Parental Occurrence of Premature Cardiovascular Disease Predicts Increased Coronary Artery and Abdominal Aortic Calcification in the Framingham Offspring and Third Generation Cohorts

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Background—Parental premature cardiovascular disease (CVD) is a risk factor for coronary heart disease (CHD). We related validated parental premature CVD with the subclinical measures of coronary artery (CAC) and abdominal aortic (AAC) calcification in the community.

Methods and Results—We studied 2 generations of Framingham Heart Study subjects who underwent multidetector computed tomography measurements of CAC and AAC and who had 2 parents in the study. Subjects included 797 Framingham Offspring (mean age, 63 years; 56% women) and 1238 Third Generation (Gen3) (mean age, 46 years; 47% women) participants free of CVD. Generalized estimating equations adjusted for major CVD risk factors were used to relate validated parental premature CVD and CHD to CAC and AAC, defined by >90th percentile age- and sex-specific cut points from a healthy subsample. Parental premature CVD was associated with CAC among Gen3 (odds ratio = 2.17 [1.41 to 3.33]; \( P < 0.001 \)) and nonsignificantly among Offspring (odds ratio = 1.42 [0.91 to 2.22]; \( P = 0.12 \)). Parental premature CHD was associated with CAC among Gen3 (odds ratio = 2.22 [1.22 to 4.01]) but not Offspring. Parental premature CVD was not associated with AAC in either cohort. Parental premature CHD was associated with AAC among Gen3 (odds ratio = 1.65 [0.99 to 2.75]; \( P = 0.05 \)) but not among Offspring. The magnitude of risk conferred was greater for paternal than maternal premature CVD.

Conclusions—Parental premature CVD is associated with CAC, and premature CHD is associated with AAC, after adjustment for risk factors, particularly in younger middle-aged adults. Risk conferred by parental premature CVD on vascular calcification may be mediated through novel mechanisms not accounted for by classic CVD risk factors known to cause atherosclerosis. (Circulation. 2007;116:1473-1481.)

Key Words: calcium ■ epidemiology ■ imaging ■ atherosclerosis ■ coronary disease ■ aorta

A reported “family history” of premature cardiovascular disease (CVD) is an independent risk factor for CVD\(^1\)\(^-\)\(^14\) and has been a recommended risk stratification marker in US guidelines for hypertension and hyperlipidemia treatment.\(^15\),\(^16\) US and European Task Force guidelines on CVD risk prevention both highlight that family history information may indicate a higher risk status than would be predicted by Framingham risk score and European SCORE risk tools.\(^17\),\(^18\)

Furthermore, data demonstrate that the addition of family history information to risk prediction based on traditional CVD risk factors may substantially improve the prediction of elevated coronary artery calcium.\(^19\) This suggests that parental CVD confers proband risk via increased susceptibility for the occurrence of atherosclerosis in key vascular beds. Indeed, coronary calcium is a well-established measure of atherosclerosis that strongly predicts future CVD events.\(^20\)\(-\)\(^22\) Whereas other major risk factors for CVD such as smoking, hyperlipidemia, and hypertension have been shown to be...
associated with coronary artery calcification (CAC), few studies have examined the effects of family history of premature CVD on CAC.\textsuperscript{23–26} It remains unclear whether parental CVD confers increased risk for subclinical atherosclerosis in probands independent of shared risk factors. Limitations of previous analyses include selected study samples and the use of unvalidated family history information based on participant recall.\textsuperscript{27}

Familial occurrence of CVD may also predict atherosclerosis in other vascular beds. For example, abdominal aortic calcification (AAC) has been shown to be an independent predictor of CVD.\textsuperscript{28} Previous studies demonstrate that genetic factors account for 52% and 20% of the variability in AAC between parent-offspring and sibling pairs, respectively.\textsuperscript{29}

Whereas traditional cardiovascular risk factors such as older age, hypertension, dyslipidemia, and smoking have been reported to be associated with AAC,\textsuperscript{30–32} the relationship between family history of premature CVD and AAC has not been well established.

With the recent completion of vascular calcification measurements with the use of multidetector computed tomography (MDCT) in both the Offspring cohort and Third Generation (Gen3) cohort of the Framingham Heart Study, we had a unique opportunity to examine the association of the validated occurrence of parental CVD with CAC and AAC in offspring in both a younger-adult cohort and a middle-aged cohort, respectively.

