), it has more than halved, from 10 to 4% (15). In many countries, smoking is a risk factor more commonly found in men and it is hypothesized to contribute to the incidence patterns with more men affected by stroke in the younger age group (1, 2, 4). In the present study, we only found a small difference with slightly more women than men smoking. The large difference of smokers in our cohort compared with the general population could indicate that smoking is an important risk factor in this age group. A recent meta-analysis estimated the odds ratio for stroke in smokers as compared with non-smokers to be 1.61 (95% CI 1.34–1.93, $P < 0.001$) (16). However, if it is smoking by itself or a combination of smoking and other risk factors such as low socioeconomic status and stress co-variating with smoking, cannot be deduced from our data as we lack information on several risk factors (17). Smoking being much more common in younger stroke patients compared to the entire stroke population was also shown in a study from the Dijon stroke registry (18). In a 27-year study, 1985–2011, of stroke incidence in people under 55 years of age, they show smoking to be the most frequent risk factor (43%). However, in contrast to our study, they found an increase in the overall stroke incidence in both men and women over the time studied (18). The difference in smoking between men and women varies substantially between countries. A Chinese study of transient ischemic attack (TIA) found 41.3% of male and 4.2% of female patients to be smokers (19).

Stroke is uncommon in younger people and thus small changes in the number of events can lead to large fluctuations in incidence. However, it shows that the worrisome rapidly increasing stroke trend particularly in young women described by Rosengren et al. in 2013 has not continued (6). In contrast to our results, a recent study by Åberg et al. showed stroke incidence among young males to be increasing in Sweden (20). Their study was based on cohorts of men enrolled for the military service in 1971–1995, with the last year of their study being in 2016. Our present study lasted 2 years longer, to 2018. The most comparable group in our study (18–44 years of age), did show a higher incidence, especially for men, in 2016 but not in 2017 compared to 2005.

A study based on insurance claims data 2001-2014 from the US showed an incidence rate ratio of 0.7 for men aged 25–44 years compared with women (21). This may reflect differences between countries and also in risk factors. In the US, the prevalence of overweight was estimated to be 42% in men and women in 2017–2018 (22). While in Sweden, the prevalence of overweight was 42% in men and 28% in women in 2016 (23). The US study included patients with health care insurance which may have introduced a bias. Furthermore, misclassification may be present (24). Riksstroke is based on discharge diagnosis and as patients receive follow-up questionnaires, the risk of misclassification may be lower (25).

Previous reports have overall shown varying results regarding sex differences in fatality in stroke. A large meta-analysis from 2013 found an overall hazard risk of 1.13 for women compared with men but was unable to analyze age-adjusted differences due to limited data (26). A study from a French stroke registry showed higher mortality in women, increasing mortality with age, and no sex differences in case fatality when the results were age-adjusted (2). Our results with no difference in 90 days case fatality between the sexes are in accordance with the latter finding.

The strengths of this study are firstly the large sample size ($n = 16{,}210$) of the unselected cohort and high coverage of cases during the entire study period. There was also a very low number of missing values. As in all observational studies, it is difficult to establish causation between measures and outcomes, and there may be unmeasured confounding not corrected for.

The included confounders were considered the most important. In a study such as this, focusing on a younger population, some other risk factors, such as migraine with aura, the use of contraceptive pill with estrogens, pregnancy complications, obesity, and different inflammatory-related diseases such as rheumatic diseases, become interesting as

many of the patients had none of the most common pre-stroke risk factors. However, to maintain a high coverage, the data collections in Riksstroke are restricted.

CONCLUSION

The result of this registry-based study indicates that there are sex differences regarding the incidence of ischemic stroke in the younger age group. Both stroke incidence and many risk factors such as atrial fibrillation, diabetes, and the use of anti-hypertensives are more common in men than women. However, in younger patients, there is no significant difference in outcome between the sexes. Also, stroke incidence in the young is not decreasing as in the older age group. However, at least in Sweden, the previously reported increase in incidence seems to be reversed. Nevertheless, stroke prevention, particularly smoking, as well as increased knowledge and recognition of more uncommon risk factors must be encouraged in younger adults for us to see a decline in stroke incidence in this age group.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from Riksstroke–The Swedish Stroke Register, the following licenses/restrictions apply: Due to the sensitive nature of the data, requests to access these datasets from qualified researchers trained in human subject confidentiality protocols must first be sent to Riksstroke for approval. Requests to access these datasets should be directed to Riksstroke, riksstroke@regionvasterbotten.se.

ETHICS STATEMENT

This study was approved by the Swedish Ethical Review Authority (reference no. 2018-02777). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KN, ME, and MvE contributed to conception and design of the study. ME organized the database. KN performed the statistical analysis with support of ME and MvE. KN wrote the first draft of the manuscript under supervision of MvE. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

Örebro University funded open access publication fees.

ACKNOWLEDGMENTS

The authors are grateful to Riksstroke and all patients, caregivers, and staff reporting to the registry.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.793181/full#supplementary-material

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frontiers in Neurology

ORIGINAL RESEARCH
published: 03 March 2022
doi: 10.3389/fneur.2022.832903

Sex-Differences in Oral Anticoagulant-Related Intracerebral Hemorrhage

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Edited by:
Svetlana Lorenzano, Sapienza University of Rome, Italy

Reviewed by:
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Marialuisa Zedde, IRCCS Local Health Authority of Reggio Emilia, Italy

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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *10 December 2021*
Accepted: *31 January 2022*
Published: *03 March 2022*

Citation:
Grundtvig J, Ovesen C, Steiner T, Carcel C, Gaist D, Christensen L, Marstrand J, Meden P, Rosenbaum S, Iversen HK, Kruuse C, Christensen T, Ægidius K, Havsteen I and Christensen H (2022) Sex-Differences in Oral Anticoagulant-Related Intracerebral Hemorrhage. Front. Neurol. 13:832903. doi: 10.3389/fneur.2022.832903

Introduction and Aim: Data remain limited on sex-differences in patients with oral anticoagulant (OAC)-related intracerebral hemorrhage (ICH). We aim to explore similarities and differences in risk factors, acute presentation, treatments, and outcome in men and women admitted with OAC-related ICH.

Method: This study was a retrospective observational study based on 401 consecutive patients with OAC-related ICH admitted within 24 h of symptom onset. The study was registered on osf.io. We performed logarithmic regression and cox-regression adjusting for age, hematoma volume, Charlson Comorbidity Index (CCI), and pre-stroke modified Ranking Scale (mRS). Gender and age were excluded from CHA_2DS_2-VASc and CCI was not adjusted for age.

Results: A total of 226 men and 175 women were identified. More men were pre-treated with vitamin K-antagonists (73.5% men *vs*. 60.6% women) and more women with non-vitamin K-antagonist oral anticoagulants (26.5% men *vs*. 39.4% women), $p = 0.009$. Women were older (mean age 81.9 *vs*. 76.9 years, $p < 0.001$). CHA_2DS_2-VASc and CCI were similar in men and women.

Hematoma volumes (22.1 ml in men and 19.1 ml in women) and National Institute of Health Stroke Scale (NIHSS) scores (13 *vs*. 13) were not statistically different, while median Glasgow Coma Scale (GCS) was lower in women, (14 [8;15] *vs*. 14 [10;15] $p = 0.003$).

Women's probability of receiving reversal agents was significantly lower (adjusted odds ratio [*aOR*] = 0.52, $p = 0.007$) but not for surgical clot removal (*aOR* = 0.56, $p = 0.25$). Women had higher odds of receiving do-not-resuscitate (DNR) orders within a week (*aOR* = 1.67, $p = 0.04$). There were no sex-differences in neurological deterioration (*aOR* = 1.48, $p = 0.10$), ability to walk at 3 months (*aOR* = 0.69, $p = 0.21$) or 1-year mortality (adjusted hazard ratio = 1.18, $p = 0.27$).

Conclusion: Significant sex-differences were observed in age, risk factors, access to treatment, and DNRs while no significant differences were observed in comorbidity burden, stroke severity, or hematoma volume. Outcomes, such as adjusted mortality, ability to walk, and neurological deterioration, were comparable. This study supports the presence of sex-differences in risk factors and care but not in presentation and outcomes.

Keywords: stroke, sex-differences, ICH, oral anticoagulation, vitamin K-antagonist, stroke in women, intracerebral hemorrhage (ICH), NOAC

INTRODUCTION

There is a growing literature documenting sex differences in risk factors, presentation, treatment interventions, and outcome in stroke. Women are in general older at the time of stroke and have a higher frequency of hypertension (1). Atrial fibrillation (AF) increases the risk of stroke more in women than it does in men (2). Women are also more likely to present with non-traditional stroke symptoms as compared to men and women possibly have a greater benefit from physical activity in the prevention of cardiovascular disease (1). It is consistently reported that women have worse outcomes after stroke, which partly results from older age, worse pre-stroke functional status, and higher comorbidity; however, after adjusting for these factors, women still have worse outcomes (1).

A recent publication demonstrated (3) that women with acute stroke were more likely to be admitted to an acute stroke unit, but less likely to be intubated, to be given treatment for fever, or be admitted to an Intensive Care Unit (ICU). On admission, women had higher odds of having received pre-stroke antihypertensive medication and lower odds of taking antiplatelets, being treated with antidiabetics or lipid-lowering drugs, while no differences in the use of oral anticoagulants were observed. In the total stroke population, case-fatality rates were higher in women than men. However, in multivariable analyses, the risk of death was lower in women than men indicating that the unadjusted estimates were due to confounding. This finding was not significant in the intracerebral hemorrhage (ICH) population alone (3). Based on the 5-dimensional EuroQol, female patients have significantly worse scores on all parameters except for mobility (3). A sub-analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Hamorrhage trials (INTERACT 1 and 2) found a higher adjusted mortality in men as compared to women (4).

Oral anticoagulant (OAC)-related ICH is a devastating presentation of stroke with very high fatality rates (5–7). Following the increased use of OAC, the number of patients with OAC-related ICH is increasing (8). So far, there are no reports available that have explored if sex-differences are present in the OAC-related ICH.

The aim of this study was to investigate that sex differences were present in risk factors, acute presentation, treatment interventions, and outcome in OAC-related ICH.

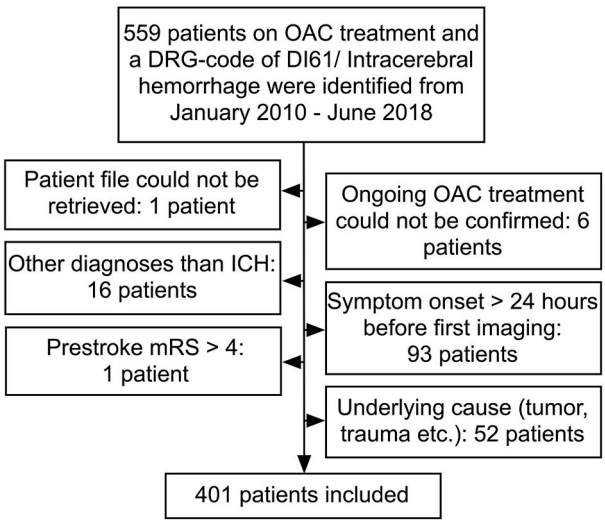

FIGURE 1 | Patient flow. Patients may be counted more than once, if they fulfilled more than one exclusion criteria. OAC, oral anticoagulant; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale.

MATERIALS AND METHODS

COOL-ICH

The analysis was performed using data from the Capital Region Anticoagulation-related ICH study (the COOL-ICH study) cohort. The cohort was based on all patients presenting with an imaging-confirmed OAC-related ICH within 24 h of symptom onset to one of five neurological or neurosurgical departments in the Capital Region of Denmark (approximate population of 1.9 million) from January 2010 to June 2018. In Denmark, the procedure for all patients with stroke is to admit them to a stroke unit and these admissions are then audited by the Danish Stroke Registry (9, 10). For this study, patients were identified for the COOL-ICH cohort using two different approaches: (1) the Danish Stroke Registry in which all departments treating stroke patients are legally obliged to report to and (2) by discharge lists from the individual neurology and neurosurgery departments. Patients with an underlying cause (e.g., vascular malformation or trauma) or a pre-stroke modified Rankin Scale (mRS) above 4 were excluded (**Figure 1**).

National Institute of Health Stroke Scale (NIHSS) was if not available in patients' files estimated (11). Female sex and age were excluded from CHA_2DS_2-VASc (12) as a predictor to be able to compare men and women. To be able to assess multimorbidity separate from age, we did not age-adjust Charlson Comorbidity Index (CCI) (13). The ability to walk at 3 months was assessed based on the note closest to 3 months after stroke in the patient's file.

All clinical imaging was systematically assessed by one senior neuroradiologist (IH). The neuroradiologist was blinded to all other information than the imaging prescription note. This would always include sex and age and may or may not have included information on OAC and concomitant diseases. Hematoma volume was assessed using the ABC/2 method (14). For each participant outcome, data (neurological deterioration and ability to walk) were adjudicated by two independent senior neurologists (LC, JM, PM, SR, HI, CK, TC, and KÆ) based on medical charts, which were blinded for admission to hospital, treating physicians and type of oral anticoagulant; in cases of disagreement, HC had the final say. Neurological deterioration was defined as a fall in Glasgow Coma Scale (GCS) of 2 points or more, and an increase in NIHSS of 4 points or more or 4 strokes. In progression (SIP) score points, using the first recorded neurological status as reference. A more comprehensive protocol is available online, which was completed before the initiation of data acquisition (15).

MEDSTAT

MEDSTAT is a publicly available online database based on all prescription drugs dispensed at Danish pharmacies, from which aggregate yearly numbers can be retrieved (16). Based on numbers from the Capital Region of Denmark, accessed in MEDSTAT, we retrieved the number of patients for each year (2010–2018) who had presented a prescription for a Vitamin-K antagonist [VKA, ATC B01AA (17)], Dabigatran [ATC B01AE07 (18)], or a direct factor Xa inhibitor [ATC B01AF (18)].

Statistical Analysis

For each group (men or women), we calculated means and medians as appropriate on numerical variables and percentages for categorical variables. Differences were tested using the *t*-test or Mann–Whitney *U* test and the chi-square or Fisher's exact test. Based on the MEDSTAT data, we made a figure, including the number of patients per year of both men and women treated with either VKAs or non-vitamin K-antagonist oral anticoagulants (NOACs) during 2010–2018, as well as a figure with number of ICHs per year, per 1,000 patients who had presented at least one prescription for either NOAC or VKA during that year. We calculated unadjusted odds ratios (ORs) between men and women for pharmacological reversal, surgical clot removal, external ventricular drains (EVD), ICU (neuro-intensive or general), intubation, and do-not-resuscitate (DNR) orders within 24 h as well as within the first week, neurological deterioration within 24 h and 7 days and finally for the ability to walk at 3 months. We also calculated adjusted ORs for men and women with the above-mentioned variables; adjusting for age, CCI, hematoma volume, pre-stroke mRS, and admission GCS. The Cox regression was performed using days from ICH admission until both 1-year death and 7-day death with sex as the independent variable. Both an unadjusted hazard ratio (HR) was calculated as well as one where we adjusted for the same variables as in the logistic regression. For pre-stroke mRS, we detected non-proportional hazards, and stratified this variable, with only a small change in the coefficient for sex.

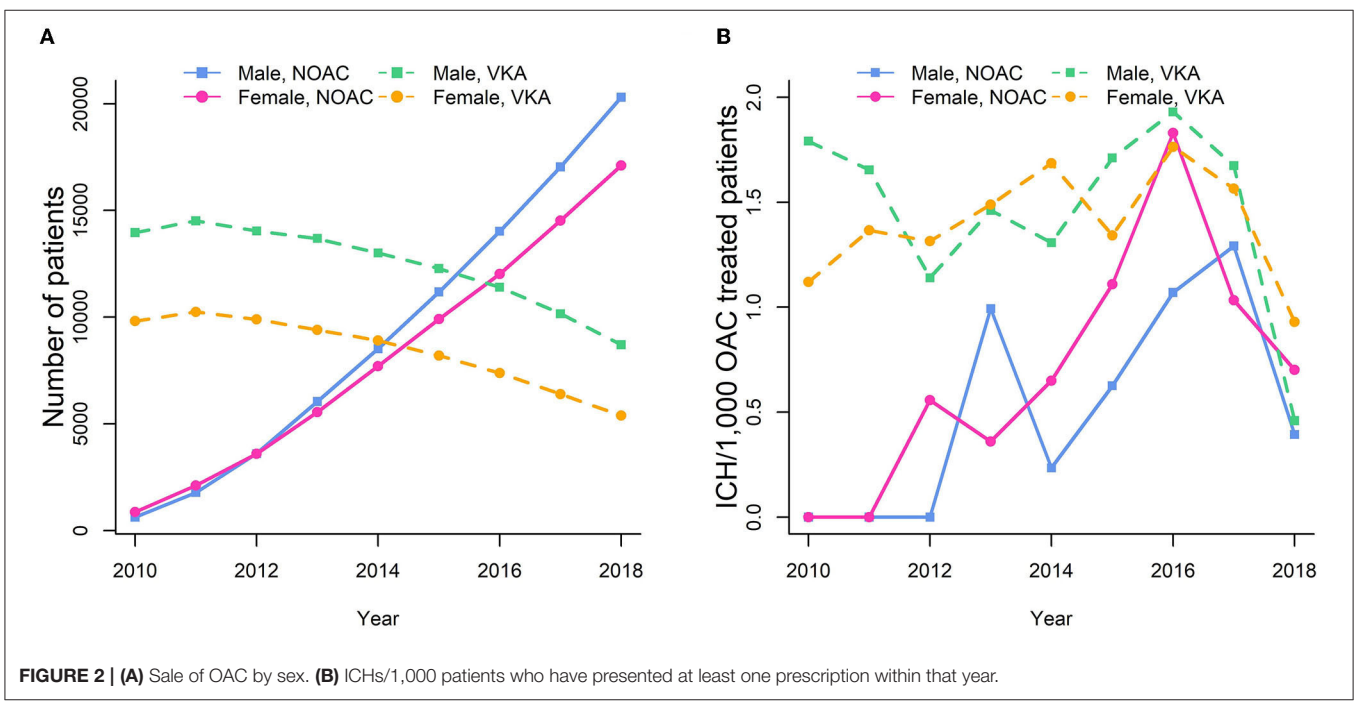

FIGURE 2 | (A) Sale of OAC by sex. **(B)** ICHs/1,000 patients who have presented at least one prescription within that year.

Ethics

The COOL-ICH study was approved by the Danish Patient Safety Authority (3-3013-2102/1) and the Danish Protection Agency (2012-58-0004). No ethical approval was needed for this study according to the Danish law. Data reporting was followed the STROBE statement.

RESULTS

Occurrence of OAC-ICH in Men and Women

In the COOL-ICH cohort, 226 (56.4%) patients were men and 175 (43.6%) patients were women. Looking at sales of OAC, more men than women were treated with both NOAC and VKA during the study period, but number of ICH per 1,000 patients treated with OAC were comparable, though most years, this was a little lower for NOAC-treated men than for NOAC-treated women (**Figure 2**).

Patient Characteristics

Female patients were significantly older and had a significantly higher pre-stroke mRS (**Table 1**). No differences were observed in risk factors (AF, hypertension, hyperlipidemia, previous ischemic stroke or transient ischemic attack, previous venous thromboembolism, diabetes, kidney disease, chronic pulmonary disease, congestive heart failure, previous myocardial infarction, and dementia) except for tobacco and alcohol use, where a significant male preponderance was observed (**Table 1**; **Figure 3**). There were no differences between men and women in CCI and CHA_2DS_2-VASc (**Table 1**; **Figure 4**).

Baseline Medications

In the COOL-ICH cohort, fewer men than women were on NOACs and more men were on VKAs (**Table 1**). Men were more frequently co-treated with antiplatelets as well as lipid-lowering drugs. There were no significant differences between men and women in the use of antihypertensive drugs or selective serotonin reuptake inhibitors (SSRI) (**Table 1**). Only three patients were concomitantly on dual antiplatelet treatment, one man and two women.

Acute ICH Event: Presentation and Interventions

Time from ICH symptom onset to admission was similar ($p = 0.56$) for male patients (median: 3.2 h, *IQR*: 1.4; 9.2) and female ones (median: 3.7 h, *IQR*: 1.6; 8.1). No significant difference in time to imaging was observed. Women had marginally more clinically severe presentations on admission, but this only reached significance in GCS and no differences were observed in hematoma volume (**Table 1**).

Men were significantly more likely to be treated with pharmacological reversal agents (e.g., prothrombin protein complex [any dose], platelet suspension, fresh frozen plasma, tranexamic acid, specific antidotes, etc.) than women (**Table 2**).

No sex differences were present in prescribing systolic blood pressure limits for the administration of acute antihypertensive treatment; however, blood pressure orders were only applied in less than half of the patients (**Table 1**).

More men than women had surgical clot removal, but this was not significant in the adjusted analysis. No differences were observed in use of EVD (**Table 2**).

Do-Not-Resuscitate Orders

Do-not-resuscitate orders (DNRs) were given more often to women both within 7 days and 24 h based on both unadjusted OR and adjusted OR. The time from admission to the DNR decision was significantly longer for men than women, $p =$

TABLE 1 | Baseline data in 401 men and women with oral anticoagulant (OAC)-related intracerebral hemorrhage (ICH).

	Male ($n = 226$)	Female ($n = 175$)	*P*-value
Mean age (SD)	76.9 (8.3)	81.9 (7.4)	<0.001
Modified Rankin Scale	0 (0; 1)	1 (0; 2)	<0.001
Comorbidity scores			
Median Charlson Comorbidity Index (IQR)	1 (0; 3)	1 (0; 2)	0.62
Median CHA_2DS_2-VASc (IQR)	2 (1; 3)	2 (1; 3)	0.74
Medicine			
NOAC	60 (26.5%)	69 (39.4%)	0.009
VKA	166 (73.5%)	106 (60.6%)	
Antiplatelets	40 (18.6%)	16 (9.9%)	0.03
Antihypertensives	156 (71.9%)	123 (75.9%)	0.44
Lipid lowering agents	94 (43.9%)	48 (29.6%)	0.006
Selective serotonin reuptake inhibitors	14 (6.5%)	20 (12.3%)	0.08
Smoking status			
Active smoker	22 (13.1%)	10 (7.8%)	<0.001
Former smoker	80 (47.6%)	37 (28.7%)	
Never smoker	66 (39.3%)	82 (63.6%)	
Alcohol/ drug use			
No alcohol use	42 (25.5%)	54 (44.3%)	<0.001
Below 14 units per week	89 (53.9%)	63 (51.6%)	
Above 14 units per week	34 (20.6%)	5 (4.1%)	
Alcohol dependency	20 (8.8%)	2 (1.1%)	0.002
Stroke severity scores			
Admission Glasgow Coma Scale	14 (10; 15)	14 (8; 15)	0.03
Admission NIHSS	8 (4; 13)	10 (5; 15)	0.09
Systolic blood pressure limit order, *n* (%)[a]			
<140 mmHg	53 (23.5%)	42 (24.0%)	0.99
140–160 mmHg	27 (11.9%)	21 (12.0%)	
160–180 mmHg	4 (1.8%)	2 (1.1%)	
No limit ordered	142 (62.8%)	110 (62.9%)	
Radiology			
Median hematoma volume, mL (IQR)	22.2 (4.6; 64.6)	19.1 (4.6; 63.8)	0.90

OAC, oral anticoagulant; ICH, intracerebral hemorrhage; SD, standard deviation; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mmHg, millimeter of mercury.

[a] *Number of patients with a systolic blood pressure limit order in the patient file.*

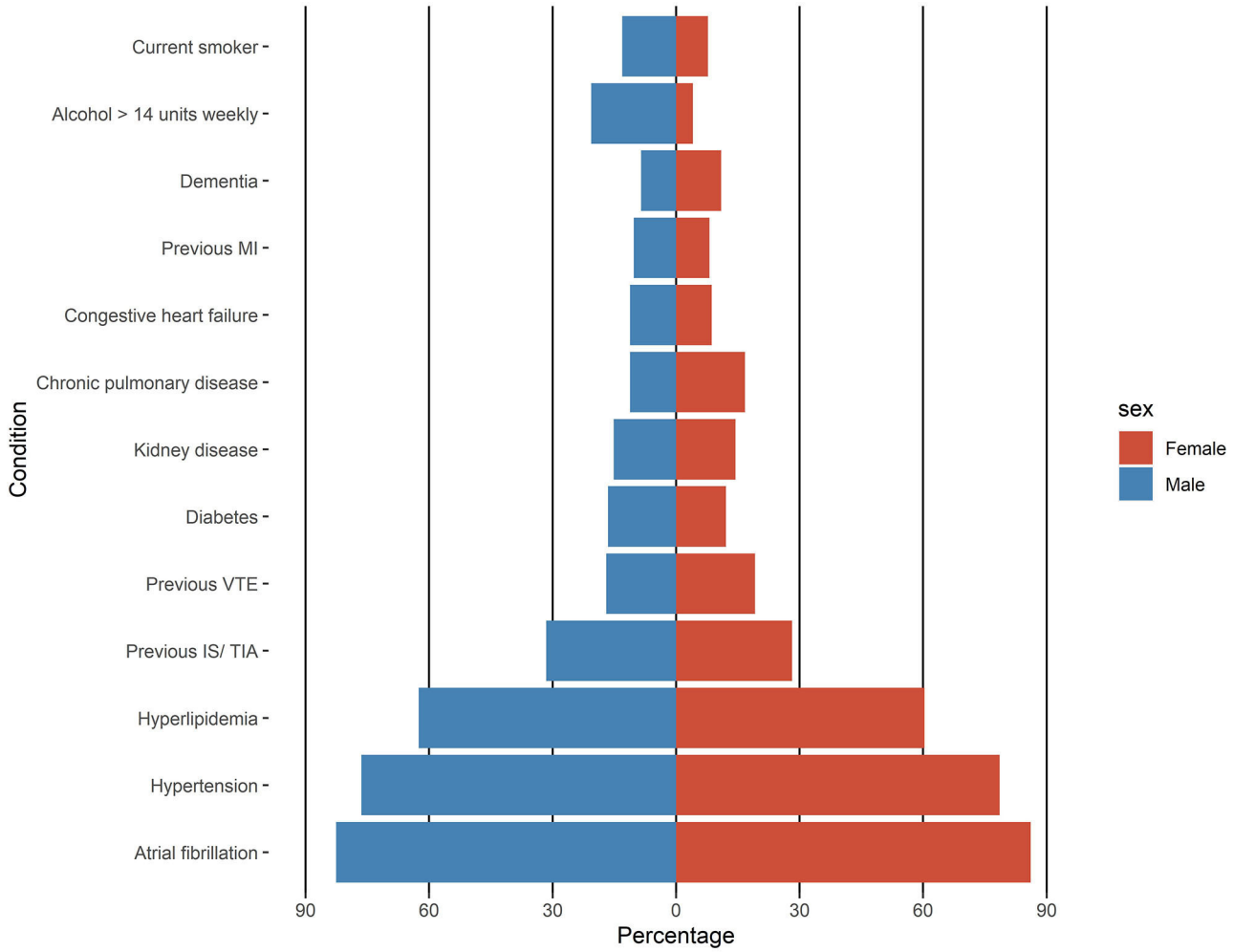

FIGURE 3 | Baseline risk factors in men and women with oral anticoagulant-related intracerebral hemorrhage. MI, myocardial infarction; VTE, venous thromboembolism; IS, ischemic stroke; TIA, transient ischemic attack.

0.01 (**Figure 5**). Of the patients that were given a DNR within 24 h, female patients were significantly older, had a significantly lower CCI as well as significantly lower hematoma volumes (57.6 ml *vs*. 50.2 ml, $p < 0.001$), with no differences between men and women with DNR orders in mRS, GCS, NIHSS, or 1-year mortality (**Table 3**).

Outcome

No differences were observed in rates of neurological deterioration. Male patients were significantly more likely to be able to walk at 3 months than female patients, but this was not the case in the adjusted analysis (**Table 2**). The median time from the admission to the evaluation of the ability to walk was 82 days for men (*IQR*: 42; 92) and 71 days for women (*IQR*: 41; 93), $p = 0.57$. Fifty percent of male patients had died within 1 year of the ICH, in comparison to 65% of women (**Figure 6**); however, in the Cox-regression analysis, female sex did not increase the risk of 1-year death significantly ($p = 0.33$) when adjusting for age, hematoma volume, CCI, and pre-stroke mRS (**Table 2**).

DISCUSSION

More men than women were exposed to OAC in the Capital Region of Denmark during the observation period, with a comparable number of OAC-related ICH per 1,000 OAC-treated patients between men and women each year. Female patients were older and had a higher pre-stroke mRS. CCI and CHA_2DS_2-VASc were comparable in men and women. Fewer men than women were pre-treated with a NOAC. More men than women were pre-treated with VKA as well as concomitantly with antiplatelets and lipid-lowering agents. Male patients also had a higher tendency toward smoking and alcohol.

Upon the admission, female patients had a marginally, but significantly, lower GCS, with no differences in NIHSS or hematoma volume. Female patients were less likely to be given pharmacological reversal and more likely to be given a DNR order. When adjusting for age, hematoma volume, pre-stroke mRS, and CCI, there were no differences between men and

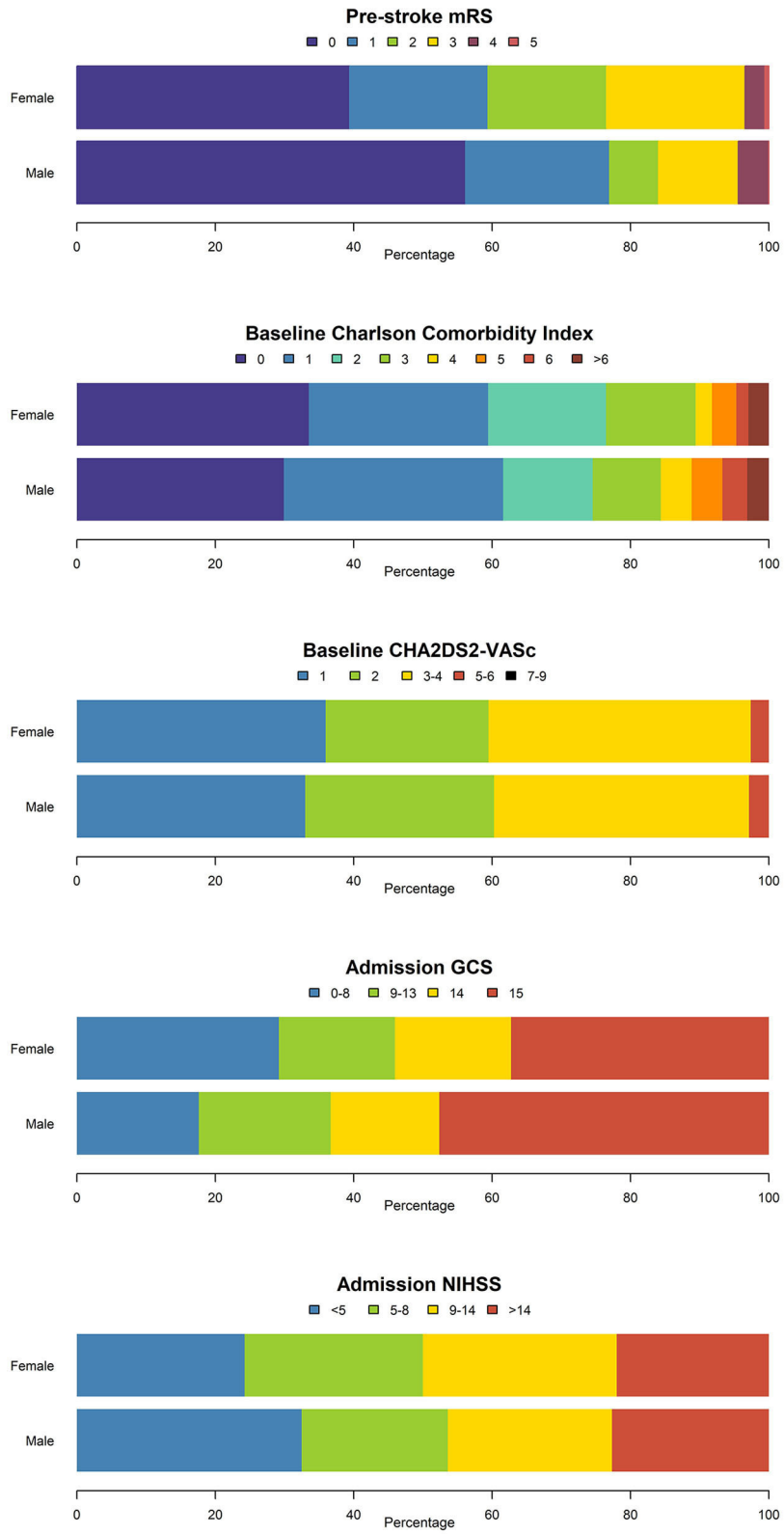

FIGURE 4 | Disability-, comorbidity-, and stroke-severity scores in men and women with OAC-ICH. mRS, modified Rankin Scale; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

TABLE 2 | Interventions and outcomes in 226 men and 175 women with OAC-related ICH.

	Unadjusted OR	95% CI	*P*-value	Adjusted OR[a,b]	95% CI	*P*-value
Pharmacological reversal	0.45	0.29; 0.70	<0.001	0.52	0.32; 0.84	0.007
Surgical clot removal	0.36	0.14; 0.83	0.02	0.56	0.20; 1.44	0.25
External ventricular drains	0.78	0.39; 1.52	0.47	1.43	0.67; 3.06	0.35
Intensive care unit (neuro or general)	0.83	0.52; 1.33	0.44	1.51	0.87; 2.62	0.14
Intubation	0.95	0.58; 1.54	0.83	1.68	0.94; 3.02	0.08
DNR within 24 h	2.13	1.42; 3.21	<0.001	1.91	1.15; 3.18	0.01
DNR within first week	1.92	1.28; 2.88	0.002	1.67	1.01; 2.77	0.04
Neurological deterioration within 24 h[c]	1.39	0.60; 3.35	0.45	1.93	0.78; 5.07	0.17
Neurological deterioration within 7 days	1.32	0.88; 1.97	0.18	1.48	0.93; 2.38	0.10
Able to walk independently at 3 months	0.58	0.36; 0.93	0.02	0.69	0.38; 1.22	0.21
	Unadjusted HR	**95% CI**	***P*-value**	**Adjusted HR[a]**	**95% CI**	***P*-value**
One-year mortality	1.48	1.14; 1.93	0.003	1.18	0.88; 1.57	0.27

Odds ratios and hazard ratios for sex, male sex being the reference.

OR, odds ratio; CI, confidence interval; HR, hazard ratio; DNR, Do-not-resuscitate order.

[a] *Adjusted for age, Charlson Comorbidity Index (CCI), hematoma volume and pre-stroke modified Rankin Scale (mRS).*

[b] *7 patients were omitted from the analysis due to missing data.*

[c] *Based on patients with neurological deterioration within 24 h opposed to within one week.*

women in neurological deterioration, ability to walk at 3 months or death.

Data from the American PINNACLE registry showed increased use of VKA in male as compared to female AF patients (19). Another study found that significantly more newly diagnosed male AF patients were treated with almost all types of OAC except for rivaroxaban. They also found a higher rate of ICH in the female patients, though this was no longer significant when adjusting for age, CCI, congestive heart failure, diabetes mellitus, region, insurance plan, and receipt of concomitant medications (20).

The observed differences in risk factors between the sexes, such as age, corroborate previous findings (1, 21). These findings are most likely determined both by biological and cultural factors.

The higher rates of the use of lipid-lowering agents and antiplatelets are in accordance to previous reports (3, 22–26). A potential explanation may be the higher frequency of atherosclerotic disease in men (22–26).

No differences were observed in NIHSS or hematoma volume, albeit GCS was somewhat lower in women. Nonetheless, women less often received reversal agents or clot removal surgery and DNR orders were more frequent. The lower frequency of women treated with clot removal surgery may be explained by the age, CCI, hematoma volume, and pre-stroke mRS of the women (**Table 2**). These factors, however, did not explain the difference in reversal agents or DNR orders. The sex difference in the use of DNR orders corresponds to previous findings in ICH patients (27) as well as patients successfully resuscitated from in-hospital cardiac arrest (28). The finding of female sex being an independent predictor of receiving a DNR order in the adjusted analyses underlines the need for further investigation into the unconscious bias in the doctors prescribing the DNR orders.

Female sex was no longer an independent predictor of neurological deterioration or inability to walk when adjusting for age, hematoma volume, CCI, and pre-stroke mRS. The observed unadjusted higher mortality in women was probably due to the sex differences in baseline characteristics, as adjusted analysis indicated no sex difference in case fatality.

Despite equal hematoma volume and NIHSS on admission, reversal therapy and surgical hematoma removal were less often applied to women in comparison to men, though in adjusted analysis, this only remained significant for reversal therapy, potentially due to less numbers in surgical treatment. This finding is in line with DNR orders being issued more frequently and earlier in female patients.

Sex differences in stroke care have previously been reported, however, adjusted survival rates are higher in women in comparison to men after stroke in most reports (1, 3, 21, 22, 24). We found no differences between sexes in adjusted 1-year mortality after ICH. However, DNR orders may worsen outcomes independently in ICH patients (29–32) and it is possible that the increased use of DNR orders in women in our study may have contributed to a decreased survival.

Our observation of few interventions in women with ICH is in accordance with previous reports (3). Guidelines in stroke care have changed during the observation period, and recommendations to proactively reverse anticoagulation were only implemented in Denmark at the end of the observation period (33). Nonetheless, this does not explain the difference in reversal attempts between the sexes. Although there is no strong evidence supporting neither reversal therapy so far, this is the case both in men and women, i.e., irrespective of gender (33, 34).

Implicit gender bias has been identified as an explanatory factor in testing in acute myocardial infarction (35), where female sex is associated with frailty and increased caution in relation to interventions. There are so far no data available if this phenomenon is also relevant to stroke.

With the well-known predictive value of DNRs (28–31), our findings underline the need for further investigation into the

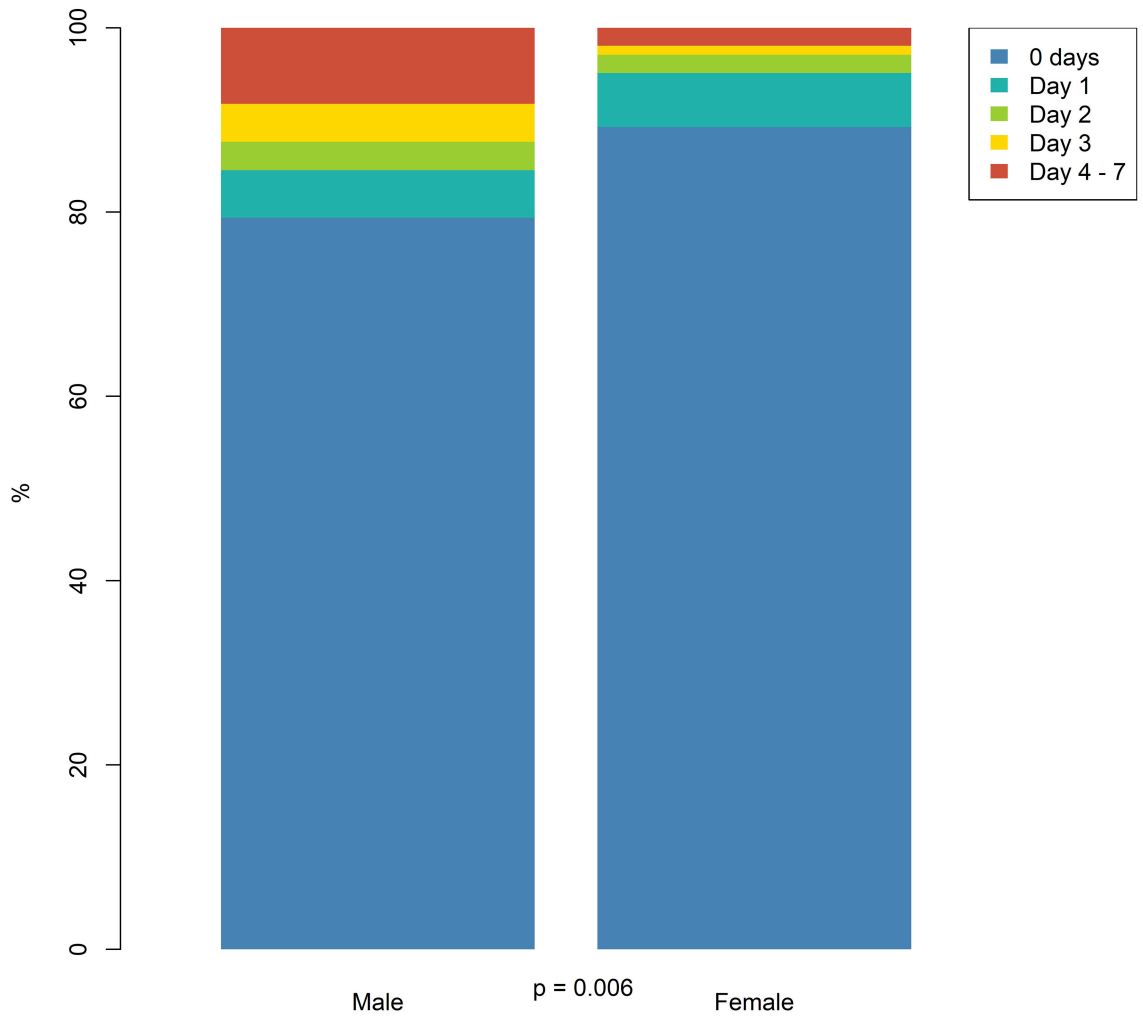

FIGURE 5 | Time from admission to do-not-resuscitate (DNR) within the first week.

TABLE 3 | Patients with OAC-related ICH given DNR orders within 24 h.

	Male, *n* = 76	**Female, *n* = 91**	***P*-value**
Age (SD)	78.5 (± 8.3)	83.1 (± 7.9)	<0.001
Charlson comorbidity index	2 (1; 4)	1 (0; 2)	0.009
Pre-stroke mRS	1.0 (0.0; 2.3)	1.0 (0.0; 3.0)	0.09
Admission GCS	9 (6; 13)	9 (5; 14)	0.92
Admission NIHSS	13 (8; 16)	13 (8; 15)	0.88
Hematoma volume	57.6 (27.6; 118.6)	50.2 (15.1; 111.1)	<0.001
One-year mortality	70 (92.1%)	86 (94.5%)	0.76

OAC, oral anticoagulants; ICH, intracerebral hemorrhage; DNR, do-not-resuscitate; SD, standard deviation; mRS, modified Rankin Scale; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

interaction of age, age bias, sex, and gender bias in treatment decisions. Our findings further support a difference in the pathophysiology of stroke in male and female patients—possibly at least partly based on lifestyle, underlining the need for including women in stroke trials but also the need for research in the pathophysiology of stroke in men and women.

