

# Female- and Male-Specific Risk Factors for Stroke

## A Systematic Review and Meta-analysis

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**IMPORTANCE** The incidence of stroke is higher in men than in women. The influence of sex-specific risk factors on stroke incidence and mortality is largely unknown.

**OBJECTIVE** To conduct a systematic review and meta-analysis of female- and male-specific risk factors for stroke.

**DATA SOURCES** PubMed, EMBASE, and the bibliographies of articles were searched for studies published between January 1, 1985, and January 26, 2015, reporting on the association between female- and male-specific characteristics and stroke.

**STUDY SELECTION** Observational studies reporting associations between sex-specific risk factors and stroke were selected.

**DATA EXTRACTION AND SYNTHESIS** Two authors performed data extraction independently. Estimates were pooled with a generic variance-based, random-effects method. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations. In addition, our study adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.


**MAIN OUTCOMES AND MEASURES** Ischemic stroke, hemorrhagic stroke, any stroke, and stroke mortality.

**RESULTS** This systematic review and meta-analysis included 78 studies (70 longitudinal and 8 case-control) comprising 10 187 540 persons. In women, the pooled relative risks of ischemic stroke were 1.80 (95% CI, 1.49-2.18) after any hypertensive disorder in pregnancy (HDP) (gestational hypertension [GH], preeclampsia, or eclampsia) and 1.81 (95% CI, 1.44-2.27) after GH vs no HDP. The pooled relative risks of hemorrhagic stroke were 2.24 (95% CI, 1.19-4.21) in women with menopause at the age of at least 55 years vs 50 to 54 years and 5.08 (95% CI, 1.80-14.34) after GH vs no GH. The pooled relative risks of any stroke were 1.42 (95% CI, 1.34-1.50) after oophorectomy vs no oophorectomy, 0.88 (95% CI, 0.85-0.90) after hysterectomy vs no hysterectomy, 1.63 (95% CI, 1.52-1.75) after any vs no HDP, 1.54 (95% CI, 1.39-1.70) after preeclampsia or eclampsia, 1.51 (95% CI, 1.27-1.80) after GH vs no HDP, 1.62 (95% CI, 1.46-1.79) after preterm delivery, and 1.86 (95% CI, 1.15-3.02) after stillbirth vs no pregnancy complications. The pooled relative risk of stroke mortality was 1.57 (95% CI, 1.04-2.39) after GH vs no GH. In men, the pooled relative risks of ischemic stroke were 1.19 (95% CI, 1.05-1.34) after androgen deprivation therapy (ADT) vs no ADT and 1.21 (95% CI, 1.00-1.46) after orchiectomy vs no orchiectomy. The pooled relative risks of any stroke were 1.21 (95% CI, 1.06-1.37) for ADT vs no ADT and 1.35 (95% CI, 1.18-1.53) for erectile dysfunction vs no dysfunction.

**CONCLUSIONS AND RELEVANCE** Female-specific characteristics increasing stroke risk include HDP for ischemic stroke, late menopause and gestational hypertension for hemorrhagic stroke, and oophorectomy, HDP, preterm delivery, and stillbirth for any stroke. Hysterectomy is possibly protective against any stroke. Male-specific characteristics increasing stroke risk include medical androgen deprivation therapy for ischemic and any stroke and erectile dysfunction for any stroke. Consideration of sex-specific risk factors can improve individualized stroke risk assessment.

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The incidence of stroke is higher in men than in women,<sup>1</sup> but this difference attenuates with increasing age.<sup>2,3</sup> Established risk factors for stroke, such as hypertension, current cigarette smoking, and ischemic heart disease, are more prevalent among men but only partly explain the difference in stroke incidence.<sup>1</sup> Current use of oral contraceptives increases the risk of ischemic stroke<sup>4</sup> and subarachnoid hemorrhage,<sup>5</sup> but it is not associated with an increased risk of intracerebral hemorrhage.<sup>4</sup> The risk of ischemic stroke is increased among users of single-agent and combination hormone therapy.<sup>6</sup> To date, the influence of sex-specific risk factors other than oral contraceptive use or hormone therapy has received little attention relative to the risk of stroke. Consideration of risk factors unique to men or women can improve the accuracy of stroke risk assessment compared with current risk scores. We systematically reviewed the literature on female- and male-specific risk factors for ischemic and hemorrhagic stroke incidence and stroke mortality.

