Sex-Specific Familial Clustering of Myocardial Infarction in Patients With Acute Coronary Syndromes

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Background—Family history of premature myocardial infarction (MI) in first-degree relatives is a risk factor for MI and an indication for primary prevention. Although excess mother-to-daughter “transmission” occurs in ischemic stroke, no published studies have considered sex-of-parent/sex-of-proband interactions in the heritability of MI.

Methods and Results—In a population-based study (Oxford Vascular Study) of all patients with acute coronary syndromes (ACS), irrespective of age, family history of all acute vascular events and related risk factors were analyzed by sex and age of both probands and first-degree relatives. Premature events were categorized as occurring at age <65 years. Of 835 probands with 1 or more ACS, 623 (420 men) had incident events and complete family history data. In probands with premature ACS, maternal history of both MI and of all vascular events were more common in female than male probands (odds ratio [OR], 2.25; 95% CI, 1.02 to 4.94; P=0.04 and OR, 3.03; 95% CI, 1.47 to 6.26; P=0.002, respectively). No such effect existed for paternal history (OR, 1.00; 95% CI, 0.46 to 2.10; P=0.99 and OR, 1.19; 95% CI, 0.58 to 2.43; P=0.63, respectively). Age at ACS in probands was highly correlated with age at MI in mothers (r=0.46, P<0.001), regardless of the proband’s sex. Consequently, history of premature maternal MI was strongly associated with premature ACS and premature MI in female (OR, 10.52; 95% CI, 2.17 to 56.6; P=0.001 and OR, 7.31; 95% CI, 1.55 to 34.6; P=0.004, respectively) and male probands (OR, 3.88; 95% CI, 1.20 to 12.6; P=0.01 and OR, 3.63; 95% CI, 1.13 to 11.60; P=0.02, respectively).

Conclusions—Important sex-of-parent/sex-of-proband interactions exist in the family history of MI in patients with ACS. Greater emphasis should be placed on maternal than paternal history of MI, particularly in women aged <65 years. (Circ Cardiovasc Genet. 2009;2:98-105.)

Key Words: epidemiology ■ myocardial infarction ■ family history ■ sex-specific ■ population

Family history of vascular disease, particularly premature myocardial infarction (MI), has been used to study the heritability of coronary heart disease (CHD) and interactions between genetic and environmental factors,1–3 and is a marker of increased cardiovascular risk in healthy individuals.4 However, although a family history of premature CHD in first-degree relatives is associated with increased risk of CHD,1–5 increased burden of risk factors, subclinical atherosclerosis,6 and metabolic syndrome,7,8 there have been very few prospective, population-based studies of family history of vascular disease in patients with MI, and prevalence of positive family history ranges from 5.3% to 34.3%, depending on the definition used9–12 (Table 1).

Clinical Perspective see p 105

Despite successive recommendations for screening of first-degree relatives of patients with premature CHD,13–16 the EUROASPIRE II study found that only 11% of siblings and 6% of children of such patients were screened in routine practice.17 Several risk-prediction tools incorporate family history of MI, including the PROCAM, QRISK, and ASSIGN scores, although definitions are variable.18–20 However, as well as ignoring the age at which the relative was affected, these scores assume that the predictive value of family history of MI is independent of sex, which might not be the case.3 For example, heritability of ischemic stroke is greater in women than in men, with an excess of affected mothers and sisters in female probands, independent of traditional risk factors.21,22 Although most previous studies have found no “sex-of-parent effect” in CHD, (ie, paternal history of CHD is at least as important as maternal history),23 no studies have reported sex-of-parent/sex-of-offspring interactions. Moreover, many studies have considered only male or only female probands,10,11,23 have excluded sibling history of MI,24 and have included unrepresentative populations.10,11,24

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Yet, sex-of-proband/sex-of-parent interactions are more likely in the heritability of CHD than stroke due to the “Carter effect.” Unlike stroke, where sex differences in incidence are relatively modest, incidence rates of acute coronary syndromes (ACS) are substantially greater in men than women, particularly at ages <65 years. The Carter effect occurs in diseases (or their intermediate phenotypes) that one sex is less prone to develop and thus may be expected in MI. Women are, on average, less likely to develop MI than men, and are therefore likely to require a greater number of genetic risk factors than men for MI to occur. Women with MI would therefore be expected to have transmitted more MI susceptibility genes to their children than would men with MI, and this effect would most clearly be manifest in female offspring, in whom the incidence of MI would be more likely to be influenced by these susceptibility genes. We therefore conducted the first population-based study of sex-of-parent and sex-of-offspring interactions in ACS.