Limitations

There are some limitations to this study: the study is retrospective and observational and restricted to hospitalized patients. This methodology may have reduced the validity of variables that are mostly narratively described in patients' files, including neurological deterioration and ability to walk at 3-months. Despite mandatory admission to the stroke unit, some patients may have been missed, e.g., due to death before hospital admission or if admitted to another specialty in case of other higher prioritized condition, or if diagnostic brain imaging was only performed at 24 h or later. Based on our data, it was not possible to assess adherence to prescribed OAC. No quality-of-life data were available; these could have provided further insights into qualitative outcomes. As to blood pressure control in the

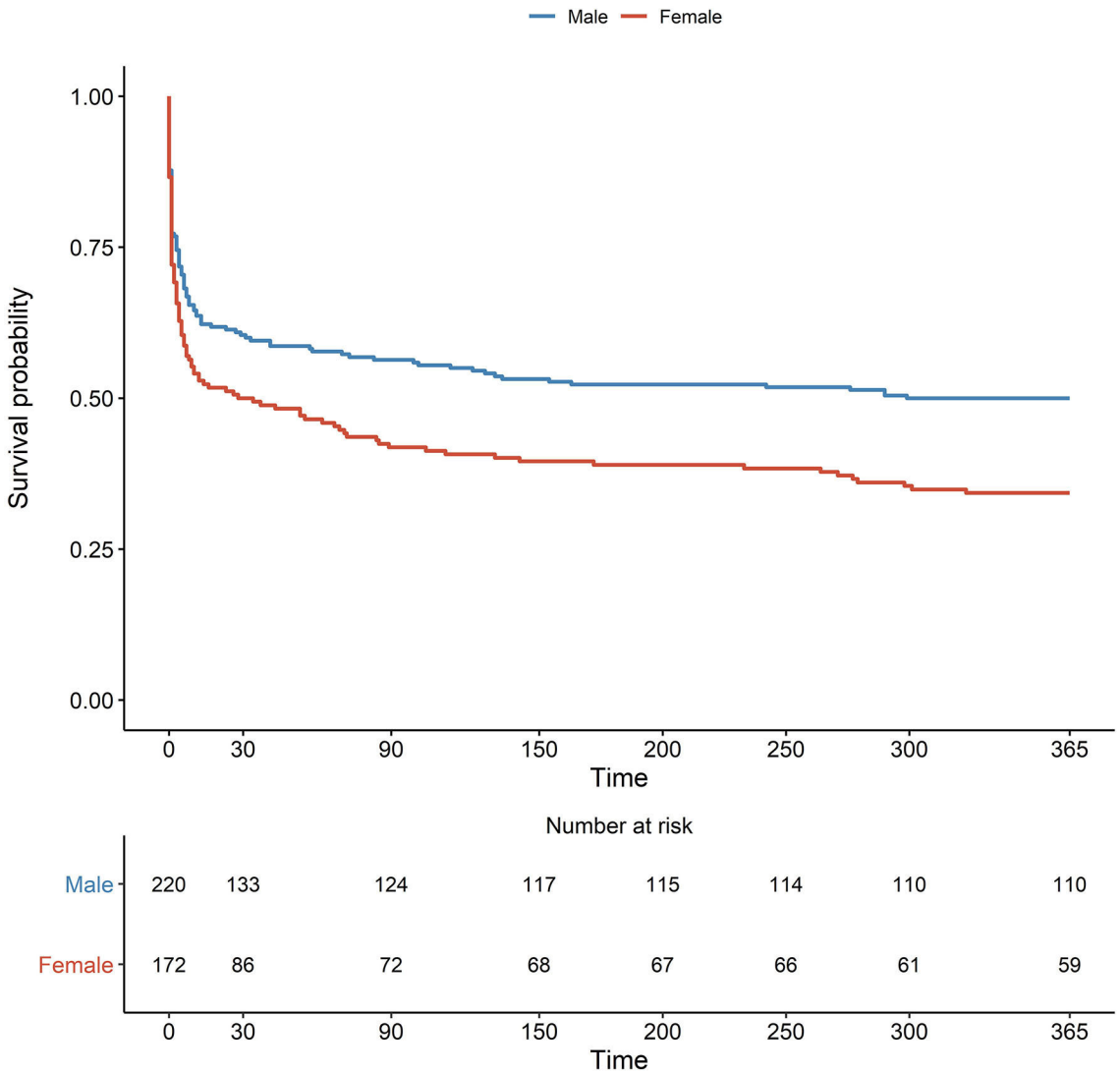

FIGURE 6 | Kaplan–Meier plot with numbers at risk and number of events.

acute phase, we only have data on the prescriptions, not on the actual blood pressure levels.

Strengths

The study is based on a well-defined catchment area (Capital Region of Denmark) with a public healthcare system providing all acute healthcare for the population free of charge and independent of personal income. The risk of selection bias is, therefore, low. All institutions have easy access to the explored interventions, such as reversal therapies. Data acquisition followed a detailed protocol, which was published before the data collection. All imaging were reassessed confirming a diagnosis, and endpoints adjudicated by senior neurologists.

Conclusions

This study demonstrated that women receive less treatment interventions and more DNR orders than men after OAC-related ICH. This cannot be fully explained by differences in the presentations of patients though age is no doubt a contributing factor. There is a need for research that can support reducing sex-based inequity in treatment and care. There were no significant differences in ICH rates between men and women.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CO and HC conceived the study. JG, CO, HC, and TS developed the protocol. HC, JG, CO, TS, and DG planned data analysis. JG, CO, and HC acquired data and performed data analysis. JG performed the statistical analysis. IH planned and performed radiological analysis. LC, JM, PM, SR, HI, CK, TC, and KÆ adjudicated outcomes and HC re-adjudicated outcomes with conflicts between first two observers. All authors reviewed the manuscript critically and approved the final version of the manuscript.

FUNDING

This work was supported by the Lundbeck Foundation and Grosserer A.V. Lykfeldt of Hustrus Legat. The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

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Conflict of Interest: CO has received a travel grant from Merck, Sharp, and Dohme. HC has received personal honoraria for speaking/educational activities from Boehringer-Ingelheim, Bristol-Myers-Squibb, Bayer, Daichi-Sanko and has received honoraria paid to her institution for services as National Lead in trials sponsored by Bayer and Alexion.

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frontiers in Neurology

ORIGINAL RESEARCH
published: 11 March 2022
doi: 10.3389/fneur.2022.831773

Pre-stroke Physical Inactivity and Stroke Severity in Male and Female Patients

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OPEN ACCESS

Edited by:
Christina Kruuse, Copenhagen University Hospital—Herlev Gentofte, Denmark

Reviewed by:
Alexander Tsiskaridze, Tbilisi State University, Georgia
Olive Lennon, University College Dublin, Ireland

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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *08 December 2021*
Accepted: *08 February 2022*
Published: *11 March 2022*

Citation:
Salmantabar P, Abzhandadze T, Viktorisson A, Reinholdsson M and Sunnerhagen KS (2022) Pre-stroke Physical Inactivity and Stroke Severity in Male and Female Patients. Front. Neurol. 13:831773. doi: 10.3389/fneur.2022.831773

Introduction: Females experience more severe ischemic strokes than do males. A higher pre-stroke physical activity level is associated with less severe stroke. The primary aim of this study was to explore the association between pre-stroke physical inactivity and stroke severity in male and female patients.

Methods: This was a retrospective, registry-based study. The data were retrieved from two stroke registries from 2014 to 2019. The primary explanatory variable was physical activity level before the stroke, assessed using the Saltin-Grimby Physical Activity Level Scale. The outcome was moderate to severe stroke at hospital admission, assessed using the National Institutes of Health Stroke Scale (NIHSS). A moderate to severe stroke was defined as a NIHSS score of ≥6. Binary logistic regression analysis was performed to explore if physical inactivity before the stroke could explain stroke severity in male and female patients.

Results: In total, we included 4,535 patients with ischemic stroke. Female patients ($n = 2{,}145$) had a mean age of 76 years, 35% had a moderate to severe stroke, and 64% were physically inactive pre-stroke. Male patients ($n = 2{,}390$) had a mean age of 72 years, 25% had a moderate to severe stroke, and 49% were physically inactive pre-stroke. Physical inactivity was associated with higher odds for moderate to severe stroke in both sexes (females' odds ratio [OR], 2.7, 95% confidence interval [CI]: 2.2–3.3, $p < 0.001$ and males' OR, 2.06, 95% CI: 1.7–2.5, $p < 0.001$). The association remained significant in the adjusted models.

Conclusions: Physically inactive females and males had higher odds of experiencing a moderate to severe stroke. However, the OR of female patients was somewhat higher than that of male patients.

Keywords: sex, sedentary behavior, physical activity, ischemic stroke, age groups, sex differences

INTRODUCTION

There are sex differences in stroke severity. Several studies have indicated that females experience greater stroke severity than do males (1–5). A recurring possible explanation for sex differences in stroke severity is that females have a longer lifespan than males and are approximately 5 years older at stroke onset (1, 4, 6–8). For individuals aged younger than 85 years, males have a higher risk of ischemic stroke than females; however, for those aged older than 85 years, females have a higher risk than males, and a 15% higher stroke mortality compared with age-matched males (9). Moreover, there is a sex difference in the risk factor profile (10), where females who have a first stroke predominantly have arterial hypertension and cardioembolic diseases, whereas males more commonly present with alcohol overuse, are smokers, and have a history of arterial peripheral disease (6). Pre-stroke physical activity (PA) level is associated with lower severity of stroke and better outcomes (11, 12). In a review, six studies reported that patients with higher pre-stroke PA had less severe strokes, whereas two studies found no association (12). A meta-analysis reported that a higher pre-stroke PA level may be more important for females than males to reduce stroke risk (13). In another study, the effect of pre-stroke PA on minor stroke was examined. Results indicated that regardless of age group only light and moderate PA were protective against more severe stroke (14). Although several studies have shown associations between pre-stroke PA and stroke severity, investigations regarding sex differences are limited.

PA promotes health for people of all ages (15). Physical inactivity is a global problem, with one-quarter of the worldwide population being insufficiently physically active (16). Well-established benefits of regular PA are reduced risk of ischemic heart disease, diabetes, and stroke (16, 17). PA is defined as any bodily movement produced by the skeletal muscles that generates energy and can be occupational, sports, conditioning, household, or other activities (18). Depending on sex and age, there appear to be differences in PA; intensity and frequency of PA decline with age in both sexes; however, females exhibit a faster decline (19). Among older people (aged $>$ 65 years), males report higher levels of PA than do females (19, 20). In another study in an older age group (aged 60–75 years), it was revealed that females had a lower frequency, shorter duration, and lighter intensity of leisure-time PA than those of males (21). In a self-reported PA questionnaire study conducted by the National Public Health Survey in Sweden in 2018, females in the younger age group (i.e., 30–44 years) were less physically active than males (64 vs. 70%). In contrast, the opposite was observed in the middle-age group (i.e., 45–64 years; 65 vs. 60%). Furthermore, in the oldest age group (65–84 years) no sex difference was reported (54% for both sexes) (22).

It is known that PA affects several risk factors for stroke and that PA habits as well as the risk factor profile differs between males and females. Additionally, associations between pre-stroke PA and a milder stroke severity have been reported in several studies, but with no study reporting associations for males and females separately, although several studies have adjusted for sex and age. Thus, the primary aim of this study was to explore the association between pre-stroke physical inactivity and stroke severity in male and female patients with ischemic stroke. The secondary aim was to explore sex differences in different age groups in relation to pre-stroke physical inactivity and stroke severity.

MATERIALS AND METHODS

Study Design and Sample

This cross-sectional and retrospective study was conducted as part of the Physical Activity Pre-Stroke in Gothenburg (PAPSIGOT) project (11). Patients who had been admitted to a stroke unit at three sites of Sahlgrenska University hospital were enrolled in the study. The hospitals provide emergency and basic care for the Gothenburg region, which has ∼850,000 inhabitants, and offer specialized care for Western Sweden, which has ∼1.7 million inhabitants (23). Patients were included if they had experienced an ischemic stroke (I63 according to the International Classification of Diseases (ICD-10), were admitted to a stroke unit from November 1, 2014, to June 30, 2019, had data available on pre-stroke PA and stroke severity at admission, and were aged $\geq$ 18 years at stroke onset.

Ethics Statement

The study was approved by the Regional Ethical Board of Gothenburg (approved 4 May 2016; registration number 346-16 and amendment approved 14 May 2020; registration number 2020-01668). Written informed consent for participation was not required. According to the Swedish Data Protection Authority, the handling of data generated within the framework of quality registries is exempt from the general rule requiring written informed consent from patients. Furthermore, the Personal Data Act (Swedish law #1998:204, issued April 29, 1998) allows data from medical charts to be collected for clinical purposes and quality control without written informed consent. Thus, the Declaration of Helsinki was not relevant to this project, which was based on data that were generated within quality registries. The collection and handling of data in this study followed the General Data Protection Regulation in Sweden (2018).

Procedure

The data were retrieved from three registries: Väststroke, Riksstroke, and Statistics Sweden (SCB). The registries were merged by statisticians at Riksstroke and SCB using personal identification numbers. Thereafter, personal identification numbers were replaced with serial numbers. SCB held the code key. The received data file was pseudonymized.

Väststroke is a quality register for stroke in Gothenburg, Sweden, and all stroke units register data on the register. Väststroke contains information on pre-stroke PA and stroke severity at admission, which are assessed using the Saltin-Grimby Physical Activity Level Scale (SGPALS) and the National Institutes of Health Stroke Scale (NIHSS) (23), respectively. Pre-stroke PA was assessed by physiotherapists working at the stroke units. Patients were asked about their PA on their first encounter with the physiotherapist. Stroke severity at admission was assessed by physicians. In cases with missing observations for SGPALS and NIHSS in the Väststroke register,

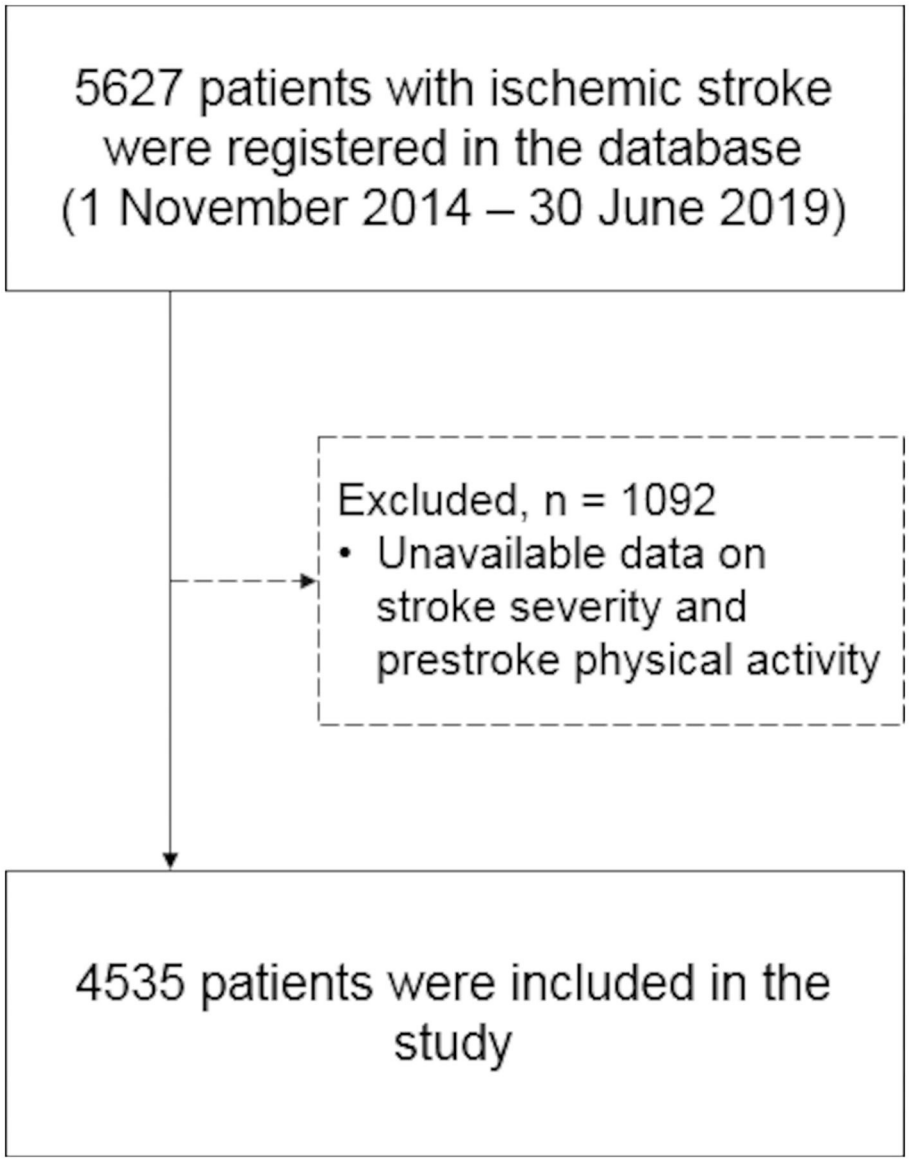

FIGURE 1 | Flow chart of the study participants with ischemic stroke.

assessments were retrieved from medical records when possible. Riksstroke is the national quality register for stroke care in Sweden (24). The coverage rate of acute stroke cases was 89% in 2019 (25). Riksstroke comprises information on patients' pre-hospital status, comorbidities, and medical treatment. Data in the Riksstroke register were recorded by trained nurses working at the stroke units. SCB covers the population statistics in Sweden. For this study, data on patients' education and country of birth were retrieved.

Variables

Stroke severity at admission was assessed using the NIHSS (26). The NIHSS score ranges from 0–42 points, with a higher score indicating more severe stroke. In this study, stroke severity was defined as mild (0–5), moderate (6–14), severe (15–24), and very severe (≥25) (27). The NIHSS was dichotomized for binary logistic regression analyses. To balance the distribution of the data between classes, stroke severity was defined as mild stroke (0–5) and moderate to severe stroke (6–42) (11).

Pre-stroke PA over the past year was assessed using the SGPALS (28). The SGPALS has four levels: (1) physical inactivity, (2) some PA for at least 4 h/week (light PA), (3) regular PA and training for at least 2–3 h/week (moderate PA), and (4) regular hard physical training for competitive sports several times per week (vigorous PA) (29). As the primary explanatory variable SGPALS was dichotomized into physically inactive (level 1) and physically active patients (levels 2–4)

TABLE 1 | Descriptive characteristics of study participants (n = 4,535, ischemic stroke) stratified by sex.

	Overall (n = 4,535)		Male (n = 2,390)		Female (n = 2,145)		P-value
Characteristics	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	
Age, years							<0.001
18–64	991	(21.9)	633	(26.5)	358	(16.7)	
65–74	1,101	(24.3)	694	(29.0)	407	(19.0)	
75–84	1,342	(29.6)	670	(28.0)	672	(31.3)	
≥85	1,101	(24.3)	393	(16.4)	708	(33.0)	
Living alone prior to stroke							<0.001[#]
Yes	2,206	(49.8)	903	(38.6)	1,303	(62.3)	
Missing	106	(2.3)	51	(2.1)	55	(2.6)	
Previous transient ischemic attack							0.412[#]
Yes	334	(7.5)	169	(7.2)	165	(7.9)	
Missing	107	(2.4)	54	(2.3)	3	(2.5)	
Previous stroke							0.043[#]
Yes	506	(11.3)	288	(12.3)	218	(10.3)	
Missing	76	(1.7)	41	(1.7)	35	(1.6)	
Atrial fibrillation							0.016[#]
Yes	799	(17.9)	390	(16.6)	409	(19.4)	
Missing	74	(1.6)	40	(1.7)	34	(1.6)	
Diabetes							< 0.001[#]
Yes	878	(19.7)	524	(22.3)	354	(16.8)	
Missing	73	(1.6)	38	(1.6)	35	(1.6)	
Smoking							0.066[#]
Yes	570	(14.6)	326	(15.5)	244	(13.5)	
Missing	624	(13.8)	292	(12.2)	332	(15.5)	
Country of birth							0.924[#]
Sweden	3,618	(80.3)	1,907	(80.3)	1,711	(80.2)	
Abroad	889	(19.7)	467	(19.7)	422	(19.8)	
Missing	28	(0.6)	16	(0.7)	12	(0.6)	
Education level							< 0.001
Pre-upper secondary school, ≤9 years	1,529	(34.7)	689	(29.6)	840	(40.4)	
Upper secondary school, 10–12 years	1,755	(39.8)	966	(41.4)	789	(38.0)	
Higher education, ≥13 years	1,125	(25.5)	676	(29.0)	449	(21.6)	
Missing	126	(2.8)	59	(2.5)	67	(3.1)	
Stroke severity, NIHSS score							<0.001
Mild stroke (0–5)	3,180	(70.1)	1,781	(74.5)	1,399	(65.2)	
Moderate stroke (6–14)	889	(19.6)	407	(17.0)	482	(22.5)	
Severe and very stroke (15–36)	466	(10.3)	202	(8.5)	264	(12.3)	
Reperfusion treatments (thrombolysis and/or thrombectomy)							0.111
Yes	875	(19.7)	482	(20.6)	393	(18.7)	
Missing	83	(1.8)	45	(1.9)	38	(1.8)	
Level of pre-stroke PA (SGPALS)							<0.001
Physically inactive	2,536	(55.9)	1,166	(48.8)	1,370	(63.9)	
Light PA	1,734	(38.2)	1,035	(43.3)	699	(32.6)	
Moderate PA	255	(5.6)	180	(7.5)	75	(3.5)	
Vigorous PA	10	(0.2)	9	(0.4)	1	(0.0)	
Blood pressure-lowering medication							<0.001[#]
Yes	2,753	(61.8)	1,389	(59.2)	1,364	(64.6)	
Missing	77	(1.7)	43	(1.8)	34	(1.6)	
Lipid-lowering medication							0.028[#]
Yes	1,165	(26.2)	646	(27.5)	519	(24.6)	
Missing	80	(1.8)	43	(1.8)	37	(1.7)	

Group comparisons were performed using [#] χ^2 and Mann-Whitney U-tests. NIHSS, national institutes of health stroke scale; PA, physical activity; SGPALS, saltin-grimby physical activity level scale.

Male Patients

	Stroke severity (NIHSS, score range 0-36)	Prestroke physical activity (SGPALS)	Age (range 18 - 103 y)	Risk factor index (range 0 - 4)	Education	Country of birth	Previous TIA	Living alone before stroke
Stroke severity (NIHSS, score range 0-36)	-	-0.17**	0.16**	0.08**	-0.07**	0.00	0.04	-0.07**
Prestroke physical activity (SGPALS)	-0.25**	-	-0.24**	-0.22**	0.16**	0.03	0.01	0.20**
Age (range 18 - 103 y)	0.23**	-0.31**	-	0.07**	-0.13**	0.10**	-0.11**	-0.10**
Risk factor index (range 0 - 4)	0.11**	-0.20**	0.05*	-	-0.12**	-0.08**	-0.03	-0.12**
Education	-0.12**	0.17**	-0.29**	-0.14**	-	0.05*	0.04	0.09**
Country of birth	-0.04	0.03	0.10**	-0.07**	0.05	-	-0.05*	-0.02
Previous TIA	0.06**	0.03	-0.11**	-0.04	0.03	-0.01	-	-0.02
Living alone before stroke	-0.09**	0.16**	-0.39**	-0.09**	0.15**	-0.08**	0.01	-

Female patients

FIGURE 2 | Correlation coefficients between explanatory variables and the outcome variable, stratified by sex (*$p < 0.05$ and **$p < 0.01$). Statistics: phi correlation coefficient for binary variables and Spearman correlation coefficient for ordinal variables. NIHSS, national institutes of health stroke scale; SGPALS, saltin-grimby physical activity level scale (range 1–4; 1 is physically inactive); TIA, transient ischemic attack.

to ensure balanced groups in the binary logistic regression models (11).

Other variables analyzed included patients' sociodemographic characteristics, comorbidities, stroke-related treatments, and outcomes. To enable group comparisons by stratifications, age was stratified into four groups: 18–64, 65–74, 75–84, and ≥ 85 years (4); education levels were defined as pre-upper secondary school (≤9 years), upper secondary school (10–12 years), and higher education, such as post-secondary education and postgraduate education (≥13 years); country of birth was defined as Sweden and outside of Sweden (because several participants were born outside of Sweden).

The risk factor index for ischemic stroke was created by grouping variables associated with an increased risk of having an ischemic stroke. In a previous study, the comorbidity burden was analyzed in pre-stroke patients with groupings of different variables (30). In the current study, the variable included conditions such as previous stroke, diabetes, smoking, and atrial fibrillation (AF) (31). The aggregated score of the risk factor index ranged from 0 to 4, where 0 indicates that the patient has no risk factors. Because previous transient ischemic attack (TIA) has been associated with lower stroke severity, it was not included in the risk factor index variable (32).

Statistical Analysis

Dropout analyses (included and excluded patients) and comparisons between male and female patients were performed using the chi-squared test (χ^2) for nominal variables and the Mann–Whitney *U*-test for continuous variables. Correlations between variables were studied by stratifying the data according to patients' sex. Spearman's rank-order correlation (r_s) was used for ordinal and scale variables, and the Phi coefficient was used for nominal variables. Correlation coefficients were interpreted as small ($< \pm 0.39$), medium (± 0.40 to ± 0.69), and large ($\geq \pm 0.70$) (33).

Binary logistic regression analyses were conducted to determine if pre-stroke physical inactivity could explain stroke severity in male and female patients. The outcome was moderate to severe stroke, which was defined as an NIHSS score of ≥6. The primary explanatory variable was pre-stroke physical inactivity defined as SGPALS level 1. Other explanatory variables were selected according to the clinical experience of the authors as well as previous literature (8, 34) and comprised age (four strata), previous TIA (yes/no), risk factor index (continuous), education (three strata), country of birth (Sweden, yes/no), and living alone prior to the stroke (yes/no).

Assumptions of the binary logistic regressions were explored prior to model building. Correlation coefficients between

TABLE 2 | Results of the univariable binary logistic regression analyses stratified by sex, showing the explanatory value of pre-stroke physical inactivity in relation to moderate to severe stroke.

	Male patients				Female patients			
	β (SE)	OR (95% CI)	*P*-value	AUC	β (SE)	OR (95% CI)	*P*-value	AUC
Pre-stroke physical inactivity (SGPALS, 1)	0.72 (0.1)	2.06 (1.71–2.50)	<0.001	0.61	1 (0.1)	2.72 (2.22–3.33)	<0.001	0.65

SE, standard error; OR, odds ratio; CI, confidence intervals; AUC, area under the receiver operating characteristic curve; SGPALS, saltin-grimby physical activity level scale. Model evaluation for male/female patients: Hosmer and Lemeshow test, 0/0; Omnibus test, <0.001/<0.001; Cox and Snell's R^2, 0.02/0.05; Nagelkerke's R^2, 0.04/0.06.

TABLE 3 | Results of the multivariable binary logistic regression analyses stratified by sex, showing the explanatory value of pre-stroke physical inactivity adjusted for age in relation to moderate to severe stroke.

	Male patients			Female patients		
	β (SE)	OR (95% CI)	*P*-value	β (SE)	OR (95% CI)	*P*-value
Pre-stroke physical inactivity (SGPALS, 1)	0.64 (0.1)	1.90 (1.57–2.30)	**<0.001**	0.83 (0.1)	2.30 (1.86–2.84)	**<0.001**
Age ≤ 64 years, Ref.			**<0.001**			**<0.001**
65–74 years	0.13 (0.1)	1.14 (0.87–1.48)	0.34	0.42 (0.2)	1.52 (1.09–2.12)	**0.014**
75–84 years	0.29 (0.1)	1.33 (1.03–1.73)	**0.031**	0.36 (0.2)	1.44 (1.06–1.95)	**0.02**
85+ years	0.59 (0.1)	1.79 (1.34–2.4)	**< 0.001**	0.93 (0.2)	2.54 (1.88–3.43)	**<0.001**

Ref, Reference; SE, standard error; OR, odds ratio; CI, confidence intervals; AUC, area under the receiver operating characteristic curve; SGPALS, saltin-grimby physical activity level scale. Bold text indicates statistical significance. Model evaluation for male/female patients. Hosmer and Lemeshow test, 0.66/0.86; Omnibus test, <0.001/<0.001; Cox and Snell's R^2, 0.03/0.07; Nagelkerke's R^2, 0.05/0.09; AUC, 0.61/0.65.

variables were explored, and variables with a correlation coefficient $\geq \pm 0.7$ were interpreted as having multicollinearity and were thus not included in the same regression model (33). Crosstables were explored between the outcome variable and all categorical explanatory variables for testing the assumption of 10 observations per outcome category.

Three binary logistic regression models were built, stratified by sex. The first univariable model explored the raw association between pre-stroke PA and stroke severity. The second model included age group with pre-stroke PA because it is known that older age is related to physical inactivity and greater stroke severity. The third model included all explanatory variables.

The results were evaluated as follows: at the variable level, we reported β coefficients with standard errors (SE), odds ratios (ORs) and 95% confidence intervals (CI), and *p*-values. The models were evaluated using the Hosmer and Lemeshow test ($p > 0.05$ indicates a good fit), the Omnibus test ($p \leq 0.05$ was desirable), and area under the receiver operating characteristic curve (AUC; a value of ≤ 0.5 indicated poor performance). The explained variance of the models was determined using Cox and Snell's R^2 and Nagelkerke's R^2 tests (higher values were desirable).

All statistical tests were two-tailed with an alpha level of 5%. The SPSS Statistics (IBM Corp. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY) was used for all statistical analyses (35).

RESULTS

A total of 4,535 patients were included in the study from the data file that comprised 5,627 patients. The dropout analyses did not show significant differences between the included ($n = 4,535$) and excluded patients ($n = 1,092$) for sex ($p = 0.765$) or age ($p = 0.164$) (**Figure 1**).

Patient Characteristics

Detailed information on the study sample is presented in **Table 1**. Briefly, there were 2,390 (52.7%) males and 2,145 (47.3%) females with mean (± standard deviation [SD]) ages of 72 years (13.1 years) and 76 years (14.0 years), respectively. Almost half (48.8%) of the males, and 63.9% of the females were physically inactive before the stroke. Median NIHSS scores were 2 and 3 for male and female patients, respectively. A higher proportion of female patients than male patients were physically inactive prior to stroke ($p < 0.001$) and had moderate to severe stroke ($p < 0.001$; **Table 1**).

Association Between Pre-stroke Physical Inactivity and Stroke Severity

Pre-stroke PA, measured using the SGPALS, was negatively correlated with stroke severity, as measured using the NIHSS, in both male and female patients. A lower level of PA was correlated with greater stroke severity. However, the strength of correlation was small: r_s −0.17 ($p < 0.01$) and r_s −0.25 ($p < 0.01$) in male and female patients, respectively (**Figure 2**). A lower level of PA was correlated with older age in both sexes (males: rs −0.24 [$p < 0.01$] and females rs −0.31 [$p < 0.01$]).

Univariable binary logistic regression models showed that physical inactivity was significantly associated with moderate to severe stroke in both male and female patients, with an OR of 2.06 (95% CI: 1.71–2.50) and 2.72 (95% CI: 2.22–3.33), respectively (**Table 2**).

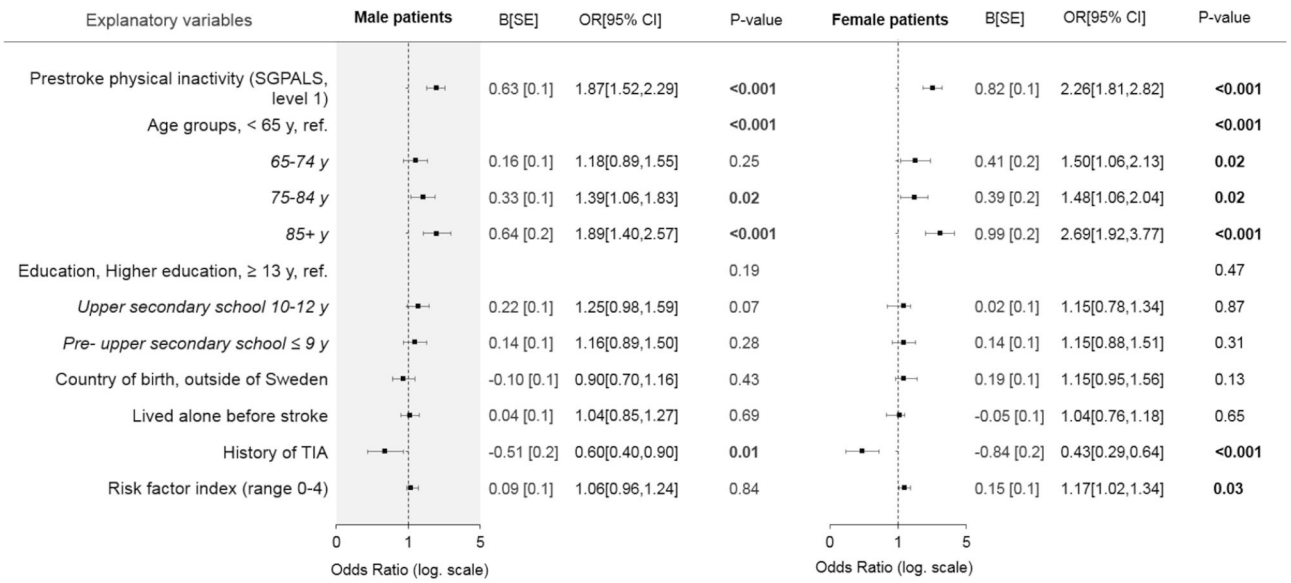

FIGURE 3 | Forest plot showing the results of the multivariable binary logistic regression models stratified by sex, with all explanatory variables in relation to moderate to severe stroke. Bold text indicates statistical significance. SGPALS, saltin-grimby physical activity level scale; TIA, transient ischemic attack. SE, standard error; OR, odds ratio; CI, confidence interval. Model evaluation metrics for male and female patients: Hosmer and Lemeshow test, 0.12/0.83; Omnibus test, <0.001/<0.001; Cox and Snell's R^2, 0.04/0.08; Nagelkerke's R^2, 0.06/0.11; area under the receiver operating characteristic curve, 0.63/0.68.

Pre-stroke physical inactivity remained a significant explanatory variable when it was adjusted for patients' age. However, the OR was lower than that of the univariable model (**Table 3**). Physically inactive male patients had 1.9 times higher odds of experiencing a moderate-severe stroke (OR: 1.90, 95% CI: 1.57–2.30) and physically inactive female patients had 2.3 times higher odds of experiencing a moderate-severe stroke (OR: 2.30, 95% CI: 1.86–2.84).

In the multivariable model that included all explanatory variables, pre-stroke physical inactivity remained a significant explanatory variable for moderate-severe stroke in both sexes (**Figure 3**). Education level and country of birth were non-significant variables (**Figure 3**).

DISCUSSION

This register-based study showed that pre-stroke physical inactivity is associated with severe stroke in both males and females. Physical inactivity was associated with a more severe stroke for both sexes, but with higher values for OR values for females. This result remained after adjusting for other variables. In addition, we found that older patients had higher odds of experiencing moderate to severe stroke, which was observed across both sexes. The highest ORs were observed in the oldest age group (≥85 years) of both sexes, although with higher values in females.

We found that more females than males were physically inactive and older before the onset of stroke, which is representative of the stroke population (19, 20). Significant associations were found between pre-stroke physical inactivity and stroke severity in both the correlation and regression analyses, although effect sizes were low. In the regression model, PA was adjusted for age groups, which slightly increased the effect size of the model. In the multivariable models that included the explanatory variables, the effect sizes were generally low. Stroke severity is a complex outcome and can depend on numerous factors. Although we included several in our analyses, data on other factors were not available in the registries. Reviews have found that cardiac diseases, stroke localization, occlusion level, stroke volume, pre-stroke dependency, pre-stroke institutionalization, and time to hospitalization are related to stroke severity (8, 34).

In the present study, females had more severe strokes than did males, which is in line with previous studies (4, 5). The higher proportion of physical inactivity could be explained by the higher age among the females. In addition, physical inactivity was related to stroke severity with higher OR values in the oldest groups for both sexes. Furthermore, the association was seen in all age groups (65–85+ years) for females, but in two age groups (75–85+ years) for males. Females having at least one risk factor (e.g., smoking, diabetes, previous stroke, or AF) had higher odds of a severe stroke. This is in line with a study where older age, AF, and pre-stroke functional dependency were possible explanations for greater stroke severity in females than males; with a 35% higher risk for females to experience a more severe stroke (8). Another study confirms that males and females differ in the prevalence of stroke risk factors (6). Females with ischemic stroke are more likely to have AF and experience thromboembolic events (5, 36), whereas males are more likely to have a history of diabetes and smoking (5). In the present study, a higher proportion of females were living alone before the stroke, this is consistent with previous findings (4, 5). Living alone is associated

with a longer time to hospitalization (5). We found that neither education level nor country of birth were associated with stroke severity. Older patients with lower education have an increased risk of stroke; however, no sex differences were observed (37). Although PA differs depending on geography (15), country of birth was not shown to be an important factor.

Limitations and Strengths

Self-reported PA, as measured by the SGPALS, can introduce recall bias because patients may experience difficulties in recalling and reporting PA levels. Recall bias was reduced by detailed follow-up questions by assessors and conversations with relatives. Another limitation of the SGPALS is the self-reported data. Although objective measures of PA are always preferred, they may not be feasible in acute stroke situations and large samples. Moreover, there were numerous assessors, which may have increased the risk of assessment bias. However, staff at stroke units have undergone local training and follow hospital routines; moreover, the SGPALS is a commonly used assessment tool that has been used in more than 600,000 subjects in numerous studies, especially in Nordic countries (38). Finally, in our study, stroke severity was measured using the NIHSS, which is a well-validated and widely used neurological stroke scale (26).

In the SGPALS, physical inactivity is defined as <4 h PA per week. In various studies, physical inactivity is referred to as sedentary behavior, and the definition of PA, especially sedentary behavior, is not consistent across previous studies (39). Thus, comparisons between studies are difficult.

Registries comprise consecutively collected data from large samples in clinical settings. Therefore, results from registry-based studies are generalizable across similar clinical settings. In Sweden, health care is tax-financed and available to everyone. In Riksstroke, 86% of the patients admitted to the Sahlgrenska University hospital were registered (25). Although the coverage is high, internal missing data are a common problem in registries, which results in selection bias. However, in this study, there were no significant differences in sex or age between the included and excluded patients. Moreover, the majority of our sample had a mild stroke, which is similar to the general Swedish population, according to the National Stroke Register (4). In addition, females in our sample were 4 years older than males at stroke onset, which is comparable with the national stroke population (4). Thus, our results have good generalizability within a similar context.

Stroke severity at admission is associated with numerous different factors. Further research including standardized measurements, sociodemographic characteristics of patients, and underlying biological mechanisms in various subgroups, such as sex, would contribute to valuable knowledge in this field and public health strategies.

CONCLUSION

Physical inactivity before stroke was associated with moderate to severe stroke in both sexes. However, female patients had higher ORs for physical inactivity, and this trend persisted even when physical inactivity was adjusted for age and other covariates. Our results suggest that PA should be encouraged in healthcare and public health sectors.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: according to the Swedish regulations the datasets generated for this study cannot be made publicly available for ethical and legal reasons. Researchers can submit requests for data to the authors (contact: ks.sunnerhagen@neuro.gu.se). Requests to access these datasets should be directed to ks.sunnerhagen@neuro.gu.se.

ETHICS STATEMENT

The study was approved by the Regional Ethical Board of Gothenburg (approved 4 May 2016; registration number 346-16 and amendment approved 14 May 2020; registration number 2020-01668). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PS: conceptualization of the study, analysis and interpretation of the data, and drafting of the manuscript. TA: conceptualization of the study, data analysis, interpretation of the data, and revising the manuscript for intellectual content. AV: acquisition of data and revising the manuscript for intellectual content. MR: acquisition of data, design and conceptualization of the study, and revising the manuscript for intellectual content. KS: design and conceptualization of the study, interpretation of the results, and revising the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

This study was financed by grants from the Swedish Research Council (VR2017-00946), NEURO Sweden, the Swedish Heart and Lung Foundation, the Swedish Brain Foundation, the Swedish state under an agreement between the Swedish government and the county councils, the ALF agreement (ALFGBG-718711 and ALFGBG-877961), the Swedish National Stroke Association, the Local Research and Development Board for Gothenburg and Södra Bohuslän (VGFOUGSB-941553), the Greta and Einar Asker's Foundation, Rune and Greta Almöv's Foundation for Neurological Research, Hjalmar Svensson's Research Foundation, Herbert and Karin Jacobson's Foundation, and Doktor Felix Neubergh's Foundation, Gun and Bertil Stohne's Foundation, and Sahlgrenska University Hospital foundations.

ACKNOWLEDGMENTS

The authors would like to thank the study participants, caregivers, and staff that collected and registered data.

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frontiers in Neurology

ORIGINAL RESEARCH
published: 21 March 2022
doi: 10.3389/fneur.2022.846690

Sex and Age Differences in Patient-Reported Acute Stroke Symptoms

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: 31 December 2021
Accepted: 11 February 2022
Published: 21 March 2022

Citation:
Eddelien HS, Butt JH, Christensen T, Danielsen AK and Kruuse C (2022) Sex and Age Differences in Patient-Reported Acute Stroke Symptoms. Front. Neurol. 13:846690. doi: 10.3389/fneur.2022.846690

Background: Identification of sex- and age-related differences in the presentation of atypical symptoms at stroke onset may reduce prehospital delay and improve stroke treatment if acknowledged at first contact.

Aim: To explore sex- and age-related differences in patient-reported typical and atypical symptoms of a stroke.

Methods: We used data from a cross-sectional survey at two non-comprehensive stroke units in the Capital Region of Denmark. Patient-reported symptoms, stroke knowledge, and behavioral response were analyzed by the Chi-square test or a Fisher's exact test separated by sex. Multivariable logistic regression adjusted for covariates were used to explore sex- and age-related differences according to each patient-reported typical or atypical symptoms.

Results: In total, 479 patients with acute stroke were included (median age 74 years [25th to 75th percentile: 64–80], and 40.1% were women). Female sex was associated with higher odds of presenting with atypical symptoms, such as loss of consciousness (OR 2.12 [95% CI 1.08–4.18]) and nausea/vomiting (OR 2.33 [95% CI 1.24–4.37]), and lower odds of presenting with lower extremity paresis (OR 0.59 [95% CI 0.39–0.89). With each year of age, the odds decreased of presenting with sensory changes (OR 0.95 [95% CI 0.94–0.97]) and upper extremity paresis (OR 0.98 [95% CI 0.96–0.99]), whereas odds of presenting with dysphagia (OR 1.06 [95% CI 1.02–1.11]) increased.

Conclusions: Patients of female sex and younger age reported on admission more frequently atypical stroke symptoms. Attention should be drawn to this possible atypical first presentation to facilitate correct identification and early stroke revascularization treatment to improve the outcome for both sexes.