## Methods

### Search Strategy and Selection Criteria

We systematically searched PubMed, EMBASE, and the bibliographies of articles published between January 1, 1985, and January 26, 2015, for observational studies reporting on the association between female- and male-specific characteristics and the risk of ischemic stroke, hemorrhagic stroke, any stroke, and stroke mortality. Eligibility was restricted to studies published after 1985 because of the widespread availability of brain imaging techniques from that year onward. Studies on hormone therapy and hormonal contraceptive use were not included in this review article because their relationship with stroke has been investigated extensively.<sup>4,6</sup> We included the following characteristics associated with female sex: menarche, menstrual cycle, polycystic ovarian syndrome, duration of reproductive period, menopause, climacteric symptoms, reproductive history, estradiol levels, sex hormone-binding globulin levels, pregnancy, gravidity, parity, breastfeeding, recurrent miscarriages, intrauterine growth retardation, preterm delivery, stillbirth, spontaneous abortion, induced abortion, gestational diabetes, gestational hypertension (GH), preeclampsia, eclampsia, ovarian hyperstimulation, in vitro fertilization, oophorectomy with or without hysterectomy, hysterectomy, subfertility, and breast vascular calcifications. We included the following characteristics associated with male sex: erectile dysfunction, testosterone levels, dihydrotestosterone levels, estradiol levels, sex hormone-binding globulin levels, androstenediol glucuronide levels, testosterone therapy, androgen deficiency, androgen deprivation therapy (ADT), orchiectomy, haplotype Y chromosome, and cryptorchidism. Finally, we also included characteristics of transgender hormone use and sex reassignment surgery. We used risk factor definitions and categories from the individual publications.

The outcome events of interest were (1) ischemic stroke, (2) hemorrhagic stroke, (3) any stroke, and (4) stroke mortality. The assessment of outcome events was based on medical

## Key Points

**Question** What are sex-specific characteristics that influence the risk of ischemic stroke, hemorrhagic stroke, any stroke, or stroke mortality?

**Findings** In this systematic review and meta-analysis, female-specific characteristics associated with increased stroke risk included hypertensive disorders of pregnancy for ischemic stroke, late menopause and gestational hypertension for hemorrhagic stroke, and oophorectomy and various pregnancy complications for any stroke; hysterectomy might be a protective factor against any stroke. Male-specific risk factors were low induced testosterone levels for ischemic stroke and any stroke and erectile dysfunction for any stroke.

**Meaning** The accuracy of risk assessment of stroke can be improved by adding female- and male-specific protective or risk factors to risk scores.

records or *International Classification of Diseases (ICD)* codes for stroke. If possible, we estimated the risk of ischemic stroke without transient ischemic attack and the risk of hemorrhagic stroke without subarachnoid hemorrhage.

A detailed search query is provided in the eAppendix in the Supplement. We cross-checked the bibliographies of included articles and review articles to identify additional studies until we could identify no further studies. We applied no language restrictions.

We used the following 6 criteria for inclusion: (1) Articles had to have a case-control, longitudinal, or case-crossover design. (2) Studies reporting crude or adjusted effect estimates with corresponding 95% CIs or results allowed calculation of risk ratios or odds ratios (ORs). (3) For longitudinal studies, the diagnosis was based on review of medical records or on ICD codes for stroke. (4) For hospital-based case-control studies, stroke diagnosis was based on medical records (in which case diagnosis had to be confirmed in  $\geq 90\%$  of the cases by neuroimaging) or on ICD codes for stroke. (5) The occurrence of stroke was not during pregnancy or the puerperium. (6) The occurrence of stroke was not a consequence of a sex-specific type of cancer.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.<sup>7</sup> In addition, our study adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.<sup>8</sup>

