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Family history of stroke and severity of neurologic deficit after stroke

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Abstract

Background—A family history of stroke is an independent risk factor for stroke.

Objective—To assess whether severity of neurologic deficit after stroke is associated with a family history of stroke.

Methods—The Ischemic Stroke Genetics Study, a five-center study of first-ever symptomatic ischemic stroke, assessed case subjects prospectively for a family history of stroke-affected first-degree relatives. Certified adjudicators used the NIH Stroke Scale (NIHSS) to determine the severity of neurologic deficit.

Results—A total of 505 case subjects were enrolled (median age, 65 years; 55% male), with 81% enrolled within 1 week of onset of symptoms. A sibling history of stroke was associated with more severe stroke. The odds of an NIHSS score of 5 or higher were 2.0 times greater for cases with a sibling history of stroke compared with cases with no sibling history (95% CI, 1.0 to 3.9). An association of family history of stroke in parents or children with stroke severity was not detected.

Conclusions—A sibling history of stroke increased the likelihood of a more severe stroke in the case subjects, independent of age, sex, and other potential confounding factors. Other family history characteristics were not associated with stroke severity.

Background genetics can influence ischemic stroke outcome as demonstrated in the spontaneously hypertensive stroke-prone rat (SHR-SP).¹ Second filial (F2) hybrid rats cross-derived from the SHR-SP and the normotensive Wistar-Kyoto (WKY) rat reference strain were subjected to permanent middle cerebral artery occlusion (MCAO) with histologic assessment of infarct volume. A genome scan identified a locus accounting for 67% of the total variance in infarct volume and co-localized with the genes encoding atrial natriuretic factor and brain

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natriuretic factor. Rat strain also may affect infarct volume after permanent MCAO as assessed by MRI in SHR-SP, WKY, and first filial (F1) hybrids.²

Few studies have examined the relationship between family history of stroke and stroke severity. The British Regional Heart Study followed 7,735 men age 40 to 59 for nearly 15 years.³ Sixty-three subjects had a fatal stroke, and 215 had a nonfatal stroke. No association was seen between parental history of stroke and fatal stroke (age-adjusted relative risk [RR], 0.8). However, a parental history of stroke was associated with nonfatal stroke (age-adjusted RR, 1.9 [95% CI, 1.3 to 2.6]). The Atherosclerosis Risk in Communities Study followed 15,792 subjects who were 45 to 64 years old at recruitment.⁴ Parental history of stroke was not associated with clinical stroke, but parental history of stroke was associated with a 1.64-fold increase in the risk of subclinical cerebral infarction detected by MRI. The relationship between family history of stroke and stroke severity as defined by neurologic status has not been studied in detail.

Methods

Study population

The original aims and methods of the Ischemic Stroke Genetics Study (ISGS) have been published.⁵ The institutional review boards at all participating centers have approved the ISGS protocol. All participants provided written informed consent. Case subjects were male and female adults (>18 years old) who presented to one of five academic stroke centers in the United States with a symptomatic first-ever ischemic stroke. Subjects had to be enrolled within 30 days after onset of stroke symptoms. Subjects were not enrolled if, in the judgment of the study neurologist, they were suspected of having, in addition to the stroke, a neurologic disorder that could measurably affect the NIH Stroke Scale (NIHSS).

Stroke was defined according to the criteria of the World Health Organization⁶ as rapidly developing signs of a focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin. A diagnosis of ischemic stroke was made only if the subject had a clinical diagnosis of stroke and a CT scan or MRI of the brain done after onset of symptoms showed the relevant infarct or failed to show an alternative etiology for the stroke symptoms. Subjects with hemorrhagic transformation of an infarct remained eligible.

Each subject with suspected stroke admitted to a participating center was evaluated according to current standards of care. The evaluation included a medical history, physical examination, CT or MRI of the head, and laboratory testing. Where clinically indicated, the evaluation also included imaging of the cervical and intracranial vessels with ultrasonography; MRI, CT, or digital subtraction angiography; imaging of the heart with transthoracic or transesophageal echocardiography; resting and ambulatory EKG; and additional blood testing.