**Methods**

The methods of the Oxford Vascular (OXVASC) Study have been published previously. Briefly, OXVASC is a population-based study of all incident or recurrent transient ischemic attacks, strokes, ACS, and acute peripheral vascular disease in a population of 91,106 people registered with 63 family physicians in Oxfordshire, United Kingdom. These general practices were selected to be representative of the urban and rural mix and the deprivation range of Oxfordshire as a whole. The OXVASC population had 94% white, 3% Asian, 2% Chinese, and 1% Afro Caribbean participants. Ascertainment combined prospective daily searches for acute events (hot pursuit) and monthly searches of hospital-care and primary-care administrative, and diagnostic coding data (cold pursuit). Multiple search methods ensure near complete ascertainment of all cases.

A physician assessed patients as soon as possible after the event using a structured questionnaire. Details of the presenting event and medical history were recorded from the patient, their relatives, family practitioner, and hospital records. Known risk factors and any previous symptomatic vascular disease were also recorded. If the patient died before assessment, we obtained an eyewitness account of the clinical event and reviewed relevant medical records.

Information about family history of stroke, MI, peripheral vascular disease or vascular risk factors, and about age at onset of disease (deceased or alive) was collated separately for the father, mother, brothers, and sisters (collectively termed first-degree relatives). An inclusive definition of family history of MI was used, including both fatal (62.2% of recorded parental MI) and nonfatal events (37.8%). Family history of known primary intracranial hemorrhage or subarachnoid hemorrhage was not included. Age at death and cause of death of relatives were noted. Assessment of the family history was based on the patient’s or relatives’ description and, when necessary, from the family practitioner’s notes. In our previous pilot study of 20 subjects, family history in a first-degree relative revealed 83.3% sensitivity and 100% specificity for medical record–confirmed events in the relative.

We defined nonfatal and fatal acute coronary events in probands with published criteria, based on history, ECG findings, cardiac biomarkers, autopsies, or death certificates. We defined ST-elevation myocardial infarction (STEMI) and non–ST-elevation myocardial infarction (NSTEMI) with standard criteria. Troponin I was measured with the Bayer Centaur assay (Bayer HealthCare Diagnostics Division, Tarrytown, NY) according to the manufacturer’s standard range.

ECGs were assessed by objective measurements based on the Minnesota criteria, but formal blinded Minnesota coding was not done. Unstable angina was defined as new cardiac symptoms or a changing symptom pattern with positive ECG findings, a positive stress test, or a relevant ischemic substrate on coronary angiography with or without subsequent percutaneous coronary intervention. Events with a suggestive clinical presentation but without any of these additional features were classified as probable unstable angina, if that was the final diagnosis made by the managing clinician.

To limit missing data, sudden cardiac deaths were excluded. Only incident cases (first-ever lifetime event) were included to allow analysis of the effect of positive family history of MI on the age of onset of first symptomatic event. Premature events were defined as occurring at <65 years, as in other studies, the expected number of cases occurring at ≤55 years being very low.

All patients with a diagnosis of ACS from April 1, 2002, to September 30, 2007, were eligible for this study. OXVASC was approved by the local ethics committee.

**Statistical Analysis**

Categorical variables were compared with Pearson χ² test, Fisher 2-tailed test, or McNemar χ² test, as appropriate. Continuous variables were compared with 2-tailed t tests or analysis of variance. Odds ratios (ORs) were calculated for positive family history of MI in ACS probands. The definition of a premature event, age at event, and sex of both probands and affected first-degree relatives all influenced the calculated ORs. ORs were calculated in the following 2 ways:

1. “Maternal history versus paternal history” for male and female probands separately.
2. “Female proband versus male proband” for positive family history of MI by each type of first-degree relative.

