Association Between Family Risk of Stroke and Myocardial Infarction With Prevalent Risk Factors and Coexisting Diseases

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Background and Purpose—Familial transmission of stroke and myocardial infarction (MI) is partially mediated by transmission of cerebrovascular and cardiovascular risk factors. We examined relationships between family risk of stroke and MI with risk factors for these phenotypes.

Methods—A cross-sectional association between the stratified log-rank family score for stroke and MI with prevalent risk factors was assessed in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort.

Results—Individuals in the fourth quartile of stratified log-rank family scores for stroke were more likely to have prevalent risk factors including hypertension (OR, 1.43; 95% CI, 1.30–1.58), left ventricular hypertrophy (OR, 1.42; 95% CI, 1.16–1.42), diabetes (OR, 1.26; 95% CI, 1.12–1.43), and atrial fibrillation (OR, 1.23; 95% CI, 1.03–1.45) compared with individuals in the first quartile. Likewise, individuals in the fourth quartile of stratified log-rank family scores for MI were more likely to have prevalent risk factors including hypertension (OR, 1.57; 95% CI, 1.27–1.94) and diabetes (OR, 1.29; 95% CI, 1.12–1.43) than the first quartile. In contrast to stroke, the family risk score for MI was associated with dyslipidemia (OR, 1.38; 95% CI, 1.23–1.55) and overweight/obesity (OR, 1.22; 95% CI, 1.10–1.37).

Conclusions—Family risk of stroke and MI is strongly associated with the majority of risk factors associated with each disease. Family history and genetic studies separating nonspecific contributions of intermediate phenotypes from specific contributions to the disease phenotype may lead to a more thorough understanding of transmission for these complex disorders. (Stroke. 2012;43:974-979.)

Key Words: cohort studies ■ family risk ■ myocardial infarction ■ REGARDS ■ stroke

Both stroke and myocardial infarction (MI) have a complex pattern of familial transmission due to multiple determinants. Family history studies have demonstrated aggregation of stroke within families, but inconsistencies have been noted with risks varying in magnitude or confined to certain subgroups.1 Genetic studies have also been conflicting with no findings replicated across studies at genomewide significance level.2-4 Few studies have adjusted associations between family history and stroke for confounding risk factors or intermediate phenotypes.5 For example, ischemic stroke shares many risk factors with MI, including hypertension, diabetes mellitus, and hypercholesterolemia. These risk factors tend to aggregate in families and have considerable genetic components.6-14 Indeed, previous studies have suggested heritability of ischemic stroke is mainly mediated through genetic influences on its risk factors and intermediate phenotypes, particularly hypertension atherosclerosis.15,16 A systematic review of all twin and family history studies identified family history of ischemic stroke as a moderate risk factor for stroke.5 Similarly, a systematic review of studies reporting family history of MI, hypertension, or diabetes mellitus as risk factors for stroke, found that most studies reported increased frequency of family history of MI or hypertension in stroke probands versus control subjects, although family history of diabetes mellitus was not associated with stroke.16 However, reliable estimates of risk were not possible due to major heterogeneity between studies as well as potential publication and reporting bias, and the majority of studies did not consider the number of affected family members. Family history of stroke and family history of MI were also related to intermediate phenotypes in 2 population-based incidence studies and 2 prospective hospital-referred cohorts restricted to patients with transient ischemic attack, potentially limiting generalizability.15 In this report, we investigate contributions of intermediate phenotypes to familial transmission of stroke and MI by exam-
ining associations between family risk and presence of specific risk factors in probands in a single large cohort. This approach avoids the effects of study heterogeneity and publication bias noted previously so that our study presents a unified description of the influence of family risk on intermediate phenotypes.

Methods

Participants
Participants were part of the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a national longitudinal cohort study of 30,329 black and European American individuals aged ≥45 years. Race was defined by self-report and by design; Hispanics and Latinos were excluded. Twenty-one percent of the sample was selected from the “buckle” of the Stroke Belt (coastal plain region of North Carolina, South Carolina, and Georgia), 35% from the Stroke Belt states (remainder of North Carolina, South Carolina, and Georgia plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and the remaining 44% from the other 48 contiguous United States. Within each region, after stratification by race and gender, individuals were recruited from commercially available lists of residents using a combination of mail and telephone contact.

