Parental Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults
A Prospective Study of Parents and Offspring

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Context  Whether parental cardiovascular disease confers increased risk independent of other risk factors remains controversial. Prior studies relied on offspring report, without complete validation of parental events.

Objective  To determine whether parental cardiovascular disease predicts offspring events independent of traditional risk factors, using a prospective design for both parents and offspring, and uniform criteria to validate events.

Design  Inception cohort study.

Setting  Framingham Heart Study, a US population-based epidemiologic cohort begun in 1948 with the offspring cohort established in 1971.

Participants  All Framingham Offspring Study participants (aged ≥30 years) who were free of cardiovascular disease and both parents in the original Framingham cohort.

Main Outcome Measures  We examined the association of parental cardiovascular disease with 8-year risk of offspring cardiovascular disease, using pooled logistic regression.

Results  Among 2302 men and women (mean age, 44 years), 164 men and 79 women had cardiovascular events during follow-up. Compared with participants with no parental cardiovascular disease, those with at least 1 parent with premature cardiovascular disease (onset age <55 years in father, <65 years in mother) had greater risk for events, with age-adjusted odds ratios of 2.6 (95% confidence interval [CI], 1.7-4.1) for men and 2.3 (95% CI, 1.3-4.3) for women. Multivariable adjustment resulted in odds ratios of 2.0 (95% CI, 1.2-3.1) for men and 1.7 (95% CI, 0.9-3.1) for women. Nonpremature parental cardiovascular disease and parental coronary disease were weaker predictors. Addition of parental information aided in discriminating event rates, notably among offspring with intermediate levels of cholesterol and blood pressure, as well as intermediate predicted multivariable risk.

Conclusions  Using validated events, we found that parental cardiovascular disease independently predicted future offspring events in middle-aged adults. Addition of parental information may help clinicians and patients with primary prevention of cardiovascular disease, when treatment decisions may be difficult in patients at intermediate risk based on levels of single or multiple risk factors. These data also support further research into genetic determinants of cardiovascular risk.

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of parental CVD on offspring risk across strata of individual risk factors is also not well understood.

We sought to determine whether validated parental occurrence of CVD is an independent, prospective predictor of offspring cardiovascular events. Accurate estimates of the relationship between parental and offspring cardiovascular events could provide stronger evidence for the clinical emphasis on prevention in patients with a positive parental history. The Framingham Heart Study is uniquely suited to perform such an analysis given its longitudinal follow-up and exhaustive documentation of events in both parents and offspring.

METHODS
Study Sample and Definitions
The Framingham Heart Study was established in 1948, when 5209 residents of Framingham, Mass, aged 28 to 62 years, were enrolled in a prospective epidemiologic cohort study. Members of this original cohort have undergone follow-up evaluations every 2 years. In 1971, an additional 5124 participants (offspring of original cohort subjects and their spouses) were enrolled in the Framingham Offspring Study (offspring cohort). These participants have undergone follow-up evaluations every 4 years. Study design and entry criteria for both cohorts have been detailed elsewhere.20,27 All participants have provided written informed consent at each examination, and all study protocols have been approved by the Institutional Review Board of Boston University School of Medicine.

We included all Framingham Offspring Study participants who were aged 30 years or older and free of prevalent CVD and for whom both parents were followed up in the original cohort. Parental subjects were followed up from 1948 to 2001, and offspring participants were followed up from 1971 to 2001. Given the structure of follow-up examinations, we elected to study the 8-year incidence of cardiovascular events in the offspring cohort. We focused on atherosclerotic cardiovascular events since atherosclerosis is believed to be the mechanism underlying familial aggregation. Using previously published Framingham Heart Study criteria28 to validate parental and offspring events, we defined a cardiovascular event as the occurrence of coronary death, myocardial infarction, coronary insufficiency, angina pectoris, atherothrombotic stroke, intermittent claudication, or cardiovascular death. Hard coronary heart disease events were defined as coronary death, myocardial infarction, or hospitalized coronary insufficiency only. Premature parental CVD was defined as the occurrence of a validated parental event prior to an offspring baseline examination and before age 55 years in a father or age 65 years in a mother. These age cut points were drawn from the recommendations of the National Cholesterol Education Program Third Adult Treatment Panel (ATP-III)1 and Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).2

