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Sibling History of Myocardial Infarction or Stroke and Risk of Cardiovascular Disease in the Elderly: The Cardiovascular Health Study

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Abstract

PURPOSE—To assess the relationship between sibling history of myocardial infarction (MI) or stroke with cardiovascular disease (CVD) and risk factors in older adults.

METHODS—Prospective cohort study of 5,888 older adults participating to the Cardiovascular Health Study (CHS). History of MI and stroke in siblings was obtained by self-report. Participants with positive sibling histories were compared to those with negative histories to determine if prevalent or incident disease (coronary heart disease [CHD], MI, stroke, angina), subclinical CVD (carotid wall thickness, left ventricular mass, hypertension, diabetes, ankle brachial index), CVD risk factors differed between groups.

RESULTS—More than 91 percent (n=5,383) of CHS participants reported at least one sibling. Sibling history of MI was associated with increased disease prevalence (CHD, MI, angina) and incidence (CHD, angina). Sibling history of stroke was associated with increased disease prevalence (CHD, angina). Sibling history of either MI or stroke was associated with increased disease prevalence and incidence for CHD, MI and angina, more subclinical disease, and a higher CVD risk profile.

CONCLUSIONS—Sibling history of MI and stroke were markers of higher CVD risk status even in older adults. Of clinical importance, participants with positive sibling history have numerous risk factors amenable to intervention.

Keywords

Epidemiology; Cardiovascular diseases; Risk Factors; Atherosclerosis; Lifestyle

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INTRODUCTION

Family history of cardiovascular disease (CVD) has been shown to be a risk factor for the subsequent development of disease, and a potential screening tool to identify individuals with increased risk who may be candidates for enhanced prevention strategies (1,2). In the elderly, parental medical history may be difficult to obtain or is often inaccurate (3), and a positive sibling history of CVD is a stronger independent predictor of incident cardiovascular events than parental history (4). Siblings' health history has been proposed as a marker to stratify populations for genetic research (5).

Familial aggregation has been shown to occur for hypertension (6–10), myocardial infarction (10–14), ischemic stroke (15,16), diabetes (17,18) and obesity (19). Family history is a predictor of risk factor levels and/or disease in studies of children, young and middle-aged adults (4,20,21). Among twins, sibling history of coronary heart disease (CHD) death predicts increase risk of CHD death before age 65 years (22), suggesting genetic components to exert stronger effects at younger ages (23). However, less is known about the importance of family history of cardiovascular disease in the elderly.

Due to a survivorship effect in older adults it is possible that substantial differences may exist in the relationship between family history and CVD risk between middle age and older populations. A positive family history may be more predictive of the risk of early CVD events rather than events in later life (24–26). The risk from a positive family history may be diminished in older adults due to reduced survivorship in high-risk families and to potential difficulties in the assessment of familial risk. However, given the older age of the participant’s parents and siblings, an advantage of assessing family history in older adults is the relatively low level of false negatives.

This study addresses the issue of whether risk factor differences exist in an elderly population between individuals with a positive as compared to a negative sibling history of myocardial infarction (MI) and of stroke. Specifically, we examined the association between a sibling history of MI and sibling history of stroke with CVD prevalence and incidence, subclinical measures of disease, and major risk factors in this cohort of older adults.

METHODS

Study Population

The Cardiovascular Health Study (CHS) cohort consists of 5,888 elderly men and women aged 65 years and older drawn from four U.S. communities. Details of the CHS study design have been published elsewhere. (27) Demographic information, laboratory tests, physical measurements, ultrasound, measures of cognitive and functional status were collected at baseline and at annual visits thereafter. Past medical histories and reported cardiovascular events were confirmed by medical record review. (27) Sibling history was collected at baseline examinations for the original CHS cohort in 1989 (n=5201) and an additional African American cohort (n=697) in 1992. Sibling history information was obtained by self-report.

