Maternal and Paternal History of Myocardial Infarction and Risk of Cardiovascular Disease in Men and Women

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Background—Few studies have examined the effects of paternal and maternal history of myocardial infarction (MI), including age at MI, on cardiovascular disease (CVD) risk, particularly among women.

Methods and Results—We prospectively studied 22 071 men from the Physicians’ Health Study and 39 876 women from the Women’s Health Study with data on parental history and age at MI. Among men, 2654 CVD cases developed over 13.0 years; among women, 563 CVD cases occurred over 6.2 years. Compared with men with no parental history, only maternal, only paternal, and both maternal and paternal history of MI conferred relative risks (RRs) of CVD of 1.71, 1.40, and 1.85; among women, the respective RRs were 1.46, 1.15, and 2.05. For men, maternal age at MI of <50, 50 to 59, 60 to 69, 70 to 79, and ≥80 years had RRs of 1.00, 1.88, 1.88, 1.67, and 1.17; for women, the RRs for maternal age at MI of <50, 50 to 59, and ≥60 years were 2.57, 1.33, and 1.52. Paternal age at MI of <50, 50 to 59, 60 to 69, 70 to 79, and ≥80 years in men had RRs of 2.19, 1.64, 1.42, 1.16, and 0.92; in women, for paternal age at MI of <50, 50 to 59, and ≥60 years, the RRs were 1.63, 1.33, and 1.13.

Conclusions—An early history of parental MI (<60 years) conferred a greater risk of CVD than did MI at older ages. However, an increased risk of CVD remained for maternal age at MI of 70 to 79 years in men and ≥60 years in women, which suggests that any maternal history of MI may be important. (Circulation. 2001;104:393-398.)

Key Words: myocardial infarction ■ risk factors ■ cardiovascular diseases ■ epidemiology ■ prevention

Epidemiological studies indicate that a parental or family history of myocardial infarction (MI) is an independent risk factor for cardiovascular disease (CVD).1 Parental history of MI is often considered a surrogate for coronary risk factors, having associations with high blood pressure, poor lipid profiles, and obesity in children2 and adults,3 as well as other biochemical and genetic markers.4–6 Limited epidemiological evidence exists in women regarding the association between parental history of MI and CVD risk. Moreover, various definitions of parental history of MI in the existing literature7 neglect the separate effects of paternal and maternal history and whether there are comparable effects on the risk of CVD. Definitions of early parental history before the age of 60 years likely underestimate the impact of maternal history of MI because of the low incidence rates of MI in women before age 60.8

Therefore, we examined the association of parental history of MI and risk of CVD in 2 large prospective cohorts of men and women. The separate effects of paternal and maternal history of MI on CVD risk were examined, as well as the effect of age of parental MI and CVD risk.

Methods

Study Populations

The Physicians’ Health Study (PHS) is a completed trial of aspirin and beta-carotene in the primary prevention of CVD and cancer.9 Briefly, 22 071 US male physicians aged 40 to 84 years and free from prior MI, stroke, transient ischemic attack, and cancer (except nonmelanoma skin cancer) were enrolled in 1982. The Women’s Health Study (WHS) is an ongoing trial of aspirin and vitamin E in the primary prevention of CVD and cancer.10 A total of 39 876 female US health professionals aged ≥45 years, postmenopausal or not intending to become pregnant and free from similar diseases as subjects in the PHS, were enrolled in 1992.

Data Collection

Men provided self-reports of baseline coronary risk factors, including age, smoking habit, alcohol, vigorous exercise, hypertension, and diabetes mellitus. Body mass index (BMI; in kg/m²) was calculated from height and weight. Women provided baseline information on the above variables plus postmenopausal status and postmenopausal hormone use.

On the PHS 12-month follow-up questionnaire, men responding yes to either “Has your mother ever had a documented MI?” or “Has your father ever had a documented MI?” provided the age of the parent at that MI. At baseline in the WHS, women were asked “Did any of these relatives ever have an MI,” including their mother or
father, plus the age category (<40 years, 40 to 49, 50 to 59, ≥60, or unknown) of that MI. Parental history of MI was classified as none, maternal only, paternal only, or both. In the PHS, age at MI was categorized as none, <50, 50 to 59, 60 to 69, 70 to 79, and ≥80 years; in the WHS, age was classified as none, <50, 50 to 59, and ≥60 years.