Defined according to the standards of Morton et al,17 the telephone response rate was 33% and the cooperation rate was 49%.18 Demographic information and medical history were obtained by computer-assisted telephone interview. Physical measures were collected at in-home examinations, including height, weight, blood pressure, blood and urine samples, electrocardiogram, and inventory of current medications. Informed consent was obtained from all participants. Study methods were approved by Institutional Review Boards at collaborating institutions. Further details about the REGARDS study design are provided elsewhere.19

Risk Factors and Disease Status
Cardiovascular health measurements were considered in 2 groups: (1) traditional cardiovascular risk factors; and (2) prevalent cardiovascular diseases. The risk factors included hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or self-reported use of antihypertensive medications), diabetes (fasting glucose >126 mg/dL, nonfasting glucose >200 mg/dL, or self-reported use of medications for diabetes control), dyslipidemia (total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >160 mg/dL, high-density lipoprotein cholesterol <55 mg/dL in women and <45 mg/dL in men, or self-reported use of treatment for elevated lipids), current cigarette smoking, atrial fibrillation (by self-report or electrocardiographic evidence), overweight or obesity (body mass index ≥25 kg/m² versus 18.5–24.9 kg/m² with individuals <18.5 kg/m² deleted from assessment), left ventricular hypertrophy (LVH; by electrocardiogram), and elevated C-reactive protein (C-reactive protein <3.0 versus C-reactive protein ≥3.0). Although described as risk factors, each has also been considered a phenotype for heritability studies.6–14 Prevalent diseases in the proband included heart disease (self-reported MI; self-reported history of coronary artery bypass grafting, bypass, angioplasty, or coronary artery stenting; or evidence of MI by electrocardiogram), chronic kidney disease (glomerular filtration rate, estimated by the Modification of Diet in Renal Disease equation, of <60 mL/min/1.73 m²), and stroke (by self-report).

Family History
Participants provided information on stroke and MI events in their parents and up to 4 siblings using a self-administered survey. Distinctions between ischemic and hemorrhagic stroke were not made. Family history data were obtained for 57,269 family members of 13,995 REGARDS participants. These data were used to determine either age of first-degree relatives at the time of their stroke or MI events or number of years first-degree relatives were stroke-free before censoring (either from death due to other diseases or to time of form completion without an event).

Risk Score
For each participant, an index of family risk was calculated separately for MI and for stroke using the stratified log-rank family score (SLFS).20 The SLFS provides a single measure of the “severity” of the family risk incorporating age of onset of family members, gender differences, and relationship among family members. SLFSs incorporate both genetic and environmental contributions to family risk and thus do not directly measure heritability.21 Briefly, separate risk scores were calculated for each of 10 types of first-degree family members (father, mother, and up to 4 brothers and 4 sisters). For each family member type, log-rank scores are computed for events with ages of family members used to construct time intervals. The individual risk score for each family member is the log-rank score for the interval into which his or her age falls. This allows a survival function to be generated for each type of family member to predict the proportion “stroke-free” and “MI-free” as a function of age (see Figure 1, shown with pooled estimates for all types of family members for brevity). The SLFS for the entire family is the mean of individual risk scores for all family members. SLFSs range from −1.0 (low risk, reflecting families with no events over a large number of person years) to 1.0 (high risk, reflecting families with multiple events at young ages).

Statistical Analysis
The primary independent variable is family risk as measured by SLFSs divided into quartiles. A logistic regression model was constructed to assess the relationship between the SLFS and the prevalent risk factors and prevalent diseases of probands, adjusting for age, race, and sex. The first quartile (Q1) was used as the reference for calculating ORs for each of the other 3 quartiles. The identification of high-risk groups through regression modeling of log-rank scores on potential risk factors has been shown to be a reasonable approach to perform survival analysis with statistical performance similar to “traditional” survival approaches such as proportional hazards analysis.22

Results
Demographic information for the study cohort is provided in Table 1. The average age of participants was 66 years (SD 8.7 years). Approximately one third of the cohort was black, and gender representation was roughly equal. The predominant vascular risk factors were dyslipidemia (76.7%), obesity (74.2%), and hypertension (55.8%). Demographics within

Figure 1. Proportion of first-degree relatives of REGARDS participants free from stroke and myocardial infarction (MI) from family history as a function of age.
each quartile of SLFSs for stroke and for MI are shown in Table 2.

Although there was a significant (P<0.0001) relationship between family risk score for stroke and family risk score for MI, the correlation of 0.18 between these 2 factors was only modest (Figure 2). This suggests that although, on average, families that reported stroke events in first-degree relatives also reported MI events, there was not a strong association in these reported events.

