Coronary Artery Calcification and Family History of Premature Coronary Heart Disease

Sibling History Is More Strongly Associated Than Parental History

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Background—The objective of the study was to assess the association of a family history (FH) of premature coronary heart disease (CHD) with coronary artery calcification (CAC) in asymptomatic individuals and to compare the effects of sibling or parental FH on the risk of subclinical atherosclerosis.

Methods and Results—CAC by electron beam tomography was performed in 8549 asymptomatic individuals (69% men; mean age, 52±9 years). The prevalence and odds of any CAC and extent of CAC stratified according to FH of premature CHD were determined. Those with (1) no FH of CHD, (2) FH of premature CHD in parents, or (3) FH in siblings had a prevalence of CAC of 55%, 64%, and 78% (P<0.0001) among men and 27%, 36%, and 56% (P<0.0001) among women, respectively. The multivariate regression analysis demonstrated that the odds ratio (95% confidence interval) for the presence of CAC was 1.3 (1.1 to 1.6) among those with positive FH of premature CHD in parents only, 2.3 (1.7 to 3.1) and 2.5 (1.8 to 3.3) among those in siblings and a combined FH compared with those without FH of CHD in men, respectively. Among women, the corresponding odds ratios were 1.3 (1.0 to 1.8), 2.3 (1.7 to 3.6), and 1.9 (1.3 to 3.1), respectively. A similar trend was observed in the association of FH of premature CHD with increasing CAC scores.

Conclusions—Our study demonstrates a highly significant association between FH of premature CHD and the presence and extent of CAC. Furthermore, within the limits of self-reporting of family history, our findings suggest that a sibling history is more strongly associated with subclinical coronary atherosclerosis than a parental history of premature CHD.

Key Words: calcium ★ arteries ★ atherosclerosis ★ tomography

A family history (FH) of premature coronary heart disease (CHD) is an independent risk factor for CHD events.1-4 The mechanisms underlying this familial clustering have not been firmly established but may include an increased susceptibility to atherosclerosis,5 an increased tendency for thrombosis,6 and proinflammatory responses suggested by high levels of C-reactive protein.7 Wang et al8 recently demonstrated a higher burden of subclinical atherosclerosis as assessed by carotid intimal thickness (IMT) in individuals with a parental history of premature CHD. Elucidating the association with subclinical atherosclerosis also may have clinical implications because many asymptomatic adults with a positive FH may benefit from subclinical disease screening to determine aggressiveness of primary preventive therapies.9

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Several studies have suggested that individuals with a FH of premature CHD in a sibling might be at higher risk than those with parental history only.10,12 The ability to confirm this association, however, has been limited because prior reports assessing the role of FH of premature CHD with subclinical atherosclerosis have mainly focused on any familial history, without distinguishing the separate effects of parental and sibling history.

Electron beam tomography (EBT) is a noninvasive tool for the detection of coronary artery calcium (CAC), a marker for atherosclerosis. The presence and extent of CAC strongly correlate with the overall magnitude of coronary atherosclerotic plaque burden13 and with the development of subsequent CHD events.14,15 The purpose of the present study was to assess the association of a FH of premature CHD with CAC in asymptomatic individuals and to determine whether a FH of premature CHD in a sibling or parent has comparable effects on the risk of atherosclerosis.

Methods

Subjects

This is a cross-sectional study on a consecutive sample of 13 389 physician-referred patients who presented to a single EBT scanning...
facility (Columbus, Ohio) between the dates of July 1999 and June 2003 for CHD risk stratification. We excluded patients who reported any personal history of CHD defined by prior myocardial infarction or coronary/peripheral arterial revascularization (n = 322) or any current symptoms potentially suggestive of angina (n = 4518) defined by self-reports of chest pain, chest pressure, or chest tightness. This study was approved by the local institutional review board and received a waiver of patient consent.

**Risk Factor Assessment**
All individuals provided details of their demographics, medical history, medication use, current symptoms, and involvement in leisure-time physical activities. A history of cigarette smoking was considered present if a subject was a current or former smoker. Dyslipidemia was coded as present for any individual self-reporting a history of high total cholesterol, high LDL, low HDL and/or high triglycerides, or current use of lipid-lowering therapy. Patients were considered to have diabetes if they reported using oral hypoglycemic agents, insulin sensitizers, or subcutaneous insulin and were considered to have hypertension if they reported a history of high blood pressure or used antihypertensive medications. Body mass index (BMI) was calculated from individuals who provided a self-report of height and weight. Individuals with BMI ≥30 kg/m² were considered obese. Leisure-time physical activities determined by the questionnaire were categorized as “none” versus “active.”