Keywords: stroke, signs and symptoms, sex diferences, prehospital delay time, behavior

INTRODUCTION

Identification of sex- and age-related differences in the presentation of atypical symptoms at stroke onset may improve stroke treatment if acknowledged at first contact and reduce prehospital delay. Failed recognition of stroke upon presentation may cause delayed treatment with reduced clinical outcome (1–4). Currently, a small but increasing proportion of all ischemic stroke patients are treated with revascularization therapy, a well-established treatment worldwide (5–7). A frequent cause of failure to receive revascularization therapy within the required time window is a prehospital delay, either patient or system related. Patient delay is often associated with failure in symptom recognition or reluctance to respond acutely to symptoms. In system delay, much has improved in door-to-needle time at comprehensive stroke units but is still largely affected by missed symptom recognition by the health professionals at first contact (8–11). Stroke symptoms can be categorized as typical (12) (e.g., hemiparesis, facial palsy, visual, or language disturbances) or atypical (e.g., headache, dizziness, confusion, or sensory symptoms) (13), where the latter induce a significant risk of missing the stroke diagnosis.

Minimizing response time and implementing fast-track treatment of stroke is the key to reducing the impact of stroke on death and disability worldwide (14). Previous studies suggest that patients of female sex present a different profile of stroke symptoms on admission compared to the male sex. However, these studies focused on symptoms identified by health professionals and not those reported by the patients or bystanders. Symptoms recognized by health professionals may be different from those experienced and reported by the patient and bystanders potentially unaware of stroke-related symptoms (15–19). Knowledge is scarce on which acute stroke symptoms are reported by the patient or the bystander on admission. In this study, we have focused on the sex- and age-related differences in patient-reported symptoms which cause them to react and present to the prehospital health system. Older patients (>80 years of age) seem to present more frequently with typical symptoms, such as aphasia and hemiplegia (18). Headache and nausea are reported more commonly in younger patients, even after controlling for concomitant migraine (19). It remains to be seen if increased age amplifies this difference in the patient-reported symptoms (9). We hypothesized that patient-reported atypical symptoms at the onset of stroke were more frequent in the female sex and that the distribution of typical and atypical stroke symptoms varied with increasing age. Accordingly, we aimed to explore the sex- and age-related differences in patient-reported symptoms of a stroke.

METHODS

Study Design and Setting

This study is a *post-hoc* analysis of data from a cross-sectional survey performed at two non-comprehensive stroke units in the Capital Region of Denmark, Herlev Gentofte Hospital, and Nordsjællands Hospital. Study design and methods have previously been published (11).

Study Population

Patients with symptoms of acute stroke or transient ischemic attack (TIA) were enrolled immediately after admission to the stroke unit, albeit before completion of a full diagnostic workup for stroke. All diagnoses [International Classification of Diseases codes: I61: non-traumatic intracerebral hemorrhage (ICH); I63: ischemic stroke (IS); or G45. TIA] were confirmed by a neurologist supported by neuroimaging (CT and MRI scans). Enrolled patients fulfilled the following inclusion criteria: (1) admitted directly to a non-comprehensive stroke unit or transferred from a comprehensive or primary stroke center after revascularization therapy, (2) age $\geq$ 18 years, and (3) obtained written consent from the patient. Exclusion criteria were patients with (1) a subarachnoid hemorrhage, (2) an in-hospital stroke, (3) a non-stroke diagnosis, or (4) symptom onsets abroad. Only the first event was included in case of recurrent stroke during the inclusion period.

Data Collection

Data were collected from February 2018 to June 2018 and September 2018 to January 2019 at Herlev Gentofte Hospital and Nordsjællands Hospital, both located in The Capital Region of Denmark. Medical records and emergency medical service (EMS) data supported patients' responses. Data were managed in a Research Electronic Data Capture, REDCAP, system (REDCap consortium, Vanderbilt University, United States of America, v9.1.0 hosted by The Capital Region of Denmark) (20).

Variables

Typical patient-reported symptoms were defined according to the American Stroke Association's stroke warning signs and symptoms "BEFAST save a life," covering Balance, Eyes, Face, Arm, Speech (and Time). BEFAST describes factors associated with the need to call EMS immediately for treatment evaluation (12). Atypical stroke symptoms were defined as symptoms not included in BEFAST (e.g., pain, loss of consciousness, unclassifiable neurological symptoms, and non-neurological symptoms) (13, 21). Patient-reported symptoms were categorized by the interviewer into predefined medical terms.

Statistical Methods

Analysis

Baseline characteristics were summarized as frequencies with percentages or medians with interquartile ranges (IQR), and differences were tested using the Chi-square test or Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables. To explore sex- and age-related differences in patient-reported typical and atypical stroke symptoms, multivariable logistic regression models were used to estimate odds ratios (OR) with 95% confidence intervals (CI) for each symptom. Models were adjusted for stoke severity assessed by the Scandinavian Stroke Scale (severe 0–25 points, moderate 26–42 points, and mild 43–58 points) (22), stroke localization (right hemisphere, left hemisphere, or bilateral, brainstem, cerebellum), a history of hypertension, diabetes (yes/no), atrial fibrillation (yes/no), and hypercholesterolemia (yes/no). Age was included as a continuous

variable. Male sex was the reference group in all statistic models. All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC, United States). A two-sided significance level was set at alpha < 0.05. There were no missing data on stroke symptoms.

Sensitivity Analysis

To test the robustness of our findings, we conducted several sensitivity analyses. In the first analysis, all symptoms were grouped into two categories: typical and atypical symptoms and examined for differences in age and sex. In the second analysis, age was included as a categorical variable with the following age groups 18–59 years, 60–74 years, and 75+. In the third analysis, age was included in 5-year intervals.

Ethics

The study was approved by the Capital Region's Ethics Committee (no. 2012-58-004) and the Danish Data Protection Agency (no. 2012-58-0004; internal reference: HGH-2017-110, I-Suite no. 06014). Patients provided written informed consent before interviews.

RESULTS

Patient Characteristics

The process of enrollment is described in detail elsewhere (11). In total, 479 patients with stroke or TIA were included (40.1% female), and the median age was 74 years (64–80) with no significant age-related difference between sexes. Baseline characteristics are summarized in **Table 1**, and **Table 2** summarizes patient-reported symptoms, stroke knowledge, behavioral response, arrival time, and treatment. The proportions of acute stroke symptoms are displayed in **Figure 1**. There were no differences between women and men with respect to stroke knowledge, behavioral response, hospital arrival within 180 min from symptom onset, or stroke treatment.

Primary Outcome

In multivariable logistic regression analyses, female sex, compared with male sex, was associated with higher odds of presenting with loss of consciousness [adjusted OR 2.12 (95% CI 1.08–4.18)] and nausea/vomiting [adjusted OR 2.33 (95% CI 1.24–4.37)], but lower odds of presenting with lower extremity paresis [adjusted OR 0.59 (95% CI 0.39–0.89)] (**Table 3**). With increase in age each year, the odds were lower of presenting with sensory changes [adjusted, OR 0.95 (95% CI 0.94–0.97)] and upper extremity paresis [adjusted OR 0.98 (95% CI 0.96–0.99)]. The odds of presenting with dysphagia [adjusted OR 1.06 (95% CI 1.02–1.11)] increased with each year of age (**Table 4**).

Sensitivity Analyses

When comparing typical vs. atypical symptoms, the male sex was not significantly associated with higher odds of presenting with either typical or atypical symptoms [adjusted OR 1.55, (95% CI 0.84–2.87)]. When age was included as a categorical variable or included in 5-year intervals (**Supplementary Tables I, IIII** online-only data supplement) our primary findings were confirmed. Including age as a categorical variable, the odds for presenting with sensory changes (atypical symptom) were lower when comparing the age group 18–59 years with 60–74 years [adjusted OR 0.52 (95% CI 0.30–0.92)], (**Supplementary Table II** online-only data supplement). When we compared the age group 18–59 years with 75+ years, the results from the primary analysis were confirmed (**Supplementary Table III** online-only data supplement). Including age in 5-year intervals, the odds of presenting with upper extremity paresis (typical symptom) and sensory changes (atypical symptom) were significantly lower with each 5-years increase in age [adjusted, OR 0.89 (95% CI 0.82–0.97)] and [adjusted, OR 0.79 (95% CI 0.72–0.87)] (**Supplementary Table V** online-only data supplement). We performed the sub-analysis according to the type of stroke by sex. In population I61, female sex was significantly associated with loss of consciousness (atypical; **Supplementary Table VI** online-only data supplement). In population I63, female sex was significantly associated with nausea + vomiting (atypical; **Supplementary Table VII** online-only data supplement). In population G45, male sex was significantly associated with affected balance (typical; **Supplementary Table VIII** online-only data supplement).

DISCUSSION

In this cross-sectional two-center survey, we explored sex- and age-related differences in patient-reported typical and atypical stroke symptoms in a stroke and TIA population. Our study yielded the following finding: Female sex was associated with higher odds of reporting atypical stroke symptoms, such as loss of consciousness and nausea/vomiting, and lower odds of reporting typical stroke symptoms, such as lower extremity paresis compared to the male sex, which confirmed our hypothesis. With increasing age, we found that sensory changes (atypical symptom) and upper extremity paresis (typical symptom) were less frequently reported, whereas dysphagia (atypical symptom) was more frequent with increasing age, which largely confirmed our hypothesis.

The chain of survival and the acute treatment of stroke and TIA have important similarities with that of acute coronary syndrome. To reduce morbidity and mortality, correct interpretation and action on acute symptoms are essential to ensure timely and correct revascularization therapy. In symptomatic manifestations of acute coronary syndrome, female sex is associated with frequent atypical presentations of symptoms, for example, unusual fatigue, dyspnea, neck and throat pain, and pain between the shoulder blades. This diversity of acute symptoms led to delay in identification and interpretation (23, 24). To which extent this diversity in symptom presentation may apply to stroke need to be addressed. In our study, female sex was associated with the initial presentation of atypical symptoms, such as loss of consciousness and nausea/vomiting at stroke onset. The findings on patient-reported symptoms were in line with studies where acute symptoms were identified by health professionals, hence female sex is associated with symptoms, such as loss of consciousness (17, 25, 26) and nausea/vomiting (27). Studies further reported

TABLE 1 | Patient characteristics.

Variables	Women *N* = 192 (40.10%)	Men *N* = 287 (59.90%)	*P*-value
Demographics			
- Age, median 25th–75th percentile	75 (65–82)	73 (64–79)	0.25
Level of education			
- Basic	78 (40.63)	112 (39.02)	<0.001
- Further	95 (49.48)	110 (38.33)	
- Higher	18 (9.38)	65 (22.65)	
- Not available	1 (0.52)	0 (0.00)	
Living arrangements			
- Living with someone	92 (47.92)	198 (68.99)	<0.001
- Living alone	100 (52.08)	89 (31.01)	
Scandinavian stroke scale score[a]			
- Mild	159 (82.81)	247 (86.06)	0.60
- Moderate	24 (12.50)	28 (9.76)	
- Severe	9 (4.69)	12 (4.18)	
Type of stroke			
- I61: Nontraumatic intracerebral hemorrhage	16 (8.33)	23 (8.01)	0.12
- I63: Cerebral infarction	114 (59.38)	195 (67.94)	
- G45: Transient cerebral ischemic attacks	62 (32.29)	69 (24.04)	
Stroke location			
- Left hemisphere	81 (42.19)	107 (37.28)	0.48
- Right hemisphere	66 (34.38)	101 (35.19)	
- Bilateral, brainstem, cerebellum	45 (23.44)	79 (27.53)	
Risk factors, history of			
- Hypertension	110 (57.29)	154 (53.66)	0.43
- Diabetes	14 (7.29)	40 (13.94)	0.02
- Atrial fibrillation	40 (20.83)	63 (21.95)	0.77
- Hypercholesterolemia	89 (46.35)	128 (44.60)	0.71
- Acute myocardial infarct	9 (4.69)	27 (9.41)	0.05
- Claudication	19 (9.90)	21 (7.32)	0.32
- Carotid stenosis	18 (9.38)	18 (6.27)	0.21
- Heart failure	7 (3.65)	30 (10.45)	0.01
- Sleep apnea	7 (3.65)	29 (10.10)	0.01
- Prior Stroke	35 (18.23)	59 (20.56)	0.53
- Smoking			
- Current	40 (20.83)	67 (23.34)	0.04
- Former	72 (37.50)	133 (46.34)	
- Never	80 (41.67)	87 (30.31)	
Pre-hospital medication for stroke comorbidity			
- ≥1	126 (65.63)	178 (62.02)	0.42
- None	66 (34.38)	109 (37.98)	

[a] *Scandinavian Stroke Scale classified as severe (0–25 points), moderate (26–42 points), and mild (43–58 points).*

that female sex, in comparison to the male sex, tended to present with other atypical symptoms identified by health professionals, such as dysphagia (25, 26, 28), headache (15, 16), mental status change (21, 29), and seizure (27). The findings that the female sex entailed a variety of atypical symptoms upon onset of stroke highlight the risk of misinterpretation symptoms as non–stroke related. In one study, female sex was associated with a longer hospital arrival time, including a decreased likelihood of reperfusion therapy, primarily due to patient-dependent delay (30). However, when adjusted for age, stroke severity, and co-habitant status, the sex difference in prehospital delay disappeared (30). In our univariate analysis 36% of both women and men arrived within 180 min from the onset. We could not confirm a significant sex difference in timely hospital arrival within 180 min. Some atypical presentations may be interpreted as severe, such as loss of consciousness or seizure, which caused

TABLE 2 | Patient-reported symptoms, stroke knowledge, behavioral response, arrival time, and treatment.

Variables	Women *N* = 192 (40.10%)	Men *N* = 287 (59.90%)	*P*-value
Typical stroke symptom			
- Affected balance	21 (10.94)	44 (15.33)	0.17
- Visual disturbance	30 (15.63)	61 (21.25)	0.12
- Eye deviation	0 (0.00)	4 (1.39)	0.10
- Facial paresis	47 (24.48)	53 (18.47)	0.11
- Paresis (arm)	70 (36.46)	112 (39.02)	0.57
- Paresis (leg)	51 (26.56)	106 (36.93)	0.02
- Ataxia (arm)	47 (24.48)	83 (28.92)	0.28
- Ataxia (leg)	38 (19.79)	69 (24.04)	0.27
- Aphasia	24 (12.50)	36 (12.54)	0.99
- Dysarthria	46 (23.96)	63 (21.95)	0.61
- Aphasia and dysarthria	18 (9.38)	16 (5.57)	0.11
Atypical stroke symptoms			
- Headache	32 (16.67)	42 (14.63)	0.55
- Pain	10 (5.21)	6 (2.09)	0.06
- Loss of consciousness	23 (11.98)	17 (5.92)	0.02
- Confusion	25 (13.02)	32 (11.15)	0.54
- Reduced attention	1 (0.52)	4 (1.39)	0.36
- Memory loss	9 (4.69)	9 (3.14)	0.38
- Vertigo	48 (25.00)	75(26.13)	0.78
- Nausea + vomiting	28 (14.58)	20 (6.97)	0.01
- Dysphagia	11 (5.73)	18 (6.27)	0.81
- Seizure	2 (1.04)	1 (0.35)	0.35
- Sensory changes	43 (22.40)	58 (20.21)	0.57
- No symptoms	0 (0.00)	1 (0.35)	0.41
- Symptoms that did not fit in the predefined symptom boxes	37 (19.27)	36 (12.54)	0.04
Typical acute stroke symptoms FAST[a]			
- ≥1	95 (49.48)	142 (49.48)	0.10
- None	97 (50.52)	145 (50.52)	
Typical acute stroke symptoms BEFAST[b]			
- ≥1	97 (50.52)	145 (50.52)	0.10
- None	95 (49.48)	142 (49.48)	
Perceived severity of symptoms[c]			
- < median 25	81 (42.19)	154 (53.66)	0.05
- ≥ median 25	100 (52.08)	120 (41.81)	
- Not available	11 (5.73)	13 (4.53)	
Stroke recognition			
- Yes	162 (84.38)	251 (87.46)	0.61
- No	28 (14.58)	33 (11.50)	
- Not available	2 (1.04)	3 (1.05)	
Prior knowledge of acute stroke therapy			
- Yes	108 (56.25)	158 (55.05)	0.79
- No	84 (43.75)	129 (44.95)	
Help seeking behavior, first contact			
- Emergency medical service	66 (34.38)	81 (28.22)	0.28
- OOH-PC	43 (22.40)	78 (27.18)	
- General practitioner	54 (28.13)	86 (29.97)	
- Home Care	6 (3.13)	5 (1.74)	
- Out-patient Clinic	9 (4.69)	7 (2.44)	
- Family, friend, neighbor, co-workers	12 (6.25)	27 (9.41)	

(Continued)

TABLE 2 | Continued

Variables	Women $N = 192$ (40.10%)	Men $N = 287$ (59.90%)	*P*-value
- Unknown bystander	1 (0.52)	0 (0.00)	
- None	1 (0.52)	3 (1.05)	
Arrival time			
- Within 180 min from onset	70 (36.46)	104 (36.24)	0.96
Treatment			
- Thrombolysis	26 (13.54)	31 (10.80)	0.36
- Thrombectomy	5 (2.60)	7 (2.44)	0.91

[a]*FAST acronym for Face, Arm, Speech, Time.*
[b]*BEFAST acronym for Balance, Eye, Face, Arm, Speech, Time.*
[c]*Patient-perceived symptom severity was rated on a scale from 0 to 100, where 100 was most severe.*

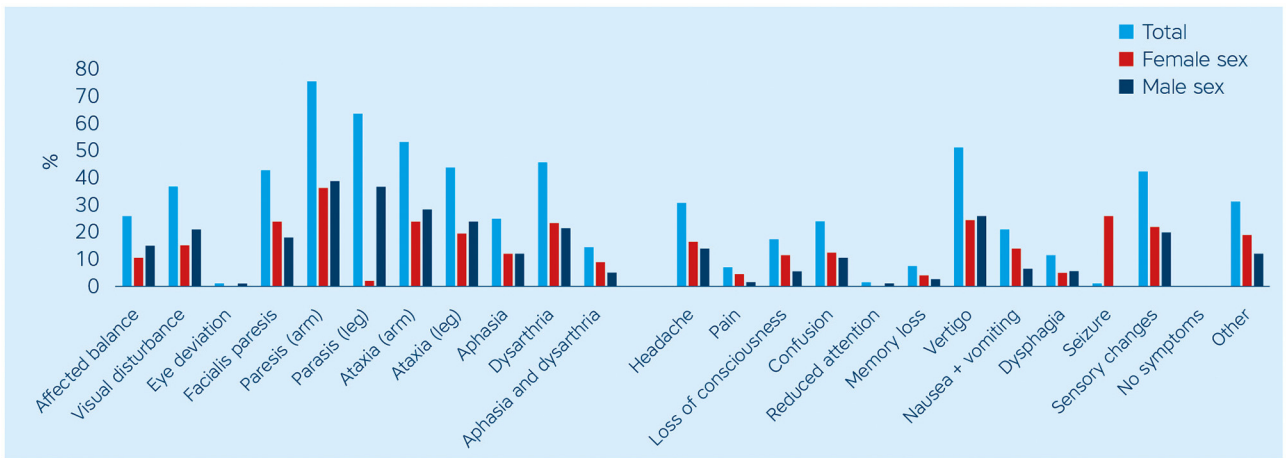

FIGURE 1 | Acute patient-reported typical and atypical stroke symptoms, %.

rapid contact to emergency services. This may contribute to why sex differences in symptoms presentation did not significantly affect arrival times in the group. Having a bystander or co-habiting at the onset of stroke was previously associated with an increased chance of stroke recognition and immediate contact to emergency medical services (31, 32). In our study, the proportion of female sex living alone at stroke onset was significantly higher compared to the male sex, but this did not affect arrival times. Nonetheless, perception of symptom severity was associated with timely hospital arrival in other studies (32, 33).

The American Heart Association warning signs for myocardial infarction included a cautionary statement in their campaign, stressing the fact that the female sex is more likely to experience atypical symptoms (34). Previous stroke awareness campaigns focused on improving knowledge of typical symptoms and increasing behavioral response, but the effect on timely arrival has so far been inconclusive (35, 36). Future stroke awareness campaigns should be tailored to address that female sex may associate also with atypical presentations of stroke, to embrace sex differences in stroke care (37). We could not confirm any sex differences in stroke recognition, prior knowledge of stroke therapy, or help-seeking behavior. This could be due to no launch of a focused stroke awareness campaign before our study, and the number of included patients was relatively small.

Stroke patients above the age of 75 years presented more frequently with dysphagia (atypical symptom) when identified by health professionals (28). This was aligned when dysphagia was patient-reported in our study. Other atypical symptoms, such as coma, aphasia, and cerebellar dysfunction, have also been associated with stroke patients above 80 years (18). These findings were not confirmed in this study. Interestingly, headache, nausea/vomiting, and sensory deficits (atypical symptoms) appeared to be more common in the female sex between 18 and 44 years, even after controlling for a diagnosis of migraine and for age (19). Results on stroke patients younger than 55 years showed that almost 25% of strokes were not identified when clustering acute stroke symptoms according to typical symptoms (19). Furthermore, it should be stressed that the outcomes of atypically presenting stroke patients are not necessarily benign, if the symptoms are misdiagnosed (38).

TABLE 3 | Sex-related differences in patient-reported stroke symptoms (continuous).

	OR	95 % confidence intervals
Typical stroke symptoms (BEFAST)		
Affected balance	0.69	0.39–1.21
Vision disturbance	0.65	0.39–1.09
Facials paresis	1.45	0.91–2.31
Paresis, (arm)	0.88	0.59–1.31
Paresis, (leg)	0.59	0.39–0.89
Ataxia, (arm)	0.81	0.53–1.23
Ataxia, (leg)	0.76	0.48–1.20
Aphasia	0.98	0.55–1.75
Dysarthria	1.05	0.67–1.65
Aphasia + Dysarthria	1.86	0.88–3.91
Atypical stroke symptoms		
Headache	1.18	0.71–1.98
Pain	2.76	0.96–7.92
Loss of consciousness	2.12	1.08–4.18
Confusion	1.21	0.68–2.14
Reduced attention	0.32	0.03–3.17
Memory loss	1.63	0.62–4.32
Vertigo	0.99	0.64–1.53
Nausea + vomiting	2.33	1.24–4.37
Dysphagia	0.82	0.36–1.86
Seizure	3.85	0.31–47.56
Sensory changes	1.20	0.76–1.92
Other	1.76	1.06–2.95

Reference category men. Adjusted for age, stroke severity, stroke localization, history of hypertension, diabetes, atrial fibrillation, and hypercholesterolemia. Eye deviation and no symptoms were removed from the analysis, due to zero observation in one of the groups.

TABLE 4 | Age-related differences in patient-reported stroke symptoms with each year increase.

	OR	95 % confidence intervals
Typical stroke symptoms (BEFAST)		
Affected balance	1.01	0.98–1.03
Vision disturbance	0.98	0.96–1.00
Facials paresis	1.00	0.98–1.02
Paresis, (arm)	0.98	0.96–1.00
Paresis, (leg)	1.00	0.99–1.02
Ataxia, (arm)	0.99	0.97.1.01
Ataxia, (leg)	1.00	0.98–1.02
Aphasia	1.01	0.99–1.04
Dysarthria	1.01	0.99–1.03
Aphasia + Dysarthria	1.02	0.98–1.05
Atypical stroke symptoms		
Headache	0.98	0.96–1.00
Pain	0.99	0.95–1.03
Loss of consciousness	1.00	0.97–1.03
Confusion	1.02	0.99–1.05
Reduced attention	0.98	0.90–1.07
Memory loss	1.01	0.97–1.06
Vertigo	0.99	0.98–1.01
Nausea + vomiting	0.99	0.96–1.02
Dysphagia	1.06	1.02–1.11
Seizure	1.04	0.93–1.16
Sensory changes	0.95	0.94–0.97
Other	0.98	0.96–1.01

Reference category men. Adjusted for sex, stroke severity, stroke localization, history of hypertension, diabetes, atrial fibrillation, and hypercholesterolemia. Eye deviation and no symptoms were removed from the analysis, due to zero observation in one of the groups.

Limitations

We aimed to reduce recall bias by including patients as early as possible after stroke onset. A selection bias cannot be dismissed as there was an overrepresentation of patients with mild stroke, either due to early patient discharge, transfer to other departments if there was a change in clinical condition before inclusion was possible which could omit mild strokes or severely affected patients. The included population represented a broad stroke population arriving at non-comprehensive stroke units. The hypothesis of this study was devised after the overall study was designed but before the end of this study. Analyses were therefore exploratory and mainly applicable as hypothesis-generating.

CONCLUSIONS

The current study confirmed our hypothesis that sex differences in patient reporting of acute stroke symptoms exist. These findings were in accordance with previous studies investigating physician-reported symptoms, where the female sex presented with atypical symptoms, such as loss of consciousness and nausea/vomiting. Recognition of stroke and correct response to symptoms pose a particular challenge in early treatment when atypical stroke symptoms are reported. It needs to be further assessed to which extent sex- and age-related differences in symptoms of acute stroke influence interpretation of symptoms, behavioral motivators, and barriers for first contact to emergency medical service.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Capital Region's Ethics Committee, Danish Data Protection Agency. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CK and AD were responsible for protocol development, gathering ethical approval, and data permission. Sub study on sex and age was conceived by HE and CK. HE and TC (only

Nordsjællands Hospital) were involved in patient recruitment and data collection. HE, JB, and CK in data analysis. HE wrote the first draft of the manuscript. All authors made critical revisions to the manuscript and approved its final version.

FUNDING

This work was supported by TrygFonden, application ID 128669 and by the Novo Nordisk Foundation Borregaard stipend, grant number NNF18OC0031840.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.846690/full#supplementary-material

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frontiers in Neurology

ORIGINAL RESEARCH
published: 24 March 2022
doi: 10.3389/fneur.2022.812647

Short-Term Prognostic Predictive Evaluation in Female Patients With Ischemic Stroke: A Retrospective Cross-Sectional Study

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OPEN ACCESS

Edited by:
Svetlana Lorenzano, Sapienza University of Rome, Italy

Reviewed by:
Tolga Daniel Dittrich, University Hospital of Basel, Switzerland
Vida Demarin, International Institute for Brain Health, Croatia

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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *10 November 2021*
Accepted: *03 February 2022*
Published: *24 March 2022*

Citation:
Eren F, Ozguncu C and Ozturk S (2022) Short-Term Prognostic Predictive Evaluation in Female Patients With Ischemic Stroke: A Retrospective Cross-Sectional Study. Front. Neurol. 13:812647. doi: 10.3389/fneur.2022.812647

Introduction and Aim: Stroke is a disease with high mortality and morbidity. Although studies are generally performed on all patients with stroke, it is known that gender has an effect on etiology and prognosis. This study aimed to determine the importance of clinical stroke scales and laboratory markers in determining the short-term prognosis of female patients with ischemic stroke of anterior circulation.

Materials and Methods: The study was planned as a retrospective and cross-sectional study. SEDAN score, the National Institutes of Health stroke scale (NIHSS), the Modified Rankin Scale (mRS), the Glasgow Coma Scale (GCS), and THRIVE score applied to the patients at the time of admission were recorded. Admission blood glucose, hemoglobin, leukocyte, urea, albumin, and blood lipid levels were evaluated. The relationship of all these parameters with in-hospital prognosis, mortality, and disability at discharge was examined. The relationship between groups and data was analyzed using the SPSS package program after the normality analysis.

Results: In this study, there were 733 female patients with stroke with a mean age of 69.53 ± 14.51 years and 858 male patients with stroke with a mean age of 64.27 ± 13.29 years. Hospitalization time, length of stay in the intensive care unit, ventilation need rate, mortality, and dependency rate were higher in female patients ($p = 0.001$). The NIHSS, SEDAN, and THRIVE scores were higher in female patients who had in-hospital mortality, had a poor prognosis, and who were discharged as dependent ($p = 0.001$). GCS was lower in this patient group ($p = 0.001$). Blood glucose, creatinine, leukocytes, urea, and CRP levels were higher; the albumin and hemoglobin levels was lower in female patients who had fatal outcomes ($p = 0.009$, 0.001, 0.001, 0.001, 0.001, and 0.020; respectively). In female patients who were dependent at discharge, blood urea, glucose, and CRP levels were higher and the albumin levels were lower than those in female patients who achieved functional independence ($p = 0.001$, 0.016, 0.002, and 0.001, respectively).

Conclusion: Our study showed that the short-term prognosis is worse in female patients who had an ischemic stroke of anterior circulation. It also revealed some clinical and laboratory parameters that could predict this situation. More intensive monitoring may be needed to improve prognosis in female patients.

Keywords: stroke, gender, prognosis, female, women, short term

INTRODUCTION

Stroke is a cerebrovascular disease that causes temporary or permanent effects and causes various neurological findings (1). Every year, varying degrees of disability and mortality occur in millions of people worldwide due to stroke. In a recent study, it was revealed that ∼80.1 million people had a stroke, and more than half of these patients were women (2). Considering the personal, social, and familial effects of stroke, it is important to identify and eliminate the risk factors. Gender is one of the most important risk factors for stroke. The effect of gender varies with age. The incidence of stroke is higher in childhood and early adulthood for men (3). Stroke rates increase in women in middle age due to hormonal factors (4). The incidence of stroke in advanced age exceeds that of men (3). Conditions such as age, comorbid diseases, and, lifestyle complicate the assessment of the effect of gender on stroke.

Many studies show that stroke-related mortality is higher in female patients, as well as disability; however, there are also studies stating that gender does not have an independent effect on mortality (5–7). Furthermore, it should be considered that women have a stroke at an older age when mortality rates are also high; therefore, it is difficult to establish a relationship between mortality and gender, to predict prognosis, and to identify markers with prognostic predictive value (8). There are studies showing the prognostic predictive value of systemic inflammatory cells, blood glucose, and blood lipid parameters in stroke (9, 10). However, these markers are easily affected by many systemic conditions, especially those related to hormonal factors. The aim of this study was to determine the in-hospital prognostic predictive value of disability scales and laboratory and clinical parameters in female patients with stroke.

MATERIALS AND METHODS

This study was planned as a retrospective and cross-sectional study. Selcuk University Clinical Researches Local Ethics Committee was obtained before the study (Ethics committee approval: 2020-473). Female patients who received inpatient treatment with a diagnosis of stroke in the Neurology Clinic of Selcuk University Medical Faculty Hospital between 2016 and 2020 were included in the study; 2,030 patients with stroke over the age of 18 were screened. Patients with a diagnosis of head trauma, intracranial hemorrhage, intraventricular or subarachnoid hemorrhage, subdural or epidural hematoma, and sinus vein thrombosis were excluded from the study. Patients with ischemic stroke of posterior circulation were also excluded from the study. Data from 611 female patients with acute ischemic stroke in the anterior circulation were included for the study. The short-term prognosis of 683 male patients followed during this period was also evaluated following the same criteria.

The patients' age, accompanying chronic diseases (diabetes mellitus, hypertension, coronary artery diseases, malignancy, chronic renal failure, dementia, hyperlipidemia, cardiac arrhythmia), and smoking were evaluated. Consciousness levels, muscle strength, presence of cranial nerve involvement, dysarthria and aphasia were evaluated. SEDAN score, the National Institutes of Health stroke scale (NIHSS), the Modified Rankin Scale (mRS), the Glasgow Coma Scale (GCS), and THRIVE score applied to the patients' record at the time of admission were recorded. The SEDAN score includes five parameters, including age, basal blood glucose, finding of early infarction, and hyperdense artery sign on CT. The GCS is especially used for assessing the state of consciousness; the mRS, the NIHSS, and THRIVE scores evaluate the current disability (11–15). Patients were divided into groups according to the following treatments: intravenous thrombolysis; endovascular thrombectomy; intravenous thrombolysis + endovascular thrombectomy.

The blood results of the patients at the time of hospitalization were analyzed. Reference blood glucose (mg/Dl), leukocytes (K/Ul), urea (K/ul), albumin (g/Dl) and blood lipid level (mg/Dl), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride values were recorded. The follow-ups of the patients during their hospitalization were examined. Requirement of intensive care hospitalization, central nervous system (CNS) complications (edema or hemorrhagic transformation), the need for mechanical ventilation, the need for decompressive surgery, and mortality were examined and grouped. The discharge status of the patients was analyzed by dividing them into independent (mRS = 0, 1, 2) and dependent groups (mRS = 3, 4, 5).

Statistical Analysis

The data were analyzed with the SPSS 18.0 Package Software Program (Statistical Package for the Social Sciences Inc.; Armonk, NY, USA). Categorical data were presented as numbers (*n*) and percent (%), and numerical data were presented as mean ± SD (minimum–maximum). The data were assumed to be normally distributed according to the central limit theorem. The chi-square (χ^2) test was used to compare categorical data. Two independent groups were analyzed with the Independent Sample *t*-test, and more than two groups were analyzed with the one-way ANOVA test. The Bonferroni correction was performed with the Tukey test for *post-hoc* analysis. The relationship between two numerical variables was examined by

Pearson's or Spearman's Correlation analysis. Spearman's rho correlation coefficients were accepted as 0.05–0.30, weak; 0.30–0.40, weak-moderate; 0.40–0.60, moderate; 0.60–0.70, strong; 0.70–0.75, very strong; and 0.75–1.00, perfect correlation. The effect of the variables on mortality and disability status was analyzed by the Binary and/or Ordinal Logistic Regression analysis. An ordinal regression analysis was indicated by mRS from 0 up to 5. Patients with mRS = 6 (death) were not included in the ordinal regression analysis. The results were evaluated at the 95% CI, and the statistical significance level was as $p < 0.05$.

RESULTS

Data from 733 female patients with ischemic stroke with a mean age of 69.53 ± 14.51 years and 858 male patients with stroke with a mean age of 64.27 ± 13.29 years were analyzed for this study. The most common comorbid chronic disease was hypertension (women = 68.5%, men = 53.6%). The most common presenting symptom of the patient was motor deficiency (women = 81.1%, men = 83.2%). The demographic characteristics, chronic diseases, presenting symptoms, ischemia localization, and treatment characteristics of the patients are shown in **Table 1**.

The need for intensive and mechanical ventilation and the length of hospitalization was higher in female patients ($p = 0.003$; $p = 0.002$; $p = 0.003$, respectively). At the same time, mortality and rates of dependency at discharge were higher in female patients ($p = 0.001$). The frequency of CNS complications and the need for decompressive surgery were similar according to gender ($p = 0.801$; $p = 0.519$, respectively). The prognostic characteristics of the patients according to the gender variable are shown in **Table 2**.

The relationship between the NIHSS score, the GCS score, SEDAN score, THRIVE score, mRS score, and blood parameters and length of stay in the hospital was investigated in female patients with acute ischemic stroke. The mean hospitalization time was 12.63 ± 10.95 (1–87 days). A low to moderate positive correlation was determined between the length of stay and the NIHSS and mRS scores (Spearman's rho = 0.339 and 0.351; $p = 0.001$ and 0.001, respectively). At the same time, a low level of positive correlation was found between hospitalization time and SEDAN score, THRIVE score, and leukocyte level; and a negative correlation was found between the GCS score and the albumin value (all $p = 0.001$; Spearman's rho = 0.143, 0.211, 0.092, −0.260, −0.234, respectively).

Three hundred forty-two female patients (46.7%) had intensive care admissions. The NIHSS score, SEDAN score, THRIVE score, the mRS, glucose, leukocytes, urea, and CRP values were found to be statistically significantly higher in patients hospitalized in the intensive care unit ($p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.048$; $p = 0.001$; $p = 0.001$; $p = 0.001$, respectively). GCS and albumin values were lower in these patients ($p = 0.001$). The NIHSS, SEDAN score, THRIVE score, mRS, and leukocyte and CRP values were found to be statistically significantly higher in female patients who developed CNS complications ($n = 71$, 9.7%) ($p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.005$; $p = 0.015$, respectively). GCS values were lower in these patients ($p = 0.001$).

TABLE 1 | Chronic diseases, presenting symptoms, and affected cerebral localizations in all patients with ischemic stroke.

	Female ($n = 733$)	Male ($n = 858$)	*p*-value
Age (year), mean ± SD	69.53 ± 14.51	64.27 ± 13.29	0.001*[a]
Scores, mean ± SD			
NIH stroke scale	8.20 ± 7.20	6.30 ± 5.35	0.001*[a]
Glasgow coma Scale	13.67 ± 2.48	14.08 ± 2.02	0.001*[a]
SEDAN score	2.05 ± 1.23	1.56 ± 1.15	0.001*[a]
THRIVE score	3.20 ± 1.87	2.27 ± 1.59	0.001*[a]
Modified Rankin Scale	3.04 ± 1.69	2.55 ± 1.68	0.001*[a]
Chronic diseases, *n* (%)			
Diabetes mellitus	297 (40.5)	244 (28.4)	0.001*[b]
Hypertension	502 (68.5)	460 (53.6)	0.001*[b]
Coronary artery disease	188 (25.2)	258 (30.1)	0.057[b]
Malignancy	46 (6.3)	61 (7.1)	0.547[b]
Chronic renal failure	31 (4.2)	39 (4.5)	0.807[b]
Dementia	44 (6.0)	15 (1.7)	0.001*[b]
Hyperlipidemia	64 (10.5)	45 (6.6)	0.048*[b]
Atrial fibrillation	208 (28.4)	119 (13.9)	0.001*[b]
Smoking, *n* (%)			
Yes	7 (0.9)	75 (8.7)	0.001*[b]
No	736 (99.1)	783 (91.3)	
Initial symptoms, *n* (%)			
Consciousness			
Alert	499 (68.1)	659 (76.8)	0.001*[b]
Other (confused, somnolence, stupor, or coma)	234 (31.9)	199 (23.2)	
Speech			
Normal	370 (43.1)	268 (36.6)	0.216[b]
Aphasia or dysarthria	363 (56.9)	590 (63.4)	
Cranial nerve involvement			
Yes	245 (33.4)	276 (32.2)	0.630[b]
No	488 (66.6)	582 (67.8)	
Motor deficiency			
Yes	587 (81.1)	714 (83.2)	0.512[b]
No	146 (19.9)	144 (16.8)	
Site of vessel occlusion			
Right	438 (59.8)	502 (58.6)	0.356[b]
Left	295 (40.2)	356 (41.4)	
Treatment			
IV thrombolysis	47 (6.4)	77 (9.0)	0.229[b]
Endovascular thrombectomy	36 (4.9)	49 (5.7)	0.224[b]
IV thrombolysis and thrombectomy	44 (6.0)	49 (5.7)	0.504[b]

*Statistically significant value. SD, Standard deviation; IV, Intravenous.
[a] Independent Sample T-test.
[b] Chi-square (χ^2) test.

TABLE 2 | Evaluation of prognostic status according to gender.

	Female ($n = 733$)	Male ($n = 858$)	p-value
Length of hospitalization			
Mean ± SD (Minimum–maximum)	12.63 ± 10.95 (1–87)	11.81 ± 12.55 (1–155)	0.003*[a]
Need for intensive care			
Yes	342 (46.7%)	336 (39.2%)	0.003*[b]
No	391 (53.3%)	522 (60.8%)	
Need for mechanical ventilation			
Yes	147 (20.1%)	123 (14.3%)	0.002*[b]
No	586 (79.9%)	735 (85.7%)	
Complication of central system			
Yes	71 (%9.7%)	87 (10.1%)	0.801[b]
No	662 (90.3%)	771 (89.9%)	
Decompressive surgery			
Yes	26 (3.5%)	37 (4.3%)	0.519[b]
No	707 (96.5%)	821 (95.7%)	
Exitus			
Yes	134 (18.3%)	103 (12.0%)	0.001*[b]
No	599 (81.7%)	755 (88.0%)	
Discharge disability			
Dependent	243 (40.7%)	199 (26.4%)	0.001*[b]
Independent	354 (59.3%)	556 (73.6%)	

SD, Standard deviation.
**Statistically significant value.*
[a]Independent Sample T-test.
[b]Chi-square (χ^2) test.
Data are expressed as numbers (percentage) unless otherwise indicated.

Female patients who needed ventilation ($n = 147$, 20.1%) had higher NIHSS score, SEDAN score, THRIVE score, mRS score, blood glucose, creatinine, leukocytes, urea, and CRP values ($p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.008$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$, respectively). GCS and albumin values were lower in these patients ($p = 0.001$). Female patients with decompressive surgery ($n = 26$, 3.5%) had higher NIHSS, SEDAN, THRIVE, mRS scores, and leukocyte values than patients without decompressive surgery ($p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.002$, respectively). Female patients who underwent decompressive surgery had lower GCS values ($p = 0.001$).

Mortality rate in female patients was 18.3% ($n = 134$). The GCS score was lower in female patients with fatal outcomes while all other scores were higher ($p = 0.001$). In this patient group, blood glucose, creatinine, leukocytes, urea, and CRP were higher; albumin and hemoglobin values were lower ($p = 0.009$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$; $p = 0.001$, respectively). Mortality rate, stroke scores, laboratory parameters, and treatment characteristics of female patients according to their mortality status are shown in **Table 3**.

Female patients who were dependent at discharge ($n = 243$, 40.7%) had lower GCS and albumin values but higher values for all the remaining scores and parameters (urea, leukocytes, CRP) ($p = 0.001$). The stroke scores, laboratory parameters, and treatment characteristics of the female patients according to their depending status are shown in **Table 4**.

TABLE 3 | Stroke scores and laboratory parameters according to mortality status in female patients with ischemic stroke.

	Mortality ($n = 134$)	Non-mortality ($n = 599$)	p-value
NIHSS	17.21 ± 7.09 (1–35)	6.19 ± 5.48 (0–25)	0.001*[a]
GCS	10.29 ± 3.45 (3–15)	14.42 ± 1.33 (7–15)	0.001*[a]
SEDAN score	2.91 ± 1.16 (0–6)	1.84 ± 1.15 (0–6)	0.001*[a]
THRIVE score	5.07 ± 1.64 (0–9)	2.79 ± 1.65 (0–8)	0.001*[a]
mRS	4.60 ± 0.83 (1–5)	2.69 ± 1.63 (0–5)	0.001*[a]
Blood glucose (mg/dL)	169.71 ± 88.54 (75–718)	152.61 ± 74.67 (71–558)	0.009*[a]
Creatinine (mg/dL)	1.06 ± 0.56 (0.39–3.69)	0.88 ± 0.57 (0.34–6.26)	0.001*[a]
Hemoglobin (g/dL)	12.26 ± 1.68 (8.20–16.90)	12.65 ± 1.72 (4.6–21.9)	0.020*[a]
Leukocyte (K/uL)	11.14 ± 5.23 (2.50–40.10)	9.00 ± 5.08 (1.4–107.8)	0.001*[a]
Urea (K/uL)	58.94 ± 28.04 (16–165)	44.11 ± 23.34 (11–228)	0.001*[a]
Albumin (g/dL)	2.94 ± 0.61 (1.5–4.30)	3.40 ± 0.50 (1.8–4.4)	0.001*[a]
C-reactive protein (mg/dL)	92.58 ± 98.71 (2.2–470.0)	41.38 ± 66.58 (0.3–476)	0.001*[a]
LDL-cholesterol (mg/dL)	114.80 ± 33.13 (59–191)	126.25 ± 41.09 (37–301)	0.150[a]
HDL-cholesterol (mg/dL)	44.92 ± 16.59 (20–91)	42.68 ± 10.58 (17–96)	0.643[a]
Triglyceride (mg/dL)	143.50 ± 58.01 (49–330)	160.59 ± 93.67 (40–627)	0.052[a]
Treatment (n, %)			
IV thrombolysis	15 (11.2)	32 (5.3)	0.841[b]
Endovascular thrombectomy	11 (8.2)	25 (4.2)	
IV thrombolysis and thrombectomy	16 (11.9)	28 (4.7)	

NIHSS, NIH stroke score; GCS, Glasgow coma score; mRS, Modified Rankin score; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; n, Number; IV, Intravenous.
**Statistical significance value.*
[a]Independent Sample T-test.
[b]Chi-square (χ^2) test.
Data are shown as mean ± SD (minimum–maximum) unless otherwise indicated.