Statistical Analysis
We used pooled logistic regression analyses to examine the risks of incident offspring cardiovascular events associated with positive parental CVD over 8 years after an examination. This person-time method of pooling person-examination data accounts for time-dependent covariance of risk factors and parental cardiovascular events and has been shown to provide valid estimates of effect similar to using time-dependent Cox analyses. This is a robust assumption, as demonstrated by D’Agostino et al.29 Participants contributed a mean of 2.2 person-examination cycles. For all logistic regression analyses, the reference group consisted of offspring participants with no parental CVD prior to the time of the offspring examination. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in unadjusted analyses, as well as after adjustment for offspring age, age with other individual categories of cardiovascular risk factors, and all other risk factors in the model. These analyses were repeated examining parental nonpremature CVD and parental hard coronary heart disease as risk factors for offspring CVD. Risk factor covariates, chosen a priori for inclusion in the models and updated using pooled logistic analyses, were: offspring age, systolic blood pressure, total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio, body mass index, presence of diabetes, current smoking, and use of antihypertensive drug therapy. In the multivariable models, there was only 1 significant first-order interaction (between maternal CVD and antihypertensive therapy in men). Inclusion of the interaction term did not alter the substance of our findings, so it was excluded from the models.

A multivariable risk score was calculated using weighted coefficients for each covariate, with the exception of parental CVD information. Offspring participants were stratified into quintiles of predicted multivariable risk for CVD. Eight-year event rates were then compared for participants in each quintile, as well as across clinical strata of individual risk factors, according to presence or absence of parental CVD, using χ² tests. C statistics were calculated for the model before and after inclusion of parental CVD information. All statistical analyses were performed using SAS statistical software version 8 (SAS Institute, Cary, NC). A 2-tailed P value less than .05 was defined as statistically significant.

RESULTS
Baseline Characteristics
The study sample included 1128 men and 1174 women offspring participants who were free of CVD at a mean age of 44 years. Characteristics of these individuals are shown in Table 1. During follow-up, 164 men and 79 women had incident cardiovascular events, of which 14 (5.7%) were coronary deaths (11 [4.5%], sudden; 3 [1.2%], nonsudden), 5 (2.1%) were other cardiovascular deaths, 76 (31.3%) were nonfatal myocardial infarction or coronary insufficiency, 71 (29.2%) were angina pectoris, 39 (16.0%) were stroke, and 38 (15.6%) were intermittent clau-
Parental CVD and Offspring Risk

The ORs for offspring cardiovascular events associated with premature parental CVD are shown in Table 2. After adjustment for offspring age, the ORs associated with parental CVD were 2.6 (95% CI, 1.7-4.1) for men and 2.3 (95% CI, 1.3-4.3) for women. Additional adjustment for individual risk factors did not substantially attenuate the risk associated with parental CVD further (Table 2). After multivariable adjustment for offspring age and all other risk factors, parental occurrence of CVD remained a significant predictor of offspring events in men. In women, the multivariable association was of borderline statistical significance. In age-adjusted and multivariable-adjusted analyses, the ORs for offspring CVD were higher for premature (Table 2) than for nonpremature parental CVD (Table 3).

The occurrence in 1 or more parent of premature hard coronary disease only was less strongly associated with risk for CVD, with multivariable ORs of 1.7 (95% CI, 1.0-2.8) for men and 1.2 (95% CI, 0.5-2.5) for women offspring. Because 1737 of the 2302 offspring were part of a sibship, a given parent's event may have been counted more than once in these analyses. When we restricted the analysis to 1 sibling per family (the oldest), the results were not changed substantially.

Offspring Event Rates by Parental CVD and Risk Factors

When we stratified participants by levels of individual risk factors, parental information added substantially to discrimination of observed 8-year event risk (Table 1). There was a similar distribution of event types among parents.

