Family History Assessment

Strategies for Prevention of Cardiovascular Disease

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Abstract: Family history assessment can be used to combine population-wide health promotion and risk-reduction efforts with a high-risk, targeted approach to help reduce the burden of cardiovascular disease (CVD). Family history is an independent predictor of CVD, and the upper portion of the family history distribution explains a larger fraction of CVD in the population than can be explained by extreme values of other risk factors (e.g., blood pressure and cholesterol). A positive family history of disease captures the underlying complexities of gene–gene and gene–environment interactions by identifying families with combinations of risk factors, both measured and unmeasured, that lead to disease expression. Family history is a useful tool for identifying most prevalent cases of CVD and for population-wide disease-prevention efforts. A positive family history also identifies the relatively small subset of families in the population at highest risk for CVD who may benefit most from targeted screening and intensive intervention. (Am J Prev Med 2003;24(2): 136–142) © 2003 American Journal of Preventive Medicine

Introduction

Two general approaches to primary prevention of cardiovascular disease (CVD) have been suggested: population-wide health promotion and targeted intervention in high-risk groups.[1–3] Public health advocates have sometimes championed one or the other approach, suggesting that they are in competition with each other. We propose that family history of disease is a unifying theme that bridges the two approaches and could overcome many of the objections to each of them. We also explain the value of population-based family history screening for identifying high-risk persons and families who are at high risk for CVD.

Population and High-Risk Screening Paradigms

Nationwide, population-based education and health promotion activities have been instrumental in helping reduce CVD incidence.[4,5] Programs that recommend healthy lifestyles and institute screening for risk factors (e.g., elevated lipids, glucose, and blood pressure) have helped identify persons at increased risk for CVD and have encouraged reductions in these risk factors. However, the substantial downward trends in CVD incidence and mortality during the 20th century appear to be leveling off for both coronary heart disease (CHD) and stroke.[6,7]

The slowing rate of decline in CVD incidence suggests that existing education and risk factor screening programs will need to be strengthened to achieve greater reductions in risk factors. Current programs have many shortcomings: Not all persons receive and understand public health messages; those who receive and understand these messages may not be successful in changing their behaviors; and recommended lifestyle changes may not be intense enough to reduce risk in persons who are at highest risk of CVD.

Targeted prevention approaches have consisted of identifying high-risk persons who can be offered more intensive intervention than is recommended for the general population. This approach raises several concerns: the cost of identifying high-risk persons may equal or exceed the cost of intervention; determining who is at high risk is difficult; and most CVD events occur in persons with risk factor levels below the extreme of the distribution. Therefore, although extreme values of specific risk factors (e.g., cholesterol) are associated with increased risk of CVD, the associated attributable risk is low because these values occur in only a small proportion of the population.[8]

The Human Genome Project has increased enthusiasm for the possibility of using specific genes to assess individual disease risk and define high-risk subgroups.[9] However, the identification of genes with a high attributable risk or even a consistently high relative risk for common diseases, including CVD, has not yet been very successful. Although many published reports have described associations of various genes with CVD, most

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Table 1. Relative risks (95% CI) of CHD[a] in family members associated with different definitions of positive family history versus no family history

Family history definition	Prevalence	Men		Women	
		20–39 yrs.	≥70 yrs.	20–39 yrs.	≥70 yrs.
1+ affected, any age	53%	2.9 (2.1–3.8)	1.3 (1.0–1.6)	1.4 (0.7–2.4)	1.1 (0.9–1.3)
1+ affected, early age[b]	32%	3.9 (2.8–5.3)	1.1 (0.8–1.5)	2.1 (1.0–3.8)	1.1 (0.8–1.5)
2+ affected, any age	24%	5.9 (2.4–12.1)	2.0 (0.9–3.7)	3.3 (0.4–12.1)	2.1 (1.1–3.6)
2+ affected, early age	11%	12.7 (4.7–27.7)	0.7 (0.1–3.6)	8.0 (1.0–29.0)	1.5 (0.3–4.4)
Family History Score[c] ≥1.0	14%	6.9 (2.8–14.2)	3.0 (0.8–7.8)	4.0 (0.5–14.4)	1.2 (0.3–3.2)

Note: Adapted from Hunt et al.[13]
[a]Relative risks of CHD after 13 years of follow-up from when family history was calculated in 1970.
[b]Onset at age <55 years (men and women).
[c]Family History Score (FHS) defined by comparing the number of CHD events (heart attack requiring hospitalization, coronary bypass surgery, or percutaneous angioplasty) in a family to the expected number of events based on the age and sex of family members and population incidence rates; FHS >1.0 requires having at least two affected persons at any age in the family.
CHD, coronary heart disease; CI, confidence interval.

still require further confirmation before clinical use is indicated. Even when more genes involved in CVD have been identified, the low penetrance of specific high-risk genotypes may make disease prediction difficult.[10] Furthermore, genes explain only a portion of the total variation in most risk factors and diseases,[11,12] suggesting that relying only on knowledge of disease pathophysiology gained through genetic advances may not provide a sufficient basis for prevention.