Findings were generally reported as “female versus male proband.” In the comparison of prevalence of maternal versus paternal history of MI, to avoid confounding because of any differences in characteristics between male and female probands, we used paired analyses. Patients were included if any relevant family history in first-degree relatives was available. For example, if sibling history was available, but parental history was absent, then that patient was included only in the analyses regarding siblings. In paired analyses of data for the mother and father, only patients from whom history of both parents was available are included.
known were included. Paired analyses were also used for first-degree relatives. Heterogeneity between ORs was assessed with the Breslow-Day test. A 1-sided test was used because the pre-hoc expectation was that maternal history would be more common in women, as we found previously in stroke\textsuperscript{21,22} and as expected on the basis of the Carter effect.

Age of proband at ACS was correlated with age of parent at MI, age of parent at death, and age of sibling at MI, using Pearson correlation coefficient. The mean age and the minimum age of siblings with MI were calculated within the sibship, where possible. Both values were correlated with the age of the proband at ACS.

A logistic regression analysis was also performed. The dependent variable was premature ACS in the proband. The independent variables were sex of proband, current smoking, hyperlipidemia, and positive maternal history of premature MI.

### Results

Eight hundred thirty-five patients with 983 ACS were enrolled. Adequate family history data for stroke and MI were unavailable for 90 (10.8\%) patients, most commonly due to cognitive impairment, rapid clinical deterioration before assessment and absence of informative relative, and adoption. Of the remaining 745 patients, 623 had an incident coronary event: 354 NSTEMI, 194 STEMI, and 75 unstable angina (only collected for the first 2 years of the study). Therefore, 623 probands (203 women and 420 men) were included in the analysis (Table 2).

Compared with men, women were older, more likely to have had unstable angina as a qualifying event, history of hypertension, strokes, and transient ischemic attacks, but were less likely to be current smokers. After adjustment for age, smoking ($P<0.0001$), and history of stroke or transient ischemic attacks ($P=0.01$) remained significantly associated with the sex of the proband (Table 2).

The total number of siblings was 1840, with a median of 2 siblings (interquartile range 1 to 4) for both male and female probands. The mean age of mothers at death was similar in male and female probands (73.8 (14.4 versus 74.4 (14.5 years; $P=0.633$) as was the mean age of fathers at death (69.5 (13.7 versus 69.6 (15.1 years; $P=0.940$). The analyses given below are for all probands with any ACS (unstable angina, NSTEMI, or STEMI) combined.

Maternal MI was less common than paternal MI in male probands (OR, 0.57; 95\% CI, 0.41 to 0.80; $P=0.001$) but not in female probands (OR, 0.86, 95\% CI, 0.53 to 1.39; $P=0.54$; difference, $P=0.13$), and the same was true for a maternal history of all vascular events (OR, 0.54; 95\% CI, 0.35 to 0.85; $P=0.007$ in male and OR, 1.22; 95\% CI, 0.76 to 1.95;
Female probands with premature ACS (<65 years) were twice as likely as male probands with premature ACS to have a maternal history of MI (OR, 2.25; 95% CI, 1.02 to 4.94; P=0.04; Table 3) or of any vascular event (OR, 3.03; 95% CI, 1.47 to 6.26; P=0.002). No such effect was seen for effect on maternal MI (OR, 1.00; 95% CI, 0.46–2.17; P=0.99; difference, P=0.09) or of any paternal vascular event (OR, 1.19; 95% CI, 0.58 to 2.43; P=0.63; difference, P=0.04). When the age cutoff for premature ACS in the proband was altered, the ORs for maternal history of MI in female versus male probands were 1.92 (95% CI, 1.03 to 3.59; P=0.03) at <70 years, 2.25 (95% CI, 1.02 to 4.94; P=0.04) at <65 years, and 2.79 (95% CI, 1.02 to 7.64; P=0.04) at <60 years.

There were no such sex-of-parent/sex-of-proband interactions in probands with ACS at age ≥65 years (Table 3). At age ≥65 years, female probands with ACS were no more likely than male probands to have a maternal history of MI (OR, 1.02; 95% CI, 0.60 to 1.75; P=0.94) or of any vascular event (OR, 1.34; 95% CI, 0.87 to 2.02; P=0.19). Trends toward similar sex-of-proband/sex-of-relative interactions were seen for family history of MI in siblings (Table 3). Consequently, the sex-of-proband/sex-of-relative interactions remained statistically significant when all first-degree relatives were considered (Table 3). For example, female probands with premature ACS were more likely than male probands with premature ACS to have a history of MI (OR, 2.31; 95% CI, 1.08 to 4.90; difference, P=0.03) or any vascular event in female first-degree relatives (OR, 3.11; 95% CI, 1.51 to 6.42; P=0.002).