Table 1. Characteristics of Offspring Subjects at Baseline Examinations*

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Offspring</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>44.1 (8.9)</td>
<td>44.3 (9.1)</td>
<td>44.1 (8.9)</td>
<td>44.3 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>126.4 (16.0)</td>
<td>119.8 (17.2)</td>
<td>126.4 (16.0)</td>
<td>119.8 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Receiving antihypertensive drug therapy, No. (%)</td>
<td>241 (9.9)</td>
<td>217 (8.3)</td>
<td>241 (9.9)</td>
<td>217 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>205.9 (37.1)</td>
<td>200.2 (38.2)</td>
<td>205.9 (37.1)</td>
<td>200.2 (38.2)</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>43.6 (11.3)</td>
<td>56.1 (14.7)</td>
<td>43.6 (11.3)</td>
<td>56.1 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Total/HDL-C ratio, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>27.0 (3.6)</td>
<td>24.9 (5.0)</td>
<td>27.0 (3.6)</td>
<td>24.9 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>78 (3.2)</td>
<td>44 (1.7)</td>
<td>78 (3.2)</td>
<td>44 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Current cigarette smoking, No. (%)</td>
<td>800 (33.2)</td>
<td>925 (35.4)</td>
<td>800 (33.2)</td>
<td>925 (35.4)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol.

SI conversion factor: to convert cholesterol to mmol/L, multiply by 0.0259; body mass index is calculated as weight in kilograms divided by the square of height in meters.

*Data are based on 2436 person-examination cycles from 1128 men and 2612 person-examination cycles from 1174 women.

Table 2. Risk for Offspring Cardiovascular Disease Over 8 Years, by Presence of Premature Parental Cardiovascular Disease

<table>
<thead>
<tr>
<th>Model Adjustment</th>
<th>None</th>
<th>Paternal CVD</th>
<th>Maternal CVD</th>
<th>Both</th>
<th>1 or Both Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offspring men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0</td>
<td>3.0 (1.7-5.0)</td>
<td>3.4 (2.1-5.6)</td>
<td>3.3</td>
<td>3.2 (2.1-5.0)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0</td>
<td>2.7 (1.6-4.7)</td>
<td>2.4 (1.5-4.0)</td>
<td>3.1</td>
<td>3.1 (1.8-5.4)</td>
</tr>
<tr>
<td>Age and SBP and antihypertensive therapy</td>
<td>1.0</td>
<td>2.5 (1.4-4.3)</td>
<td>2.2 (1.3-3.7)</td>
<td>2.7</td>
<td>2.6 (1.7-4.1)</td>
</tr>
<tr>
<td>Age and total/HDL cholesterol ratio</td>
<td>1.0</td>
<td>2.8 (1.6-4.9)</td>
<td>2.1 (1.2-3.4)</td>
<td>2.9</td>
<td>2.3 (1.5-3.7)</td>
</tr>
<tr>
<td>Age and smoking</td>
<td>1.0</td>
<td>2.4 (1.4-3.5)</td>
<td>2.2 (1.3-3.7)</td>
<td>2.8</td>
<td>2.4 (1.5-3.8)</td>
</tr>
<tr>
<td>Age and diabetes and body mass index</td>
<td>1.0</td>
<td>2.5 (1.4-4.3)</td>
<td>2.2 (1.3-3.7)</td>
<td>2.7</td>
<td>2.4 (1.5-3.8)</td>
</tr>
<tr>
<td>Multivariable-adjusted*</td>
<td>1.0</td>
<td>2.2 (1.2-3.9)</td>
<td>1.7 (1.0-2.9)</td>
<td>2.4</td>
<td>2.0 (1.2-3.1)</td>
</tr>
<tr>
<td>Offspring women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.0</td>
<td>2.7 (1.3-5.8)</td>
<td>3.2 (1.7-6.0)</td>
<td>4.3</td>
<td>2.9 (1.6-5.3)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0</td>
<td>2.8 (1.3-6.1)</td>
<td>2.3 (1.2-4.5)</td>
<td>4.1</td>
<td>2.9 (1.4-4.3)</td>
</tr>
<tr>
<td>Age and SBP and antihypertensive therapy</td>
<td>1.0</td>
<td>2.3 (1.1-5.1)</td>
<td>1.9 (0.9-3.7)</td>
<td>3.1</td>
<td>1.9 (1.0-3.6)</td>
</tr>
<tr>
<td>Age and total/HDL cholesterol ratio</td>
<td>1.0</td>
<td>1.9 (0.9-3.3)</td>
<td>2.0 (1.0-3.9)</td>
<td>3.8</td>
<td>2.1 (1.0-3.6)</td>
</tr>
<tr>
<td>Age and smoking</td>
<td>1.0</td>
<td>2.8 (1.3-3.6)</td>
<td>2.3 (1.2-4.4)</td>
<td>4.5</td>
<td>2.3 (1.2-4.2)</td>
</tr>
<tr>
<td>Age and diabetes and body mass index</td>
<td>1.0</td>
<td>2.4 (1.1-5.3)</td>
<td>2.2 (1.1-4.3)</td>
<td>3.5</td>
<td>2.2 (1.2-4.1)</td>
</tr>
<tr>
<td>Multivariable-adjusted*</td>
<td>1.0</td>
<td>1.7 (0.7-3.6)</td>
<td>1.7 (0.8-3.4)</td>
<td>2.8</td>
<td>1.7 (0.9-3.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; OR, odds ratio; SBP, systolic blood pressure.

