

# Sex Differences in Heritability of Ischemic Stroke

## A Systematic Review and Meta-Analysis

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**Background and Purpose**—Using data from Oxfordshire, UK, we recently showed that women are more likely than men to have a family history of stroke in female versus male first degree relatives. To test the generalizability of this finding, we did a comprehensive systematic review of all available published and unpublished data.

**Methods**—Studies were included in the present review if they reported the frequency of family history of stroke in relation to sex of parent or proband. Where necessary, we contacted authors of studies to obtain unpublished data. Data from the Oxford Vascular Study (OXVASC) and 3 other Oxford cohorts (1925 patients) were secondarily pooled with the data from other studies.

**Results**—We obtained data from 18 studies (7941 patients), including unpublished data from 7 studies. Female probands were slightly more likely to have a parental history of stroke than male probands (pooled OR=1.15; 95% CI: 1.03 to 1.29;  $P_{(\text{sig})}=0.028$ ;  $P_{(\text{het})}=0.45$ ). Maternal history of stroke was more common than paternal history (pooled OR=1.25; 1.15 to 1.37;  $P_{(\text{sig})}<0.00001$ ;  $P_{(\text{het})}=0.12$ ). However, the maternal excess was only present in female probands (pooled OR=1.47; 1.27 to 1.70;  $P_{(\text{sig})}<0.00001$ ;  $P_{(\text{het})}=0.11$ ). In contrast, male probands were no more likely to have maternal than paternal history of stroke (pooled OR=1.02; 0.88 to 1.17,  $P_{(\text{sig})}=0.43$ ;  $P_{(\text{het})}=0.09$ ).

**Conclusions**—Women with stroke are more likely than men to have a parental history of stroke, which is accounted for by an excess maternal history of stroke. This finding could be explained by sex-specific genetic, epigenetic, or nongenetic mechanisms. (*Stroke*. 2008;39:16-23.)

**Key Words:** cerebrovascular accident ■ epidemiology ■ genetics ■ risk factors ■ family history

Several studies have shown that ischemic stroke is, at least in part, a heritable disease.<sup>1,2</sup> However, the relative importance of genetic and environmental factors is uncertain. Although some genetic polymorphisms have been associated with stroke,<sup>3,4</sup> the mechanisms remain to be determined and most of the subsequent studies have failed to replicate the findings.<sup>5</sup> In fact, heritability of stroke could also be explained by inheritance of intermediate phenotypes,<sup>6,7</sup> or by exposure to early life environmental factors.<sup>8</sup> The transmission of stroke in families is clearly not in accordance with a classic mode of inheritance. However, whether or not transmission of stroke could be sex-specific has been very rarely investigated. Yet, it cannot be assumed that heritability will necessarily be similar in both sexes. First, there are differences between stroke in males and females in relation to risk factors, frequency of subtypes, and outcome, which could reflect transmission of sex-specific factors.<sup>9</sup> Second, several epidemiological studies have suggested that the risk of future vascular disease and that of vascular risk factors development could be programmed during the fetal life.<sup>10,11</sup> An ecological correlation between low birth weight and risk of later coronary artery disease, hypertension, type 2 diabetes, and stroke notably

supports this latter hypothesis.<sup>8,10</sup> Greater maternal-offspring transmission of type 2 diabetes is also well established.<sup>12</sup>

Using data from the Oxford Vascular Study (OXVASC) population-based study, we have recently shown that women are more likely than men to have a history of stroke in mothers than in fathers and in sisters than in brothers.<sup>13</sup> This female excess in women was independent of traditional vascular risk factors and was also found in 2 independent datasets from previous Oxford studies. However, the mechanisms of such a transmission remain unclear and the generalizability of the finding to other populations needs to be tested. Therefore, in collaboration with many original investigators who provided us unpublished data on family history, we did a comprehensive systematic review and meta-analysis of all available data.

### Methods

We sought all available previous published studies in which family history of stroke was analyzed as a risk factor for stroke or TIA, as reported elsewhere.<sup>1</sup> Briefly, studies were identified by 2 independent observers from MEDLINE and EMBASE from 1966 with the following search terms: (family history OR twin) AND (stroke OR cerebrovascular accident OR TIA OR cerebrovascular OR transient ischemic attack). We considered studies in any language. The electronic literature search

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**Table 1. Main Characteristics of Oxford Data, and the Other Studies Included in the Systematic Review (Published and Unpublished Data)**