FH of CHD in parents and siblings was obtained by asking patients whether any member of their immediate family (parents or siblings) had a fatal or nonfatal myocardial infarction and/or coronary revascularization before or after 55 years of age by the questionnaire. The event was considered premature if it occurred before the age of 55 years.

**Electron Beam Tomography**
Each patient underwent EBT scanning with the use of an Imatron scanner. Coronary arteries were imaged with rapid acquisition of approximately 30 to 40 contiguous images of 3-mm slice thickness (with a 26-cm field of view) during end-diastole, with ECG triggering used during a single 30- to 35-second breath hold. CAC was quantified by means of the previously described Agatston scoring method. Calcium was considered present in a coronary artery when a density of >130 Hounsfield units was detected in >3 contiguous pixels (≥1 mm²) overlaying that coronary artery. The CAC score was computed from the product of the attenuation factor and the area of calcification (mm²), with the total CAC score of each coronary artery being equal to the sum CAC of all the lesions from that artery. The total calcium score was calculated by summing CAC scores from the left main, left anterior descending, left circumflex, and right coronary arteries.

**Statistical Analysis**
Participants were first examined by categories of FH of premature CHD with ANOVA to compare mean values or χ² tests to compare proportions of baseline coronary risk factors. To facilitate data interpretation, the CAC score was classified into the following categories: 0, 0.0 to 9.9, 10.0 to 99.9, 100 to 399.9, and ≥400 (no identifiable plaque, minimal plaque, mild plaque, moderate plaque, and extensive atherosclerotic plaque burden, respectively). These categories of the CAC score have been used to differentiate between very low, low, moderate, moderately high, and high cardiovascular risk.

Median CAC scores according to FH were compared by median test. The association between FH of premature CHD and the extent of subclinical atherosclerosis as measured by CAC was examined by means of multivariable logistic regression (with 95% CI). For each model, the reference group consisted of negative scores (CAC = 0); this approach has been used previously. In the full multivariate model (adjusted for age, hypertension, smoking status, diabetes, dyslipidemia, obesity, and physical activity), statistical differences were calculated between the associations of premature FH of CHD in sibling versus parent with any CAC as well as advanced CAC by means of an adjusted Wald test. The association of FH of premature CHD with CAC did not differ substantially in the age-adjusted models and the age + CHD risk factors, including BMI-adjusted models; as a result, we have described the analyses on the basis of the full multivariate adjustments only.

The likelihood ratio χ² statistics were obtained to determine whether the addition of FH of premature CHD contributed significantly to the models predicting presence and extent of CAC. In a separate model, we also evaluated the role of reported FH of CHD at ≥55 years of age as a predictor of coronary atherosclerosis. We also examined whether FH of premature CHD stratified asymptomatic adults for the presence of advanced CAC with increasing number of major risk CHD risk factors (smoking, dyslipidemia, hypertension, diabetes mellitus, and obesity). The association of CHD risk factors with CAC was also assessed across FH of premature CHD categories to assess interaction. All statistical analyses were performed with the use of Stata version 8.0.

**Results**
The study population consisted of 8549 asymptomatic individuals (69% men; mean age, 52±9 years). The majority of the population (67%) was 45 to 64 years of age; 20% were younger than 45 years and 13% were 65 years or older, respectively. For 4882 participants (1619 women), a CHD event was reported in either a parent or sibling. For 2283 (826 women), the familial CHD event was premature. Among men reporting a FH of premature CHD, only a parental history, a sibling history, or a history in both were seen in 71%, 18%, 11%; for women, the respective proportions were 64%, 20%, and 16%. Women reported a FH of premature CHD more often than men (P<0.0001), a disparity that existed within all age groups. Both younger men and women reported FH of premature CHD more frequently than those who were older. Table 1 compares the baseline characteristics of men and women according to a FH of premature CHD. Statistically significant differences in age, prevalence of dyslipidemia, and hypertension by category of FH of premature CHD were seen in both men and women, whereas a difference in current smoking status was observed only in women.

CAC scores in this population ranged from 0 to 7108, with a median (interquartile range) of 4 (0 to 85). Median scores were significantly higher in individuals with a FH of premature CHD, especially those reporting sibling history, compared with those without any FH of CHD (Table 2). A similar trend of difference across FH of premature CHD in median score was observed when individuals with no CAC were excluded from the analysis.

