Sex Differences in Stroke Epidemiology
A Systematic Review

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Background and Purpose—Epidemiological studies, mainly based on Western European surveys, have shown that stroke is more common in men than in women. In recent years, sex-specific data on stroke incidence, prevalence, subtypes, severity and case-fatality have become available from other parts of the world. The purpose of this article is to give a worldwide review on sex differences in stroke epidemiology.

Methods—We searched PubMed, tables-of-contents, review articles, and reference lists for community-based studies including information on sex differences. In some areas, such as secular trends, ischemic subtypes and stroke severity, noncommunity-based studies were also reviewed. Male/female ratios were calculated.

Results—We found 98 articles that contained relevant sex-specific information, including 59 incidence studies from 19 countries and 5 continents. The mean age at first-ever stroke was 68.6 years among men, and 72.9 years among women. Male stroke incidence rate was 33% higher and stroke prevalence was 41% higher than the female, with large variations between age bands and between populations. The incidence rates of brain infarction and intracerebral hemorrhage were higher among men, whereas the rate of subarachnoidal hemorrhage was higher among women, although this difference was not statistically significant. Stroke tended to be more severe in women, with a 1-month case fatality of 24.7% compared with 19.7% for men.

Conclusions—Worldwide, stroke is more common among men, but women are more severely ill. The mismatch between the sexes is larger than previously described. **(*Stroke*. 2009;40:1082-1090.)**

Key Words: stroke ■ epidemiology ■ sex ■ gender

A previous review article, mainly based on studies from Western Europe, showed that stroke incidence was about 30% higher in men than in women. For cerebral infarction the excess was 45%, whereas there was little difference between the sexes regarding intracerebral hemorrhage. For subarachnoidal hemorrhage, the relationship between the sexes was opposite, with a male deficit of about 50%.[1] Male patients are on average younger than female when they got their first stroke.[2] During recent years, a considerable number of articles have been published which add knowledge on epidemiological differences between the sexes in different parts of the world. The purpose of this review is to give an update on the current knowledge within this field. We have extended this review to also include data on stroke prevalence, severity, trends and case fatality, which hitherto have been given little attention in review articles.

Methods

We searched PubMed using the algorithms (incidence[ti] OR epidemiology[ti] OR prevalence[ti]) AND (cerebrovascular[ti] OR stroke[ti]); subtype[ti] AND (cerebrovascular[ti] OR stroke[ti]). We also used existing review articles on community-based incidence and prevalence studies,[3–11] as well as reference lists in articles. Furthermore, tables-of-contents in relevant journals have been scrutinized. The period of manual search reached from the year 2000 and lasted until the end of 2007, while the above mentioned review articles cover earlier periods. The names of the journals that were manually searched are listed in the supplemental Appendix (available online at http://stroke.ahajournals.org). The ambition was to include comparable community-based studies only.[3,12] The main criteria of such studies are: complete community-based case ascertainment, multiple overlapping sources, standard definition of stroke (WHO), first-ever strokes only, prospective design, all ages included, standard presentation (mid-decade age bands). All incidence studies (except one, see below) fulfilled these criteria. For prevalence studies, we required a community-based procedure using telephone interviews or questionnaires. Regarding stroke trends and ischemic subtypes, other studies than community-based have been accepted as well. When noncommunity-based studies have been referred to, this has been emphasized. Only articles in English have been included in this review.