Study (year)	Type	Setting	Country	N cases	IS only	Men, n (%)	Mean age (y)	FHx Parents, n (%)		FHx Mother, n (%)			FHx Father n (%)		
								Women	Men	All	Women	Men	All	Women	Men
Oxford data															
OxVASC	Cases	Population	UK	781	Yes	371 (48)	75	100 (13)	82 (22)	118 (15)	71 (17)	39 (10)	82 (10)	47 (13)	43 (12)
OCSP <sup>15</sup>	Cases	Population	UK	663	Yes	340 (51)	71	49 (15)	46 (14)	66 (10)	42 (13)	24 (7)	41 (6)	14 (4)	27 (8)
TIA-series <sup>6</sup>	Cases	Hospital	UK	481	Yes	312 (65)	63	34 (18)	56 (18)	55 (11)	23 (14)	32 (10)	44 (9)	14 (8)	30 (10)
Other data															
Gifford (1966) <sup>32</sup>	Case-Control	Hospital	USA	126	No	66 (52)	...	...	...	28 (22)	...	...	20 (16)	...	...
Alter (1967) <sup>27</sup>	Case-Control	Hospital	USA	44	Yes	?	...	...	...	7 (16)	...	...	6 (14)	...	...
Gertler (1968) <sup>37</sup>	Cases	Hospital	USA	133	Yes	109 (82)	61	...	...	24 (18)	...	...	22 (17)	...	...
Marshall (1971) <sup>33</sup>	Cases	Hospital	UK	201	No	146 (70)	...	4 (7)	24 (17)	19 (27)	3 (5)	16 (11)	9 (4)	1 (2)	8 (6)
Welin (1987) <sup>35</sup>	Cohort	Other	Sweden	57	No	57 (100)	...	NA	21 (37)	NA	NA	17 (30)	NA	NA	4 (7)
Lindenstrom (1993) <sup>29</sup>	Cohort	Population	Denmark	696	No	428 (61)	...	...	...	89 (13)	...	...	66 (9)	...	...
<b>Vitullo (1996)<sup>19</sup></b>	Case-Control	Hospital	Italy	237	Yes	157 (66)	30-69*	<b>31 (39)</b>	<b>48 (31)</b>	<b>44 (19)</b>	<b>15 (19)</b>	<b>29 (18)</b>	<b>49 (21)</b>	<b>22 (28)</b>	<b>27 (17)</b>
Jousilahati (1997) <sup>36</sup>	Cohort	Population	Finland	453	No	249 (55)	...	24 (12)	23 (19)	25 (6)	13 (7)	12 (5)	22 (21)	11 (6)	11 (5)
<b>Liao (1997)<sup>23</sup></b>	Case-Control	Population	USA	103	No	64 (61)	62	<b>15 (41)</b>	<b>22 (33)</b>	<b>19 (18)</b>	...	...	<b>18 (17)</b>	...	...
<b>Berger (1998)<sup>22</sup></b>	Cohort	Other	Germany	129	Yes	95 (73)	52	<b>5 (19)</b>	<b>16 (17)</b>	...	...	...	...	...	...
<b>Caicoya (1999)<sup>24</sup></b>	Case-Control	Population	Spain	470	No	247 (53)	71	<b>47 (21)</b>	<b>58 (23)</b>	66 (14)	...	-	48 (10)	...	...
Reed (2000) <sup>30</sup>	Case-Control	Population	USA	83	Yes	83 (100)	72	NA	36 (43)	NA	NA	19 (23)	NA	NA	17 (20)
Starr (2001) <sup>34</sup>	Case-Control	Hospital	UK	293	No	143 (49)	70	...	...	54 (18)	...	...	33 (11)	...	...
<b>Tentschert (2003)<sup>21</sup></b>	Cases	Hospital	Austria	1564	Yes	853 (55)	69	224 (32)	234 (27)	253 (16)	136 (19)	117 (14)	245 (16)	<b>103 (14)</b>	<b>142 (17)</b>
Kim (2004) <sup>28</sup>	Case-Control	Population	USA	49	Yes	0 (0)	36	11 (22)	NA	NA	5 (10)	NA	NA	6 (12)	NA
<b>Lindgren (2005)<sup>18</sup></b>	Case-Control	Population	Sweden	447	No	254 (57)	76	<b>68 (35)</b>	<b>92 (36)</b>	<b>97 (22)</b>	<b>45 (23)</b>	<b>52 (20)</b>	<b>86 (19)</b>	<b>33 (17)</b>	<b>53 (21)</b>
<b>Lisabeth (2005)<sup>20</sup></b>	Cases	Population	USA	444	Yes	197 (44)	73	<b>75 (30)</b>	<b>41 (21)</b>	74 (17)	<b>49 (20)</b>	<b>25 (13)</b>	52 (12)	<b>30 (12)</b>	<b>22 (11)</b>
MacClellan (2006) <sup>31</sup>	Case-control	Population	USA	487	Yes	0	39	118 (24)	NA	NA	70 (14)	NA	NA	48 (10)	NA

IS indicates ischemic stroke only (proband), including TIA. NA, not applicable. ... means that either data were not published (studies published <1995), no reply from authors, or data not collected. \*Range of ages.