In this study population, 35% of individuals had no major CHD risk factor, whereas 36%, 20%, and 9% of adults had 1, 2, and ≥3 major risk factors, respectively. The prevalence of moderate calcification (CAC ≥100) significantly increased with increasing number of CHD risk factors in this population (P =0.015, 1 =0.23, 2 =0.31, ≥3 =0.45; P<0.0001 for trend). In each category, the prevalence of CAC ≥100 was significantly higher among individuals with a sibling history, followed by a parental history of premature CHD, and lowest among those without a FH of CHD, respectively (Figure 1). The distribution of CAC scores by FH status for each gender is shown in Figure 2. Individuals with no FH of CHD were more likely to have no CAC (CAC =0). On the other hand, the prevalence of moderate-extensive CAC was significantly higher in individuals with a FH in siblings followed by FH of...
premature CHD in parents, with the lowest presence among those without a FH of CHD (Figure 2).

The association between FH of premature CHD categories and the presence as well as the extent of CAC was examined by means of multivariable logistic regression. The results of the regression analysis are summarized in Table 3. In both men and women, all of the associated odds ratios increased in proportion to the magnitude of CAC. However, a FH of premature CHD in men was not associated with minimal CAC scores (1.0 to 9.9). The likelihood ratio \( \chi^2 \) statistics demonstrated that the addition of premature FH of CHD to traditional risk factors in both genders contributed significantly to predicting the presence of CAC as well extent of CAC \( P<0.001 \). The odds ratios for presence of any CAC and extent of CAC, with a FH in a sibling, were significantly higher than with a parental FH in both genders \( P<0.001 \), except for association with minimal (0 to 9.9) and mild CAC (10 to 99.9) in women. In all models, there was no difference in the association of premature FH in a sibling only compared with a combined FH in both parents and siblings. In separate multivariate analysis, the reported FH of CHD at \( \geq 55 \) years of age was not significantly associated with either the presence of any CAC or extent of CAC in both men and women (data not shown).

The risk of moderate CAC with a FH of premature CHD was also assessed according to age of the participants (Table 4). Although higher odds were observed in older men (\( \geq 55 \) years) and older women (\( \geq 65 \) years), the difference was not statistically significant. Table 5 displays the association of the major CHD risk factors with moderate CAC in individuals with and without FH of premature CHD. The odds ratios for CHD risk factors were similar in both genders \( P>0.1 \) for interaction.

**Discussion**

Our study supports the contention that premature CHD in a first-degree relative identifies individuals with a strong predisposition to any and/or significant subclinical atherosclerosis. Consistent with prior published studies using both subclinical8,18–20 and clinical end points,1–4 our data reinforce current recommendations to include information on FH of premature CHD in practice guidelines.21 Finally, we demonstrate for the first time that sibling history of premature CHD is more strongly associated with coronary atherosclerosis than a parental FH of premature CHD.

**Sibling Versus Parental Family History of Premature CHD**

Most prior studies have reported CHD risk associated with family history by using the definition of either “any” first-degree relatives or based on the participant’s reports of “parental” CHD status. A recent study has demonstrated that a FH of premature CHD in first-degree relatives was independently associated with the presence of CAC in both men and women.18 In addition, Wang et al19 have also established a strong association of specifically the presence FH of premature CHD in parents with carotid IMT thickness. The results of the present study confirm the association of a FH of premature CHD with subclinical atherosclerosis and extend the findings of previous studies by describing in detail the association of a sibling history of premature CHD with CAC. In our study, even after adjustment for confounding risk factors, the presence of a FH of premature CHD was associated with an increased CAC burden.

**TABLE 1. Baseline Demographics According to Family History of Premature CHD Categories in Men and Women**

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (n=2668)</td>
<td>Parental Only (n=1036)</td>
</tr>
<tr>
<td>Age, y</td>
<td>51±7</td>
<td>47±8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Obesity (BMI ≥30), %</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Leisure-time physical activity (none), %</td>
<td>26</td>
<td>25</td>
</tr>
</tbody>
</table>