### Selection of Studies and Data Extraction

One author (M.H.F.P.) screened titles and abstracts for eligible studies and subsequently reviewed full-text versions of the potentially eligible studies. In case of doubt, studies were discussed in consensus meetings with 2 other authors (A.M.A. and C.J.M.K.). If multiple publications originated from the same center or population, we included the study with the largest sample size. Two authors (M.H.F.P. and A.M.A.) independently extracted the relevant data from included studies and completed data extraction forms. We collected data on study period, study design, setting, size of the study population, stroke diagnosis criteria, case-finding methods, assessment of

exposure, sex-specific characteristics of interest, risk estimates, and adjustment factors. If necessary, we asked the authors to provide us with additional unpublished data. Any discrepancies in extracted data between the 2 reviewers were resolved in consensus meetings with 3 of the authors (M.H.F.P., A.M.A., and C.J.M.K.).

### Statistical Analysis

For each included study, we obtained risk ratios, ORs, or hazard ratios (HRs) with 95% CIs for the various female- and male-specific characteristics. Risk estimates greater than 1 indicate an increased risk of the defined outcome, and risk estimates less than 1 indicate a decreased risk of the defined outcome. We assessed statistical significance using the 95% CIs. If the 95% CI did not include the neutral value 1, we considered the risk statistically significant.

To compare the data from different studies, definitions and cutoffs of risk factors were harmonized between studies whenever possible. We pooled estimates using a generic variance-based, random-effects method, weighting individual study results by the inverse of their variance. Heterogeneity was assessed with  $\chi^2$  statistics, and we considered results heterogeneous at  $P < .10$ . Our primary analyses focused on female- and male-specific characteristics for the risk of ischemic and hemorrhagic stroke separately. Secondary analyses were based on studies reporting any type of stroke. Tertiary analyses were based on studies reporting stroke mortality. We combined estimates from case-control studies and longitudinal studies and used the most adjusted estimate available per study because we considered adjusted estimates to be the most valid.

## Results

After screening 7819 publications, we identified 78 eligible studies (eFigure 1 and eTable 1 in the [Supplement](#)), comprising 10 187 540 persons. Seventy studies had a longitudinal design, and 8 studies had a case-control design. The assessment of stroke as an outcome event was based on medical records in 28 studies and on ICD classification codes in 50 studies (eTable 2 in the [Supplement](#)). Characteristics of included studies are listed in eTable 3 in the [Supplement](#), and an overview of adjustment factors is summarized in eTable 4 in the [Supplement](#). Risk factors that could be pooled are shown at the top of eFigures 2, 3, 4, 5, and 6 in the [Supplement](#). Individual risk factors that could not be included in meta-analyses are shown at the bottom of the figures.

### Female-Specific Risk Factors for Ischemic Stroke

With age at natural menopause between 50 and 54 years taken as the reference, the pooled relative risks (RRs) of ischemic stroke for age at natural menopause were 0.72 (95% CI, 0.46-1.12) for 55 years or older, 1.09 (95% CI, 0.87-1.37) for 45 to 49 years, 0.97 (95% CI, 0.52-1.78) for 40 to 44 years, and 0.90 (95% CI, 0.22-3.74) for younger than 40 years (eFigure 2 in the [Supplement](#), top). The pooled RRs were 1.80 (95% CI, 1.49-2.18) in women with a history of any hypertensive disorder in

pregnancy (HDP) (GH, preeclampsia, or eclampsia), 1.34 (95% CI, 0.95-1.89) in women with a history of preeclampsia or eclampsia, and 1.81 (95% CI, 1.44-2.27) in women with a history of GH vs no HDP. We found statistically significant heterogeneity for GH ( $P = .04$  for heterogeneity) (eTable 5 in the [Supplement](#)).