The relationship between treatment and short-term prognosis was evaluated in female patients with ischemic stroke. Mortality was similar in the treatment groups (intravenous thrombolysis = group 1; endovascular thrombectomy = group 2; intravenous thrombolysis + endovascular thrombectomy = group 3) ($p = 0.841$). However, the frequency of independency at discharge was higher in all treatment groups (intravenous thrombolysis; endovascular thrombectomy; intravenous thrombolysis + endovascular thrombectomy) ($p = 0.016$). Logistic regression

TABLE 4 | Stroke scores and laboratory findings according to short-term disability status in female patients with ischemic stroke.

	Independent (n = 354) (mRS = 0–2)	Dependent (n = 243) (mRS = 3–5)	p-value
NIHSS	3.01 ± 2.96 (0–22)	10.77 ± 5.05 (2–25)	0.001*[a]
GCS	14.90 ± 0.41 (8–15)	11.72 ± 1.82 (5–15)	0.001*[a]
SEDAN score	1.50 ± 1.10 (0–6)	2.26 ± 1.08 (0–5)	0.001*[a]
THRIVE score	2.22 ± 1.32 (0–5)	3.60 ± 1.75 (0–8)	0.001*
mRS	1.62± 1.15 (0–5)	4.24 ± 0.74 (3–5)	0.001*[a]
Blood Glucose (mg/dL)	149.86 ± 76.26 (73–558)	156.85 ± 74.04 (71–534)	0.016*
Creatinine (mg/dL)	0.89 ± 0.60 (0.37–6.26)	0.88 ± 0.56 (0.34–5.55)	0.828[a]
Hemoglobin (g/dL)	12.66 ± 1.61 (4.6–16.3)	12.66 ± 1.88 (7.50–21.9)	0.793[a]
Leukocyte (K/uL)	8.71 ± 5.95 (1.4–107.8)	9.44 ± 3.43 (3.4–26.8)	0.001*[a]
Urea (K/uL)	41.84 ± 21.42 (13–221)	47.46 ± 25.64 (11–228)	0.001*[a]
Albumin (g/dL)	3.57 ± 0.39 (2.3–4.3)	3.30 ± 0.53 (1.8–4.4)	0.001*[a]
C-reactive protein (mg/dL)	31.61 ± 58.72 (0.3–476)	48.99 ± 71.40 (1.11–471)	0.002*[a]
LDL-cholesterol (mg/dL)	124.75 ± 42.90 (49–301)	129.30 ± 37.64 (37–249)	0.080
HDL-cholesterol (mg/dL)	43.17 ± 10.11 (24–96)	41.94 ± 11.33 (17–73)	0.196[a]
Triglyceride (mg/dL)	167.35 ± 98.08 (48–627)	158.14 ± 84.42 (49–459)	0.082[a]
Treatment (n, %) IV thrombolysis	16 (4.5)	15 (6.2)	0.016*[b]
Endovascular thrombectomy	4 (1.1)	21 (8.6)	
IV thrombolysis and thrombectomy	8 (2.3)	20 (8.2)	

NIHSS, NIH stroke score; GCS, Glasgow coma score; mRS, Modified Rankin score; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; n, Number; IV, Intravenous.
**Statistical significance value.*
[a]Independent Sample T test.
[b]Chi-square (χ^2) test.
Data are shown as mean ± SD (minimum–maximum unless otherwise indicated).

analysis was performed according to the model established by the NIHSS, GCS, SEDAN scores, THRIVE score, and the mRS score of female patients to predict the mortality. Model fit was good (Nagelkerke R Square = 0.49). According to the results of this analysis, one unit increase in the GCS score reduced the risk of mortality 0.61 times (p = 0.001, adjusted OR = 0.611, %95 CI = 0.534–0.701). An increase of one unit in the SEDAN score increases the mortality risk by 1.30 times (p = 0.031, adjusted OR = 1.307, 95%CI = 1.024–1.669). An increase of one unit in the mRS score increases the mortality risk by 1.42 times (p = 0.011, adjusted OR = 1.424, 95%CI = 1.085–1.870).

TABLE 5 | Prediction of the mortality status and dependency at the discharge with initial disability scores.

Parameter	Exp (B)	Standard error (SE)	95% Confident interval		p
			Lower	Upper	
Prediction for mortality					
GCS*[a]	0.611	0.070	0.534	0.701	0.001
SEDAN*[a]	1.307	0.125	1.024	1.669	0.031
mRS*[a]	1.424	0.139	1.085	1.870	0.011
Prediction for dependency					
NIHSS**[a]	1.611	0.045	1.474	1.762	0.001
NIHSS***[b]	1.726	0.035	1.612	1.847	0.001

GCS, Glasgow coma score; mRS, Modified Rankin score; NIHSS, NIH stroke score.
**Model established with by the NIHSS, the GCS, the SEDAN, THRIVE, and the mRS score to predict mortality.*
***Model established with the NIHSS, the GCS, SEDAN, and THRIVE scores to predict dependency (independent or dependent).*
****Model established with the NIHSS, the GCS, SEDAN, and THRIVE scores to predict dependency (mRS: 0–5).*
[a]Logistic regression analysis.
[b]Ordinal regression analysis.

The logistic regression analysis was performed in the model established by female patients' NIHSS, GCS, SEDAN, and THRIVE scores to predict the dependency status [mRS 0–2 = functional independence, mRS 3–5 = functional dependency]. Model fit was good (Nagelkerke R Square = 0.610). According to the results of this analysis, one unit increase in the NIHSS increased the risk of being fully dependent by 1.61 times (p = 0.001, adjusted OR = 1.611, 95% CI = 1.474–1.762). An ordinal regression analysis was also performed in the model established by female patients' NIHSS, GCS, SEDAN, and THRIVE scores to predict the dependency status. Model fit was good (Nagelkerke R Square = 0.735). According to the results of this analysis, one unit increase in the NIHSS increased the risk of being fully dependent by 1.72 times (p = 0.001, adjusted OR = 1.726, 95% CI = 1.612–1.847). The prediction of the mortality status and dependency at the discharge with initial disability scores are shown in **Table 5**.

DISCUSSION

Although the etiology, mechanisms, and risk factors of diseases have been mostly understood, estimating the prognosis of diseases is one of the most important issues in medicine due to the existence of several relevant factors such as common comorbidities, habits, genetic, and environmental factors. It is important to predict the prognosis in patients with stroke because of high mortality and morbidity. Studies are generally conducted on all patients with stroke. However, the prognostic factors for the female gender, which has specific risk factors, should also be investigated. Women have a stroke at a later age than men and had comorbid diseases during stroke more commonly than men (8); it is known that these factors have an impact on prognosis. Especially in western countries, stroke develops at a younger age; while in countries such as China and Iran, stroke occurs at an

older age (16–18). The mean age of female patients with stroke in our study was 68.97 ± 14.61 years. This situation showed us that stroke in women in Turkey occurs in middle-advanced ages. At the same time, female patients with ischemic stroke were older than male patients. When the literature is evaluated in terms of comorbid diseases, the most common chronic disease in women and men is hypertension. Diabetes mellitus and atrial fibrillation are the other most frequent accompanying risk factors (8, 19). In our study, similar to the literature, the most common comorbid chronic diseases in female patients with stroke were hypertension (68.9%) and diabetes mellitus (41.4%). Stroke is a disease with high mortality and disability. The mortality rate in patients varies between 8 and 20%. This rate is quite high, and deaths occur frequently in the first year (7, 19). In our study, the in-hospital mortality rate was determined as 18.3% in women and 12.0% in men, and it was relatively higher in female patients. Considering that stroke-related mortality is higher in female patients in the literature, findings consistent with the literature were also determined in our study (5). The worse prognosis in female patients with stroke suggested that there is a relationship between gender and the severity of stroke.

Many clinical scales are frequently used in the selection of treatment, clinical follow-up, and prognosis in stroke. The most frequently used ones among these are the NIHSS and mRS scores. Another frequently used scale is the GCS, which is used especially in intensive care units. SEDAN and THRIVE scores are the other scales that have been determined to have prognostic importance in the current literature. Decreased GCS and all other increased scores are associated with stroke severity (11–15). In the literature, studies using scales for prognostic evaluation generally included all patients with stroke. Studies in which gender-specific evaluation is performed are rare (20, 21). In our study, NIHSS, SEDAN, and THRIVE scores were higher in female patients who had a fatal outcome, were discharged as functionally dependent, required intensive care unit admission, developed CNS complications, and needed ventilation, while the GCS score was lower. Since scores of these scales can predict prognosis and the need for intensive care in female stroke patients, these scales should also be evaluated for treatment options.

Prolonged hospital stay is a poor prognostic indicator in patients with stroke. Patients with severe stroke tend to stay in the hospital for a long time. This situation increases rates and negatively affects the prognosis of stroke. Therefore, individuating outcome predictors in these patients can guide the disease and treatment process (22, 23). In our study, a statistically significant correlation was found between the length of hospital stay and all scales, while the highest correlation coefficients were with the NIHSS and the mRS. Higher scores on these scales were associated with longer hospital stays.

Changes in hematological values can predict stroke prognosis and may be associated with mortality and disability (24, 25). In particular, leukocyte count changes are frequently affected by many clinical conditions, especially infection and inflammation. However, studies on patients with stroke have shown that the leukocyte count can be an important blood marker in predicting mortality and prognosis (24, 26). Elevated serum glucose level has been determined as a strong indicator of poor prognosis in stroke (27). While glucose elevation is an important risk factor in etiology, especially in patients with diabetes mellitus, it is also associated with increased cerebral ischemic volume and poor functional status (28). As a result, it was determined that hyperglycemia was associated with the size of the lesion and the severity of the neurological deficit (29). It has been shown that there is a relationship between high renal function tests and low serum albumin levels and prognosis, and increased values are associated with poor functional outcomes (30). While high serum lipids can be an important risk factor in the etiology of stroke, it has been stated that high serum cholesterol levels can be associated with favorable outcomes (31). In this study, it was shown that there is a relationship between high inflammatory values (especially leukocytes and C-reactive protein) and poor in-hospital prognosis. The elevated blood glucose level at admission was associated with increased mortality and the need for ventilation. Similarly, increased serum urea and creatinine levels were associated with mortality. Low albumin level was also found to be an indicator of poor in-hospital prognosis. Urea and albumin levels were associated with disability at discharge; indeed, the increased value of urea and the decreased value of albumin were associated with worse functional outcomes. There was no relationship between blood lipid levels and prognosis. These prognostic markers should be confirmed with multicenter studies.

In conclusion, female patients with ischemic stroke of anterior circulation have a worse short-term prognosis, higher mortality, and a higher rate of disability. The NIHSS and the mRS can be used to predict prognosis, higher mortality, and disability. Although the NIHSS and the mRS can be used to predict prognosis in these patients, the GCS, SEDAN, and THRIVE scores are also important measures in short-term prognosis. In addition, higher levels of blood glucose, creatinine, urea, leukocytes, and CRP and lower levels of albumin and hemoglobin predict poor prognosis.

This study has several limitations. First, this is a retrospective and cross-sectional study. Second, the national and geographic features could not be evaluated because data from a single center were used. Third, the patients were not divided into groups according to ischemic stroke localization (frontal, temporal, etc.). Fourth, the serum markers evaluated in the study are frequently affected by many clinical and structural conditions. Fifth, female patients were not divided into groups according to their menstrual cycle, pregnancy, or menopause status. Sixth, long-term (3rd month, 6th month, or 1st year) prognosis and causes of mortality were not assessed. Seventh, factors, such as infection, that might have an adverse impact on morbidity and mortality during hospitalization (pneumonia, etc.) were not evaluated. Importantly, other variables, such as stroke subtype, the presence of vessel occlusion, lesion volume, the collateral circulation status, and recanalization, were not taken into account. Multivariate analyses for mortality and dependency were adjusted only for the stroke scales, which were under investigation in this study for prognosis prediction (NIHSS, mRS, GCS, SEDAN, and THRIVE). Additionally, blood parameters and disability scores of male patients with ischemic stroke were not evaluated for comparison.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Selcuk University Clinical Research Local Ethics Committee (approval number: 2020-473).

AUTHOR CONTRIBUTIONS

FE: planning, organization, writing, and editing. SO: planning, organization, and editing. CO: planning, organization, data collection, writing, and editing. All authors contributed to the article and approved the submitted version.

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frontiers | Frontiers in Neurology

REVIEW
published: 07 April 2022
doi: 10.3389/fneur.2022.833933

Detection to Hospital Door: Gender Differences of Patients With Acute Stroke Symptoms

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Although prehospital stroke management is challenging, it is a crucial part of the acute stroke chain to enable equal access to highly specialised stroke care. It involves a critical understanding of players usually not specialized in acute stroke treatments. There is contradictory information about gender inequity in prehospital stroke detection, dispatch, and delivery to hospital stroke centers. The aim of this narrative review is to summarize the knowledge of gender differences in the first three stages of acute stroke management. Information on the detection of acute stroke symptoms by patients, their relatives, and bystanders is discussed. Women seem to have a better overall knowledge about stroke, although general understanding needs to be improved. However, older age and different social situations of women could be identified as reasons for reduced and delayed help-seeking. Dispatch and delivery lie within the responsibility of the emergency medical service. Differences in clinical presentation with symptoms mainly affecting general conditions could be identified as a crucial challenge leading to gender inequity in these stages. Improvement of stroke education has to be applied to tackle this inequal management. However, specifically designed projects and analyses are needed to understand more details of sex differences in prehospital stroke management, which is a necessary first step for the potential development of substantially improving strategies.

Keywords: prehospital, acute stroke, management, women, gender inequity

OPEN ACCESS

Edited by:
Christina Kruuse, Copenhagen University Hospital-Herlev Gentofte, Denmark

Reviewed by:
Serefnur Ozturk, Selcuk University, Turkey
Krystyna Jaracz, Poznan University of Medical Sciences, Poland

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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *12 December 2021*
Accepted: *09 March 2022*
Published: *07 April 2022*

Citation:
Walter S, Phillips D, Wells B, Moon R, Bertsch T, Grunwald IQ and Fassbender K (2022) Detection to Hospital Door: Gender Differences of Patients With Acute Stroke Symptoms. Front. Neurol. 13:833933. doi: 10.3389/fneur.2022.833933

INTRODUCTION

Acute stroke care and access to timely treatment strongly depend on efficiently organized prehospital management. The stroke chain of survival with its first 3 "Ds", detection, dispatch, and delivery, based in the prehospital setting emphasizes the importance of optimal pathways before the patients arrive at the hospital (1). There is contradictory information about gender inequity in acute stroke treatment. A German nationwide cohort analysis with >1 million patients identified a higher probability of men receiving stroke unit treatment (OR, 1.11; 95% CI, 1.09–1.12) with a lower in-hospital mortality (OR, 0.91; 95% CI, 0.89–0.93) compared to women (2). However, intravenous thrombolysis (IVT) treatment numbers were similar in this study and more women received endovascular treatment (EVT). A Swedish analysis confirmed significantly lower numbers of women receiving stroke unit care in their cohort (3). In contrast, a retrospective analysis of

patients with acute ischemic stroke (AIS) arriving at hospital within 2 h after symptom onset from the American Get-With-The-Guidelines-Stroke registry identified female sex as a risk factor for not receiving IVT (4). It is unclear whether these differences are caused by an already existing gender inequity in the very first prehospital stages of acute stroke care in different regions. This review gives insights into available knowledge on gender differences from symptom onset until arrival at the hospital emergency department and discusses available information on detection, dispatch, and delivery of the acute stroke management cascade.

DETECTION OF ACUTE STROKE SYMPTOMS

Identification of acute symptoms of stroke can be challenging even for specialists. However, this is the first crucial step in gaining access to modern stroke treatment, especially to recanalizing therapies with a time-limited treatment window for the best outcome. Most of the current literature describes a better recognition and identification of acute stroke symptoms by women, but there are also publications emphasizing their lack of stroke understanding.

Differences in Stroke Knowledge

A meta-analysis of 22 studies, of which 20 were cross-sectional and 2 pretest–posttest design surveys, mainly conducted in the USA and Canada, identified a greater knowledge of stroke symptoms and related risk factors in women compared to men (5). In a Spanish randomized study, in which knowledge about stroke symptoms and risk factors was collected with structured face-to-face questionnaires, no sex difference could be detected in general knowledge about stroke, but women showed a higher understanding of risk factors. However, they were less likely to call an ambulance (6). In contrast, in a cross-sectional Chinese study, in which men and women with stroke and hypertension were questioned regarding their stroke knowledge and behavior, men demonstrated a better knowledge about stroke but had a worse pre-stroke health behavior than women (7). An American stroke survey performed with a limited number of stroke survivors detected women as significantly more likely compared to men to identify all the five traditional warning signs of stroke and subsequently take the correct action by calling the Emergency Medical Service [EMS; (8)]. In 4 Canadian cross-sectional surveys, in which public awareness campaigns including information about stroke preceded a stroke-knowledge questionnaire about face, arm, speech symptoms, a clear association of limited knowledge with male sex was found [Odds ratio 0.68; 95% CI: 0.53, 0.86; (9)].

In addition, the overall perception of stroke knowledge in women is poor. A survey of 1,024 women contacted by randomly selected telephone numbers in the USA in 2003 identified that only one-fourth of all women felt well informed about stroke and stroke risk and just below a quarter reported to be very concerned about the disease. Standing out was that younger women aged 25–34 years had the highest rate of nescience (37%). Hispanic or Black ethnicity was associated with less knowledge, but correct identification of acute stroke symptoms was low for all age groups and independent of racial backgrounds (10).

The above examples of available evidence (summarized in **Table 1**) emphasize that in many countries women are not generally underprivileged in their knowledge about stroke and understanding of the necessary actions to take. But, knowledge in general still needs improvement and differs not only between the countries but also between different ethnic groups. Both latter stress the need for tailored regional educational programmes involving women of all ethnic groups. A one-fit-all approach will not reach the aim.

Another possibility to increase stroke knowledge is to address pupils rather than only adults and to integrate medical education into school programmes. There is only limited information about the potential benefits of an early school education about stroke and stroke symptoms. However, there seems to be no gender difference. In an 11-question multiple-choice stroke awareness survey with >600 American High school pupils, no difference in stroke symptom knowledge between girls and boys was detected (14). A randomized controlled, multiethnic school-based intervention study called "Kids Identifying and Defeating Stroke" (KIDS), which was started in middle schools enrolling 8,827 pupils in Texas, USA investigated whether a structured stroke education campaign for their year 6 to year 8 pupils could improve stroke knowledge and necessary emergency actions. The programme was performed as four 1-h classes each year, taught by health teachers and neurologists, and included a homework assignment involving parents. A significant increase in stroke knowledge and correct reaction to witnessed symptoms of students' in the KIDS group compared with controls could be observed. The result did not show any gender differences (12). No information could be found from other countries. Also, it stays unclear whether school educational programmes can lead to a longer-lasting increase in the overall understanding of stroke symptoms, and emergency actions needed. This requires further investigation.

Educational Effect of Public Awareness Campaigns

Public awareness campaigns, comparable to advertisements promoting products or services, are general means that use mass media and new media to transfer information.

It is very well described that most public awareness campaigns can improve stroke knowledge only for a short amount of time, usually lasting between 3 and 6 months (25). Interestingly, it seems that there is a gender difference in susceptibility to such campaigns. A randomized study analyzing the effect of a posted information letter about stroke symptoms showed that the outcome of reduction of prehospital times was only significant for women (13). This could be explained by the finding from a cohort analysis in the Czech Republic, where a sample of 1,004 people were interrogated about their stroke knowledge. Women showed significantly higher interest in the information than men (11). Nevertheless, it stays unclear whether permanently repeated public awareness campaigns in the spirit of "Groundhog Day"

TABLE 1 | Studies addressing gender in prehospital stroke management.

Reference	Location	Study design	Participants n	Results for women
Detection				
Bártlová et al. (11)	Czech Republic	Cohort study	1,004	Women show more interest in stroke information
Ferris et al. (10)	USA	Telephone survey with randomly selected women	1,024	Only 25% women feel well informed
Focht et al. (8)	USA	Cohort survey	71	Women know more stroke signs and more likely to take correct actions
Li et al. (7)	China	Cross-sectional survey	272 men and 118 women	Women less knowledge about men, but better pre-stroke health behavior
Morgenstern et al. (12)	USA	RCT	573	Girls and boys show equal knowledge after stroke education
Mueller-Nordhorn et al. (13)	Germany	RCT	75,720	Women show reduced prehospital times after posted stroke information
Ramírez-Moreno et al. (6)	Spain	RCT	2,409	Women show higher understanding of risk factors, but EMS alerted less often, no difference in general stroke knowledge
Rioux et al. (9)	Canada	Cross-sectional survey	2,451	Women show better knowledge after awareness campaign
Stroebel et al. (5)	USA, Canada	Metaanalysis	20 cross-sectional, 2 pre-posttest surveys	Women show greater knowledge about stroke and risk factors
Umar et al. (14)	USA	Cohort survey	608	No difference in stroke knowledge of girls and boys
Dispatch				
Barr et al. (15)	Australia	Cohort study	150	Fewer women recognized the importance of immediate transfer to hospital
Buck et al. (16)	USA	Cohort study	871	More women than men were misidentified by EMS dispatcher
Mainz et al. (17)	Denmark	Cohort study	5,356	Women living alone have longer total prehospital time delay
Mochari-Greenberger et al. (18)	USA	GWTG registry	398,798	Hispanic, Asian, Black women less likely to use the EMS
Springer and Labovitz (19)	USA	Cohort study	1,940	Women more often found down, leads to admission delay
Delivery				
Govindarajan et al. (20)	USA	Registry cohort	3,787	Fewer women are correctly diagnosed by EMS
Hsieh et al. (51)	Taiwan	Cohort study	928	More men are pre-notified to hospital
Leung et al. (21)	Hong-Kong	Cohort study	298	More men are pre-notified to hospital, pre-notification associated with shorter treatment times
Lin et al. (22)	USA	GWTG registry	371,998	Fewer women are transferred with pre-notification
Madsen et al. (23)	USA	Cohort study	1,991	Females living alone are at higher risk to have delayed hospital arrival combreaked to men
Mould-Millman et al. (24)	USA	Cohort study	548	Women have lower sensitivity to be correctly diagnosed at the emergency site

could lead to a more solid understanding of stroke of all genders and ethnicities.

DISPATCH: INVOLVEMENT OF EMS

Early activation and dispatch of EMS is a vital element in the acute stroke chain of survival (26). The use of EMS is associated with shorter times to treatment (27); however the existing literature evidences a large degree of variation in how quickly patients alert the EMS and the subsequent dispatch of a medical resource. Prehospital delays can range from 20 min to >150 h based on a number of factors, including the patient's awareness of the severity of their symptoms with data suggesting that female patients with stroke experience an increased delay time in calling for help (15).

There is a paucity of contemporary evidence surrounding sex differences in activation and dispatch of EMS; however there is

a recognized inequity in emergency care access in women with stroke, which may be a result of delay in EMS dispatch (28). In a study of 5,515 patients with stroke in the Netherlands, symptom onset to door time was found to be on average 27 min longer in women than in men (29). This finding can be caused by multiple different underlying reasons, of which some are discussed below and are summarized in **Table 1**.

Willingness to Call

Existing literature presents an inconsistent picture of sex differences in the activation of EMS. Ramirez-Moreno et al. (6) studied responses from 2,409 participants aged 18 and over, who were surveyed through face-to-face interviews consisting of open-ended questions about the respondent's hypothetical answer to presenting or witnessing signs of a stroke and upon suspecting stroke or transient ischemic attack (TIA) in a family member or themselves. An appropriate response to a suspected stroke was indicated by 83.4% of men compared to only 77.5% of women. These findings are corroborated by further research which suggest that women are more likely to delay accessing emergency care than men, with some literature suggesting that the odds of being admitted to hospital within 3 h of symptom onset was 10% lower for women than men (30). Possible reasons for the disparity in the response to stroke symptoms between men and women may include a difference in perceived severity of the symptoms with women underestimating the urgency of the situation (6). But there are also intrasexual differences. Data analyzed from 398,798 American Get-with-the-guideline stroke registry patients, identified Hispanic or Asian or Black women compared to White women as less likely to use the EMS when stroke symptoms occurred [aOR, 95%CI: Black: 0.87, 0.84–0.91; Hispanic: 0.71, 0.67–0.74; Asian: 0.71, 0.67–0.76; (18)].

Reasons for Delayed Calling

Delayed calling for help might have multiple underlying causes. An American questionnaire study assessing attitudes toward response to stroke onset found that women, who arrived at hospital over 3 h after symptom onset, cited reasons such as not wanting to trouble others, opting to see if their symptoms might resolve, hiding their symptoms from others, and trying to continue with their normal actives for a delay in seeking emergency care (31). This finding demonstrates some plausible reasons for the delay in EMS dispatch, and therefore hospital arrival, that impacts the eligibility for recanalizing treatments due to arriving outside the treatment window (17).

Whilst the study did not include men and therefore provides no opportunity for comparison with regard to responses, it is recognized that there are sex-specific differences in the way in which medical assistance is summoned following the onset of stroke symptoms, which can result in a delay in dispatch for women (32). In a study of 150 patients with stroke in Australia, it was found that women experienced a delay in symptom onset to presentation to ED that was a mean average of 1.4 h longer than men, with knowledge and recognition of stroke symptoms and not recognizing the importance of their symptoms significantly impacting this delay (15).

Impact of Difference in Social Situations

If a stroke is witnessed, the activation of EMS is substantially shorter than if symptom onset was unwitnessed (33). It is, therefore, reasonable to suggest that living alone may result in a higher incidence of stroke with an unwitnessed symptom onset and therefore delayed EMS dispatch. Mainz and collaborators published in 2020 (17) the higher proportion of women living alone at the time of their stroke as a likely cause for a longer delay in symptom onset to EMS call. Their study found that this "patient-dependent delay" for women was 19.8 min longer than for men, with living alone being associated with a longer total prehospital time delay. About 50.4% of women lived alone compared to only 31.7% of men.

A retrospective cohort analysis of 1,904 hospital patients with stroke in New York, USA identified that women are significantly more often found with severe stroke symptoms unable to seek help on their own ("found down") and that this led to all of them arriving 3 h or later after onset (19).

If the onset of stroke symptoms is witnessed, it is most commonly by the patient's partner (34); however more women than men are widowed at the time of stroke and therefore live alone, with a delay in EMS dispatch a plausible consequence of this (35). The caller was the patient themselves in only 3% of cases based on a study of 198 patients transported to the emergency department (ED) by EMS in Melbourne (34), further supporting the hypothesis that women are susceptible to delays in EMS dispatch.

Another reason adding to the gender difference in EMS activation might be that women are older than men at the time of stroke, particularly in Europe, Australia, and South America (36). This results in a higher level of functional limitation prior to their stroke (35, 37), which may impact their physical ability to summon help.

Role of the Emergency Medical Service Dispatch Center

The identification of stroke symptoms at the point of EMS dispatch is key in optimizing the chain of survival in acute stroke and this remains one of the least investigated elements of the chain (38). It is critical that dispatch centers accurately identify stroke to avoid the assignment of an incorrect "code" and cause subsequent delays in EMS dispatch (39). There are many differences in the organization of EMS worldwide (40); however findings show a stark variation in the proportion of strokes correctly identified at the point of dispatch with successful identification ranging from 45 to 83% (16, 41).

In some countries, the Medical Priority Dispatch System (MPDS) is used for EMS dispatch. This system is based on a structured caller interrogation with additional instructions on what to do until EMS arrival. In a Los Angeles study of 871 patients, 58 were assigned the stroke MPDS code by the dispatcher, but only 45% received a confirmed in-hospital stroke diagnosis (16). A total of 56.2% of female patients with stroke were misidentified in this study. In a review of existing literature, Oostema and collaborators (42) found that despite the use of a stroke screening tool, the recognition of stroke

by the dispatch center was inadequate and it is suggested that many subtle stroke presentations may be misidentified (39). A barrier to the identification of stroke symptoms at the point of dispatch is the variety of presenting symptoms that may fall outside of the screening system adopted by the communication center. With women more likely to experience non-traditional stroke symptoms, an inherent risk not only of incorrect call coding at the point of dispatch with subsequent delays in timely EMS care but also of EMS identification of a woman with stroke, decelerating the delivery to the stroke center, has to be considered.

DELIVERY TO HOSPITAL

There are many reports on differences in clinical presentation between men and women [**Table 1**; (43)]. This likely not only affects stroke patient's identification at the dispatch center level but also at the scene, influencing the delivery step of the acute stroke chain of survival. Delivery comprises of rapid EMS identification of stroke symptoms, management of the patient on the scene, and timely transportation and prenotification to the hospital, as defined by the American Heart Association (44).

Gender Differences in Stroke Presentation and EMS Recognition

Women are reported to often present with unusual stroke symptoms such as generalized weakness, fatigue, and mental status change. In an analysis of 461 patients, 52% of women compared to 44% of men presented with a non-traditional stroke symptom (43). This result was primarily driven by the number of women with mental status changes, a symptom caused by many other differential diagnoses (45). Further studies confirmed that non-traditional stroke symptoms were present in 51.8% of women compared to 43.9% of men (46). In addition, disorientation, visual disturbance, dizziness headache, general pain, urinary incontinence, or changes in consciousness are specifically described to be shown in female stroke (47, 48).

These reported differences in the clinical presentation of stroke between genders can therefore be of challenge for the EMS when diagnosing stroke in the prehospital environment with only limited diagnostic tools available. This is supported by multiple studies (49). A recent systematic meta-analysis of 21 observational studies with 6,934 stroke and transient ischemic attack patients identified that 26% of all patients with stroke, who were missed by the EMS, presented with non-FAST symptoms like speech abnormalities, nausea/vomiting, dizziness, changes in mental status, and visual disturbance (41). A study with 3,787 patients transported by EMS found that only 30% of women compared to 35% of men received a correct diagnosis of stroke, with these findings perceived to be based on the non-traditional stroke symptoms displayed more frequently by women (20).

Various measures have been previously discussed to enhance prehospital stroke recognition, including the use of validated stroke scales (50). A retrospective analysis of 548 emergency patients in Atlanta, USA evaluated that paramedics were more likely to positively identify stroke when the Cincinnati Prehospital Stroke Scale (CPSS) was positive. However, sensitivity to be diagnosed at the scene was lower for women than men [odds ratio 0.53, 95%CI 0.17–1.63; (24)].

It is likely that different presentations of women with acute stroke lead to a wrong working diagnosis by the EMS in the prehospital phase, which could impact further stroke management. However, more prospective studies are needed to understand the real impact.

Gender Differences in EMS On-Scene Time Metrics and Prenotification to Hospital

A large study of nearly 2,000 patients presenting with AIS found that before adjustment, the time of symptom onset to arrival at the hospital *via* the EMS was slightly longer in women (mean 337 min vs. 297 min in men); however, they subsequently found that gender was not associated with a delayed time to arrival when considering age and National Institute Of Health Stroke Severity (NIHSS) score. It was demonstrated that 30% of women in the study (324/1097) lived alone compared to 22% of men (200/894), and that this was a factor in delayed arrival at the hospital, potentially due to the lack of self-recognition of symptoms (23). A study of 5,356 patients identified that 40.5% of women and 44.4% of men arrived at the stroke unit within 3 h of symptom onset, and similarly living alone was deemed to be a contributory factor involved in this finding. About 54.4% (1,256) of women were documented as living alone, leading to an average delay of 20 min longer than their male counterparts (17).

A study from 2016 demonstrated an association not only between pre-notification and faster door to computed tomography (CT) scan in patients presenting within 3 h of symptom onset but also a shorter door-to-needle (DTN) time. This study comprised of 928 patients, of whom 727 received pre-notification to the hospital. There was a significantly higher number of men who were transported with pre-notification (64.5%), and more pre-notified patients had a DTN of < 60 min (45.1 vs. 28%) compared to those not pre-notified (51). A similar pattern was shown in a study from Hong Kong, which found that the ratio of men to women receiving pre-notification to hospital for stroke was 1.22:1. Pre-notification was also demonstrated to improve door-to-CT and DTN time (21).

An analysis of the American Get-with-the-Guideline stroke registry of 371,998 enrolled patients with stroke in 1,585 hospitals over 8 years showed a pre-notification rate of 67%. Patients with EMS pre-notification to the hospital were more likely to be younger, white, and male. In the 122,791 patients eligible for pre-notification where none was given, 54.3% were women (22).

These differences in prehospital management of women with acute stroke might be caused by a higher number of misdiagnoses, subsequently leading to lower numbers with accurately initiated stroke alert to the hospital. But clearly, further research is required to understand unbiased differences in prehospital treatment and outcomes.

DISCUSSION

This review addresses gender differences in the very first stages of acute stroke management, the detection of disease symptoms to the delivery of the suspected stroke patient to the specialized

center. It highlights some of the available evidence with the aim to raise awareness and identify a pattern, hinting toward areas of necessary improvement to guarantee gender equity in prehospital acute stroke treatment.

Detection of acute stroke and initiation of the necessary steps, which enable health care specialists to administer up-to-date and high-quality stroke care, is incumbent to the patient and or relatives or bystanders. There is a lot of evidence coming from different countries that women have a better knowledge about acute stroke symptoms, risk factors, and the necessary actions to take than men. However, the overall public level of knowledge about stroke, the number three disease cause for disability is still poor (52, 53). Gender inequity in the detection of stroke seems to show geographical differences, but further systematic evaluations are needed to understand where and what differences exist.

Despite often having a higher and better knowledge about stroke, women seem to feel uncertain about many aspects of the disease. Women's confidence in their own knowledge differs from that of men (54), which needs to be considered and addressed in educational programmes.

The idea to implement health education in standard school programmes would be one possibility to establish gender-independent knowledge transfer in the future. But, to reach girls and young women in countries with relevant sex inequity would need strong collaboration between health services and educational sectors with strong political and governmental support.

It is well described that public campaigns do not lead to a sustainable solution to improve health awareness (1); however it seems that women are more likely and willing to pick up information provided by mass media campaigns (55).

However, equal knowledge and awareness alone do not lead to equal acute stroke care. The available evidence suggests that women arrive at the hospital later than men, indicating an inequity in dispatch and delivery of acute stroke care. Relevant confounders like social disparity with more women living alone at an older age, when the risk of stroke increases, have to be considered. Management of women seeking help at an emergency medical dispatch center does not seem to show any gender-based differences. But many countries use systematized interrogation programmes, like the Medical Priority Dispatch System to identify stroke suspects, which could be prone to errors and disadvantageous to women with stroke, who often present with non-traditional symptoms (43).

There is no information available on whether a criteria-based dispatch, used in many Nordic and European countries (56), which relies on the experience of the telecommunicator, is less prone to misidentify women with suspected strokes. More studies comparing both modes of emergency service dispatch are needed to identify gender-related challenges of different dispatch systems.

The differences in the clinical presentation of women compared to men can make it difficult for paramedics to quickly conclude a stroke working diagnosis at the emergency site. This likely presents the biggest challenge in the delivery of equal care. There is evidence for an inequity in pre-notification of cases to the receiving hospital. To tackle this, paramedic and EMS stroke-specific training have to be considered and addressed. A correlation between high-quality medical education and patient outcome has been demonstrated for nurse care (57, 58), but data for the EMS or, more important, training programme adjustment for prehospital staff is lacking.

To conclude, more structured data and results from specifically designed clinical trials are needed to understand gender inequity in the first stages of acute stroke care and to develop solutions to overcome potential gender disbalances. Identified gender inequity is mostly caused by unawareness of gender-specific aspects of stroke, which are not considered in acute prehospital pathways.

AUTHOR CONTRIBUTIONS

SW, BW, RM, and KF contributed to the conception and design of the review. SW, BW, and RM wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Neurology

REVIEW
published: 11 April 2022
doi: 10.3389/fneur.2022.833215

Trends in the Incidence and Risk Factors of Pregnancy-Associated Stroke

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Pregnancy is a female-specific risk factor for stroke. Although pregnancy-associated stroke (PAS) is a rare event, PAS leads to considerable maternal mortality and morbidity. It is estimated that 7.7–15% of all maternal deaths worldwide are caused by stroke and 30–50% of surviving women are left with persistent neurological deficits. During last decade, several studies have reported an increasing incidence of PAS. The objective of this review is to summarize studies on time trends of PAS in relation to trends in the prevalence of stroke risk factors in pregnant women. Seven retrospective national healthcare register-based cohort studies from the US, Canada, UK, Sweden, and Finland were identified. Five studies from the US, Canada, and Finland reported an increasing trend of PAS. Potential biases include more sensitive diagnostics and improved stroke awareness among pregnant women and professionals toward the end of the study period. However, the concurrent increase in the prevalence of several stroke risk factors among pregnant women, particularly advanced age, hypertensive disorders of pregnancy, diabetes, and obesity, indicate that the findings are likely robust and should be considered seriously. To reduce stroke in pregnancy, increased awareness among all medical specialties and pregnant women on the importance of risk-factor management during pregnancy and stroke symptoms is necessary. Important preventive measures include counseling for smoking cessation and substance abuse, treatment of hypertensive disorders of pregnancy, use of aspirin in women at high risk for developing preeclampsia, and antithrombotic medication and pregnancy surveillance for women with high-risk conditions. Epidemiological data from countries with a high risk-factor burden are largely missing. National and international registries and prospective studies are needed to increase knowledge on the mechanisms, risk factors, management, and future implications for the health of women who experience this rare but devastating complication of pregnancy.

Keywords: stroke, cerebrovascular disease, pregnancy, postpartum, prevention

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *10 December 2021*
Accepted: *22 March 2022*
Published: *11 April 2022*

Citation:
Ijäs P (2022) Trends in the Incidence and Risk Factors of Pregnancy-Associated Stroke. Front. Neurol. 13:833215. doi: 10.3389/fneur.2022.833215

INTRODUCTION

Pregnancy, along with postpartum period (puerperium), is a female-specific risk factor for stroke (1). Pregnancy-associated stroke (PAS) accounts for 18% of strokes in women aged <35 years (2). During pregnancy, the female body undergoes significant physiological changes to adapt to the growth of the fetus and to prepare for delivery (**Figure 1A**) (3–5). Many of these changes

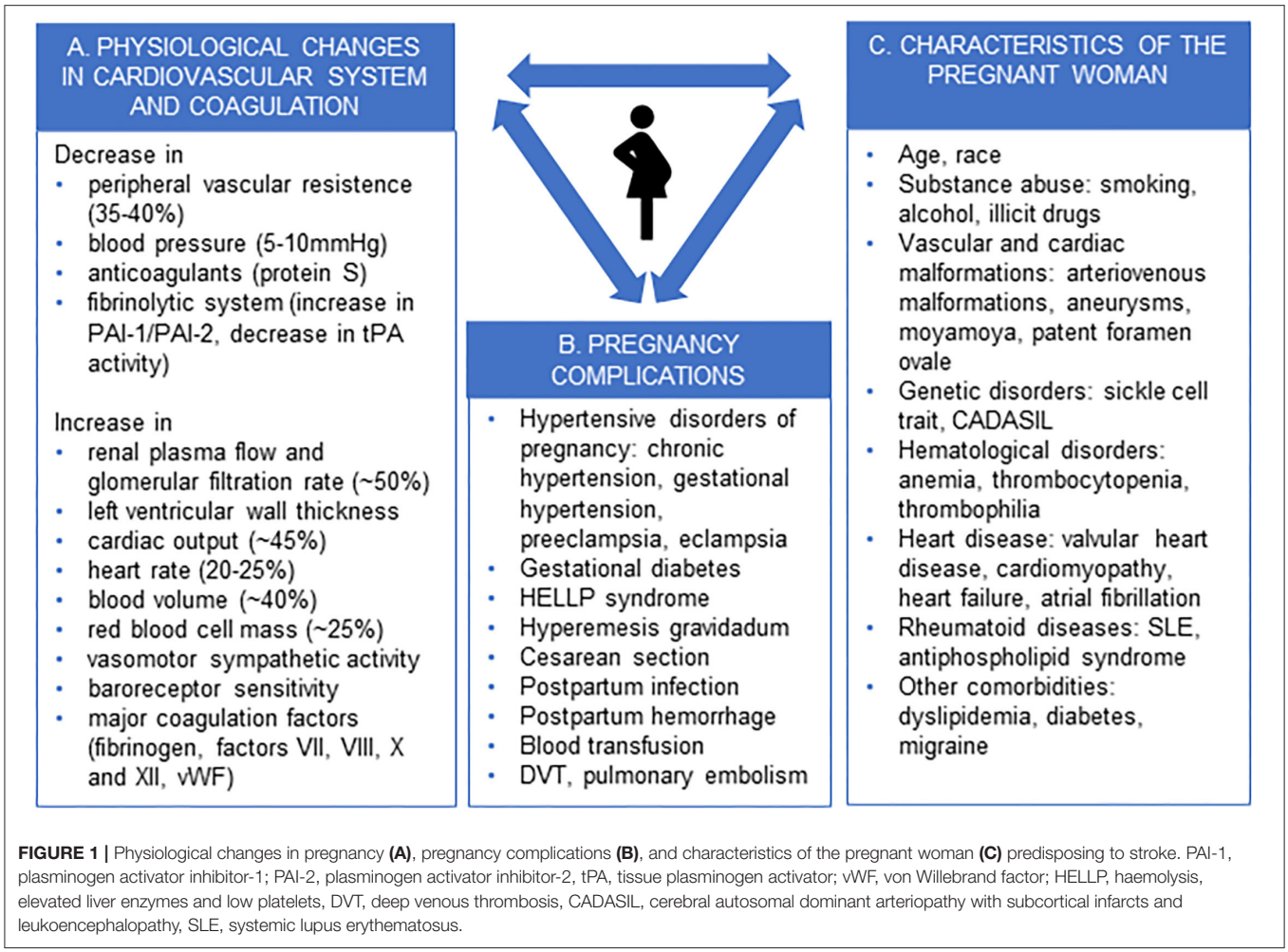

FIGURE 1 | Physiological changes in pregnancy **(A)**, pregnancy complications **(B)**, and characteristics of the pregnant woman **(C)** predisposing to stroke. PAI-1, plasminogen activator inhibitor-1; PAI-2, plasminogen activator inhibitor-2, tPA, tissue plasminogen activator; vWF, von Willebrand factor; HELLP, haemolysis, elevated liver enzymes and low platelets, DVT, deep venous thrombosis, CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, SLE, systemic lupus erythematosus.

may render the woman more vulnerable to thromboembolism and cardiovascular events to such an extent that pregnancy has been called Nature's stress test (3, 5). Pregnancy and its complications may reveal pre-existing maternal characteristics and comorbidities that predispose to cardiovascular diseases and stroke, such as heart disease, genetic and coagulation disorders, and malformations of cerebral vasculature (**Figures 1B,C**) (3, 5, 6).