Maternal age at MI strongly correlated with proband age at ACS, regardless of sex of proband (r=0.46, P=0.001 overall; r=0.49, P=0.004 in females versus r=0.45, P<0.001 in males). Consequently, female probands with premature ACS were 10 times as likely as female probands with ACS at age ≥65 years to have a premature maternal history of MI (OR, 10.52; 95% CI, 2.50 to 44.3; P<0.001) and 5 times as likely to have premature maternal history of any vascular event (OR, 5.60; 95% CI, 2.05 to 15.36; P=0.0003). This association was also found in male probands (OR, 3.88; 95% CI, 1.37 to 10.99; P=0.006 and OR, 1.99; 95% CI, 0.90 to 4.40; P=0.08, respectively; difference, P=0.32). When probands with unstable angina only are excluded, premature maternal MI was 7 times more common in women with premature MI than in women presenting with MI at age ≥65 years (OR, 7.31; 95% CI, 1.55 to 34.6; P=0.004). A similar association was also found in male probands (OR, 3.63; 95% CI, 1.13 to 11.60; P=0.02).

Age of proband at ACS weakly correlated with age of maternal MI (r=0.18, P=0.037), but only in male probands (r=0.28, P=0.05). There was a correlation between age of sibling at MI and age of proband at ACS, whether the mean age or the minimum age of siblings at MI was considered (r=0.44, P<0.001 and r=0.40, P<0.001, respectively). Age of maternal death correlated weakly with proband age at ACS (r=0.16, P<0.0001), but no correlation was found for age at paternal death (r=0.09, P=0.06).

Risk factor profiles of probands with parental history of MI and probands without parental history showed very few differences (Table 4). When probands were analyzed by maternal versus paternal history of MI, no differences in ACS subtype, risk factors, or vascular history were found. Table 5 shows the hazard ratios calculated when all probands were considered together in a regression analysis. When probands were stratified by sex, the hazard ratios for premature maternal MI were 2.82 (95% CI, 1.16 to 6.85; P=0.02) in female probands and 1.48 (95% CI, 0.94 to 2.34; P=0.09) in male probands, respectively. The hazard ratios for current smoking were 6.49 (95% CI, 2.65 to 15.89; P<0.0001) in female probands and 3.62 (95% CI, 2.44 to 5.38; P<0.0001) in male probands, respectively.

### Table 3. Family History of MI in Male and Female Probands Presenting With ACS

<table>
<thead>
<tr>
<th>Age</th>
<th>Female Probands</th>
<th>Male Probands</th>
<th>Female vs Male Proband, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;65 (n=37)</td>
<td>≥65 (n=166)</td>
<td>&lt;65 (n=182)</td>
</tr>
<tr>
<td>Family history of MI parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one</td>
<td>21 (56.8)</td>
<td>77 (42.3)</td>
<td>1.79 (0.88–3.65)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (8.1)</td>
<td>9 (4.9)</td>
<td>1.70 (0.44–6.59)</td>
</tr>
<tr>
<td>Mother</td>
<td>12 (32.4)</td>
<td>32 (17.6)</td>
<td>2.25 (1.02–4.94)</td>
</tr>
<tr>
<td>Father</td>
<td>11 (29.7)</td>
<td>54 (29.7)</td>
<td>1.00 (0.46–2.17)</td>
</tr>
<tr>
<td>Siblings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>9/92 (9.8)</td>
<td>27/509 (5.3)</td>
<td>1.94 (0.88–4.26)</td>
</tr>
<tr>
<td>Any female</td>
<td>3/46 (6.5)</td>
<td>7/226 (3.1)</td>
<td>2.18 (0.54–8.78)</td>
</tr>
<tr>
<td>Any male</td>
<td>5/38 (13.2)</td>
<td>21/231 (9.1)</td>
<td>1.52 (0.53–4.30)</td>
</tr>
<tr>
<td>FDRs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>23 (62.2)</td>
<td>92 (50.5)</td>
<td>1.61 (0.78–3.32)</td>
</tr>
<tr>
<td>Any female</td>
<td>14 (37.8)</td>
<td>38 (20.9)</td>
<td>2.31 (1.08–4.90)</td>
</tr>
<tr>
<td>Any male</td>
<td>13 (35.1)</td>
<td>69 (37.9)</td>
<td>0.89 (0.42–1.86)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise indicated. Denominators are given where data were not available for all patients. For sibling analyses, the total number of siblings was used as the denominator rather than the number of probands. *P<0.04; †P<0.03.
Discussion

