Should Your Family History of Coronary Heart Disease Scare You?

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OUTLINE

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ABSTRACT

Traditional risk factors explain most of the risk associated with coronary heart disease, and after adjustment for risk factors family history was believed to contribute very little to population-attributable risk of coronary heart disease. However, the INTERHEART study demonstrated an independent association of family history of coronary heart disease with acute myocardial infarction. To assess this relationship more comprehensively in multiple datasets in different populations, we carried out a detailed review of the available evidence. Case-control studies involving 17,202 cases and 30,088 controls yielded a pooled unadjusted odds ratio (random-effects model, overall \(I^2 = 64.6\%\), \(P = 0.000\)) of 2.03 (95% confidence interval: 1.79–2.30), whereas cohort studies that included 313,837 individuals yielded an unadjusted relative risk for future coronary heart disease (random-effects model, overall \(I^2 = 88.7\%\), \(P = 0.000\)) of 1.60 (95% confidence interval: 1.44–1.77). Although the presence of family history of coronary heart disease indicates a cumulative exposure of shared genes and environment, the risk estimates for family history did not attenuate significantly after adjustment for conventional coronary heart disease risk factors in several studies. It is probably an oversimplification to dichotomize the family history variable into a simple “yes” or “no” risk factor, as the significance of family history is influenced by several variables, such as age, sex, number of relatives, and age at onset of disease in the relatives. Moreover, a quantitative risk-assessment model for the family history variable, such as the “family risk score,” has a positive linear relationship with the risk of coronary heart disease.
relationship with coronary heart disease. More studies are warranted to assess the benefits and risks of intensive interventions, both targeted individually and at the family level, among individuals with a valid family history and borderline elevated risk factors. 

Key Words: coronary heart disease, family history, risk factors.

Although cardiovascular diseases (CVD) accounted for <10% of all deaths worldwide at the beginning of the 20th century, it was responsible for nearly one-half of all deaths in the developed world and more than a quarter in the developing world during the first decade of the 21st century. Of the 16.7 million CVD deaths in 2002, 7.2 million were due to coronary heart disease (CHD). Although CHD is decreasing in many industrialized countries, it is increasing in developing and transitional countries, partly as a result of increasing longevity, urbanization, and lifestyle changes.

Traditional risk factors such as elevated blood pressure, adverse lipid profile, smoking, and diabetes explain most of the CHD mortality and morbidity burden and have been used in risk-prediction models. However, a higher concordance for CHD trait and CHD risk factors among monozygotic twins, as demonstrated in the studies from Denmark, Sweden, and Norway, highlights the potential genetic contributions to CHD. Furthermore, the importance of family history in premature CHD is well studied, and familial aggregation (as defined in Table 1) has been frequently cited as evidence for the role of genetic factors in the development of CHD.

Although family history is an accepted risk factor for CHD and is independent of common CHD risk factors, it has not been used in several of the available risk-prediction tools. Accurate assessment of cardiovascular risk is essential for clinical decision-making, because the benefits, risks, and costs of alternative management strategies must be weighed to choose the best treatment options for individual patients. Deeper understanding of patterns of CHD risk in families may help to identify a subset of the population that is at high risk for CHD events. There is need for creation of concrete evidence to promote family-based risk assessment and prevention. In this regard, we systematically reviewed the available evidence on the magnitude and strength of association between family history and prevalent or incident CHD and assessed the clinical utility of incorporation of family-oriented preventive cardiology into standard clinical practice.

