Familial Aggregation of Stroke
The Framingham Study
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Background and Purpose: Family history is perceived to be an important risk factor for stroke despite conflicting published data. We examined patterns of familial aggregation of stroke among three generations using data from the Framingham Study.

Methods: Cox proportional hazards analyses, adjusting for known stroke risk factors, were used to examine familial concordance in three groups: (1) members of the original Framingham cohort using reported parental stroke death; (2) members of the Framingham Offspring Study and their parents (members of the original Framingham Study); and (3) siblings within the original Framingham cohort.

Results: We found no association between stroke or transient ischemic attack among original cohort members and their reported parental stroke death (n=4933; relative risk [RR]=1.07). Using verified cases of parental stroke or transient ischemic attack, the Offspring analyses revealed that both paternal (n=1762; RR=2.4; 95% confidence interval [CI], 0.96 to 6.03) and maternal (n=2074; RR=1.4; 95% CI, 0.60 to 3.25) histories were associated with an increased risk. Parental history of coronary heart disease was strongly associated with stroke or transient ischemic attack among Offspring Study members (RR=3.33; 95% CI, 1.27 to 8.72). Sibling history of stroke or transient ischemic attack was not associated with stroke or transient ischemic attack among original cohort members, although a non–statistically significant increased risk associated with sibling history of atherothrombotic brain infarction was observed (RR=1.8; 95% CI, 0.68 to 4.94).

Conclusions: These analyses suggest that parental history of stroke may be a risk factor for stroke. As more stroke or transient ischemic attack events develop among the Offspring Study members, it will be valuable to reexamine these associations. (Stroke. 1993;24:1366-1371.)

KEY WORDS • cerebral infarction • cerebral ischemia, transient • genetics • risk factors

Despite a more than 50% decline in stroke mortality in the United States since 1970, cerebrovascular disease is likely to continue to be a major source of death and disability among the elderly. The most effective strategy to combat this disease involves prevention achieved by identifying risk factors and detecting persons at high risk of stroke.1

Through prospective epidemiologic study, a number of risk factors for stroke or transient ischemic attack (TIA) were identified and subsequently used in the development of a risk profile.1,2 The risk profile provides an individual's probability of stroke, thereby identifying high-risk candidates for stroke and risk factor modification.2

Family history is perceived to be an important predisposing risk factor for stroke both by physicians and the lay public. However, definitive data on family history of stroke are meager, and the importance of family history as a predisposing factor for stroke remains unresolved.3-9 Using data from the Framingham Study, we examined patterns of familial aggregation of stroke among first-degree relatives.

Subjects and Methods

The Framingham Study is an ongoing prospective study of cardiovascular disease in a cohort of 5209 persons (2336 men and 2873 women) representing a two-thirds sample of adults resident in the town of Framingham, Mass, in 1948 who were 28 to 62 years old at entry. Original cohort members have been systematically evaluated every 2 years since 1948. Previous publications provide detail concerning study design, cohort composition, and examination procedures.10,11

The Offspring cohort (hereafter referred to as Offspring), initially evaluated in 1971, consists of 5124 descendants or spouses of descendants (2483 men and 2641 women) of the original Framingham cohort members (hereafter referred to as Cohort). After entry in 1971, the Offspring have been examined every 4 years with the exception of the first exam cycle, which lasted 8 years. The Offspring examinations are very similar to their progenitors’ examinations and include medical and lifestyle histories, physical examinations, noninvasive cardiac studies, and blood chemistry measurements. Further details of the Offspring composition and examinations have been published.12
We investigated patterns of familial aggregation of stroke in three distinct groups: (1) members of the original Framingham cohort (using the reported cause of death of their parents); (2) members of the Framingham Offspring Study (using their parents in the original Framingham cohort); and (3) sibships within the original Framingham cohort. In each of these groups, we determined if history of stroke or TIA in a first-degree relative was associated with stroke or TIA in the other relative (Figure).

For our purposes here, the original cohort analysis included those 4933 subjects who were at least 30 years of age at entry; free of stroke, TIA, and death at the second examination (baseline) in 1952 to 1954; and whose reported parental cause of death was not missing. A follow-up of 36 years was used in these analyses.

Among the 5124 Offspring, 2317 Offspring members with at least one parent in the Cohort, no history of stroke or TIA before entry into the study, and who were at least 30 years of age at entry were included in these analyses. The follow-up period was 16 years.