While research continues to pursue more specific genetic information that could be relevant to prevention of CVD and other common diseases, the use of family history to capture genetic information can help overcome the drawbacks of both population-based and high-risk approaches to disease prevention.

The Importance of Using Family History to Assess Risk of CVD

Family history has been used successfully to evaluate risk of CHD in the high school–based Health Family Tree Study in Utah (Table 1).[13] Family history of early-onset disease was much more predictive of early CHD in unaffected family members than was family history without respect to age. Older persons were at no more risk for CHD than the general population unless they had at least two family members who had been diagnosed with CHD (Table 1). A similar pattern of risks was observed in families with a positive family history of hypertension.[13] Because some diseases appear to share certain environmental risk factors and common pathophysiologic pathways, a family history of one of these diseases may be relevant to assessing risk of the others. For example, families with a history of CHD are also more likely to have a history of hypertension or diabetes.[14]

Throughout the United States, many community-based programs screen for chronic diseases or risk factors. Most of these programs target only one disease (e.g., CHD or diabetes) or one risk factor (e.g., cholesterol or glucose) at a time. However, because an estimated 45% of families have a positive family history of one or more common chronic diseases,[15] taking a family history can capture information about many diseases and risk factors simultaneously. To assess risk of CHD, information about smoking, alcohol consumption, exercise, weight, hypertension, and diabetes in multiple family members can be correlated with incidence of CHD and stroke in the family.

Family history of disease is important not only because it is an independent predictor of future disease incidence, but because it also defines the relatively small subset of families in the population that account for the most cases. Table 2 summarizes data from the Utah Health Family Tree Study, in which a quantitative family history score (FHS) was calculated for each family by comparing the number of CHD events (heart

Table 2. Family history of CHD and stroke in Health Family Tree Study[a]

Family History Score[b]	% families	% early disease	% all disease
CHD			
≥0.5	14	72	48
≥1.0	3.2	35	18
≥2.0	1.0	17	6
Stroke			
≥0.5	11	86	68
≥1.0	1.4	22	16
≥2.0	1.0	19	12

Note: Adapted from Williams et al.[16]
[a]Includes data from 122,155 families; 16,602 early CHD cases; 54,182 cases of CHD at any age; 4600 early stroke cases; and 22,425 cases of stroke at any age.
[b]Family history calculated using events in families at time of data collection (1983–1999). Family History Score (FHS) defined by comparing the number of CHD events (heart attack requiring hospitalization, coronary bypass surgery, or percutaneous angioplasty) in a family to the expected number of events based on the age and sex of family members and population incidence rates; FHS >1.0 requires having at least two affected persons at any age in the family.
CHD, coronary heart disease.

attack requiring hospitalization, coronary bypass surgery, or percutaneous angioplasty) and stroke events (requiring hospitalization, with symptoms persisting after hospitalization) that occurred in the family, with the expected number of events based on the age and gender of family members and population incidence rates.[16] Events occurring before age 55 were characterized as "early." Family history was considered positive if the FHS was ≥0.5, corresponding roughly to one event at any age in small- to medium-sized nuclear families or one early event in large nuclear families. An FHS of ≥1.0 could be assigned only if the family had at least two affected members. Further discussion of the FHS is provided in Hunt et al.[13]

Only 1% of Utah families had a strongly positive family history of CHD (FHS ≥2.0, corresponding roughly to ≥2 early CHD events), but they accounted for 17% of all early CHD events. Overall, 14% of Utah families had a positive family history of CHD (FHS ≥0.5); these families accounted for 72% of all early CHD events and 48% of CHD events at any age. The 11% of families with a positive family history of stroke (FHS ≥0.5) accounted for 86% of all early strokes.

These results demonstrate that early CVD is concentrated in families with a positive family history of CVD. Clearly, these families need rigorous intervention to prevent disease in additional family members. Because family history can be used to predict risk of future disease and to identify the subset of families that account for the majority of prevalent cases in the population, it is an excellent tool that combines population and high-risk approaches to disease prevention. New American Heart Association guidelines for primary prevention of CHD and stroke recommend regular updating of a person's family history of CHD.[17]

Several published studies have found that family history of CHD remains an independent predictor of CHD when controlling for other known risk factors.[16,18–28] Three large studies have estimated directly (without using statistical models) that as much as 75% of CHD occurs in individuals with any combination of elevated blood pressure, high cholesterol, and smoking (Figure 1), and the percentage of CHD increases further if diabetes and obesity are included.[29–31] Combining these results with the results of Table 2, in which half of all CHD can be explained by family history, suggests that there is clearly overlap in subgroups with a positive family history and subgroups with elevated blood pressure or high cholesterol or who smoke. Therefore, finding an independent effect for family history of CHD seems paradoxical if such a large percentage of CHD is due to known risk factors, especially because these risk factors also tend to cluster in families. One possible explanation—that interactions among risk factors confound their relationships in linear models—has not been substantiated by studies that included statistical interaction terms.[19,21,22,24,26,27]