Family history

The family history was obtained by interviewing the case subject or, when necessary, an alternate informant. A family history of stroke was taken for all living or deceased first-degree relatives (FDRs). The family history interviewer instructed the informant on the distinctions between a biologic parent and an adoptive parent, foster parent, or stepparent; a full sibling and a half sibling or stepsibling; and a biologic child and an adopted child or stepchild. Subjects had the option to initiate contact with their FDRs and clarify points of history within 30 days of enrollment. The interviewer recorded the total number of living and deceased full siblings and the total number of living and deceased biologic children so that analyses could be adjusted for pedigree size. Family history was verified with the medical record.

Deficit severity

The severity of the neurologic deficit was assessed within 48 hours of enrolling a case subject by means of the NIHSS⁷ administered by an examiner who was trained and certified through the American Stroke Association using video-recorded live patient vignettes in a manner previously described.⁸ Severity was also assessed in terms of the effects of stroke on global functioning using the Oxford Handicap Scale (OHS)⁹ and Glasgow Outcome Scale (GOS)¹⁰ and the effects on ability to perform activities of daily living using the Barthel Index (BI).¹¹

Stroke subtyping

A single neurologist adjudicator, blinded to genotype data and personal health identifiers, assigned subtype diagnoses to the ischemic stroke by reviewing medical records compiled in a standard fashion. Because the final subtype diagnosis has been shown to vary from initial diagnosis in approximately one-third of cases,¹² the adjudicator reviewed all available and relevant information obtained after completion of the stroke workup. Standardized and reliable classification systems were used: the Trial of Org 10172 in Acute Stroke Treatment (TOAST), which uses all available clinical and radiographic information,¹³ and the Oxfordshire Community Stroke Project (OCSP) system, which uses the clinical syndrome for classification.¹⁴

Statistical analysis

Enrolled subjects were asked how many parents had previous strokes, how many siblings they had and how many of those siblings had strokes, and how many children they had and how many had strokes. A case subject was considered positive for a parent, sibling, or child history of stroke if one or more of those specific relatives had a previous stroke. Analyses of the specific histories were limited to those with one or more relatives at risk for stroke. A family history was determined on the basis of combined answers to the parent, sibling, and child questions. The number of FDRs was calculated as the sum of the number of parents, siblings, and children, when those questions were answered. A case subject was considered positive for an FDR history of stroke if any FDR had a previous stroke.

Wilcoxon rank sum test were used to assess the effect of having a parent, sibling, child, or family history of stroke on stroke severity as quantified by the NIHSS, BI, OHS, and GOS. Separate analyses were done by classifying affected history as none, one affected relative, and more than one affected relative. Rank analysis of covariance was used to assess the effect of specific histories adjusted for baseline covariates, including age at stroke (in years), number of relatives, sex, race/ethnicity, site, prestroke OHS score (with levels 3 to 5 combined), hypertension, and presence of diabetes mellitus.

Stroke severity is sometimes reported in the literature by dichotomizing one or more of the instruments mentioned above, so we also performed exploratory analyses to assess the effect of stroke history on stroke severity by dichotomizing each of the stroke severity measures. Although no cut-point for any of these scales is universally accepted, we chose values that have been used previously by other investigators. Stroke was considered severe if the NIHSS score was 5 or higher, BI was less than 80, OHS was 3 or higher, or GOS was 3 or higher. The χ^2 test was used to assess the unadjusted associations between stroke history and stroke severity for each of the dichotomized measures. Logistic regression was applied to assess these associations after adjusting for other covariates, using the same variables mentioned above for the analysis of covariance. Separate analyses were done to assess the impact of the particular cut-points chosen.