**Methods**

Participants for this study were drawn from the MDCT substudy of the community-based Framingham Heart Study, including both Offspring and Gen3 cohorts. The original Framingham Heart Study cohort was enrolled beginning in 1948.\textsuperscript{33} Beginning in 1971, 5124 participants for this study were drawn from the MDCT substudy of the Framingham Heart Study, including both cohort was enrolled beginning in 1948.\textsuperscript{33} Beginning in 1971, 5124 participants for this study were drawn from the MDCT substudy of the Framingham Heart Study, including both.

Between June 2002 and April 2005, 3483 participants (n=1390 Offspring participants and n=2093 Gen3 participants) underwent assessment of coronary artery and aortic calcium. Inclusion in this study was weighted toward participants from larger Framingham Heart Study families and those who resided in the Greater New England area. Men were at least 35 years of age and women at least 40 years of age and not pregnant, and all participants weighed <320 pounds. Of these, 1303 Offspring and 2087 Gen3 participants had interpretable CAC measurements. We excluded participants with only 1 parent participating in the Framingham Heart Study (because validated parental CVD information was not available on the other parent who did not participate in the Framingham Heart Study) (Offspring, n=425; Gen3, n=558); with a father younger than 55 years or a mother younger than 65 years, irrespective of whether they had experienced a CVD event before that age (Gen3, n=276); or with prevalent CVD at the time of the MDCT test (Offspring, n=81; Gen3, n=15). After these exclusions, 797 Offspring and 1238 Gen3 participants remained eligible for analysis of CAC outcomes.

Among these 3483 participants in the MDCT study, 1384 Offspring and 2093 Gen3 had interpretable AAC measurements. We excluded participants with only 1 parent participating in the Framingham Heart Study (Offspring, n=461; Gen3, n=562), with a father younger than 55 years or a mother younger than 65 years, irrespective of whether they had experienced a CVD event before that age (Gen3, n=274), or with prevalent CVD at the time of the MDCT test (Offspring, n=115; Gen3, n=21). After exclusions, 808 Offspring and 1236 Gen3 participants remained eligible for analysis of AAC outcomes.

**MDCT and Calcium Measurements**

All subjects were imaged with an 8-slice MDCT (Lightspeed Ultra, GE, Milwaukee, Wis). Each subject underwent 2 chest scans that were performed according to a sequential scan protocol with a slice collimation of 8\times2.5 mm (120 kVp, 320/400 mA for \textless 220 and \textgreater 220 lb body weight, respectively) during a single end-inspiratory breath hold (typical duration, 18 seconds). Image acquisition (330 ms) was prospectively initiated at 50% of the cardiac cycle. Thirty contiguous 5-mm-thick slices of the abdomen were acquired covering 150 mm above the level of S1. Calcium measurements were performed on an offline workstation (Acquarius, Terarecon, San Mateo, Calif) by 4 experienced observers (3 trained physicians and 1 trained technician). A calcified lesion in either the coronary arteries or the aorta was defined as an area of at least 3 connected pixels with CT attenuation \textgreater 130 Hounsfield units with the use of 3-dimensional connectivity criteria (6 points). Each scan was evaluated for the presence of CAC and AAC. A modified Agatston score (because the Agatson score was originally devised from electron beam computed tomography (CT) scans and then “modified” to MDCT) was determined, as has been described previously.\textsuperscript{35}

**Definition of CAC and AAC**

The presence of both CAC and AAC was defined as \textgreater 90th percentile age-, sex-, and cohort-specific cut points based on a healthy referent sample (free of hyperlipidemia, diabetes, hypertension, smoking, and prevalent CVD). In secondary analyses, we defined CAC as \textgreater 75th percentile age-, sex-, and cohort-specific cut points based on a healthy referent sample.

**Risk Factor Assessment**

At the baseline examination cycle (Offspring examination cycle 7 from 1998 to 2001; Gen3 examination cycle 1 from 2002 to 2005), participants underwent a routine physical examination, anthropometry, and laboratory assessment of vascular risk factors. Plasma glucose, total and high-density lipoprotein cholesterol, and triglycerides were measured on morning samples obtained after an 8-hour fast. Diabetes was defined as a fasting plasma glucose \textgreater 126 mg/dL or treatment with either insulin or an oral hypoglycemic agent. Participants were considered to be current smokers if they smoked at least 1 cigarette per day for the last year. Women were considered to be menopausal if their periods had stopped for at least 1 year. The median duration between baseline examination and MDCT measure was 4 years for Offspring participants and 0 years for Gen3 participants.