Although a rare event, PAS accounts for considerable maternal mortality and morbidity. Approximately 7.7–15% of all maternal deaths worldwide are caused by stroke, with the highest mortality related to intracerebral hemorrhage (ICH) (7, 8). The estimated case fatality rate is 13.8% for ICH and 3.9% for ischemic stroke (9). Furthermore, stroke is a major cause of disability, as 30–50% of the mothers who experience stroke have persistent neurological deficits, which subsequently affects their ability to care for themselves and the newborn, to participate in family life, and to return to work (10).

Published estimates on the incidence of PAS are highly variable and range from 3.8 to 98.4 per 100 000 hospitalizations. This can be explained by differences between studies regarding source data (single institution, pregnancy or stroke registry, insurance or healthcare registry, questionnaire-based), inclusion criteria (stroke types, antenatal/postpartum), and geographical and population factors (healthcare system and income of the country, population genetics) (6, 11). In a recent meta-analysis including 11 studies from seven countries, the incidence of pregnancy-related stroke was estimated as 30.0 per 100 000 pregnancies (95% confidence interval [CI] 18.8–47.9), which is approximately 2–3 times greater than the rate in non-pregnant young adults (11). The rates were approximately equal between ischemic stroke (12.2, 95% CI 6.7–22.2), cerebral venous thrombosis (CVT) (9.1, 95% CI 4.3–18.9), and haemorrhagic stroke (12.2, 95% CI 6.4–23.2). The crude stroke rate was 18.3 (95% CI 11.9–28.2) for antenatal/perinatal stroke and 14.7 (95% CI 8.3–26.1) for postpartum stroke.

During the last decade, reports on the increasing incidence of stroke during pregnancy and puerperium have been published from several countries (12–17). The objective of this non-systematic review is to summarize the results from these recent studies on the incidence trends of PAS and to discuss the findings in relation to trends on the prevalence of stroke risk factors in pregnant women. Potential areas for future research are discussed.

METHODS

This was a non-systematic or narrative review. For the review on incidence trends of PAS, an electronic search included PubMed, Medline, and Google Scholar and used the search terms 'stroke', and 'pregnancy' or 'postpartum' or 'puerperium' and 'incidence'. Titles and (if required) abstracts were screened for relevant articles. Original articles reporting incidence rate trends in time for stroke during pregnancy or the postpartum period up to 12 weeks after delivery were included in the review. The exclusion criteria were articles for which full text was not available, articles not in English, or articles that reported incidence data only for a restricted subpopulation of pregnant women (e.g., women with hypertensive disorders of pregnancy or women with subarachnoid hemorrhage). From the articles retrieved in the first search round, additional references were identified by a manual search among the cited references. For the review on trends in the prevalence of stroke risk factors, an additional electronic search was performed using the search terms 'stroke' and 'pregnancy' or 'postpartum' or 'puerperium' and 'risk factors'. Additional references were identified by a manual search among the cited references from both searches. Searches were performed in December 2021.

INCIDENCE TRENDS OF PREGNANCY-ASSOCIATED STROKE

The literature search identified eight studies. Three were from the Nationwide Inpatient Sample in the US (12–14), two were national healthcare register-based studies from Canada (15), and one each were from the UK (18), Sweden (19), and Finland (16). One study on temporal trends of severe maternal morbidity in Canada (20) was excluded as it analyzed the same dataset and time period as the study specifically focused on PAS (15). The remaining seven studies are summarized in **Table 1**.

All studies from the US utilized data on pregnancy-related stroke hospitalizations in the Nationwide Inpatient Sample database, the largest all-payer, publicly available database of inpatient hospitalizations in the US. Their results cannot be directly compared due to different study outcomes and time periods between 1994 and 2015 (12–14). The earliest study that compared incidence rates of hospitalizations with antenatal or postpartum stroke between 1994–95 and 2006–07 reported increases both in antenatal strokes (from 15 to 22 per 100 000 deliveries, $p < 0.001$) and postpartum strokes (from 12 to 22 per 100,000 deliveries, $p < 0.001$) (12). A later study investigated the effect of hypertensive disorders of pregnancy (HDP) on the risk of stroke during pregnancy and noted that the incidence of stroke increased significantly both in women with and without HDP (13). In the most recent study, the incidence of acute stroke and TIA remained relatively unchanged between 2007 and 2015 (14). However, in the secondary analysis, in which TIA and pregnancy-specific codes were excluded, the incidence of acute stroke increased from 29.8 to 33.0 per 100 000 pregnancy-related hospitalizations ($p_{trends} < 0.0001$).

In the data from the Canadian Institute of Health Information, the incidence of stroke, TIA, and cerebrovascular disease rose from 10.8 per 100 000 in 2003–04 to 16.6 per 100 000 deliveries in 2015–16 ($p = 0.002$) (15). Most cases were haemorrhagic strokes (58.6%) and occurred in the postpartum period (51.5%). This study included a wide spectrum of diagnostic codes related to cerebrovascular disease and it was not possible to verify whether the identified strokes were first-time events or complications of an earlier event. Nevertheless, the incidence was lower than in the earlier studies from the US. A recent Finnish population-based study that covered a 30-year time period from 1987 to 2016 revealed an increasing incidence of PAS from 11.1 to 25.2 per 100 000 deliveries from 1987–91 to 2012–16 ($p < 0.0001$) (16). Among stroke subtypes, the rising trend was significant for ischemic stroke and CVT but not for subarachnoid hemorrhage (SAH) or ICH. The main strength of this study was that the stroke cases were verified from medical records, resulting in the exclusion of 70% of register-identified cases. The main reasons for exclusion were history of stroke not associated with pregnancy (36.6%), neurologic symptoms and suspicion of stroke during pregnancy or postpartum period leading to an alternative diagnosis after evaluation (stroke mimics, 17.2%), and anomalies of cerebral vasculature without an acute cerebrovascular event (9.5%).

Two other studies, one from Sweden (19) and another from the UK (18), examined incidence rates during an approximate 20-year time period but did not specifically report on trends in time. The incidence rates reported from the UK for the 5-year time periods 1997–2002 and 2009–2014 increased slightly (18). In the Swedish study, which reported only peripartum or early postpartum stroke, a decreasing incidence was revealed (19).

Summary

Seven studies on incidence trends of PAS over time were identified by the literature search. All the studies specifically addressing incidence trends over time, reported an increasing incidence of PAS. Studies were retrospective cohort studies from national healthcare registers, where stroke cases were identified by stroke ICD codes. One study verified diagnoses from medical records. The Finnish and Swedish registers are nationwide. The Canadian register included hospitalizations from all Canadian provinces except Quebec. The US Nationwide Inpatient Sample is the largest all-payer, publicly available database of inpatient hospitalizations in the US and includes all discharge data from 1,050 hospitals in 44 states, approximating a 20% stratified sample of US community hospitals. Thus, the register-based studies have good coverage and generalizability over the studied populations. The incidence rates are difficult to compare due to different diagnostic inclusion criteria and incidence rate definitions. However, the incidence rates in Canada and Finland appear lower than those in the US. Studies on incidence trends were only found from a few high-income countries, and data from middle- and low-income countries are lacking.

TABLE 1 | Studies reporting long-term incidence trends of pregnancy-associated stroke.

Country	Study years	Data source; N	Outcome	Change during the study period*
US (12)	1994–95 vs. 2006–07	Nationwide Inpatient Sample; not specified	Hospitalizations with antenatal or postpartum stroke, incl. TIA	Antenatal: 15 to 22 per 100 000 deliveries ($p < 0.001$); postpartum: 12 to 22 per 1000,000 deliveries ($p < 0.001$)
US (13)	1994–95 vs. 2010–11	Nationwide Inpatient Sample; 81,983,216 pregnancy hospitalizations	Pregnancy-related stroke hospitalizations with or without HDP, incl. TIA	Stroke with HDP: 8 to 16 per 100 000 hospitalizations ($p < 0.001$); stroke without HDP: 22 to 32 per 100,000 hospitalizations ($p < 0.001$)
US (14)	2007 vs. 2015	Nationwide Inpatient Sample; 37,360,772 pregnancy hospitalizations	Pregnancy-related acute stroke hospitalizations, incl. TIA	TIA included: 42.8 to 42.2 per 100 000 hospitalization ($p = 0.10$); TIA excluded: 29.8 to 33.0 per 100,000 hospitalizations ($p < 0.0001$)
Canada (15)	2003–04 vs. 2015–16	Canadian Institute of Health Information; 3,907,262 deliveries	Pregnancy-related stroke hospitalizations, incl. TIA and other cerebrovascular diseases	10.8 to 16.6 per 100,000 deliveries ($p = 0.002$)
Sweden (19)	1992–96 vs. 2007–12	National healthcare registers (Medical Birth Register, National Patient Registry); 1,124,541 women	Incidence rates for first incident stroke per 100,000 person-years, IRR for pregnancy periods and non-pregnant time, excl. TIA	Peripartum or early postpartum stroke: 106.5 to 93.5 per 100,000 person-years†
UK (18)	1997–2002 vs. 2009–14	National healthcare registers (Clinical Practice Research Datalink, Hospital Episode Statistics); 2,046,048 women	Incidence rates for first incident stroke per 100 000 person-years, IRR for pregnancy periods and nonpregnant, excl. TIA	49.8 to 59.7 per 100,000 person-years†
Finland (16)	1987–91 vs. 2012–16	National healthcare registers (Medical Birth Register, Hospital Discharge Register, Register of Causes of Death), cases chart-verified; 1,773,728 deliveries	Incident stroke per 100 000 deliveries, excl. TIA	11.1 to 25.2 per 100 000 deliveries ($p < 0.0001$)

*HPD, hypertensive disorders of pregnancy; IRR, incidence rate ratio. *p-value from time-trend analysis reported in the study. †Time-trend analysis was not performed in the study.*

TRENDS IN THE PREVALENCE OF RISK FACTORS OF PREGNANCY-ASSOCIATED STROKE

Stroke during pregnancy and postpartum often arises from an adverse interaction between normal physiological changes related to pregnancy, complications of pregnancy or delivery, and baseline characteristics of the pregnant woman (**Figure 1**) (6, 14, 16, 21, 22). Lifestyle factors and diseases of the pregnant woman that increase stroke risk include substance abuse (smoking, alcohol, illicit drugs), obesity, diabetes, dyslipidaemia, chronic hypertension, heart disease, migraine, antiphospholipid syndrome and systemic lupus erythematous, coagulopathy, certain genetic traits (sickle cell disease, CADASIL), and cerebrovascular malformations (aneurysms, arteriovenous malformations, moyamoya disease) (6, 14, 16, 21, 22). Among demographic factors, advanced age and African-American race are associated with an increased risk of PAS (14–16, 21). Complications of pregnancy and delivery, such as hyperemesis gravidarum, post-partum hemorrhage and infection, and Cesarean section, may precipitate stroke by exaggerating a prothrombotic state and fluid-electrolyte-acid-base disturbances (21, 22).

The prevalence of several known risk factors for PAS is increasing. Age is the most important non-modifiable risk factor for stroke and also increases the risk of stroke in pregnancy. In the Finnish population-based study, the incidence was three times higher in women >40 years than in those between 20 and 24 years (16). In many middle- and high-income countries, the mean maternal age at first birth has increased by several years. In the US, the percentage of first births for women 40–44 years increased by 70% between 1991 and 2001 (23). Advanced age increases the risk of stroke by multiple mechanisms. Women with advanced age typically have more classical vascular risk factors and may be less able to adapt to pronounced cardiovascular changes related to pregnancy, which renders them more vulnerable to pregnancy complications, particularly HDP (24). Less evident associations have also been described; a systematic review and meta-analysis of long-term cardiovascular effects of fertility therapy revealed a trend of a higher incidence of stroke (HR 1.27; 95% CI 0.96–1.68). It is not known if this applies to PAS.

Several modifiable stroke risk factors have also become more common among pregnant women. Obesity among pregnant women is a global problem, particularly in upper middle and lower middle income countries, where sharp increases in the proportions of overweight and obese pregnant women have been observed. In 2014, one fifth of women in India and a third of women in the US were obese (25). At the same time, an over 2-fold increase in the prevalence of pre-existing diabetes

in pregnant women, particularly among younger women, was noted between 1999 and 2005 in the US (26). Overweight women have significantly higher blood pressure at any point during the pregnancy and postpartum than women with lower body mass and are more prone to develop HDP (27). These trends were also observed in the reviewed incidence trend studies. In the earliest study by Kuklina and colleagues, the increases in the prevalence of HDP and heart disease were considered to almost exclusively explain the increase in postpartum hospitalizations (12). In the later study on the Nationwide Inpatient Sample database, there was an increase in the prevalence of obesity, smoking, hyperlipidaemia, migraine, atrial septal defects, prior stroke, and gestational hypertension among women with pregnancy-associated acute stroke or TIA (14). The interaction between many risk factors, such as obesity, diabetes, and HDP, may lead to clustering of several minor stroke risk factors, while pregnancy acts as a trigger for stroke.

Probably the most significant risk factor for PAS worldwide is HDP, which includes pre-existing hypertension (chronic hypertension), hypertension developing after week 20 in pregnancy (gestational hypertension), and preeclampsia/eclampsia (28). The reported prevalence of preeclampsia/eclampsia among women with PAS varies between 73% in India (29), 47% in France (10), 31% in the US (13), and 22% in Taiwan (9). HDP is associated with all stroke subtypes (9, 10, 16, 30). Women with HDP are approximately five-times more likely to have a stroke than those without; the presence of traditional stroke risk factors further increased this risk (13). Women hospitalized with HDP and stroke also had higher rates of complications than women without HDP, including the need for mechanical ventilation, seizure, pneumonia, prolonged hospital stay, and death during hospitalization (13). In data from the Global Burden of Disease 2019 Study, covering populations from 204 countries and territories, the total number of incident cases of HDP increased by 10.92% from 1990 to 2019 but the age-standardized incidence rate decreased (31). The authors suggested that this is related to population growth, advanced maternal age, and multiple pregnancies. The highest incidence rates of HDP were found in South Asia, western sub-Saharan Africa, and eastern sub-Saharan Africa.

The prevalence of several other potential risk factors for PAS is also increasing. Heart disease is an important risk factor for stroke (14, 32). Although the number of persons with heart diseases is not increasing due to better management, they more often become pregnant and thus encounter the risks associated with pregnancy. The same may apply to other patients with severe pre-existing conditions. Cesarean section is more commonly used and may promote thrombotic events (22).

Summary

The prevalence of several well-known risk factors for PAS has increased worldwide. The age of first-time mothers has increased, when they are more likely to have pre-existing comorbid conditions and are also more susceptible to pregnancy complications, notably HDP. The increasing incidence worldwide of obesity and diabetes also increases the risk of HDP and thromboembolism. Advancements in the management of certain medical conditions, such as heart and autoimmune diseases, increase the number of women with high-risk conditions who wish to become pregnant. Collectively, these factors may contribute to the increasing trend of PAS.

DISCUSSION

The incidence of PAS and its major risk factors has shown increasing trends during the last few decades. The incidence of stroke during pregnancy and puerperium is increasing in several high-income countries (12–16). Epidemiological data on pregnancy-associated stroke from many countries with high risk factor burden (25, 31) is largely missing. Older age accompanied with major stroke risk factors, such as hypertensive disorders of pregnancy, obesity, and diabetes, is becoming more prevalent among pregnant women.

There may be some alternative explanations for the incidence findings. It cannot be excluded that the identification of stroke cases has become more accurate over time. The general awareness of stroke and its symptoms has improved since the 1990s and thus there may be a lower threshold to seek medical attention for neurological symptoms (33). Furthermore, the development of efficient acute treatments for stroke has likely prompted clinicians to refer their patients with suspected stroke to specialists. Accordingly, patients with minor stroke may be more readily diagnosed. More sensitive imaging-based diagnostics by magnetic resonance imaging (MRI) are increasingly available, even in smaller hospitals in rural areas. This is particularly apparent in the case of minor stroke and local CVT, where diagnosis would not be possible without MRI (34). However, in the case of ischemic stroke, MRI can more readily diagnose stroke mimics and functional neurological disorders in addition to minor strokes. This was reflected in the Finnish population-based study, where 17% of the register-identified cases were excluded as stroke mimics after chart review (16). Evidence for a real increase in the incidence of PAS is the concomitant prominent increasing trends in stroke risk factors in pregnant women.

The improved general management of stroke and declining trend of stroke in older age groups suggests that the increasing prevalence of PAS can be reversed. For example, the Tromsø study showed that changes in cardiovascular risk factors explained 57% of the decrease in ischemic stroke incidence in the general population from 1995 to 2012. Reduction in systolic blood pressure and prevalence of smoking accounted for 26 and 17% of the observed decline, respectively (35). Since younger women are generally considered at low risk of cardiovascular diseases, the recognition of pregnancy as a stroke risk factor requires education of women and healthcare professionals working with pregnant women to achieve similarly efficient screening and management of blood pressure and other stroke risk factors in pregnant women.

Very little research data and no randomized controlled trials exist on preventative treatment or acute management

of stroke in pregnancy. Despite the rising incidence, stroke in pregnancy remains rare and it is highly unlikely that randomized controlled trials will be conducted. In recent years, guidelines and statements based on case series and expert opinion have been published in the US (36) and Canada (37, 38). Furthermore, extensive international and national guidelines exist on the management of HDP (28), diabetes (39), and cardiovascular diseases (32, 40) during pregnancy. As a general guideline, counseling for women with pre-existing cardiovascular disease should begin before pregnancy. Such women should be managed by multidisciplinary teams, high-risk patients should be treated in specialized centers, and diagnostic procedures and interventions should be performed in centers of expertise. Low-threshold maternal services and preventive pregnancy surveillance systems are important for screening and identifying women at high risk of PAS. Important measures of prevention include counseling for smoking cessation, screening and treatment of HDP, use of aspirin in women at high risk for developing preeclampsia, and antithrombotic medication and pregnancy surveillance for women with high-risk conditions (such as thrombophilias, heart diseases, previous stroke, or cerebrovascular malformation). Follow up after delivery should continue for at least 6 weeks or women should haver low-threshold maternal services to contact if neurological symptoms develop after delivery.

Several open questions and knowledge gaps remain. Very little is known on the exact pathogenic mechanisms responsible fo acute stroke during pregnancy and puerperium; such knowledge is needed to improve treatment. Preeclampsia is an established risk factor for long-term cardiovascular disease and stroke, and guidelines recommend following women with preeclampsia or gestational hypertension for cardiovascular risk factors after delivery (36, 38). Whether the increased risk of future stroke and cardiovascular disease applies to women with PAS and TIA is not known but is plausible. This suggests that more rigorous follow-up and management of women with PAS is necessary. National and international registries and prospective studies, such as the SiPP study (41), are urgently needed to improve knowledge on this rare but devastating complication of pregnancy.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 28 April 2022
doi: 10.3389/fneur.2022.853513

Comparison of Sex Differences in Outcomes of Patients With Aneurysmal Subarachnoid Hemorrhage: A Single-Center Retrospective Study

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OPEN ACCESS

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Reviewed by:
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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *12 January 2022*
Accepted: *09 March 2022*
Published: *28 April 2022*

Citation:
Cai YK, Liu Z, Jia CG, Zhao JW, Chai SS, Li Z, Xu CS, Zhang TB, Ma YH, Ma C, Chen XJ, Jiang PC, Zhao WY, Chen JC and Xiong NX (2022) Comparison of Sex Differences in Outcomes of Patients With Aneurysmal Subarachnoid Hemorrhage: A Single-Center Retrospective Study. Front. Neurol. 13:853513. doi: 10.3389/fneur.2022.853513

Background: Sex differences in the outcomes of patients with aneurysmal subarachnoid hemorrhage (aSAH) remain controversial. The aim of this study was to evaluate sex differences in the outcomes of patients with aSAH.

Method: This study retrospectively analyzed the clinical data of consecutive patients with aSAH, admitted to the Department of Neurosurgery, Wuhan University Zhongnan Hospital, from May 1, 2020 to December 31, 2020. The modified Rankin Scale (mRS) score was used to evaluate the prognosis of patients at discharge. Outcome indicators included cerebral ischemia, hydrocephalus, and mRS $\geq$ 2 at discharge.

Results: The majority (65%) of the 287 patients with aSAH included in the study were females. Patients were divided into female ($n = 184$) and male ($n = 99$) groups; the female patients were significantly older than the male patients (61.3 $\pm$ 8.5 years vs. 60.0 $\pm$ 8.5 years, $p = 0.032$). The incidence of comorbidities (hypertension, diabetes, and heart disease) was higher in the female group than in the male group, but the difference was not statistically significant. Although more female patients than male patients underwent endovascular treatment, there was no statistical difference in the treatment approach between the two groups. Comparison of post-operative complications and mRS scores at discharge revealed that the rate of cerebral ischemia and mRS $\geq$ 2 at discharge were significantly higher among female patients than among male patients. Moreover, this difference persisted after propensity adjustment for age and treatment approach. Analysis of risk factors for poor prognosis at discharge in both pre- and post-adjustment patients revealed cerebral ischemia and high mFisher score (mFisher = 3/4) to be independent risk factors.

Conclusion: Female patients with aSAH have a worse prognosis than male patients, and this difference may be because women are more susceptible to cerebral ischemia.

Keywords: aneurysmal subarachnoid hemorrhage (aSAH), gender, propensity adjustment, outcome, aneurysm

INTRODUCTION

Stroke is the second leading cause of mortality and disability-adjusted life-years lost worldwide, affecting almost 14 million individuals annually (1). Epidemiological studies have found that there are sex differences in many aspects of stroke, such as female patients having different vascular risk factors (2) and a greater likelihood of a poor prognosis (3) when compared with male patients. Aneurysmal subarachnoid hemorrhage (aSAH) is a common type of hemorrhagic stroke with a mortality rate of up to 30%, and a higher mortality rate in survivors even after successful treatment when compared to the general population (4). A previous study showed that female patients were more likely to develop intracranial aneurysms, especially seen among elderly patients (5). Furthermore, women also have a higher incidence and mortality rate of aSAH (6, 7). However, sex differences in aSAH outcomes remain controversial. The main reason for the different conclusions may be the different basic characteristics of male and female patients and the large number of confounding factors (8). Female patients, on average, are older than male patients and have more comorbidities. Moreover, different treatment approaches may also have different effects on patient outcomes (9).

Therefore, this study retrospectively analyzed the clinical data of consecutive patients with aSAH treated in our institution. Propensity scores were used to adjust for age and treatment approach between male and female patients. We compared the differences in outcomes between the two groups before and after adjustment.

METHOD

Material Collection and Variables

Institutional Review Board/Ethics Committee approval was not required for this retrospective analysis of de-identified Medicare data. Likewise, patient consent was not necessary in our study. Patients diagnosed with aSAH from May 1, 2020 to December 31, 2020, in the Department of Neurosurgery, Wuhan University Zhongnan Hospital, were collected. To ensure the accuracy of the analysis, the patients who were considered to have aSAH on admission but had no definite aneurysm on digital subtraction angiography (DSA) were excluded. Patients younger than 18 years of age were also excluded. Patients who had already undergone aneurysm surgery at other hospitals and were transferred to our hospital for further treatment were excluded.

Patients' basic characteristics, comorbidities, smoking and drinking status, aneurysm characteristics, treatment approach, and inpatient logs were reviewed in detail. The location and number of aneurysms were clarified by reviewing the patient's computed tomography angiography (CTA) or DSA. If the patient has multiple intracranial aneurysms, the one that ruptured is recorded as the responsible aneurysm. Aneurysms originating from all segments of the vertebral artery and basilar artery and their branch aneurysms were recorded as posterior circulation artery (PCA) aneurysms. The treatment of aneurysm is divided into craniotomy, interventional treatment, and conservative treatment. Various endovascular treatment approaches, such as coiling and flow direction, are collectively referred to as interventional treatments. Very few patients treated with a combination of clipping and intervention or bypass were classified as receiving craniotomy. Those who underwent only extraventricular drainage and/or decompressive craniectomy were classified as having received conservative treatment.

Management and Assessment

Cranial computed tomography (CT) and CTA were performed when a patient was considered to have aSAH in the emergency department. If there was no clear diagnosis or characterization of aneurysm, further DSA was performed. All patients diagnosed with aSAH in our department were treated with nimodipine, an anti-vascular spasm agent, after admission. Aneurysm management was performed by two chief surgeons specializing in craniotomy and intervention, respectively. Patient admission and imaging findings were reviewed to obtain the Hunt–Hess grade, Glasgow Coma Scale (GCS), and modified Fisher score. The presence of cerebral ischemia and hydrocephalus was assessed using the patient's pre-discharge cranial CT imaging and clinical manifestations. The patient's clinical symptoms, antibiotic use, and cerebrospinal fluid examination results were used to determine whether the patient had complications of intracranial infection.

Inpatient and discharge data and patient discharge condition assessed using the modified Rankin Scale (mRS) score were reviewed. An mRS of 2 represents mild disability, an inability to perform all tasks and activities, yet able to live normally without depending on others. Therefore, we chose the more stringent criterion of mRS 0–1 as an indicator of prognostic excellence. Patients with an mRS $\geq$2 were defined as having a poor outcome. The above scoring and assessments were performed independently by two individuals and reviewed and finalized by the supervising physician.

Statistics Analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Patient age and body mass index (BMI) are continuous variables described as mean ($\pm$SD) or median (interquartile range), while comorbidities, smoking and drinking status, aneurysm characteristics, and treatment approach and complications are count variables and represented as rates. Differences between sexes were assessed using chi-squared analysis, Fisher's exact test, Student's *t*-test, and the Kruskal–Wallis one-way analysis of variance, as appropriate. A value of $p \leq 0.05$ was considered statistically significant. Patients were divided into age classes at 10-year intervals, and propensity matching was performed for male and female groups according to both "age class" and "treatment approach." Univariate analysis of poor prognosis was first performed, and the results were then included in a multivariate logistic regression analysis system to analyze the independent risk factors for poor patient prognosis. Microsoft Excel software was used for graphing.

RESULTS

Patient Characteristics

A total of 287 patients with a diagnosis of aSAH were reviewed in this study; four patients were excluded because no definite aneurysm was found on either CTA or DSA after admission. A predominantly female population (65.0%) of 283 patients with a mean age of 60.5 ± 8.6 years (range, 34–85 years) was included in the analysis (**Table 1**). Approximately half of the patients were overweight or obese (BMI ≥ 24 kg/m^2), and more than half had comorbid hypertension. Approximately a quarter of the patients were smokers or drinkers, the majority of whom were men. Aneurysms mainly originated from arteries in the anterior circulation (87.3%) and were found most commonly in the internal carotid artery (ICA) (51.6%), followed by the anterior cerebral artery (ACA) (19.8%). Multiple aneurysms were present in approximately one fifth of the patients (n = 49, 19.8%). A clear majority of patients underwent aggressive surgical treatment; 60% underwent craniotomy and 31% underwent interventional treatment. The Hunt–Hess grades of patients were predominantly low grade (I and II), with a high grade (III–V) present in ∼30% of the patients, and the mFisher score was almost equally divided in each score (**Figure 1**).

TABLE 1 | The overall characteristics of the patients and the comparison of gender differences.

	Total (n = 283)	Female (n = 184)	Male (n = 99)	*P*
Age (mean ± SD)	60.5 ± 8.6	61.3 ± 8.5	60.0 ± 8.5	0.032*
BMI (mean ± SD)	23.8 ± 3.4	23.9 ± 3.6	23.6 ± 3.0	0.505
<18.5	14 (4.9%)	11 (6.0%)	3 (3.0%)	0.044*
18.5 ∼ 23.9	131 (46.3%)	80 (43.5%)	51 (51.5%)	
24 ∼ 27.9	109 (38.5%)	68 (37.0%)	41 (41.4%)	
≥28	29 (10.2%)	25 (13.6%)	4 (4.0%)	
Comorbidities				
Hypertension	162 (57.2%)	110 (59.8%)	52 (52.5%)	0.239
Diabetes	18 (6.4%)	15 (8.2%)	3 (3.0%)	0.092
Heart disease	22 (7.8%)	17 (9.2%)	5 (5.1%)	0.209
Smoking	73 (25.8%)	7 (3.8%)	66 (66.7%)	<0.001*
Drinking	60 (21.2%)	12 (6.5%)	48 (48.5%)	<0.001*
Multiple aneurysms	49 (17.3%)	35 (19.0%)	14 (14.1%)	0.301
Aneurysm location				<0.001*
ACA	56 (19.8%)	22 (12.0%)	34 (34.3%)	
ICA	146 (51.6%)	111 (60.3%)	35 (35.4%)	
MCA	45 (15.9%)	28 (15.2%)	17 (17.2%)	
PCA	36 (12.7%)	23 (12.5%)	13 (13.1%)	
Treatment				0.29
Craniotomy	170 (60.1%)	106 (57.6%)	64 (64.6%)	
Endovascular	88 (31.1%)	63 (34.2%)	25 (25.3%)	
Conservative	25 (8.8%)	15 (8.2%)	10 (10.1%)	

*BMI, Body mass index; ICA, Internal carotid arteries; ACA, Anterior cerebral artery; MCA, Middle cerebral artery; PCA, Posterior circulation artery. *p < 0.05, with a statistical difference.*

Sex Differences and Adjustment

The patients were divided into a female group (n = 184) and male group (n = 99) according to their sex, with a ratio of ∼2:1 in group size (**Table 1**). Female patients were significantly older than male patients (p = 0.032) and a greater proportion was obese (13.6 vs. 4.0%). Although female patients had higher rates of comorbidities, this difference was not statistically significant. The proportion of smokers and drinkers was significantly higher in male patients than in female patients (p < 0.001). There was no significant difference in the proportion of patients with multiple aneurysms between the two groups; however, there was a significant difference in the origin of aneurysms. Most female patients (60.3%) had aneurysms originating from the ICA, whereas male patients had a similar proportion of aneurysms originating from the ICA and the ACA. Both groups were mainly treated with craniotomy. However, the proportion of patients who received interventional treatment was higher in the female group than in the male group (34.2 vs. 25.3%).

The difference in mFisher scores between the two groups was not significant and was evenly distributed between scores (**Table 2**, **Figure 1**). The comparison of complications showed that female patients were significantly more likely to have cerebral ischemia than male patients (27.2 vs. 15.2%, p = 0.022). There was no significant difference between the two groups regarding the incidence of mortality, hydrocephalus, or intracranial infection. The proportion of female patients with an mRS score ≥2 was significantly higher than that of male patients at discharge (p = 0.013).

In the real world, as well as in previously published articles, intracranial aneurysms are more common in women. Therefore, patients were matched on a 1:2 propensity score based on patient "age class" and "treatment approach," for male and female patients (**Table 2**). The mean age of patients was similar in both groups after matching (61.8 ± 7.9 years vs. 60.2 ± 7.4 years, p = 0.105), and the proportions were the same for the different age subgroups (p = 1; **Figure 2**). Similarly, the proportion of male and female patients with different treatment approaches was the same after adjustment (p = 1). After adjustment, there was still no significant difference in mFisher scores, hydrocephalus, mortality, or intracranial infection between the two groups. Furthermore, the incidence of cerebral ischemia and mRS score ≥2 at discharge remained higher in the female group when compared to the male group.

Risk Factors of Poor Prognosis

Univariate analysis of patients with poor prognosis (mRS ≥ 2) at discharge showed that age, sex, hypertension, mFisher score, treatment, location, ischemia, and hydrocephalus affected patients' prognosis at discharge. Multivariate analysis including the above factors in a logistic regression analysis revealed high mFisher score (mFisher = 3/4) and ischemia as independent risk factors for poor patient prognosis at discharge (**Table 3**).

Analysis of risk factors for poor prognosis was performed again after propensity score matching. Univariate analysis revealed that sex, mFisher, treatment, and ischemia influenced prognosis at discharge. Multivariate analysis including the above factors in a logistic regression analysis system found that high

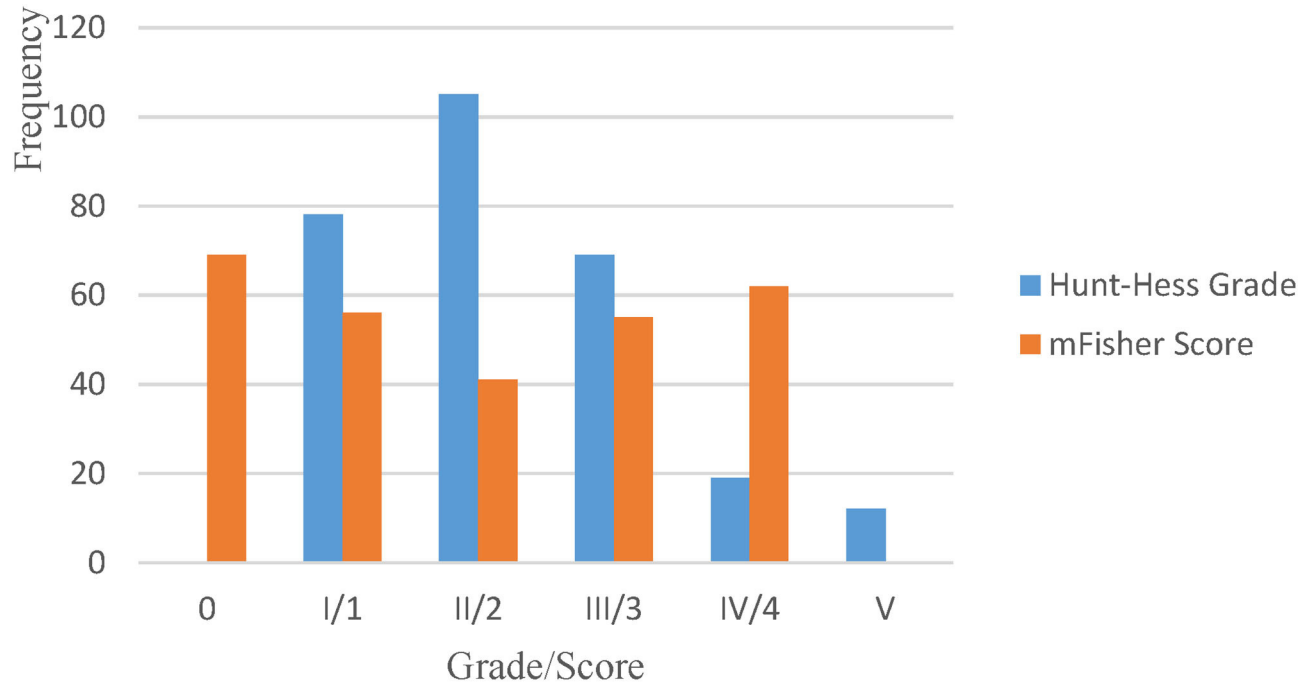

FIGURE 1 | The overall distribution of patients' Hunt–Hess grades and mFisher scores.

TABLE 2 | Comparison of differences in outcomes between male and female patients before and after propensity adjustment.

	Before the adjustment		*P*	After the adjustment		*P*
	Female (*n* = 184)	Male (*n* = 99)		Female (*n* = 168)	Male (*n* = 63)	
mFisher						
0	50 (27.2%)	19 (19.2%)	0.225	43 (25.9%)	19 (22.9%)	0.68
1	37 (20.1%)	19 (19.2%)		36 (21.7%)	15 (18.1%)	
2	22 (12.0%)	19 (19%2)		19 (11.5%)	14 (16.9%)	
3	32 (17.4%)	23 (23.2%)		30 (18.1%)	18 (21.7%)	
4	43 (23.4%)	19 (19.2%)		38 (22.9%)	17 (20.5%)	
Complications						
Mortality	18 (9.8%)	11 (11.1%)	0.725	16 (9.6%)	10 (12.0%)	0.558
Ischemia	50 (27.2%)	15 (15.2%)	0.022*	47 (28.3%)	14 (16.9%)	0.048*
Hydrocephalus	25 (13.6%)	12 (12.1%)	0.727	24 (14.5%)	9 (10.8%)	0.428
Intracranial infection	1 (0.5%)	2 (2.0%)	0.247	1 (0.6%)	2 (2.4%)	0.218
mRS ≥ 2	110 (59.8%)	44 (44.4%)	0.013*	100 (60.241)	39 (46.988)	0.047*

*mRS, Modified rankin scale. *p < 0.05, with a statistical difference.*

mFisher score (mFisher = 3/4) and ischemia were independent risk factors for poor patient prognosis at discharge (**Table 4**).

DISCUSSION

The main finding of this study was that there were significant sex differences in aSAH outcomes, with female patients having a higher incidence of cerebral ischemia and worse prognosis at discharge. This result is consistent with most previous literature reports. This trend persisted after propensity score adjustment for patient age class and treatment approach. However, risk factor analysis of poor prognosis in patients with aSAH revealed that ischemia and high mFisher score were independent risk factors for poor patient prognosis and not the female sex.

Sex Differences in aSAH Incidence

Women are more vulnerable to intracranial aneurysms than men, and this difference becomes more pronounced with increasing age, especially after menopause (5, 10), and may be associated with a decrease in estrogen after menopause (11). As there

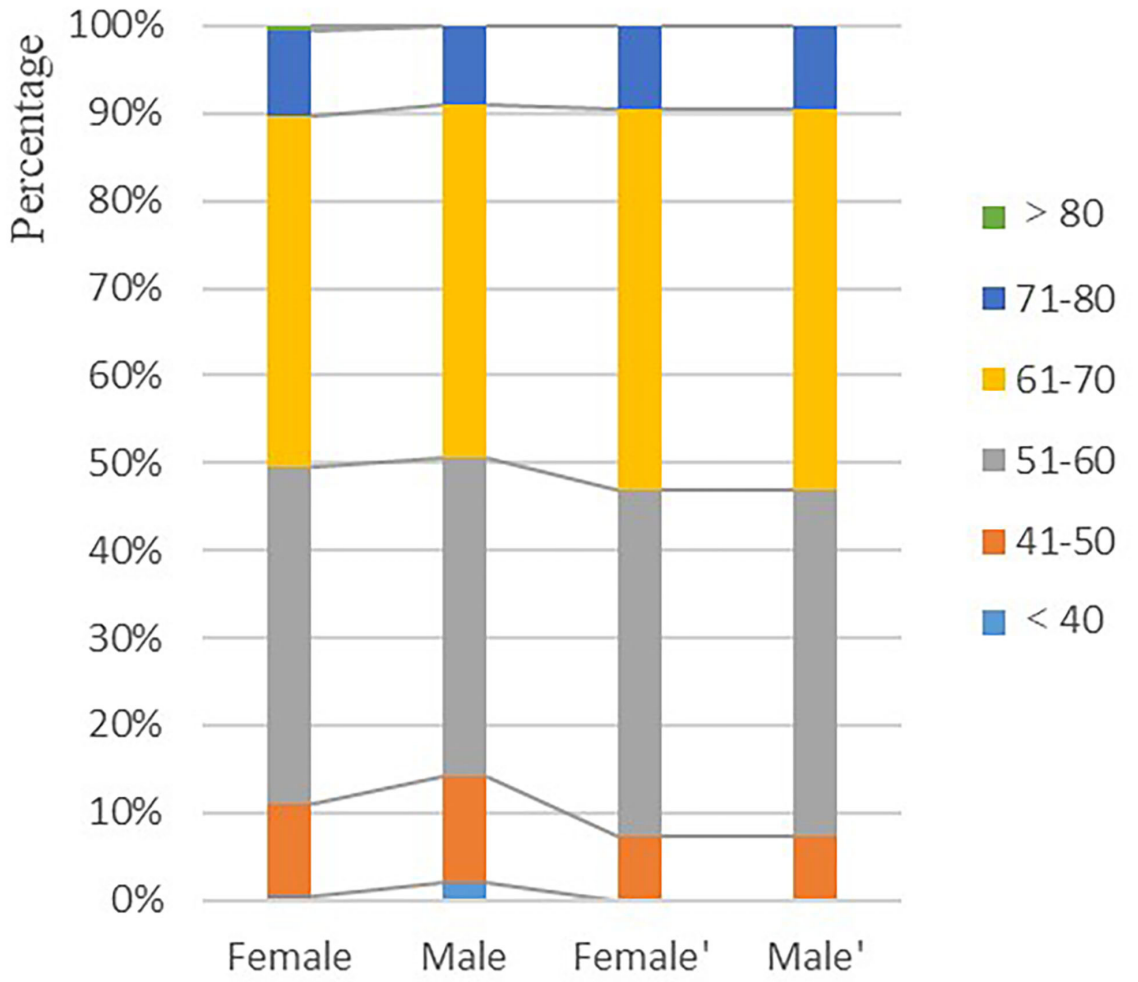

FIGURE 2 | Comparison of the proportion of men and women in different age classes before and after propensity score adjustment. Female and male are pre-adjustment and female′ and male′ are post-adjustment.

are sex differences in the incidence, more patients with aSAH in clinical practice are females. In addition, studies have also shown that female sex is a risk factor for ruptured intracranial aneurysm (12). Female patients in our study were approximately twice as likely as male patients to have intracranial aneurysm rupture, which is comparable to rates reported in a previous study (12).

There are also sex differences in the characteristics of intracranial aneurysms, with female patients more often having aneurysms originating from the ICA, especially the posterior communicating artery, while male aneurysms are more commonly found in the ACA (13). Women also seem to be more likely than men to have multiple aneurysms (14). In this study, although the proportion of female patients with multiple aneurysms was also higher than that of male patients, the difference was not statistically significant. As in previous studies, however, aneurysms in female patients more commonly originated from the ICA.

Sex Differences in aSAH Complications

Studies have shown that cerebral ischemia and hydrocephalus are two important complications that affect the prognosis of aSAH (4). As with other studies (15, 16), our study found that the likelihood of cerebral ischemia was significantly higher in female patients with aSAH than in male patients with aSAH. This phenomenon could be because female patients with aSAH are more vulnerable to vasospasm (12). Studies have shown that early vasospasm predicts a higher incidence of SAH-related cerebral ischemia and a poorer prognosis (17). Female sex has been reported to be an independent risk factor for cerebral vasospasm after aSAH (18, 19). Moreover, it has also been found that catecholamine metabolites, which reflect sympathetic excitation, have a higher level in the cerebrospinal fluid of female patients with SAH, which also suggests that they are more vulnerable to vasospasm (20). However, it has also been reported that there are no sex differences in SAH cerebral vasospasm (21). In addition, studies have shown that SAH vasospasm is also associated with inflammatory and genetic factors (22, 23), the characteristic

TABLE 3 | Multivariate logistic regression analysis of patients with poor prognosis at discharge before propensity adjustment.