Among the 22,071 randomized men in PHS, subjects were excluded if they had missing data on parental history of MI or had prerandomization angina, CABG, or PTCA. These exclusions resulted in a study population of 20,515 men. Similar exclusions in the WHS reduced the study population from 39,876 to 37,985 women.

### Outcome Ascertainment

Follow-up in PHS consisted of annual questionnaires on which participants reported CVD events (MI, CABG, PTCA, stroke, or cardiovascular death) since the last questionnaire. Medical records were obtained and reviewed by an independent committee of physicians for reports of MI or stroke. MI was confirmed with World Health Organization criteria. Stroke was defined as a typical neurological deficit, sudden or rapid in onset, lasting >24 hours. CVD death was documented by convincing evidence of a cardiovascular mechanism from death certificates and medical records. All analyses are based on the first confirmed CVD event. After a median follow-up of 13.0 years (maximum follow-up, 14.4 years), morbidity and mortality follow-up rates were 99.2% and 99.99% complete.9

Follow-up in WHS was accomplished by similar methods and annual follow-up questionnaires. Total CVD was defined in WHS in a manner similar to that in the PHS but with CABG and PTCA also confirmed by hospital records. After a median follow-up of 6.0 years (maximum follow-up, 6.9 years), morbidity and mortality follow-up rates were 98.9% and 99.9% complete.

### Data Analyses

Separate analyses were done for men and women. Participants were first examined by categories of parental history with ANCOVA to compare mean values or χ² tests to compare proportions of baseline coronary risk factors. Cox proportional hazards models estimated the relative risk (RR) and 95% CI of CVD, MI, and stroke. Three separate sets of models were fitted for parental history of MI, age of maternal MI, and age of paternal MI. We first examined crude models, then added age, and then further adjusted for BMI, smoking status, exercise, and alcohol intake. Additional covariates in models for men included randomized aspirin and beta-carotene treatment; for women, randomized aspirin and vitamin E treatment, postmenopausal status, and postmenopausal hormone use were included. In secondary analyses, we examined whether variables potentially on the causal pathway (hypertension, blood pressure, and diabetes) altered the findings. The parameter estimates of maternal versus paternal history of MI were compared by the inclusion of terms for maternal age at MI (mean centered), maternal history, paternal age at MI (mean centered), and paternal history in a multivariate model. Likelihood ratio tests compared models with maternal, paternal, and both maternal and paternal history of MI.

### Results

The proportions of men with no parental history of MI, only a maternal history, only a paternal history, or a history in both parents were 65.5%, 5.6%, 25.3%, and 3.5%, respectively; for women, the respective proportions were 65.9%, 7.9%, 21.8%, and 4.4%. Table I compares baseline characteristics of men and women according to parental history of MI. Statistically significant differences in age and history of hypertension by category of parental history of MI were found for both men and women, whereas significant differences in diabetes, smoking, exercise, and alcohol were found for either men or women.

There were 2654 CVD events (including 653 MI cases and 613 stroke cases) in men and 563 CVD events (including 159 MI cases and 195 stroke cases) in women during follow-up. We examined the effect of parental history on the risk of total CVD, MI, and stroke (Table 2). The addition of hypertension, diabetes, and blood pressure resulted in similar RRs (data not shown). The higher magnitude of RRs for maternal versus paternal history of MI was significantly different in men (P = 0.01) but not women (P = 0.13). Considering CVD subtypes, maternal history of MI was strongly associated with risk of MI (both P < 0.05) but not stroke (both P > 0.05) in men and women.

We next examined the effect of maternal age at MI (Table 3). A total of 9.6% of women reported a maternal history with a maternal age of <50 years compared with only 2.2% of men. In men, even a maternal age at MI of 70 to 79 years was associated with a significant 67% increased risk of CVD (test for negative linear trend in maternal age, P = 0.02). When stratified by paternal history of MI, men with no paternal history had a similar pattern to the overall RRs except that the significant increased risk of CVD extended through an age at maternal MI of ≥80 years. Women with a maternal age at MI ≥60 years also had a significant multivariate RR of 1.52, which suggests that history of maternal MI may be important regardless of maternal age at MI (test for negative linear trend in maternal age, P = 0.16). In a model stratified by paternal history of MI, the association between maternal age at MI and risk of CVD closely approximated the overall results among women with no paternal history.