In addition, we did an exploratory analysis to test the association between stroke history and a combined stroke severity measure (CSSM). Although the four scales could be combined in numerous ways, we used a principal components analysis to obtain the linear combination of the four measures that accounts for the greatest variance (i.e., the combination that captures as much of the information as possible in the original four variables). For this analysis, we first subtracted BI from 100 so that higher scores on all scales reflected more severe strokes. Each measure was then standardized by subtracting its mean and dividing by its SD, and the weights were determined for these standardized variables. Analysis of variance was used to assess the unadjusted effect of stroke history on this CSSM. Analysis of covariance (ANCOVA) was used to assess the effect of stroke history adjusted for the covariates mentioned above. Least squares estimates and SEs were calculated from the fitted ANCOVA model.

Results

Between December 2002 and June 2005, a total of 505 case subjects with first-ever ischemic stroke were prospectively accrued to this study, with approximately equal numbers accrued at each of the five sites (table 1). These subjects ranged in age from 19 to 94 years, with a median of 65 years; 40% were aged 70 years or older. Sixty-eight percent were white, 55% were male, and 71% were overweight (body mass index [BMI] >25 and <30 kg/m²) or obese (BMI >30 kg/m²). The majority of subjects were not current smokers (73%). Before the current stroke, most subjects (76%) had no symptoms that interfered with their lifestyle; 12% had minor to severe handicaps. The majority (71%) had hypertension, 45% had hyperlipidemia, and 27% had diabetes mellitus. Other medical conditions (e.g., TIA, congestive heart failure, angina, myocardial infarction, and atrial fibrillation) occurred in less than 20% of the case subjects. Thirty-two percent of the case subjects were recruited within 2 days of their stroke, 60% within 4 days, 81% within 1 week, and 94% within 2 weeks.

Of the 488 case subjects who provided parent data, 143 (28%) reported that one parent and 24 (5%) reported that both parents had experienced a stroke. Four hundred thirty-eight case subjects had siblings and provided data regarding sibling stroke history. The number of siblings ranged from 1 to 15, with a median of 3; 41 subjects (9%) had 1 sibling and 13 (3%) had 2 or more siblings with previous strokes. Four hundred twenty-seven case subjects had children and provided data regarding child stroke history. The number of children ranged from 1 to 12, with a median of 3; 11 case subjects (3%) had 1 child and 6 (1%) had 2 or more children with previous strokes. All but one case subject provided some family history data. The number of FDRs ranged from 2 to 20, with a median of 8. Altogether, 207 case subjects (41%) had some family history of stroke; 149 (30%) had 1, 41 (8%) had 2, and 17 (3%) had 3 or more affected FDRs. Twenty case subjects had parent and sibling history of stroke, 5 had parent and child history, 2 had sibling and child history, 2 had parent, sibling, and child history, 140 had a parent history only, 8 had a child history only, and 30 had a sibling history only. Family history data are summarized in table E-1 on the *Neurology* Web site (www.neurology.org).

Stroke characteristics and severity

Stroke characteristics are summarized in table E-2. Forty-two case subjects had strokes that were not visualized on CT or MRI. The remainder had stroke diameters that were approximately equally distributed among the categories of less than 1.5 cm, 1.5 to 3.0 cm, and larger than 3.0 cm. The majority (76%) of strokes were supratentorial (equal numbers in the left and right hemispheres), 15% were infratentorial, and 1% were in multiple locations (four of these infratentorial and supratentorial and one right and left supratentorial). According to the TOAST classification, 19% of case subjects had strokes that were due to large-artery atherosclerosis, 18% due to small-vessel occlusions, 24% due to cardioembolism, 4% due to other causes, and 35% due to undetermined etiology. According to the OCSP classification,

28% of the case subjects had lacunar infarcts, 10% had total anterior circulation infarcts, 44% had partial anterior circulation infarcts, and 18% had posterior circulation infarcts.

