Family History as a Risk Factor for Carotid Artery Stenosis

Mahyar Khaleghi, MD; Iyad N. Isseh, MBBS; Hayan Jouni, MD; Sunghwan Sohn, PhD; Kent R. Bailey, PhD; Ifitkhar J. Kullo, MD

Background and Purpose—We investigated whether family history of stroke or coronary heart disease (CHD) is associated with presence of carotid artery stenosis (CAS).

Methods—The study cohort included 864 patients (72±8 years; 68% men) with CAS and 1698 controls (61±11 years; 55% men) referred for noninvasive vascular testing. CAS was defined as ≥70% stenosis in the internal carotid artery on ultrasound or history of carotid revascularization. Controls did not have CAS or history of cerebrovascular disease or CHD. Family history of stroke and CHD was defined as having ≥1 first-degree relative who had stroke or CHD before age 65 years. Logistic regression analysis was used to evaluate whether family history of stroke or CHD was associated with presence of CAS, independent of conventional risk factors.

Results—Family history of stroke and CHD was present more often in patients with CAS than in controls, with a resulting odds ratios (95% confidence interval) of 2.02 (1.61–2.53) and 2.01 (1.70–2.37), respectively. The associations remained significant after adjustment for age, sex, body mass index, smoking, diabetes mellitus, hypertension, and dyslipidemia; odds ratios: 1.41 (1.06–1.90) and 1.69 (1.35–2.10), respectively. A greater number of affected relatives with stroke or CHD was associated with higher odds of CAS; adjusted odds ratios: 1.25 (0.91–1.72) and 1.46 (1.14–1.89) versus 2.65 (1.35–5.40) and 2.13 (1.57–2.90) for patients with 1 and ≥2 affected relatives with stroke and CHD, respectively.

Conclusions—Family history of stroke and of CHD were each associated with CAS, suggesting that shared genetic and environmental factors contribute to the risk of CAS. (Stroke. 2014;45:2252-2256.)

Key Words: atherosclerosis ▪ carotid stenosis ▪ coronary heart disease ▪ risk factors ▪ stroke

Carotid artery stenosis (CAS) is one of the main causes of ischemic stroke, a major public health burden in the United States. Several population-based studies have estimated the prevalence of CAS (defined as ≥70% narrowing of the internal carotid artery (ICA) based on ultrasound) to be in the range of 0.0% to 3.1% with a higher prevalence in patients >65 years of age. The annual stroke risk for patients with CAS is ~2% to 5%. Although multiple studies have shown that family history is a significant risk factor for coronary heart disease (CHD) and stroke, the association between family history of atherosclerotic vascular disease with presence of CAS is largely unknown. In the Tromso study, family history of CHD was marginally associated with CAS in men (P=0.03) but not in women (P=0.3). Small sample size was a limitation of this study, and whether family history of stroke/CHD is associated with CAS has not been examined in a large cohort of patients with CAS. The present study was designed to investigate whether family history of stroke or CHD was associated with the presence of CAS. We also assessed whether number of affected relatives with stroke or CHD was associated with CAS. In addition, we assessed whether parental versus sibling history of atherosclerotic vascular disease are differently associated with CAS.

Materials and Methods

Study Population

In October 2006, a biorepository of plasma and DNA of vascular disease patients and controls was initiated by recruiting patients referred for noninvasive vascular testing at the Mayo Clinic, Rochester, MN. Between October 2006 and June 2012, 10206 patients were recruited. All participants gave informed consent, and the study protocol was approved by the Institutional Review Board of the Mayo Clinic.

Case and Control Status

Patients at Mayo Clinic suspected of having CAS are referred for carotid artery Doppler ultrasound. Angle-corrected velocity measurements of the neck vessels are performed and recorded as peak systolic and end-diastolic velocity, respectively. Measurement of carotid stenosis, if present, is based on velocity parameters that compare the residual internal carotid luminal diameter with that of the normal distal ICA in accordance with North American Symptomatic Carotid Endarterectomy Trial (NASCET). An algorithm based primarily on natural language processing of unstructured text in the carotid ultrasound report was used to extract the required velocities and other study variables (available in Material and Methods in the online-only Data Supplement). The carotid ultrasound report closest to recruitment date was used, and the severity of stenosis recorded was the higher degree of stenosis from either side. Twenty-five randomly selected carotid ultrasound reports were manually reviewed by one of the study investigators to confirm the presence of CAS. The study was approved by the Institutional Review Board of the Mayo Clinic. The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.006245/-/DC1.