Unpublished data are in bold.

was updated using the same search terms until October 1st, 2006 and supplemented by hand-searching of reference lists, reviews, and specialist journals. Studies which had a high proportion of patients with hemorrhagic stroke but for which data were not available for ischemic stroke separately were excluded. Case-control, cohort, twin, and case studies were included in the current review if they reported the frequency of a parental history of stroke in relation to sex of parent or proband. Two independent reviewers used a standardized form to extract available data on family history separately for mother, father, and female and male probands.

We contacted authors of studies published within the last 10 years that reported parental history of stroke but which lacked sex-specific data and asked them to provide data on family history in father and

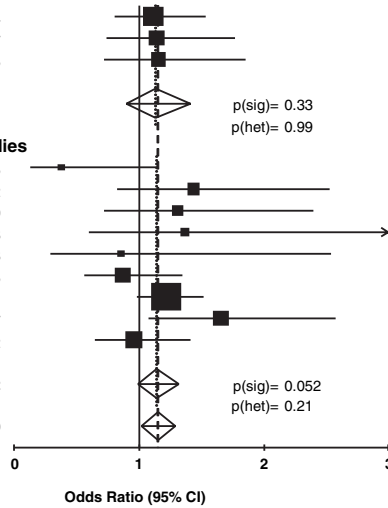
mother separately for male and female probands. Apart from the OxVASC study, no study has reported on family history in sisters and brothers separately. In addition, analyses on siblings would have required obtaining individual data to take into account intrafamily correlations. Therefore, we did not seek data on siblings from authors.

Data from the OxVASC study,<sup>13,14</sup> the Oxfordshire Community Stroke Project (OCSP),<sup>15</sup> and those of Oxford hospital-referred TIA patients (TIA-series)<sup>6</sup> were analyzed separately and secondarily pooled with the other data.

### Statistical Analysis

Odds ratios (OR) for positive family history of stroke in women versus men and in mother versus father were calculated in all

	FHx+ / Patients		OR	95% CI
	Women	Men		
<b>Oxford data</b>				
OXVASC	104 / 423	87 / 383	1.11	0.80-1.54
OCSP	49 / 323	46 / 340	1.14	0.74-1.77
TIA-series	34 / 169	56 / 312	1.15	0.72-1.85
<b>Subtotal</b>	<b>187 / 915</b>	<b>189 / 1035</b>	<b>1.13</b>	<b>0.90-1.41</b>
<b>Published and unpublished data from previous studies</b>				
Marshall (1971)	4 / 55	24 / 140	0.38	0.13-1.15
<b>Vitullo (1996)</b>	<b>31 / 80</b>	<b>48 / 157</b>	<b>1.44</b>	<b>0.82-2.52</b>
Jousilahati (1997)	24 / 204	23 / 249	1.31	0.72-2.40
<b>Liao (1997)</b>	<b>15 / 37</b>	<b>22 / 66</b>	<b>1.36</b>	<b>0.59-3.13</b>
<b>Berger (1998)</b>	<b>5 / 34</b>	<b>16 / 95</b>	<b>0.85</b>	<b>0.29-2.53</b>
<b>Caicoya (1999)</b>	<b>47 / 223</b>	<b>58 / 247</b>	<b>0.87</b>	<b>0.56-1.35</b>
Tentschert (2003)	224 / 711	234 / 853	1.22	0.98-1.51
<b>Lisabeth (2005)</b>	<b>75 / 247</b>	<b>41 / 197</b>	<b>1.66</b>	<b>1.07-2.57</b>
<b>Lindgren (2005)</b>	<b>68 / 193</b>	<b>92 / 254</b>	<b>0.96</b>	<b>0.65-1.42</b>
<b>Subtotal</b>	<b>493 / 1784</b>	<b>558 / 2258</b>	<b>1.16</b>	<b>0.99-1.32</b>
<b>TOTAL</b>	<b>680 / 2699</b>	<b>747 / 3293</b>	<b>1.15</b>	<b>1.03-1.29</b>
<b>Significance</b>	<b>p= 0.028</b>			
<b>Heterogeneity</b>	<b>p= 0.45</b>			
	<b>I<sup>2</sup>= 31%</b>			