Stroke severity was quantified by four separate measures as described above: NIHSS, BI, OHS, and GOS. The NIHSS scores ranged from 0 to 30, with a median of 2 and a mean (SD) of 4.0 (4.9). Seventeen percent of the subjects had scores of 0, 18% had scores of 1, 35% had scores between 2 and 4, 22% had scores between 5 and 10, and 8% had scores of 11 or higher. The BI ranged from 0 to 100, with a median of 90 and a mean (SD) of 78.2 (27.9). Forty-two percent of the subjects scored 100 on this test, 21% scored between 80 and 95, 16% scored between 60 and 75, 16% scored between 20 and 55, and 5% scored less than 20. OHS scores at enrollment ranged from 0 (no symptoms) to 5 (severe handicap). Fourteen percent had no symptoms, 26% had minor symptoms, 28% had minor handicaps, 18% had moderate handicaps, 11% had moderately severe handicaps, and 3% had severe handicaps. Fifty-one percent of the subjects had GOS scores of 1 (good recovery) at enrollment, 30% had scores of 2 (moderately disabled), and 19% had scores of 3 (severely disabled). Correlations were high among the four severity measures, with Spearman rank correlations ranging from 0.61 (NIHSS and GOS) to 0.82 (OHS and GOS).

Stroke severity, stratified by family history, is summarized in table 2. In this table, the severity measures are considered continuously, and rank statistics (Wilcoxon rank sum test and rank ANCOVA for unadjusted and adjusted tests) were used to assess the association between history and severity. An association of parent history of stroke with stroke severity was not detected with any of the stroke severity measures, unadjusted or adjusted for other case subject and stroke characteristics. The same was true for a history of stroke in the case subject's children and in any FDRs. However, a sibling history of stroke was significantly associated with each severity measure except NIHSS. Cases with a sibling history of stroke had a mean (SD) NIHSS score of 4.6 (4.6), and cases without a sibling history of stroke had a mean (SD) NIHSS of 3.9 (4.9) ($p = 0.09$). Cases with a sibling history of stroke had a mean BI score of 68.0 (27.2), and cases without a sibling history of stroke had a mean BI score of 79.7 (27.5) ($p = 0.001$). Cases with a sibling history of stroke had a mean OHS score of 2.4 (1.4), and cases without a sibling history of stroke had a mean OHS score of 1.9 (1.3) ($p = 0.005$). Cases with a sibling history of stroke had a mean GOS score of 1.9 (0.8), and cases without a sibling history of stroke had a mean GOS score of 1.6 (0.8) ($p = 0.005$). The relationships of sibling history with BI, OHS, and GOS remained significant after adjustment for other covariates ($p = 0.02$ for BI, $p = 0.04$ for OHS, and $p = 0.02$ for GOS). The relationship of sibling history and NIHSS remained nonsignificant after adjustment for covariates ($p = 0.08$). There was no evidence that having multiple affected relatives increased the risk of having more severe strokes (data not shown).

Exploratory analyses

We also considered each severity measure dichotomized above and below certain cut-points, as described in Methods. These results are summarized in table 3. As with the previous analyses, there is no significant association between stroke severity and a history of stroke in parents, children, or any FDRs. Those case subjects with a sibling history of stroke, however, tended to have more severe strokes. Forty-three percent of case subjects with a sibling history had NIHSS scores of 5 or higher compared with 28% of case subjects without a sibling history ($p = 0.03$). Likewise, the percentages of case subjects with BIs less than 80 were 59% for cases with a sibling history of stroke and 34% for cases without a sibling history of stroke ($p < 0.001$). A total of 48% of cases with a sibling history of stroke and 30% of cases without a history of stroke had OHS scores of 3 or higher ($p = 0.007$). A total of 31% of cases with a sibling history of stroke and 16% of cases without a history of stroke had GOS scores of 3 or higher ($p = 0.007$). These relationships remained significant, or nearly significant, after adjustment for other covariates ($p = 0.04$ for NIHSS, $p = 0.004$ for BI, $p = 0.06$ for OHS, and $p = 0.05$ for

GOS). Again, no evidence suggested that having multiple affected siblings increased the risk of a severe stroke.