We next considered the effect of paternal age at MI on CVD risk (Table 4). A greater proportion of women with a paternal history of MI reported a younger (<50 years) paternal age at MI than did men (16.4% for women, 9.6% for men). Compared with men with no paternal history of MI, younger paternal ages at MI conferred greater magnitudes of CVD risk that decreased as paternal age increased (test for negative linear trend in paternal age, P < 0.001). However, a paternal age at MI of 70 to 79 years was still associated with a small, significantly increased risk of CVD. Women with a paternal age at MI ≥60 years had no increased risk of CVD (test for negative linear trend in paternal age, P = 0.04). In a model stratified by maternal history of MI, the association between paternal age at MI and risk of CVD weakened among women with no maternal history. Still, women with both a paternal age at MI of <60 years and maternal age at MI of ≥60 years had an RR of CVD of 3.68 (2.29 to 5.93; data not shown).

Other analytic issues were considered. First, multivariate models simultaneously included maternal and paternal age at MI and maternal and paternal history and found no difference between maternal and paternal history of MI and CVD in men (P = 0.09) or women (P = 0.89). The negative slopes for maternal and paternal age were marginally different in men (P = 0.048) but similar in women (P = 0.85). A model with both maternal and paternal history of MI added information beyond maternal history alone (men, P < 0.05; women, P = 0.06) and paternal history alone (men and women, P < 0.05). We addressed potential survival bias by stratifying results by age dichotomized at 60 years. The RRs associated with maternal or paternal history of MI increased in magnitude among all subjects aged <60 years, with the exception...
of no differences for maternal history of MI when younger versus older men were compared (data not shown).

Discussion
These data confirm previous findings for an independent effect of parental history of MI on the risk of CVD. However, a maternal history of MI may be more strongly associated with risk of CVD than a paternal history of MI, primarily owing to its association with MI. Our study reinforces the notion that a premature (younger than 60 years of age) history of paternal MI confers a greater risk of CVD than does MI at older ages. However, maternal age at MI continued to confer a significantly increased risk of CVD for maternal ages as great as 70 to 79 years for men and ≥60 years for women.
These differences in risk for paternal versus maternal age at MI may simply reflect the inherent differences in incidence rates of MI for men and women.

A positive family history of MI is usually interpreted as early family history. The National Cholesterol Education Program defines a positive history as having a close blood relative with an MI younger than 55 years (father or brother) or younger than 65 years (mother or sister). Epidemiological studies embrace numerous similar definitions, commonly assuming that a positive parental history of MI occurs before age 60 years. However, on the basis of our data, a parental history of MI beyond age 60 still strongly predicts risk of CVD. This finding may be more important for maternal history of MI, because few women younger than 60 years of age have MIs. Thus, the more meaningful comparison may be to compare RRs for maternal age at MI versus paternal age at MI that is a decade younger. However, among men, we found that the decrease in magnitude of RRs across ages of parental MI was greater for paternal versus maternal history of MI. Furthermore, a greater magnitude of risk for MI persisted across a wider range of maternal ages. Therefore, any maternal history of MI, regardless of age at the event, may provide clinically relevant information in the assessment of CVD risk.

Parental history of MI reflects the genetic, biochemical, and behavioral components whereby an individual may be predisposed to be at higher risk of CVD. The present study is consistent with others that support an independent effect of parental history of MI with CVD. Family history of MI affects lipids, inflammatory markers, and hemostatic markers. Higher RRs for maternal versus paternal history of MI may reflect phenotypic evidence that birth weight affects subsequent hypertension, diabetes, and insulin resistance syndrome. Alternatively, mothers may have greater influences on their children’s dietary and behavioral patterns retained later in life. No study has incorporated the entire array of genetic, biochemical, and behavioral risk factors to examine the extent to which the independent effects on CVD would be attenuated.

