Should Your Family History of Coronary Heart Disease Scare You?

Dorairaj Prabhakaran, MD, DM, FRCP[1,2] and Panniyammakal Jeemon, MPH, PhD Fellow[1,3,4]

[1]Centre for Chronic Disease Control, New Delhi, India
[2]Centre of Excellence in Cardio-metabolic Risk Reduction in South Asia, New Delhi, India
[3]Public Health Foundation of India, New Delhi, India
[4]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

OUTLINE

Address Correspondence to:

Dorairaj Prabhakaran
Centre for Chronic Disease Control
New Delhi, India
Email: dprabhakaran@ccdcindia.org

Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI:10.1002/msj.21348

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 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. ***Mt Sinai J Med 79:721–732, 2012.*** *© 2012 Mount Sinai School of Medicine*

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.[1] Of the 16.7 million CVD deaths in 2002, 7.2 million were due to coronary heart disease (CHD).[2] Although CHD is decreasing in many industrialized countries, it is increasing in developing and transitional countries,[3] 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.[4] 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.[5–9] 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.[10–14]

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.[15] 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[16–27] and the remaining 12 were cohort studies.[28–39] 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%

Table 1. *Definitions.*

Familial aggregation: Any trait more common in relatives of an affected individual than in the general population due to genetic factors or shared environment.
Family risk score: A quantitative risk score for CHD computed from observed and expected CHD events using family data.
Odds ratio: 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.
P value: The probability that a variable would assume a value greater than or equal to the observed value strictly by chance.
Meta-analysis: A statistical method to compile the results of several studies that address a set of common or related hypothesis.
Random-effects model in meta-analysis: 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.
Fixed-effect model in meta-analysis: In this model, we assume that there is one true effect size that is shared by all individual studies.

Abbreviation: CHD, coronary heart disease.

DOI:10.1002/MSJ

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.

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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 CHD did not attenuate significantly after adjusting for the traditional risk factors of CHD. However, this 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 may not have reached the conventional risk-factor threshold needed to satisfy the definitions of CHD risk factors).

Although the presence of family history of coronary heart disease indicates a cumulative exposure of shared genes and environment, only a small fraction of the familial aggregation of coronary heart disease was accounted for by the familial aggregation of traditional risk factors. 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 al*[46] 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