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Stroke is available at http://stroke.ahajournals.org

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the authors (I.I.). Validation showed a positive and negative predictive value of 100%. CAS was defined as having ≥70% stenosis in either ICA on ultrasound (the cutoff at which revascularization is indicated) or history of carotid artery endarterectomy/stenting. Carotid stenosis ≥70% on ultrasound was established based on predefined criteria of ICA peak systolic velocity ≥230 cm/s, or ICA end-diastolic velocity >100 cm/s, or ICA/common carotid artery peak systolic velocity ratio >4.0.13,14 Controls were patients without CAS or history of atherosclerotic vascular disease (stroke, myocardial infarction, and peripheral arterial disease).

We excluded 40 patients who identified themselves as having been adopted. Several nonatherosclerotic vascular diseases can result in arterial disease.

Family History
Family history of stroke and CHD was obtained via questionnaire given to the patients at the time of recruitment. Participants were asked about presence of stroke and CHD in first-degree relatives, including mother, father, full siblings, sons, and daughters, before age 65 years. Family history of CHD was considered to be present if a first-degree relative had myocardial infarction or coronary revascularization or stent placement before age 65 years.

Demographic Factors
Specific data elements of potential relevance to CAS were abstracted from the electronic health record. These include birth date, sex, and race. Height, weight, and body mass index closest to index date (defined as the date of vascular laboratory evaluation) were abstracted from the electronic health record record directly.

Cardiovascular Risk Factors and Comorbidities
Smoking status was ascertained from the study questionnaire and ever smoking defined as having smoked >100 cigarettes. To ascertain other risk factors and comorbidities, we used ICD-9-CM codes, medication use, and laboratory data in the electronic health record as previously detailed.15

Statistical Methods
Continuous data are summarized as either mean±SD or median and quartiles. Between-group differences were assessed by an unpaired 2-tailed Student t test or Wilcoxon rank-sum test. Categorical data were expressed as percentages, and between-group differences were assessed by χ² test statistic. We constructed multivariable logistic regression models that adjusted for conventional risk factors and other potential confounding variables to assess whether family history of stroke or CHD was independently associated with CAS. Adjustments were performed for age and sex, body mass index, smoking history, diabetes mellitus, hypertension, and dyslipidemia. To compare the association of parental and sibling history of stroke and CHD with presence of CAS, we stratified study participants based on family history (parental or sibling history) and repeated the above analyses for each group separately. We also checked for interactions between conventional risk factors and family history in the prediction of CAS. A 2-sided P<0.05 was deemed statistically significant. Statistical analyses were performed using the SAS v 9.1 (SAS Institute, Cary, NC) software package.

Results
Participant characteristics are shown in Table 1. Patients with CAS were older and included higher proportion of men and had a higher prevalence of increased body mass index, dyslipidemia, diabetes mellitus, history of smoking, and hypertension (Table 1).

Prevalence of family history of stroke was significantly higher in patients with CAS compared with controls (19.8% versus 10.9%; P<0.001; Table 2). Both parental and sibling history of stroke were more often present in cases than controls (9.3 versus 6.4%, P=0.01 and 10.6 versus 4.8%, P<0.001, respectively). In univariable logistic regression analysis, family history of stroke was associated with a higher odds ratio (OR): 2.02 (95% confidence interval, 1.61–2.53) of having CAS (Figure 1). This association was attenuated but remained significant after adjustment for age, sex, body mass index, ever smoking, diabetes mellitus, hypertension, and dyslipidemia; OR: 1.41 (1.06–1.90; Table 3). In a subset analysis, similar results were observed for sibling history of stroke; OR: 1.48 (1.00–2.20). However, the association between parental history of stroke and presence of CAS was not statistically significant; OR: 1.23 (0.83–1.82). A greater number of affected relatives with stroke was associated with a higher odds of presence of CAS. In logistic regression models, the adjusted ORs were 1.25 (0.91–1.72) and 2.65 (1.35–5.40) for patients with 1 and ≥2 affected relatives with stroke, respectively (Figure 2).