**Figure 1.** Any parental history of stroke in women vs men. Unpublished data are in bold. Heterogeneity: the probability value corresponds to the Breslow-Day test.

individual studies. In the comparison between the prevalence of maternal and paternal history of stroke, to avoid confounding attributable to any differences in characteristics between male and female probands, we used a paired analysis, OR simply being the ratio between the number of probands with a maternal history of stroke and the number of those with a paternal history.<sup>16</sup> However, we also performed a separate analysis comparing the prevalence of parental history of stroke in female and in male probands using a nonpaired analysis. OR from separate studies were combined by fixed-effects meta-analysis according to the Mantel-Haenszel method which is also valid for paired-OR.<sup>16</sup> Heterogeneity between studies was assessed by the Breslow-Day  $\chi^2$  test and  $I^2$  statistic.<sup>17</sup> The  $I^2$  statistic describes the percentage of total variation across studies that is attributable to heterogeneity rather than chance. Compared with the classical Breslow-Day  $\chi^2$  test, its interpretation is more intuitive and the value does not depend on the number of studies. There is no simple categorization of values of  $I^2$  although values over 75% are usually considered as meaning high heterogeneity.<sup>17</sup>

### Results

We identified 28 studies which were potentially relevant for the present systematic review (22 from our previous systematic review and 6 among 267 references obtained from the updated electronic search). We contacted authors of 17 studies published  $\geq 1995$  with no (n=13) or partial (n=4) data in relation to parent or proband sex. Authors of 4 studies provided all requested data,<sup>18-21</sup> 3 gave partial data,<sup>22,23,24</sup> 2 did not collect the necessary data,<sup>25,26</sup> and 8 did not reply. Thus, we obtained data from 18 studies (10 case-control studies, 4 case series, and 4 cohort studies), including unpublished data from 7 studies (Table 1). Family history information was obtained by structured interview in 11 studies,<sup>18-22,24,27-31</sup> death certificates in 4 studies,<sup>32-35</sup> self-administered questionnaire in 2 studies,<sup>23,36</sup> and the method used to collect this information was not given in 1 study.<sup>37</sup> The main characteristics of Oxford studies are also given in Table 1.<sup>13</sup>

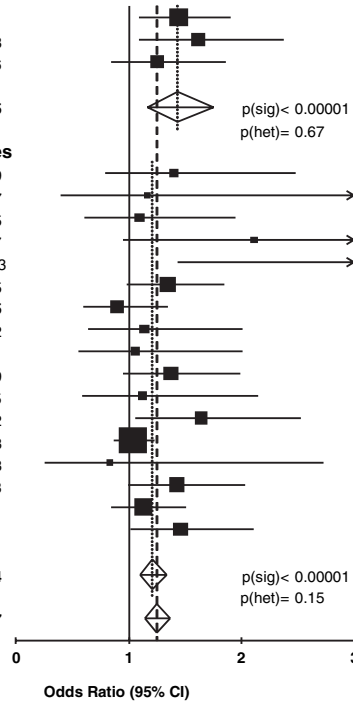
There was no significant difference between female and male probands in the prevalence of family history of stroke in any parent in Oxford data (OR=1.13; 0.90 to 1.41; Figure 1)

and in other data from 9 studies (4042 patients, unpublished data from 6 studies; OR=1.16; 95% CI, 0.99 to 1.32;  $P=0.05$ ; Figure 1). The pooled analysis showed that female probands were slightly, but significantly, more likely to have a positive family history of stroke in any parent than male probands (pooled OR=1.15; 1.03 to 1.28,  $P=0.028$ ; Figure 1) with no heterogeneity across studies. In Oxford data, a maternal history of stroke was more common than a paternal history (Figure 2). Separate data for maternal and paternal history of stroke were available from 17 further studies (5710 patients, unpublished data from 3 studies). There was also a maternal excess of stroke in these studies (OR=1.21; 1.10 to 1.34; Figure 2). The pooled analysis showed a significant excess of maternal history of stroke (pooled OR=1.25; 1.15 to 1.37; Figure 2) without significant heterogeneity across studies.

However, as shown in Figures 3 and 4, the maternal excess was only present in female probands in Oxford cohorts (OR=2.03; 1.50 to 2.76). Although smaller, a similar excess was found in data from 8 studies identified in the literature from which data stratified by both sex of proband and sex of affected parent(s) were available (2002 women, unpublished data from 4 studies): OR=1.29 (1.12 to 1.56,  $P=0.0004$ ). The pooled analysis of all available data showed that women were more likely to have a maternal than a paternal history of stroke (OR=1.47; 1.27 to 1.70) with no significant heterogeneity across studies. Figures 3 and 4 also shows that, in contrast to female probands, male probands were no more likely to have maternal than paternal history of stroke in either the Oxford cohorts or in the other available studies (1967 patients from 8 studies, including unpublished data from 4 studies): pooled OR=1.02 (0.88 to 1.17).