Data analysis

CVD risk factors used in these analyses were limited to "major" risk factors available in CHS and included age, gender, race, blood pressure, body size, lipids and lipoproteins, smoking status, creatinine, plasma glucose and insulin, medication use and measures of coagulation factors. Individuals were considered to have a positive sibling history for MI if any of their siblings had experienced an MI. Sibling history for stroke was constructed in a similar manner. A “combined” sibling history for MI or stroke was positive if they had a positive sibling history

for MI or a positive sibling history for stroke. All measures used in the analysis were collected at baseline.

The STATA version 9.2 (StataCorp, College Station, TX) statistical package was used for data analysis. Associations between continuous and dichotomous measures of CVD and sibling history factors (i.e., MI, stroke and the combined sibling history factor) were investigated using regression analysis with robust variance estimates. Continuous measures of CVD include subclinical measures (carotid intima-media thickness [IMT], left ventricular [LV] mass, ankle-brachial index [ABI]) and other risk factors (blood pressure, lipids/lipoproteins, body size, coagulation factors, creatinine, fasting glucose and fasting insulin levels). Dichotomous measures of CVD risk factors include: gender, black race, medication use, aspirin use (greater than two times per two weeks) current smoking, ECG abnormalities, uncontrolled blood pressure (more than 140 mm Hg systolic blood pressure to 90 mm Hg diastolic blood pressure), and high low density lipoproteins (LDL > 130 mg/dL). Associations were adjusted by age, gender and race. Multivariable logistic regression with robust variance estimates was used to investigate the relationship between prevalent disease (CHD, MI, stroke, angina) and the sibling history factors. Multivariable Cox regression with robust variance estimates was used to investigate incident disease (CHD, MI, stroke, angina) and the sibling history factors. Each disease outcome was modeled separately. In logistic models, unadjusted and adjusted odds ratios (OR) were used to summarize prevalent disease associations and sibling history. In Cox models, unadjusted and adjusted hazard ratios (HR) were used to summarize the associations between incident disease associations and sibling history. Test statistics were Wald statistics. All p-values were two-sided.

RESULTS

Sibling History of Disease

The number of siblings reported by participants ranged from 0 to 10 (Table 1). The sibling questionnaire allowed information for up to 10 siblings. Participants with more than 10 siblings were effectively grouped at 10. Six CHS participants were missing sibling data; 499 participants reported no siblings and were excluded from the remaining analyses. There were more than 91 percent (n=5,383) of participants reporting one or more siblings. The presence of at least two siblings was reported by 77% of the cohort. A history of sibling MI was reported in 32% of participants. A history of sibling stroke was reported by 15% of participants. A sibling history of either MI or stroke was reported by 39% of participants.

Association between CVD risk factor profile and sibling history of MI or stroke

Participants who reported a positive sibling history of MI differed from participants who reported a negative sibling history for a number of CVD risk factors (Table 2). Mean internal carotid IMT, LDL, fibrinogen, glucose and creatinine were significantly higher for participants who reported a positive sibling history of MI than participants who reported a negative sibling history of MI. Mean ABI and HDL were significantly lower for participants with a positive sibling history of MI. Participants with a positive sibling history of MI were more likely to be hypertensive, have higher medication and aspirin use, less likely to be black and less likely to be male than participants who reported a negative sibling history.

Participants with a positive sibling history of stroke were older and their mean ABI was lower compared to participants who reported a negative sibling history. Participants with a positive sibling history of stroke were also more likely to be hypertensive and to be taking medications.

Associations between CVD risk factors and a positive sibling history for either MI or stroke were similar to the associations observed between these risk factors and a positive sibling

history of MI alone. It revealed, additionally, that mean age was significantly higher for participants with a positive sibling history of either MI or stroke. Mean common carotid IMT and mean of log insulin were significantly higher for participants with a positive sibling history of either MI or stroke.