FAMILY HISTORY AS RISK FACTOR FOR CORONARY HEART DISEASE

Clinically relevant sources of evidence on association of family history and CHD include data from observational studies, such as case-control and cohort studies. We identified 24 case-control or cohort studies reporting the association of family history and CHD through MEDLINE, PubMed, and Embase search from 1966 to 2011 and by searching cross-references from published articles. Some of the common epidemiological terms used in this article and their definitions are provided in Table 1. Of the identified studies, 12 were case-control studies and the remaining 12 were cohort studies. We were able to extract data for pooled estimate of odds ratio (OR) or relative risk (RR) imposed by family history from all identified studies. Case-control studies involving 17,202 cases and 30,088 controls (Figure 1) yielded a pooled unadjusted OR (random-effects model, overall $I^2 = 64.6\%$, $P = 0.000$) of 2.03 (95% confidence interval [CI]: 1.79–2.30), whereas the cohort studies, which included 313,837 individuals (Figure 2) yielded an unadjusted RR for future CHD (random-effects model, overall $I^2 = 88.7\%$, $P = 0.000$) of 1.60 (95% confidence interval [CI]: 1.49–1.71).

### Table 1. Definitions.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Familial aggregation</td>
<td>Any trait more common in relatives of an affected individual than in the general population due to genetic factors or shared environment.</td>
</tr>
<tr>
<td>Family risk score</td>
<td>A quantitative risk score for CHD computed from observed and expected CHD events using family data.</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>A measure of effect size describing the strength of association. It is the ratio of the probability of an event occurring in one group to the probability of it occurring in another group.</td>
</tr>
<tr>
<td>P value</td>
<td>The probability that a variable would assume a value greater than or equal to the observed value strictly by chance.</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>A statistical method to compile the results of several studies that address a set of common or related hypothesis.</td>
</tr>
<tr>
<td>Random-effects model</td>
<td>In this model, we assume that the true effect could vary from study to study. The studies included in the analysis are assumed to be a random sample of the relevant distribution of effects, and the combined effect estimates the mean effect in the distribution.</td>
</tr>
<tr>
<td>Fixed-effect model</td>
<td>In this model, we assume that there is one true effect size that is shared by all individual studies.</td>
</tr>
</tbody>
</table>

**Abbreviation:** CHD, coronary heart disease.
CI: 1.44–1.77). However, we did not have access to the original data to do a meta-regression and dissect out the independent effect of family history over and above the traditional risk factors of CHD.

Case-control studies involving 17,202 cases and 30,088 controls yielded a pooled unadjusted odds ratio (random-effects model, overall $I^2 = 64.6\%, P = 0.000$) of 2.03 (95% confidence interval: 1.79–2.30), whereas the cohort studies, which included 313,837 individuals, yielded an unadjusted relative risk for future coronary heart disease (random-effects model, overall $I^2 = 88.7\%, P = 0.000$) of 1.60 (95% confidence interval: 1.44–1.77).

Natural-history studies of atherosclerosis have demonstrated higher serum concentrations of lipoproteins and homocysteine and higher blood pressure among children with a parental history of premature CHD in comparison with children without such a background.40–43 It is generally believed that familial aggregation of CHD can be explained by the aggregation of established risk factors of CHD. For example, in an analysis of National Health and Nutrition Examination Survey (NHANES) data, adults with parental history of CHD were more likely to have multiple CHD risk factors (OR: 2.9, 95% CI: 1.4–6.3).44 Although the presence of family history of CHD indicates a cumulative exposure of shared genes and environment, only a small fraction of the familial aggregation of CHD was accounted for by the familial aggregation of traditional risk factors.27,36,39 The risk estimates for family history of coronary heart disease did not attenuate significantly after adjusting for the traditional risk factors of coronary heart disease.

Evidence for familial aggregation of premature CHD also comes from a large study carried out in the state of Utah, in the United States.45 In this study involving 121,555 families, familial aggregation was documented using a quantitative family risk score (FRS). The FRS was calculated for each family by comparing the observed number of affected persons in the family with the number expected, based on applying total number of age-specific and sex-specific person-years of experience calculated from 167,447 adults aged ≥30 years. A score of ≥0.5, which was considered as an indicator of moderate to strong family history, was seen in only 14% of the Utah families that were surveyed for these studies. However, 72% of all early CHD (onset before age 55 years in men and 65 years in women) in Utah occurred in these families, highlighting the aggregation of CHD in a small group of high-risk families. Cipriani et al46 studied the familial aggregation of early-onset MI in a group of relatives of Italian patients who had survived a myocardial infarction (MI) that occurred at age ≤45 years; they concluded that early-onset MI aggregates in families and being a relative of an early-onset MI patient increases the risk of MI by 3-fold. The findings from these studies suggest that we should concern ourselves with family history of CHD.

