Family History, Subclinical Atherosclerosis, and Coronary Heart Disease Risk

Barriers and Opportunities for the Use of Family History Information in Risk Prediction and Prevention

Christopher J. O’Donnell, MD, MPH

With completion of the human genome sequence, expectations are rising that a detailed catalogue will soon be available of all important common genetic susceptibility variants for human diseases, including coronary heart disease (CHD) and related atherosclerotic cardiovascular disease (CVD). In light of this seminal event in medical research, it is curious that the family history of CHD has not been accorded a more central role in risk prediction and disease prevention by clinicians and public health professionals. A positive family history of CHD is present in the majority of cases of premature-onset CHD. In cases of familial hypercholesterolemia and other rare forms of premature-onset CVD, CHD clearly segregates in a mendelian fashion. For most cases of premature-onset CHD, the mode of genetic transmission in families is less clear. Although the family history of CHD has been considered a putative risk factor for decades, it has not been incorporated along with other established risk factors such as hyperlipidemia, hypertension, and cigarette smoking in some widely applied multivariable risk algorithms, though other risk algorithms do incorporate family history information.

See p 2150

This cautious approach to widespread application of family history information is not due to insufficient evidence. Risks for CHD death are greatest in monozygotic (identical) compared with dizygotic (nonidentical) twins, particularly when there is a premature (<65 years) age of onset in the initially affected twin. In multiple prospective studies involving hundreds of thousands of men and women, a parental history of premature CHD is a significant risk factor for CVD even after multivariable adjustment. Relative risk estimates generally range from 1.2 to 2.0, as noted in the Physician’s Health Study and Women’s Health Study, although the estimated magnitude of risk associated with early-onset parental disease is substantially higher in some studies. However, what has remained unclear are the pathophysiological/genetic mechanisms of the familial risk, the extent to which familial risk is independent of other established risk factors (including hyperlipidemia, hypertension, and tobacco use, which have a familial component), the magnitude of excess risk after adjustment for other risk factors, and the extent to which risk conferred by a positive family history of CHD is modifiable.

In this context, Nasir et al in this issue of Circulation provide a fascinating and timely contribution to the family history literature. The authors examined the association of a reported family history of early-onset (before age 55 years) CHD with the presence and burden of coronary artery calcium (CAC) in electron beam computed tomography in 8549 asymptomatic men and women referred for testing. CAC is a surrogate measure of the presence and burden of coronary atherosclerosis that has consistently been associated with increased risks for CHD in selected cohorts. CAC was significantly more common in subjects with a sibling or parental history of CHD. After adjustment for other risk factors, the odds ratio for the presence of CAC was 2.5 (95% confidence interval 1.8 to 3.3) in men and 1.9 (95% confidence interval 1.3 to 3.1) in women with a positive family history in both a sibling and a parent. Interestingly, the magnitude of effect associated with a sibling history was consistently greater than that for a parental history. The elevated odds for CAC conferred by the presence of a family history were not significantly different by strata of individual modifiable risk factors, although the prevalence of CAC in subjects with 3 or more risk factors was higher in those with than in those without a family history.

Nasir et al add an important, large study of CAC to a growing literature demonstrating the association of familial CHD with subclinical atherosclerosis. Studies in population-based cohorts have reported that parental history of CHD is associated with increased carotid intima-media thickness, even after adjustment for established risk factors. Notably, both CAC score and carotid intima-media thickness scores are heritable, suggesting that approximately 40% of the interindividual variability in these measures is attributable to the effects of individual genes even after adjusting for other shared established risk factors. Collectively, the results of these studies provide strong support for the hypothesis that the sharing of unmeasured risk factors and/or genetic variants may predispose to susceptibility to clinically apparent CVD via the development and progression of subclinical athero-
sclerosis in the coronary and carotid arterial beds. These data certainly justify further research to identify the important genetic variation underlying this familial risk.

Aside from genetic research considerations, why hasn’t family history entered more front and center into the practice of risk prediction? There are several potentially important limitations of most studies to date relating family history to outcomes or to subclinical atherosclerosis. For one, the family history in most prior studies has been ascertained by an unvalidated report by the offspring or first-degree relative rather than by strict validation of familial events. Misclassification from a self-reported family history may lead to overestimation of risk due to recall bias, particularly in case-control studies in which disease status is known by the reporter, or underestimation if there is random misclassification. Secondly, if self-reported risk factors, which may themselves be inaccurate, are used in multivariable models, the multivariable risk models may underestimate the risk conferred by the risk factors and inflate the impact of the self-reported family history independent of the other risk factors.