Separate analyses were done to look at how changing the cut-points would affect the results. The results for NIHSS were more sensitive to the cut-point chosen compared with the other three measures. The univariate association between a sibling stroke history and NIHSS was only significant using 5 or 6 as the cut-point, and the association with BI was significant using any cut-point higher than 40. For GOS, all cut-point choices resulted in a significant association, and cut-points of 2, 3, or 4 for OHS resulted in significant associations.

Hypertension was not associated with stroke severity as measured by NIHSS, OHS, or GOS (all $p > 0.05$). History of hypertension was associated with a small mean (SD) reduction in the BI (76.5 [28.4] vs 82.5 [26.5]), which predicted a slightly worse stroke outcome ($p = 0.005$). Among the case subjects with siblings, 49 of 309 with hypertension reported a sibling with a history of stroke; in contrast, only 5 of 127 nonhypertensive individuals reported a sibling history of stroke ($p = 0.001$). There were no differences in parent (123/347 vs 43/139; $p = 0.34$) or child (14/303 vs 3/122; $p = 0.30$) history of stroke for hypertensive and nonhypertensive individuals.

A principal components analysis was used to create the CSSM, as described in Methods. The first principal component accounted for 80% of the variability in the original four measures and had weights of 0.464, 0.520, 0.510, and 0.504 for NIHSS, BI, OHS, and GOS, standardized by subtracting their means and dividing by their SDs. Values of CSSM ranged from -2.00 to 5.98 with a mean (SD) of 0 (1.79) and a median of -0.47, where higher scores represented more severe strokes. As with the individual stroke severity measures, histories of stroke in parents ($p = 0.35$), children ($p = 0.97$), and FDRs ($p = 0.79$) were not significantly associated with CSSM. Sibling history, however, was significantly associated with CSSM. The mean (SD) CSSM for those cases with a sibling history of stroke was 0.60 (1.81) vs -0.11 (1.78) for cases without a sibling history of stroke ($p = 0.006$).

ANCOVA was used to assess which factors were significantly associated with CSSM (table 4) and to assess the effect of sibling history after adjustment for those covariates. Sibling history was still significant after adjustment for other covariates ($p = 0.003$), with those with a sibling history having more severe strokes. Other factors that were significantly associated with CSSM were age, prestroke OHS score, and site. Older age and prestroke disabilities were predictive of more severe strokes.

Discussion

In this multicenter prospective study of recent first-ever ischemic stroke, stroke severity, as assessed by the NIHSS, BI, OHS, and GOS, was associated with sibling history of stroke. An association of stroke severity with history of stroke in a child, parent, or FDR was not detected. A modest association of stroke and family history of stroke is well recognized.^{15,16} Our study demonstrates the association of sibling history of stroke and stroke severity. These data are supported by evidence from animal studies that genetic milieu influences infarct size^{1,2} and susceptibility to cerebral ischemia.¹⁷ In humans, variants of specific candidate genes have been tentatively linked to susceptibility to cerebral ischemia.¹⁸ Genetic determinants of stroke severity may differ substantially from the genetic determinants of stroke susceptibility. In fact, genetic factors could affect stroke severity in many ways, including influencing recanalization or collateralization, differential ischemic vulnerability, or ability to recover rapidly from deficits. To the extent that there may be genetic determinants of infarct volume, finding an association between family history and stroke severity is confounded by the imperfect correlation between infarct volume and stroke severity.^{19,20}