Prevalence of family history of CHD was higher in patients with CAS than in controls (50.6% versus 33.7%; P<0.001; Table 2). Similar results were observed for parental and sibling history of CHD (26.7% versus 22.7%, P=0.028 and 33.8 versus 15.8%, P<0.001, respectively). In univariable logistic

<table>
<thead>
<tr>
<th>Table 1. Participant Characteristics</th>
<th>CAS (n=864)</th>
<th>Control (n=1698)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean±SD or n (%)</td>
<td>Mean±SD or n (%)</td>
</tr>
<tr>
<td>Men</td>
<td>72±8</td>
<td>61±11*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.2±5.2</td>
<td>28.3±5.3*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>834 (36.3)</td>
<td>701 (16.0)*</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>655 (75.8)</td>
<td>700 (41.2)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>629 (72.8)</td>
<td>555 (32.7)*</td>
</tr>
<tr>
<td>Previous history of stroke</td>
<td>156 (18.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Previous history of MI</td>
<td>199 (23.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Number of first-degree relatives with stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>693 (80.2)</td>
<td>1513 (89.1)*</td>
</tr>
<tr>
<td>1</td>
<td>135 (15.6)</td>
<td>167 (9.8)</td>
</tr>
<tr>
<td>2</td>
<td>31 (3.6)</td>
<td>17 (1.0)</td>
</tr>
<tr>
<td>≥3</td>
<td>5 (0.6)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Number of first-degree relatives with CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>427 (49.4)</td>
<td>1125 (66.3)*</td>
</tr>
<tr>
<td>1</td>
<td>248 (28.7)</td>
<td>428 (25.2)</td>
</tr>
<tr>
<td>2</td>
<td>106 (12.3)</td>
<td>92 (5.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>83 (9.6)</td>
<td>53 (3.1)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as means±SD or median and interquartile range, whereas categorical variables are presented as counts and percentages. BMI indicates body mass index; CAS, carotid artery stenosis; CHD, coronary heart disease; and MI, myocardial infarction.

*Statistically significant differences at P<0.001.
regression analysis, family history of CHD was associated with a higher OR of having CAS: 2.01 (1.70–2.37; Figure 1). This association remained significant after adjustment for the above mentioned covariates; OR: 1.69 (1.35–2.10; Table 3). Adjustment also showed similar results for parental and sibling history of CHD; OR: 1.46 (1.14–1.89) and 1.65 (1.29–2.11), respectively. A greater number of affected relatives with CHD was also associated with higher odds of presence of CAS. In logistic regression models, the adjusted ORs were 1.46 (1.14–1.89) and 2.13 (1.57–2.90) for patients with 1 and ≥2 affected relatives with CHD, respectively (Figure 2).

When we assessed the combined effect of family history of stroke and CHD on the odds of presence of CAS, the combination of greater number of affected relatives with stroke and CHD lead to markedly increased odds of presence of CAS (Figure 3). For example, patients with ≥2 affected relatives with stroke, as well as ≥2 affected relatives with CHD (n=84), had an OR 7.22 (3.11–18.71) compared with those without such history.

**Discussion**

In the present study, we demonstrated that (1) family history of stroke, as well as of CHD, were significantly associated with presence of CAS, independent of conventional risk factors; (2) sibling history of stroke or CHD was a stronger risk factor than parental history; (3) the association was stronger in individuals with greater number of affected relatives, independent of the size of the family. These findings suggest that shared genetic and environmental factors contribute to the risk of CAS and that carotid atherosclerosis shares several genetic variants with CHD.

The American Society of Neuroimaging recommends (grade A) screening in patients with cardiovascular risk factors (patients aged ≥65 years with ≥3 cardiovascular risk factors: hypertension, coronary artery disease, current cigarette smoking, or hyperlipidemia).16 The results of our study suggest that family history of stroke or CHD is another risk factor for presence of CAS and should be considered when contemplating ultrasound screening in asymptomatic individuals.