Parental history of premature MI is a well-documented risk factor for MI in offspring, but most previous studies of the family history of MI have not reported sex-of-parent effects. Two studies did report sex-of-parent effects for family history of MI in patients with MI, but they were not population based, were restricted to younger age groups, and did not report sex-of-offspring/sex-of-parent interactions. One study attempted to determine sex-of-offspring/sex-of-parent interactions, but it was a retrospective comparison of 2 separate single-sex cohorts in which data were collected by different methods. None of the previously published studies have considered sex-of-offspring/sex-of-parent interactions in a single population.

Our study has several original findings. First, history of maternal MI was twice as common in women with premature ACS as men with premature ACS. Second, age at maternal MI was strongly correlated with age at ACS in probands of both sexes. Third, as a consequence of the above, premature maternal MI was 10 times more common in women with premature ACS than in women presenting with ACS at age 65 years. However, premature maternal MI was also associated with premature ACS in men.

Genetic and nongenetic factors may explain the excess of maternal MI in probands with premature ACS, as with diabetes mellitus and hypertension which have a higher maternal transmission. Epigenetic phenomena (ie, changes in gene expression that do not entail a change in DNA sequence) are more likely to explain mother-daughter transmission of stroke than classic genetic mechanisms. However, the higher prevalence of maternal MI in women with ACS and the strong correlation of premature maternal MI with premature MI in men and women, implicate the Carter effect in sex-specific heritability of MI. Women have lower incidence of MI than men, and therefore require more genetic risk factors than men for MI to occur. Women with MI would therefore be expected to have transmitted more MI susceptibility genes to their children than would men with MI, and this effect

Table 4. Association Between Family History of MI in Mother and Father and Different Patient Characteristics According to Patient’s Sex

<table>
<thead>
<tr>
<th>Family History of MI</th>
<th>Female Probands</th>
<th>Male Probands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No FH (n=110)</td>
<td>FH Mother (n=39)</td>
</tr>
<tr>
<td>Age, y</td>
<td>77.5 (9.9)</td>
<td>69.1 (12.7)</td>
</tr>
<tr>
<td>ACS subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>14 (12.7)</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>64 (58.2)</td>
<td>20 (51.3)</td>
</tr>
<tr>
<td>STEMI</td>
<td>32 (29.1)</td>
<td>10 (25.6)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (54.5)</td>
<td>23 (59.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (14.7)</td>
<td>10 (25.6)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>30 (27.3)</td>
<td>16 (41.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (13.6)</td>
<td>8 (21.1)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>53 (48.2)</td>
<td>14 (36.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (10.1)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>23 (20.9)</td>
<td>7 (17.9)</td>
</tr>
</tbody>
</table>

Table 5. Independent Predictors of Premature ACS in All Probands

<table>
<thead>
<tr>
<th>Proband</th>
<th>Independent Variable</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Sex (female vs male)</td>
<td>0.31 (0.20–0.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Current smoking</td>
<td>3.23 (2.15–4.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Premature maternal MI</td>
<td>1.60 (1.00–2.55)</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
<td>0.66 (0.44–0.98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>Current smoking</td>
<td>6.49 (2.85–15.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Premature maternal MI</td>
<td>2.82 (1.16–6.85)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
<td>0.59 (0.24–1.46)</td>
<td>0.25</td>
</tr>
<tr>
<td>Male</td>
<td>Current smoking</td>
<td>3.62 (2.44–5.38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Premature maternal MI</td>
<td>1.48 (0.94–2.34)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
<td>0.67 (0.43–1.05)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
is greatest in female offspring. It is also entirely plausible, however, that the cause-effect relationship is actually the other way around: the low risk of MI in women is due to a combination of sex-specific genetic factors (eg, hormone-gene interactions or X-chromosome–related factors), and mother-daughter pairs with MI are more likely to lack these protective genes.