Association between prevalent CVD and sibling history of MI, stroke, or MI and stroke combined

Figure 1 presents both unadjusted and adjusted ORs comparing positive with negative sibling histories to the prevalent CVD outcomes (CHD, MI, stroke, angina). Adjusted analyses included baseline characteristics presented in Table 2.

Prevalent CHD—A positive sibling history of MI was associated with a 56% increase in the odds of having prevalent CHD relative to those with a negative sibling history of MI for participants with the same observed CVD risk profile. A positive sibling history of stroke was not associated with prevalent CHD (OR=1.19, p=0.111). A positive history of either MI or stroke was associated with a 53% increase in the odds of having prevalent CHD compared to participants with negative sibling histories.

Prevalent MI—A positive sibling history of MI was associated with a 52% increase in the odds of having prevalent MI relative to those with a negative sibling history of MI. A positive sibling history of stroke was not significantly associated with prevalent MI (OR=1.19, p=0.242). A positive sibling history of either MI or stroke was associated with a 46% increase in the odds of having prevalent MI compared to participants with negative sibling histories.

Prevalent stroke—Sibling history of MI and sibling history of stroke were not significantly associated with prevalent stroke in unadjusted or adjusted analyses.

Prevalent angina—A positive sibling history of MI was associated with a 55% increase in the odds of having prevalent angina relative to those with a negative sibling history of MI. A positive sibling history of stroke was marginally associated with 23% increase in the odds of prevalent angina compared to participants with a negative sibling history of stroke (p=0.074). A positive sibling history of either MI or stroke was associated with a 56% increase in the odds of having prevalent angina compared to participants with negative sibling histories.

Association between incident CVD and sibling history of MI, stroke, or MI and stroke combined

Figure 2 presents both unadjusted and adjusted hazard ratios (HRs) comparing positive to negative sibling histories to incident CVD outcomes. Adjusted analyses include the same baseline characteristics noted previously.

Incident CHD—A positive sibling history of MI was associated with a 22% increased risk of incident CHD relative to those with a negative sibling history of MI for participants with the same observed CVD risk profile. A positive sibling history of stroke was associated with a 29% increased risk of incident CHD compared to participants with a negative sibling history of stroke. A positive sibling history of either MI or stroke was associated with a 28% increased risk of incident CHD compared to participants with negative sibling histories.

Incident MI—A positive sibling history of either MI or stroke was marginally associated with a 17% increased risk of incident MI (HR=1.17, p =0.058) compared to participants with negative sibling histories. A positive sibling history of MI and a positive sibling history of stroke were associated with an increased risk of incident MI (HRs=1.11 and 1.13). These associations, however, were not significant (p=0.246 and 0.257, respectively).

Incident stroke—Sibling history for MI, sibling history for stroke and the two factors combined were not significantly associated with incident stroke in adjusted analyses.

Incident angina—A positive sibling history of MI was associated with a 23% increased risk of incident angina relative to those with a negative sibling history of MI. A positive sibling history of stroke was associated with a 32% increased risk of incident angina compared to participants with a negative sibling history of stroke. A positive sibling history of either MI or stroke was associated with a 28% increased risk of incident angina compared to participants with negative sibling histories.

DISCUSSION

Sibling history of MI and sibling history of stroke in this sample of older adults was associated with a greater prevalence of CVD risk factors, subclinical and clinical disease in the participant. Specifically, the prevalence of CHD was associated with a positive sibling history of MI and marginally associated with a positive sibling history stroke. Prevalent MI was associated with a positive sibling history of MI and was marginally associated with a positive sibling history of stroke. Prevalence of angina was associated with a positive sibling history of MI and a positive sibling history of stroke. No significant associations were observed between sibling history of MI or sibling history of stroke and prevalent stroke. Incident CHD and angina, but not incident MI, were associated with a positive sibling history of MI or a positive sibling history of stroke. A combined positive sibling history (either MI or stroke) was marginally associated with incident MI. Sibling history of MI and sibling history of stroke were not associated with incident stroke.