*Adjusted for age, total/HDL cholesterol ratio, SBP, antihypertensive therapy, diabetes, body mass index, and current smoking.
rates. Table 4 shows the 8-year cardiovascular event rates for offspring men and women, separately and combined, without and with premature parental CVD. The overall event rate was 44/1000 (4.4%) over 8 years. Although absolute event rates were lower for women than they were for men, the overall pattern of effect was similar. When we stratified by offspring age, parental CVD was associated with significantly higher event rates with a 3-fold difference for offspring aged 30 to 59 years, and a 2-fold difference for older offspring.

Parental CVD increased offspring risk across all strata of total cholesterol levels and blood pressure measurements. The greatest relative differences in event rates were observed among participants with borderline levels of cholesterol and high-normal blood pressure. Premature parental CVD increased risk in these intermediate subsets to the point that the 10-year risks of CVD would exceed 10%, a threshold for treatment used in some clinical guidelines. Premature parental CVD was also associated with increased risk among both smokers and nonsmokers, as well as among those who did not have diabetes. However, parental CVD did not significantly increase risk among diabetic participants, who already had substantially higher event rates.

Eight-year cardiovascular event rates are displayed in the Figure for offspring according to quintile of predicted multivariable risk. Observed 8-year event rates increased markedly and in a stepwise fashion from lowest to highest quintile. At very low and very high predicted risk, the increase in event rates associated with the presence of premature parental CVD was modest: offspring with favorable risk factor profiles were not at substantially increased risk despite parental CVD, and offspring with very unfavorable risk factor profiles remained at high risk even in the absence of parental CVD. In the intermediate quintiles, premature parental CVD was associated with significantly higher cardiovascular event rates (Figure).

In a separate analysis, we stratified offspring according to their predicted absolute 10-year risk for hard coronary events, as estimated by the ATP-III risk equations. Premature parental CVD presence vs absence was associated with increased events among offspring predicted to be at low risk by ATP-III (n = 3093; 54/1000 vs 18/1000 events over 8 years, respectively; \( P < .001 \)). There was a nonsignificant difference in the ATP-III intermediate-risk group (n = 153; 200/1000 vs 138/1000, respectively; \( P = .33 \)), but there were few participants, particularly women, in the ATP-III intermediate-risk (n = 9 women) and high-risk (n = 29 women) groups due to the young age of the offspring sample.

Receptor Operating Characteristic Analyses and Attributable Risk
Inclusion of premature parental CVD as a covariate altered the \( c \) statistic (area under the receiver operating characteristic curve) for our multivariable model predicting offspring CVD from 0.80 to 0.81 for men and from 0.81 to 0.82 for women. When men and women were combined, inclusion of premature parental CVD in the multivariable model altered the \( c \) statistic from 0.82 to 0.83. The attributable risk percentages for premature parental CVD were 29.0% in men and 20.6% in women offspring; for nonpremature parental CVD, they were 20.5% and 3.8%, respectively.