These findings must be considered in the context of some potential limitations. First, questions on the age of parental MI in the WHS had an upper category of $60$ years. It remains unclear whether the strong magnitude of effect for older ages of maternal MI in men extends to women. History of MI in other first-degree relatives (eg, siblings) or family history of other cardiovascular outcomes was not assessed. Additional details on family history of MI may further improve the definition of a positive family history and efforts to target high-risk individuals for CVD risk.

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The magnitude of the RRs of CVD associated with parental history of MI tended to be greater for younger versus older men, which suggests that younger individuals are more likely to manifest the deleterious consequences of a parental history of MI. Individuals aged in their 40s may have parents with impending MIs after the age of 70. Some misclassification is likely, because younger subjects free of parental history of MI may later develop a positive history. Premature death also prevents MI from becoming manifested. Because we neither updated information on parental history of MI nor ascertained parental age or mortality status, we likely underestimated our RRs. Such competing risks would nominally affect the RRs for earlier parental ages of MI, because all subjects would have parents, if alive, who contributed data to those categories.

**TABLE 3. Effect of Age of Maternal MI and the RR (95% CI) of CVD, as Well as Its Joint Association With Paternal History of MI**

<table>
<thead>
<tr>
<th>Age of Maternal MI</th>
<th>None</th>
<th>&lt;50 y</th>
<th>50–59 y</th>
<th>60–69 y</th>
<th>70–79 y</th>
<th>≥80 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted RR</td>
<td>1.00 (ref)</td>
<td>1.05 (0.40–2.81)</td>
<td>1.94 (1.42–2.65)</td>
<td>1.89 (1.56–2.29)</td>
<td>1.69 (1.42–2.03)</td>
<td>1.18 (0.92–1.51)</td>
</tr>
<tr>
<td>Multivariate-adjusted RR†</td>
<td>1.00 (ref)</td>
<td>1.00 (0.38–2.68)</td>
<td>1.88 (1.37–2.58)</td>
<td>1.88 (1.55–2.29)</td>
<td>1.67 (1.39–2.00)</td>
<td>1.17 (0.91–1.51)</td>
</tr>
<tr>
<td>Joint association with paternal MI†</td>
<td>None</td>
<td>1.00 (ref)</td>
<td>0.99 (0.25–3.97)</td>
<td>2.01 (1.35–2.99)</td>
<td>1.77 (1.37–2.29)</td>
<td>1.66 (1.31–2.10)</td>
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<tr>
<td></td>
<td>&lt;60 y</td>
<td>1.82 (1.59–2.09)</td>
<td>...</td>
<td>2.79 (1.25–6.22)</td>
<td>3.39 (2.13–5.40)</td>
<td>1.94 (1.17–3.23)</td>
</tr>
<tr>
<td></td>
<td>≥60 y</td>
<td>1.23 (1.10–1.37)</td>
<td>1.84 (0.46–7.38)</td>
<td>1.89 (0.94–3.79)</td>
<td>2.36 (1.61–3.46)</td>
<td>2.29 (1.64–3.19)</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00 (ref)</td>
<td>2.59 (1.52–4.41)</td>
<td>1.50 (0.93–2.44)</td>
<td>1.55 (1.21–1.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted RR†</td>
<td>1.00 (ref)</td>
<td>2.57 (1.51–4.37)</td>
<td>1.33 (0.80–2.23)</td>
<td>1.52 (1.18–1.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint association with paternal MI†</td>
<td>None</td>
<td>1.00 (ref)</td>
<td>2.70 (1.44–5.07)</td>
<td>1.26 (0.65–2.45)</td>
<td>1.32 (0.94–1.85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 y</td>
<td>1.18 (0.86–1.60)</td>
<td>5.08 (1.63–15.9)</td>
<td>1.67 (0.54–5.22)</td>
<td>3.68 (2.29–5.93)</td>
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</tr>
<tr>
<td></td>
<td>≥60 y</td>
<td>1.15 (0.88–1.50)</td>
<td>1.04 (0.15–7.42)</td>
<td>1.56 (0.50–4.86)</td>
<td>1.29 (0.76–2.21)</td>
<td></td>
</tr>
</tbody>
</table>

ref indicates referent.