Among traditional risk factors shown in Table 3, there is a clear monotonic trend observed for each of prevalent hypertension, LVH, and diabetes, with increasing odds of the risk factor being prevalent with increasing SLFSs for stroke. Differences were particularly striking for hypertension (16%, 23%, and 43% greater odds in Q2, Q3, and Q4 versus Q1 of stroke SLFS, respectively) and prevalent LVH (22%, 32%, and 42% greater odds in Q2, Q3, and Q4 versus Q1, respectively) with a less dramatic increase for diabetes (7%, 18%, and 26% in Q2, Q3, and Q4 versus Q1). Odds of atrial fibrillation were increased for increasing quartiles of SLFS (23% increased risk from Q4 to Q1; P=0.033) with differences in prevalence of atrial fibrillation being primarily between Q1 versus Q2 through Q4 (ie, similar odds across the top 3 quartiles). Although there were significant differences in odds of current smoking (P=0.016) as a function of stroke SLFS, there was no clear pattern observed between the quartiles of stroke SLFS and the likelihood of being a current smoker. Finally, there was not a significant association between any of prevalent dyslipidemia (P=0.14), overweight or obesity (P=0.074), or elevated C-reactive protein (P=0.19) and stroke SLFS.

The association between MI SLFS and prevalent traditional risk factors significantly (P<0.0062) increased for all risk factors with the exceptions of LVH (P=0.12) and elevated C-reactive protein (P=0.11). For each of the risk factors significantly associated with MI SLFS, the trend indicated that odds of that particular risk factor increased with increasing quartile of the SLFS. This was particularly dramatic for hypertension (25%, 38%, and 57% increase in Q2, Q3, and Q4 versus Q1), dyslipidemia (12%, 11%, and 38% increase in Q2, Q3, and Q4 versus Q1), and atrial fibrillation (24%, 29%, and 36% increase in Q2, Q3, and Q4 versus Q1). A sizable difference was also noted for diabetes (26% increase), current smoking (25% increase), overweight and obesity (22% increase), and LVH (24% increase).

Models assessing the relationship between each of the stroke and MI SLFS and each of prevalent heart disease and stroke indicated strong associations (P<0.0004 for all models). However, there was not a clear association between either of these family risk scores and prevalent chronic kidney disease. Although there was a similar increase in

Table 1. Description of the Study Population (n=13 995)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td></td>
</tr>
<tr>
<td>Age (y; mean±SD)</td>
<td>66.2±8.7</td>
</tr>
<tr>
<td>Black</td>
<td>29.5%</td>
</tr>
<tr>
<td>Female sex</td>
<td>50.9%</td>
</tr>
<tr>
<td>“Traditional” risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>55.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.1%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>76.7%</td>
</tr>
<tr>
<td>Smoking</td>
<td>12.7%</td>
</tr>
<tr>
<td>Atrial fibrillation (electrocardiogram)</td>
<td>8.7%</td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>74.2%</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>6.2%</td>
</tr>
<tr>
<td>Elevated C-reactive protein</td>
<td>38.8%</td>
</tr>
<tr>
<td>Prevalent coexisting diseases</td>
<td></td>
</tr>
<tr>
<td>Prevalent heart disease</td>
<td>23.5%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>45.3%</td>
</tr>
<tr>
<td>Prevalent stroke</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

Table 2. Demographics of the Study Population by SLFS Quantiles

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>3485</td>
<td>3504</td>
<td>3466</td>
<td>3484</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y; mean±SD)</td>
<td>71.5±8.1</td>
<td>66.7±7.9</td>
<td>63.3±7.8</td>
<td>63.3±8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black (%)</td>
<td>25.3%</td>
<td>26.1%</td>
<td>31.3%</td>
<td>35.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>46.7%</td>
<td>47.7%</td>
<td>52.6%</td>
<td>56.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>3485</td>
<td>3486</td>
<td>3484</td>
<td>3486</td>
<td></td>
</tr>
<tr>
<td>Age (y; mean±SD)</td>
<td>71.1±8.2</td>
<td>66.3±8.0</td>
<td>63.4±8.2</td>
<td>63.9±8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black (%)</td>
<td>27.9%</td>
<td>29.6%</td>
<td>31.5%</td>
<td>29.2%</td>
<td>0.07</td>
</tr>
<tr>
<td>Female sex</td>
<td>46.3%</td>
<td>50.3%</td>
<td>53.0%</td>
<td>54.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SLFS indicates stratified log-rank family score; Q, quantile; MI, myocardial infarction.
prevailant stroke of approximately 50% with increasing family risk for each of MI or stroke, there was a much larger increase in odds of prevalent heart disease with increasing family risk for MI (81% increase between Q4 and Q1) than for increasing family risk for stroke (33% increase between Q4 and Q1).