In the nonpaired analyses, comparing female and male probands, females were more likely than males to have a maternal history of stroke (OR=1.42; 1.22 to 1.66,  $P_{(sig)} < 0.00001$ ,  $P_{(het)} = 0.52$ ), whereas they were no more likely to have a paternal history of stroke than males

	FHx+ / Patients Mother	FHx+ / Patients Father	OR	95% CI
<b>Oxford data</b>				
OxVASC	118 / 781	82 / 781	1.44	1.09-1.91
OCSP	66 / 663	41 / 663	1.61	1.09-2.38
TIA-series	55 / 481	44 / 481	1.25	0.84-1.86
<b>Subtotal</b>	<b>239 / 1925</b>	<b>167 / 1925</b>	<b>1.43</b>	<b>1.17-1.75</b>
<b>Published and unpublished data from previous studies</b>				
Gifford, 1966	28 / 126	20 / 126	1.40	0.79-2.49
Alter (1967)	7 / 44	6 / 44	1.17	0.39-3.47
Gertler (1968)	24 / 133	22 / 133	1.09	0.61-1.95
Marshall (1971)	19 / 192	9 / 192	2.11	0.96-4.67
Welin (1987)	17 / 57	4 / 57	4.25	1.43-12.63
Lindenstrom (1993)	89 / 696	66 / 696	1.35	0.98-1.85
<b>Vitullo (1996)</b>	<b>44 / 237</b>	<b>49 / 237</b>	<b>0.90</b>	<b>0.60-1.35</b>
Jousilahati (1997)	25 / 453	22 / 453	1.14	0.64-2.02
<b>Liao (1997)</b>	<b>19 / 103</b>	<b>18 / 103</b>	<b>1.06</b>	<b>0.55-2.01</b>
Caicoya (1999)	66 / 470	48 / 470	1.38	0.95-1.99
Reed (2000)	19 / 83	17 / 83	1.12	0.58-2.15
Starr (2001)	54 / 225	33 / 225	1.64	1.06-2.52
Tentschert (2003)	253 / 1564	245 / 1564	1.03	0.87-1.23
Kim (2004)	5 / 49	6 / 49	0.83	0.25-2.73
Lisabeth (2005)	74 / 444	52 / 444	1.42	1.00-2.03
<b>Lindgren (2005)</b>	<b>97 / 347</b>	<b>86 / 347</b>	<b>1.13</b>	<b>0.84-1.51</b>
MacClellan (2006)	70 / 487	48 / 487	1.46	1.01-2.11
<b>Subtotal</b>	<b>910 / 5710</b>	<b>751 / 5710</b>	<b>1.21</b>	<b>1.10-1.34</b>
<b>TOTAL</b>	<b>1149 / 7635</b>	<b>918 / 7635</b>	<b>1.25</b>	<b>1.15-1.37</b>
<b>Significance</b>	<b>p &lt; 0.00001</b>			
<b>Heterogeneity</b>	<b>p = 0.18</b> <b>I<sup>2</sup> = 65%</b>			



**Figure 2.** Maternal vs paternal history of stroke. Unpublished data are in bold. Heterogeneity: the probability value corresponds to the Breslow-Day test.

(OR=0.87, 0.74 to 1.03;  $P_{(sig)}=0.13$ ,  $P_{(het)}=0.27$ ) (data not shown).

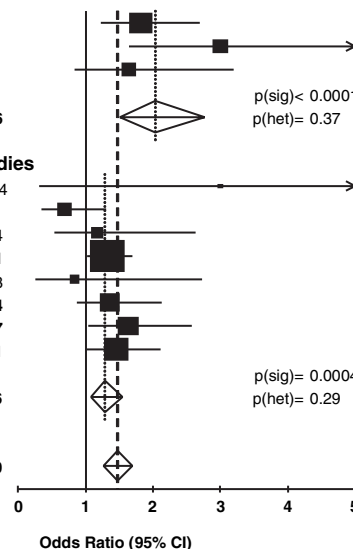
Although, in the OxVASC study, we found that female probands were also more likely to have a history of stroke in sisters than in brothers, no similar data were available in previous published studies. Similarly, maternal excess in female probands was consistent across age group and stroke

subtypes in the Oxfordshire studies,<sup>13</sup> but we did not find any similar data in the literature.

