

# Sex differences in the incidence of cerebrovascular disease

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**SUMMARY** Incidence rates for cerebrovascular disease reported by community-based and hospital-based studies during the past 15 years are analysed. The range of variation between areas is wide, with Japan and Finland experiencing the highest age-adjusted rates. Of 16 studies reporting incidence rates by sex, 15 showed a male excess, and nine of these were significant when the incidence rate was age-adjusted. Overall, the excess is about 30% for both community-based and hospital-based studies. For cerebral infarction the excess is about 45%. Intracerebral haemorrhage shows little difference between the two sexes and subarachnoid haemorrhage shows a male deficit of about 50%. These findings are self-consistent.

We review here all studies that have reported incidence rates of cerebrovascular disease with particular reference to differences between the two sexes.<sup>1–27</sup> The main sources of these data are from community-based and hospital-based longitudinal studies of the disease.

The variation of incidence rates with age is well-documented for all cerebrovascular disease and for the principal diagnostic subdivisions.<sup>28–29</sup> Work is in hand to represent this age variation formally by mathematical curves.

The results discussed in this review are concerned with the variation in incidence rates by sex. A broader discussion of sex differences in stroke, embracing national cause-of-death mortality rates and survival rates after the onset of stroke, is in the course of being published.<sup>30</sup>

## Method

To compare age- and sex-specific incidence rates in different epidemiological studies may involve the comparison of a large quantity of data. However, with a condition like cerebrovascular disease, which has a low crude incidence rate, such a procedure could involve calculating specific rates based on few person-years of exposure, and hence it could be subject to considerable statistical fluctuation. Comparison between studies is also hindered by the

different methods of age grouping used. Therefore there are advantages in using a single-figure index to summarise and compare studies, accepting that some statistical information is likely to be lost in this process.

The use of crude indices has disadvantages. These problems can be reduced by age-standardisation procedures when both numerator and denominator data are available for all strata in each population; when the aim is primarily descriptive, the usual approach is by direct standardisation. The England and Wales home population for both sexes for 1973 has been used as the standard.<sup>31</sup>

Since the level of annual incidence is approximately 2–3 per 1000, the number of new cases in any single investigation is likely to be small, so that estimates of incidence rates should be qualified by confidence limits. Following the suggestion of Lew,<sup>32</sup> it is assumed that the number of new cases follows a Poisson distribution, and corresponding formulae for approximate 95% confidence limits for age-adjusted incidence rates are given in the Appendix.

To test the significance of the difference between two age-adjusted incidence rates, a method proposed by Armitage,<sup>33</sup> based on Cochran,<sup>34</sup> has been used, and the formulae are presented in the Appendix.

Both direct and indirect methods of standardisation have attracted criticism in the literature<sup>35</sup> on the grounds that they place too much

weight on absolute rather than relative differences, and hence, in this context, that the indices respond more to differences at the oldest ages than at the youngest. Such criticisms are not crucial when, as with cerebrovascular disease, the age-specific rates are negligible at ages under 45.

## Results

The community-based studies reported in the last 15 years are summarised in Table 1 giving age-adjusted incidence rates (adjusted to the England and Wales 1973 population) and approximate confidence intervals.

Table 1 Age-adjusted incidence rates for all cerebrovascular disease (in 100 000 a year) from different community-based studies, for both sexes of all races

Study	Years covered	No. of cases	Age-adjusted rates	95% confidence interval
Rochester, USA <sup>1</sup>	1945-54	584 (whites only)	284	±24
Rochester, USA <sup>2</sup>	1955-69	993 (whites only)	236	±15
Middlesex Co, USA <sup>3</sup>	1957-58	191 (whites only)	277	±39
Evans Co, USA <sup>4</sup>	1960-69	94	303	±34
Fargo Moorhead, USA <sup>5</sup>	1965-66	408	355	±22
Mid-Missouri, USA <sup>6</sup>	1965-66	195 (whites only)	278	±40
Mid-Missouri, USA <sup>7</sup>	1966-67	189	228	±35
W. Pennsylvania, USA <sup>8</sup>	1968	774	437	—
Oxford, UK <sup>9</sup>	1963-64	630	222	±27
Farnham and Frimley, UK <sup>10</sup>	1971-72	380	191	—
Carlisle, UK <sup>11</sup>	1978	251	230	±29
Frederiksberg, Denmark <sup>12</sup>	1971-73	556	180	±15
Dublin, Ireland <sup>13</sup>	1972-74	543	249	±33
Espoo, Finland <sup>14</sup>	1972	153	332	±58
Tartu, USSR <sup>15</sup>	1970-73	667	231	±18
Hiroshima, Japan <sup>16</sup>	1963-64	175	518	±28

Within the United States of America the range of variation is 1.92, measured by the ratio between the extreme levels. The weighted average age-adjusted incidence rate for the USA is 310 per 100 000 a year (using weights proportional to the number of cases in each study). Within Europe, the range of variation similarly calculated is 1.84, and the weighted average age-adjusted incidence rate is 223 per 100 000 a year.