Comment
Principal Findings
Using a prospective design to ascertain both parental and offspring events, we found that the occurrence of paren-

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**Table 3. Risk for Offspring Cardiovascular Disease Over 8 Years, by Presence of Nonpremature Parental Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Model Adjustment</th>
<th>None</th>
<th>Paternal CVD</th>
<th>Maternal CVD</th>
<th>Both</th>
<th>1 or Both Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offspring men Unadjusted</td>
<td>1.0</td>
<td>3.0 (1.9-4.6)</td>
<td>4.1 (2.4-6.8)</td>
<td>5.2 (2.8-9.8)</td>
<td>3.0 (2.0-4.6)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0</td>
<td>2.0 (1.2-3.1)</td>
<td>1.8 (1.0-3.2)</td>
<td>2.4 (1.2-4.8)</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>Age and SBP and antihypertensive therapy</td>
<td>1.0</td>
<td>1.8 (1.1-2.8)</td>
<td>1.5 (0.8-2.8)</td>
<td>2.1 (1.0-4.3)</td>
<td>1.7 (1.1-2.7)</td>
</tr>
<tr>
<td>Age and total/HDL cholesterol ratio</td>
<td>1.0</td>
<td>1.8 (1.2-2.9)</td>
<td>1.8 (1.0-3.3)</td>
<td>2.6 (1.3-5.1)</td>
<td>1.8 (1.1-2.8)</td>
</tr>
<tr>
<td>Age and smoking</td>
<td>1.0</td>
<td>1.9 (1.2-2.9)</td>
<td>1.6 (0.9-2.9)</td>
<td>2.1 (1.1-4.2)</td>
<td>1.8 (1.1-2.8)</td>
</tr>
<tr>
<td>Age and diabetes and body mass index</td>
<td>1.0</td>
<td>1.8 (1.2-2.9)</td>
<td>1.6 (0.8-2.9)</td>
<td>2.1 (1.1-4.3)</td>
<td>1.8 (1.1-2.8)</td>
</tr>
<tr>
<td>Multivariable-adjusted*</td>
<td>1.0</td>
<td>1.6 (1.0-2.5)</td>
<td>1.3 (0.7-2.4)</td>
<td>1.8 (0.9-3.7)</td>
<td>1.5 (0.9-2.4)</td>
</tr>
</tbody>
</table>

| Offspring women Unadjusted   | 1.0           | 2.6 (1.5-4.6)| 3.5 (1.7-6.9) | 3.9 (1.7-9.0) | 2.6 (1.5-4.6)    |
| Age-adjusted                 | 1.0           | 1.6 (0.9-3.0)| 1.7 (0.8-3.7) | 1.7 (0.7-4.1) | 1.6 (0.9-2.9)    |
| Age and SBP and antihypertensive therapy | 1.0 | 1.4 (0.7-2.6) | 1.3 (0.6-3.0) | 1.3 (0.5-3.2) | 1.4 (0.7-2.5)    |
| Age and total/HDL cholesterol ratio | 1.0 | 1.4 (0.7-2.6) | 1.4 (0.6-3.2) | 1.5 (0.6-3.6) | 1.3 (0.7-2.4)    |
| Age and smoking              | 1.0           | 1.5 (0.8-2.8) | 1.7 (0.8-3.9) | 1.5 (0.6-3.6) | 1.5 (0.8-2.8)    |
| Age and diabetes and body mass index | 1.0 | 1.6 (0.9-3.0) | 1.7 (0.8-3.7) | 1.7 (0.7-4.2) | 1.6 (0.9-2.9)    |
| Multivariable-adjusted*      | 1.0           | 1.1 (0.6-2.1)| 1.2 (0.5-2.9) | 1.0 (0.4-2.7) | 1.1 (0.6-2.1)    |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; OR, odds ratio; SBP, systolic blood pressure.