Several studies provided data on female risk factors for ischemic stroke that could not be pooled (eFigure 2 in the [Supplement](#), bottom). One study<sup>9</sup> found an increased risk of ischemic stroke in women with a reproductive period of less than 34 vs 34 years or longer. The same study<sup>9</sup> reported a decreased risk of ischemic stroke in women with a reproductive period of more than 40 vs less than 34 years. Another study<sup>10</sup> found that women with parity categories of 3, 4, and 5 or more were at an increased risk of ischemic stroke vs women in parity category 2, while there was an increased risk of ischemic stroke in women with parity categories of 1 or 0 vs 2. Finally, a study<sup>11</sup> found an increased risk of ischemic stroke in women with vascular calcifications in breast tissue vs no calcifications.

### Female-Specific Risk Factors for Hemorrhagic Stroke

With age at natural menopause between 50 and 54 years taken as the reference, the pooled RRs of hemorrhagic stroke for age at natural menopause were 2.24 (95% CI, 1.19-4.21) at 55 years or older and 1.16 (95% CI, 0.72-1.87) at 45 to 49 years (eFigure 3 in the [Supplement](#), top). The pooled RR of hemorrhagic stroke in women with a history of GH was 5.08 (95% CI, 1.80-14.34) vs no GH. We observed no statistically significant heterogeneity (eTable 5 in the [Supplement](#)).

Several studies provided data on female risk factors for hemorrhagic stroke that could not be pooled (eFigure 3 in the [Supplement](#), bottom). One study<sup>12</sup> found a decreased risk of hemorrhagic stroke in women with menarche at age 16 to 17 vs 14 years or younger and in women with menarche at the age of at least 18 vs 14 years or younger. Another study<sup>10</sup> found that women with parity categories of 3, 4, and 5 or more were at increased risk of hemorrhagic stroke vs women in parity category 2. In the same study,<sup>10</sup> an increased risk of hemorrhagic stroke was found in women with parity categories of 1 or 0 vs 2.

### Female-Specific Risk Factors for Any Stroke and Stroke Mortality

With age at natural menopause between 50 and 54 years taken as the reference, the pooled RRs of any stroke for age at natural menopause were 0.91 (95% CI, 0.67-1.23) at 55 years or older, 1.11 (95% CI, 0.93-1.31) at 45 to 49 years, 0.95 (95% CI, 0.69-1.30) at 40 to 44 years, and 0.86 (95% CI, 0.42-1.74) at younger than 40 years (eFigure 4 in the [Supplement](#), top). The pooled RRs of any stroke in women who underwent oophorectomy vs no oophorectomy were 1.42 (95% CI, 1.34-1.50) and 0.88 (95% CI, 0.85-0.90) in women who underwent hysterectomy vs no hysterectomy. The pooled RRs of any stroke were 1.63 (95% CI, 1.52-1.75) in women with a history of any HDP, 1.54 (95% CI, 1.39-1.70) in women with a history of preeclampsia or eclampsia, and 1.51 (95% CI, 1.27-1.80) in women with a history of GH vs no HDP. The pooled RRs of any stroke were

1.62 (95% CI, 1.46-1.79) in women with a history of preterm delivery, 1.86 (95% CI, 1.15-3.02) in women with a history of stillbirth, and 1.25 (95% CI, 0.95-1.63) in women with a history of spontaneous abortion vs no pregnancy complications. We found statistically significant heterogeneity for the following risk factors: oophorectomy ( $P < .001$  for heterogeneity), hysterectomy ( $P = .004$  for heterogeneity), preeclampsia or eclampsia ( $P = .04$  for heterogeneity), and history of spontaneous abortion ( $P = .02$  for heterogeneity) (eTable 5 in the Supplement).

Several studies provided data on female risk factors for any stroke that could not be pooled (eFigure 4 in the Supplement, bottom). One study<sup>10</sup> found an increased risk of any stroke in women with parity categories of 3, 4, and 5 or more vs 2, while an increased risk of any stroke was found among women with parity categories of 1 or 0 vs 2. Another study<sup>13</sup> found an increased risk of any stroke in women with 4 or 5 or more pregnancies vs 1 pregnancy.