The hospital-based studies reported in the last 25 years are summarised in Table 2 with age-adjusted incidence rates, as in Table 1. The variation is again wide and significant.

The data in Tables 1 and 2 are based on all new cases of cerebrovascular disease with the different types of pathology considered together. In some reports no attempt was made to distinguish between them, but where such attempts were made the criteria often differed between studies. Table 3 gives the

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Table 2 Age-adjusted incidence rates for all cerebrovascular disease (in 100 000 a year) from different hospital-based studies, for both sexes of all races

Study	Years covered	No. of cases	Age-adjusted rates	95% confidence interval
Harlem, USA <sup>17</sup>	1971	328 (non-whites only)	228	—
Monroe Co, USA <sup>18</sup>	1971	383	214	±13
Manitoba, Canada <sup>19</sup>	1970-71	1367	199	±12
Carlisle, UK <sup>20</sup>	1955-61	694	157	±12
Frederiksberg, Denmark <sup>21</sup>	1940-53	1000	76	±18
Jerusalem, Israel <sup>22</sup>	1960-67	1517	170	±9

Table 3 Age-adjusted incidence rates for cerebral infarction (in 100 000 a year) from different community-based studies, for both sexes

Study	Years covered	No. of cases	Age-adjusted rates	95% confidence interval
Rochester, USA <sup>1</sup>	1945-54	428	218	±21
Rochester, USA <sup>2</sup>	1955-69	777	186	±13
Middlesex Co, USA <sup>3</sup>	1957-58	91	131	±27
Framingham, USA <sup>23</sup>	1950-72	174	102*	—
Oxford, UK <sup>9</sup>	1963-64	251	90	±11
Frederiksberg, Denmark <sup>12</sup>	1971-73	164	57	±9
Tartu, USSR <sup>15</sup>	1970-73	532	185	±16
Hisayama, Japan <sup>24</sup>	1961-65	32	364	—
Hiroshima, Japan <sup>16</sup>	1958-64	80	261	±64

\*Based on ages under 85

age-adjusted incidence rates for community-based studies of cerebral infarction.

The range of variation between these rates is wide and statistically significant. The weighted average age-adjusted incidence rates for cerebral infarction for the three principal geographical regions studied were:

USA 193 (per 100 000 a year)  
Japan 290 (per 100 000 a year)  
Europe 138 (per 100 000 a year)

Tables 4 and 5 present the age-adjusted incidence rates for cerebrovascular disease in the two sexes in several studies.

The significance of the difference between each pair is tested using a method due to Cochran.<sup>33 34</sup> All but one of the comparisons between male and female rates are greater than 1 in Table 4 and all are greater than 1 in Table 5. This apparent male excess is significant in six out of 13 possible comparisons from Table 4, and three out of three in Table 5. The weighted average age-adjusted incidence rates show a male excess of 29% in Table 4 and 26% in Table 5.

Table 6 shows comparisons of male and female incidence rates for cerebral infarction. In all seven studies there is a male excess, which is significant for five of the six comparisons. The weighted average age-adjusted incidence rates show a male excess of 46%.

Table 4 Sex differences in age-adjusted incidence rates for cerebrovascular disease (in 100 000 a year) from different community-based studies

Study	Male rate	Female rate	SD*	Male/ Female
Evans County, USA				
Whites	402	150	p < 0.005	2.68
Non-whites	401	429	p > 0.05	0.93
Rochester, USA				
1955-69	322	194	p < 0.00005	1.66
Middlesex, Co, USA	300	254	p > 0.05	1.18
Fargo Moorhead, USA	369	344	p > 0.05	1.07
Mid-Missouri, USA				
1966-67				
Whites	255	215	p > 0.05	1.19
Non-whites	656	367	p > 0.05	1.79
Jefferson Co, USA <sup>38</sup>				
Whites	245	124	—	1.98
Non-whites	359	344	—	1.04
Oxford, UK	228	219	p > 0.05	1.04
Farnham and Frimley, UK	212	175	—	1.21
Frederiksberg, Denmark	221	154	p < 0.0005	1.44
Dublin, Ireland	274	231	p < 0.05	1.19
Espoo, Finland	364	305	p > 0.05	1.19
Tartu, USSR	274	208	p < 0.001	1.32
Hiroshima, Japan	563	483	p < 0.005	1.17
WEIGHTED AVERAGE	293	227	—	1.29

\*Significance of difference

Table 5 Sex differences in age-adjusted incidence rates for cerebrovascular disease (in 100 000 a year) from different hospital-based studies