FAMILY HISTORY AND SUBCLINICAL ATHEROSCLEROSIS

Recently, structural and functional alterations (assessed by brachial and carotid ultrasound) have been demonstrated among healthy offspring (mean DOI:10.1002/MSJ
age, 19 years; range, 6–30 years) of parents who had premature MI (at $\leq 60$ years) as compared with age-matched and sex-matched controls. $^{47,48}$ A positive family history of coronary artery disease is an important predictor of impaired endothelium-dependent coronary blood-flow regulation in humans. $^{49}$ The prevalence of atheromatous plaques was significantly higher in subjects with a positive family history of premature deaths from CHD. In the 21-year follow-up of the Cardiovascular Risk in Young Finns Study in 2265 white adults aged 24–39 years, individuals with a positive family history of CHD had significantly increased carotid intima-media thickness. $^{50}$ Furthermore, positive parental history of premature MI was independently associated with elevated intima-media thickness. $^{51}$ Nasir et al$^{52}$ studied the extent of coronary artery calcium (CAC) in 8549 asymptomatic individuals using electron-beam computed tomography. The elevated odds for CAC conferred by the presence of a positive family history in this study were not significantly different by strata of individual modifiable risk factors. Importantly, the magnitude of effect associated with a sibling history was consistently greater than that of parental history. Furthermore, familial propensity to subclinical atherosclerosis interacts with the presence of traditional risk factors and exacerbates the risks for those exposed to both. $^{53}$ Later, in 2007, Nasir et al studied the association of family history of premature CHD with CAC in 5347 asymptomatic individuals in the Multi-Ethnic Study of Atherosclerosis (MESA). $^{54}$ This study reported an independent association of family history of premature CHD with CAC, after accounting for other risk factors and Framingham risk score. Furthermore, in the Dallas Heart Study, a positive family history of premature MI was independently associated with CAC among women (OR: 2.0, 95% CI: 1.0–4.1). $^{55}$ In the overall cohort, family history of premature MI was an independent predictor of CAC (OR: 1.3, 95% CI: 1.1–1.7) and the relationship was more pronounced in younger age group. $^{56}$ Though statistical adjustments do not account for all the residual confounders, it is attractive to speculate that the increased risk among individuals with a positive family history operates independently of traditional risk factors. However, this excludes the continuous relationship of risk factors, and sophisticated analyses are needed to clearly eliminate the role of cardiovascular risk factors among families with high risk.