Other studies have shown a similar association between sibling history and CVD in adults, but these reports have not focused on this older age group (10,14,17). Similar to our findings, a recent report combining the Siblings With Ischemic Stroke Study (Swiss cohort) (28) and the Umeå cohort (29) observed a lack of aggregation of ischemic stroke subtypes in affected sibling pairs (30).

Given the above association between sibling history of MI and participant prevalent subclinical disease, we were interested in assessing if risk factor differences could be observed between positive and negative sibling history. Our data show associations between CVD risk factor levels in these older adults and sibling history of MI. The associations are weaker for sibling history of stroke. Sibling history of MI and sibling history of stroke were associated with a more abnormal risk profile for major CVD risk factors. Similarly, an association between family history of CVD and more abnormal levels of known risk factors has been observed in children (11,13) and also in younger and middle-aged adults (7,10,12,14,31,32).

Our data suggest that the increased prevalence of CHD in participants with positive sibling histories of MI or stroke persisted after adjustment for known CVD risk factors. Other studies of adult populations have observed that the increased susceptibility of adults with a family history of CHD may be independent of lipids and blood pressure levels (32–34).

We did not observe an association between sibling history of stroke and stroke in this elderly population, despite prior suggestion of a genetic contribution to cerebral susceptibility to ischemia (35–37). Likewise, recent data from a population-based cohort of patients with recent transient ischemic attack indicated that family history of stroke does not predict future risk of ischemic stroke (38). The discrepancy between these findings could possibly be explained by different predisposition in subjects with different ethnicity (37), stroke subtype (36), and elderly individuals. Few subjects with prevalent stroke were recruited into this study; these subjects were probably at lower risk of having stroke events. It is also possible that due to a

limited number of events, our study did not have sufficient power to detect such associations. However, the size of the effect did not appear to be very strong.

There are a number of limitations of this study. A potential drawback is the lack of medical record validation data on sibling's disease status. However, other investigators have detected a relatively good concordance (78%) between a reported family history of MI and medical record validation, suggesting that, despite some imprecision, the reported history gives a reasonably good estimate of family history for the diseases we have assessed (39). It is possible that an ascertainment bias may have occurred with those individuals with a positive sibling history of MI having a greater likelihood of diagnoses (hypertension, diabetes, CHD) than participants with a negative sibling history due to increased awareness of the condition by participants and their medical care providers. It is also possible that recall bias might affect the results to some extent. If differential misclassification occurs, due to more active investigations in participants with positive sibling histories, this could have led to some degree of bias. However, risk factors and events in the CHS cohort were sought prospectively, at regular intervals through the study visits, and it is unlikely that participants had different likelihood of being diagnosed with risk factors for CVD or CVD. Our study emphasizes the clinical importance of sibling history as an easily ascertained risk factor for CVD, and a potential feature able to identify subjects amenable to primary prevention.

Given our definition of sibling history, individuals from large families may have a slightly higher risk of being categorized into the positive history group. We investigated confounding by family size by including a covariate for the number of siblings in all fitted logistic and Cox regression. Family size did not appear to confound the associations between the CVD outcomes and sibling history. The relative change in odds ratios was between 1–2% and the relative change in hazard ratios was between 2–4% after adjustment for the number of siblings. The conclusions drawn from the reported results were unchanged. We were also unable to identify half-sibs or step-sibs in our analyses. Given these relationships are aggregated in our data, it is likely the association between sibling history and outcome would be stronger if the half-sibs and step-sibs were excluded from the analysis if the associations observed were genetic in nature. Including non full siblings in the analyses likely bias our results toward the null.

In addition, we did not attempt to obtain family history data on parents and other CVD events. This was done due to concern about the reliability of self-reported data and the comparability of diagnostic methods for ascertaining disease 40–50 years ago.