Study	Male rate	Female rate	SD*	Male/ Female
Harlem, USA	248	217	—	1.14
Manitoba, Canada	223	175	p < 0.00005	1.27
Frederiksberg, Denmark				
1940-53	83	73	p < 0.05	1.14
Jerusalem, Israel	193	150	p < 0.00005	1.29
WEIGHTED AVERAGE	181	144	—	1.26

\*Significance of difference

Table 6 Sex differences in age-adjusted incidence rates for cerebral infarction (in 100 000 a year) from different community-based studies

Study	Male rate	Female rate	SD**	Male/ Female
Rochester, USA				
1955-69	248	147	p < 0.005	1.69
Middlesex Co, USA	133	130	p > 0.05	1.02
Framingham, USA	108*	97*	—	1.11
Oxford, UK	102	81	p < 0.05	1.23
Frederiksberg, Denmark <sup>38</sup>				
1971-72	85	48	p < 0.01	1.79
Tartu, USSR	221	171	p < 0.0005	1.29
Hiroshima, Japan	304	229	p < 0.0005	1.33
WEIGHTED AVERAGE				
(except Framingham)	210	144	—	1.46

\*Based on ages under 85

\*\*Significance of difference.

In Table 7 male and female incidence rates for intracerebral haemorrhage are compared. In three of the five cases there is a male excess, and in two a female excess. None of the differences are significant.

In Table 8 male and female incidence rates for subarachnoid haemorrhage are compared. Both studies show a male age-adjusted rate which is 52% of the female rate. The difference is significant in one of the comparisons.

## Discussion

The variation in the rates in Table 1 is wide, partly because of significant differences in factors other than age, such as the sex and racial composition of the study population, geographical location, and the years in which the study occurred. Alternatively, as Kurtzke<sup>36</sup> suggests, the wide variation may be due to statistical causes, including differences in disease definitions as well as methods of case ascertainment and confirmation of diagnosis. By tabulating the confidence limits, an attempt is made to quantify the effect of random fluctuations arising from the small size of numbers of cases reported, relative to the number of persons exposed to the risk of incidence.

Examples of the inherent technical differences between studies can be given by comparing the Evans County<sup>4</sup> and Rochester<sup>2</sup> investigations. In the former, the diagnostic criteria could be questioned, particularly as necropsy confirmation is largely absent. The latter investigation is based on the records of the Mayo Clinic. These records are among the most accurate available because the population of

Table 7 Sex differences in age-adjusted incidence rates for intracerebral haemorrhage (in 100 000 a year) from different community-based studies

Study	Male rate	Female rate	SD*	Male/ Female
Rochester, USA <sup>27</sup>	24	17	—	1.37
Middlesex Co, USA	103	94	p > 0.05	1.10
Oxford, UK	70	83	p > 0.05	0.85
Frederiksberg, Denmark				
1971-72	27	23	p > 0.05	1.18
Hiroshima, Japan	16	17	p > 0.05	0.94

\*Significance of difference

Table 8 Sex differences in age-adjusted incidence rates for subarachnoid haemorrhage (in 100 000 a year) from different community-based studies

Study	Male rate	Female rate	SD*	Male/ Female
Oxford, UK	11	22	p < 0.05	0.52
Hiroshima, Japan	1.7	3.2	p > 0.05	0.52

\*Significance of difference

Rochester is, in medical terms, unique: the Mayo Clinic provides all medical services, and the studies have been continuing for several decades; in addition, a high quality index and retrieval system has been operative there for many years.<sup>37</sup>

As a further example, we note that the study design of the Oxford investigation<sup>9</sup> was unusual. The study included all cases with cerebrovascular disease who had spent at least one night in hospital during the investigation period and all persons not admitted to hospital for whom the death certificate gave the underlying cause of death as cerebrovascular disease. It thus excluded those cases of stroke treated at home who either survived their first year of follow-up or died within one year from another underlying cause. It was argued by the authors that such an approach saved time and expense without much loss of accuracy. However, as pointed out by Cochrane,<sup>38 39</sup> such an approach could involve an understatement of up to 45% in the incidence rates derived. We would therefore expect age-adjusted incidence rates calculated for this study as in Tables 1, 3, 4, and 6 to be underestimates.

It seems reasonable to assume that technical differences between the studies such as those described above will affect the two sexes to the same extent, so that the data available are of epidemiological value for the purpose of elucidating the sex differences in incidence of cerebrovascular disease.

Apart from the Hiroshima study,<sup>16</sup> most of the other age-adjusted incidence rates in Table 1 fall within the range 200–350 per 100 000 a year. The high levels of incidence shown for Japan<sup>16</sup> and Finland<sup>14</sup> are consistent with the high levels of cause-specific mortality rates ascribed to cerebrovascular disease in those countries.