**TABLE 2. Median (Interquartile Range) CAC Scores According to Categories of Family History of Premature CHD**

<table>
<thead>
<tr>
<th>Category</th>
<th>No FH</th>
<th>FH of Premature CHD in Parents Only</th>
<th>FH of Premature CHD in Siblings Only</th>
<th>FH of Premature CHD Both</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population including CAC=0, n</td>
<td>3667</td>
<td>1561</td>
<td>419</td>
<td>303</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7 (0–122)</td>
<td>26 (0–189)</td>
<td>67 (4–249)</td>
<td>59 (2–223)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>0 (0–5)</td>
<td>3 (0–32)</td>
<td>6 (0–78)</td>
<td>8 (0–91)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Excluding individuals with CAC=0, n</td>
<td>1737</td>
<td>852</td>
<td>291</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>49 (11–273)</td>
<td>61 (19–321)</td>
<td>107 (30–355)</td>
<td>102 (23–401)</td>
<td>0.006</td>
</tr>
<tr>
<td>Women</td>
<td>21 (5–130)</td>
<td>34 (8–173)</td>
<td>61 (9–210)</td>
<td>67 (10–231)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
factors, the odds of any CAC was approximately 2.5-fold higher in those with a sibling history of premature CHD. The prevalence of CAC ≥100 was similar in those with sibling history with ≥3 risk factors compared with high-risk individuals (≥3 risk factors) but no FH of CHD. Interestingly, the results also indicate that the atherosclerosis burden is more strongly related to sibling rather than parental FH of premature CHD.

It is not entirely clear why a sibling history is more strongly associated with CAC as compared with parental history. For a trait the variation of which is attributable entirely to additive genetic effects, the magnitude of the sibling and parent–child correlations should be similar. However, atherosclerosis is influenced by a complex interplay among numerous environmental and genetic factors. Sibling–sibling correlations for most CHD risk factors are larger than parent–offspring correlations; also, shared environmental effects on CHD risk factors are stronger for sibling pairs than for parent–offspring pairs. Adverse circumstances in childhood (likely to be shared by siblings) have also shown to have specific influence on CHD risk. A higher burden of subclinical coronary atherosclerosis among patients with sibling history as opposed to a parental history as seen in our study may suggest that there is a greater sharing of environmental determinants between siblings than between parents and offspring or that dominant as well additive genetic effects are involved.

Validation of Reported Family History of Premature CHD

Before considering the implications of the above findings, it is appropriate to consider the validity of the indexes of FH, which was based on data obtained from a self-reported questionnaire in our study. The optimal method of validation of a reported FH of disease is through review of medical records, with direct clinical assessment of the individual(s) reportedly affected. However, medical records are often not available, and it may not be practical (or possible) to interview and/or examine the affected family member(s). In that case, a family history obtained by the individual may be the only available source of information. Studies have demonstrated for reported FH of CHD a sensitivity of 68% to 86% and specificities ranging from 86% to 98%, and most likely the bias in recall of FH of CHD is toward the null. The underestimation might be more pronounced for a parental FH for two reasons. The study participants are more likely to be close in age to a sibling with a CHD event, whereas a parental event may have occurred decades in the past and may be subject to recall bias. Murabito et al have also recently demonstrated a poor positive predictive value of reported CHD deaths in parents, which as a result can

![Figure 1. Age-adjusted prevalence (%) of CAC ≥100 by FH of premature CHD category and increasing number of risk factors.](image1)

![Figure 2. Distribution (%) of CAC scores by FH of premature CHD category and gender.](image2)
potential lead to an underestimation of the associated risk for cardiovascular disease in the offspring. The other possible reason could be that CHD of siblings is probably more valid as a risk marker than the history of the disease in parents because the lack of diagnostic resources and premature deaths caused by infectious diseases may lead to underestimation of the disease in the latter group. These viewpoints may explain some of the apparently greater risk conferred by self-reported sibling versus parental CHD. However, one study has shown almost similar sensitivities and specificities for reporting CHD in parents and siblings.25

**Additional Findings**

There are additional important findings of the study that warrant explanation in the context of previous published reports. Several case-control studies have shown the odds ratio for CHD events to be higher for younger individuals.1,31,32 Interestingly, the Tromso study of 6408 men and women (20% with known myocardial infarction and angina) demonstrated greater effect of premature FH on carotid IMT with aging.19 To the best of our knowledge, none of the other published literature describing the relation of FH of premature CHD with subclinical atherosclerosis has shown a varied effect with the age of the participants.8,20 In our study, a slightly higher association, although not statistically significant, of a FH of premature CHD with CAC was observed in the older individuals (men ≤55 years, women ≥65 years): First, the results may imply a time-dependent expression of genes, a gene–environment interaction, or a familial aggregation of environmental factors19; second, survival and selection biases might have occurred as subjects with a positive FH might have clinically manifested CHD at early ages and thus were excluded from our study.20 The risk of FH of premature CHD on the manifestation of subclinical atherosclerosis and clinical CHD with aging needs to be further evaluated in longitudinal studies.