**Validated CVD Assessment**

For Offspring and Gen3 cohorts, parental CVD and CHD information was drawn from physician-adjudicated outcomes from the Framingham Original cohort and the Offspring cohort, respectively. Using previously published Framingham Heart Study criteria to validate parental events,\textsuperscript{16} we defined a cardiovascular event as the occurrence of coronary death, myocardial infarction, stable or unstable angina pectoris, atherothrombotic stroke, intermittent claudication, or cardiovascular death. Hard coronary heart disease (CHD) events were defined as coronary death, myocardial infarction, or hospitalized coronary insufficiency only. Parental occurrence of premature CVD was defined as the occurrence of a validated parental event before the offspring MDCT examination and before age 55 years in a father and/or age 65 years in a mother. These age cut points were based on recommendations of the National Cholesterol Education Program Third Adult Treatment Panel\textsuperscript{15} and Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.\textsuperscript{16} We chose to study premature parental CVD in addition to premature parental CHD because we have previously demonstrated that premature parental CVD and premature parental CHD are independent risk factors for offspring CVD.\textsuperscript{37} This study was approved by the institutional review boards of the Boston University Medical Center and Massachusetts General Hospital. All subjects provided written consent.
Statistical Analysis
Parental (either maternal, paternal, or both) occurrence of premature CVD and premature CHD, and the separate paternal and maternal occurrence of these outcomes, were related to dichotomous variables for CAC and AAC. Generalized estimating equation logistic regression analysis was used to assess relations between parental occurrence of premature CHD/CVD and calcification. Generalized estimating equation models were employed to account for related observations given the presence of siblings in both the Offspring and Gen3 cohorts. Multivariable models were adjusted for age, sex, total/high-density lipoprotein cholesterol, lipid treatment, systolic blood pressure, hypertension treatment, body mass index, diabetes, smoking, hormone replacement therapy, and menopausal status. In secondary analyses, among Gen3, we assessed the association between parental premature CVD and parental CHD.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Baseline Characteristics and CAC/AAC Prevalence
Baseline characteristics of the Offspring and Gen3 cohorts, including the prevalence of the occurrence of parental CVD and mean CAC and AAC scores, are shown in Table 1. The mean age of Offspring and Gen3 cohort participants was 63 and 46 years, respectively. Offspring cohort participants tended to have a higher prevalence of CVD risk factors including hypertension, diabetes, and a higher prevalence of hormone replacement therapy and lipid medication use compared with Gen3 participants. Both Offspring and Gen3 participants had mean body mass index values in the overweight range. Current cigarette smoking was reported by 13% of Gen3 and 11% of Offspring cohort participants. The positive parental occurrence of either CVD or CHD was 26% and 9%, respectively, in Offspring participants and 16% and 7%, respectively, in Gen3 participants. As expected, given the substantial difference in ages, the mean and median CAC and AAC scores were higher in Offspring than in Gen3 participants.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic and risk factor characteristics</th>
<th>Offspring (Total n=797)</th>
<th>Gen3 (Total n=1238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.5±8.5</td>
<td>46±5.5</td>
</tr>
<tr>
<td>Female sex, n</td>
<td>444 (55.7)</td>
<td>583 (47.1)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>202.5±35.3</td>
<td>193.8±33.7</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>54.2±15.7</td>
<td>53.8±17.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2±5.1</td>
<td>27.6±6.9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124.8±17.3</td>
<td>119.5±18.6</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75.1±9.3</td>
<td>77.8±24.3</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>65 (8.2)</td>
<td>33 (2.7)</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>283 (35.5)</td>
<td>220 (17.8)</td>
</tr>
<tr>
<td>Lipid treatment, n</td>
<td>113 (14.2)</td>
<td>125 (10.1)</td>
</tr>
<tr>
<td>Hypertension treatment, n</td>
<td>194 (24.3)</td>
<td>144 (11.6)</td>
</tr>
<tr>
<td>Menopause (women), n</td>
<td>360 (81.1)</td>
<td>170 (29.2)</td>
</tr>
<tr>
<td>Hormone replacement therapy (women), n</td>
<td>162 (20.3)</td>
<td>59 (4.8)</td>
</tr>
<tr>
<td>Current cigarette smoking, n</td>
<td>84 (10.5)</td>
<td>162 (13.1)</td>
</tr>
</tbody>
</table>