Cohort members with at least one sibling in the Cohort and free of stroke or TIA before entry in the study were included in the sibling analysis. Within a sibship, one sibling was randomly chosen to be the proband (dependent variable).

### Outcomes and Risk Factors

Stroke is defined as the first occurrence of atherothrombotic brain infarction, cerebral embolism, subarachnoid hemorrhage, intracerebral hemorrhage, or other type. In addition to family history of stroke or TIA, the following risk factors were included in multivariate analyses: age, sex, systolic blood pressure, serum cholesterol (milligrams per 100 milliliters), cigarettes smoked per day, and left ventricular hypertrophy by electrocardiogram (ECG) (coded none, borderline, or definite). Glucose intolerance (for the Cohort) or diabetic status (for the Offspring) were also included. Offspring were classified as diabetic if (1) their blood glucose was 140 mg/100 mL or greater or (2) they were on insulin or oral hypoglycemic agents.

For the Cohort, risk factors other than sex and family history of stroke or TIA were taken from the second biennial examination. Examination 1 risk factors were used in those few cases in which examination 2 risk factors were missing. For the Offspring, risk factors from the first examination were used in the analyses because this was the most complete examination. Stroke or TIA among Cohort and Offspring members has been validated by a panel of study physicians after review of all available medical information including hospital and physician records and the application standard criteria.

### Parental History of Stroke or Transient Ischemic Attack

Cohort. The cause of death for parents of Cohort members was reported by the subject on entry to the study and was updated on each subsequent biennial examination. Parental cause of death was classified as coronary heart disease (CHD), stroke, other cardiovascular disease, cancer, accident, suicide, infection, other, or unknown. In 6% of fathers (n=287) and 11% of mothers (n=558) the cause of death was not reported.

Cohort members who reported stroke as the cause of death of either parent were considered to have a positive parental history of stroke. Those in whom neither parent succumbed to stroke were coded as negative.

There were 178 Cohort members whose parents were also Cohort members. Using these subjects, there was an opportunity to compare reported cause of death with the cause of death as validated by study criteria. The predictive value positive was calculated using reported cause of parental death due to stroke and the actual cause of their parents’ death as determined by the Framingham Study. This value was used to estimate the accuracy of the reported cause of parental death.

Offspring. Offspring members with at least one parent (Cohort member) who had experienced a validated stroke or TIA, according to study criteria for stroke on review, were considered to be positive for having a parental history of stroke, and those with neither parent experiencing a verified stroke or TIA were negative.

### Sibling History of Stroke or Transient Ischemic Attack

Sibling history was considered positive if any of the other siblings in the Cohort experienced a stroke or TIA; if not, sibling history was considered negative. Adjustment for sibship size was made in all sibling analyses because the probability of having a sibling with a stroke or TIA increases with increasing sibship size. This adjustment was accomplished by including an
independent variable in the model that contained the number of siblings in the sibship.

Statistical Procedures

Cox proportional hazards linear regression was used to examine familial patterns of stroke or TIA. Univariate (crude), sex- and age-adjusted, and multivariate analyses (age, sex, and the five risk factors cited previously) were performed. Crude and adjusted risk ratios and corresponding 95% confidence intervals were computed. When possible, separate analyses were performed by parental sex and stroke type.

Results

Cohort

Among the 4933 subjects used in this analysis who reported parental death due to stroke, there were 604 stroke or TIA events. One hundred forty-six subjects had missing values on other variables and could not be used in the multivariate analysis.

Among Cohort members there was no increased risk of stroke or TIA associated with reported parental stroke death (Table 1). Examination of family history according to maternal or paternal fatal stroke history separately yielded similar results (Table 1). It was not possible to stratify family history according to type of stroke; these data were not available for the parents of the original Cohort members (who had died in the late 19th and early 20th century and in whom stroke subtype could not be determined).

The predictive value positive for reported cause of parental death due to stroke was .77 for those 178 Cohort members who had both reported and verified parental cause of death recorded. In other words, 23% of reported causes of death due to stroke were discordant with actual cause of death due to stroke as determined by the Framingham Study. The predictive value positive is .87 for reported cause of paternal death due to stroke and .63 for reported cause of maternal death due to stroke.

Offspring

Among the 2317 Offspring, there were 34 stroke or TIA events. Forty-nine subjects had missing values on other variables and could not be used in the multivariate analysis.