Variables	OR (95%CI)	*P*
Age	1.021 (0.981–1.062)	0.304
Male	0.54 (0.267–1.068)	0.081
Hypertension	1.22 (0.648–2.302)	0.537
mFisher		
1	1.444 (0.585–3.585)	0.424
2	1.664 (0.62–4.445)	0.308
3	5.378 (1.979–15.368)	0.001*
4	9.322 (3.282–28.907)	<0.001*
Treatment		
Conservative	3.154 (0.966–10.907)	0.061
Craniotomy	1.157 (0.552–2.434)	0.699
Location		
ICA	1.241 (0.503–3.097)	0.64
MCA	2.5 (0.89–7.221)	0.085
PCA	0.673 (0.193–2.292)	0.528
Ischemia	10.261 (3.958–31.182)	<0.001*
Hydrocephalus	NA	NA

*ICA, Internal carotid arteries; MCA, Middle cerebral artery; PCA, Posterior circulation artery; NA, Not applicable. *p < 0.05, with a statistical difference.*

TABLE 4 | Multivariate logistic regression analysis of patients with poor prognosis at discharge after propensity adjustment.

Variables	OR (95% CI)	*P*
Male	0.625 (0.32–1.196)	0.159
mFisher		
1	1.521 (0.63–3.712)	0.352
2	2.374 (0.89–6.474)	0.087
3	6.797 (2.64–18.642)	<0.001*
4	9.972 (3.74–29.07)	<0.001*
Treatment		
Conservative	3.488 (1.02–13.208)	0.052
Craniotomy	1.284 (0.63–2.633)	0.492
Ischemia	9.219 (3.78–26.332)	<0.001*
Hydrocephalus	NA	NA

*NA, Not applicable. *p < 0.05, with a statistical difference.*

effects of which in women are not well known. Therefore, the reasons and mechanisms for this difference and whether it is associated with estrogen remain uncertain (24, 25).

In addition, some experimental studies have shown sex differences in the occurrence of hydrocephalus after aSAH (26). Some clinical studies have also found female sex to be a risk factor for hydrocephalus after SAH (27). This difference may be related to the ability of estrogen to induce more neutrophils leading to more severe ventricular dilatation and white matter damage (28). However, most studies of sex differences in the prognosis of aSAH did not find that female patients were more likely to develop hydrocephalus (8, 29). In our study, female patients with aSAH were more likely to have hydrocephalus than male patients, but the difference was not statistically significant.

Sex Differences in aSAH Prognosis

In our study, a higher proportion of female patients had an mRS $\geq$ 2 at discharge and worse prognosis than the male patients. Although we chose the more stringent criterion of mRS $\geq$ 2 for poor prognosis, our results are similar to the results of previous studies (30). By contrast, in other studies, they found no significant differences in the prognosis of male and female patients with aSAH (31). They suggested that the difference in age classification between female and male patients may have biased the comparison between the two groups (8). Moreover, different treatment option choices related to surgeon and patient selections may influence the comparison between the two groups (32). However, in our study, the proportion of female patients discharged with an mRS score $\geq$2 was still significantly higher than that of male patients after adjustment for "age class" and "treatment approach." Therefore, we suggest that although male and female aSAH patients may have different demographic characteristics and receive treatment using different modalities, the prognosis between sexes is different.

In addition, as in previous studies, our study showed that the occurrence of cerebral ischemia and high mFisher score were independent risk factors for poor patient prognosis (33). As the incidence of cerebral ischemia after aSAH was significantly higher in female patients than in male patients in our study, and there was no significant difference in mFisher score between the two groups, we believe that the poor prognosis of female patients correlates with their higher incidence of cerebral ischemia.

LIMITATIONS

As a retrospective study, our study has inherent limitations. For instance, some information relevant to sex comparisons was not collected (e.g., pregnancies and births), which could suggest changes in estrogen levels in female patients and facilitate the exploration of the role of estrogen in female SAH. Moreover, smoking was not quantified, which might have helped determine the dose-effect relationship between smoking and incidence of aSAH in women (34). In addition, the limited sample size may have prevented us from identifying smaller sex differences, for example, the sex difference in hydrocephalus after aSAH mentioned in the article, which may mean that our results ignore the specific effect of hydrocephalus on the prognosis of female patients.

CONCLUSION

Female patients with aSAH have a worse prognosis at discharge compared with that of male patients, and this difference may be because female patients are more vulnerable to cerebral ischemic complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NX, JC, PJ, and WZ contributed to the study concept and design. YC, JZ, ZLi, TZ, CX, ZLiu, YM, CM, and XC contributed to the acquisition and analysis of data. YC, CJ, JZ, SC, and ZLiu contributed to the image review and drafting figures of the manuscript. NX was responsible for the overall content as guarantor. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We thank John Holmes, MSc, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
published: 19 May 2022
doi: 10.3389/fneur.2022.878759

Sex Differences in Collateral Circulation and Outcome After Mechanical Thrombectomy in Acute Ischemic Stroke

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Background: Collateral circulation is known to lead to smaller infarct volume and better functional outcome after mechanical thrombectomy (MT), but studies examining sex differences in collateral circulation are scarce. The aim of this study was to investigate if collateral circulation has a different impact on outcome in women and men.

Methods: A single-center retrospective study of 487 patients (230 men and 257 women) treated with MT for acute ischemic stroke in the anterior cerebral circulation. Collateral circulation was assessed on computed tomography angiography images. The outcome was evaluated at 90 days according to the modified Rankin Scale (mRS).

Results: Women were older, median age 76 years (IQR 68-83) vs. 71 years (IQR 63–78). Stroke severity and time to recanalization were comparable. More women had moderate or good collaterals in 58.4 vs. 47.0% for men ($p = 0.01$). Among patients with moderate and good collaterals significantly more men (61%) were functionally independent (mRS 0–2) than women (41.5%) ($p = < 0.01$). This difference remained significant after correcting for age by linear weighting, 60.4 vs. 46.8% ($p = 0.03$).

Conclusion: Women had better collateral flow but showed worse functional outcomes, while good collateral flow led to better outcomes in men, even after correcting for age. Further clinical studies on peri- and post-interventional care, factors affecting recovery after hospital discharge as well as basic research on the neurovascular unit are needed to find modifiable targets to improve clinical outcomes for women.

Keywords: ischemic stroke, mechanical thrombectomy, collateral flow, outcome, sex differences

OPEN ACCESS

Edited by:
Zilong Hao,
Sichuan University, China

Reviewed by:
Qiwen Deng,
Nanjing Medical University, China
Juan Chen,
Beijing Hospital, China

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Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *18 February 2022*
Accepted: *19 April 2022*
Published: *19 May 2022*

Citation:
Lagebrant C, Ramgren B, Hassani Espili A, Marañon A and Kremer C (2022) Sex Differences in Collateral Circulation and Outcome After Mechanical Thrombectomy in Acute Ischemic Stroke. Front. Neurol. 13:878759. doi: 10.3389/fneur.2022.878759

INTRODUCTION

There is a growing awareness that stroke etiology, incidence, and outcome differ between men and women. Women have a higher lifetime risk of stroke than men due to their longer life expectancy and a higher incidence of stroke at older ages (1–3). There are also differences in stroke risk factors, where women have a higher prevalence of hypertension and atrial fibrillation, whereas cardiovascular disease, large artery atherosclerosis, smoking, and alcohol use are more prevalent among men (2). Furthermore, women have worse functional outcomes compared to men. A large part of these differences could be explained by age, stroke severity, and pre-stroke comorbidity. But

even after adjustment for these factors, women have a higher disability and lower quality of life after stroke than men (1–3).

In 2015, randomized controlled trials (RCTs) proved that mechanical thrombectomy (MT) is more effective than IVT in stroke caused by occlusion of the anterior cerebral circulation if administered within 6 h after stroke onset (4, 5). Since the publication of these studies, the utilization of MT has increased widely (6). Recent studies also demonstrated that MT is effective up to 24 h after onset of stroke in selected patients with radiological imaging showing ischemic but not yet infarcted brain tissue (7, 8). There has been some uncertainty about whether the outcome after MT is affected by the sex of the patient. One *post-hoc* analysis of data from a large RCT found that women were less likely to benefit from MT and that women had higher mortality and more adverse events than men (9). Another prospective cohort study reported that women were less likely to be functionally independent 90 days after MT compared to men (10). However, several other studies, including one large recently published meta-analysis of seven RCTs, did not confirm these findings and concludes that sex does not influence clinical outcome after MT (11–13).

It has been shown that collateral circulation influences outcome after MT, where a good collateral status leads to smaller infarct volume and better functional outcome (14, 15). The anatomy of these alternative pathways differs greatly between individuals. Experimental studies in rodents have found no structural or functional differences in leptomeningeal collateral circulation between sexes, nor any anatomical differences in the circle of Willis between men and women (16, 17). In animal studies, the amount of cerebral collaterals is determined by multiple factors, genetic as well as environmental. Age and comorbidities such as hypertension, endothelial dysfunction, diabetes, and obesity are known to cause loss of collateral number, a decrease in collateral vessel diameter, and impaired autoregulation of cerebral vasculature (17, 18). Just a few studies include collateral circulation as a prognostic parameter for outcomes like the meta-analysis of seven RCTs by Chalos et al. (12). In this study, they found that women included in the randomized MT trials had better collateral status than men. Interestingly, this did not improve the functional outcomes for these women.

This study aims to evaluate collateral circulation in patients receiving MT for stroke in the anterior cerebral circulation and to investigate if the collateral status has a different impact in women and men.

METHOD

This study is a retrospective evaluation of patients receiving MT between 1 January 2014 and 31 December 2018. The medical imaging program Picture Archiving and Communication System (PACS) was used to identify all referrals for MT within this period. Only patients with stroke in the anterior cerebral circulation were included in the study. Cases, where no attempt of MT was made, were excluded. Patients who suffered a second stroke and had a second MT during the 90-day follow-up were also excluded from this study. Cases with missing or technically failed computed tomography angiography (CTA) were also excluded.

Clinical Data

Clinical baseline data included: age, sex, initial National Institute of Health Stroke Scale (NIHSS) score, time of stroke onset, time from onset to recanalization—if the time of onset was unknown, a time when the patient was last seen well was used—and neurological impairment at admission according to NIHSS was evaluated (19). Clinical data were evaluated by assessing the local database, and time from onset and time to recanalization were reviewed in PACS together with the recanalization outcome.

Radiological Data

Computed tomography angiography was performed on multidetector-CT scanners from different companies in place at the 13 referral hospitals within the catchment area, and a standard CTA protocol was used with bolus-tracking software to acquire images at the peak contrast arrival. Collateral circulation was assessed with axial view CTA imaging. In one case, the axial view was missing and the coronal view was used instead. The amount of intra-arterial contrast in the area distal to the occlusion was evaluated. The contralateral side of the brain was used as a baseline for comparison. Collateral circulation was graded and given a score of 0–3 with a method described by Tan et al. (20):

0 = No collateral circulation = absent collaterals in the vascular territory supplied by the occluded arterial segment.

1 = Poor collateral circulation = collaterals filling <50% of the vascular territory supplied by the occluded arterial segment.

2 = Moderate collateral circulation = collaterals filling more than 50%, but <100% of the vascular territory supplied by the occluded arterial segment.

3 = Good collateral circulation = collaterals filling 100% of the vascular territory supplied by the occluded arterial segment.

Computed tomography angiography imaging was reviewed using PACS on computers and monitors used professionally in clinical practice by radiologists in SUS Lund. Collateral circulation was assessed by the authors (CL and BR) in all included patients. All inconclusive cases were reviewed together with a senior neuroradiologist (BR) to ensure high-quality assessments throughout the material (**Supplementary Figure 1**).

Outcome Data

One measure of outcome analyzed in this study was thrombolysis in cerebral infarction (TICI) after recanalization with MT. TICI is a radiological scale describing perfusion past an occlusion on angiography ranging from 0 to 3. TICI 2B, 2C, and 3 are defined as successful recanalization (21, 22). TICI-scores were collected from post-interventional charts in PACS.

The main outcome in this study was patient functional status and independence 90 days after stroke according to the modified Rankin Scale (mRS) (23).

A 90-day mRS-score was obtained by interpreting data from Riksstroke, a Swedish national quality registry for stroke care.

TABLE 1 | Clinical characteristics by sex.

Characteristics	Men, median ($n = 230$)	IQR	Women, median ($n = 257$)	IQR	*P*-value[a]
Age (years)	71 ($n = 230$)	63–78	76 ($n = 257$)	68–83	<0.01
NIHSS at admission (points)[b,c]	15 ($n = 217$)	11–19	15 ($n = 246$)	10–18	0.41
Time from onset to recanalization (h:min)[d]	4:39 ($n = 181$)	3:40–5:56	4:41 ($n = 198$)	3:39–5:49	0.76

[a]*Mann Whitney U-test for differences in median value between men and women.*
[b]*NIHSS, National Institutes of Health Stroke Scale.*
[c]*Data missing for 24 patients, 11 women and 13 men.*
[d]*Data missing for 108 patients, 59 women and 49 men.*

All hospitals treating acute stroke in Sweden are submitting data to this register in a standardized manner (6). Information on activities of daily living (ADL), such as personal hygiene, dressing, and mobility, is recorded in a 90-day follow-up. By using syntax, we converted the ADL-data into the mRS.

For patients with no 90-day follow-up recorded in the Riksstroke registry, mRS-scores were obtained, if available, by interpreting patient medical records.

Statistical Analysis

Baseline demographics and clinical characteristics were expressed as median values with an inter-quartile range (IQR). The Mann-Whitney *U*-test was used to compare average ranks for clinical baseline data between men and women.

The chi-square test was used to test for dependence between sex and distribution of collateral status and TICI-score. The chi-square test was also used to test for sex differences in the mRS score 90 days after MT for different degrees of collateral circulation. Analysis of collateral circulation was made for each separate group of collateral circulation as well as for dichotomized groups of none and poor vs. moderate and good collateral circulation. To correct for age, we applied linear weighting and matching. Essentially the algorithm tries to find the optimal set of weights with minimal variance so that the resulting weighted means and standard deviations for age, as well as the percentage distributions for the age quartile groups, are similar in both gender categories. The weights are obtained using the GfK linear weighting and matching program.

The SPSS Statistics for Windows version 27 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. $P < 0.05$ were considered to be significant.

This study was approved by the Research Ethics Committee in Lund with registration numbers 2013/466 and 2018/53.

RESULTS

A total of 487 of 751 referrals for MT met inclusion criteria, 230 (47%) men and 257 (53%) women. (PRISMA flow chart, **Supplementary Figure 2**). Clinical characteristics are summarized in **Table 1**.

Women in our study were significantly older with a median age of 76 years (IQR 68–83) vs. 71 years (IQR 63–78) for men ($p = < 0.01$). The severity of stroke did not differ between the sexes. Median NIHSS before MT was 15 points for both men (IQR 11–19) and women (IQR 10–18). The time from onset of stroke to recanalization was similar between the groups.

TABLE 2 | Collateral circulation in patients receiving mechanical thrombectomy.

Collateral status	Men ($n = 230$)	Women ($n = 257$)	*P*-value
No collateral circulation	28 (12.2%)	24 (9.3%)	
Poor collateral circulation	94 (40.9%)	83 (32.3%)	
Moderate collateral circulation	43 (18.7%)	64 (24.9%)	
Good collateral circulation	65 (28.3%)	86 (33.5%)	0.09[a]
No/poor collateral circulation	122 (53.0%)	107 (41.6%)	
Moderate/good collateral circulation	108 (47.0%)	150 (58.4%)	0.01[b]

[a]*Chi 2-test for sex difference in distribution among collateral circulation groups.*
[b]*Chi-2 test for sex difference after dichotomization of collateral circulation groups.*

TABLE 3 | Functional status 90 days after mechanical thrombectomy.

Modified rankin scale[a]	Men ($n = 208$)	Women ($n = 246$)	*P*-value[b]
0–2	94 (45.2%)	86 (35.0%)	
3	22 (10.6%)	36 (14.6%)	
4	34 (16.3%)	34 (13.8%)	
5	19 (9.1%)	31 (12.6 %)	
Dead	39 (18.8%)	59 (24.0%)	0.11

[a]*Data missing for 33 patients, 11 women and 22 men, who had no 90-day follow up recorded in Riksstroke.*
[b]*Chi 2-test for sex differences in distribution among groups of mRS90.*

Women had better collateral circulation status (**Table 2**). When dichotomized into groups of no or poor collateral circulation and moderate or good collateral circulation, more women had moderate or good collateral 58.4 vs. 47.0% for men ($p = 0.01$).

Outcome Measures

There was no sex difference in radiological outcome after MT according to TICI-scale. Seventy-seven percent of women had successful recanalization, with a TICI-score of 2B, 2C, or 3, compared to 79.0% for men.

More men were functionally independent 90 days after MT, with mRS 0–2, 45.2% compared to 35.0% for women. A 90-day mortality, mRS 6, was higher for women, 24.0 vs. 18.8%. The proportion of disabled patients, mRS 3–5, was higher for women, 41.0 vs. 36.0% for men (**Table 3**).

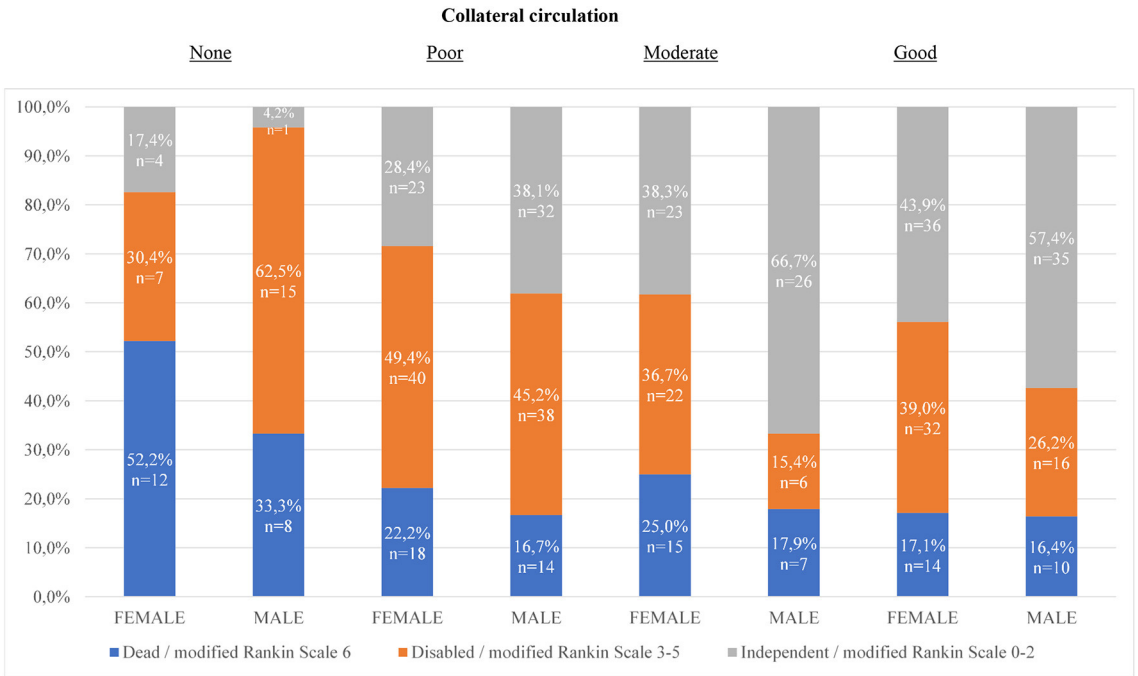

FIGURE 1 | Distribution of functional outcomes 90 days after mechanical thrombectomy for different degrees of collateral circulation. Chi 2-test for sex differences in proportion of functionally independent outcome: 1. ($p = 0.14$) 2. ($p = 0.19$) 3. ($p = 0.01$) 4. ($p = 0.11$) For dichotomization moderate and good collaterals together ($p = < 0.01$). For dichotomization none and poor collaterals together ($p = 0.46$).

In **Figure 1**, the distribution of functional outcomes 90 days after MT is presented for different degrees of collateral circulation. In the groups with poor, moderate, and good collateral circulation, men were functionally independent to a higher extent than women. The differences in outcome were particularly evident in the groups with moderate and good collateral circulation. When these two groups were combined into one, 61.0% of men were functionally independent compared to women 41.5% ($p = < 0.01$). In the group of patients with no collateral circulation, women were independent to a higher extent than men. This difference was however not significant.

Since the age distributions were significantly different for the gender groups of patients, we investigated if controlling for age in both gender groups can affect the percentages of functional independence among patients with moderate and good collateral circulation after the application of linear weighting and matching on the 487 patients. Applying the derived linear weights, the results for the percentages of functionally independent outcomes 90 days after MT were as follows: 60.4% of the male patients were functionally independent 90 days after MT, while the corresponding percentage for women was estimated at 46.8%. The difference was found to be statistically significant, following the chi-square test, with $p = 0.034$.

DISCUSSION

In this single-center study, women treated with MT had better collateral status than men, but with worse outcomes. These differences remained significant even after correcting for age. Our results are comparable with the results from the recently published meta-analysis by Chalos et al. (12). This is the largest study on outcome after MT to this date and one of few studies specifying collateral status in their baseline characteristics. Furthermore, using the grading system by Tan et al. (20), they reported that more women had moderate or good collateral circulation grades, 88% of women compared to 80% of men ($n = 1{,}290$, $p = <0.01$). The proportion of moderate or good collateral circulation in this meta-analysis is higher for both men and women than in our study (12).

Women showed even better collaterals in the Defuse 3 cohort, a cohort selected by neuroimaging for thrombectomy presenting between 6 and 16 h after stroke (24).

The reasons for these observed disparities in collateral flow between men and women receiving MT are not known. It is interesting that women in our study had better collateral status even though they were 6 years older by median age than the included men. However, it is known that smoking, alcohol use, large vessel atherosclerosis, and peripheral vascular disease are more prevalent in men with stroke than in women with stroke (2). These factors lead to early vessel aging and impaired autoregulation and could potentially explain men's lower collateral scores. Several agents or mechanisms such as steroid- and sex-hormones, sex chromosomes, differences in cell death, differences in immune pathways, epigenetic regulation, and sex-specific microRNAs have all been proposed to cause sex differences in stroke (17, 18). However, the regulation of cerebral vasculature is still poorly understood, and much effort is needed to fully comprehend these mechanisms. Further

research to clarify the question of potential sex differences in collateral circulation is of utmost importance, as pharmacological regulation of collateral vessels has been proposed as a possible therapeutic approach in acute stroke treatment (25).

Rates of successful recanalization were similar between men and women in our study. This is in line with the results from several other investigations of outcomes after MT, where no sex difference in TICI-score after MT was found (11–13). Altogether this suggests that it is not the intervention itself that causes disparities in outcomes and that women should not be withheld from MT treatment on the sole basis of their sex.

There might also be aspects of peri- and post-interventional care explaining sex differences. Blood pressure during and after stroke is known to affect the outcome. Both hypotension and hypertension are prognostic factors for poor outcomes (26). Current guidelines recommend permissive hypertension, that is allowing blood pressure up to 180/105 mm Hg in the first 24 h after IVT or MT to ensure increased perfusion to the affected area (27). However, specific evidence on blood pressure after MT is lacking. One study has found that high peak values of systolic blood pressure during the first 24 h after MT correlated with the worse functional outcomes as well as with higher rates of hemorrhagic complications (28). Another study found that variabilities in systolic blood pressure after MT are associated with worse clinical outcomes (29). In some women, there could also be a risk of hypotension due to heart failure induced by atrial fibrillation, a disease more common among women with stroke (2). It is therefore possible that difficulties in regulating peri- and post-interventional blood pressure in these women could be a factor contributing to sex difference in the outcome.

The differences seen in our study are likely multifactorial, where age and pre-stroke comorbidity might offer some causative explanations. But it is also possible that the worse functional outcome seen in women is a result of unmeasured contributors affecting recovery post-stroke and after hospital discharge. Except for the already discussed factors, some researchers have proposed musculoskeletal comorbidities such as arthritis and osteoporosis (10). These diseases are known to be more common in women than in men and could influence the mRS 90 days after stroke by increasing complications as well as limiting the possibilities for rehabilitation and mobilization.

Our study has several limitations. The sample size of included patients is relatively low, and the study could be underpowered to properly detect differences between men and women.

Another weakness is that we had limited information on the pre-morbid status or cognitive decline of patients. Some differences in outcomes might have been influenced by factors not captured in the analysis, even though this might not explain the differences in recruitment of collateral flow and affect the 3-month outcome.

Assessment of collateral circulation was made by the CL after training and, in non-conclusive cases, with the assistance of a senior neuroradiologist. The images were not blinded to clinical data or outcome. The CTA images used to assess collateral circulation were of varying quality. The purpose of CT and CTA exams performed in an acute stroke care setting is primarily to find hemorrhage and site of occlusion and not to assess collateral circulation. Thus, CTA imaging with poorly timed contrast delivery—for example, due to technical problems with the CT machine, due to low cardiac output in a patient with chronic heart failure, or due to asymptomatic stenosis on the extracranial part of the carotid artery—could be enough to visualize the occluded vessel but at the same time not enough to properly display collateral circulation. We excluded all such CTA images of low technical quality from the analysis. But it might still be possible that temporal delay in the filling of collateral vessels could have caused inaccurate visualization of collateral circulation in some cases.

CONCLUSION

In summary, women in our study had better collateral circulation but worse functional outcomes.

No collateral circulation led to a high proportion of poor outcomes for both men and women. Women do not have the same beneficial effect of an increasing degree of collateral circulation as men do. Among patients with moderate and good collateral circulation, a significantly higher proportion of men reached functional independence.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee Lund University 2013/466 and 2018/53. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CK and BR contributed to the conception of the study. AH collected and analysed the data. CL and BR reviewed the radiological data. CL wrote the first draft. AM performed the statistical analysis. All authors contributed to the revision of the manuscript.

ACKNOWLEDGMENTS

The authors thank all patients and caregivers for participating in the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.878759/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
published: 21 June 2022
doi: 10.3389/fneur.2022.856239

Aspirin for Primary Stroke Prevention; Evidence for a Differential Effect in Men and Women

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Background: The use of aspirin for primary prevention of cardiovascular events in men and women remains controversial. Our study aimed to investigate the role of aspirin in primary stroke prevention in men and women and the effect of aspirin on risk of ischemic stroke in patients with covert cerebral small vessel disease (ccSVD).

Methods: We performed systematic searches of the PubMed, and Cochrane Library databases, covering the period from the inception of each database to May 2021. The incidence of any ischemic stroke (IS) or hemorrhagic stroke (HS) was the main outcome. The incidence of stroke overall, both ischemic (IS) and hemorrhagic (HS), was the main outcome.

Results: From 531 abstracts, 11 randomized control trials which assessed primary prevention of cardiovascular events in men and women were included. Only one study assessed the risk of aspirin in people with ccSVD. In women, there was significant decrease in the risk of stroke (OR 0.85 [95% CI 0.73, 0.99], $p = 0.03$) and IS (OR 0.76 [0.63, 0.93], $p = 0.008$) with aspirin compared to placebo while no increase in the risk of HS was found (OR 1.78 [0.61, 5.19], $p = 0.29$). In men, aspirin did not affect the risk of stroke (OR 1.13 [0.97, 1.31], $p = 0.12$) and IS (OR 0.94 [0.67, 1.32], $p = 0.72$) but increased the risk of HS with borderline statistical significance (OR 1.99 [0.99, 4.03], $p = 0.05$) compared to placebo. Aspirin significantly increased major bleedings in both sexes ($p < 0.05$). We found no evidence to support the use of aspirin in patients with ccSVD.

Conclusion: Our meta-analysis suggests aspirin is effective in primary prevention of stroke and IS in women with no clear increased risk of HS. However, it was associated with an overall increased risk of bleeding. Aspirin is not recommended in ccSVD.

Keywords: aspirin, primary prevention, ischemic stroke, hemorrhagic stroke, men, women

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Edited by:
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University Hospitals Leuven, Belgium

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *16 January 2022*
Accepted: *20 May 2022*
Published: *21 June 2022*

Citation:
Gdovinova Z, Kremer C, Lorenzano S, Dawson J, Lal A and Caso V (2022) Aspirin for Primary Stroke Prevention; Evidence for a Differential Effect in Men and Women. Front. Neurol. 13:856239. doi: 10.3389/fneur.2022.856239

INTRODUCTION

The use of aspirin for the primary prevention of cardiovascular events in men and women remains controversial (1–7). The antithrombotic effect of aspirin is primarily related to the irreversible inhibition of the enzyme cyclooxygenase in platelets resulting in a decreased production of prostaglandins and thromboxane A2. Furthermore, aspirin reduces inflammation by forming nitric

oxide radicals and protects endothelial cells from oxidative stress. Sex hormones are known to have differential effects on platelet function, with testosterone promoting platelet activity and estrogen inhibiting (8–10).

Based on these premises, our study aimed to investigate the role of aspirin in primary prevention in men and women. In addition, because the risk benefit ratio of antiplatelets may differ in people with cerebral small vessel disease, we also explored the effect of aspirin on risk of stroke risk in people with covert cerebral small vessel disease (ccSVD). Covert small vessel disease was defined as: Cerebral small vessel disease (SVD) with the presence of brain lesions found on CT or MR brain imaging or pathology examination, thought to have resulted from disease of the small blood vessels that perforate into the brain, primarily affecting the white matter and deep gray matter. The full spectrum includes covert cerebral SVD (ccSVD) detected incidentally on neuroimaging, and SVD-related clinical presentation with stroke, cognitive decline or dementia, mood or physical dysfunction (11).

We performed systematic searches of the PubMed, and Cochrane Library databases, covering the period from the inception of each database to May 2021; the incidence of stroke, both ischemic (IS) and hemorrhagic (HS), was the main outcome.

METHODS

Literature Search and Study Selection

A comprehensive search of Medline, EMBASE, CINAHL, SCOPUS was performed. The search terms aspirin, stroke, women and their corresponding Medical Subject Heading (MeSH) terms were used. The search strategy was (((Aspirin OR antiplatelet* OR dual antiplatelet therapy OR DAPT) AND (stroke OR TIA OR CVA OR cerebrovascular accident OR cerebrovascular apoplexy OR transient ischemic attack OR cerebrovascular infarct* OR cerebrovascular embolism OR brain ischaemia OR wind stroke OR cerebral embolism OR brain infarct* OR intracranial hemorrhages) AND (women OR females OR men OR male OR sex difference OR gender difference OR sex factor* OR gender factor*)).ti,ab.). The exclusion criteria were as follows: (i) people without stroke; (ii) Intervention: no aspirin, no antiplatelets therapy; (iii) Outcome: non-relevant outcomes; (iv) Study designs: narrative reviews, letter to editor, case report, commentary, or editorial.

A total of 531 abstracts were identified from different searches and uploaded on the COVIDENCE software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). This systematic review and meta-analysis were conducted by following the guidelines of PRISMA (12). After removing the duplicates, 258 abstracts were screened by title and abstract. Of these, 31 articles were selected for full text screening and 12 articles (11 studies) published before April 2020 were selected for data extraction and meta-analysis (**Figure 1** and **Table 1**). The selection of the abstracts and articles were performed independently and in duplicate. The data extraction was done by one person and checked by others. The incidence of stroke, both ischemic and hemorrhagic, was considered the primary outcome. Secondary outcomes were ischemic stroke, hemorrhagic stroke, and bleeding episodes.

Data Analysis and Statistical Methods

Meta-analysis was performed using Review Manager (RevMan) 5.3 COCHRANE Collaboration software when more than one study reported the outcome and number of subjects were ≥ 6 in each group. Odds ratio (OR) and 95% confidence intervals (CI) for dichotomous variables were calculated. I^2 statistic, an expression of inconsistency of studies' results and describing the percentage of variation across studies due to heterogeneity rather than by chance, was calculated. A high value of I^2 (>50%) and p-value <0.05 indicate statistically significant heterogeneity among the studies for an outcome. The reasons for high heterogeneity were explored. A random effects model was used for all outcomes. The publication bias was assessed by looking at the asymmetry of a funnel plot. The funnel plot was generated if at least 10 studies were included in a meta-analysis.

RESULTS

From 531 abstracts, 31 articles were selected for full text screening and of these, 12 met the eligibility criteria and contained the results of 11 randomized control trials (RCTs) (**Table 1**) (13–24). The flowchart of the study is shown in **Figure 1**. In all included studies except for WHS, both men and women were enrolled (representation of women was 29.5–70%) and heterogenous populations were studied. Three of the RCT compared ASA with placebo and were published in four articles 2018 (21–24).

Another study sought to detect if aspirin reduces the risk of ischemic stroke or increases hemorrhagic stroke risk in patients with covert cerebral small vessel disease (25). One RCT included patients $\geq$ 45 years with at least one silent brain infarct (SBI) but no previous clinical cerebrovascular events for randomization to aspirin 100 mg or placebo. The primary endpoint was the combined endpoint of ischemic stroke, TIA, and new silent brain infarcts detected by MRI (25).

RCTs on Aspirin as the Primary Prevention of Stroke

The WHS (Women's Health Study) trial was the only trial which included only women. In this trial 100 mg of aspirin on alternate days or placebo was prescribed to 39 876 initially asymptomatic women 45 years of age or older, who were followed up for 10 years for a first major vascular event (non-fatal MI, non-fatal stroke, or cardiovascular death). Although there was a non-significant 9% reduction (RR, 0.91; 95% CI, 0.80–1.03; $P = 0.13$) in the combined primary endpoint among women, the study found a statistically significant 17% reduction in the risk of stroke (RR, 0.83; 95% CI, 0.69–0.99; $P = 0.04$) There was a 24% reduction in the risk of ischemic stroke (RR, 0.76; 95% CI, 0.63–0.93; $P = 0.009$) and a non-significant increase in the risk of hemorrhagic stroke (RR, 1.24; 95% CI, 0.82–1.87; $P = 0.31$). Aspirin therapy was associated with a 22% reduction in the risk of transient ischemic attack (RR, 0.78; 95% CI, 0.64–0.94; $p = 0.01$).

Occurrence of gastrointestinal hemorrhage requiring transfusion, was more frequent in the aspirin group (RR, 1.40;

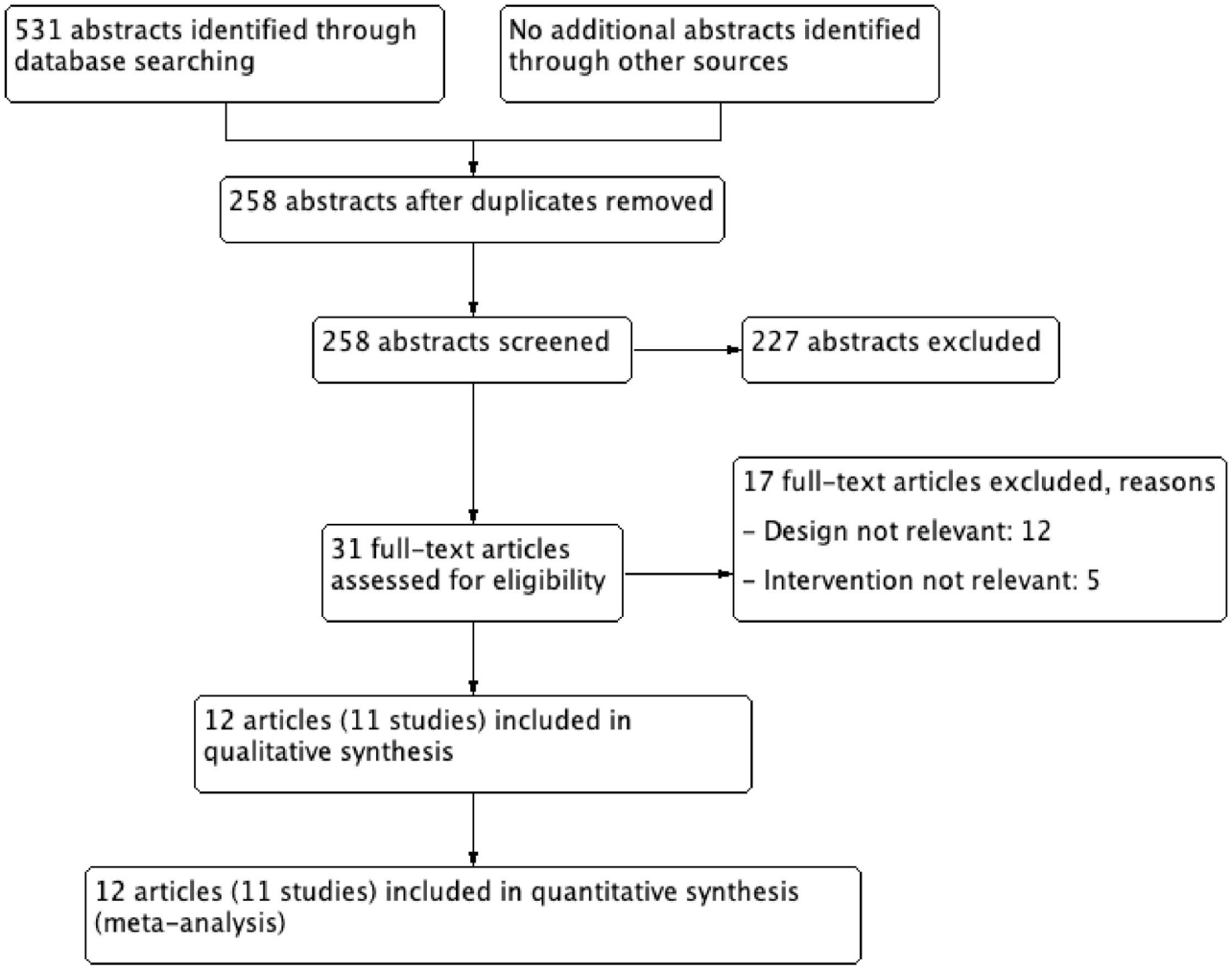

FIGURE 1 | Study flow chart. A total 531 abstracts identified through database searching (PubMed, and Cochrane Library databases), finally 11 studies (12 articles) were included in quantitative synthesis (meta-analysis).

95% CI, 1.07–1.83; $P = 0.02$). The most consistent benefit for aspirin was in women ≥ 65 years of age at study entry, among whom the risk of major cardiovascular events was reduced by 26% (RR, 0.74; 95% CI, 0.59–0.92; $P = 0.008$), including a 30% reduction in the risk of ischemic stroke (RR, 0.70; 95% CI, 0.49–1.00; $P = 0.05$). However, there was no significant benefit when the combination of IS and hemorrhagic stroke was considered (RR, 0.78; 95% CI, 0.57–1.08; $P = 0.13$). Based on the WHS results, aspirin is recommended for primary prevention for women after consideration of the 10-year risk of cerebrovascular disease (CVD) and of whether this and age outweigh the risk of hemorrhage (13).

In the AAA (Aspirin for Asymptomatic Atherosclerosis) trial 100 mg aspirin once daily was compared with placebo in men and women free of clinical cardiovascular disease and with low (≤0.95) Ankle Brachial Index (ABI). Approximately, 70% of trial participants (3, 350) were women. Participants were followed up for a mean (SD) of 8.2 (1.6) years A primary endpoint event (fatal or non-fatal coronary event or stroke or revascularisation) occurred in 357 participants (13.5 per 1,000 person/years, 95% CI, 12.2–15.0) and no statistically significant difference was found in event rates over time between the groups (aspirin, 13.7; 95% CI, 11.8–15.9 vs. placebo, 13.3; 95% CI, 11.4–15.4 events per 1 000 person/years; hazard ratio [HR], 1.03; 95%CI, 0.84–1.27) There was no difference between the groups also for secondary endpoints: all initial vascular events defined as a composite of a primary endpoint event or angina, intermittent claudication, or transient ischemic attack and all-cause mortality. The comparison of the primary endpoint by sex, age, and ABI, found lower event rates in women than in men, but in both groups, the difference was higher in aspirin group (men, event rate in aspirin group 27.4 [22.2–33.5)] vs. placebo group 23.9 [19.0–29.6], 95% CI 1.15 [0.86–1.54]; women in aspirin group 8.8 [7.0–10.8] vs. placebo group 9.6 [7.7–11.7], 95% CI 0.92 [0.68–1.23]) and in patients < 62 years of age. Although no statistically significant effect of aspirin on major events was found, the HR

TABLE 1 | Randomized control trials included in the meta-analysis.

Studies	Included participants
WHS	Asymptomatic women, 45 years of age or older
AAA	Patients with a low ankle brachial index (ABI) indicating atherosclerosis, aged 55–75 years
ETDRS	Patients with DM 1 and DM 2 and aged 18–70 years
JPAD	Patients with DM 2
POPADAD	Patients with DM and asymptomatic peripheral arterial disease, aged 40 or more years, aspirin was combined with antioxidants
JPPP	Patients aged 60 to 85 years with DM, hypertension and dyslipidemia
HOT	Patients allocated to a target blood pressure level and randomly assigned to aspirin or placebo group
PPP	Vitamin E was added to low dose of aspirin in patients with hypertension, hypercholesterolemia, diabetes, obesity, family history of premature myocardial infarction, or individuals who were elderly
ASCEND	Patients ≥ 40 years old with DM1 and DM2 without ASCVD, randomised to aspirin 100 mg/D or placebo
ASPREE*	Patients ≥ 70 years old (≥ 65 years old for Hispanic and African American patients) without life-limiting chronic illness, dementia, physical disability or documented cardiovascular or cerebrovascular disease, randomised to aspirin 100 mg/D or placebo
ARRIVE	Men ≥ 55 years and 2–4 risk factors, women aged ≥ 60 years and with ≥ 3 risk factors

*WHS, Women's Health Study; AAA, Aspirin for Asymptomatic Atherosclerosis; ETDRS, Early Treatment Diabetic Retinopathy Study; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; POPADAD, The prevention of progression of arterial disease and diabetes; JPPP, The Japanese Primary Prevention Project; HOT, Hypertension Optimal Treatment Trial; PPP, Primary Prevention Project; ASCEND, A Study of Cardiovascular Events in Diabetes; ASPREE, Aspirin in Reducing Events in the Elderly; ARRIVE, Use of Aspirin to Reduce Risk of Initial Vascular Events in patients at moderate risk of cardiovascular disease. * results published in 2 articles.*

and 95% CIs did not rule out the possibility of a risk reduction of up to 16% (or an increased risk up to 27%). To achieve this, it means that 500–600 people from the general population would need to be screened and prescribed aspirin to prevent a single major cardiovascular event over an 8-year period. Adverse effects such as major hemorrhage, gastrointestinal ulcer and fatal intracranial hemorrhage are of particular concern in the context of screening the healthy general population and when the absolute effects of aspirin in reducing major vascular events may be small (14).

In the ETDRS (Early Treatment Diabetic Retinopathy Study) trial only patients with diabetes mellitus (DM 1 and DM2), between the ages of 18 and 70 years with different categories of diabetic retinopathy were included, randomly assigned to aspirin 650 mg daily or placebo, and followed up for 5 years. The primary endpoint was mortality from all causes. Among the 3,711 patients enrolled in EDTRS, 1 615 (44%) were women and only a slightly higher relative risk for stroke was reported for females (RR, 1.31; 99% CI, 0.71–2.39) than for males (RR, 1.07; 99% CI, 0.63–1.83) (15).