Most results in this review are given as male/female (m/f) ratios (eg, incidence rate ratios and prevalence ratios). When calculating the overall age-standardized m/f ratios, it is not possible to divide the overall (all ages) male rate with the overall female rate because males and females have different age distributions. To obtain the total incidence rate ratio for each study, the male and female crude incidence rates have to be standardized to the age structure of the total (male+female) population. In our case, standardization was performed to the WHO world standard population[13] using the direct method.[14] The number of strokes as well as the number of people at risk (person-years) has to be known for each age band. If this information was not

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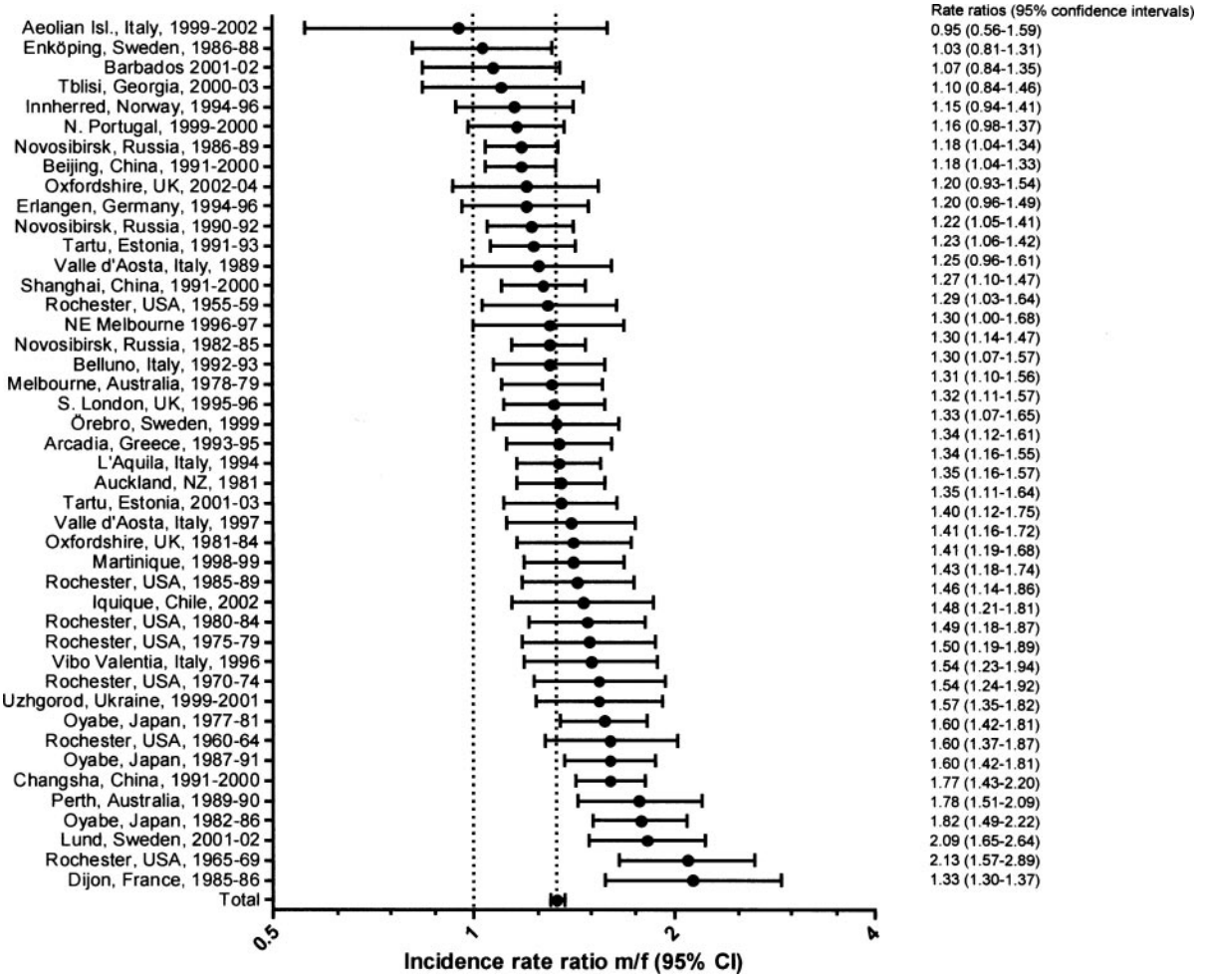


Figure 1. Male/female stroke incidence rate ratios with 95% CIs for different populations. Ages ≥45 years are included. (Adjusted to the WHO world population.) Test for heterogeneity: $\chi^2=144.18$, $df=43$, $P<0.00001$, $I^2=70\%$; test for overall effect: $Z=6.48$ ($P<0.00001$).

obtainable, the study could not be included in the overall age-standardized results.