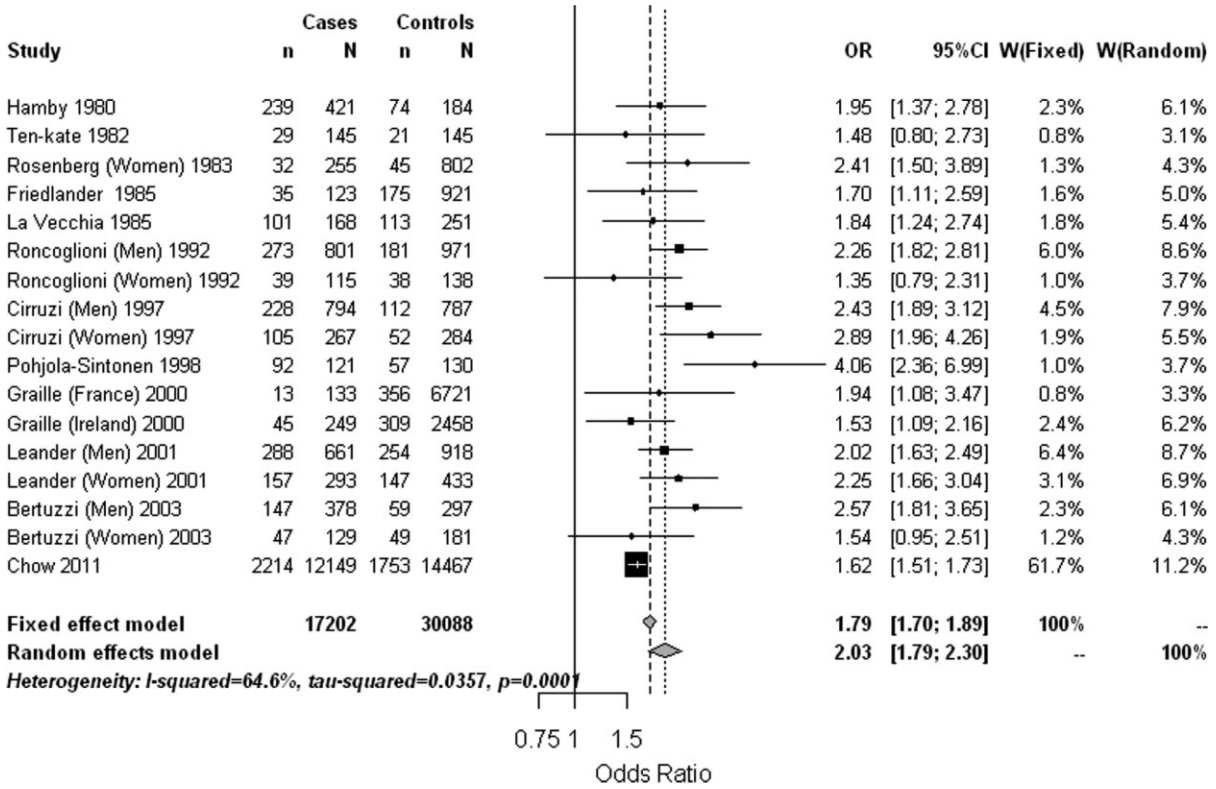

Fig 1. Family history and risk of CHD (case-control studies). **Abbreviations:** CHD, coronary heart disease; CI, confidence interval; OR, odds ratio.

age, 19 years; range, 6–30 years) of parents who had premature MI (at ≤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.

DOI:10.1002/MSJ

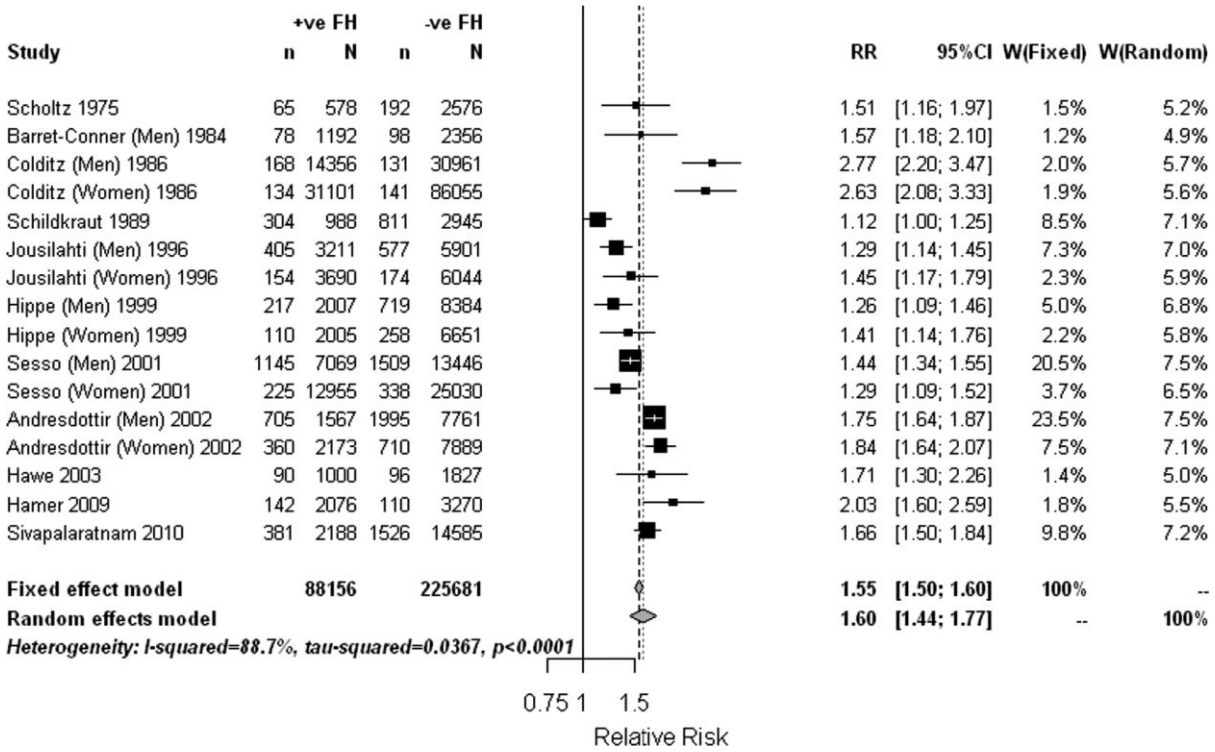

Fig 2. Family history and risk of CHD (cohort studies). **Abbreviations:** CHD, coronary heart disease; CI, confidence interval; FH, family history; RR, relative risk; W, weight.