Prior premature parental CVD and parental CHD

| Parental CVD, n                              | 203 (25.5)              | 197 (15.9)          |
| Parental CHD, n                              | 71 (8.9)                | 88 (7.1)            |
| Paternal CVD <55 y, n                        | 88 (11.0)               | 106 (8.6)           |
| Paternal CHD <55 y, n                        | 39 (4.9)                | 55 (4.4)            |
| Maternal CVD <65 y, n                        | 131 (16.4)              | 100 (8.1)           |
| Maternal CHD <65 y, n                        | 34 (4.3)                | 35 (2.8)            |

Values of CAC and AAC

| Mean CAC, modified Agatston score             | 226.2±562.4             | 34.9±167.9         |
| Mean AAC, modified Agatston score             | 1428.4±2436.8           | 198.2±731.4        |
| CAC ≥90th percentile cut point               | 133 (16.7)              | 174 (14.1)         |
| AAC ≥90th percentile cut point               | 173 (21.7)              | 230 (18.6)         |

Value are expressed as mean±SD or n where indicated; percentages are in parentheses. HDL indicates high-density lipoprotein.
Table 2 shows the unadjusted prevalence of premature CVD and premature CHD by presence of CAC and AAC (defined by the 90th percentile age- and sex-specific cut point from a healthy referent group). For both Offspring and Gen3 CAC, there was generally a greater proportion of participants with a positive parental occurrence of premature CVD or of CHD above the CAC cut point compared with below the CAC cut point. Similarly, for both Offspring and Gen3 AAC, there was generally a greater proportion of participants with a positive parental occurrence of premature CVD or of CHD above the AAC cut point compared with below the AAC cut point (Table 2).

### Odds Ratios for Association of Premature Parental CVD With Vascular Calcification

Among Gen3 participants, parental premature CVD and parental premature CHD were both associated with a 2.2-fold increased odds of CAC (odds ratio [OR] = 2.17 [1.41 to 3.33]; \( P = 0.009 \), and 2.22 [1.22 to 4.01]; \( P < 0.001 \), respectively), after adjustment for age and other CVD risk factors (Table 3). Among Offspring participants, the multivariable-adjusted ORs were also increased but not statistically significant for association of parental premature CVD with CAC or parental premature CHD with CAC (OR = 1.42 [0.91 to 2.22]; \( P = 0.12 \)) and for parental premature CHD with AAC (OR = 1.44 [0.80 to 2.59]; \( P = 0.22 \)).

Among Gen3 participants, parental premature CVD was associated with AAC in age- and sex-adjusted models (\( P = 0.001 \) and \( P = 0.02 \), respectively); however, the strength and statistical significance of these associations were diminished after further adjustment for CVD risk factors (Table 3). Among Gen3 participants, parental premature CHD was associated with a 1.6-fold increased odds of AAC, of borderline statistical significance (OR = 1.65 [0.99 to 2.75]; \( P = 0.05 \)). There was a more modest association of parental premature CVD with AAC in Offspring participants (OR = 1.38 [0.78 to 2.45]; \( P = 0.27 \)), an association that was not statistically significant (Table 3).

We further examined these associations according to the occurrence of premature parental and premature maternal CVD. Among Gen3 participants, premature parental CVD was associated with a 2.9-fold increased odds of CAC (\( P = 0.0001 \)) and a 2.2 increased odds of AAC (\( P = 0.02 \)) (Table 3). Similarly, among Gen3 participants, premature paternal CHD was associated with a 2.2-fold increased odds of CAC (\( P = 0.04 \)) and a 2.1 increased odds of AAC (\( P = 0.009 \)). Premature paternal CHD was not associated with CAC or AAC among Offspring participants. There was no significant association of premature maternal CVD or premature maternal CHD with CAC or AAC in either Offspring or Gen3 participants.

### Adjustment for CVD Risk Factor Subgroups

We further examined the impact of adjustment for specific risk factors subgroups on the association between premature parental CVD outcomes with CAC and AAC in Gen3 (Table 4). The age- and sex-adjusted association between parental premature CVD and CAC among Gen3 was modestly attenuated by the addition of lipid covariates to age- and sex-adjusted models (age- and sex-adjusted OR = 2.39 [\( P < 0.001 \)]; age-, sex-, total/HDL cholesterol, and lipid treatment–adjusted OR = 2.29 [\( P = 0.002 \]); multivariable-adjusted OR = 2.17 [\( P = 0.004 \)]. Similar findings of attenuation by lipid covariates were found for the association between maternal CVD and CAC among Gen3. The age- and sex-adjusted association between parental premature CVD and AAC among Gen3 was modestly attenuated by the addition of cigarette smoking to the statistical model (age- and sex-adjusted OR = 1.80 [\( P = 0.002 \]); age-, sex-, and smoking-adjusted OR = 1.58 [0.02]; multivariable-adjusted OR = 1.39 [\( P = 0.1 \)].