The STATA software[15] was used to calculate the standardized m/f rate ratios. For the stroke incidence studies, only studies which have given number of strokes separately for men and women, along with person-years at risk for the age bands—45 to 54, 55 to 64, 65 to 74, 75 to 84, and ≥85—were included in the results. Because of the lack of information in many studies, the age bands below 45 years could not be included in this calculation. Theoretically, this means that the total rate ratio is biased against younger individuals, but in practice, these age bands have little influence on the total rate ratio, as only 2.9% of all strokes occur in ages below 45 in these studies. (For example: for Örebro, Sweden, the world standardized m/f rate ratio is 1.33, whether ages <45 years are included or not.) For stroke subtypes, however, we chose to also include ages below 45 years, because in these populations as many as 36% of all subarachnoidal hemorrhages (SAH) occurred in ages below 45 years, and therefore this age group may heavily influence the total m/f SAH rate ratio.

To achieve the total age-specific ratios, data were pooled from individual studies (number of stroke cases for each study, as well as denominators were summarized). Confidence intervals (CIs) for different age bands were calculated according to the method described by Morris and Gardner.[16]

For the prevalence studies, as well as for main stroke types, the STATA software[15] was used to calculate ratios with CIs. For tests of heterogeneity, Review Manager (RevMan)[17] was used. Non–age-standardized data were used for the tests of heterogeneity.

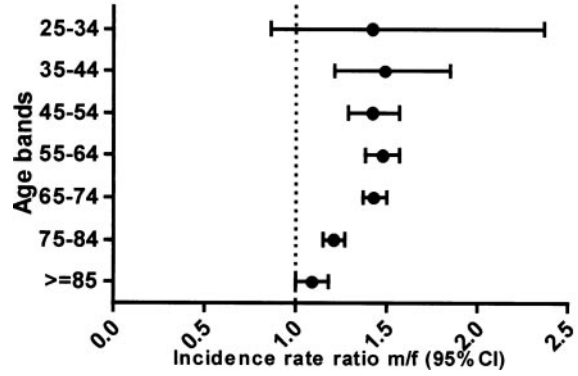
Results

Incidence

In total, we found 59 different incidence studies from 19 countries and 5 continents which fulfilled our inclusion criteria.[18–59] With the exception of the Rochester study from the United States, which was included because of its long duration and careful design, these studies essentially comply with the requirements of comparable community-based studies described above.[3,12] There were 14 149 male and 16 255 female strokes, which means that females outnumbered men by the factor 1.15.

Figure 1 shows the world population age-adjusted m/f incidence rate ratios for 44 different populations, with 95% CIs, as well as the pooled result. The pooled age-adjusted rate ratio was 1.33 (95% CI, 1.30 to 1.37), meaning that stroke is 33% more incident in males than in females. For Europe (24 studies, 11 687 cases), the pooled age adjusted rate ratio was 1.24 (95% CI, 1.20 to 1.29), and for the Australasia and the Americas (20 studies, 10 304 cases) the rate ratio was 1.45 (95% CI, 1.39 to 1.51).