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.[30,31] 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).[57] 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.[38]

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.[31] The risk for CHD appears to be 2.5× higher for offspring of parents who suffered an MI or developed CHD before age 60.[21,30,31]

The age of onset of the coronary heart disease event in parents also appears to influence the risk of coronary heart disease.

Family studies have also demonstrated an increased risk for CHD among siblings of individuals who developed premature CHD. In the family study of Rissanen *et al*[58] involving 309 men and their relatives, the RR of CHD among brothers of probands (index cases) who were diagnosed before age 46 years was 11.4, as compared with 1.3 when diagnosis in the proband was made after age 51 years. Similarly, in another family case-control study (a substudy of the Honolulu Heart Study)

DOI:10.1002/MSJ

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 descendants 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

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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.

DOI:10.1002/MSJ

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.[30] 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.[62,63] 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.[64] 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.[63] 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.[65] 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.[15] 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.[66] 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.[67] 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.[68]

Another important ethical angle in family history research is related to the obligation of investigators to notify people who are at high risk of disease. Is it important to notify individuals that they have a strong family history of CHD? Do we need to notify only the study subject, or all family members? These issues need to be addressed satisfactorily by incorporating the views of all stakeholders, and a general consensus should be reached based on the perceived risk-benefit scenarios.

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.[69] Despite this elevated risk, family history is not included in any version of the Framingham risk score to estimate CHD risk, owing to both the imprecision in its measurement in the original Framingham cohorts and the lack of statistical significance in meeting the model-building criteria. Although 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.[70] Realizing that ignoring

DOI:10.1002/MSJ

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 (eg, Framingham risk score) as input data.[71] The latest cardiovascular risk scores, such as Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network (ASSIGN),[72] the QRESEARCH Cardiovascular Risk Algorithm (QRISK),[73–75] and the Reynolds Risk Score in women[76] and men,[77] include positive family history as a predictive variable for future events.

The latest cardiovascular risk scores, such as Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network (ASSIGN), the QRESEARCH Cardiovascular Risk Algorithm (QRISK), and the Reynolds Risk Score in women and men, include positive family history as a predictive variable for future events.

Despite a significantly excess risk contributed by family history, the population-attributable risk (PAR) is not large. In the INTERHEART study,[27] 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

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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.[41] 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.

DOI:10.1002/MSJ

This has been demonstrated in a couple of studies looking at modification of cardiovascular risk factors in families.[78,79] Similar studies need to be replicated in different settings using culturally sensitive and context-specific resources for management of CHD.

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.

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.

Future epidemiologic studies should collect detailed family history data in a systematic manner so that absolute global coronary heart disease 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 coronary heart disease 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.

DOI:10.1002/MSJ

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.

ACKNOWLEDGMENTS

Dorairaj Prabhakaran is supported by research grants from National Heart, Lung, and Blood Institute (HHSN286200900026C) and National Institutes of Health (1D43HD065249). Panniyammakal Jeemon is supported by a Wellcome Trust Capacity Strengthening Strategic Award to the Public Health Foundation of India and a consortium of UK universities.

DISCLOSURES

Potential conflict of interest: Nothing to report.