Other studies have suggested that sibling history of stroke may be a more potent risk factor than parent history for ischemic stroke. A case-control study of young women ages 18 to 44 years demonstrated a significant twofold increase in FDRs with stroke (OR, 2.04 [95% CI, 1.15 to 3.62]).²¹ Among subgroups, women with ischemic stroke were 3.2 times more likely than age-matched controls to report a sibling with a history of stroke but only 1.8 times more likely to report a parent with a history of stroke. However, neither of these was significant. In a retrospective analysis of a prospectively collected Japanese cohort,²² sibling history of stroke was associated with an increased risk of ischemic stroke; the OR was 2.7 (95% CI, 2.6 to 2.9) after adjusting for age, sex, and other risk factors. By comparison, the OR was 2.0 (95% CI, 1.8 to 2.2) for parent history of stroke. Co-aggregation of stroke and hypertension was much stronger among siblings (OR, 7.7 [95% CI, 7.3 to 8.1]) than across generations (OR, 2.3 [95% CI, 2.2 to 2.4]).²²

The interactions of hypertension, stroke, and family history add complexity to genetic and family history research on ischemic stroke.²³ Family history of stroke is associated with proband hypertension in community-based and hospital-based populations with ischemic stroke.²⁴ In a pooled analysis of four populations with either stroke or TIA, family history of stroke was strongly related to history of hypertension in the proband, with an OR of 1.8 (95% CI, 1.3 to 2.5; $p = 0.0008$).²⁵ Several authors caution that hypertension may account for a significant component of the heritability of ischemic stroke.

Hypertension is a risk factor for both large- and small-vessel strokes, but its relationship to ischemic stroke severity is poorly characterized.²⁶ Hypertension may be associated with favorable outcomes in patients with stroke and carotid occlusion.²⁷ Others have found prestroke hypertension to have no relationship to stroke severity and perhaps an inverse relationship with 28-day mortality in a community-based cohort of first-ever stroke patients.²⁸ In the cohort of first-ever stroke patients from the following year, the same investigators found no relationship between hypertension and stroke severity and mortality.²⁹

In our study, individuals with hypertension were four times more likely to report a sibling with a history of stroke, whereas no such increase was observed with parent or child history of stroke. There is little evidence in our results suggesting that prestroke hypertension has a major impact on stroke severity. We do not have data on family history of hypertension for all subjects in the current study. In future trials we will collect detailed data on family history of hypertension, which will allow further analysis of the interrelationship of hypertension and ischemic stroke.

Information regarding sibling history of stroke may be more accurate than that regarding parental history of stroke. Accordingly, we have not ruled out an association between parental history and stroke severity. Moving back in time one generation, 25 to 35 years, increases the potential for error in recalling historical medical facts. Public knowledge regarding definition of stroke was limited, and diagnostic tools were limited (e.g., CT was introduced in 1973). Methods of communication among family members were more restricted than they are today and were considerably more expensive. In addition, stroke-affected status was assessed by informant interview and not by examination and medical record review of family members. The Framingham Heart Study found that offspring with a paternal history of stroke before the age of 65 years had a positive likelihood ratio of 11.2, and offspring with a maternal history of stroke before the age of 65 years had a positive likelihood ratio of 22.4.³⁰ Offspring parent history of stroke at any age has a greater positive predictive value than history of early stroke.³¹ We did not obtain family history information by directly interviewing family members. However, Family Heart Study Investigators found that the proband-reported family histories for common diseases generally showed specificities higher than 90% when relatives' self-reports were used as a benchmark.³¹

The finding of an association of sibling history of stroke with more severe stroke may reflect a uniquely potent interaction of genetic and environmental factors shared by siblings. However, the quality of the data may differ across generations. Parental strokes may have occurred before the age of modern neuroimaging, data collected longer ago may be inherently less complete, and there is greater potential for misclassification and less opportunity to validate data (e.g., by speaking with the affected relative). The number of strokes among children of case subjects was very small, and our analysis may be underpowered to detect a real association.

Another potential limitation is that the relative importance of genetic factors may diminish with increasing age as other acquired factors become more dominant. We found an association of family history and stroke severity after adjusting for age and other factors. However, we cannot exclude an interaction between age and family history of stroke. A family history of stroke has been associated with a young age at onset, with the highest rates in patients aged 60 years or younger (OR, 1.7 [95% CI, 1.0 to 2.9]).²⁴ This study also found a trend toward a higher frequency of family history of stroke in patients younger than 60 years for each stroke subtype.