Further, because of the Atomic Bomb Casualty Commission's basic responsibilities, the Hiroshima population<sup>16</sup> was carefully defined and the necropsy rate among fatalities was in excess of 70%.

Despite the likelihood of wide variation in patient selection procedures and rates of completeness of identification of cases for hospital-based studies, the age-adjusted rates in Table 2 fall within the range 150–230 per 100 000 a year, with one exception. The rate for Frederiksberg<sup>21</sup> is very low, but a later community-based study in the same city<sup>12</sup> reported an age-adjusted rate of 180 (Table 1).

The results in Table 3 also show a wide variation between studies. An important factor affecting these age-adjusted rates is the ability to effect an accurate differential diagnosis, in particular between cerebral infarction and cerebral haemorrhage. Those studies

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with low incidence rates for cerebral infarction<sup>3 9</sup> have reported relatively high incidence rates for other pathologies, as illustrated in Tables 7 and 8. The data for the Framingham study<sup>23</sup> is anomalous in that only ages under 85 are included.

The patient selection and lack of complete ascertainment of cases in hospital-based studies is unlikely to affect the two sexes differently, so that the results of Tables 4 and 5 may be combined. In this situation, nine of the 16 possible sex differences in age-adjusted incidence rates were significant ( $p < 0.05$ ). These results are inconclusive but seem to suggest that the male age-adjusted incidence rate is about 30% higher than the rate for females. Thus the weighted average rates in Tables 4 and 5 show a strikingly similar male excess incidence of about 30%.

The results in Table 6 for cerebral infarction only are more striking. Five of the possible six sex differences are significant, which suggests that the male age-adjusted incidence rate is significantly higher than that for females. The weighted average figures suggest that the male excess is about 46%, which is higher than that reported for all the pathologies combined.

The results in Table 7 for intracerebral haemorrhage indicate only a negligible difference between the two sexes. The results for subarachnoid haemorrhage in Table 8 indicate that the male age-adjusted incidence rate is about 50% of the female age-adjusted rate.

The hospital-based studies of Melamed *et al*<sup>22</sup> and Abu-Zeid *et al*<sup>19</sup> support these conclusions for intracerebral haemorrhage, neither finding significant differences between the sexes.

The consistency of the results described in Tables 4–8 may be shown by using the findings of the epidemiology study group<sup>28</sup> who estimated the frequency distribution of new strokes for either sex by diagnostic type to be:

Subarachnoid haemorrhage	10%
Intracerebral haemorrhage	15%
Cerebral infarction	75%

Using these proportions as weights, and the results from Tables 6–8, we estimate the sex ratio for all new strokes to be:

$$0.10 \times 0.52 + 0.15 \times 1.00 + 0.75 \times 1.46 = 1.30$$

which agrees with the aggregate results for Tables 4 and 5 quoted above.

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Appendix

(1) Consider two populations denoted by A and B with age-specific incidence rates given respectively by  $q_x^A$  and  $q_x^B$ . Let  $N_x$  denote the age structure of the standard population (that is, the number of persons aged  $x$  to  $x+1$ ) and let  $N$  denote the total size of the standard population. Then the age-adjusted incidence rates  $q^A$  and  $q^B$  are given by:

$$q^A = \sum \frac{N_x}{N} q_x^A \quad q^B = \sum \frac{N_x}{N} q_x^B$$

For population A, let  $i_x^A$  denote the number of incidence cases between ages  $x$  and  $x+1$ , and let  $n_x^A$  denote the number of population A aged between  $x$  and  $x+1$  and exposed to the risk of incidence. Then:

$$q_x^A = \frac{i_x^A}{n_x^A}$$

and approximate 95% confidence limits for  $q^A$  are given by:

$$q^A \pm 1.96 \text{ se}(q^A)$$

where

$$\text{se}(q^A) = \sqrt{\left(\frac{N_x}{N}\right)^2 \frac{i_x^A}{(n_x^A)^2}}$$

We have assumed that the number of incident cases in each age group follows a Poisson distribution, which is independent of the number of cases in the other age groups.

(2) For testing the significance of the difference  $d = q^A - q^B$  we compute  $\text{se}(d)$  and consider  $z = d/\text{se}(d)$  which may be shown to follow approximately the standard normal distribution.

Here  $\text{se}(d) =$

$$\sqrt{\sum \left(\frac{N_x}{N}\right)^2 \frac{(n_x^A + n_x^B)}{n_x^A n_x^B} q_x^0 (1 - q_x^0)}$$

where  $q_x^0$  is the pooled incidence rate:  $\frac{i_x^A + i_x^B}{n_x^A + n_x^B}$

Since  $q_x^0 \ll 1$ , we use the following approximation:

$$\text{se}(d) = \sqrt{\sum \left(\frac{N_x}{N}\right)^2 \frac{(i_x^A + i_x^B)}{n_x^A n_x^B}}$$

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