*Adjusted for age, total/HDL cholesterol ratio, SBP, antihypertensive therapy, diabetes, body mass index, and current smoking.
tal CVD is an independent predictor of offspring cardiovascular events in middle-aged men and women. After adjustment for other risk factors, premature CVD in at least 1 parent was associated with a significant doubling in cardiovascular risk for men and a 70% increase (nonsignificant) in risk for women over 8 years. Premature parental CVD was found to discriminate risk best among offspring with intermediate levels of cardiovascular risk as pre-

### Table 4. Eight-Year Cardiovascular Disease Event Rates per 1000 for Men and Women Separately and Combined, According to Presence or Absence of Parental Premature Cardiovascular Disease, Stratified by Individual Risk Factor Levels

<table>
<thead>
<tr>
<th>Offspring Characteristic</th>
<th>No. of Person-Examinations</th>
<th>Offspring Men</th>
<th>1 or Both Parents</th>
<th>P Value</th>
<th>Offspring Women</th>
<th>1 or Both Parents</th>
<th>P Value</th>
<th>Combined</th>
<th>1 or Both Parents</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3346</td>
<td>33</td>
<td>97</td>
<td>&lt;.001</td>
<td>17</td>
<td>44</td>
<td>&lt;.001</td>
<td>25</td>
<td>72</td>
<td>&lt;.001</td>
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<tr>
<td>30-59</td>
<td>3217</td>
<td>29</td>
<td>94</td>
<td>&lt;.001</td>
<td>16</td>
<td>36</td>
<td>.01</td>
<td>22</td>
<td>65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥60</td>
<td>129</td>
<td>160</td>
<td>158</td>
<td>.98</td>
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<td>Cholesterol, mg/dL</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
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**Abbreviations:** CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

SI conversion factor: to convert cholesterol to mmol/L multiply by 0.0259; body mass index is calculated as weight in kilograms divided by the square of height in meters.

### Figure. Offspring Cardiovascular Disease Event Rates by Predicted Risk and Presence of Premature Parental CVD

Offspring participants were stratified into quintiles of predicted risk of cardiovascular disease based on factors listed in the “Methods” section.
dicted by individual traditional risk factors or multivariable risk equations.

We focused on a cohort of middle-aged offspring because parental CVD is likely to be a greater factor in determining relative CVD risk in younger than older individuals, as our findings confirm (Table 4). Adjustment for offspring age markedly attenuated the association of parental and offspring CVD. This may reflect the fact that older subjects also have older parents, who have had a longer lifespan in which to experience a cardiovascular event unrelated to familial aggregation. Multivariable adjustment for age and other traditional risk factors further attenuated the risk associated with parental CVD, and these covariates accounted for the majority of the crude risk associated with parental CVD. A significant, but modest, residual risk remained associated with parental occurrence of CVD, suggesting that parental CVD is a clinically important aggregate marker of both heritable risk factors and as yet unmeasured genetic risk factors.

Clinical Implications

These results should help to inform clinicians and patients about use of parental history in risk stratification and treatment decisions. It should be noted that the validation of parental events available for this study is not available in most clinical settings. Nevertheless, our results shed important light on the true magnitude of the association between offspring and parental CVD. It is likely that clinicians place greater importance on positive parental CVD in younger compared with older patients, which appears appropriate in terms of relative risk. However, at present it is difficult for clinicians and patients to know how to assess and incorporate into clinical practice the risk associated with parental CVD, independent of shared risk factors. As expected, we observed a substantial, stepwise increase in the incidence of CVD across quintiles of multivariable risk as estimated by multivariable equations using a combination of traditional, modifiable risk factors (Figure). Recent studies confirm that these traditional risk factors are present in almost all patients who develop CVD, and that they account for the majority of risk. Thus, clinicians and patients must continue to focus on proven lifestyle and drug therapies to modify traditional risk factors and reduce risk.