We noted that the number of affected relatives with stroke was associated with higher odds of presence of CAS. Individuals with ≥2 affected relatives had an OR higher than that associated with diabetes mellitus (OR: 2.38 [1.82–3.12]) or dyslipidemia (OR: 1.98 [1.53–2.58]) and almost similar to that associated with hypertension (OR: 2.91 [2.31–3.67]). We observed a similar association between the number of affected relatives with CHD and presence of CAS. To adjust for differences in family size between cases and controls, we included the size of family (number of all first-degree relatives) in the regression models. Adjustment for family size did not change the strength of associations (analyses not shown).

**Table 2. Prevalence of Family History of Stroke and CHD in Cases and Controls**

<table>
<thead>
<tr>
<th></th>
<th>CAS (n=864) n (%)</th>
<th>Control (n=1698) n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>171 (19.8)</td>
<td>185 (10.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental history of stroke</td>
<td>80 (9.3)</td>
<td>108 (6.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sibling history of stroke</td>
<td>92 (10.6)</td>
<td>81 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Offspring history of stroke</td>
<td>11 (1.3)</td>
<td>6 (0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>437 (50.6)</td>
<td>573 (33.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental history of CHD</td>
<td>231 (26.7)</td>
<td>386 (22.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>Sibling history of CHD</td>
<td>292 (33.8)</td>
<td>268 (15.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Offspring history of CHD</td>
<td>39 (4.5)</td>
<td>20 (1.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenosis; and CHD, coronary heart disease.

**Table 3. Multivariable Associations of Family History of Stroke/CHD With Presence of CAS**

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.41 (1.06–1.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Parental history of stroke</td>
<td>1.23 (0.83–1.82)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sibling history of stroke</td>
<td>1.48 (1.00–2.20)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>1.69 (1.35–2.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental history of CHD</td>
<td>1.46 (1.14–1.89)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sibling history of CHD</td>
<td>1.65 (1.29–2.11)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Models were adjusted for age, sex, hypertension, diabetes mellitus, smoking, dyslipidemia, and body mass index. CAS indicates carotid artery stenosis; CHD, coronary heart disease; CI, confidence interval; and OR, odds ratio.
The association of family history of stroke/CHD and presence of CAS could be because of familial aggregation of conventional risk factors. Participants with CAS were older and had a higher prevalence of conventional risk factors than controls. The associations between family history of stroke/CHD and CAS were attenuated (the ORs went from 2.0 to 1.4–1.7) after adjustment for conventional risk factors but remained significant. This suggests that the association of family history of stroke/CHD with CAS may be because of genetic factors acting independent of conventional risk factors.

In a small (n=394) selected population, Jacobowitz et al found that history of stroke in a first-degree relative was inversely associated with the prevalence of CAS (the authors attributed this finding to the lack of reliable patient history). In the Tromso study, family history of CHD was marginally associated with stenosis in men (P=0.03) but not in women (P=0.3). Small sample size leading to lack of power was a major limitation of these studies. In the present study, we did not find a significant interaction between family history and sex or any other conventional risk factors in predicting the presence of CAS. There was only a weak interaction (P=0.05) between age and family history of stroke in predicting presence of CAS, indicating that the association is stronger in younger individuals. However, the interaction was not significant in a fully adjusted model.

In a subset analysis, when we adjusted our models for both family history of stroke and of CHD, family history of CHD remained significantly and independently associated with presence of CAS, whereas family history of stroke was no longer associated with presence of CAS (analysis not shown). The independent association of family history of CHD with presence of CAS suggests that shared genetic factors influence susceptibility to CAS and CHD.

We found sibling history of stroke/CHD to be a stronger risk factor than parental history for presence of CAS. In a subset analysis, when we adjusted models for both sibling and parental history of stroke/CHD, sibling history of stroke/CHD was associated with presence of CAS, independent of parental history (analysis not shown). This is consistent with several previous studies that have shown sibling history of early-onset CHD to be a stronger risk factor than parental history. This may be because of greater sharing of environmental factors between sibling pairs than between parent–offspring pairs. It has been shown that maternal transmission of CHD is stronger than paternal transmission. In subset analysis, we found that maternal history of CHD to be a stronger risk factor than paternal history for presence of CAS; ORs: 2.05 (1.37–3.11) and 1.30 (0.99–1.71), respectively (Table I in the online-only Data Supplement).