### Secondary Analyses

When we utilized age-, sex-, and cohort-specific 75th percentile cut points derived from the entire Offspring and Gen3 samples undergoing MDCT scanning, premature parental CVD and premature parental CHD were both associated with a 2-fold increase in CAC in Gen3 (\( P < 0.05 \)), but in Offspring participants the odds ratios for association were substantially lower (1.3- to 1.5-fold increase) and not statistically significant for associations with CAC (Table I in the online-only Data Supplement).

Among the 1230 Gen3 participants having both AAC and CAC measurements, the prevalence of the following mutually exclusive categories was as follows: both CAC and AAC <90th percentile, 73.7%; only AAC ≥90th percentile, 12.3%; only CAC ≥90th percentile, 7.7%; and both CAC and AAC ≥90th percentile, 6.3%. The ORs for associations of
premature parental CVD and CHD with only AAC ≥90th percentile, only CAC ≥90th percentile, and both CAC and AAC ≥90th percentile, with the referent category being both CAC and AAC <90th percentile, are shown in the Figure. Premature parental CVD and CHD were most strongly and significantly associated with having only CAC ≥90th percentile.

TABLE 3. Association of Premature CVD/CHD With CAC/AAC (Based on 90th Percentile Age- and Sex-Specific Cut Points From a Healthy Referent Subset)

<table>
<thead>
<tr>
<th>Model (Adjustment)</th>
<th>Offspring</th>
<th>Gen3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>P</td>
</tr>
<tr>
<td>CAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental premature CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.52 0.99–2.35 0.058</td>
<td>2.39 1.56–3.68 &lt;0.0001</td>
</tr>
<tr>
<td>All variables</td>
<td>1.42 0.91–2.22 0.12</td>
<td>2.17 1.41–3.33 0.0004</td>
</tr>
<tr>
<td>Parental premature CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.54 0.88–2.69 0.13</td>
<td>2.37 1.32–4.24 0.004</td>
</tr>
<tr>
<td>All variables</td>
<td>1.44 0.80–2.59 0.22</td>
<td>2.22 1.22–4.01 0.009</td>
</tr>
<tr>
<td>Paternal premature CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.88 1.02–3.45 0.04</td>
<td>2.91 1.68–5.03 0.0001</td>
</tr>
<tr>
<td>All variables</td>
<td>2.01 1.13–3.58 0.02</td>
<td>2.89 1.69–4.92 0.0001</td>
</tr>
<tr>
<td>Paternal premature CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.57 0.76–3.25 0.22</td>
<td>2.18 1.02–4.68 0.05</td>
</tr>
<tr>
<td>All variables</td>
<td>1.79 0.87–3.70 0.11</td>
<td>2.17 1.02–4.61 0.04</td>
</tr>
<tr>
<td>Maternal premature CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>0.99 0.61–1.66 0.99</td>
<td>1.54 0.90–2.62 0.11</td>
</tr>
<tr>
<td>All variables</td>
<td>0.86 0.51–1.45 0.57</td>
<td>1.27 0.72–2.22 0.41</td>
</tr>
<tr>
<td>Maternal premature CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.30 0.59–2.90 0.52</td>
<td>2.20 0.96–5.04 0.06</td>
</tr>
<tr>
<td>All variables</td>
<td>1.02 0.43–2.39 0.97</td>
<td>1.93 0.80–4.70 0.15</td>
</tr>
<tr>
<td>AAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental premature CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.16 0.79–1.70 0.46</td>
<td>1.80 1.25–2.60 0.002</td>
</tr>
<tr>
<td>All variables</td>
<td>0.98 0.66–1.46 0.91</td>
<td>1.39 0.93–2.09 0.11</td>
</tr>
<tr>
<td>Parental premature CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.47 0.87–2.47 0.15</td>
<td>1.81 1.11–2.93 0.02</td>
</tr>
<tr>
<td>All variables</td>
<td>1.38 0.78–2.45 0.27</td>
<td>1.65 0.99–2.75 0.05</td>
</tr>
<tr>
<td>Paternal premature CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.13 0.66–1.95 0.65</td>
<td>1.94 1.23–3.06 0.004</td>
</tr>
<tr>
<td>All variables</td>
<td>1.06 0.59–1.92 0.83</td>
<td>1.77 1.10–2.84 0.02</td>
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<tr>
<td>Paternal premature CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.00 0.48–2.11 0.99</td>
<td>2.11 1.21–3.67 0.009</td>
</tr>
<tr>
<td>All variables</td>
<td>1.11 0.45–2.73 0.81</td>
<td>2.08 1.21–3.60 0.009</td>
</tr>
<tr>
<td>Maternal premature CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.05 0.67–1.65 0.83</td>
<td>1.57 0.95–2.60 0.08</td>
</tr>
<tr>
<td>All variables</td>
<td>0.87 0.56–1.37 0.55</td>
<td>1.09 0.61–1.96 0.77</td>
</tr>
<tr>
<td>Maternal premature CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.90 0.97–3.74 0.06</td>
<td>0.83 0.36–1.92 0.66</td>
</tr>
<tr>
<td>All variables</td>
<td>1.59 0.81–3.15 0.18</td>
<td>0.88 0.37–2.12 0.78</td>
</tr>
</tbody>
</table>