*Excluding 836 men (132 CVD cases) and 453 women (14 CVD cases) having maternal or paternal history of MI but missing data on parental age.
†Adjusted for age, BMI, smoking status, exercise, and alcohol intake. Additional covariates for men included aspirin and beta-carotene treatment; for women, aspirin and vitamin E treatment, postmenopausal status, and postmenopausal hormone use.

**TABLE 4. Effect of Age of Paternal MI and the RR (95% CI) of CVD, as Well as Its Joint Association With Maternal History of MI**

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<th>70–79 y</th>
<th>≥80 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted RR</td>
<td>1.00 (ref)</td>
<td>2.22 (1.80–2.75)</td>
<td>1.66 (1.43–1.93)</td>
<td>1.39 (1.22–1.59)</td>
<td>1.19 (1.02–1.38)</td>
<td>0.94 (0.74–1.20)</td>
</tr>
<tr>
<td>Multivariate-adjusted RR†</td>
<td>1.00 (ref)</td>
<td>2.19 (1.77–2.72)</td>
<td>1.64 (1.42–1.91)</td>
<td>1.42 (1.24–1.62)</td>
<td>1.16 (1.00–1.36)</td>
<td>0.92 (0.72–1.18)</td>
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<tr>
<td>Joint association with maternal MI†</td>
<td>None</td>
<td>1.00 (ref)</td>
<td>2.17 (1.71–2.74)</td>
<td>1.71 (1.45–2.01)</td>
<td>1.43 (1.24–1.65)</td>
<td>1.13 (0.96–1.34)</td>
</tr>
<tr>
<td></td>
<td>&lt;60 y</td>
<td>1.87 (1.28–2.74)</td>
<td>6.86 (2.84–16.5)</td>
<td>0.52 (0.07–3.67)</td>
<td>2.73 (1.30–5.74)</td>
<td>0.92 (0.23–3.69)</td>
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<tr>
<td></td>
<td>≥60 y</td>
<td>1.65 (1.41–1.94)</td>
<td>2.80 (1.55–5.07)</td>
<td>2.19 (1.49–3.20)</td>
<td>1.83 (1.30–2.57)</td>
<td>1.96 (1.39–2.77)</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00 (ref)</td>
<td>1.76 (1.22–2.55)</td>
<td>1.30 (0.94–1.80)</td>
<td>1.07 (0.84–1.36)</td>
<td></td>
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</tr>
<tr>
<td>Multivariate-adjusted RR†</td>
<td>1.00 (ref)</td>
<td>1.63 (1.12–2.39)</td>
<td>1.33 (0.96–1.84)</td>
<td>1.13 (0.89–1.43)</td>
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</tr>
<tr>
<td>Joint association with paternal MI†</td>
<td>None</td>
<td>1.00 (ref)</td>
<td>1.50 (0.96–2.32)</td>
<td>0.98 (0.65–1.49)</td>
<td>1.15 (0.88–1.50)</td>
<td></td>
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<tr>
<td></td>
<td>&lt;60 y</td>
<td>1.76 (1.10–2.79)</td>
<td>2.66 (0.66–10.7)</td>
<td>2.45 (0.91–6.58)</td>
<td>1.39 (0.52–3.72)</td>
<td></td>
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<tr>
<td></td>
<td>≥60 y</td>
<td>1.32 (0.94–1.85)</td>
<td>3.16 (1.30–7.66)</td>
<td>3.93 (2.26–6.85)</td>
<td>1.29 (0.76–2.21)</td>
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†Adjusted for age, BMI, smoking status, exercise, and alcohol intake. Additional covariates for men included aspirin and beta-carotene treatment; for women, aspirin and vitamin E treatment, postmenopausal status, and postmenopausal hormone use.
The identification of individuals with a parental history of MI provides important information for the clinician by which to target primary prevention efforts. A premature paternal history of MI was an important, independent predictor of CVD in both men and women. In contrast, maternal history of MI follows a different age distribution because CVD predominantly occurs in older, postmenopausal women. In fact, maternal history of MI appears to predict CVD at least as strongly as paternal history, and at older ages of maternal MI. Therefore, any maternal history of MI may provide valuable clinical information, perhaps challenging the assumption that only an early maternal history of MI is important and warranting other studies.

Acknowledgments
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References
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