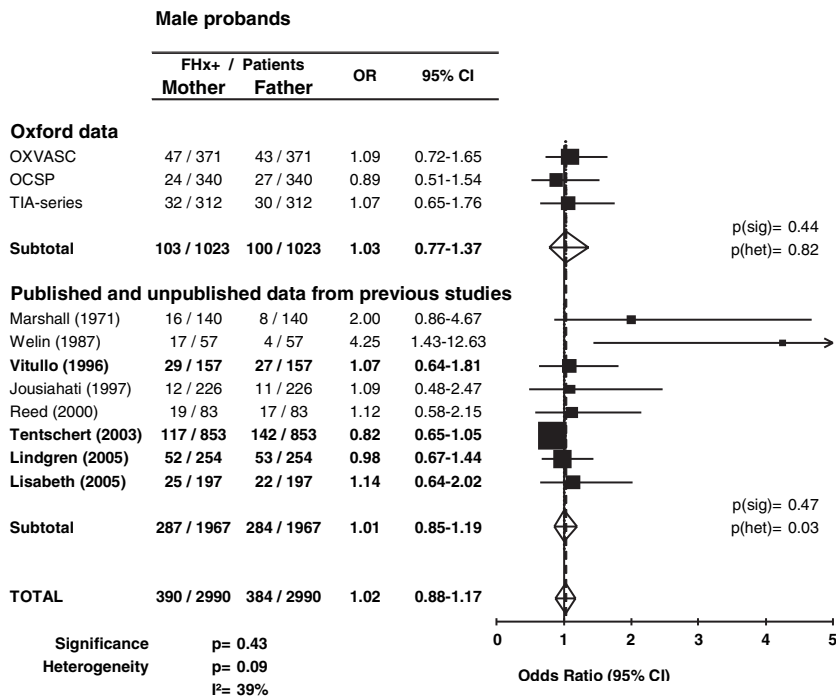
Finally, to test whether the maternal excess of stroke could be explained by some artifact attributable to previous sex- and age-specific differences in stroke incidence, we used the data from the OCSP, which ascertained all incident strokes in our population from 1981 to 1986, ie, corresponding approx-

**Female probands**

	FHx+ / Patients Mother	FHx+ / Patients Father	OR	95% CI
<b>Oxford data</b>				
OxVASC	71 / 410	39 / 410	1.82	1.2-2.7
OCSP	42 / 323	14 / 323	3.00	1.6-5.5
TIA-series	23 / 169	14 / 169	1.64	0.8-3.2
<b>Subtotal</b>	<b>136 / 902</b>	<b>67 / 902</b>	<b>2.03</b>	<b>1.50-2.76</b>
<b>Published and unpublished data from previous studies</b>				
Marshall (1971)	3 / 55	1 / 55	3.00	0.31-28.84
<b>Vitullo (1996)</b>	<b>15 / 80</b>	<b>22 / 80</b>	<b>0.68</b>	<b>0.35-1.31</b>
Jousilahati (1997)	13 / 180	11 / 180	1.18	0.53-2.64
<b>Tentschert (2003)</b>	<b>136 / 711</b>	<b>103 / 711</b>	<b>1.32</b>	<b>1.02-1.71</b>
Kim (2004)	5 / 49	6 / 49	0.83	0.25-2.73
<b>Lindgren (2005)</b>	<b>45 / 193</b>	<b>33 / 193</b>	<b>1.36</b>	<b>0.87-2.14</b>
<b>Lisabeth (2005)</b>	<b>49 / 247</b>	<b>30 / 247</b>	<b>1.63</b>	<b>1.04-2.57</b>
MacClellan (2006)	70 / 487	48 / 487	1.46	1.01-2.11
<b>Subtotal</b>	<b>336 / 2002</b>	<b>254 / 2002</b>	<b>1.29</b>	<b>1.12-1.56</b>
<b>TOTAL</b>	<b>808 / 4906</b>	<b>575 / 4906</b>	<b>1.47</b>	<b>1.27-1.70</b>
<b>Significance</b>	<b>p &lt; 0.00001</b>			
<b>Heterogeneity</b>	<b>p = 0.11</b> <b>I<sup>2</sup> = 80%</b>			



**Figure 3.** Maternal vs paternal history of stroke in female probands. Unpublished data are in bold. Heterogeneity: the probability value corresponds to the Breslow-Day test.