All variables include age, sex, total/high-density lipoprotein cholesterol, lipid treatment, systolic blood pressure, hypertension treatment, body mass index, diabetes, smoking, hormone replacement therapy, and menopausal status.

Discussion
Main Findings
In 2 contemporary Framingham Heart Study cohorts with mean ages of 63 (Offspring cohort) and 46 (Gen3 cohort) years, respectively, we found that a validated parental occurrence of premature CVD was strongly and significantly associated with an elevated risk of CAC in the younger of the
2 cohorts, even after adjustment for risk factors. The parental occurrence of premature CVD and of premature CHD was also associated with AAC among Gen3 participants, although these associations were largely attenuated and not significant after adjustment for CVD risk factors. Our analyses suggest a stronger relationship of paternal versus maternal premature CVD with both CAC and AAC.

Parental CVD and CAC in Offspring
Our finding that validated parental CVD is significantly associated with CAC in our younger subjects, using a 90th percentile cut point, substantially extends prior evidence. Our results are similar to recent findings in the Dallas Heart Study that demonstrated a significant association between family history of myocardial infarction and coronary calcium among younger (men <45 years, women <55 years) but not among older study participants ($P$ for interaction $<0.02$).37 Furthermore, previous epidemiological studies demonstrated larger relative risks of CVD associated with parental myocardial infarction in younger versus older probands.3 8–4 0 The multivariable-adjusted 2-fold magnitude of increased risk for parental premature CHD with CAC in Gen3 participants is consistent with prior studies of populations with a similar age distribution (aged 32 to 47 years).41 A previous study of 8549 asymptomatic men and women (mean age, 53 $\pm$ 9 years) referred by their physicians for subclinical atherosclerosis screening by electron beam CT demonstrated a very similar association between premature parental CHD and both the presence of CAC, CAC $>75$th percentile, and the presence of at least moderate coronary calcification.26 Because we use validated parental CVD outcome information, our study extends these previous findings, which were recorded in a

<table>
<thead>
<tr>
<th>Model (Adjustment)</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
</table>
| Parental premature CVD with CAC | Age and sex | 2.39 | 1.56–3.68 | $<0.0001$
| | Age, sex, SBP, hypertension treatment | 2.36 | 1.55–3.60 | $<0.0001$
| | Age sex, total/HDL cholesterol, lipid treatment | 2.29 | 1.49–3.53 | 0.0002
| | Age, sex, cigarette smoking | 2.31 | 1.50–3.56 | 0.0002
| | Age, sex, diabetes, BMI | 2.37 | 1.54–3.62 | $<0.0001$
| | All variables | 2.17 | 1.41–3.33 | 0.0004
| Parental premature CHD with CAC | Age and sex | 2.37 | 1.32–4.24 | 0.004
| | Age, sex, SBP, hypertension treatment | 2.33 | 1.33–4.07 | 0.003
| | Age, sex, total/HDL cholesterol, lipid treatment | 2.27 | 1.26–4.11 | 0.007
| | Age, sex, cigarette smoking | 2.35 | 1.31–4.22 | 0.004
| | Age, sex, diabetes, BMI | 2.34 | 1.28–4.26 | 0.006
| | All variables | 2.22 | 1.22–4.01 | 0.009
| Parental premature CVD with AAC | Age and sex | 1.80 | 1.25–2.60 | 0.002
| | Age, sex, SBP, hypertension treatment | 1.75 | 1.20–2.54 | 0.004
| | Age, sex, total/HDL cholesterol, lipid treatment | 1.72 | 1.19–2.48 | 0.004
| | Age, sex, cigarette smoking | 1.58 | 1.07–2.33 | 0.02
| | Age, sex, diabetes, BMI | 1.77 | 1.22–2.56 | 0.003
| | All variables | 1.39 | 0.93–2.09 | 0.11
| Parental premature CHD with AAC | Age and sex | 1.81 | 1.11–2.93 | 0.016
| | Age, sex, SBP, hypertension treatment | 1.74 | 1.07–2.83 | 0.025
| | Age, sex, total/HDL cholesterol, lipid treatment | 1.75 | 1.07–2.85 | 0.03
| | Age, sex, cigarette smoking | 1.80 | 1.10–2.93 | 0.02
| | Age, sex, diabetes, BMI | 1.80 | 1.08–3.01 | 0.03
| | All variables | 1.65 | 0.99–2.75 | 0.05