Figure 2 shows rate ratios for different age bands. There was a significant drop in the m/f incidence rate ratio between the 65 to 74 and the 75 to 84 age bands, and a tendency to further drop in the ≥85 age band. Further details of individual



Rate ratios (95% confidence intervals)	No. of studies	No. of patients m/f
1.42 (0.86-2.37)	19	41/29
1.49 (1.21-1.85)	31	221/148
1.42 (1.29-1.57)	44	945/711
1.48 (1.38-1.57)	44	2099/1665
1.43 (1.37-1.50)	44	3423/3327
1.21 (1.15-1.27)	44	2845/4150
1.09 (1.00-1.18)	44	850/1976

Figure 2. Male/female stroke incidence rate ratios for different age bands with 95% CIs. Summary estimates. The same populations as in Figure 1 form the basis for this figure. Tests for heterogeneity: Ages 25 to 34: χ^2=13.70, *df*=15, *P*=0.55, I^2=0%; test for overall effect: *Z*=1.49 (*P*=0.14). Ages 35 to 44: χ^2=19.92. *df*=30, *P*=0.92, I^2=0%; test for overall effect: *Z*=3.92 (*P*<0.0001). Ages 45 to 54: χ^2=46.52, *df*=43, *P*=0.33, I^2=8%; test for overall effect: *Z*=8.00 (*P*<0.00001). Ages 55 to 64: χ^2=80.65, *df*=43, *P*=0.0004, I^2=47%; test for overall effect: *Z*=12.97 (*P*<0.00001). Ages 65 to 74: χ^2=78.00, *df*=43, *P*=0.0009, I^2=45%; test for overall effect: *Z*=15.23 (*P*<0.00001). Ages 75 to 84: χ^2=65.05, *df*=43, *P*=0.02, I^2=34%; test for overall effect: *Z*=8.18 (*P*<0.00001). Ages 85+ : χ^2=64.73, *df*=43, *P*=0.02, I^2=34%; test for overall effect: *Z*=1.81 (*P*=0.07).

studies are given in supplemental Table I (available online at http://stroke.ahajournals.org).

Mean Age at First-Ever Stroke

Overall, the weighted mean age (according to study size) for men was 68.6 years, and 72.9 years for women, which means that women get their first strokes on an average 4.3 years later than men. The mean age for male patients varies between 60.8 years (Uzhgorod, Ukraine) and 75.3 years (Innherred, Norway), and for females between 65.3 years (Matão, Brazil) and 80.4 years (Lund, Sweden).

The studies from Eastern Europe (Novosibirsk, Tartu, Uzhgorod, Tblisi) average at 63.6/69.1 years (m/f), the studies from Western Europe at 71.8/76.0 years, and the studies from North America and Australasia average at 68.6/73.3.

Secular Trends

In many populations, during the last 3 decades, there has been a decrease in stroke incidence in both sexes.[20,32,60–63] Some studies have found the declining stroke incidence to be greater in men.[64–66] A few studies did not find any significant changes over time.[67,68]

Although one study found that mean age at first stroke increased among women, and was unchanged among men,[20] many studies have shown a trend toward higher age in both sexes with time.[24,39,67] Some studies have shown an unchanged mean age,[30,32] and one study even a declining age at first-ever stroke.[66]

Prevalence

We found 13 different prevalence studies which had given prevalence figure for men and women separately.[5,9,69–78] Figure 3 shows 9 of these studies presenting sex-specific data for the age bands 55 to 64, 65 to 74, 75 to 84 and ≥85 years. Age-adjusted[13] m/f prevalence ratios are shown for individual studies, as well as the pooled estimate (with 95% CIs). The pooled ratio was 1.41 (95% CI, 1.12 to 1.59), meaning that stroke was 41% more prevalent among men than women in these studies.

Supplemental Table II gives age-specific data for all 13 studies with 95% CIs, as well as pooled ratios. The m/f ratio peaks in the age band 65 to 74, while it tends to drop in the 75 to 84 age band, and significantly so in the ≥85 year age band.