**Figure 4.** Maternal vs paternal history of stroke in male probands. Unpublished data are in bold. Heterogeneity: the probability value corresponds to the Breslow-Day test.

imately to the period during which strokes were occurring in the parents of OxVASC patients.<sup>38</sup> As shown in Table 2, the expected ratio of maternal to paternal strokes was less than 1 for events occurring under the age of 75 years, but the ratio reversed for strokes at older ages. In female probands under the age of 75 years in OxVASC, the observed excess of strokes in mothers was opposite to that expected. In male probands with stroke under age 75 years, the sex ratio for parental stroke was approximately unity but this possibly also represented a small excess of maternal stroke compared with that expected on the basis of OCSF incidence data.

### Discussion

This systematic review and meta-analysis of published and unpublished data shows that women are about 50% more likely to have a maternal than a paternal history of stroke whereas no similar excess exists in men. The present replication of our previous findings in Oxford studies across different continents and in various study designs shows that the finding is unlikely to be attributable to chance or to be a consequence of some unknown selection biases. The maternal excess that we have demonstrated in female probands but not in males is unlikely to be explained by any sex difference in life-time risk of stroke, which is very similar in women and

men in incidence studies.<sup>14,39</sup> Moreover, any explanation based on a greater incidence of ischemic stroke in women of the parental generation would not be consistent with our finding of no excess of maternal stroke in male probands. Although in earlier data from the Framingham cohort paternal history of stroke appeared to be a more potent risk factor for stroke in offspring than maternal history,<sup>40</sup> other studies found that maternal and paternal history of stroke provided a relatively similar increase in risk of stroke.<sup>24,36</sup> However, sex-specific data are very scarce,<sup>36</sup> and therefore, differences in risk of stroke associated with maternal or paternal history between male and female probands could not be excluded. Our result supports previous findings of distinct maternal and paternal influences on the risk of cardiovascular diseases.<sup>8,10,11,41</sup> It is also plausible given that there are several other well-recognized differences between males and females with stroke and TIA.<sup>9</sup>

A higher maternal transmission has been observed in several other conditions predisposing to vascular diseases including diabetes mellitus, hypertension, and low HDL-cholesterol concentration,<sup>12,42-44</sup> and has also been recently documented in coronary artery disease.<sup>45</sup> As in these conditions, genetic and nongenetic factors could explain the excess maternal transmission and are not mutually exclusive. How-

**Table 2. Comparison Between Ratio Women-Men in OCSF and Ratio Mothers-Fathers in OxVASC (Ratios of Crude Numbers)**

Age of Stroke in Parents (Years)	Expected Mothers/Fathers Ratios (OCSF Data)	Observed Mothers/Fathers Ratios (95% CI) (OxVASC Data)			
		Female Probands		Male Probands	
<65	0.7	15/9	1.67 (0.73-3.81)	10/10	1.00 (0.42-2.40)
65-74	0.6	19/9	2.11 (0.96-4.67)	13/11	1.18 (0.53-2.58)
≥75	1.5	30/17	1.76 (0.97-3.20)	19/19	1.00 (0.53-1.89)
TOTAL	0.9	64/35	1.83 (1.21-2.76)	42/40	1.05 (0.68-1.62)

ever, mother-to-daughter transmission cannot be explained easily by classical genetic mechanisms. Mitochondrial transmission of a genetic profile that had greater penetrance in females is theoretically possible but, to our knowledge, such an interaction between mitochondrial genome and sex of the proband has never been documented. Epigenetic phenomena could also account for our findings.<sup>46</sup> They are changes in gene expression that do not entail a change in DNA sequence but have sufficient stability to be transmitted from parental cell to daughter cells. This occurs by altering the chromatin structure and includes covalent modifications of DNA and histones. Genomic imprinting is a subtype of epigenetic regulation in which the activity of a gene is reversibly modified depending on the sex of the parent that transmits it, leading to unequal expression of the maternal and the paternal alleles for a diploid locus. There is evidence that epigenotype, in particular imprinting genes, could be more susceptible to environmental factors (including maternal behavior in animal) than genotype,<sup>46,47</sup> and interactions between imprinting phenomena and sex of the offspring have been suggested in other diseases.<sup>48</sup>