Offspring with parents who had a stroke or TIA had a 90% increased risk of experiencing a stroke or TIA compared with those without a positive parental history; this increased risk was marginally significant (P=.067). After adjusting for age, sex, and other potentially confounding risk factors, a smaller and not statistically significant increased risk was still evident (Table 2).

Separate analyses were performed for maternal and paternal history of stroke or TIA. Offspring with a positive paternal history of stroke or TIA had 2.3 times the risk (P=.066) of developing a stroke or TIA compared with those with a negative paternal history. After adjustment for other risk factors, the analyses yielded similar results (Table 2).

Maternal stroke or TIA was associated with Offspring stroke or TIA in the univariate analysis but not in the adjusted analyses. In the crude analysis, Offspring whose mother experienced a stroke or TIA were 2.3 times as likely to experience a stroke or TIA when compared with those with a negative maternal history (P=.03) (Table 2). After adjusting for potential confounders, the risk was attenuated and no longer statistically significant. This suggests that the association between maternal history of stroke or TIA and stroke or TIA in Offspring members is confounded by age, sex, and the other potential confounders adjusted for in the multivariate model.

The multivariate-adjusted risk ratio was 2.4 in the paternal analysis and 1.4 in the maternal analysis. This suggests that the effect of parental history of stroke or TIA on stroke or TIA in the Offspring is modified by parental sex. We considered investigating a parental sex and parental history of stroke or TIA interaction, but, after removing those Offspring with both parents having a history of stroke or TIA, the numbers were too small for any reliable analysis.

Because parental history of CHD may confound the relation between parental history of stroke or TIA in Offspring, an analysis was performed to examine this possibility. Some of the Offspring had been recruited because one of their parents experienced CHD between exam 1 and exam 10. If Offspring members had a parent who experienced CHD during this time, parental hist-
history of CHD was coded as positive; otherwise, it was coded as negative.

Separate multivariate analyses (including parental history of CHD in addition to the previously included set of multivariate risk factors) were run to investigate this possibility. The risk ratio was virtually unchanged in the parental and paternal analyses and only slightly altered in the maternal analysis (Table 2). Parental history of CHD does not appear to be a confounding factor in the association between parental history of stroke or TIA and stroke or TIA in the Offspring.

Parental history of CHD was examined as a potential risk factor for stroke or TIA in Offspring (Table 3). In the unadjusted analysis, Offspring with a parental history of CHD were 3.6 times more likely to have a stroke or TIA compared with those Offspring without a parental CHD history (*P*=.004). Similarly, the age- and sex-adjusted and multivariate-adjusted analyses showed a statistically significant threefold increased risk of developing a stroke or TIA associated with parental history of CHD.

Separate analyses of paternal and maternal history of CHD and occurrence of stroke disclosed that those Offspring with a paternal history of CHD were 2.5 times as likely to experience a stroke or TIA compared with those Offspring without such a history (*P*=.046) (Table 3). Similar risks ratios were seen in the adjusted analyses, although they were not statistically significant.

Maternal history of CHD was a strong predictor of stroke or TIA in the Offspring. Offspring with a maternal history of CHD were 3.5 times as likely to experience a stroke or TIA as those without this history (*P*=.001). The adjusted analyses revealed that Offspring with a maternal history of CHD were approximately 2.5 times as likely to experience a stroke or TIA compared with those without this history. The adjusted analyses yielded risk ratios substantially smaller than the crude risk ratio, indicating that the association between ma-

### Table 2. Parental, Paternal, and Maternal History of Stroke or Transient Ischemic Attack and Stroke or Transient Ischemic Attack in Offspring Cohort

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>No. of events</th>
<th>P</th>
<th>RR</th>
<th>95% CI</th>
</tr>
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<td><strong>Parental</strong></td>
<td></td>
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<td>Crude</td>
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<tr>
<td>Multivariate adjusted including parental history of CHD</td>
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<td>.27</td>
<td>1.50</td>
<td>0.73-3.06</td>
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<tr>
<td><strong>Paternal</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
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<td>.066</td>
<td>2.34</td>
<td>0.95-5.80</td>
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<tr>
<td>Age and sex adjusted</td>
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<td>0.93-5.72</td>
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<tr>
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<td>2.40</td>
<td>0.96-6.03</td>
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<tr>
<td>Multivariate adjusted including parental history of CHD</td>
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<td>.06</td>
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<td>0.95-6.02</td>
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</tr>
<tr>
<td>Crude</td>
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<tr>
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<tr>
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<td>1.40</td>
<td>0.60-3.25</td>
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<tr>
<td>Multivariate adjusted including maternal history of CHD</td>
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<td>29</td>
<td>.65</td>
<td>1.22</td>
<td>0.52-2.87</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; CHD, coronary heart disease.