With age at natural menopause between 50 and 54 years taken as the reference, the pooled RRs of stroke mortality for age at natural menopause were 0.77 (95% CI, 0.47-1.25) at 55 years or older, 1.02 (95% CI, 0.94-1.11) at 45 to 49 years, 0.97 (95% CI, 0.85-1.10) at 40 to 44 years, and 1.54 (95% CI, 0.89-2.66) at younger than 40 years (eFigure 6 in the Supplement). The pooled RRs of stroke mortality were 0.99 (95% CI, 0.91-1.07) in women who underwent oophorectomy vs no oophorectomy and 1.57 (95% CI, 1.04-2.39) in women with a history of GH vs no GH. We found no statistically significant heterogeneity (eTable 5 in the Supplement). An overview of female-specific risk factors for stroke mortality is shown in eFigure 6 in the Supplement.

### Male-Specific Risk Factors for Ischemic Stroke

The pooled RRs of ischemic stroke in men were 1.19 (95% CI, 1.05-1.34) in those treated with medical ADT vs no ADT and 1.21 (95% CI, 1.00-1.46) in those who underwent orchiectomy vs no orchiectomy (eFigure 5 in the Supplement). We found statistically significant heterogeneity for orchiectomy ( $P = .05$  for heterogeneity) (eTable 5 in the Supplement). Findings from an individual study<sup>14</sup> included a decreased risk of ischemic stroke after testosterone therapy, with a RR of 0.42 (95% CI, 0.29-0.59).

### Male-Specific Risk Factors for Hemorrhagic Stroke

The available data did not allow us to pool estimates of male-specific risk factors for hemorrhagic stroke. Findings from individual studies are shown in eFigure 5 in the Supplement.

### Male-Specific Risk Factors for Any Stroke and Stroke Mortality

The pooled RR of any stroke in men treated with medical ADT vs no ADT was 1.21 (95% CI, 1.06-1.37) (eFigure 5 in the Supplement). The pooled RR of any stroke in men with erectile dysfunction vs no dysfunction was 1.35 (95% CI, 1.18-1.53). We found no statistically significant heterogeneity (eTable 5 in the Supplement). Findings from an individual study<sup>15</sup> included an increased risk of any stroke in men with the lowest quartile of total testosterone levels vs the upper 3 quartiles and an in-

creased risk of any stroke in men with the lowest quartile of free testosterone levels vs the upper 3 quartiles.

The available data did not allow us to pool estimates of male-specific risk factors for stroke mortality (eFigure 6 in the Supplement). Findings from an individual study<sup>16</sup> included no association between testosterone levels and stroke mortality and no association between androstenediol glucuronide levels and stroke mortality.

## Discussion

The data from our systematic review and meta-analysis indicate that HDP increase the risk of ischemic stroke. In women with late menopause or a history of gestational hypertension, we found an increased risk of hemorrhagic stroke. Oophorectomy, HDP, and pregnancy complications increase the risk of any stroke, whereas hysterectomy possibly reduces the risk of any stroke. We found an increased risk of ischemic stroke and of any stroke in men treated with medical ADT and an increased risk of any stroke in men with erectile dysfunction.

Our findings are consistent with a previous study<sup>17</sup> that showed an increased risk of cardiovascular events after preeclampsia or eclampsia. The basis of the association between HDP and stroke, or cardiovascular disease in general, is not fully understood, but several possible theories have been proposed. For instance, it has been hypothesized that HDP and stroke have shared risk factors, such as hypertension and dyslipidemia, or that they may share genetic risk factors.<sup>18</sup> Alternatively, the cardiovascular abnormalities resulting from HDP may persist in the long term, although GH usually resolves by 12 weeks postpartum.<sup>19</sup> Finally, HDP may be a marker of vascular disease and unmask underlying cerebrovascular disease.<sup>18</sup> One study<sup>20</sup> identified spontaneous preterm delivery as an independent risk factor for cardiovascular disease despite substantial between-study heterogeneity, and another study<sup>21</sup> found an increased risk of coronary heart disease in women with a history of spontaneous abortion, with little between-study heterogeneity. In our systematic review and meta-analysis, a history of spontaneous preterm delivery and a history of stillbirth increased the risk of any stroke. A history of spontaneous abortion was not associated with the risk of any stroke, although the pooled estimate was in the direction of an increased risk.