The strengths of this study include a large cohort of CAS cases and controls and assessment of family history based on an in-depth questionnaire: the response rate to the questionnaire was relatively high at 69%. Using the electronic health record, we were able to compare the characteristics of responders versus nonresponders (Table II in the online-only Data Supplement). Responders were older, but there was similar proportion of men and women in both groups. Conventional risk factors were similar in the 2 groups.

Several limitations of our study need to be considered. Selection of the study population from patients who were referred to Mayo Clinic may limit the external validity of the study. Our study sample consists predominantly of non-Hispanic whites (>95%) and the extent to which our findings may be generalizable to subjects of other ethnic backgrounds is not known. Personal history of stroke or myocardial infarction may increase the risk of presence of CAS. However, in a subset analysis that included CAS cases without such history, we found similar results (Table III in the online-only Data Supplement). We cannot exclude the presence of asymptomatic CAS in control participants not assessed by ultrasound. In a subset of controls (n=248) who were evaluated by carotid artery Doppler ultrasound, only 5 patients (2%) had CAS, which is in range of the estimated prevalence of CAS in several population-based studies. Similar to other case–control studies, we cannot exclude the effect of recall bias in our study. The optimal method of validation of a reported family history of disease is through review of medical records. However, it is not practical to interview and examine affected relatives in a large cohort study. Previous studies have shown that reported family history of CHD has a high sensitivity and specificity and most likely the recall bias is toward the null. It was not possible to distinguish between family history of ischemic versus hemorrhagic stroke in the questionnaire. However, inclusion of hemorrhagic stroke would be expected to attenuate the observed associations.

Conclusions
We report for the first time results of an in-depth investigation of family history as a risk factor for CAS. We show that (1) family history of stroke or CHD is independently associated with presence of CAS; (2) sibling history of stroke or CHD confers greater risk than parental history; and (3) the magnitude of the association is greater in those with greater number of affected relatives, independent of the size of the family. These findings motivate additional studies to a) identify genetic susceptibility variants for CAS; and b) assess the utility of screening asymptomatic individuals with family history of vascular disease for early detection of CAS and prevention of ischemic stroke.

Sources of Funding
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Disclosures

None.

References

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World Wide Web at:
http://stroke.ahajournals.org/content/45/8/2252

An erratum has been published regarding this article. Please see the attached page for:
/content/45/9/e198.full.pdf

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/07/08/STROKEAHA.114.006245.DC1
The version of the article, “Family History as a Risk Factor for Carotid Artery Stenosis” by Khaleghi et al that published online ahead-of-print on July 8, 2014, and appears in the August issue (Stroke. 2014;45:2252–2256) contained an error in the Abstract and Conclusions. The conclusion of the abstract should read, “Family history of stroke and of CHD were each associated with CAS, suggesting that shared genetic and environmental factors contribute to the risk of CAS.” The second sentence of the conclusions should read, “We show that (1) family history of stroke or CHD is independently associated with presence of CAS; (2) sibling history of stroke or CHD confers greater risk than parental history; and (3) the magnitude of the association is greater in those with greater number of affected relatives, independent of the size of the family.” The authors regret the error.

This correction has been made to the online version of the article, which is available at http://stroke.ahajournals.org/content/45/8/2252.

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Natural Language Processing Methods

Natural Language Processing (NLP) has been widely employed in various clinical applications including pathology information extraction,\(^1\) patient medical status extraction,\(^2,\,3\) sentiment analysis,\(^4\) and genome-wide association studies.\(^5,\,6\) In this study, NLP was used to extract required variables from the narrative electronic health record (EHR). We used basic NLP techniques from the clinical Text Analysis and Knowledge Extraction System (cTAKES)\(^7\) to preprocess unstructured text. The information extraction module from MedTagger (http://sourceforge.net/projects/ohnlp/files/MedTagger/) was used to extract velocities and other variables. In the NLP pipeline, the EHR was initially preprocessed to parse clinical narratives into sentences and word tokens. Since the variables required in this study are described in various ways in the EHR, we manually created customized pattern matching rules using regular expressions for each variable. We then implemented those rules into the MedTagger framework to extract the required variables systematically.
### Supplement Table I. Associations of maternal vs. paternal history of stroke/CHD with presence of CAS