### Table: Family History and Risk of CHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
<th>W(Fixed)</th>
<th>W(Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamby 1980</td>
<td>239</td>
<td>421</td>
<td>1.95</td>
<td>[1.37; 2.70]</td>
<td>2.3%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Ten-kate 1982</td>
<td>29</td>
<td>145</td>
<td>1.48</td>
<td>[0.80; 2.73]</td>
<td>0.8%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Rosenberg (Men)</td>
<td>32</td>
<td>255</td>
<td>2.41</td>
<td>[1.50; 3.89]</td>
<td>1.3%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Friedlander 1985</td>
<td>35</td>
<td>123</td>
<td>1.70</td>
<td>[1.11; 2.59]</td>
<td>1.6%</td>
<td>5.0%</td>
</tr>
<tr>
<td>La Vecchia 1985</td>
<td>101</td>
<td>168</td>
<td>1.64</td>
<td>[1.24; 2.74]</td>
<td>1.8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Roncaglioni (Men)1992</td>
<td>273</td>
<td>610</td>
<td>2.26</td>
<td>[1.02; 2.81]</td>
<td>6.0%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Roncaglioni (Women) 1992</td>
<td>39</td>
<td>115</td>
<td>1.35</td>
<td>[0.79; 2.31]</td>
<td>1.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Ciruzi (Men) 1997</td>
<td>226</td>
<td>794</td>
<td>2.43</td>
<td>[1.89; 3.12]</td>
<td>4.5%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Ciruzi (Women) 1997</td>
<td>105</td>
<td>267</td>
<td>2.89</td>
<td>[1.96; 4.26]</td>
<td>1.9%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Pohjola-Sintonen 1998</td>
<td>92</td>
<td>121</td>
<td>4.06</td>
<td>[2.36; 6.99]</td>
<td>1.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Graille (France) 2000</td>
<td>13</td>
<td>133</td>
<td>1.94</td>
<td>[1.06; 3.47]</td>
<td>0.8%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Graille (Ireland) 2000</td>
<td>45</td>
<td>249</td>
<td>1.53</td>
<td>[1.09; 2.16]</td>
<td>2.4%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Leander (Men) 2001</td>
<td>269</td>
<td>661</td>
<td>2.02</td>
<td>[1.63; 2.49]</td>
<td>6.4%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Leander (Women) 2001</td>
<td>157</td>
<td>293</td>
<td>2.25</td>
<td>[1.66; 3.04]</td>
<td>3.1%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Bertuzzi (Men) 2003</td>
<td>147</td>
<td>378</td>
<td>2.57</td>
<td>[1.81; 3.65]</td>
<td>2.3%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Bertuzzi (Women) 2003</td>
<td>47</td>
<td>129</td>
<td>1.54</td>
<td>[0.95; 2.51]</td>
<td>1.2%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Chow 2011</td>
<td>2214</td>
<td>12149</td>
<td>1.62</td>
<td>[1.51; 1.73]</td>
<td>61.7%</td>
<td>11.2%</td>
</tr>
</tbody>
</table>

**Fig 1.** Family history and risk of CHD (case-control studies). **Abbreviations:** CHD, coronary heart disease; CI, confidence interval; OR, odds ratio.
OTHER ISSUES RELEVANT TO FAMILY HISTORY AND ITS ASSOCIATION WITH CORONARY HEART DISEASE

Family History and Risk of Coronary Heart Disease: Role of Age of Onset of Disease

The role of family history in enhancing the risk of CHD is particularly evident among younger individuals with CHD or among individuals whose parents develop CHD at a younger age. For example, the frequency of family history is markedly high among those who suffer MI or develop CHD at younger ages. A positive family history was independently associated with recurrent events (hazard ratio [HR]: 1.31, 95% CI: 1.01–1.72) in individuals with premature CVD (<51 years in men and <56 years in women). In a 7-year follow-up study of 5946 Scottish individuals, a parental history of CVD independently increases the risk of CVD events (a composite of fatal and nonfatal events incorporating acute MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, stroke, and heart failure), especially in individuals aged <65 years.

The age of onset of the CHD event in parents also appears to influence the risk of CHD. Family history of CHD before age 60 years in a first-degree relative has been demonstrated to be an independent risk factor for developing early MI, after controlling for traditional risk factors. The risk for CHD appears to be 2.5× higher for offspring of parents who suffered an MI or developed CHD before age 60.
involving 3981 families, the RR of CHD for a male sibling was 2.5 when the index sibling died before age 52 years.59

Are There Differences in Risk Associated with Paternal and Maternal History of Coronary Heart Disease?