The relationship of the duration of exposure to endogenous estrogens with cardiovascular disease and cardiovascular disease mortality has been investigated extensively.<sup>22-24</sup> One study<sup>23</sup> found an increased risk of cardiovascular morbidity in women with early menarche (<12 years), whereas another study<sup>22</sup> found no difference between the earliest vs the median menarcheal age groups with respect to death from cardiovascular disease and death from stroke. In our systematic review and meta-analysis, we found an increased risk of hemorrhagic stroke in women with age at natural menopause of 55 years or older but no association between age at natural menopause and ischemic stroke, any stroke, or stroke mortality. We do not have an explanation for these discrepancies, although heterogeneity in definitions of age categories and ref-



erence groups for natural menopause, age at menarche, and reproductive period may hamper appropriate interpretation of the data. The finding that late age at natural menopause increases the risk of hemorrhagic stroke has not been reported before, to our knowledge.

An increased risk of cardiovascular disease has been described in women with premature ovarian insufficiency.<sup>24</sup> In contrast, exogenous hormones (oral contraceptive use and hormone therapy) have been shown to increase risk of ischemic stroke. In the present systematic review and meta-analysis, we report that oophorectomy was associated with an increased long-term stroke risk. However, this finding was predominantly driven by a single study<sup>25</sup> in women younger than 50 years undergoing oophorectomy, and we were unable to adjust for possible confounders. Similarly, the finding that hysterectomy is associated with a decreased risk of long-term stroke risk was driven by just one study<sup>25</sup> with an unadjusted risk estimate. In the original study,<sup>25</sup> the authors adjusted for the co-occurrence of oophorectomy and hysterectomy and found, in contrast to our self-estimated risk, that in women younger than 50 years, hysterectomy increased the risk of long-term stroke and that oophorectomy at or before hysterectomy further increased this risk. After oophorectomy, patients enter menopause, and circulating endogenous hormones (estrogens and testosterone) decrease. Hysterectomy may result in premature ovarian failure by disruption of ovarian blood flow.

Similar to female hormones, the relationship of endogenous and exogenous male hormones with cardiovascular risk is complex. Two large prospective studies<sup>14,26</sup> found a higher risk of future cardiovascular disease in men receiving exogenous testosterone therapy. However, both studies have methodological limitations: one analyzed the data using a method that has not been validated, and the other compared preprescription and postprescription of testosterone.<sup>27</sup> In the present systematic review and meta-analysis, we found an increased risk of ischemic stroke and any stroke in men treated with medical ADT, as well as a suggestion that orchiectomy may also increase long-term risk of ischemic stroke. Results for medical ADT have to be interpreted with caution because of limited power due to differences in type and duration of ADT,<sup>28</sup> as well as the possibility of immortal time bias introduced by the method of selecting the exposure group. Men receiving gonadotropin-releasing hormone antagonists by injection are more often seen by physicians, which may lead to a higher incidence of the outcome measure. Moreover, the various types of medical ADT have different castrate levels of testosterone and different adverse effect profiles, including central obesity, lipid alteration, and insulin resistance. Such adverse effects may alter stroke risk. Finally, the association between ADT and stroke may be biased by physiological changes in patients with prostate cancer, specifically hypercoagulability.