We have shown that a positive sibling history of MI and a positive sibling history of stroke in older adults were associated with a significantly worse cardiovascular disease prevalence and incidence, more subclinical measures of CVD, and a more adverse risk factor profile. Given that this older cohort of adults represents the "survivors" from early onset of CVD events, it is interesting to note that sibling history of MI and sibling history of stroke remain associated with a more adverse risk factor profile. We have shown that differences were observed in modifiable factors such as lipoprotein levels in older adults with a positive sibling history of disease. The observed differences in prevalent and subclinical CVD remained after adjusting for the major risk factors, suggesting an independent effect of sibling history of MI and sibling history of stroke beyond the direct effects of the risk factors. These data also suggest that these sibling history factors may be markers for other genetic/familial factors that may be poorly or inadequately measured using traditional CVD risk factors in older adults. These data provide additional guidance in the interpretation of siblings' history and could help reduce barriers to the recognition of positive family history (40). Accurate history taking and increasing awareness of siblings' cardiovascular disease, even among older adults, might promote the identification of subjects at risk of cardiovascular disease and potentially improve the access to care and motivate subjects to follow a healthier lifestyle.

List of Abbreviations and Acronyms

ABI	Ankle Brachial Index
CHD	Coronary Heart Disease
CHS	Cardiovascular Health Study
CVD	Cardiovascular Disease
HR	Hazard Ratio
IMT	Intima Media Thickness
LDL	Low Density Lipoproteins
LV	Left ventricle
MI	Myocardial Infarction
OR	Odds Ratio

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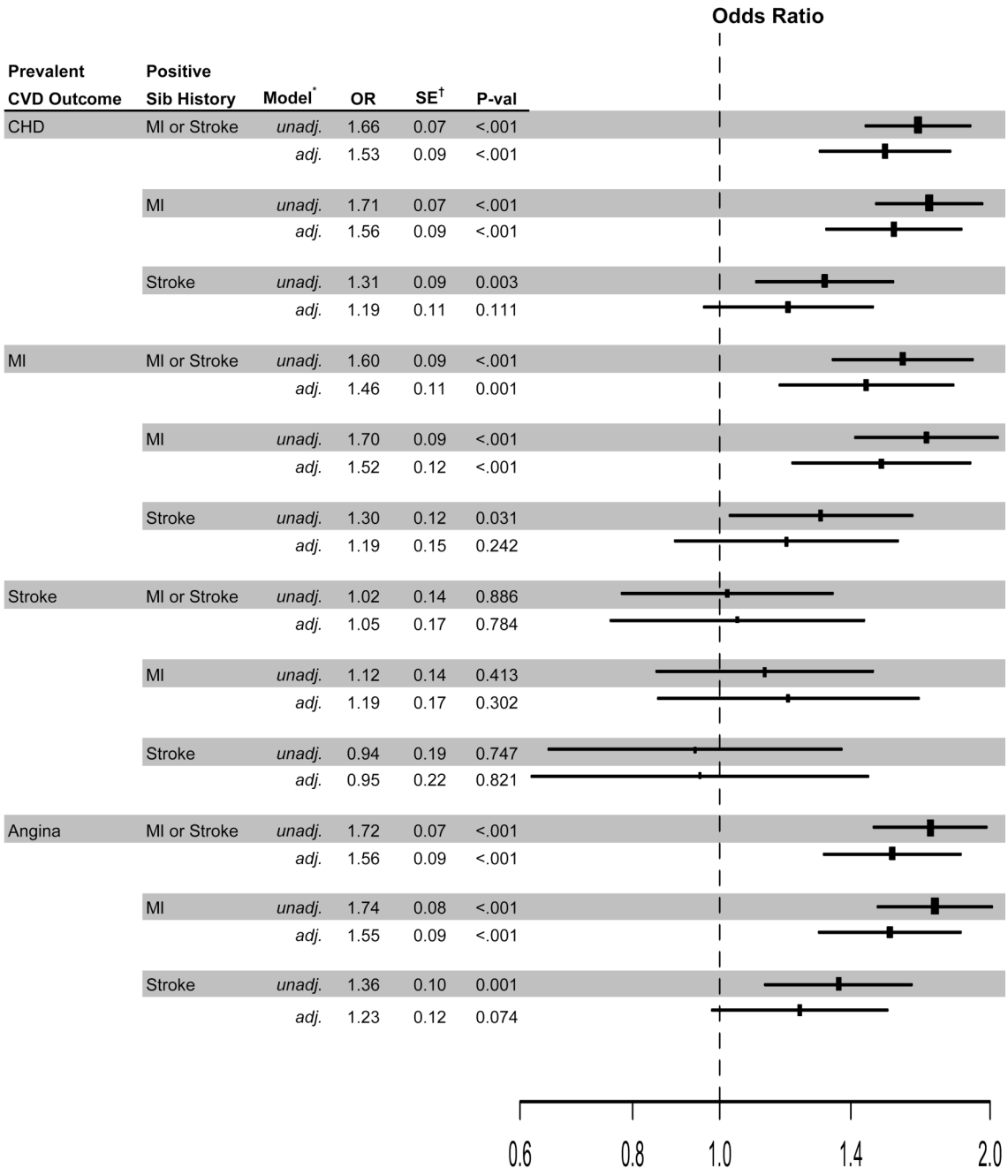