There are 3 implications of this study for candidate gene and genome-wide association studies of MI. First, such studies should be sex-stratified to establish whether any genes are particularly important in women (eg, estrogen-responsive genes). Second, subanalyses of women with premature CHD may also be especially fruitful in candidate gene studies. Third, the correlation between age of ACS in parent and offspring might also partly reflect heritability of longevity, rather than heritability of CHD. Existing data suggest significant heritable components of both ageing and CHD, and overlap between the heritability of CHD and ageing, particularly in terms of maternal transmission.

Our study does have some limitations. First, family history data were not fully validated. However, reported family history of MI has 70% sensitivity and >95% specificity for MI confirmed by medical records, and our small validation study showed 83.3% sensitivity and 100% specificity. Moreover, in the clinical setting, reported family history is most pertinent. Second, knowledge of family history in men and women may differ, but is unlikely to differ substantially for maternal versus paternal history. Third, nonpaternity may lead to underestimation of the relative risk associated with paternal history of MI, but the United Kingdom estimates suggest that rates on nonpaternity are relatively low (1.35% in 521 families with cystic fibrosis, and 1.59% in 744 families with multiple sclerosis). The extent to which nonpaternity might affect results can be examined statistically, but given the low rates in the United Kingdom, such sensitivity analyses would have little effect on our findings. Fourth, family history is also influenced by shared environmental factors, such as childhood socioeconomic or psychological environment. It is also plausible that the observed effects are a consequence of programming during fetal life by maternal intrauterine environment or during early infancy. Fifth, there were only 37 female probands with premature MI in the study period, and so the statistical power of our study was limited. Sixth, we tested the statistical significance of the difference in the excess of affected mothers in female probands versus male probands using a 1-sided Breslow-Day test rather than a 2-sided test. We used a 1-sided test because of the pre hoc expectation that maternal history would be more common in women, as we found previously in stroke and as expected on the basis of the Carter effect. Finally, our case-control approach did not allow us to estimate the absolute risk of ACS based on different patterns of family history.

Family history is a risk factor for CHD that is easily available to clinicians. Regardless of mechanism, sex-of-parent/sex-of-proband interactions, particularly the strong associations of maternal and female sibling MI in women, seem to be important risk factors for ACS. However, family history data are currently underutilized in risk scores. Even risk prediction tools designed for low-resource settings, where other technology-dependent risk factors are not available, have usually excluded family history.

In conclusion, important sex-of-parent/sex-of-proband interactions exist in the family history of MI in patients with ACS. Greater emphasis should be placed on primary prevention in young women with family history of MI in mothers or sisters. Although young women have a low incidence of MI, case fatality is more than double that for young men, and young women with family history of MI demonstrate less CHD risk awareness and worse lifestyle choices than men.

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Disclosures
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Family history of premature myocardial infarction (MI) is an important risk factor for MI, but it is seldom included in risk prediction tools. Also, published family history studies have not included the full spectrum of acute coronary syndromes (ACS). Although excess mother-to-daughter “transmission” occurs in ischemic stroke, no published studies have considered sex-of-parent/sex-of-proband interactions in the context of family history of MI. Within the Oxford Vascular Study, our study of the familial basis of ACS showed 3 important results. First, history of maternal MI was twice as common in women with premature ACS as in men with premature ACS. Second, age at maternal MI was strongly correlated with age at ACS in probands of both sexes. Third, as a consequence, premature maternal MI was 10 times more common in women with premature ACS than in women presenting with ACS at age ≥65 years. However, premature maternal MI was also associated with premature ACS in men. Regardless of mechanism, sex-of-parent/sex-of-proband interactions, particularly the strong associations of maternal and female sibling MI in women, seem to be important risk factors for ACS. Appropriate emphasis should be placed on primary prevention in young women with family history of MI in mothers or sisters. Although young women have a low incidence of MI, case fatality is more than double that for young men, and young women with family history of MI demonstrate less coronary heart disease risk awareness than men.