Types of Stroke

We found 17 studies which have given sex- and age-specific data on the main types of stroke, comprising 7783 male strokes and 8371 female strokes.[41–43,45,48,52,55,58,59,79–84] Figure 4 shows the age-adjusted m/f incidence rate ratios for different main types of stroke, with 95% CIs. For ischemic stroke, the ratio was 1.55 (95% CI, 1.48 to 1.61), for intracerebral hemorrhage 1.60 (95% CI, 1.47 to 1.74), for SAH 0.84 (95% CI, 0.69 to 1.04), and for stroke of undetermined cause 1.08 (0.98 to 1.20). Supplemental Table III gives age-specific values for individual populations, as well as the pooled results with CIs.

Studies on ischemic subtypes often give proportions or rates that are difficult to compare. Very few such studies have included age bands for subtypes. In supplemental Table IV we have compiled studies that have included information on numbers of strokes per sex for each subtype.[25,52,82,85–94] The table is based on 4808 male and 3869 female strokes. The most consistent finding is that cardioembolic stroke is proportionally more common in women, while large vessel and small vessel strokes are proportionally more common in men.

Stroke Severity

Several studies have shown that women have more severe strokes than men,[90,95,96] although there were only trends in some studies.[97,98] The differences are modest—in our local study, the average score on the National Institutes of Health Stroke Scale (range 0 to 42)[99] was 10.0 for women and 8.2 for men (*P*=0.06, n=377).[100]

Case Fatality

Figure 5 shows community-based studies that have accounted for 28-day (in some cases 30-day or 1-month) case fatality

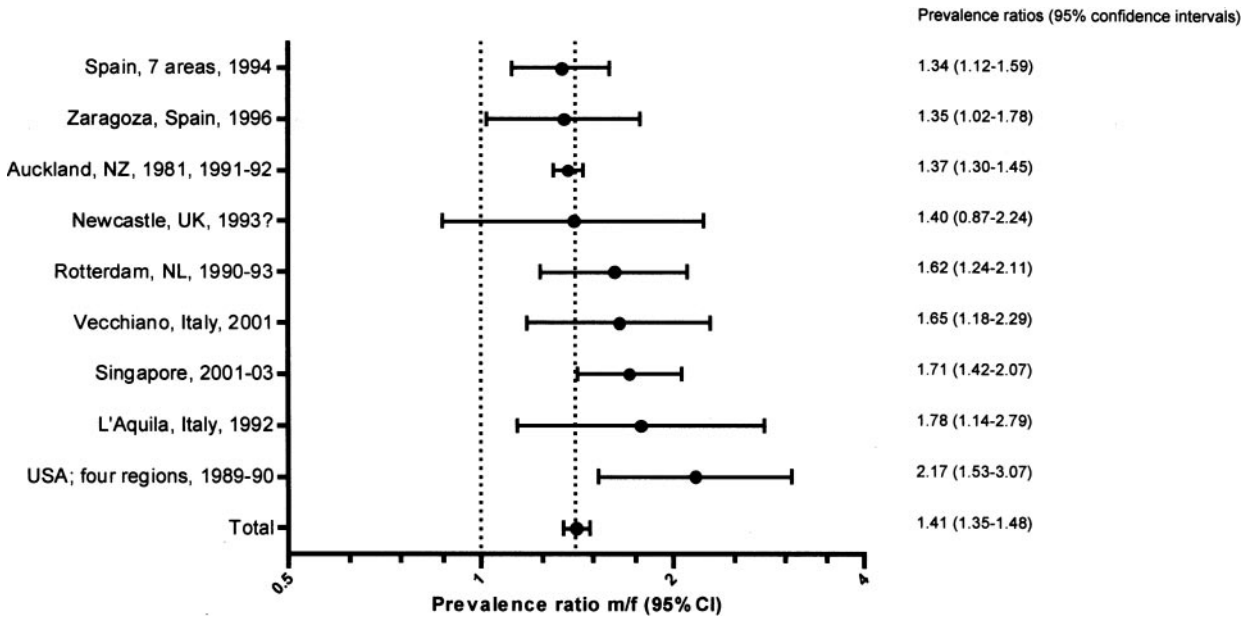


Figure 3. Male/female stroke prevalence ratios for different populations with 95% CIs. Ages ≥55 years are included. (Adjusted to the WHO world population.) Test for heterogeneity: $\chi^2=35.53$, $df=8$, $P<0.0001$, $I^2=77\%$; test for overall effect: $Z=9.55$ ($P<0.00001$).