CHD risk has been shown to be related to the number of relatives who are affected22,33 in some but not all studies.2,34 In the present study, there was no significant difference between the risk of CAC with FH of premature CHD in siblings alone compared with both in siblings and parents. The small number of individuals with FH of premature CHD in both parent and sibling may explain the lack of “additive” effect of the “both” exposure in CAC. However, the lack of augmented association with increasing number of first-degree relatives affected and subclinical atherosclerosis have also been reported in the Framingham Heart Study8 and the Tromso Study.19

Several prior studies have suggested that the effect of FH on CHD risk differs between men and women.21,32 We found

### TABLE 3. Multivariable Association Between Categories of Family History and Presence and Severity of CAC in Men and Women

<table>
<thead>
<tr>
<th></th>
<th>CAC &gt;0</th>
<th>CAC &gt;0 to 9.9</th>
<th>CAC 10 to 99.9</th>
<th>CAC ≥100 to 399.9</th>
<th>CAC ≥400</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No FH of CHD (n=2668)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FH of premature CHD in parents only (n=1036)</td>
<td>1.3 (1.1–1.6)†</td>
<td>1.1 (0.9–1.5)</td>
<td>1.4 (1.2–1.7)*</td>
<td>1.9 (1.5–2.5)†</td>
<td>2.4 (1.7–3.3)†</td>
</tr>
<tr>
<td>FH of premature CHD in siblings only (n=257)</td>
<td>2.3 (1.6–3.1)†</td>
<td>1.5 (0.8–2.7)</td>
<td>2.6 (1.8–3.9)*</td>
<td>3.3 (2.3–5.1)†</td>
<td>3.7 (2.1–6.5)†</td>
</tr>
<tr>
<td>FH of premature CHD in both (n=164)</td>
<td>2.5 (1.8–3.3)†</td>
<td>1.4 (0.9–3.5)</td>
<td>2.7 (1.8–4.1)*</td>
<td>3.8 (2.3–7.2)†</td>
<td>3.9 (2.2–8.9)†</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No FH of CHD (n=999)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FH of premature CHD in parents only (n=525)</td>
<td>1.3 (1.0–1.8)*</td>
<td>1.2 (1.0–2.2)*</td>
<td>1.4 (1.0–2.5)*</td>
<td>1.8 (1.1–2.6)†</td>
<td></td>
</tr>
<tr>
<td>FH of premature CHD in siblings only (n=162)</td>
<td>2.4 (1.7–3.6)†</td>
<td>1.4 (1.1–3.2)*</td>
<td>2.1 (1.8–3.7)*</td>
<td>2.9 (1.8–5.9)†</td>
<td></td>
</tr>
<tr>
<td>FH of premature CHD in both (n=139)</td>
<td>1.9 (1.3–3.1)†</td>
<td>1.3 (0.7–4.7)</td>
<td>1.9 (1.3–4.6)*</td>
<td>2.7 (1.6–7.1)†</td>
<td></td>
</tr>
</tbody>
</table>

Values are OR (95% CI). For each model, the reference group consisted of negative scores (CAC=0). Dyslipidemia, hypertension, smoking, diabetes mellitus, BMI, and physical activity were adjusted covariates in the multivariate models. Women with CAC ≥400 were combined with those with CAC ≥100.

*P<0.05, †P<0.001.

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### TABLE 4. Multivariable Association Between Categories of Family History and CAC ≥100 in Men and Women According to Age Groups

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI) by Age in Years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) by Age in Years</td>
</tr>
<tr>
<td></td>
<td>&lt;55 (n=2675)</td>
</tr>
<tr>
<td>No FH of CHD</td>
<td>2668 1 1 999 1 1</td>
</tr>
<tr>
<td>FH of premature CHD in parents only</td>
<td>1036 2.2 (1.3–2.7) 1.9 (1.5–2.5) 525 1.3 (1.0–2.8) 2.4 (1.1–5.4)</td>
</tr>
<tr>
<td>FH of premature CHD in siblings only</td>
<td>257 2.8 (2.1–4.4) 3.6 (2.3–5.3) 162 2.4 (1.4–4.9) 3.3 (1.6–7.7)</td>
</tr>
<tr>
<td>FH of premature CHD in both</td>
<td>164 3.4 (1.4–5.8) 4.1 (1.6–7.3) 139 1.9 (1.3–5.7) 3.6 (1.1–7.9)</td>
</tr>
</tbody>
</table>