Surprisingly, few validation studies exist to document the accuracy of proband report. In one study of the concordance between (unvalidated) reports of both proband and first-degree relatives, the concordance of reports was 70% to 80%, and there were differences in the degree of concordance with siblings and parents. Murabito et al compared offspring reports of parental outcomes with actual validated CVD outcomes, taking advantage of the long-term follow-up, office-based measurement of established risk factors, and validation of outcomes by a 3-physician end-point panel in both parents and offspring of the Framingham Heart Study to examine this misclassification. Offspring men and women accurately reported their own risk factor status, but they inaccurately reported the occurrence of a premature parental myocardial infarction (positive predictive value 28%) or stroke (positive predictive value 43%). In a companion outcomes study, the occurrence of a (validated) premature-onset CVD event in at least one parent was associated with a 2-fold CVD risk in men and a 1.7-fold risk in women even after adjustment for measured CVD risk factors. This study suggests that premature parental CVD is truly an important risk factor with a magnitude of increased risk that is in line with more conservative estimates from prior prospective studies. Interestingly, the excess risk appeared strongest in those at borderline to mildly elevated levels of risk as judged by blood pressure, total cholesterol, or multivariable risk.

The potential hazards of inaccurate reporting of family history have been well acknowledged by Nasir et al. The reliability of reporting of sibling CHD events may be greater than that for parental events because of the occurrence near the time of the CAC test, or referral for CAC testing may have been more likely to occur on the basis of the recent occurrence of a sibling CHD event. More accurate reporting of sibling events might lead to underestimation of the parental (relative to sibling) odds for CAC. Despite these potential limitations, an explanation, posed by Nasir et al, might be that shared childhood environment leads to increased odds for CAC from sibling rather than parental CHD. However, the provocative finding of a stronger association of sibling compared with parental CHD with CAC should be interpreted with caution and warrants detailed replication in other studies. Despite these considerations, the overall magnitude and direction of odds ratios in the study by Nasir et al are consistent with many of the prior estimates using validated parental information. Future studies of family history should strive to provide validation data that are as rigorous as possible for the accuracy of family history information in the cohort of interest. Research is needed to define the most accurate family history instruments, factors that predict the most accurate family history ascertainment, and methods to calibrate and correct for misclassification.

More generally, the large and growing body of evidence suggests there is a golden opportunity to more rigorously investigate the role of valid family history information in risk prediction and prevention. Subclinical atherosclerosis testing is actively underway in several ongoing, large, community-based studies in multiple ethnic cohorts and 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 newer risk markers such as C-reactive protein. Family history instruments such as the “family risk score” may be applicable to population screening to identify families at greatest risk who might be amenable to intervention. Studies of patients and populations are warranted to assess the benefits and risks of intensive interventions, such as intensive lipid-lowering therapy, in persons with a valid family history and borderline elevated risk factors, perhaps initially in persons with prevalent subclinical atherosclerosis.

If relatively low-cost genome-wide tests are soon available for genotyping or sequencing to identify disease-associated genetic variants, will the family history one day become obsolete? Several genome-wide linkage studies have been conducted in populations of families affected by myocardial infarction, yielding evidence for the existence of chromosomal segments harboring genetic susceptibility variants for myocardial infarction. Similarly, a parallel strategy of genome-wide searches using large numbers of single-nucleotide polymorphisms has become feasible, and preliminary screens have begun to identify candidate single-nucleotide polymorphisms for further study. An examination of these ongoing studies is outside the scope of this editorial, and evidence for or against conclusive replication of each of these studies is eagerly awaited. Before any such genetic results can be reliably applied to genetic risk assessment, extensive and time-consuming prospective replication studies will be required to assess whether these and other genetic variants are reproducibly associated with CHD and other CVDs and to test for important genetic modifier effects. To accomplish these ends, it has been suggested that an extremely large, diverse American cohort might be essential. Even when genome-wide genetic tests eventually become available, an accurate family history will likely still have an important role in effective clinical practice and public health decision-making.
Acknowledgments

I gratefully acknowledge Dr Thomas J. Wang for his thorough review and comment. I also acknowledge the collaboration and expertise of my many outstanding research colleagues at the NHLBI’s Framingham Heart Study.

References


Key Words: Editorials  genetics  risk factors  coronary disease  prevention
Family History, Subclinical Atherosclerosis, and Coronary Heart Disease Risk: Barriers and Opportunities for the Use of Family History Information in Risk Prediction and Prevention
Christopher J. O'Donnell

_Circulation_. 2004;110:2074-2076
doi: 10.1161/01.CIR.0000145539.77021.AC
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/15/2074

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/