separately for men and women[20,24,30,32,34,39,42,43,52–54,56,58,101–103] Case fatality was higher among women than among men in 26 of 31 studies, and higher in male patients in only 3 studies. Supplemental Table V shows the case fatality in more detail for individual populations.

The pooled case fatality for men was 19.7%, and for women 24.7%. Thus, case fatality was 1.25 times higher among women (95% CI, 1.17 to 1.34). Twenty-one of the populations are included in this calculation (7561 male and 8639 female strokes).

Discussion

Male sex may be a stronger risk factor for stroke than previously stated. Textbooks have often mentioned the incidence rates to be about 25% to 30% higher among men,[104] but the present review accounts for an overall risk increase for men by 33%. An explanation may be that community-based studies from new parts of the world have been published, and that these studies have changed the picture. There was a significantly larger male predominance in studies from Australasia and the Americas compared to studies from Europe.

The ≥85-year age band is open-ended, which has certain implications. In Sweden, the expected remaining length of life at 85 years is 5.24 years among men, and 6.50 years among women.[105] Thus, at 85 years, women have a 24% longer remaining lifetime than men that they are exposed to the risk of getting a stroke. The implication is that the male and female rates are not directly comparable in this age band. For example, in Örebro, Sweden, for ages ≥85 years, the age-specific incidence rate is 2878 per 100 000 per year for men, and 3285 for women.[52] In order to compensate for a shorter exposition time, the incidence rate for men has to be multiplied with 1.24. The adjusted incidence rate for men would then be 3569, which also would affect the total age adjusted rate ratios (m/f), in this case from 1.33 to 1.39. Consideration has not been taken to the ≥85 year age band