### Table 3. Parental, Paternal, and Maternal History of Coronary Heart Disease and Stroke or Transient Ischemic Attack in Offspring Cohort

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>No. of events</th>
<th>P</th>
<th>RR</th>
<th>95% CI</th>
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<td><strong>Parental</strong></td>
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<td></td>
<td></td>
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<tr>
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<td>1.23-7.26</td>
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<tr>
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<td>33</td>
<td>.01</td>
<td>3.33</td>
<td>1.27-8.72</td>
</tr>
<tr>
<td><strong>Paternal</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
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<td>.046</td>
<td>2.52</td>
<td>1.02-6.25</td>
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<td>.09</td>
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<td>.11</td>
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<td>0.84-5.35</td>
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<tr>
<td><strong>Maternal</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
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<td>30</td>
<td>.001</td>
<td>3.45</td>
<td>1.64-7.24</td>
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<td>.01</td>
<td>2.57</td>
<td>1.21-5.47</td>
</tr>
<tr>
<td>Multivariate adjusted</td>
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<td>29</td>
<td>.03</td>
<td>2.48</td>
<td>1.11-5.53</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval.
ternal history of CHD and stroke or TIA in the Offspring is confounded by the variables in the multivariate model. In all Offspring analyses (Tables 2 and 3), the low number of stroke or TIA events in the Offspring cohort precluded separate analyses by type of stroke.

**Siblings**

There were 604 sibships, in which there were 71 stroke or TIA events among the Cohort members and 87 stroke or TIA events among their siblings. There were 38 atherothrombotic brain infarctions among the probands and 45 among their siblings. Nineteen subjects had missing values on other variables and could not be used in the multivariate analysis.

Cohort members with a sibling history of stroke or TIA were 1.5 times as likely to experience a stroke or TIA compared with those without such a sibling history, although the association was not statistically significant ($P = .21$). Both the age- and sex-adjusted and multivariate-adjusted analyses showed weaker associations that were not statistically significant (Table 4).

Atherothrombotic brain infarction in siblings was strongly related to atherothrombotic brain infarction in Cohort members, indicating a threefold increased risk ($P = .01$). The age-, sex-, and sibship-size-adjusted analyses yielded a 2.5-fold increased risk ($P = .04$); the multivariate-adjusted analyses showed approximately a twofold increased risk, which was not statistically significant ($P = .23$) (Table 4).

**Discussion**

Because of conflicting results from published data on familial patterns of stroke, the role of family history remains controversial. Marshall et al. compared the frequency of death certified as due to cerebral hemorrhage among the brothers and sisters of 180 index patients with its frequency in the general population of the same age and sex. He found statistically significant excess of death due to cerebral hemorrhage among the brothers of female index patients. Using a case-control study involving 132 stroke patients and 239 age- and sex-matched control subjects, Herman et al. reported that a stroke among one’s parents or siblings did not appear to influence stroke risk. Khaw and Barrett-Connor found family history of stroke in any first-degree relative to be an independent predictor of stroke mortality in 1924 women 50 to 79 years of age after controlling for standard risk factors. Diaz et al. examined the frequency of stroke among 76 siblings of 41 patients hospitalized for cerebral infarction and TIA and found no significant difference when compared with 55 siblings of the hospitalized patients’ spouses. Welin et al. analyzed certified parental death from stroke and other potential risk factors in relation to the incidence of stroke among 789 men born in 1914, all 54 years old at baseline examination. They reported that men whose mothers had died of stroke had a 3.6-fold increase in their incidence of stroke compared with men without such a maternal history. Boysen et al. followed 13,088 persons who were at least 35 years of age and free of stroke at entry for 5 years. After adjusting for associated risk factors, they found no association between family history of stroke and the development of stroke. Brass and Shaker examined the association of reported family history of stroke with reported personal history of TIA among 85 respondents diagnosed with TIA and found no significant association for the entire cohort, although a significant association was observed in an elderly age group.