Our study has several strengths. The multicenter design yielded a demographically diverse case subject population. Because enrollment was restricted to subjects with first-ever symptomatic ischemic stroke, there was no potential for confounding that could have occurred if we had included subjects with recurrent stroke. Patients with recurrent stroke might have inflated measures of severity relative to patients with first-ever stroke. Another strength of our study was that it did not rely on record review alone. Family history of stroke and stroke severity were assessed prospectively by interview and record review, and stroke severity was assessed by interview, observation, and examination.

Our finding that sibling history imparted risk of more severe stroke but parent history did not suggest that one or more genetic factors are acting through a recessive rather than dominant inheritance pattern. Our findings should be tested in other populations. Future studies should also assess the relationship between sibling history of stroke and the pathophysiologic features of acute cerebral infarction such as infarct volume and markers of the ischemic penumbra. Such studies might provide insight into how inherited factors may be exerting their effects on stroke severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary of case subject characteristics

Characteristic	Subjects	
	No.	%
Total	505	100
Age, y		
<45	64	13
45-54	88	17
55-64	97	19
65-74	118	23
75-84	103	20
≥85	35	7
Sex		
Male	276	55
Female	229	45
Race		
White	343	68
African American	148	29
Other	14	3
BMI,* kg/m ²		
Underweight (<18.5)	10	2
Normal (18.5-24.9)	136	27
Overweight (25-29.9)	168	33
Obese (≥30.0)	189	38
Case subject history [†]		
TIA	75	15
Congestive heart failure	53	11
Angina	51	10
Myocardial infarction	78	15
Atrial fibrillation	72	14
Hypertension	359	71
Hyperlipidemia	228	45
Diabetes mellitus	137	27
Smoking history		
Never	158	31
Prolonged abstainer	182	36
Recent abstainer	31	6
Active	134	27
Prestroke OHS score		
0	385	76
1	60	12
2	48	10
3	7	1
4	4	1
5	1	<1
Stroke to NIHSS, d		
0-7	408	81
8-14	65	13
15-30	32	6

BMI = body mass index; NIHSS = NIH Stroke Scale; OHS = Oxford Handicap Scale.

* Data were missing for two case subjects.

[†] Each subject may have had more than one disorder. Data were missing for one subject with TIA, two with congestive heart failure, one with angina, one with myocardial infarction, four with atrial fibrillation, two with hypertension, and three with hyperlipidemia.

Table 2

Effect of stroke family history on stroke severity^{*}

Characteristic	No. [†]	NIHSS	BI	OHS	GOS
Total	505	4.0 (4.9)	78.2 (27.9)	2.0 (1.3)	1.7 (0.8)
Parent					
No	321	4.1 (5.0)	77.9 (27.7)	2.0 (1.3)	1.7 (0.8)
Yes	167	3.7 (4.2)	79.5 (28.2)	1.9 (1.3)	1.6 (0.8)
Sibling [‡]					
No	384	3.9 (4.9)	79.7 (27.5)	1.9 (1.3)	1.6 (0.8)
Yes	54	4.6 (4.6)	68.0 (27.2)	2.4 (1.4)	1.9 (0.8)
Child					
No	410	3.9 (4.8)	78.1 (28.0)	1.9 (1.3)	1.7 (0.8)
Yes	17	3.4 (4.5)	78.2 (25.8)	2.1 (1.0)	1.6 (0.7)
FDR					
No	297	4.2 (5.1)	78.4 (28.4)	2.0 (1.3)	1.7 (0.8)
Yes	207	3.7 (4.4)	78.0 (27.4)	2.0 (1.3)	1.7 (0.8)

BI = Barthel Index; FDR = first-degree relative; GOS = Glasgow Outcome Scale; NIHSS = NIH Stroke Scale; OHS = Oxford Handicap Scale.