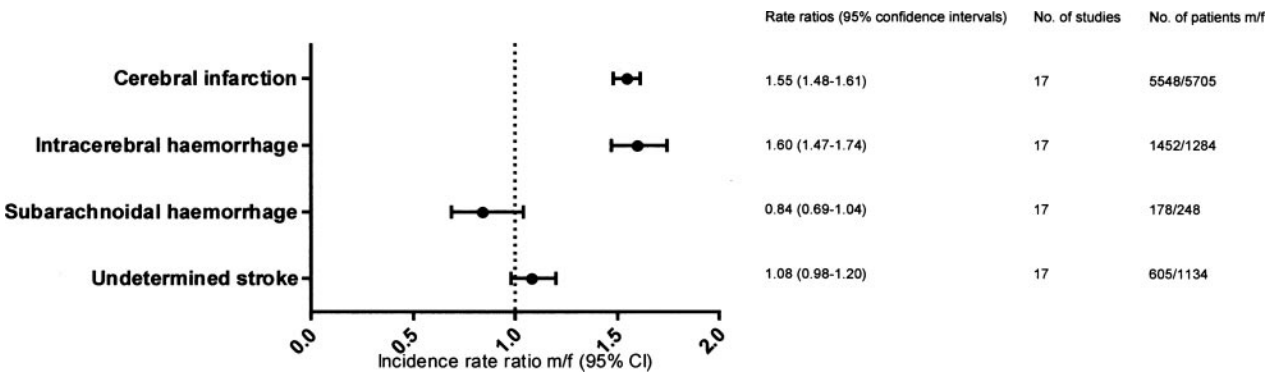
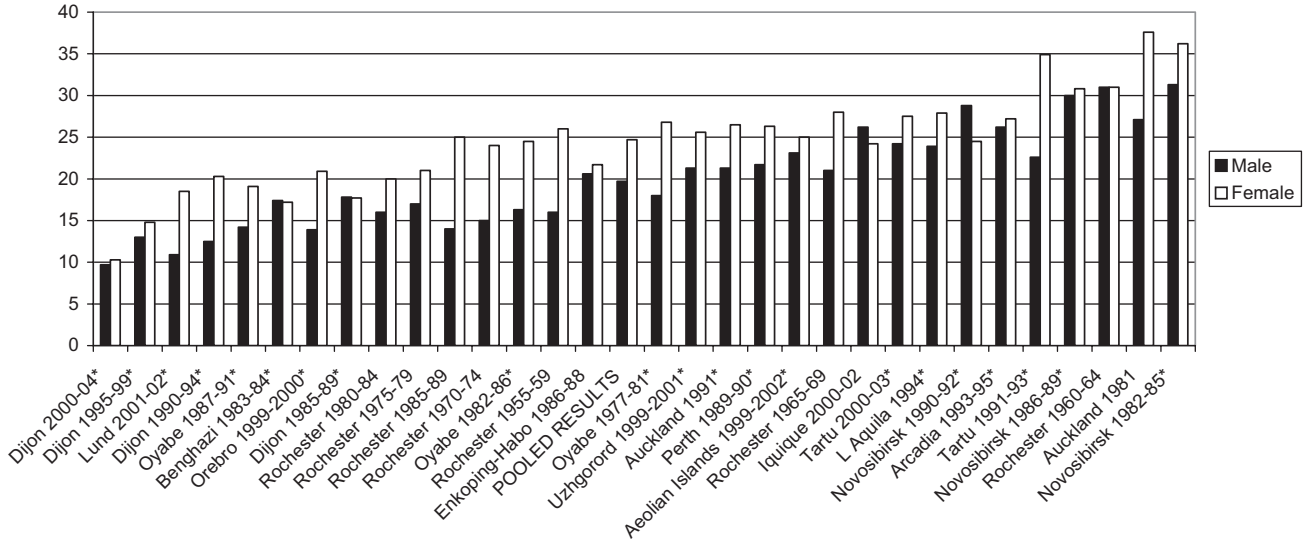


Figure 4. Male/female incidence rate ratios for main types of stroke with 95% CIs. (Adjusted to the WHO world population.) Summary estimates. Tests for heterogeneity: cerebral infarction: $\chi^2=33.26$, $df=16$, $P=0.007$, $I^2=52\%$; test for overall effect: $Z=3.15$ ($P=0.002$); intracerebral hemorrhage: $\chi^2=22.14$, $df=16$, $P=0.14$, $I^2=28\%$; test for overall effect: $Z=4.69$ ($P<0.00001$); subarachnoidal hemorrhage: $\chi^2=16.11$, $df=16$, $P=0.45$, $I^2=1\%$; test for overall effect: $Z=2.47$ ($P=0.01$); undetermined stroke: $\chi^2=16.95$, $df=16$, $P=0.26$, $I^2=17\%$; test for overall effect: $Z=10.60$ ($P<0.00001$).



*Studies with an asterisk are included in the pooled results.

Figure 5. Male and female case fatality percentages at 1 month for different stroke populations. The order is based on average m/f case fatality. *Studies with an asterisk are included in the pooled results.

problem in our review, however, because the population structure in the age band ≥85 years is not available for individual studies. Because of the different life expectancy in the sexes in ages ≥85 years, the overall m/f rate ratio is likely to be a few percentage units higher than the value accounted for.