There are also potential nongenetic explanations for our findings. First, mothers and daughters could share environmental risk factors for stroke. In our previous analysis of OXVASC data, we did not find any relation with the traditional vascular risk factors, but there are other factors such as those related to childhood socioeconomic or psychological environment that could be relevant. For example, maternal influence on stress reactivity is well documented in rodents and humans.<sup>49</sup> It has been hypothesized that childhood maternal environment influences the development of responses to stress, which form the basis for vulnerability/resistance to diseases in adulthood.<sup>49</sup> Second, consequences of programming during the fetal life by maternal intrauterine environment or during early infancy are also plausible explanations.<sup>50,51</sup> The fetal origins hypothesis proposes that coronary artery disease, type 2 diabetes, stroke, and hypertension originate in developmental plasticity, in response to adverse intrauterine environment during fetal life or rapid gains in weight during infancy.<sup>10</sup> A number of sex-specific effects have been described in animal models of fetal programming, with females appearing to be more sensitive to some programming effects, and these results have been supported in a few human studies.<sup>41</sup> Interestingly, there is evidence that fetal or early life programming and responses to stress are related to epigenetic modifications (ie, interactions between epigenotype and environmental factors).<sup>41,49</sup>

The maternal excess in women was greater in the 2 earliest studies (Figure 3)—the OCSF and Marshall study.<sup>33</sup> This could be attributable to chance or to differences in the way of collecting family history data, but might also reflect changes over time in the prevalence of environmental factors which could interact with epigenotype or early life programming. Although the strength of the association was weaker in other data than in ours, the association was still highly significant in other data. The  $I^2$  value found in this analysis suggested high heterogeneity across studies. However, estimates showed the same direction of effect, with almost all studies showing a maternal excess in women.<sup>17</sup>

Several potential limitations need to be addressed. First, the accuracy and exhaustiveness of family history data may be questioned. Studies in which family history data were collected from patients' reports could have inappropriately considered hemorrhagic strokes in parents as a positive family history. However, hemorrhagic strokes account for a small proportion of strokes and although probands could be unaware of the exact diagnosis in their parent, this potential bias is unlikely to be related to the sex of the proband. There is also potential differential accuracy in recall of family history between men and women, with women tending to report family history more accurately than males in some diseases.<sup>52</sup> However, the Framingham offspring study showed that the accuracy of parental history reports did not differ between men and women for any risk factor or vascular disease, nor between maternal and paternal conditions.<sup>53</sup> More importantly, because recall-bias can be a major problem in case-control studies we restricted our study to case-case comparisons. Anyway, it is unlikely that female probands would be expected to recall stroke in their mother to a substantially greater extent than stroke in their fathers. Therefore, none of these potential recall biases are likely to explain our findings. Second, some studies of our meta-analysis included a proportion of hemorrhagic strokes. However, we only included studies with a small proportion of hemorrhagic strokes (see Methods) and there was no heterogeneity across studies. Moreover, exclusion of studies in which hemorrhagic strokes were included did not change our results (data not shown). Third, it has been suggested that apparent maternal transmission of diabetes could partly be explained by coding "don't know" responses as indicating no family history, with unknown paternal status being more common than unknown maternal status in that study.<sup>54</sup> However, the bias was unrelated to the sex of the proband. Moreover, in OXVASC, we found that "don't know" responses were rare and in fact slightly more common in female probands.<sup>13</sup> Fourth, another potential bias could result from patients with severe or fatal stroke for whom family history is usually unknown. Yet, as suggested by a recent study, those patients may be more likely to have a positive family history.<sup>55</sup> However, in that study, the association with severity was found with sibling history of stroke only and there was no evidence for interaction with the sex of the proband. Fifth, the longer average life span in women and the strong relation between age and stroke incidence result in bigger numbers of old women at risk of stroke and higher crude numbers of strokes in women than in men in the oldest categories of age ( $\geq 75$  years). This could have explained a slight excess of maternal strokes in our analyses. However, the age-specific incidence of ischemic stroke is higher in men and overall incidences are the same in men and in women. Moreover, in OXVASC for example, the mean age of death of mothers was similar in male and female probands, and the maternal excess in women was observed across all categories of age.<sup>13</sup> Considering an expected prevalence higher in fathers than in mothers from OCSF data, the excess of maternal history of stroke  $< 75$  years was in fact greater than twice in females. Although the analysis comparing OCSF data to OXVASC findings may have some limitations, it does not support that

our results could be explained by any artifact due to sex- and age-specific differences in stroke incidence. Nevertheless, it remains to be demonstrated that there is no similar maternal excess in females in an appropriate control population. Finally, a small bias might be expected because of nonpaternity. However, rates of nonpaternity are not sufficiently high to account for the effect sizes that we observed and although they could lead to small apparently increased maternal heritability, this effect would not be dependent on the sex of the proband.

In summary, we have shown that women with stroke are more likely than men to have a parental history of stroke, and that this is accounted for by an excess maternal history of stroke in female probands. This finding is consistent across all available published and unpublished data and could be explained by sex-specific genetic, epigenetic, or nongenetic mechanisms.

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### Disclosures

None.

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