<table>
<thead>
<tr>
<th></th>
<th>OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal history of stroke</td>
<td>1.46 (0.84-2.56)</td>
<td>0.2</td>
</tr>
<tr>
<td>Paternal history of stroke</td>
<td>1.14 (0.68-1.89)</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal history of CHD</td>
<td>2.05 (1.37-3.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paternal history of CHD</td>
<td>1.30 (0.99-1.71)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Models were adjusted for age, sex, hypertension, diabetes, smoking, dyslipidemia, and body mass index. CAS, carotid artery stenosis; CHD, coronary heart disease; CI, confidence interval; OR, odds ratio
Supplement table II. Characteristics of respondents vs. non-respondents

<table>
<thead>
<tr>
<th></th>
<th>Respondents (n=6883)</th>
<th>Non-respondents (n=3179)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD or n (%)</td>
<td>Mean ± SD or n (%)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>67.0 ± 11.1</td>
<td>64.0 ± 13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>4258 (61.9)</td>
<td>1919 (60.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.9 ± 5.5</td>
<td>29.3 ± 5.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4993 (72.5)</td>
<td>2341 (73.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1589 (23.1)</td>
<td>799 (25.1)</td>
<td>0.025</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3699 (53.7)</td>
<td>1760 (55.4)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Continuous variables are presented as means ± standard deviation, whereas categorical variables are presented as counts and percentages. BMI: body mass index
### Supplement Table III. Associations of family history of stroke/CHD with presence of CAS

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong> (excluding 156 cases with personal history of stroke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.41 (1.04-1.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>Parental history of stroke</td>
<td>1.21 (0.80-1.84)</td>
<td>0.36</td>
</tr>
<tr>
<td>Sibling history of stroke</td>
<td>1.51 (1.00-2.28)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>CHD</strong> (excluding 199 cases with personal history of myocardial infarction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>1.65 (1.31-2.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental history of CHD</td>
<td>1.45 (1.11-1.89)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sibling history of CHD</td>
<td>1.61 (1.24-2.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Models were adjusted for age, sex, hypertension, diabetes, smoking, dyslipidemia, and body mass index. CAS, carotid artery stenosis; CHD, coronary heart disease; CI, confidence interval; OR, odds ratio.
33. Have you ever been told by a physician that you had:
(Please mark one response per line.)
- emphysema, chronic bronchitis, or chronic obstructive lung disease?
- thyroid disease?
- kidney disease?
- a blood clot in the veins of your legs or arms?
- A blood clot that went to the lungs?
- connective tissue disorder (such as rheumatoid arthritis, SLE)?
- any form of cancer, including melanoma (but excluding other forms of skin cancer)?

34. Have you had radiotherapy to the chest for treatment of cancer?
- No
- Yes
  How old were you the first time this happened?
  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] Age

35. Have you had radiotherapy to the abdomen for treatment of cancer?
- No
- Yes
  How old were you the first time this happened?
  [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] Age

36. Are you adopted?
- No
- Yes
  Can you tell us any information about one or more of your blood-related family members?
  - No
    - Skip to question 44 on page 14.
  - Yes
    - Continue with question 37 on page 10.
The following questions are about your blood-related family members.

37. How many of each of the following blood-related family members do you have?

<table>
<thead>
<tr>
<th>Family Members</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7 or more</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full sisters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full brothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half sisters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half brothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood-related daughters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood-related sons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mother's side:

<table>
<thead>
<tr>
<th>Family Members</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7 or more</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aunts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cousins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Father's side:

<table>
<thead>
<tr>
<th>Family Members</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7 or more</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aunts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cousins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

38. For each of your blood-related family members below, please tell us how many of them have had any of the listed conditions before age 65. (For each condition, please fill in one bubble per family member.)