Figure 1.

Odds ratios of prevalent outcomes and sibling history of mi or sibling history of stroke. The size of the rectangles is proportional to the reciprocal of the variance of the odds ratio. *Adjusted analyses include age, gender, black race, IMT of common & internal carotid arteries, ECG LV mass, ankle-brachial index, fibrinogen, Factor VII, LDL & HDL cholesterols, body mass index, log insulin, log glucose, log creatinine, systolic blood pressure, diabetes, hypertension, medication use, aspirin use greater than two times per two weeks, ECG abnormalities. †Estimated standard errors are for log (OR) estimates.

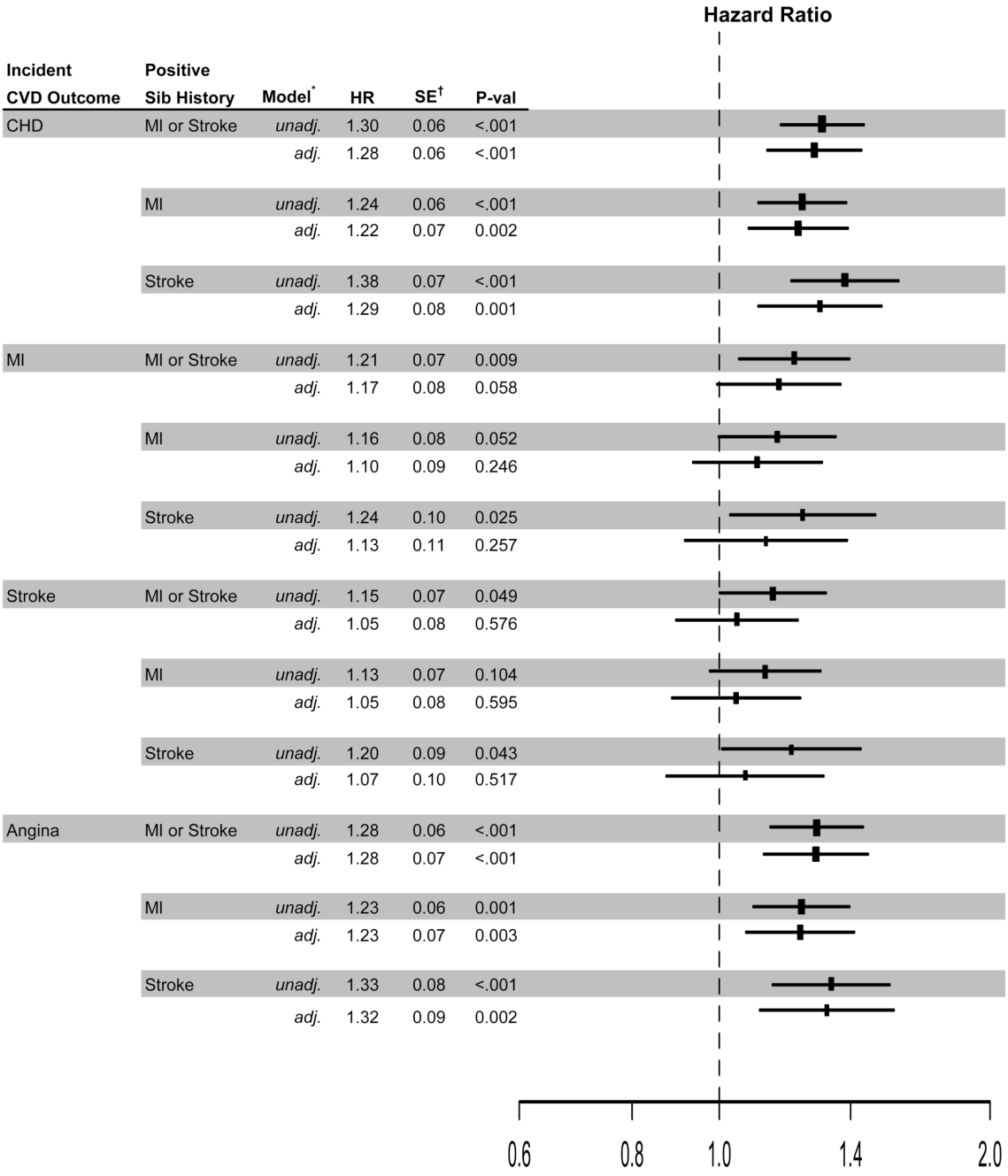

Figure 2.

Hazard ratios of incident outcomes and sibling history of mi or sibling history of stroke. the size of the rectangles is proportional to the reciprocal of the variance of the odds ratio. *Adjusted analyses include age, gender, black race, IMT of common & internal carotid arteries, ECG LV mass, ankle-brachial index, fibrinogen, Factor VII, LDL & HDL cholesterols, body mass index, log insulin, log glucose, log creatinine, systolic blood pressure, diabetes, hypertension, medication use, aspirin use greater than two times per two weeks, ECG abnormalities. †Estimated standard errors are for log (HR) estimates.

Table 1

Distribution of Number of Siblings, Sibling History of MI and Sibling History of Stroke for the CHS Participants.

No. of siblings	N	Percent
0	499	8.5
1	847	14.4
2	973	16.5
3	793	13.5
4	695	11.8
5	509	8.7
6	445	7.6
7	380	6.5
8	264	4.5
9	187	3.2
10 or more	290	4.9
Total	5882*	100
Sibling History of MI		
No	3659	68
Yes	1724	32
Total	5383 †	100
Sibling History of Stroke		
No	4567	85
Yes	816	15
Total	5383 †	100
Sibling History of MI and/or Stroke		
No	3292	61
Yes	2091	39
Total	5383 †	100

*Six participants had missing values for information pertaining to their siblings.

†Data exclude 499 participants with no siblings or have missing data.

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Table 2

Baseline Characteristics of CHS Participants, Comparing Positive versus Negative Sibling History of Myocardial Infarction (MI), Sibling History of Stroke, or Sibling History of either MI or Stroke.