REFERENCES

1. Lopez AD, Mathers CD, Ezzati M, et al. *Global Burden of Disease and Risk Factors*. New York, NY: World Bank, Oxford University Press; 2006.
2. Mackay J, Mensah G. *The Atlas of Heart Disease and Stroke*. Geneva: World Health Organization; 2004.
3. Mirzaei M, Truswell AS, Taylor R, et al. Coronary heart disease epidemics: not all the same. *Heart* 2009; 95: 740–746.
4. Dent TH. Predicting the risk of coronary heart disease I: the use of conventional risk markers. *Atherosclerosis* 2010; 213: 345–351.
5. Scheuner MT. Genetic predisposition to coronary artery disease. *Curr Opin Cardiol* 2001; 16: 251–260.
6. Berg K. Twin studies of coronary heart disease and its risk factors. *Acta Genet Med Gemellol (Roma)* 1984; 33: 349–361.
7. Retterstol L, Eikvar L, Berg K. A twin study of C-reactive protein compared to other risk factors for coronary heart disease. *Atherosclerosis* 2003; 169: 279–282.
8. Marenberg ME, Risch N, Berkman LF, et al. Genetic susceptibility to death from coronary heart disease in a study of twins. *N Engl J Med* 1994; 330: 1041–1046.
9. Allen G, Harvald B, Shields J. Measures of twin concordance. *Acta Genet Stat Med* 1967; 17: 475–481.
10. Scheuner MT. Genetic evaluation for coronary artery disease. *Genet Med* 2003; 5: 269–285.
11. Grant PJ. The genetics of atherothrombotic disorders: a clinician's view. *J Thromb Haemost* 2003; 1: 1381–1390.
12. Cooper RS. Gene-environment interactions and the etiology of common complex disease. *Ann Intern Med* 2003; 139: 437–440.
13. Eaton CB, Bostom AG, Yanek L, et al. Family history and premature coronary heart disease. *J Am Board Fam Pract* 1996; 9: 312–318.
14. De Bacquer D, De Backer G, Kornitzer M, et al. Parental history of premature coronary heart disease mortality and signs of ischemia on the resting electrocardiogram. *J Am Coll Cardiol* 1999; 33: 1491–1498.
15. Kardia SL, Modell SM, Peyser PA. Family-centered approaches to understanding and preventing coronary heart disease. *Am J Prev Med* 2003; 24: 143–151.
16. Hamby RI. Hereditary aspects of coronary artery disease. *Am Heart J* 1981; 101: 639–649.
17. Ten Kate LP, Boman H, Daiger SP, et al. Familial aggregation of coronary heart disease and its relation to known genetic risk factors. *Am J Cardiol* 1982; 50: 945–953.
18. Rosenberg L, Miller DR, Kaufman DW, et al. Myocardial infarction in women under 50 years of age. *JAMA* 1983; 250: 2801–2806.
19. Friedlander Y, Kark JD, Stein Y. Family history of myocardial infarction as an independent risk factor for coronary heart disease. *Br Heart J* 1985; 53: 382–387.
20. La Vecchia C, Franceschi S, Decarli A, et al. Risk factors for myocardial infarction in young women. *Am J Epidemiol* 1987; 125: 832–843.
21. Roncaglioni MC, Santoro L, D'Avanzo B, et al; GISSI-EFRIM Investigators. Role of family history in patients with myocardial infarction: an Italian case-control study. *Circulation* 1992; 85: 2065–2072.
22. Ciruzzi M, Schargrodsky H, Rozlosnik J, et al; Argentine FRICAS (Factores de Riesgo Coronario en America del Sur) Investigators. Frequency of family history of acute myocardial infarction in patients with acute myocardial infarction. *Am J Cardiol* 1997; 80: 122–1227.
23. Pohjola-Sintonen S, Rissanen A, Liskola P, et al. Family history as a risk factor of coronary heart disease in patients under 60 years of age. *Eur Heart J* 1998; 19: 235–239.
24. Graille V, Ferrières J, Evans A, et al. Associations between classical cardiovascular risk factors and coronary artery disease in two countries at contrasting risk for myocardial infarction: the PRIME study. *Int J Cardiol* 2000; 74: 191–198.
25. Leander K, Hallqvist J, Reuterwall C, et al. Family history of coronary heart disease, a strong risk factor for myocardial infarction interacting with other cardiovascular risk factors: results from the Stockholm Heart Epidemiology Program (SHEEP). *Epidemiology* 2001; 12: 215–221.
26. Bertuzzi M, Negri E, Tavani A, et al. Family history of ischemic heart disease and risk of acute myocardial infarction. *Prev Med* 2003; 37: 183–187.
27. Chow CK, Islam S, Bautista L, et al. Parental history and myocardial infarction risk across the world: the INTERHEART Study. *J Am Coll Cardiol* 2011; 57: 619–627.