In the JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial only patients with type 2 diabetes mellitus without history of atherosclerotic disease were enrolled. A low-dose aspirin (81–100 mg) was used, and the median follow-up duration was 4.37 years. The primary endpoint was any atherosclerotic event, which was a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; non-fatal acute myocardial infarction; unstable angina; newly developed exertional angina; non-fatal ischemic and hemorrhagic stroke; transient ischemic attack; or non-fatal aortic and peripheral vascular disease during the follow-up period. Overall, mean (SD) age was 65 (10) years, 44% of 2,539 patients were women. Out of a total of 154 atherosclerotic events, 68 (5.4%) were in the aspirin group and 86 (6.7%) in the non-aspirin group (HR, 0.80; 95%CI, 0.58–1.10; log-rank test, $P = 0.16$) and there was no difference in occurrence of hemorrhagic strokes (6 in the aspirin group, 7 in the non-aspirin group) There were no significant differences between the aspirin group and non-aspirin group in other subgroup analyses, including that by sex (16).

In the POPADAD (The Prevention Of Progression of Arterial Disease And Diabetes) trial 1 276 patients (female 56%) with DM1 and DM2 without symptomatic cardiovascular disease aged 40 or more years were included, aspirin 100 mg daily was used with and without antioxidant and compared with placebo alone or with antioxidant. Overall, 233 participants experienced the composite primary endpoint, with an event rate of 2.9 per 100 patient years. No significant differences were found between aspirin and no aspirin in the primary and secondary endpoints In the subgroup analysis, the difference in treatment effect between men and women was not statistically significant (men, event rate in aspirin group 68 [23.8%] vs. placebo group 62 [22.4%], 95% CI 1.04 [0.74–1.47]; women in aspirin group 48 [13.6%] vs. placebo group 55 [15.2%], 95% CI 0.89 [0.60–1.31]) (17).

In the JPPP (The Japanese Primary Prevention Project) trial 14 464 patients (women 58%) were aged 60 to 85 years and presenting with DM and also hypertension and dyslipidaemia. Low-dose aspirin (100 mg) once-daily was compared with placebo. The study was terminated prematurely owing to futility; regression analyses indicated that the risk of a primary endpoint event (composite death from cardiovascular causes, non-fatal stroke and non-fatal myocardial infarction) was higher in patients aged 70 years or older vs. those younger than 70 years (parameter estimate, 0.92; HR, 2.51 [95%CI, 2.00–3.14]; $p < 0.001$) and, in terms of sex, in men vs. women (parameter estimate, 0.34; HR, 1.41; 95% CI, 1.14–1.74; $P = 0.002$) (18).

In the HOT (Hypertension Optimal Treatment Trial) trial the potential benefit of a low dose of acetylsalicylic acid in the treatment of hypertension was studied. Overall, 18 790 patients (male/female−53%/47%) aged 50–80 years, with hypertension

and diastolic blood pressure between 100 and 115 mm Hg (mean 105 mm Hg), were included in the study and randomly assigned to a target diastolic blood pressure. Acetylsalicylic acid 75 mg/day was used in 9 399 patients and 9 391 patients were assigned to placebo. Primary outcomes were major cardiovascular events, defined as all (fatal and non-fatal) myocardial infarctions, all (fatal and non-fatal) strokes, and all other cardiovascular deaths. Aspirin significantly ($p = 0.03$) reduced the major cardiovascular events by 15%, all myocardial infarction was 36% less frequent in the aspirin group with a significant difference ($p = 0.002$). No difference in stroke incidence between patients randomized to acetylsalicylic acid or placebo was observed. However, while fatal bleeds (including cerebral) were equally common in the two groups, non-fatal major bleeds were significantly more frequent among patients receiving aspirin than in those receiving placebo (risk ratio 1.8, $p < 0.001$); minor bleeds were also 1.8 times more frequent among patients who were on aspirin. A specific comparison of the treatment effect in men and women was not made (19).

In the PPP (Primary Prevention Project) trial vitamin E 300 mg/day was added to low dose of Aspirin 100 mg/day in patients with hypertension, hypercholesterolemia, diabetes, obesity, family history of premature myocardial infarction, or individuals who were elderly. Slightly more women (57%) out of a total 4 495 patients were included, but a subgroup analysis by sex was not performed. Aspirin lowered the frequency of all the endpoints (major fatal and non-fatal cardiovascular events) being significant for cardiovascular death (from 1.4 to 0.8%; RR, 0.56; 95% CI, 0.31–0.99) and total cardiovascular events (from 8.2 to 6.3%; RR, 0.77; 95% CI, 0.62–0.95). Severe bleedings were more frequent in the aspirin group than in the no-aspirin group (1.1% vs. 0.3%; $p < 0.0008$). Vitamin E showed no effect on any pre-specified endpoint (20).

In the ASCEND (A Study of Cardiovascular Events in Diabetes) trial adults who had diabetes but no evident cardiovascular disease were randomly assigned to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer. A total of 15 480 participants of at least 40 years of age (female 37.5%) were randomized. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; $P = 0.01$). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; $P = 0.003$), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned.

Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard (21).

In the ASPREE (Aspirin in Reducing Events in the Elderly) trial, of the 19,114 healthy persons (female 56.4%), who did not have cardiovascular disease, dementia, or disability, of over 70 years of age who were enrolled. Of these, 9 525 were assigned to receive 100 mg of enteric-coated aspirin and 9,589 to receive placebo. The primary composite endpoint was derived from the first endpoint events of death, dementia, and persistent physical disability. A total of 1 052 deaths occurred during a median of 4.7 years of follow-up. The risk of death from any cause was 12.7 events per 1,000 person-years in the aspirin group and 11.1 events per 1 000 person-years in the placebo group (HR, 1.14; 95% CI, 1.01 to 1.29). Cancer was the major contributor to the higher mortality in the aspirin group, accounting for 1.6 excess deaths per 1,000 person-years. Cancer-related death occurred in 3.1% of the participants in the aspirin group and in 2.3% of those in the placebo group (hazard ratio, 1.31; 95% CI, 1.10 to 1.56) (22). The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo (23). Differences between men and women were not analyzed. In a *post hoc* analysis the risk of incident dementia and cognitive decline was analyzed. There was evidence that sex modified the association with incident dementia (interaction $P = 0.02$), with increased risk in men (HR, 1.68; 95% CI, 1.19–2.39) but not women (HR, 1.01; 95% CI, 0.72–1.42) (26).

The ARRIVE (Use of Aspirin to Reduce Risk of Initial Vascular Events in patients at moderate risk of cardiovascular disease) trial was a randomized, double-blind, placebo-controlled, multicentre study conducted in seven countries. Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate based on the number of specific risk factors. Patients at high risk of gastrointestinal bleeding or other bleeding, or diabetes were excluded. The total number of patients was 12,546 patients (female 29.5%) and they were randomly assigned to receive enteric-coated aspirin tablets (100 mg) or placebo, once daily. Median follow-up was 60 months. The primary efficacy endpoint was a composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack. In the intention-to-treat analysis, the primary endpoint occurred in 269 (4.29%) patients in the aspirin group vs. 281 (4.48%) patients in the placebo group (HR 0.96; 95% CI 0.81–1.13; $p = 0.6038$). There were 321 documented deaths ($n = 160$ [2.55%] of 6,270 patients in the aspirin group and n=161 [2.57%] of 6,276 patients in the placebo group; HR 0.99, 95% CI 0·80–1.24; $p = 0.9459$). Of these deaths, 108 patients had fatal myocardial infarction, fatal stroke, or other vascular death ($n = 49$ [0.78%] in the aspirin group and $n = 59$ [0.94%] in the placebo group) (24). Gastrointestinal bleeding

events occurred in <1% of patients in each group and were predominantly mild but were more frequent for those assigned to aspirin (HR, 2.11; 95%CI, 1.36–3.28, $p = 0.0007$).

From 11 trials only one RCT studied the effect of aspirin in primary prevention in women (WHS), and based on their results aspirin is recommended for primary prevention for women after consideration of the 10-year risk of cerebrovascular disease (CVD) and whether this and age outweigh the risk of hemorrhage (13). In other studies, women were represented relatively well-compared to men (44–70%), except the last 2 trials, where they were underrepresented—ASCEND (37.4%) (21) and ARRIVE (29.5%) (24), however, only in 5 trials men and women were compared with no significant difference (14–18).

Meta-Analyses

Meta-analyses of 11 RCTs (135 641 patients) comparing aspirin with placebo showed significant decreases (prevention) in the risk of major cardiovascular events in women and men (**Figure 2**).

In women, there was significant decrease in the risk of stroke (OR 0.85 [95% CI 0.73, 0.99], $p = 0.03$) (**Figure 3**) and ischemic stroke (OR 0.76 [0.63, 0.93], $p = 0.008$) (**Figure 4**) with aspirin compared to placebo and there was no significant increase in risk of hemorrhagic stroke (OR 1.78 [0.61, 5.19], $p = 0.29$) (**Figure 5**) with aspirin compared to placebo. Aspirin also significantly decreased the risk of transient ischemic attack (OR 0.78 [0.64, 0.95], $p = 0.01$), compared to placebo, though only one study was included in the analysis (**Table 2**).

In men, aspirin did not affect the risk of stroke (OR 1.13 [0.97, 1.31], $p = 0.12$) (**Figure 3**) and ischemic stroke (OR 0.94 [0.67, 1.32], $p = 0.72$) (**Figure 4**), but increased the risk of hemorrhagic stroke with a borderline statistical significance (OR 1.99 [0.99, 4.03], $p = 0.05$) (**Figure 5**) compared to placebo (**Table 2**). There were no marked effects of aspirin compared to placebo on overall mortality and cardiovascular mortality in women and men.

Compared to placebo, aspirin significantly increased the major bleeding in both, women (OR 1.43 [1.19, 1.72], $p = 0.002$) and men (OR1.37 [1.26, 1.49], $p < 0.00001$) (**Figure 6**), while gastrointestinal (GIT) bleeding was significantly increased only in women (OR 1.40 [1.07, 1.83], $p = 0.01$) (**Figure 7**) taking aspirin (**Table 2**).

In women, aspirin did not affect the risk of myocardial infarction (OR 0.92 [0.77, 1.11], $p = 0.38$) while in men aspirin significantly decreased this risk (OR 0.68 [0.58, 0.81], $p < 0.0001$) compared to placebo (**Table 2**).

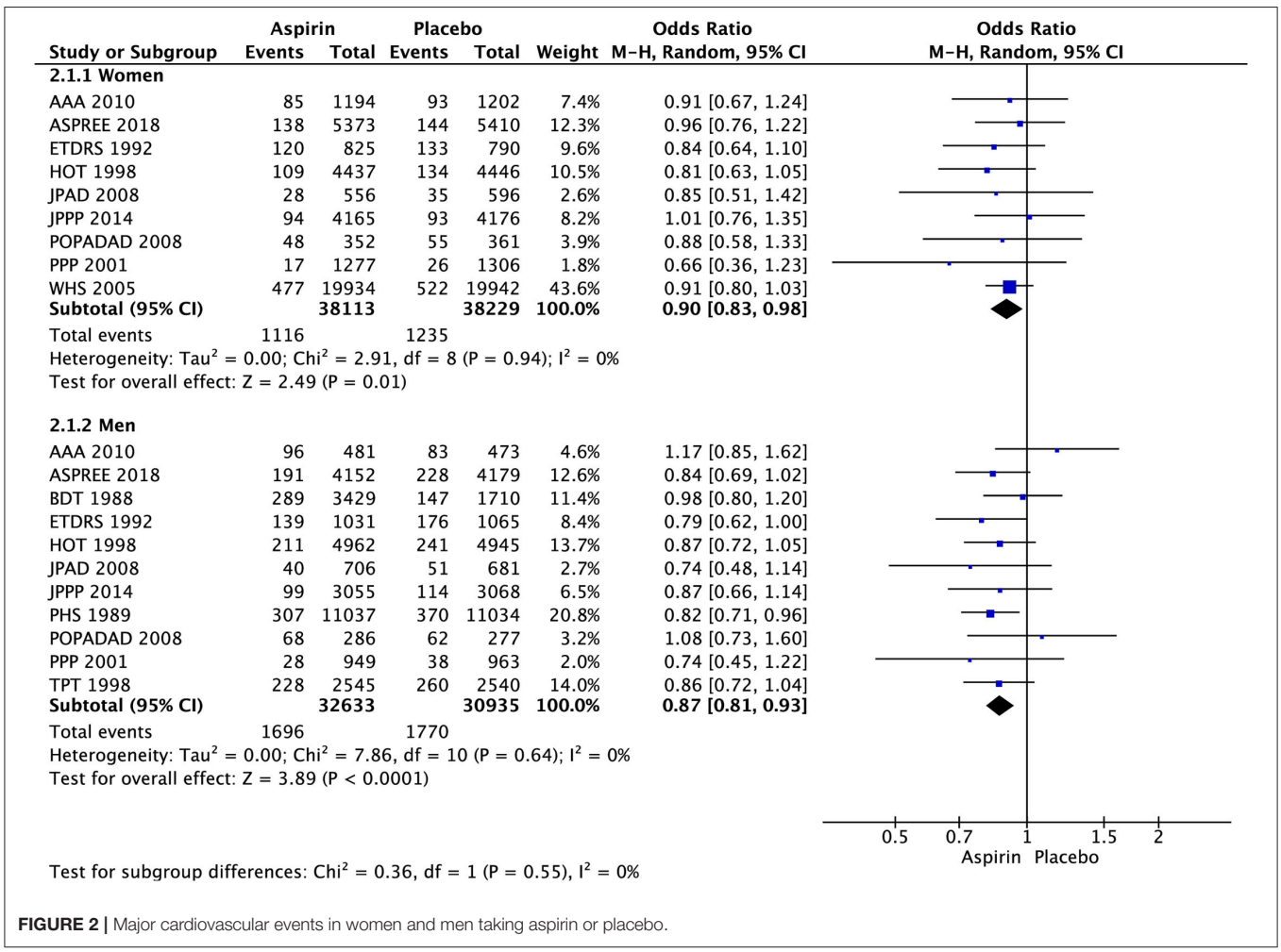

FIGURE 2 | Major cardiovascular events in women and men taking aspirin or placebo.

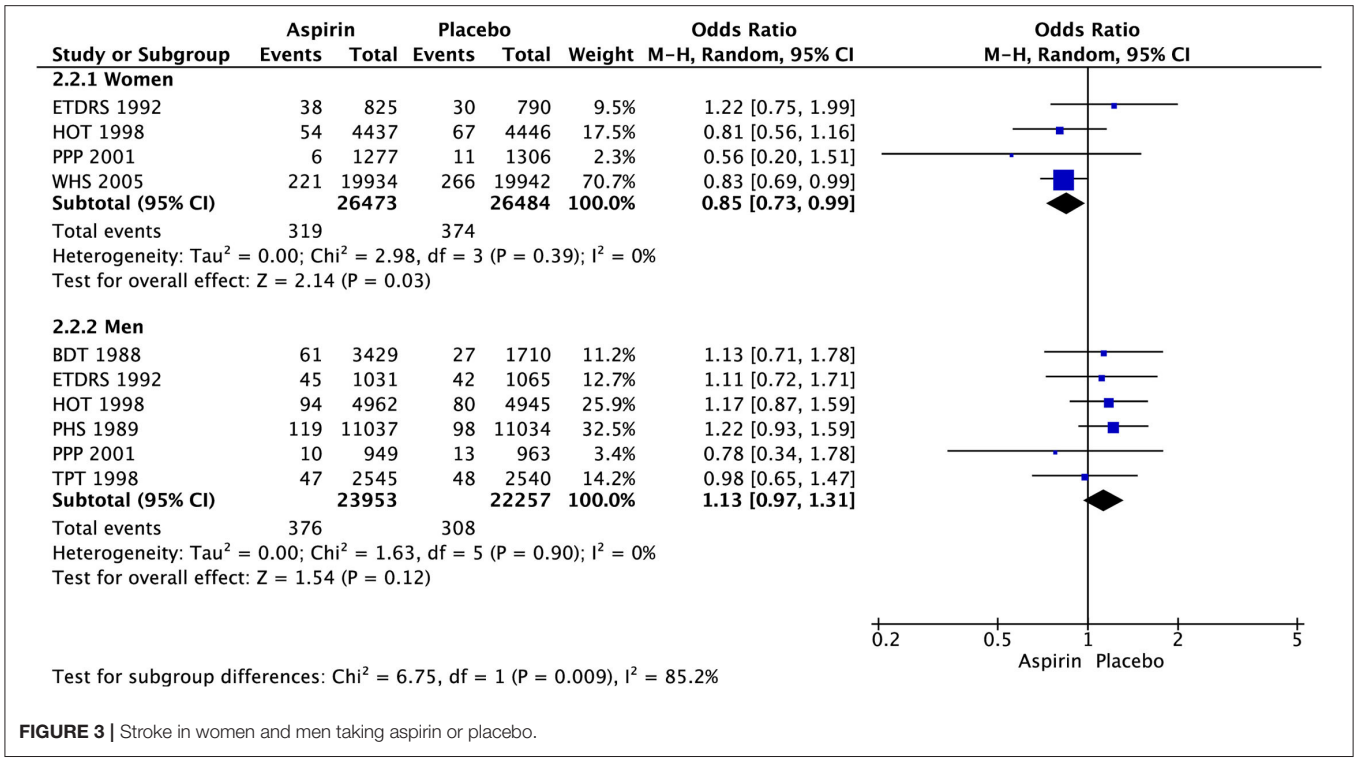

FIGURE 3 | Stroke in women and men taking aspirin or placebo.

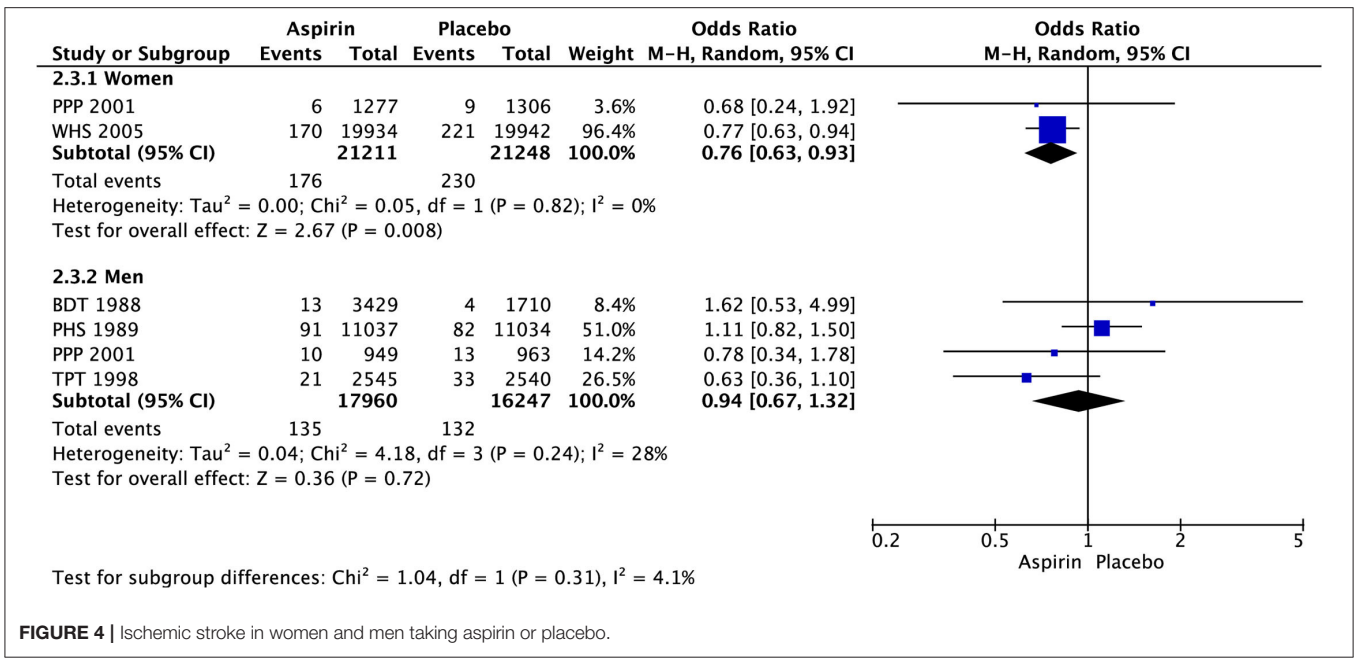

FIGURE 4 | Ischemic stroke in women and men taking aspirin or placebo.

Mortality was not reduced in either women or men taking aspirin (**Table 2**).

In the meta-analysis of event rates in women and men taking aspirin, the risk of major cardiovascular events (3.5% vs. 5.6%, OR 0.59 [0.45, 0.78], $p = 0.0002$) (33 801 patients) in 8 RCTs (**Figure 8**), mortality (4.0% vs. 5.9%, OR 0.64 [0.48, 0.86], $p = 0.003$) in 23 006 patients from 4 RCTs (**Figure 9**), and major bleeding (2.6% vs. 3.0%, OR 0.83 [0.69, 1.00], $p = 0.05$) in 32 248 patients from 7 RCTs (**Figure 10**) (**Table 3**) were significantly lower in women compared to men (**Table 3**). On meta-analyzing the Hazard ratio, there was no marked effect of aspirin on composite outcome compared to placebo in women HR 0.94 [0.83, 1.07] and men HR 0.95 [0.85, 1.05]. In addition, there was no difference in the effect of aspirin vs. placebo in women and

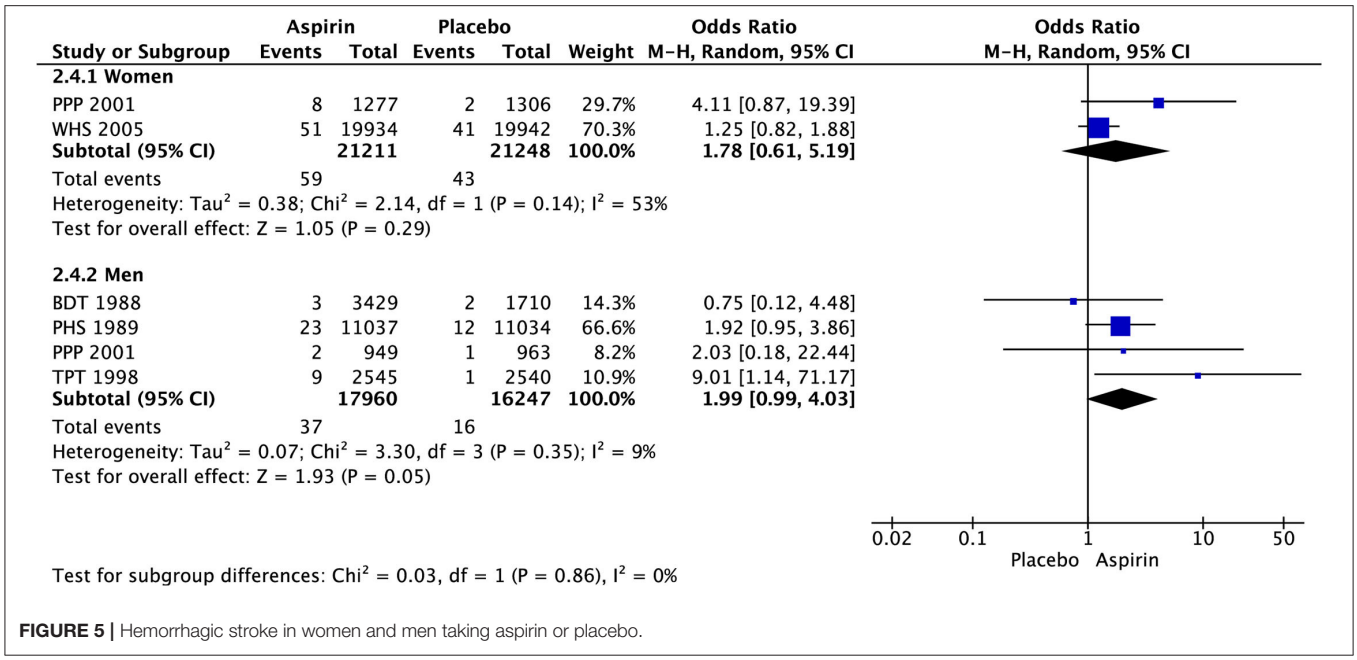

FIGURE 5 | Hemorrhagic stroke in women and men taking aspirin or placebo.

men, $p = 0.95$. There was no statistically significant heterogeneity among the studies (**Figure 11**). The HR of major bleeding was significantly greater in women taking aspirin, HR 1.58 [1.25, 1.99], $p = 0.0001$ and tend to be greater in men taking aspirin, HR 1.21 [0.97, 1.51], though data was not statistically significant. Compared to placebo, there was no significant difference in the effect of aspirin in women and men on the risk of major bleeding ($p = 0.10$) (**Figure 12**).

There were no differences in event rates between women and men taking aspirin for stroke, ischemic stroke or hemorrhagic stroke, cardiovascular mortality, or myocardial infarction. For hemorrhagic stroke, stroke and systemic embolism, cardiovascular disease and vascular event/revascularisation there was only one RCT for each outcome, so we cannot draw and generalize any conclusions from these results; moreover, no differences were found between men and women in terms of risk of hemorrhagic stroke and primary outcome in these RCTs (**Table 3**).

In ASPREE the risk of cardiovascular disease was significantly decreased in women compared to men (3.9% vs. 5.7%, OR 0.68 [0.56, 0.82], $p < 0.0001$) in 9 525 patients (**Figure 13**) and in the ASCEND trial the risk of vascular event/revascularization was also significantly decreased in women (9.0% vs. 11.8%, OR 0.73 [0.63, 0.86], $p < 0.0001$) in 7 740 of patients (**Figure 14**), however, representation of women in ASCEND was only 37.4%.

Study of Aspirin on Risk of Ischemic Stroke in Patients With Covert Cerebral Small Vessel Disease (CcSVD)

Another study sought to detect if aspirin reduces the risk of ischemic stroke or increases hemorrhagic stroke risk in patients with covert cerebral small vessel disease (ccSVD). Only one RCT included patients aged ≥ 45 years with at least one silent brain infarct (SBI) but no previous clinical cerebrovascular events for randomization to aspirin 100 mg (36 patients) or placebo (47 patients). The primary endpoint was the combined endpoint of ischemic stroke, TIA, and new silent brain infarcts detected by MRI which had occurred in 9 controls (19.1%) and in two subjects (5.6%) in the ASA group ($p = 0.10$) after 4 years (26). A new stroke was observed in 1/36 (2.8%) in the ASA group compared to 2/47 (4.3%) subjects in control group (OR 0.64 [0.06–7.38]) There were no (0/36 [0%]) deaths in the aspirin-treated group and 1/47 (2.1%) death in the control group (O: 0.64 [0.06–7.38]) (11, 25), gastrointestinal adverse effects were reported in 2 (5.6%) aspirin-treated patients compared to 1 (2.1%) in the control group. There was no significant difference in the incidence of cognitive impairment between treated and non-treated patients during the 4-year follow-up (25). The findings should be interpreted with caution, taking into account a small sample of the population investigated, the imbalance in the prevalence of hypertension between the aspirin-treated patient group (17/36 [47.2%]) and the control group (29/47 [61.7%]) ($p = 0.188$) and, in relation to cognitive impairment, also the relatively young age (median of 66 years in the aspirin group vs. 68 years in the control group) and the relatively short period of follow-up.

DISCUSSION

In primary prevention, the role of aspirin remains controversial and net benefit less certain for women, moreover only in five studies women and men were compared (14–18).

In a meta-analysis of 11 trials enrolling 135 641 participants in primary prevention with aspirin we found a significant decrease in the risk of major cardiovascular events in both sexes with a decreased risk of stroke and ischemic stroke in women taking

TABLE 2 | Role of aspirin in primary prevention of stroke, major cardiovascular events, mortality, myocardial infarction (MI), and bleeding in women and men.

Outcome	Incidence (%)		*n* (*N*)	OR [95% CI]	I^2	*P*-value
	Aspirin	Placebo				
Major cardiovascular events						
Women	2.9%	3.2%	9 (76,342)	0.90 [0.83, 0.98]	0%	0.01
Men	5.2%	5.7%	11 (63,568)	0.87 [0.81, 0.93]	0%	<0.0001
Stroke						
Women[a]	1.2%	1.4%	4 (52,957)	0.85 [0.73, 0.99]	0%	0.03
Men	1.6%	1.4%	6 (46,210)	1.13 [0.97, 1.31]	0%	0.12
Ischemic stroke						
Women	0.8%	1.1%	2 (42,459)	0.76 [0.63, 0.93]	0%	0.008
Men	0.8%	0.8%	4 (34,207)	0.94 [0.67, 1.32]	28%	0.72
Hemorrhagic stroke						
Women	0.3%	0.2%	2 (42,459)	1.78 [0.61, 5.19]	53%	0.29
Men	0.2%	0.1%	4 (34,207)	1.99 [0.99, 4.03]	9%	0.05
TIA						
Women	0.9%	1.2%	1 (39,876)	0.78 [0.64, 0.95]	NA	0.01
Men	NR	NR	NR	NR	NR	NR
Mortality						
Women	3.4%	3.5%	5 (63,740)	0.92 [0.77, 1.10]	66%	0.37
Men	4.8%	4.7%	7 (54,541)	0.97 [0.87, 1.08]	39%	0.57
Cardiovascular mortality						
Women	1.0%	1.1%	5 (53,670)	0.90 [0.74, 1.09]	15%	0.26
Men	2.2%	2.1%	7 (46,773)	0.97 [0.85, 1.10]	4%	0.64
Myocardial infarction						
Women	1.2%	1.3%	4 (52,957)	0.92 [0.77, 1.11]	13%	0.38
Men[b]	2.2%	3.2%	6 (46,210)	0.68 [0.58, 0.81]	47%	<0.0001
Vascular events/ revascularization						
Women	9.0%	9.6%	1 (5,796)	0.93 [0.78, 1.11]	NA	0.42
Men	11.8%	13.6%	1 (9,684)	0.85 [0.76, 0.96]	NA	0.009
Coronary revascularisation						
Women	2.0%	1.9%	1 (39,876)	1.04 [0.90, 1.20]	NA	0.58
Men	NR	s	NR	NR	NR	NR
Major bleeding						
Women	3.7%	2.8%	5 (67,921)	1.43 [1.19, 1.72]	52%	0.0002
Men	3.3%	2.5%	8 (84,200)	1.37 [1.26, 1.49]	0%	<0.00001
GIT bleeding						
Women	0.6%	0.5%	1 (39,876)	1.40 [1.07, 1.83]	NA	0.01
Men	3.4%	3.2%	2 (27,156)	1.05 [0.92, 1.20]	0%	0.46
Cardiovascular outcome						
Women	3.9%	3.8%	1 (10783)	1.05 [0.86, 1.28]	NA	0.64
Men	5.7%	6.5%	1 (8331)	0.87 [0.73, 1.04]	NA	0.14

CI, Confidence interval; GIT, Gastrointestinal; I^2, Heterogeneity; MI, myocardial infarction, n, Number of studies; N, Number of patients; NA, Not applicable; NR, Not reported; p, Statistical significance value; OR, Odds Ratio; TIA, transient ischemic attack, a: Women vs. Men (improvement of outcome with aspirin; P = 0.009); b: Men vs. Women (improvement of outcome with aspirin; p = 0.02).

aspirin compared to placebo with no significantly increased risk of hemorrhagic stroke.

In men, aspirin did not affect the risk of stroke and ischemic stroke, but significantly increased the risk of hemorrhagic stroke compared to placebo.

Compared to placebo, aspirin significantly increased major bleeding in both, men and women, while gastrointestinal (GIT) bleeding was significantly increased only in women receiving aspirin.

In women, aspirin did not affect the risk of MI while in men it significantly decreased the risk of MI compared to placebo. These findings are consistent with other published meta-analyses on the effect of aspirin on primary stroke prevention (27–29). In meta-analysis of 13 trials, Zheng et al. found that the use of aspirin in

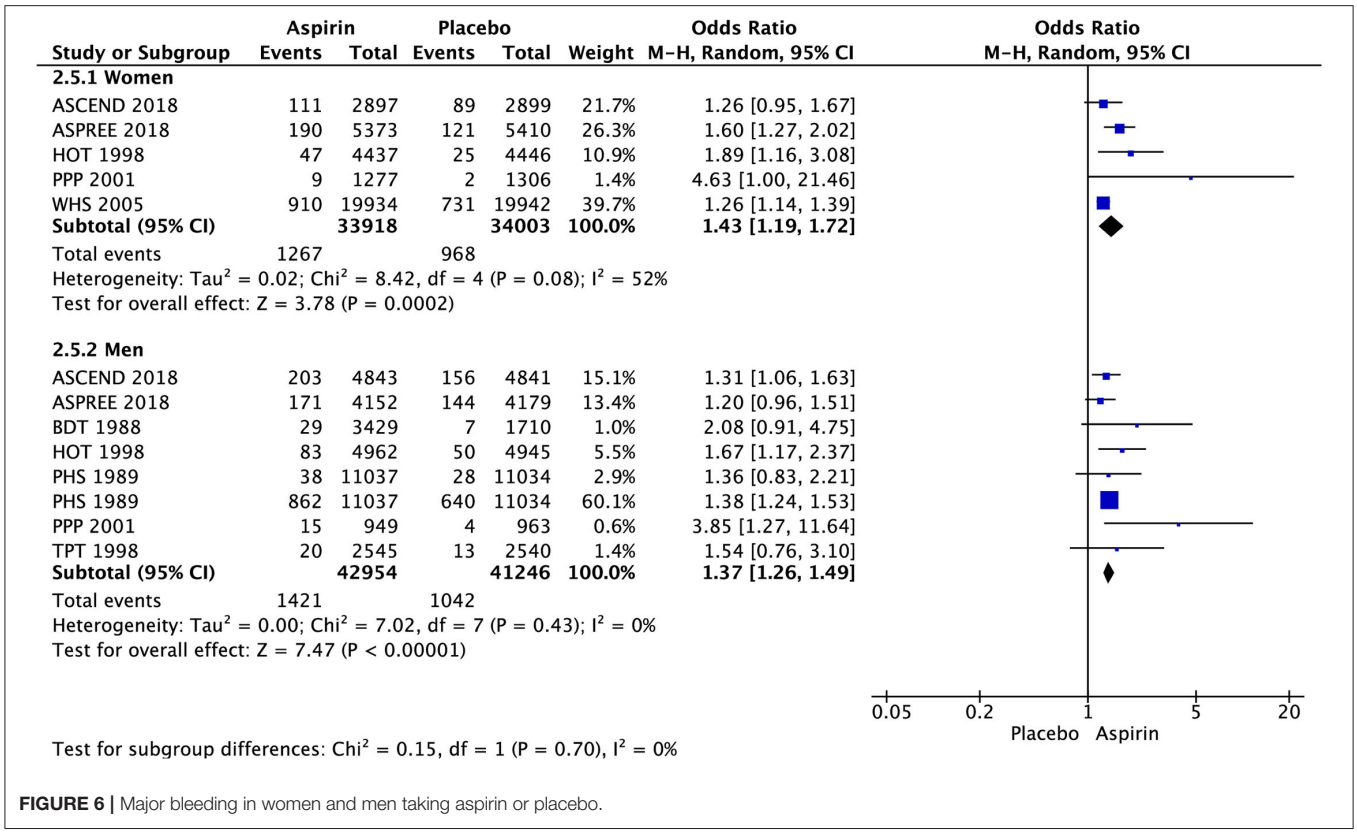

FIGURE 6 | Major bleeding in women and men taking aspirin or placebo.

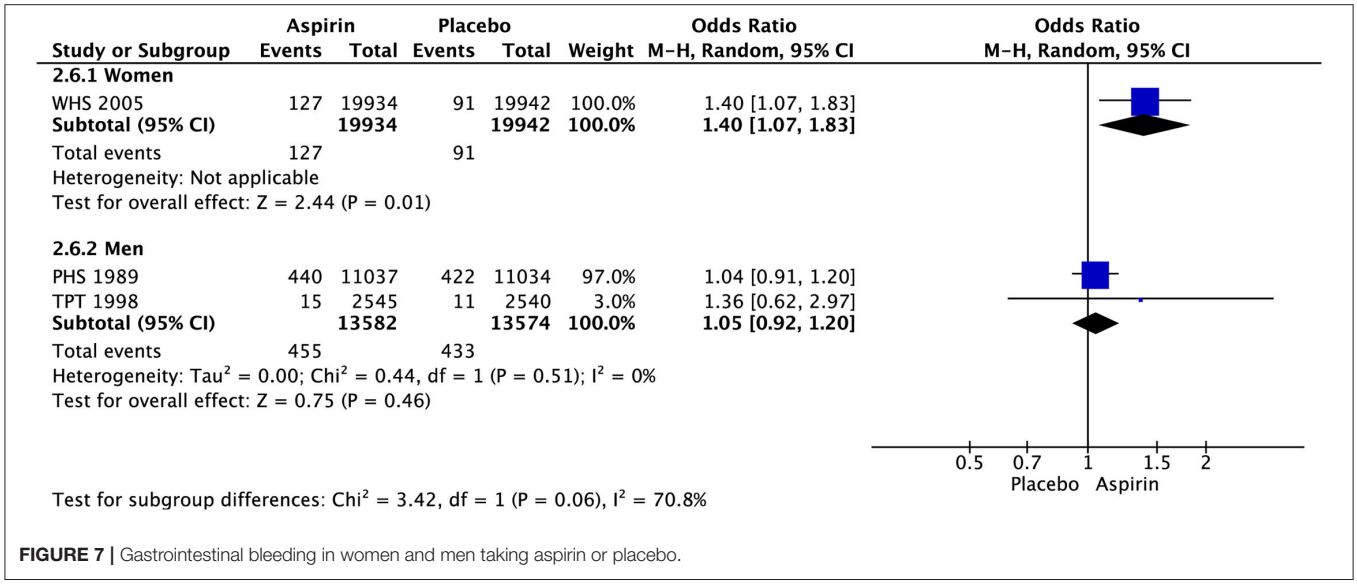

FIGURE 7 | Gastrointestinal bleeding in women and men taking aspirin or placebo.

individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and with an increased risk of major bleeding, and that the number needed to treat to cause major bleeding was lower than number needed to treat to prevent an ASCVD (atherosclerotic cardiovascular disease) event (210 vs. 265) (27). Based on this, according to the authors, the use of aspirin indicates more harm than benefit (27). This was confirmed by a meta-analysis published by Lei et al. (28) showing that in healthy adults and patients with cardiovascular diseases the little protective benefit from aspirin is offset by the increased risk of severe bleeding events (28).

Therefore, even the current guidelines recommend aspirin for, primary prevention only with restrictions and the strength of the recommendations is mostly weak (30).

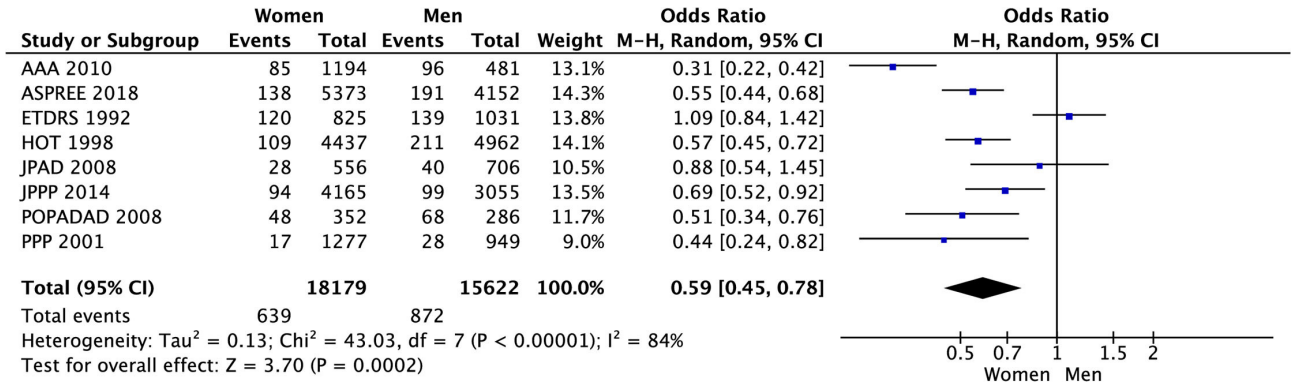

FIGURE 8 | Major cardiovascular events in women and men taking aspirin.

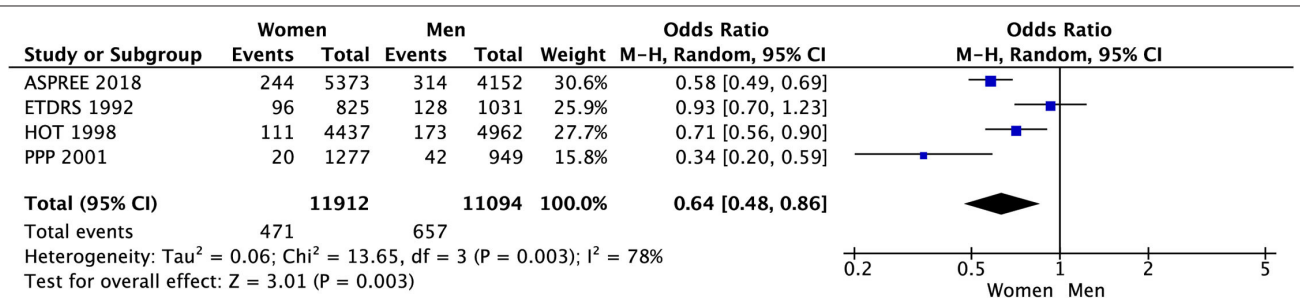

FIGURE 9 | Mortality in women and men taking aspirin.

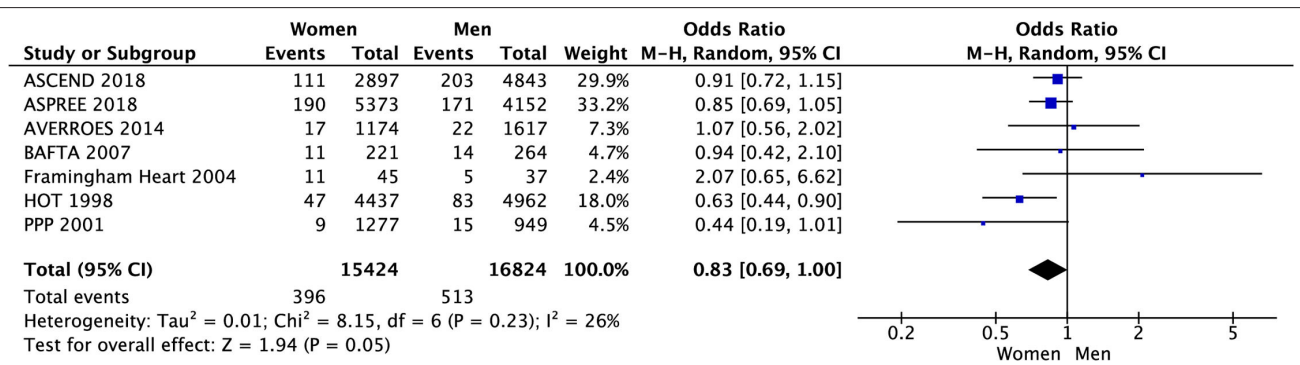

FIGURE 10 | Major bleeding in women and men taking aspirin.