There is a general belief that positive maternal history influences the risk of CHD among male offspring more than female offspring, and positive paternal history influences both offspring sexes equally. However, in the Physician's Health Study and the Women's Health Study, women with both parents affected are at similar risk (RR: 2.05, 95% CI: 1.60–2.91) as men with both parents affected (RR: 1.85, 95% CI: 1.56–2.19), in comparison with individuals with a negative family history.35 Furthermore, history of maternal MI at any age was associated with excess risk for both sons and daughters; in contrast, paternal MI at any age confers excess risk for sons, but only premature MI (at <50 years) confers excess risk for daughters. More importantly, a 5-fold increase in risk was observed in descendents with a joint association of both paternal and maternal history of premature MI. In INTERHEART, a case-control study of acute MI involving 15,152 cases and 14,820 controls matched for age and sex,27 the ORs for MI associated with paternal and maternal history of MI were 1.84 (95% CI: 1.69–2.0) and 1.72 (95% CI: 1.56–1.96), respectively, and they were not significantly different.

Family History and Risk of Coronary Heart Disease: Are There Any Differences Related to Race/Ethnicity?

The excess risk imposed by family history has been noted in all the major ethnic groups. In the subgroup analysis of the INTERHEART study,27 the ORs for MI in individuals with a positive family history of MI, after adjustment for all other risk factors, were similar among those of European, Chinese, South Asian and other Asian, and Middle Eastern descent. However, black Africans had a higher point estimate of OR for MI with a wide CI due to smaller sample size (OR: 10.95, 95% CI: 1.83–65.72). In an analysis of data from 3034 African American and 9048 white participants in the National Heart, Lung, and Blood Institute's Atherosclerosis Risk in Communities (ARIC) study, after adjusting for established risk factors and preclinical carotid atherosclerosis, the HR of CHD associated with a 1-SD increase of FRS was 1.52 in African American women and 1.46 in African American men; this was similar in magnitude to that of white participants.41,60 Therefore, it appears that putative ethnic differences in some studies may be related to design and smaller sample sizes, and there are no real ethnic differences in the risk of CHD imposed by family history.

Is It Oversimplifying to Dichotomize the Family History Variable?

In the INTERHEART study,27 there was a significant graded relationship between family history and MI even after adjustment for the 9 major risk factors (current smoking, diabetes, hypertension, abdominal obesity, psychosocial index, consumption of fruits and vegetables, physical activity, alcohol intake, and apolipoprotein B/apolipoprotein A ratio). For example, compared with those with no family history, persons with a family history of MI at an age ≥50 years in 1 parent had an OR for MI of 1.67 (95% CI: 1.55–1.81), persons with a family history of MI at an age ≤50 years in 1 parent had an OR for MI of 2.36 (95% CI: 1.89–2.95), persons for whom both parents had an MI at an age ≥50 years had an OR for MI of 2.90 (95% CI: 2.30–3.66), persons for whom both parents had an MI but 1 event occurred at an age <50 years had an OR for MI of 3.26 (95% CI: 1.72–6.18), and persons for whom both parents had a premature MI had an OR for MI of 6.56 (95% CI: 1.39–30.95).

Family risk score for CHD is a continuous variable and computed based on comparison of the number of observed or reported CHD events with the number expected. The HR per 1-SD increase in FRS was 1.4–1.7 in different population groups for incident CHD after adjusting for traditional CHD risk factors.60 In a modeling study using data from the Santé-Québec heart health survey, a comparison was made between different predictive models for CHD that incorporates family history as either a binary variable or ordinal family history indices in terms of predictive ability.61 The study concludes that use of more sophisticated definitions of the family history variable, compared with a simple binary approach, leads to significant improvements in the predictive ability of CHD risk models.

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Use of more sophisticated definitions of the family history variable, compared with a simple binary approach, leads to significant improvements in the predictive ability of coronary heart disease risk models.