* All variables include age, sex, total/high-density lipoprotein (HDL) cholesterol, lipid treatment, systolic blood pressure (SBP), hypertension treatment, body mass index (BMI), diabetes, smoking, hormone replacement therapy, and menopausal status. AAC and CAC cut points are based on 90th percentile age- and sex-specific cut points from a healthy referent subset.
higher-risk population that was not drawn from a general population and that utilized retrospective participant reports of family history data.

Use of 75th Percentile Cut Points Derived From the Broad Study Sample
To facilitate comparison of our results with those of Nasir and colleagues from the Multiethnic Study of Atherosclerosis (MESA), we analyzed our data utilizing CAC and AAC cut points similar to the cut points of their study. Among white participants in MESA, a positive family occurrence of CHD conferred an elevated odds of CAC ≥75th percentile of 1.97 (95% CI, 1.51 to 2.57).41 This estimate is nearly identical to our corresponding OR of 2.15 (95% CI, 1.02 to 4.52) for the association of parental premature CHD and AAC among Framingham Heart Study Gen3 participants.

Self-Reported Versus Validated Family History Data
Self-reported family history may be highly inaccurate because of significant reporter bias and/or misclassification compared with a family history validated by a physician adjudication panel. In the Framingham Offspring Cohort, the positive predictive value for a reported myocardial infarction in a father before age 55 years was only 28% when participant report was validated with medical records.42 Although use of the validated family history provides a state of the art exposure measure for the present study and as such provides the strongest level of evidence for the associations of family history with CAC, the family history in clinical practice is usually elicited by report and not by the use of primary medical records. The association of validated family occurrence of premature CVD with CAC/AAC in the context of aging should be explored in further investigations.

Parental Premature CVD and AAC in Offspring
Our finding that parental premature histories of CVD and CHD are associated with AAC in a younger and relatively low-risk cohort is a relatively novel finding. These associations are largely attenuated by multivariable adjustment except in the younger Gen3 cohort, suggesting that these associations, in older persons in particular, are largely a result of shared CVD risk factors. Future studies are needed to confirm these findings and to determine in other population settings whether family history consistently adds to prediction of AAC above and beyond classic CVD risk factors.

Differences in Association of Paternal Versus Maternal Occurrence of Premature CVD With CAC
Our finding that paternal premature CVD and CHD was associated with CAC and AAC, particularly in Gen3, is consistent with previous data linking paternal CHD with proband CHD. Our finding that maternal premature CVD/CHD was unrelated to CAC is surprising in light of previous data relating maternal premature myocardial infarction to offspring CHD,13 including some studies that suggest a stronger risk conferred by history of maternal versus paternal CVD.43 The magnitude and consistency of differences in risk conferred by maternal CVD versus paternal CVD on offspring CVD outcomes are still uncertain, but it may be that the mechanism of association of parental CVD with clinically apparent disease in offspring differs from the mechanism for increased risk for subclinical atherosclerosis in the coronary arteries or aorta. There may be significant sex-related differences between inherited triggers of CVD events versus inherited susceptibility to endothelial damage and atherogenesis. However, it remains uncertain whether maternal CVD confers CHD risk through mechanisms unrelated to atherosclerosis and therefore unrelated to vascular calcification. Further studies are needed to confirm any differential effect of premature paternal and maternal history of CVD/CHD on both outcomes and subclinical atherosclerosis manifested by vascular calcification.