The question is: Why do women have lower stroke incidence than men? One possible answer is genetic factors. We have not found support for this assumption in the literature. On the contrary, a recent systematic review found that women with stroke are more likely than men to have a parental history of stroke.[106] Another answer might be the positive effects of estrogen on the cerebral circulation.[107] A lifetime exposure to ovarian estrogens may protect against ischemic stroke, at least of the noncardioembolic type,[108] an effect that seems to cease with menopause.[109] These observations have been one reason for the use of postmenopausal hormone replacement therapy. Randomized controlled trials have, however, failed to show advantages for treated groups,[110] and the current recommendation is that postmenopausal hormone therapy should not be used in the primary prevention of stroke.[111] A third factor may be blood pressure. Studies have shown that blood pressure values are higher in men than women of similar ages.[112,113] Moreover, ischemic heart disease,[86,95,114,115] peripheral artery disease,[86,90] and cigarette smoking[86,90,95,116,117] are more prevalent among male stroke patients. These conditions are associated with large-vessel disease.

Textbook knowledge states that SAH is more common among women than men,[104] although this may not be the case in all populations. In a study from the WHO MONICA project, the populations from Eastern Europe and Finland had higher incidence rates of SAH in men than in women.[118] The MONICA study covers ages 25 through 64 years in most populations. A recent systematic review has shown that the female predominance begins in the upper part of this age band, at the age of 55 through 64, and is most pronounced in the age band 75 through 85 years.[11] The same review found that the incidence of SAH was 1.24 times higher in women than in men, which in its inverted form, 1/1.24=0.81, is not far from our figure of 0.84. It is not known why SAH is more common among women, but hormonal factors have been proposed.[119]

Atrial fibrillation is more prevalent among elderly people, and female stroke patients are older when they get their first stroke.[86,90,114,120] Several studies have shown that women are generally at higher risk than men for atrial fibrillation–related, cardioembolic stroke,[115,121–124] but a few studies also have failed to show any significant sex difference.[125,126] A biological reason for an increased risk for stroke in women with atrial fibrillation is still lacking,[127] but a study from the Swedish Stroke Register has shown that female patients with atrial fibrillation receive oral anticoagulant therapy less often than men.[117] The higher prevalence of embolic strokes among women may to a large part explain their higher stroke severity.

The compilation of ischemic subtypes (supplemental Table IV) suffers from low numbers and varying definitions, and that some studies have included an undetermined group as well (not accounted for in the table). Nonetheless, most studies show that embolic stroke is proportionally more common among women. Whether the incidence of cardioembolic stroke among higher in women is still an open question. Unfortunately, few studies have given age specific data on men and women separately for ischemic subtypes. We have only been able to find one such study,[82] and data from that study, as well as unpublished data from our own incidence study,[52] do not support that cardioembolic stroke is more common among women.

In almost all studies reviewed here, women have higher 1-month case fatality than men. It must be observed that confounders have not been adjusted for. Women are older

when they get their first stroke, and SAH and cardioembolic strokes are proportionally more common among women. Also, the results are not adjusted for differences in other baseline characteristics (eg, risk factors), which may play a role. Therefore, this result is not in conflict with prognostic studies, where multivariate analysis emphasizes other factors, and in which sex rarely becomes an independent factor.[128]

One obvious limitation of this review is that the distribution of contributing studies is geographically uneven. Africa, Asia and South America are underrepresented. This is of importance, because our results show that the m/f ratios may differ between different parts of the world. Also, because of limitations in our search strategy, we may have missed some studies. Despite this, we think that the main trends in this review are supported by most studies. Some of these epidemiological factors, as for example age distribution and distribution of stroke types, may however vary considerably between places. The case fatality ratios are not age-standardized, and age differences may therefore bias the results. Differences in stroke care may also strongly affect case fatality.

Our review has confirmed that stroke is more common among men than women. The difference tends to decrease with age. Women get their first stroke about four and a half years later than men. The incidence of SAH tends to be higher in women, even if the results of our review were not statistically significant. Both brain infarction and intracerebral hemorrhage are more common in men, but cardioembolic stroke, which is more severe, accounts for a larger proportion of strokes among women. Strokes are more severe in women, and case fatality at one month is higher among women.

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Disclosures

None.

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