### Discussion

Both stroke and MI are complex disorders with multiple genetic and environmental determinants associated with intermediate phenotypes that are themselves complex diseases. Thus, familial transmission patterns likely reflect both aggregation of these intermediate phenotypes, which nonspecifically increase the risk of stroke and MI as well as other disorders, and aggregation of the stroke and MI phenotypes, which are specific for each disorder. We have shown that a family risk of stroke or MI is associated with substantially increased prevalence of many risk factors in the proband. In particular, family risk of stroke is associated with increased odds of an individual being hypertensive, having LVH, or being diabetic and is also associated in an inconsistent manner with atrial fibrillation and current smoking. The pattern of increasing prevalence of risk factors in an individual was more dramatic and more consistent between family risk of MI and each of these risk factors.

This study has several notable strengths. The sample size is an order of magnitude greater than prior studies, giving greater statistical power to detect meaningful associations. Our results reinforce previous findings of the association between family risk of stroke and hypertension in the proband; in addition, we report new associations between family risk of stroke and other risk factors such as diabetes that have not been observed in earlier, smaller studies.15,16

Furthermore, the novel statistical methodology of the SLFS offers many advantages over other methods for measuring family risk, including: (1) providing a continuous index of family risk; (2) differentiating among families with no events by reflecting person-years of exposure; and (3) differentiating among families with events on the basis of the number of events and age of the events. The SLFS also avoids the bias that occurs with use of dichotomous indicators for presence of disease among first-degree relatives, which emphasize absolute counts rather than mean number of occurrences in a family; larger families will be more likely to have a first-degree relative with a positive history, introducing false associations with any risk factor associated with larger family risk.
sizes. Such information is often not included in studies examining family risk of stroke, raising potential concerns that results of previous studies may be driven by events in younger individuals and large families.⁵,¹⁵

Our research does have some limitations. Some details of the family history of stroke were not available, particularly classification as ischemic or hemorrhagic. However, hypertension has a similarly strong association between the 2 subtypes, making a spurious finding due to the inclusion of hemorrhagic strokes among family members unlikely. An association of diabetes with hemorrhagic stroke has been reported but less consistently observed; however, this would tend to dilute the relationship observed in our study rather than strengthen it if large numbers of hemorrhagic strokes were included in family members. The use of self-report data could also introduce recall bias in both family and individual proband medical histories, although previous studies have found self-report reliable for the conditions we studied.²⁴

Another limitation is that we cannot separate the associations between family risk scores attributable to genetic versus environmental processes. Although family history provides information on transmission of disorders that follow a complex, non-Mendelian pattern,⁴⁻⁵ it represents an integrated assessment of risk that encompasses both genetic and environmental factors. Although family risk undoubtedly includes environmental influences, it would also indicate that the associations observed in this study are partially due to genetic sources with only the relative contribution of each being indeterminate.

Finally, we cannot rule out survivorship bias, in which more severely ill individuals died before reaching the age for inclusion in the REGARDS study. This would lead to healthier individuals being part of the cohort and would again tend to dilute the results of our study if this type of bias occurs.

Our results are consistent with previous studies demonstrating that the heritability of stroke and MI is largely mediated through the heritability of risk factors and intermediate phenotypes. Most of the intermediate phenotypes we examined are not specific for stroke or MI but give an increased risk for both disorders as well as other illnesses. However, the significant but modest association between family risk score for stroke and family risk score for MI indicates that the same intermediate phenotypes will lead to differential manifestion of 1 disorder or the other in many families. Although this finding could be due to problems in the collection of family history data, it is consistent with the existence of additional disease-specific influences on the non-specific factors. These disease-specific influences tend to run in families but could be genetic or environmental. This is similar to previous studies, in which the effect of family risk of stroke on the risk of stroke in the proband was significantly attenuated by adjustment for risk factors.⁵ Thus, recommendations by other authors that family history and genetic studies of stroke adjust for differences in intermediate phenotypes remain valid, although such an approach would necessarily remove the contribution of intermediate phenotypes and only identify disease-specific influences. Our findings would also add weight to the proposal to identify potential stroke-related genes using intermediate phenotypes followed by validation of these genes for stroke itself.²⁷

In conclusion, we have shown that family risk of either stroke or MI is strongly associated with increased odds of many common prevalent risk factors in probands. This observation has important scientific implications for understanding the aggregation of stroke and MI in family history and genetic studies. Researchers should carefully consider whether their goal is to identify genetic and environmental influences having specific effects on stroke (or MI), general effects on stroke (or MI) through intermediate phenotypes, or both. Such an approach would naturally lead to a richer, more thorough understanding of the familial transmission of these complex disorders.

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Disclosures
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References


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