DOI:10.1002/MSJ

28. Sholtz RI, Rosenman RH, Brand RJ. The relationship of reported parental history to the incidence of coronary heart disease in the Western Collaborative Group Study. *Am J Epidemiol* 1975; 102: 350–356.
29. Barrett-Connor E, Khaw K. Family history of heart attack as an independent predictor of death due to cardiovascular disease. *Circulation* 1984; 69: 1065–1069.
30. Colditz GA, Rimm EB, Giovannucci E, et al. A prospective study of parental history of myocardial infarction and coronary artery disease in men. *Am J Cardiol* 1991; 67: 933–938.
31. Colditz GA, Stampfer MJ, Willett WC, et al. A prospective study of parental history of myocardial infarction and coronary heart disease in women. *Am J Epidemiol* 1986; 123: 48–58.
32. Schildkraut JM, Myers RH, Cupples LA, et al. Coronary risk associated with age and sex of parental heart disease in the Framingham Study. *Am J Cardiol* 1989; 64: 555–559.
33. Jousilahti P, Puska P, Vartiainen E, et al. Parental history of premature coronary heart disease: an independent risk factor of myocardial infarction. *J Clin Epidemiol* 1996; 49: 497–503.
34. Hippe M, Vestbo J, Hein HO, et al. Familial predisposition and susceptibility to the effect of other risk factors for myocardial infarction. *J Epidemiol Community Health* 1999; 53: 269–276.
35. Sesso HD, Lee IM, Gaziano JM, et al. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation* 2001; 104: 393–398.
36. Andresdottir MB, Sigurdsson G, Sigvaldason H, et al; Reykjavik Cohort Study. Fifteen percent of myocardial infarctions and coronary revascularizations explained by family history unrelated to conventional risk factors. *Eur Heart J* 2002; 23: 1655–1663.
37. Hawe E, Talmud PJ, Miller GJ, et al; Second Northwick Park Heart Study. Family history is a coronary heart disease risk factor in the Second Northwick Park Heart Study. *Ann Hum Genet* 2003; 67: 97–106.
38. Hamer M, Chida Y, Stamatakis E. The role of conventional and novel mechanisms in explaining increased risk of cardiovascular events in offspring with positive parental history. *J Hypertens* 2009; 27: 1966–1971.
39. Sivapalaratnam S, Boekholdt SM, Trip MD, et al. Family history of premature coronary heart disease and risk prediction in the EPIC-Norfolk prospective population study. *Heart* 2010; 96: 1985–1989.
40. Freedman DS, Srinivasan SR, Shear CL, et al. The relation of apolipoproteins A-I and B in children to parental myocardial infarction. *N Engl J Med* 1986; 315: 721–726.
41. Srinivasan SR, Dahlen GH, Jarpa RA, et al. Racial (black-white) differences in serum lipoprotein (a) distribution and its relation to parental myocardial infarction in children: Bogalusa Heart Study. *Circulation* 1991; 84: 160–167.
42. Bao W, Srinivasan SR, Wattigney WA, et al. The relation of parental cardiovascular disease to risk factors in children and young adults: the Bogalusa Heart Study. *Circulation* 1995; 91: 365–371.
43. Greenlund KJ, Srinivasan SR, Xu JH, et al. Plasma homocysteine distribution and its association with parental history of coronary artery disease in black and white children: the Bogalusa Heart Study. *Circulation* 1999; 99: 2144–2149.
44. Brown DW, Giles WH, Burke W, et al. Familial aggregation of early-onset myocardial infarction. *Community Genet* 2002; 5: 232–238.
45. Williams RR, Hunt SC, Heiss G, et al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the Health Family Tree Study and the NHLBI Family Heart Study). *Am J Cardiol* 2001; 87: 129–135.
46. Cipriani V, Mannucci PM, Ardissino D, et al. Familial aggregation of early-onset myocardial infarction. *Eur J Intern Med* 2010; 21: 511–515.
47. Gaeta G, De Michele M, Cuomo S, et al. Arterial abnormalities in the offspring of patients with premature myocardial infarction. *N Engl J Med* 2000; 343: 840–846.
48. Zureik M, Touboul PJ, Bonithon-Kopp C, et al. Differential association of common carotid intima-media thickness and carotid atherosclerotic plaques with parental history of premature death from coronary heart disease: the EVA study. *Arterioscler Thromb Vasc Biol* 1999; 19: 366–371.
49. Schächinger V, Britten MB, Elsner M, et al. A positive family history of premature coronary artery disease is associated with impaired endothelium-dependent coronary blood flow regulation. *Circulation* 1999; 100: 1502–1508.
50. Juonala M, Viikari JS, Räsänen L, et al. Young adults with family history of coronary heart disease have increased arterial vulnerability to metabolic risk factors: the Cardiovascular Risk in Young Finns Study. *Arterioscler Thromb Vasc Biol* 2006; 26: 1376–1382.
51. Barra S, Gaeta G, Cuomo V, et al. Parental history of premature myocardial infarction is a stronger predictor of increased carotid intima-media thickness than parental history of hypertension. *Nutr Metab Cardiovasc Dis* 2011; 21: 391–397.
52. Nasir K, Michos ED, Rumberger JA, et al. Coronary artery calcification and family history of premature coronary heart disease: sibling history is more strongly associated than parental history. *Circulation* 2004; 110: 2150–2156.
53. Michos ED, Nasir K, Rumberger JA, et al. Relation of family history of premature coronary heart disease and metabolic risk factors to risk of coronary arterial calcium in asymptomatic subjects. *Am J Cardiol* 2005; 95: 655–657.
54. Nasir K, Budoff MJ, Wong ND, et al. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2007; 116: 619–626.
55. Patel MJ, de Lemos JA, Philips B, et al. Implications of family history of myocardial infarction in young women. *Am Heart J* 2007; 154: 454–460.
56. Philips B, de Lemos JA, Patel MJ, et al. Relation of family history of myocardial infarction and the presence of coronary arterial calcium in various age and risk factor groups. *Am J Cardiol* 2007; 99: 825–829.
57. Mulders TA, Meyer Z, van der Donk C, et al. Patients with premature cardiovascular disease and a positive family history for cardiovascular disease are prone to recurrent events. *Int J Cardiol* 2011; 153: 64–67.
58. Rissanen AM. Familial occurrence of coronary heart disease: effect of age at diagnosis. *Am J Cardiol* 1976; 44: 60–66.