The addition of parental data may aid in discriminating risk most among men and women at intermediate levels of predicted risk. Knowledge of parental CVD status may not change the magnitude of risk substantially for those at very high or very low predicted risk. For patients with intermediate predicted risk, however, the additional information provided by positive parental CVD may change the posttest probability enough to consider altering the treatment of the patient. Treatment decisions in current guidelines are based on absolute risk levels. We demonstrate significantly higher 8-year absolute rates of CVD among participants with borderline cholesterol or blood pressure levels and premature compared with no parental CVD (Table 4). It is precisely these patients in whom decisions about lifestyle modification or drug treatment may be the most difficult. Thus, our data support the emphasis placed by the ATP-III and JNC 7 guidelines on ascertainment of parental history to help guide treatment decisions for primary prevention. Furthermore, our findings support consideration of clinical trials to assess the benefits of aggressive risk-factor modification in intermediate risk patients with parental CVD.

Our data also suggest that incorporation of validated parental data into multivariable functions predicting 10-year absolute risks for cardiovascular or coronary disease may increase the predictive accuracy of such functions, although perhaps only to a small extent. The overall c statistic for our multivariable model increased from 0.82 to 0.83 by adding parental CVD information. It has proved difficult to make marked improvements in risk stratification over and above incorporation of traditional risk factors, even with novel markers such as C-reactive protein.

Ongoing work is examining the utility of including parental occurrence of CVD or other novel risk markers in updated Framingham coronary risk functions. The addition of parental information to traditional risk factors must certainly be considered in the development of these risk functions. However, in the formulation of updated risk functions, a number of novel risk markers should also be considered. It may well be that inclusion of such markers will improve risk prediction better than incorporation of family history.

Research Implications

There is ample evidence for familial aggregation of traditional risk factors, as well as associations of parental and sibling CVD with adverse lipids and other risk factors in offspring. Parental history has also been associated with novel markers of inflammation, lipoprotein(a) and fibrinogen, and measures of subclinical atherosclerosis. Ongoing work is examining the utility of including parental occurrence of CVD or other novel risk markers in updated Framingham coronary risk functions. The addition of parental information to traditional risk factors must certainly be considered in the development of these risk functions. However, in the formulation of updated risk functions, a number of novel risk markers should also be considered. It may well be that inclusion of such markers will improve risk prediction better than incorporation of family history.

Current Study in Perspective

Numerous case-control studies have reported approximately 2- to 5-fold higher prevalence of a positive familial history among subjects with manifest CVD than among control subjects. Large, prospective cohort studies have generally found a positive association between self-reported parental or familial history and multivariable-adjusted relative risks for offspring CVD, with estimates ranging from 0.8 to 2.2. Our results shed further light on the true magnitude of this association.

Our study benefited from several unique methodologic strengths. First, as
this was a prospective study, parental events were ascertained and validated independently and prior to the occurrence of offspring events, avoiding recall bias and inaccuracy inherent in offspring self-report.21-23 Both parental and offspring events were validated using consistent, standardized definitions after review of all medical records by a panel of 3 physicians.28 Many studies have relied on death certificate data to identify or confirm parental events, which may lead to substantial overdiagnosis of coronary disease, especially in older decedents.51

Our study also benefited from the long duration of follow-up of both the parental and offspring family members. Shorter studies would miss parental events that have not yet occurred. At this point, ascertainment of premature events in parents is complete, and ascertainment of later parental events, near-complete. Our study design allowed for updating of parental history information and repeated measurements of offspring risk factors independent of parental history. Given these strengths, our estimates of the magnitude of the association between parental and offspring CVD may represent the most accurate published to date.

Limitations

The Framingham cohorts are almost exclusively white, which may limit the generalizability of our findings to other ethnic groups. Rates of use of preventive medications were fairly low, but could have contributed to reduction in risk associated with parental CVD if subjects with parental CVD were more likely to receive them. If anything, this would bias our results toward the null. We had relatively little power to find an independent relationship in women and to comment on any potential differences between paternal and maternal CVD as risk factors. Apparent differences in the effect of between offspring men and women may reflect the low number of cases and lower prevalence of risk factors in women. Finally, an unvalidated offspring report of parental history may not have the same clinical utility as the validated parental events used in the current study. However, risk estimates from studies using offspring self-report fall within the bounds of our study. With the current study design, we attempted to determine the most accurate possible representation of the association between parental and offspring CVD.

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Writing is nothing more than a guided dream. 
—Jorge Luis Borges (1899-1986)