<table>
<thead>
<tr>
<th>Heart attack</th>
<th>Heart artery angioplasty or bypass surgery</th>
<th>Leg artery angioplasty or bypass surgery</th>
<th>Stroke</th>
<th>Aortic aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full sisters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full brothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half sisters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half brothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sons</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
39. For each of your blood-related family members below, please tell us how many of them have had any of the listed conditions before age 65. (For each condition, please fill in one bubble per family member.)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mother's side</th>
<th>Father's side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attack</td>
<td>Aunts</td>
<td>Aunts</td>
</tr>
<tr>
<td>Heart artery angioplasty or bypass surgery</td>
<td>Uncles</td>
<td>Uncles</td>
</tr>
<tr>
<td>Leg artery angioplasty or bypass surgery</td>
<td>First cousins</td>
<td>First cousins</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

40. Do you have any full sisters or brothers or half sisters or brothers?

- [ ] No
- [ ] Yes
- [ ] Don’t know

Did any of your full or half sisters or brothers die before the age of 65?

- [ ] No
- [ ] Yes

How many of them died of a heart attack or stroke?

- [ ] None
- [1]
- [2]
- [3]
- [4 or more]
- [Don’t know]

41. Do you have any daughters or sons?

- [ ] No
- [ ] Yes
- [ ] Don’t know

Did any of your daughters or sons die before the age of 65?

- [ ] No
- [ ] Yes

How many of them died of a heart attack or stroke?

- [ ] None
- [1]
- [2]
- [3]
- [4 or more]
- [Don’t know]
42. Please provide the following information about your blood-related MOTHER.

Is your blood-related MOTHER alive or deceased?

- [ ] Alive
- [ ] Deceased
- [ ] Don't know

Go to question 43 on page 13.

What is her current age?

- [ ] Age
- [ ] Don't know

What was her age at death?

- [ ] Age
- [ ] Don't know

What was the cause of her death?

- [ ] Accident
- [ ] Heart attack
- [ ] Congestive heart failure
- [ ] Stroke
- [ ] Emphysema
- [ ] Cancer
- [ ] Other, specify: 
- [ ] Don't know

Please tell us if your blood-related mother has had any of the conditions below by marking the bubble to the left of the condition. If she has had the condition, please tell us her age when the condition was first diagnosed.

- [ ] Heart attack or myocardial infarction
- [ ] Heart bypass surgery
- [ ] Heart artery angioplasty or stent placement
- [ ] Stroke
- [ ] Carotid artery surgery (carotid endarterectomy)
- [ ] Angioplasty or stent placement in a leg artery
- [ ] Bypass surgery for poor circulation in the legs
- [ ] Aortic aneurysm
- [ ] Diabetes or high blood sugar
- [ ] High blood pressure or hypertension
- [ ] High cholesterol

Has/did your mother ever smoked/smoke cigarettes on a regular basis?

- [ ] No
- [ ] Yes
- [ ] Don't know

What is/was your mother's usual weight?

- [ ] Slender or average
- [ ] Mildly overweight
- [ ] Moderately overweight
- [ ] Markedly overweight

Please do not write in this area.

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43. Please provide the following information about your blood-related FATHER.

Is your blood-related FATHER alive or deceased?

- Alive
  - What is his current age?
    - Age
    - Don't know

- Deceased
  - What was his age at death?
    - Age
    - Don't know

- Don't know

Go to question 44 on page 14.

Please tell us if your blood-related father has had any of the conditions below by marking the bubble to the left of the condition. If he has had the condition, please tell us his age when the condition was first diagnosed.

- Heart attack or myocardial infarction
- Heart bypass surgery
- Heart artery angioplasty or stent placement
- Stroke
- Carotid artery surgery (carotid endarterectomy)
- Angioplasty or stent placement in a leg artery
- Bypass surgery for poor circulation in the legs
- Aortic aneurysm
- Diabetes or high blood sugar
- High blood pressure or hypertension
- High cholesterol

Has/did your father ever smoked/smoke cigarettes on a regular basis?

- No
- Yes
- Don't know

What is/was your father's usual weight?

- Slender or average
- Mildly overweight
- Moderately overweight
- Markedly overweight
Supplemental References