DOI:10.1002/MSJ

59. Phillips RL, Lilienfeld AM, Diamond EL, et al. Frequency of coronary heart disease and cerebrovascular accidents in parents and sons of coronary heart disease index cases and controls. *Am J Epidemiol* 1974; 100: 87–100.
60. Li R, Bensen JT, Hutchinson RG. Family risk score of coronary heart disease (CHD) as a predictor of CHD: the Atherosclerosis Risk in Communities (ARIC) study and the NHLBI family heart study. *Genet Epidemiol* 2000; 18: 236–250.
61. Ciampi A, Courteau J, Niyonsenga T, et al. Family history and the risk of coronary heart disease: comparing predictive models. *Eur J Epidemiol* 2001; 17: 609–620.
62. Silberberg JS, Wlodarczyk J, Fryer J, et al. Correction for biases in a population-based study of family history and coronary heart disease: the Newcastle Family History Study I. *Am J Epidemiol* 1998; 147: 1123–1132.
63. Kee F, Tiret L, Robo JY, et al. Reliability of reported family history of myocardial infarction. *BMJ* 1993; 307: 1528–1530.
64. Walter FM, Emery J, Braithwaite D, et al. Lay understanding of familial risk of common chronic diseases: a systematic review and synthesis of qualitative research. *Ann Fam Med* 2004; 2: 583–594.
65. Cook-Deegan RM. Privacy, families, and human subject protections: some lessons from pedigree research. *J Contin Educ Health Prof* 2001; 21: 224–237.
66. Botkin J. Protecting the privacy of family members in survey and pedigree research. *JAMA* 2001; 285: 207–211.
67. Austin MA. Ethical issues in human genome epidemiology: a case study based on the Japanese American Family Study in Seattle, Washington. *Am J Epidemiol* 2002; 155: 585–592.
68. Lounsbury DW, Reynolds TC, Rapkin BD, et al. Protecting the privacy of third-party information: recommendations for social and behavioral health researchers. *Soc Sci Med* 2007; 64: 213–222.
69. Myers RH, Kiely DK, Cupples LA, et al. Parental history is an independent risk factor for coronary artery disease: the Framingham Study. *Am Heart J* 1990; 120: 963–969.
70. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486–2497.
71. Crouch MA, Gramling R. Family history of coronary heart disease: evidence-based applications. *Prim Care* 2005; 32: 995–1010.
72. Woodward M, Brindle P, Tunstall-Pedoe H; SIGN Group on Risk Estimation. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007; 93: 172–176.
73. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007; 335: 136.
74. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008; 336: 1475–1482.
75. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *BMJ* 2010; 341: c6624.
76. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score [published correction appears in *JAMA* 2007;297:1433]. *JAMA* 2007; 297: 611–619.
77. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation* 2008; 118: 2243–2251.
78. Pyke SD, Wood DA, Kinmonth AL, et al. Change in coronary risk and coronary risk factor levels in couples following lifestyle intervention: the British Family Heart Study. *Arch Fam Med* 1997; 6: 354–360.
79. Thompson SG, Pyke SD, Wood DA. Using a coronary risk score for screening and intervention in general practice: British Family Heart Study. *J Cardiovasc Risk* 1996; 3: 301–306.

DOI:10.1002/MSJ