^{*} All values are means (SD) unless indicated otherwise.[†] Some case subjects had no siblings or children, and some cases were missing stroke history data.[‡] Unadjusted and adjusted *p* values are 0.09 and 0.08 for NIHSS, 0.001 and 0.02 for BI, 0.005 and 0.04 for OHS, and 0.005 and 0.02 for GOS. For all other comparisons, *p* > 0.1.

Table 3

Effect of stroke family history on stroke severity^{*}

Stroke history	No. [†]	NIHSS (≥5)	BI (<80)	OHS (≥3)	GOS (≥3)
Total	505	153 (30)	186 (37)	163 (32)	94 (19)
Parents					
No	321	96 (30)	123 (38)	108 (34)	63 (20)
Yes	167	49 (29)	55 (33)	47 (28)	28 (17)
OR (95% CI)					
Unadjusted		1.0 (0.6-1.5)	0.8 (0.5-1.2)	0.8 (0.5-1.2)	0.8 (0.5-1.3)
Adjusted		1.0 (0.6-1.5)	0.8 (0.5-1.2)	0.7 (0.5-1.1)	0.8 (0.5-1.4)
Siblings [‡]					
No	384	108 (28)	131 (34)	115 (30)	63 (16)
Yes	54	23 (43)	32 (59)	26 (48)	17 (31)
OR (95% CI)					
Unadjusted		1.9 (1.1-3.4)	2.8 (1.6-5.0)	2.2 (1.2-3.9)	2.3 (1.2-4.4)
Adjusted		2.0 (1.0-3.9)	2.6 (1.4-4.9)	1.9 (1.0-3.5)	2.1 (1.0-4.3)
Children					
No	410	120 (29)	152 (37)	128 (31)	76 (19)
Yes	17	4 (24)	7 (41)	6 (35)	2 (12)
OR (95% CI) [§]					
Unadjusted		0.7 (0.2-2.3)	1.2 (0.4-3.2)	1.2 (0.4-3.3)	0.6 (0.1-2.6)
FDR					
No	297	90 (30)	108 (36)	96 (32)	55 (19)
Yes	207	62 (30)	77 (37)	66 (32)	39 (19)
OR (95% CI)					
Unadjusted		1.0 (0.7-1.4)	1.0 (0.7-1.5)	1.0 (0.7-1.4)	1.0 (0.6-1.6)
Adjusted		1.1 (0.7-1.6)	1.0 (0.7-1.5)	0.9 (0.6-1.4)	1.0 (0.6-1.7)

BI = Barthel Index; FDR = first-degree relative; GOS = Glasgow Outcome Scale; OHS = Oxford Handicap Scale; OR = odds ratio.

^{*} Values are numbers (percentage) unless specified otherwise.[†] Some case subjects had no sibling or children, and some cases were missing stroke history data.[‡] Unadjusted and adjusted *p* values are 0.03 and 0.04 for NIHSS, <0.001 and 0.004 for BI, 0.007 and 0.06 for OHS, and 0.007 and 0.05 for GOS. For all other comparisons, *p* > 0.1.[§] Only unadjusted results are provided for children because of the small number of children with strokes.

Table 4

Adjusted effect of stroke family history on combined stroke severity measure

Characteristic	Effect (SE)	<i>p</i> Value
Sibling stroke	0.56 (0.26)	0.03
Age (per decade)	0.17 (0.07)	0.01
Sex (M vs F)	-0.18 (0.17)	0.28
Race		0.17
Other vs white	-0.13 (0.56)	
Black vs white	-0.54 (0.29)	
OHS base score		0.001
1 vs 0	0.06 (0.26)	
≥2 vs 0	0.96 (0.26)	
Site		0.001
1 vs 5	-0.12 (0.27)	
2 vs 5	0.67 (0.28)	
3 vs 5	1.35 (0.37)	
4 vs 5	0.63 (0.27)	
Diabetes mellitus	0.27 (0.19)	0.16
Hypertension	-0.14 (0.20)	0.84

OHS = Oxford Handicap Scale.