	Sibling History								
	MI			Stroke			MI or Stroke		
Characteristic	**No (N=3655)**	**Yes (N=1722)**	**P-val**	**No (N=4562)**	**Yes (N=815)**	**P-val**	**No (N=3288)**	**Yes (N=2089)**	***p*-val**
Mean age (years)	72.8 ± 5.7	73.1 ± 5.5	0.075	72.7 ± 5.6	73.7 ± 5.8	<.001	72.7 ± 5.7	73.1 ± 5.5	0.004
Male gender (%)	44	39	0.001	42	42	0.870	44	40	0.025
African American (%)	17	12	<.001	15	16	0.590	17	13	<.001
Mean body mass index (kg/m^2)	26.6 ± 4.8	26.8 ± 4.6	0.260	26.7 ± 4.8	26.5 ± 4.5	0.207	26.7 ± 4.8	26.7 ± 4.6	0.624
Diabetic (%)	16	18	0.116	17	15	0.356	16	17	0.215
Current smoking (%)	12	11	0.362	12	13	0.304	12	12	0.768
Mean common carotid IMT (mm)	1.06 ± 0.22	1.07 ± 0.22	0.056	1.06 ± 0.22	1.08 ± 0.23	0.172	1.06 ± 0.22	1.07 ± 0.22	0.039
Mean internal carotid IMT (mm)	1.42 ± 0.57	1.47 ± 0.57	0.004	1.43 ± 0.56	1.46 ± 0.60	0.143	1.42 ± 0.56	1.45 ± 0.58	0.001
Mean left ventricular mass (g)	154 ± 36	155 ± 32	0.661	154 ± 35	156 ± 36	0.256	154 ± 36	155 ± 33	0.454
ECG Abnormalities (%)	30	31	0.436	30	32	0.313	30	31	0.751
Mean systolic blood pressure (mmHg)	136 ± 21	136 ± 21	0.921	136 ± 21	136 ± 22	0.520	136 ± 21	136 ± 21	0.751
Controlled BP (< 140/90) (%)	6	6	0.886	6	6	0.722	6	6	0.471
Medication use (%)	76	81	<.001	77	80	0.052	76	80	<.001
Aspirin use (> 2 days/2 weeks) (%)	33	37	0.002	34	34	0.889	33	36	0.007
Hypertensive (%)	42	48	<.001	44	48	0.028	42	47	<.001
Mean ankle brachial index	1.07 ± 0.17	1.05 ± 0.18	0.001	1.07 ± 0.17	1.05 ± 0.18	0.011	1.07 ± 0.17	1.05 ± 0.18	0.001
Mean LDL (mg/dL)	129 ± 35	131 ± 36	0.014	130 ± 36	130 ± 35	0.904	129 ± 35	131 ± 36	0.021
LDL < 130 mg/dL (%)	52	50	0.117	51	52	0.729	52	50	0.148
Mean HDL (mg/dL)	54.9 ± 16.0	52.3 ± 15.0	<.001	54.2 ± 15.7	53.4 ± 15.5	0.140	54.9 ± 16.0	52.7 ± 15.2	<.001
Mean fibrinogen (mg/dL)	322 ± 69	328 ± 65	0.005	324 ± 67	325 ± 69	0.553	322 ± 69	327 ± 66	0.010
Mean Factor VII (mg/mL)	123 ± 29	124 ± 30	0.075	123 ± 30	123 ± 29	0.507	123 ± 29	124 ± 30	0.191
Mean *log* insulin (pmol/L)	3.72 ± 0.79	3.81 ± 0.81	0.097	3.75 ± 0.79	3.75 ± 0.81	0.877	3.72 ± 0.79	3.79 ± 0.81	0.002

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Mean *log* glucose (mg/dL)	6.74 ± 0.35	6.76 ± 0.34	0.041	6.75 ± 0.34	6.75 ± 0.36	0.855	6.74 ± .35	6.76 ± .34	0.073
Mean *log* creatinine (mg/dL)	.025 ± 0.40	.052 ± 0.41	0.007	.033 ± 0.40	.041 ± 0.41	0.549	.027 ± 0.41	.044 ± 0.40	0.070

Values represent mean ± raw SD or percent. MI indicates myocardial infarction; IMT, intima media thickness; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Baseline characteristics are adjusted for age, gender and race. Summaries for age, gender and race are unadjusted.