Issues in Interpretation of Family History of Coronary Heart Disease and Variations in Definitions of Family History

Reported family history is influenced by several factors. Major limitations include noninclusion of fatal cases in case-control studies and recall bias. Colditz et al have suggested that the influence of family history may be stronger in cases of fatal MI than nonfatal MI. Therefore, the RR imposed by family history is more likely to be underestimated. Recall bias may result in both under-reporting and over-reporting of family history. However, validation studies indicate that recall bias in case-control studies is unlikely to exert any substantial bias on the estimated risk associated with a positive family history of CHD. A recent systematic review of all published qualitative research articles addressing the question of family history in chronic diseases suggests that reporting of a family history of chronic disease depends on an individual’s personal sense of vulnerability and interpretation of personal models of disease causation and inheritance. Other factors that may influence the reporting of family history include family size, the age of the person reporting the family history (younger individuals are less likely to recall adverse events of parents that occurred prior to their births or when they were very young), personal attributes and beliefs of individuals, and their socioeconomic status. Despite the above limitations, if family history is obtained in a standardized fashion, it should be useful in stratifying the general population into different risk groups.

Ethical Issues in Collecting Family History

In general, family members are considered third parties in most studies. Therefore, consent is not required because the information is obtained from someone else, and the risk from holding and using the information is minimal. The counter view is that an investigator’s interaction with a family member or obtaining private information about them automatically makes the family member a “human subject,” and therefore consent is required. In a case involving Virginia Commonwealth University, the father of a woman being recruited for a twin study sued the university for breach of his privacy arising out of the collection of family history information. The federal ruling in favor of the father’s position, along with further debates on this topic, urged the American Society of Human Genetics to issue a membership alert motivating investigators to pay close attention to the information being obtained on family members and whether it represents more than minimal risk. The latest recommendation for protecting the privacy of third-party information demands that investigators and institutional review boards be more conscious of how a proposed study design may affect the rights and welfare of third parties and ensure that they have minimized the potential risks for third parties.

Family History in Coronary Heart Disease Risk Prediction

The independent effect of positive family history of CHD death on CHD incidence in offspring was shown in the Framingham Heart Study cohort. For example, when participants were classified according to multivariate quintiles of risk score based on traditional risk factors, CHD incidence was greater in those with parental history of CHD in all but those in the highest quintile of risk. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines include family history of premature CHD as a dichotomous variable when counting major risk factors, it was omitted from estimating the short-term (10-year) CHD risk. Realizing that ignoring
family history definitely underestimates CHD risk in individuals with family history of CHD and leads to below-par treatment of many high-risk individuals, the recent update to the ATP III guidelines partially corrects this by lowering the low-density lipoprotein goal to 100 mg/dL for moderate-risk subjects (10%–20% 10-year risk) and a strong family history of premature CHD. Although some of the computerized CHD risk calculators take family history into account while estimating the CHD risk, none include quantitative family history (e.g., Framingham risk score) as input data. The latest cardiovascular risk scores, such as Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network (ASSIGN), the QRESEARCH Cardiovascular Risk Algorithm (QHRISK), and the Reynolds Risk Score in women and men, include positive family history as a predictive variable for future events.

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Despite a significantly excess risk contributed by family history, the population-attributable risk (PAR) is not large. In the INTERHEART study, the PAR for family history in the overall population was 10.1% (95% CI: 8.5–12.1). For younger individuals, the PAR was significantly higher, at 14.8% (95% CI: 11.7–18.5). It is also possible that the positive impact of family history could be in the interaction with intermediate factors to lead to the development of CHD events.

**Family History in Primary Prevention of Coronary Heart Disease**

**Implications for Individuals**

Family history of premature CHD is useful in clinical decision-making to identify high-risk patients and risk stratification among individuals with multiple CHD risk factors for intensive blood pressure, blood glucose, and cholesterol management. In general, primary-care physicians routinely triage, prioritize, and manage multiple medical issues with each patient during a clinic visit. A detailed family history of CHD can be used as an instrument to prioritize patient concerns and focus on disease prevention. For example, a patient with family history of premature CHD events ideally should be motivated to control or eliminate other modifiable CHD risk factors more intensively and beyond the conventional risk-factor thresholds.