The reference group consisted of negative scores (CAC=0). Dyslipidemia, hypertension, smoking, diabetes mellitus, BMI, and physical activity were adjusted covariates in the multivariate models. Interaction with age not significant.
the association of FH to be similar in both genders with CAC, and this is consistent with reports describing the association of FH with subclinical atherosclerosis.8,19,20 Finally, individuals with a positive FH may also be more susceptible to the deleterious effects of the traditional risk factors and may have greater atherosclerosis risk through smoking or dyslipidemia than individuals with similar risk factor exposure but without a family history.34 Consistent with other reports, we found traditional risk factors to be equally predictive of CHD risk for persons with and without a FH of premature CHD.33,35

Limitations
The results of our study should be interpreted in the context of several limitations. In our study, CHD risk factors were self-reported. Hoff et al18 has shown a good reliability of self-reported histories of CHD risk factors in self-referred individuals for EBT scanning. However, because the CHD risk factors were self-reported, the potential "residual confounding" cannot be ruled out. Asymptomatic adults, like those enrolled in our study, are also less likely to have recall bias than those who present acutely with cardiac symptoms. The study population is fairly homogeneous in the sense that subjects were highly motivated to assess their CHD risk and that they could afford the expense associated with the EBT scan. These findings raise the possibility that such a physician-referred population differs from the general population in use of screening procedures and other preventive measures.18 Also, the study population was mainly composed of whites, and the finding may not apply to other ethnic groups. Third, the Third Report of the National Cholesterol Education Program Expert Panel considers a FH of premature CHD positive if CHD occurs in first-degree male relatives 65 years of age and first-degree female relatives <65 years of age.21 Our initial choice of exposure categories was arbitrary rather than based on any biological mechanism. Finally, we could not determine the differential association of the affected relative’s gender (parent or sibling) because the information was not collected. Notably, in the Framingham Heart Study, no difference in degree of carotid IMT was observed between subjects with maternal or paternal FH of premature CHD.11

Summary and Implications
In summary, data from our study suggest that within the limits of self-reporting of FH, a sibling history is more strongly associated with subclinical atherosclerosis than a parental history of premature CHD. Current guidelines count a positive family history for CHD as an additional risk factor that physicians should use to determine the intensity of LDL-lowering therapy.21 On the basis of our data, we believe it is reasonable to consider selective noninvasive quantification of subclinical atherosclerosis among middle-aged adults with a FH of premature CHD to help determine the appropriate aggressiveness of risk factor modifications in those classified as being at low or intermediate risk for CHD events.

Acknowledgments
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References

### TABLE 5. Odds Ratios With 95% CI of Association of CAC $\geq$100 (Moderate Calcification) With Major CHD Risk Factors Among Individuals With and Without FH of Premature CHD

|                   | Hypertension* | Diabetest† | Smoker‡ | Dyslipidemia§ | Obesity|| |
|-------------------|---------------|------------|---------|---------------|--------|
|                   | OR 95% CI     | OR 95% CI  | OR 95% CI| OR 95% CI     | OR 95% CI|
| No FH of CHD (n=3667) | 1.9 (1.5–2.6) | 2.7 (1.9–4.7) | 2.5 (1.7–4.4) | 2.3 (1.5–2.6) | 1.6 (1.2–2.0) |
| FH of premature CHD in parents only (n=1561) | 2.2 (1.1–2.9) | 2.2 (1.3–4.8) | 2.2 (1.1–4.3) | 2.9 (1.8–4.5) | 1.8 (1.3–2.9) |
| FH of premature CHD in siblings only (n=419) | 1.7 (1.1–3.2) | 3.7 (1.5–8.6) | 4.1 (1.1–11.6) | 2.4 (1.4–5.3) | 2.9 (1.3–5.4) |
| FH of premature CHD in both (n=303) | 1.4 (0.8–3.1) | 1.9 (0.9–5.2) | 4.4 (1.3–10.1) | 2.4 (1.0–5.1) | 1.9 (0.9–5.1) |

The reference group consisted of negative scores (CAC=0). In all models, variables adjusted were age, gender, physical activity, hypertension, diabetes, smoking status, dyslipidemia, and obesity.

*Hypertensive vs normotensive.
†Diabetic vs nondiabetic.
‡Smoker vs nonsmoker.
§Dyslipidemic vs normal lipid levels.
||Obese (BMI $\geq$30 kg/m²) vs nonobese (BMI <30 kg/m²).
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