In part, the discrepancies between these findings of various studies of family history of stroke can be attributed to differences in and problems with study design. First, some of the studies were case-control studies (Diaz et al, Marshall, and Herman et al.), one cross-sectional (Brass and Shaker), and others prospective (Khaw and Barrett-Connor, Welin et al, and Boysen et al.). Case-control and cross-sectional studies are subject to recall bias and are likely to result in some degree of misclassification (differential or nondifferential) of family history of stroke. Second, except in the studies of Marshall and Welin et al, family history was determined by questionnaire or interview. Although this method of determining family history is economically feasible and often the only option available, the accuracy of the information recollected may be suspect and likely to result in some degree of misclassification. Third, the studies of Marshall and Welin et al used death certificate information to determine family history of stroke. This method may have limited accuracy for various reasons. Selection bias could result if age at death is not considered because those whose death was not related to a stroke event may have been too young to express stroke. The death certificate may not have recorded any information on nonfatal strokes or, if so, only for severe cases. Furthermore, there could be an error in the diagnosis of death as recorded on the certificate. Corwin et al. examined the validity of death certification of stroke in the Framingham Study cohort. They found that 113 of 280 descendants with certified stroke (40% false-negative rate) had no mention of
stroke on the death certificate and that the false-negative rate increased significantly with increasing age at death and increasing interval from last stroke to death. They questioned the accuracy of studies dependent on this source of information.

An advantage of the Offspring and sibling analyses in this study is that family history of stroke was determined based on detailed clinical evaluation by a study neurologist and reviewed by a panel of physicians including a neurologist rather than by questionnaire, unsubstantiated self-report, or solely by the death certificate.

Unlike the Offspring analyses, which used clinically reviewed and documented information on the development of stroke or TIA in their parents, the Cohort analysis had only information on stroke as the reported cause of parental death. Unfortunately, this analysis cannot account for those parents who, for example, developed a stroke but whose death certificate reported myocardial infarction or cancer as the cause of death. Furthermore, approximately one fourth of the reported causes of death due to stroke were estimated to be discordant with their cause of death as recorded in the Framingham Study. This misclassification is likely to be nondifferential because ascertainment of family history occurred before the onset of disease and therefore the true risk ratio is likely to be underestimated. This degree of misclassification could explain why the risk ratios are close to 1 in the Cohort analysis (Table 1).

The results of the parental history, maternal history, and paternal history Offspring analysis suggest that there is an increased risk of experiencing a stroke associated with a parental history of stroke or TIA but, because Offspring members are relatively young and have yet to experience many stroke or TIA events, we may not currently have the statistical power to detect these relations. As more strokes and TIAs develop, it will be important to reexamine these associations. The resulting statistical power and tighter confidence intervals will present a truer description of these relations. The same is true for the sibling atherothrombotic brain infarction analysis.

One factor not considered in any of the previously mentioned studies is common lifestyles. Cultural and/or personal behavior patterns such as diet and physical activity may partially account for the familial aggregation of stroke. Parents who subscribe to minimal physical exercise and diets rich in sodium and fat are likely to have high blood pressure, and their offspring who presumably adapt similar behavioral patterns are also more likely to be hypertensive. Because elevated blood pressure is a risk factor for stroke, these familial behavior patterns could account for some proportion of familial stroke aggregation.

Familial clustering of risk factors for stroke due to environmental and/or genetic influences may partially explain familial aggregation of stroke. In a related analysis, we used linear and logistic regression to investigate the association between risk factors for stroke or TIA among the Offspring and risk factors for stroke or TIA among their parents, adjusting for Offspring sex and age. Offspring systolic blood pressure values were strongly associated with their parents' systolic blood pressure values after adjusting for Offspring sex and age (P<.0001); the same was true for diastolic blood pressure (P=.0001). Diabetic status in the Offspring was strongly associated with glucose intolerance in their parents (P=.0004). Left ventricular hypertrophy by ECG among the Offspring was marginally associated with left ventricular hypertrophy by ECG in their parents (P=.09). Serum cholesterol values among the Offspring were strongly associated with serum cholesterol values in their parents (P<.001).

The results of this study suggest that parental and sibling history of stroke or TIA may be risk factors for the development of stroke or TIA. As more stroke or TIA events develop among the Offspring, it will be valuable to reexamine these associations. More research will be needed to determine the influences of environmental and genetic influences on the familial aggregation of stroke and to determine if the association between family history of stroke and the development of stroke is causal. Only then can this association be clarified and family history of stroke be considered a significant risk factor and component of a stroke risk profile.

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