Although endogenous serum total testosterone levels and serum free testosterone levels decrease with increasing age, termed the *andropause* by some authors,<sup>29-33</sup> other studies<sup>34,35</sup> found no association between endogenous serum total testosterone levels and ischemic stroke. No association between total dihydrotestosterone levels and

ischemic stroke was found, but an inverse relationship with free dihydrotestosterone levels was observed.<sup>35</sup> In contrast, a higher risk of any stroke has been described in men with low levels of total testosterone and low levels of free testosterone, and the risk of any stroke was decreased in men with high levels of total testosterone and high levels of calculated free testosterone.<sup>15,36</sup>

We found an increased risk of stroke in men with erectile dysfunction. Men with erectile dysfunction and cardiovascular disease share common risk factors, including diabetes, hypertension, hyperlipidemia, and physical inactivity, although erectile dysfunction also exists independent of systemic vascular disease.<sup>37</sup> Whether erectile dysfunction and stroke must both be considered as vascular complications due to atherosclerosis or whether other factors, such as hormonal and neural paths, contribute to the etiology of these diseases needs further investigation. The same holds true for the increased risk of ischemic stroke and breast vascular calcifications in women.<sup>11</sup>

### Limitations

This systematic review and meta-analysis has some limitations. In general, different biases should be considered in observational studies. The allocation of treatment is not random, which may lead to confounding by indication. Studies that did not adjust for age should be interpreted with caution because of changes in prevalence of age-related risk factors across the life span. In case-control studies, recall bias may have influenced results. In addition, comparability of the individual studies was hampered by the use of different definitions and various cutoffs of risk factors and heterogeneity in reference groups. Because of these differences in reference groups and outcome events, we were unable to pool almost half of the included risk factor data. To give a complete overview of all the included data, we have provided detailed analyses of individual risk factor data to reliably identify all potentially important effects on long-term stroke risk and outcome. Another limitation is that stroke diagnosis was based on ICD codes in 50 of the 78 included studies. These 50 studies were generally of lower quality than the studies that based case definition on medical records because the case definition is often a composite of different stroke subtypes. To make our review article as comprehensive as possible, we did not exclude these studies.

Frequently, risk estimates were based on a composite of the different types of stroke, sometimes including subarachnoid hemorrhage or transient ischemic attack (eTable 2 in the Supplement). Future research on sex-specific risk factors for stroke should apply clear and unequivocal definitions of risk factors, the reference groups, and the different types of stroke.

The main strength of our systematic review and meta-analysis is its extensive and comprehensive literature search and overview of all data, with most sources being longitudinal studies. To date, it provides the first systematic overview of female- and male-specific risk factors, besides hormone therapy and oral contraception, for ischemic stroke, hemorrhagic stroke, any stroke, and stroke mortality. In addition, by including studies with stroke diagnosis based

on ICD codes, we were able to provide a complete overview of female- and male-specific risk factors. In contrast to previous studies,<sup>20,24,38</sup> we distinguished between fatal and nonfatal events. In 2014, the guidelines for the prevention of stroke in women emphasized the need for more prospective research on risk factors specific to women, including pregnancy-related risk factors and changes in hormone status across the life span.<sup>39</sup> Consistent reporting of definitions is needed to improve future research for sex-specific risk factors. By summarizing and presenting both the pooled and individual findings from eligible published studies on risk factors that are unique to women and men, we have been able to strengthen the evidence for specific risk factors within patient groups.

## Conclusions

Female-specific characteristics that increase stroke risk include various pregnancy complications and oophorectomy. Hysterectomy was the only factor that was protective against any stroke. Male-specific risk factors for stroke are associated with low induced testosterone levels and erectile dysfunction. These sex-specific variables could be helpful in identifying specific patient groups with an increased risk of stroke, and individual risk factors should be considered in recommendations on primary prevention of stroke and in secondary prevention of stroke in patients with manifest cardiovascular disease.

## ARTICLE INFORMATION

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**Author Contributions:** Dr Klijn had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Poorthuis, A. Algra, Kappelle, Klijn.

**Acquisition, analysis, or interpretation of data:** Poorthuis, A. M. Algra, A. Algra, Klijn.

**Drafting of the manuscript:** Poorthuis, A. M. Algra.  
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**Administrative, technical, or material support:** A. M. Algra, Klijn.

**Study supervision:** A. Algra, Kappelle, Klijn.

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