Clinical Implications of Our Findings
The appropriate clinical role for CAC in risk screening is still being defined. Recent expert guidelines recommend coronary artery calcium screening only for individuals specifically having an “intermediate” 10-year CHD risk (ie, those with a 10% to 20%, 10-year CHD risk15 based on presence of conventional CVD risk factors).44 Our findings that parental history of premature CVD and CHD is associated with CAC, accounting for major CVD risk factors, suggest that family history information should be further investigated as a simple clinical indicator, in addition to the other risk factors in the Framingham risk algorithm, to identify individuals who might benefit from coronary artery calcium screening. Our study underscores the need for further observational and interventional studies to identify the appropriate patient subgroups in which CAC screening will add incremental information in addition to family history information and established risk factors to identify at-risk individuals in whom effective lowering of risk can be achieved.

Limitations
Several limitations should be acknowledged as well. Our study sample is limited both geographically and ethnically. Because our study sample is of largely white, European descent, generalizability to other ethnic groups may be limited. Because the distribution of CAC differs across various ethnic groups,45 and the risk of CAC given parental CVD varies across ethnicity,46 our findings should be confirmed in other populations. Among Offspring participants, the MDCT scans were done a median of 4 years after baseline examination (compared with Gen3, among whom the median was 0 years). Therefore, there was a greater opportunity for covariate misclassification in Offspring participants, which would have biased associations toward the null. Although we adjusted for most known traditional CVD risk factors in our analysis, residual confounding from covariates not measured in our study cannot be excluded. Survival bias could have attenuated associations between exposure and outcome in our study, especially among our older Offspring cohort participants. Additionally, we had limited power to detect very modest effect sizes for maternal and paternal premature CVD and CAC/CAC. We did not have adequate power to undertake sex-specific analyses among our study sample. We did
not analyze sibling history of premature CVD and CHD because sibling information was incomplete for several study participants (not all siblings participated in the Framingham Heart Study in several families). Accordingly, we chose to focus on the premature parental CVD and CHD occurrence. We could not combine the Gen3 and Offspring cohorts to formally assess an age interaction because of insufficient overlap in their respective age distributions.

In this study we used an 8-slice MDCT scanner, and we reported an Agatston score averaged from 2 sequential chest MDCT scans. Since the study inception, the temporal resolution and volume coverage of MDCT scanners has improved, with the introduction of 32- and 64-slice scanners from 330 ms to ~165 to 210 ms and from 18 seconds to ~10 to 14 seconds, respectively. However, in a recent report from the MESA study, the differences between different CT scanners appear negligible, at least on a population basis, and thus we do not believe that the use of an 8-slice scanner significantly decreased the accuracy of our calcium measurements. Finally, our MDCT coverage of the abdominal aorta may have differed slightly among participants given that we used a spinal landmark (scans were preformed 150 mm above S1).

Conclusions

A validated parental occurrence of premature CVD and of premature CHD was significantly associated with increased coronary atherosclerosis, independent of traditional risk factors. We found that the relationship between parental premature CVD and CHD with CAC and AAC was strong and significant, particularly in our younger Framingham Heart Study subjects, suggesting possible age-dependent effects of parental premature CVD/CHD on atherosclerosis. The parental occurrence of premature CVD and of premature CHD was associated with AAC, although shared CVD risk factors appear to underlie much of these associations. Our analyses also suggest stronger relationships with CAC and with AAC of paternal premature CVD versus maternal premature CVD. These findings may have clinical implications as further evidence accrues regarding the appropriate use of family history information and subclinical disease screening over and above established risk factors.

Sources of Funding

This work was supported by the National Heart, Lung, and Blood Institute’s Framingham Heart Study (N01-HC-25195).

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

We determined that parental history of premature cardiovascular disease and premature coronary heart disease is associated with high levels of coronary artery calcification after accounting for major cardiovascular disease risk factors. Additionally, we found that a positive history of parental premature cardiovascular disease and coronary heart disease was a risk factor for coronary artery calcification in middle-aged persons compared with elderly individuals. Prospective outcome studies are warranted to confirm that family history information considered in addition to other established coronary heart disease risk factors may identify individuals who might benefit from coronary artery calcium screening. Our findings may have clinical implications as further evidence accrues regarding the appropriate use of family history information together with subclinical atherosclerosis screening over and above established risk factors.
Parental Occurrence of Premature Cardiovascular Disease Predicts Increased Coronary Artery and Abdominal Aortic Calcification in the Framingham Offspring and Third Generation Cohorts

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*Circulation.* 2007;116:1473-1481; originally published online September 4, 2007;
doi: 10.1161/CIRCULATIONAHA.107.705202

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/116/13/1473

Data Supplement (unedited) at:
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