A detailed family history of coronary heart disease can be used as an instrument to prioritize patient concerns and focus on disease prevention. For example, a patient with family history of premature coronary heart disease events ideally should be motivated to control or eliminate other modifiable coronary heart disease risk factors more intensively and beyond the conventional risk-factor thresholds.

**Implications for Populations**

Recognizing patterns of CHD risk in families can help identify individuals who may have the most to gain from preventive interventions. As pointed out earlier in the Utah study, nearly three-fourths of early CHD occurred in 14% of families and 86% of early stroke occurred in 11% of families. This clearly indicates that implementation of family-based strategies to assess CHD or stroke risk can potentially influence early disease detection. Encouraging primary prevention efforts in these families would potentially affect the health benefits at the population level. Furthermore, lifestyle changes are likely to be more effective when delivered to the whole family rather than to individuals, as they work within the framework of biological and cultural relationships to effect risk-factor reduction.
This has been demonstrated in a couple of studies looking at modification of cardiovascular risk factors in families.\(^7\) Similar studies need to be replicated in different settings using culturally sensitive and context-specific resources for management of CHD.

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**FUTURE RESEARCH RECOMMENDATIONS**

The available absolute CHD risk-prediction models consider only limited family history or do not consider family history at all in deriving the risk estimates, as these models were developed with data from epidemiological studies that did not ascertain family history comprehensively. Although these models work well in predicting risk for most people, they underestimate disease risk among people who have strong family history. Therefore, future epidemiologic studies should collect detailed family history data in a systematic manner so that absolute global CHD risk-prediction models can be developed that adequately address family history as a risk factor. Policy recommendations on widespread adoption of family-based risk assessment of CHD and its prevention are only possible if adequate evidence is generated from studies evaluating the feasibility, validity, reliability, and effectiveness of this approach.

The subclinical atherosclerosis testing actively underway in several ongoing large, community-based studies in multiple ethnic cohorts will provide a tremendous opportunity to evaluate whether the family history predicts risk over and above subclinical atherosclerosis measures, such as CAC and carotid intima-media thickness, in addition to established risk factors and nontraditional risk markers such as C-reactive protein.

**CONCLUSION**

A positive family history is undeniably an independent risk factor for CHD and is an important unit for investigating the roles of nature and nurture in promoting cardiovascular health and preventing CHD outcomes. Early-onset CHD aggregates in families, and being a relative of someone with early-onset CHD increases the risk of CHD by several-fold. Even though some of this clustering can be explained by concomitant aggregation of known risk factors, the risk estimates for family history did not attenuate significantly after adjustment for conventional CHD risk factors. It could be partly due to the early onset of disease in individuals with family history of CHD (CHD generally occurs in older ages) and the continuous relationship of risk factors and CHD (ie, younger individuals not reaching the conventional threshold for risk factors). Adjustment of conventional risk factors often ignores the continuous relationship of these risk factors with CHD and may not clearly eliminate the role of cardiovascular risk factors among families with high risk.

It is probably an oversimplification to dichotomize the family history variable into a simple “yes” or “no” risk factor, as the significance of family history is influenced by several variables, such as age, sex, number of relatives, and age at onset of disease in the relatives. Moreover, a quantitative risk assessment model for the family history variable, such as the “family risk score,” has a positive linear relationship with CHD. Coronary heart disease risk assessment and prediction are improved when a quantitative risk score is used or when a comprehensive family history takes into account the number of affected relatives and the age at onset of CHD.
The available evidence suggests there is a great opportunity to rigorously investigate the role of valid family history information in risk prediction and prevention. More studies are warranted to assess the benefits and risks of intensive interventions, both targeted individually and at the family level among individuals with a valid family history and borderline elevated risk factors. In order to ensure widespread adoption of family-based risk assessment in CHD and its prevention, evidence must be gathered from studies evaluating the feasibility, validity, reliability, and effectiveness of this approach.

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DISCLOSURES

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