Recently published trials (ASCEND, ASPREE, ARRIVE) were focused on the effect of aspirin in primary prevention in three risk groups of patients, i.e., patients with diabetes mellitus, older patients without life-limiting chronic illness, and patients at intermediate risk of a future atherosclerotic event (21, 22, 24). The meta-analysis of the former three trials did not report a significant survival benefits with aspirin in primary prevention (risk ratio, 0.98; 95% CI, 0.93–1.02, $p = 0.30$) and confirmed the increased risk of major bleeding (risk ratio, 1.47; 95% CI, 1.31–1.65; $p < 0.0001$ (29).

The effect of aspirin in primary prevention in women was specifically addressed by only one RCT (WHS) and similarly only 1 meta-analysis (from 2006) was focused on determining if the benefits and risks of the treatment with aspirin in primary prevention of cardiovascular disease vary by sex (31). Based on WHS trial, the most consistent benefit for aspirin was in women ≥ 65 years of age at study entry (14). According to a

TABLE 3 | Role of aspirin in primary prevention of MACE, stroke, mortality, and bleeding in Women compared with Men.

Outcome	Incidence (%)		*n* (N)	OR [95% CI]	I^2	*P*-value
	Women	Men				
Major cardiovascular events	3.5%	5.6%	8 (33,801)	0.59 [0.45, 0.78]	84%	0.0002
Stroke	1.5%	2.1%	3 (13,481)	0.74 [0.48, 1.14]	53%	0.17
Ischemic stroke	2.4%	2.0%	2 (5, 017)	0.96 [0.25, 3.73]	84%	0.96
Hemorrhagic stroke	0.6%	0.2%	1 (2,226)	2.99 [0.63, 14.09]	NA	0.17
Mortality	4.0%	5.9%	4 (23, 006)	0.64 [0.48, 0.86]	78%	0.003
Cardiovascular mortality	2.3%	2.9%	4 (14,119)	0.71 [0.44, 1.12]	72%	0.14
Myocardial infarction	1.8%	2.2%	3 (13,481)	0.77 [0.45, 1.32]	70%	0.35
Major bleeding	2.6%	3.0%	7 (32,248)	0.83 [0.69, 1.00]	26%	0.05
Major and clinically relevant bleeding	4.9%	4.5%	2(2,873)	1.19 [0.58, 2.44]	47%	0.64
Intracranial bleeding	0.6%	0.4%	2(2,873)	1.28 [0.45, 3.60]	0%	0.64
Stroke and systemic embolism	5.5%	3.0%	1(2,791)	1.85 [1.26, 2.70]	NA	0.002
Primary outcome	9.5%	10.1%	1(488)	0.93 [0.51, 1.70]	NA	0.82
Cardiovascular disease	3.9%	5.7%	1 (9,525)	0.68 [0.56, 0.82]	NA	<0.0001
Vascular event/Revascularization	9.0%	11.8%	1 (7,740)	0.73 [0.63, 0.86]	NA	<0.0001

CI, Confidence interval; I^2, Heterogeneity; n, Number of studies; N, Number of patients; NA, Not applicable; p, Statistical significance value; OR, Odds Ratio; Primary outcome: Fatal or non-fatal disabling stroke (ischemic or hemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism.

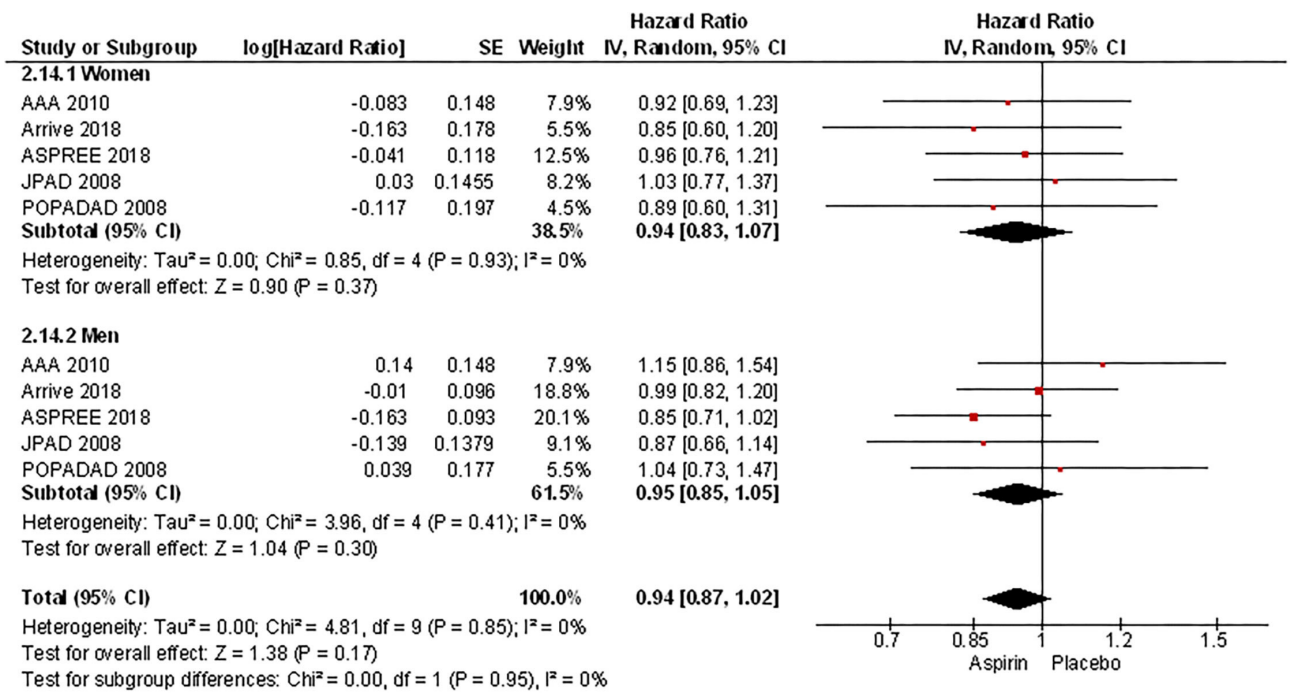

FIGURE 11 | Hazard ratio of composite outcome women and men taking aspirin.

meta-analysis, for both women and men, aspirin therapy reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischemic stroke in women and MI in men and significantly increased the risk of bleeding to a similar degree among women and men. When the benefits and risks for women were compared, the average absolute benefit in women receiving aspirin therapy was ∼2 stroke events per 1,000 women treated and the risk of major bleeding was 2.5 per 1,000 treated women (31). The Southern Community Cohort Study analyzed low-dose aspirin in primary prevention by race/ethnicity and found decreased risk of ischemic cardiac death in white participants, especially women. The history of peptic ulcer was not associated with low-dose aspirin, whereas it was associated to the concomitant use of NSAIDs (32).

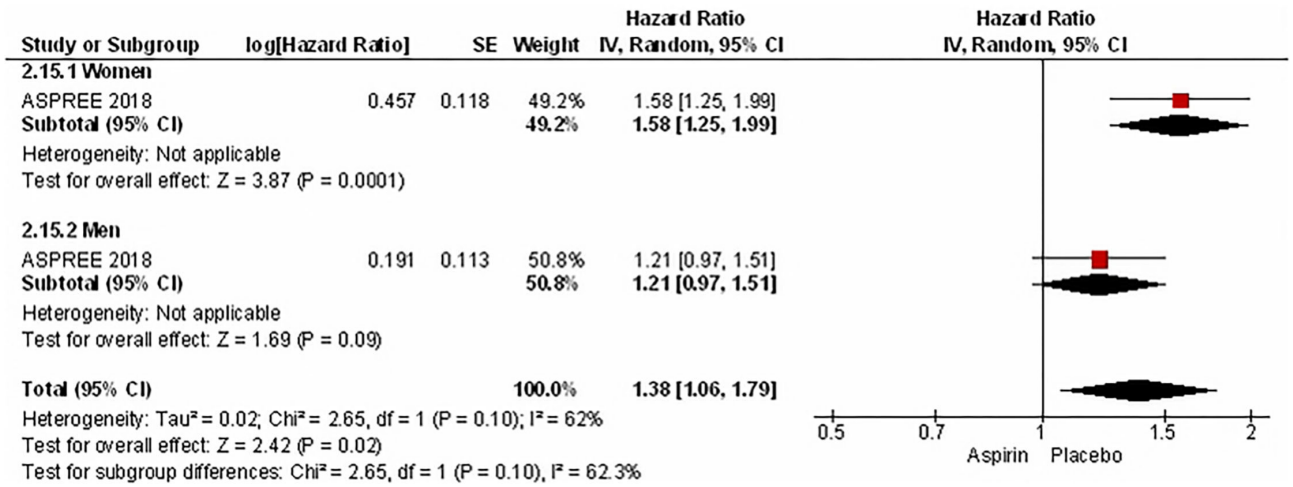

FIGURE 12 | Hazard ratio of major bleeding in women and men taking aspirin.

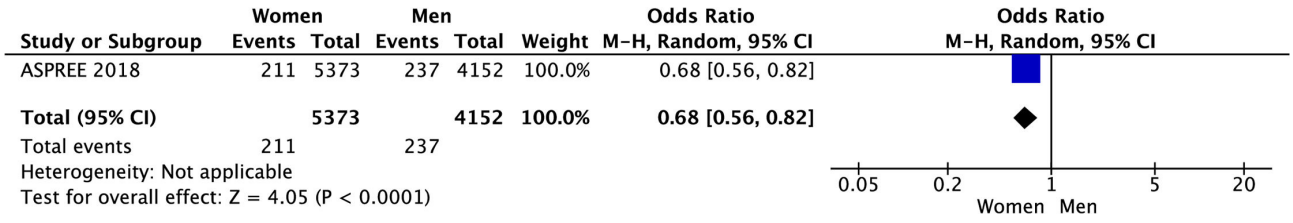

FIGURE 13 | Cardiovascular disease in women and men taking aspirin.

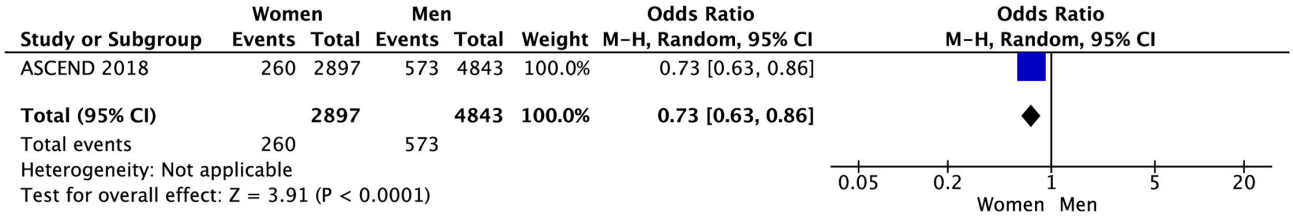

FIGURE 14 | Vascular event/Revascularization in women and men taking aspirin.

According the American Heart Association Effectiveness-Based Guidelines for Prevention of cardiovascular Disease in Women-2011 Update: (i) aspirin (75–325 mg) is deemed reasonable to be used in women with diabetes mellitus without known CVD unless contraindicated; (ii) aspirin therapy can be useful in women ≥ 65 years of age without known CVD (81 mg/d or 100 mg every other day) if blood pressure is controlled and the benefit for ischemic stroke and myocardial infarction prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke; iii) aspirin (81 mg/d or 100 mg every other day) may be reasonable for ischemic stroke prevention in women aged < 65 years without known CVD (1).

In our meta-analysis on the role of aspirin in primary prevention in men and women, we found that the risk of major cardiovascular events, mortality and major bleeding were significantly lower in women compared to men.

There were no marked differences between women and men taking aspirin regarding the risk of stroke, ischemic stroke or hemorrhagic stroke, cardiovascular mortality, or myocardial infarction. However, for hemorrhagic stroke, stroke and systemic embolism, primary outcome, cardiovascular disease and vascular event/revascularisation there was only one RCT for each outcome.

In the ASPREE trial, in patients aged > 75 years the risk of cardiovascular disease was significantly decreased in women compared to men. This confirmed the results from the WHS trial, where the most consistent benefit for aspirin was in women ≥ 65 years of age at study entry, among whom the risk of

major cardiovascular events was reduced by 26% (20). In the ASCEND trial the risk of vascular event/revascularisation was also significantly decreased in women but representation of women in ASCEND was only 37.4% (21).

Although we have found significant decreases in the primary prevention of the risk of major cardiovascular events in both women and men and in women a decreased risk of stroke and ischemic stroke with aspirin compared to placebo with no significantly increased risk of hemorrhagic stroke, it is apparent that this benefit is associated with an overall increased risk of bleeding. Indeed, aspirin significantly increased the major bleeding in both men and women. In contrast, gastrointestinal (GIT) bleeding was significantly increased only in women treated with aspirin.

Some works reported that co-prescription of aspirin with a proton pump inhibitor (PPI) might limit the risk of significant gastrointestinal bleeding; the use of PPIs was inconsistently reported in most of the studies and this strategy has not been adequately tested in RCTs (27). Therefore, we do not have sufficient evidence to recommend a concomitant treatment with PPI to reduce the risk of bleeding.

With regards to patient care, it should be considered that most of the cited trials were conducted in an era where pharmacological preventive measures available nowadays were less widespread (e.g., lipid lowering therapies). Therefore, the results of these aspirin trials, which showed minimal benefits and consistent bleeding risks, should be considered alongside the results of statin trials (33), recommendations for blood pressure control (34) and treatment of diabetes mellitus (35). In primary prevention trials, the use of statins was associated with a decreased risk of major vascular events (36). This statistically and clinically relevant benefit was associated with a favorable safety profile, in particular, it was not associated with the bleeding complications observed with aspirin (33). Given the increased cardiovascular risk, all patients with DM require aggressive risk factor reduction. In primary prevention, a combination of tight controls of blood pressure, lipids and diabetes is certainly crucial. However, studies have consistently shown that women are underdiagnosed and undertreated compared with men (37, 38). Furthermore, women with DM have poorer blood pressure, lipid and DM control compared with their male counterparts (35, 39).

We found no evidence to support the use of aspirin in patients with ccSVD which is in line with the ESO guideline on covert cerebral small vessel disease published in 2021 (25), where, given the low quality of evidence, only Expert Consensus Statement was formulated as follows: (i) Most group members advised against the use of antiplatelet drugs to prevent clinical outcomes in subjects with ccSVD when no other indication for this treatment exists; (ii) with current available knowledge, the use of antiplatelet drugs to prevent progression of cerebral SVD may be harmful in older patients (from around $\geq$ 70 years of age) if no other indication for this treatment exists (11).

CONCLUSION

In both women and men aspirin reduced the risk of major cardiovascular events and in women it decreased the risk of stroke and ischemic stroke with no significantly increased risk of hemorrhagic stroke.

In men, aspirin did not affect the risk of stroke and ischemic stroke but significantly increased the risk of hemorrhagic stroke compared to placebo. Aspirin increased the risk of major bleeding in both women and men, while gastrointestinal bleeding was significantly increased only in women treated with aspirin.

Based on the current ESO guidelines, aspirin is not recommended in covert cerebral small vessel disease.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 12 January 2023
DOI 10.3389/fneur.2022.1052401

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

RECEIVED 23 September 2022
ACCEPTED 16 December 2022
PUBLISHED 12 January 2023

CITATION
Pavlovic A, Pekmezovic T, Mijajlovic M, Tomic G and Zidverc Trajkovic J (2023) Is the female sex associated with an increased risk for long-term cognitive decline after the first-ever lacunar stroke? Prospective study on small vessel disease cohort. *Front. Neurol.* 13:1052401. doi: 10.3389/fneur.2022.1052401

Is the female sex associated with an increased risk for long-term cognitive decline after the first-ever lacunar stroke? Prospective study on small vessel disease cohort

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Background: Sex is a significant determinant of survival and functional outcome after stroke. Long-term cognitive outcome after acute lacunar stroke in the context of sex differences has been rarely reported.

Methods: A cohort of small vessel disease (SVD) patients presenting with first-ever acute lacunar stroke and normal cognitive status has been evaluated 4 years after the qualifying event for the presence of cognitive impairment (CI) with a comprehensive neuropsychological battery. Differences in baseline clinical and neuroimaging characteristics were compared between sexes in relation to cognitive status.

Results: A total of 124 female and 150 male patients were analyzed. No difference was detected between the groups regarding age ($p = 0.932$) or frequency of common vascular risk factors ($p > 0.1$ for all). At the baseline assessment, women had more disabilities compared to men with a mean modified Rankin scale (mRS) score of 2.5 (1.5 in men, $p < 0.0001$). Scores of white matter hyperintensities (WMH) of presumed vascular origin and a total number of lacunes of presumed vascular origin on brain MRI were higher in women compared to men ($p < 0.0001$ for all). As many as 64.6% of patients had CI of any severity on follow-up, women more frequently (77.4%) than men (54.0%; $p < 0.0001$). Univariate logistic regression analysis showed that female sex, higher NIHSS and mRS scores, presence of depression, and increasing WMH severity were associated with an increased risk for CI. Multivariate regression analysis indicated that only depression (OR 1.74, 95%CI 1.25–2.44; $p = 0.001$) and WMH severity (OR 1.10, 95%CI 1.03–1.17; $p = 0.004$) were independently associated with the CI.

Conclusion: At the long-term follow-up, women lacunar stroke survivors, compared to men, more frequently had CI in the presence of more severe vascular brain lesions, but this association was dependent on the occurrence of depression and severity of WMH, and could not be explained by differences in common vascular risk factors.

KEYWORDS

small vessel disease (SVD), lacunar stroke, vascular cognitive impairment, white matter lesions, female sex

Introduction

Due to the high survival and low recurrence rate, lacunar ischemic stroke is considered to have a favorable prognosis in the short term, with lower mortality, shorter hospital stays, and functional independence at discharge (1, 2). However, in the long-term follow-up, a history of previous lacunar stroke is associated with an increased risk for cardiovascular mortality, stroke recurrence, and functional and cognitive decline, particularly in older patients, those with multiple vascular risk factors, and initially more severe strokes (3, 4). The burden of underlying cerebral small vessel disease (SVD) worsens the long-term prognosis after lacunar stroke by increasing the risk of disability, rate of recurrence, the occurrence of cognitive impairment, and depression (5–7).

Sex is a significant determinant of long-term survival and functional outcome after stroke (8, 9). Stroke has a greater clinical effect on women, although age-specific incidence and mortality are higher among men (10, 11). Compared with men, women experience worse post-stroke functional and quality-of-life outcomes, which is partially explained by their older age at stroke onset and greater stroke severity (12).

Several studies reported that the female sex was an independent predictor of post-stroke cognitive impairment (CI) (13–17). The female sex has been also associated with both worse pre-stroke functioning and pre-stroke dementia (18, 19). In addition, women are more likely than men to experience post-stroke depression, which is a risk factor for cognitive decline, although the results are conflicting and age-related (20, 21). A variable proportion of patients after a lacunar stroke had been reported to have CI of any severity (mild cognitive impairment or dementia), ranging from 24 to 47%, with most of the studies referring to early post-event assessment, which may be influenced by acute complications and interventions and may even be reversible to a certain extent (4, 22). There is still a lack of knowledge regarding sex differences in post-stroke cognitive outcomes in the long term, as studies are few and heterogeneous in their designs (16, 19). Therefore, we aimed to investigate sex effect on long-term outcomes in patients with clinical and MRI evidence of cerebral SVD who initially presented with first-ever lacunar stroke.

Methods

A cohort of consecutive patients with SVD hospital-treated for first-ever acute lacunar stroke and free of cognitive decline and depression was recruited and evaluated at the baseline, and then reevaluated 4 years after the qualifying event for the presence of CI in a single-center prospective study. Patients with pre-existing CI ($n = 12$), a severe motor deficit that precluded full neuropsychological assessment ($n = 13$), recurrent stroke during follow-up ($n = 18$), and lost for follow-up ($n = 9$) were not included in the final analysis. All patients underwent baseline brain MRI scanning per previously reported protocol (23, 24). Diagnosis of lacunar stroke was based on clinical and neuroimaging assessment. The functional, cognitive, and affective statuses were documented in all participants as described (23, 24). Standard neuropsychological testing was done in all patients at the baseline and at the follow-up, comprising the Mini-Mental State Examination (25), the Trail Making Test A and B (26), the Wisconsin Card Sorting Test (27), the Rey-Osterreith Complex Figure (28), the Rey Auditory Verbal Learning Test (29), the 60-item Boston Naming Test (30), and the Animal Naming Test (31). Standard age-, sex-, and/or education-adjusted norms were applied as appropriate. The neuropsychological battery is following the Neuropsychological Test Protocol proposed by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Decline Impairment Harmonization Standards (32). Instrumental Activities of Daily Living were documented in all patients (33). Only patients without recurrent stroke during the follow-up period were included in the study.

Baseline demographic data and vascular risk factors were compared between sexes. The admission NIH Stroke Scale (NIHSS) score was analyzed for all patients. Functional status was assessed using the modified Rankin Scale (mRS) score (23) at the recruitment. The patients with the lowest (0, $n = 8$) and highest (4, $n = 12$) mRS scores were excluded

TABLE 1 Demographic data and vascular risk factor distribution in all patients.

	Female ($n = 124$)	Male ($n = 150$)	All participants ($n = 274$)	p-value
Age (yrs.)	63.0 ± 11.0	62.6 ± 10.1	62.8 ± 10.4	0.932
Education (yrs.)	11.8 ± 2.0	11.9 ±2.4	11.9 ± 2.2	0.742
Hypertension	110 (88.7)	135 (90.0)	245 (89.4)	0.888
Diabetes mellitus	39 (31.4)	33 (22.0)	72 (26.3)	0.103
Hypercholesterolemia	101 (81.4)	127 (84.7)	228 (83.2)	0.584
Smoking	40 (32.2)	49 (32.7)	89 (32.5)	0.999
CAD	21 (16.9)	22 (14.7)	43 (15.7)	0.729
PAD	9 (7.3)	10 (6.7)	19 (6.9)	0.999
AF	10 (8.0)	13 (8.7)	23 (8.4)	0.999
Carotid stenosis >50%	10 (8.0)	9 (6.0)	19 (6.9)	0.663
Total number of risk factors	3.6 ± 1.4	3.5 ± 1.1	3.6 ± 1.2	0.932

Data are given as n, % or mean ± SD.
CAD, coronary artery disease; PAD, peripheral artery disease; AF, atrial fibrillation.

from the analysis to reduce study group heterogeneity in terms of stroke severity. During follow-up evaluation, patients were classified according to the findings of cognitive assessment as having: (1) normal cognitive status, (2) cognitive decline-no dementia, which included patients with evidence of a significant decline in at least one cognitive domain, but exclusion of dementia if impairment was not sufficiently severe to interfere with instrumental activities of daily living, or (3) vascular dementia with evidence of a significant decline in at least two cognitive domains and disturbance in instrumental activities of daily living, as reported before (23, 24). Data for patients with cognitive decline-no dementia and vascular dementia were jointly analyzed as CI. The presence of major depressive disorder was identified according to the DSM-IV criteria and patients were classified as depressed or not-depressed (34). The study has been approved by the Ethics Committee of the Clinical Center of Serbia and all patients consented to evaluation and follow-up.

Magnetic resonance imaging and image analysis

Baseline brain MRI, performed on the 1.5-T scanner (Siemens Avanto, Germany), was evaluated by a trained neurologist blinded to clinical data with two visual rating scales of the severity of cerebral white matter hyperintensities (WMH) of presumed vascular origin on fluid-attenuated inversion recovery (FLAIR) and T2*-weighted axial scans (35–37). The total score on the Age-Related White Matter Changes (ARWMC) scale (tARWMC) was used as a measure of the whole brain (WMH) load (35). Basic ARWMC scores were rated on a four-point scale for brain regions, including frontal, parieto-occipital, temporal, basal ganglia, and infratentorial areas bilaterally, and were then summed to obtain the tARWMC (23, 35). Therefore, the tARWMC score was applied as a measure of the whole brain WMH and lacunes load, with the score ranging from 0 (no lesions) to a maximum of 30 (23, 35). In addition, the Fazekas visual rating scale was used for separate assessment of periventricular (PV) and deep subcortical (DS) WMH in all participants on FLAIR axial images, with scores ranging from 0 (no lesions) to a maximum of 3 (36). We identified lacunes of presumed vascular origin on FLAIR and T2 axial images as focal hyperintense lesions with a diameter of 3–15 mm (23, 36, 37), and included the total number of lacunes in the analysis.

Statistical analysis

The normality of data distribution was tested by the Kolmogorov–Smirnov test, and data not normally distributed were presented as a median with an interquartile range. Statistical analysis comprised analysis of variance (ANOVA) for continuous variables and the Chi-squared test for categorical variables. In case of deviation from a normal distribution, a non-parametric Mann–Whitney U-test was used for testing differences between groups. Logistic regression analysis was used to compare data on clinical and MRI characteristics between sex groups. Multivariate logistic regression analysis was applied to identify independent parameters associated with the CI at follow-up, with risks shown as odds ratio (OR) estimated for each selected variable with a 95% confidence interval (95%CI). A value of $p < 0.05$ was considered statistically significant.

TABLE 2 Baseline clinical and neuroimaging characteristics of patient subgroups.

	Female ($n = 124$)	Male ($n = 150$)	All participants ($n = 274$)	p-value
NIHSS score, mean ± SD	6.6 ± 2.3	5.3 ± 2.3	5.9 ± 2.4	<0.0001
mRS, mean ± SD	2.5 ± 0.5	1.5 ± 0.6	2.0 ± 0.8	<0.0001
tARWMC scale score	15.9 ± 5.8	11.3 ± 4.8	13.4 ± 5.3	<0.0001
Fazekas PV score	3 (0–3)	2 (0–3)	2 (0–3)	<0.0001
Fazekas DS score	3 (1–3)	2 (0–3)	2 (0–3)	<0.0001
Number of lacunes, total	10.8 ± 3.9	8.2 ± 3.6	9.4.±3.90	<0.0001

Data are given as *n*, % or median (range) unless stated otherwise.
NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; tARWMC, total Age-Related White Matter Changes; PV, periventricular; DS, deep subcortical.

Results

The group consisted of 124 female (45.3%) and 150 male (54.7%) patients, with a mean age of 62.8 ± 10.4 years. Male and female groups did not differ regarding age ($p = 0.932$) and education ($p = 0.742$, Table 1). No difference was found in the frequency of vascular risk factors (Table 1). Furthermore, the total number of vascular risk factors was the same between groups ($p = 0.932$) (Table 1). Only a minority of patients ($n = 5$) were on hormone-replacement therapy for menopause.

The clinical presentation did not differ between sexes ($p =$ p.981), with most of the patients exhibiting pure motor stroke (76 or 61.2% in women vs. 99 or 66.0% in men), followed up by sensorimotor stroke (17 or 13.7% in women and 26 or 17.3% in men) and ataxic hemiparesis (12 or 9.7% in women and 13 or 8.7% in men), while the rest of the patients experienced a pure sensory stroke, dysarthria clumsy hand syndrome, and atypical lacunar syndrome. At the baseline, women had more severe strokes than men with an admission NIHSS score of 6.6 compared to 5.3 in men ($p < 0.0001$, Table 1). In addition, the mean mRS was also higher in women (2.5) compared to men (1.5) ($p < 0.0001$, Table 1). All measures of SVD-related lesions on MRI scans were more severe in female patients, including tARWMC score, Fazekas PV and DS scores, and the total number of lacunes ($p < 0.0001$ for all, Table 2).

A follow-up assessment was performed after a mean time of 47.4 ± 6.9 months, with no difference between sexes in the time of reassessment ($p = 0.764$). On follow-up, no difference in depression rate was detected between sexes (45 or 37.2% depressed female patients vs. 61 or 40.7% male patients, $p = 0.791$). Overall, any CI was detected in 177 or 64.6% of stroke survivors, more frequently in women than men (96 or 77.4% of female patients vs. 81 or 54.0% of male patients, $p < 0.0001$) (Figure 1). A total of 46 (37.1%) female patients met the criteria for diagnosis of dementia, and only 12 (8.0%) male patients (Figure 1). In patients with CI on follow-up, the most frequently affected cognitive domains were: attention (in 96 or all female and 76 or 93.8% male patients), processing speed (in 92 or 95.8% female and 78 or 96.3% of male patients), executive functions (in 86 or 89.6% female and 57 or 70.4% male patients), and visuospatial functions (in 57 or 59.4% female and 34 or 42.0% male patients), followed by memory (25 or 26.0% female and 5 or 6.2% male patients) and language (14 or 14.6% female and 1 or 1.2% male patients). The decline in global cognitive functioning was detected in 49 (51.0%) female patients and 9 (11.1%) male patients with CI.

Univariate regression analysis adjusted for age and vascular risk factors indicated that female sex, presence of depression, baseline total number of lacunes, and initial overall severity of WMH (tARWMC scale score, Fazekas PV, and Fazekas DS scores) were significantly associated with CI at follow-up (Table 3). Multivariate regression analysis adjusted for age and vascular risk factors revealed variables independently associated with the female sex in patients with SVD: depression with OR 1.74 (95%CI 1.25–2.44; $p = 0.0001$) and tARWMC with OR 1.30 (95%CI 1.03–1.17); $p = 0.004$ (Table 4).

Discussion

In this prospective study of patients with first-ever lacunar stroke and imaging evidence of SVD but with normal cognitive status, more than half (64.6%) of surviving patients met the criteria for CI 4 years after the qualifying event, likely as a predictor of subcortical vascular dementia in the medium-long term. Patients with CI were more frequently women, with more severe baseline strokes, more disability after stroke, and more advanced cerebral SVD lesions according to the MRI-based scoring systems. At the baseline assessment, after the initial lacunar stroke in our cohort, sex differences were noted, with female patients having a more severe functional impairment and more extensive baseline MRI markers of SVD, including both WMH and the number of lacunes of presumed vascular origin. After a mean follow-up of 4 years, a significant difference in cognitive status between sexes was detected, with evidence for CI being significantly more frequent in women than men. These

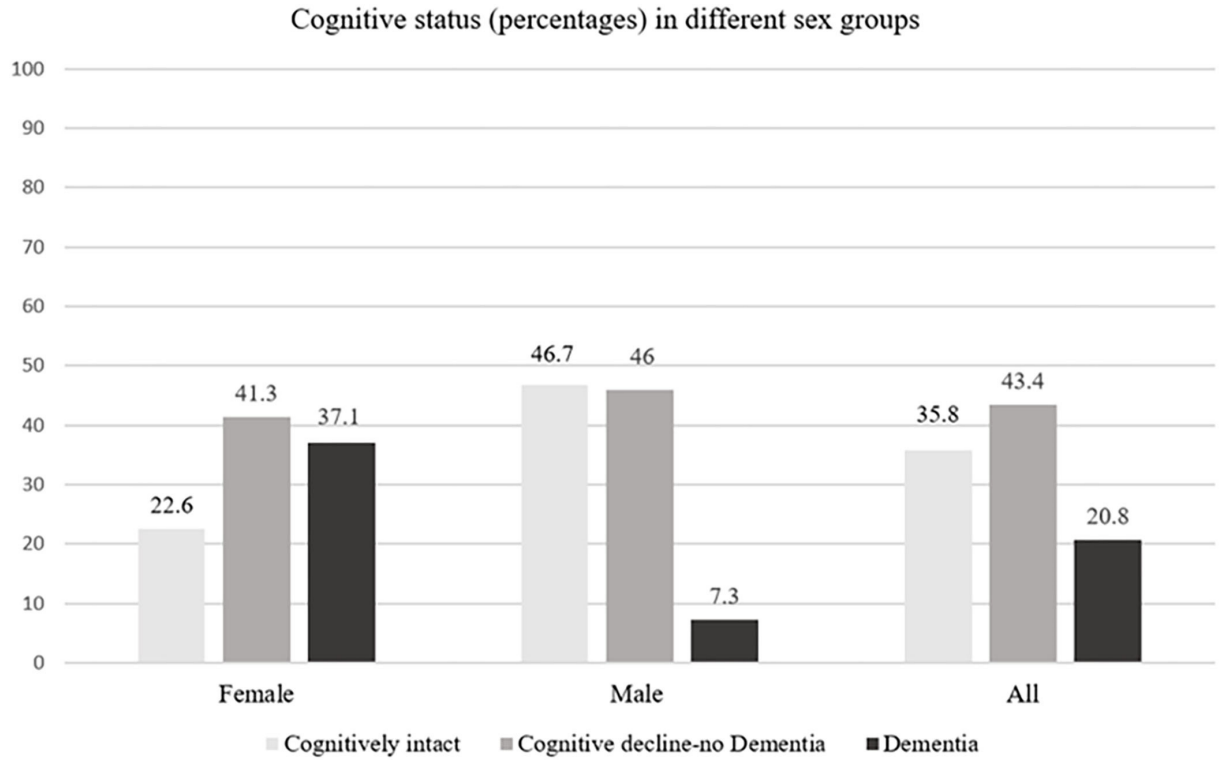

FIGURE 1
Distribution of cognitive status in female patients, male patients, and all patients with SVD.

sex disparities could not be explained by differences in common vascular risk factors or age but were independently associated with the occurrence of depression and the burden of WMH of presumed vascular origin.

There is increasing evidence of sex-specific differences in stroke symptoms, diagnosis, treatment, and preventive strategies (10, 11, 38). Currently, specific recommendations for the prevention and management of stroke in women are available (39, 40). Although sex-specific differences in common vascular risk factors have been recognized, this was not observed in our cohort of patients nor was any particular risk factor associated with cognitive outcome (39, 41, 42). Other possible factors adding to the risk of SVD and cognitive outcomes, such as serum homocysteine levels, immunological or inflammation markers, blood pressure variability, and the influence of genetic factors, were not assessed in this study. Sex-hormone influence may be less relevant in this post-menopausal population (female patients' mean age was 62.5 years) and only a minority of patients were on the hormone-replacement treatment (40).

Cognitive impairment appears to be common after lacunar strokes despite their small size, suggesting that underlying SVD may increase their impact (4, 7, 43). Cerebral SVD burden has been strongly associated with post-stroke cognitive and functional outcomes (44, 45). Most studies have been focusing on the early post-stroke period but also indicating that women more frequently than men experienced cognitive deficits (16). In the Health and Retirement Study, Bako et al. detected a significant short-term acceleration of cognitive decline for the overall population (4.2 percentage points) and among female participants (5.0 percentage points), but no evidence of long-term acceleration of the cognitive decline after stroke was noted (16). We found a significant association between medium-to-long-term CI and the female sex, which is in accordance with studies reporting female sex was an independent predictor of post-stroke CI (13–15), although there are conflicting results as well (46–48). In their systematic review and meta-analysis, Pendlebury and Rothwell indicated that the female sex was confounded by age and was strongly associated rather with pre-stroke than with post-stroke dementia (18). In a prospective follow-up of 1,227 patients surviving a first-ever ischemic stroke or intracerebral hemorrhage, at 90 days after stroke, women had worse cognitive outcomes than men, with differences attributed to sociodemographic and pre-stroke characteristics (19). The rates of dementia were lower than in our study with 27.6% for men and 35.6% for women with an unadjusted odds ratio of dementia comparing women with men of 1.45, but the follow-up assessment in our study was done much later (19).

TABLE 3 Variables associated with CI at follow-up; univariate logistic regression analysis adjusted for age and vascular risk factors.

	OR (95% CI)	*p*-value
Female sex	1.44 (1.07–1.94)	0.015
mRS	1.14 (0.95–1.36)	0.163
NIHSS	1.02 (0.96–1.08)	0.591
Depression	2.09 (1.54–2.82)	<0.0001
Number of lacunes	1.07 (1.04–1.11)	<0.0001
tARWMC scale score	1.08 (1.01–1.0.16)	0.046
Fazekas PV score	1.34 1.17–1.53	<0.0001
Fazekas DS score	1.67 (1.34–2.08)	<0.0001

OR, odds ratio; mRS, modified Rankin Scale; tARWMC, total Age-Related White Matter Changes; PV, periventricular; DS, deep subcortical.

TABLE 4 Variables associated with CI at follow-up; multivariate logistic regression analysis adjusted for age and vascular risk factors.

	OR (95% CI)	*p*-value
Depression	1.74 (1.25–2.44)	0.001
tARWMC scale score	1.10 (1.03–1.17)	0.004

OR, odds ratio, tARWMC, total Age-Related White Matter Changes.

Andersen et al. also did not find evidence of a sex modifier for vascular dementia, in contrast to the female predominance of Alzheimer's type of dementia (49). Preexisting degenerative pathology may be more frequent in female stroke survivors developing cognitive impairment post-stroke (50), but none of our patients met the criteria for other types of dementia on follow-up assessment. Similarly, the increased burden of vascular changes attributable to SVD registered in our study in female patients compared to male participants led to an increased risk for CI. Interestingly, in our dataset of patients, the co-existence of depression was independently associated with the occurrence of CI post-lacunar stroke. Female stroke survivors may be facing additional challenges of post-stroke depression and unmet social needs, such as living alone or being a caregiver themselves before the stroke (19, 21, 24, 51–53). We were not able to determine the exact onset of depressive symptoms in our patients, and could not conclude whether depression preceded cognitive decline or developed as a parallel trajectory. Although cognitive trajectories post-stroke have been well-described, there is a need to increase our knowledge of affective status trajectories post-stroke, in patients with SVD in particular (54, 55). The presence of both cognitive and mood deterioration in patients with SVD may be indicative of a more severe vascular burden, as was the case in our study. Unfortunately, we did not control for other potential confounders, such as major life stressors and socioeconomic status (54, 55).

The impact of stroke subtypes on cognitive outcomes has been rarely studied, particularly in a long-term setting. Although lacunar strokes are considered a leading cause of vascular CI and vascular dementia, in a meta-analysis by Makin and co-workers, there were no differences in the proportion of patients with CI after lacunar and non-lacunar strokes (4). Corriani and co-workers examined the long-term risk of dementia among survivors of incident stroke of any type and recorded high rates of CI among survivors of hemorrhagic stroke comprising intracerebral and subarachnoid hemorrhage (56). In our study, all MRI markers of SVD were more severe in female than in male patients. This is in accordance with the Rotterdam Scan Study reporting tendency for women to have more severe WMH of presumed vascular origin (57) but also the more marked progression of subcortical WMH and incident lacunar infarcts compared with men (58). Similar were the findings of the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study (59, 60). Contrary to this, in a recent cross-sectional study, male sex was significantly and independently associated with the proposed total SVD score which combines individual MRI features of the SVD in one measure (61). A possible explanation for these sex differences was that postmenopausal estrogen reduction might make the female brain more vulnerable by reduction of cerebral blood flow and ischemia (62), but mechanisms are still largely unknown. In a community-based cohort followed up for 9 years, women with migraine had a higher incidence of deep white matter hyperintensities but did not have significantly higher progression of other MRI-measured brain changes (63). We did not analyze the data on the frequency of migraine in our patients or hormonal status. Overall, differences in common risk factors could not explain differences in WMH severity between sexes in our study.

Our female patients with SVD and lacunar stroke had on average mild to moderate disability compared to men who were significantly less disabled (mean mRS 2.5 in women, 1.5 in men). Most studies have indicated that stroke is more severe in women than in men, although this finding has been confounded by age (64–68). A subanalysis of the Framingham Heart Study showed that women were more disabled and 3.5 times as likely to be institutionalized at 3–6 months post-stroke compared with men, even in the first-ever stroke cases present in our study (69). After adjustment for cardiovascular risk profile, socioeconomic status, and age, stroke remained more severe in women in a study by Dehlendorff et al. (70). Lacunar stroke severity and outcome have been reported to be similar in men and women in some cohorts, while others documented a higher admission NIHSS in women compared to men (41, 68). The other possible explanation for the sex difference in functional outcome could also be related to the pre-stroke functional status, which appeared lower in women, and possibly differences in acute lacunar stroke location and volume which we did not analyze (68, 71). However, our findings are associated with a

higher burden of pre-existing SVD in female patients compared to male patients with the cognitive outcome, which may be reflected in the functional score (mRS) as well.

There are several limitations to our study, comprising the size of the cohort, lack of monitoring for other imaging markers of SVD, such as cerebral microbleeds, perivascular spaces, and cerebral atrophy, single-center design, and engagement of a single though blinded MRI reader (72, 73). In addition, we did not analyze other confounding factors, such as the impact of the medications used by our patients or the development of new comorbidities, including the occurrence of new vascular risk factors during the follow-up period. However, we focused on a very well-defined cohort of a particular stroke subtype patients experiencing lacunar stroke and performed a close long-term follow-up to understand specific stroke subtype influence on cognitive outcome. Our findings have clinical implications of keeping in focus cognitive outcome even in long-term post-acute lacunar stroke to detect early susceptible patients, and in identifying a subgroup of post-lacunar stroke patients particularly prone to developing cognitive decline. The optimal management of post-stroke CI remains controversial both in general terms as well as regarding the sex differences in interventions for its prevention and treatment (51, 74).

Conclusion

The female sex is associated with more severe vascular brain lesions secondary to SVD and cognitive deterioration long-term after acute lacunar stroke. The independent predictors of cognitive decline were the co-existence of depression and the severity of vascular WM changes. Mechanisms of these differences are beyond common vascular risk factors and are still to be explained. The cognitive outcome as well as affective status post-lacunar stroke should be actively monitored even in the long term, in women particularly, and could be a signal of more severe underlying SVD markers on neuroimaging.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Clinical Center of Serbia, Belgrade, Serbia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AP designed the study, conducted research, and wrote the paper. TP performed the statistical analysis and contributed to the writing of the paper. MM, GT, and JZ contributed to the research and writing of the paper. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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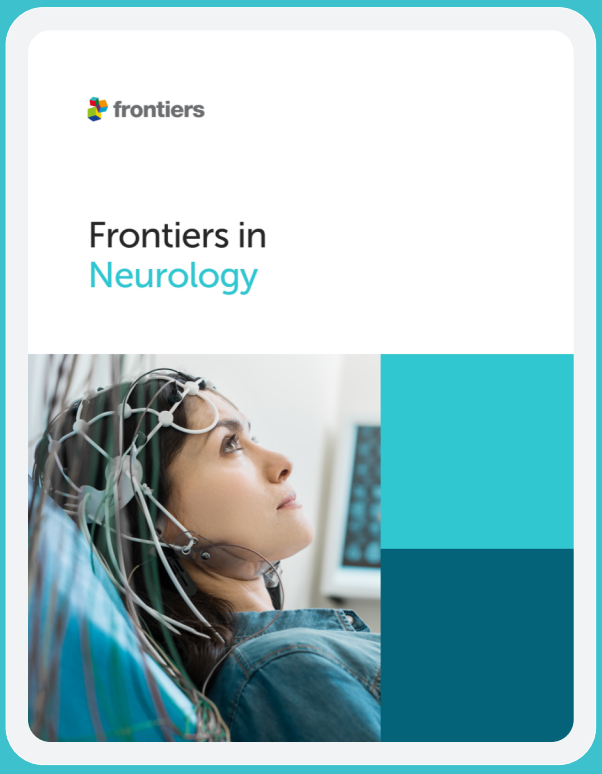

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