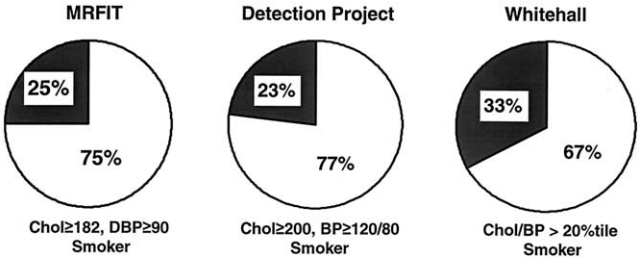

Figure 1. Percentage of coronary heart disease (CHD) explained by major risk factors from three different studies.[29–31] White areas are the percentage of persons with CHD with any combination of the three risk factors; black areas represent the percentage of persons with CHD who have none of the risk factors. Cutpoints for each of the risk factors are shown at the bottom of the pie chart for each study. BP, blood pressure; Chol, cholesterol; DBP, diastolic blood pressure; 20%tile, above the 20th percentile; MRFIT, Multiple Risk Factor Intervention Trial.

However, physiological interactions are probably much more complicated than can be modeled by simple linear and interaction terms. Family history may capture these additional effects of CHD risk factors (including unmeasured factors and interactions) that family members have in common, either because of inheritance or shared environment.

Perhaps an equally important explanation of family history as an independent predictor for CVD is the large degree of interfamily heterogeneity in the familial prevalence of other risk factors. If a particular risk factor is shared in only a subset of families, its effect could be underestimated by regression analysis of the entire study sample. However, incorporating family history into the analysis can overcome the problem of interfamily heterogeneity because it measures disease expression without regard to the underlying causes. Thus, family history provides a surrogate measure of physiologic processes leading to CHD without requiring complete understanding of their underlying complexity.

Family History Is Useful for Population and High-Risk Approaches

The cost-effectiveness of screening the population to identify persons with abnormal risk factors (e.g., cholesterol levels greater than 90th percentile) has been questioned because of the cost of screening and the limited effectiveness of focusing intervention only on a high-risk subset.[3] Most CHD events occur in persons with risk factor measurements in the middle of the distribution (e.g., total cholesterol between 200 and 240 mg/dl) rather than at the extremes. For example, in the Multiple Risk Factor Intervention Trial (MRFIT), 41% of all CHD events occurred in persons with cholesterol levels between 203 and 244 mg/dl.[29]

Although persons with very high cholesterol levels are at greatly increased risk of CHD, they constitute a small group and thus account for only a small proportion of CHD events in the population. This low attributable fraction favors a population-based intervention rather than one directed to the highest-risk group.[8] One study that contrasted population-based and high-risk approaches to CHD prevention estimated that lowering total cholesterol in the entire population by 10% and blood pressure by 5% would lower CHD mortality by 31%; a high-risk approach that lowered total cholesterol by 20% only in the top 10% of the cholesterol distribution (>325 mg/dl) and lowered diastolic blood pressure to 90 mmHg would reduce CHD mortality by an estimated 28%.[3] The more effective a population approach is in reducing cholesterol and blood pressure, the more it will out-perform the high-risk approach using individual risk factors.[3]

Family history evaluation can be used effectively to define a subpopulation in which CHD expression is clustered. While persons with extreme values of individual risk factors may or may not express disease because of protective levels of other factors, a positive family history identifies families who express the disease. These families include people with risk factor values in the middle of the distribution as well as those with extreme values. Family history is thus able to capture the effects of measured and unmeasured factors that interact to cause CHD.

Therefore, the high-risk subset defined by the extreme of the family history distribution accounts for more CVD events in the population than the subset defined by extreme values of individual risk factors and results in a higher attributable risk. Furthermore, because values of other risk factors (e.g., cholesterol and blood pressure) in persons with a positive family history of CVD are typically not extreme, less costly and intensive interventions may be adequate in these families to produce the changes in risk factor levels needed to reduce risk. Only a much smaller subset of families with a positive family history will have extreme levels of risk factors that require more intensive interventions.

Family History and Gene–Environment Interactions

Families at highest risk will generally require medical assistance because behavior changes recommended for the general population are usually inadequate to reduce their risk. For example, even the best diet only reduces cholesterol 20% to 25% in persons with familial hypercholesterolemia (FH).[32] Because this reduction is not enough to normalize cholesterol levels in persons with FH, they require prescribed medication in addition to diet modification for proper control. Identifying a strong family history of early-onset CHD, followed by cholesterol testing, may identify families who have FH and can be adequately treated. Current estimates from more than 30 countries suggest that 80% of patients with FH remain undiagnosed and that only 7% have controlled cholesterol levels.[33] The diagnosis of FH in one family member allows confirmation of FH in close and extended relatives using validated FH cholesterol criteria.[34] If persons with FH can be found and adequately treated, most will enjoy average life spans instead of dying prematurely. A recent analysis suggests that treating hypercholesterolemia could prevent 95% of 5-year CHD mortality in first-degree relatives aged <40 years of people with diagnosed FH; reducing cholesterol in first-degree relatives of any age could prevent 44% of all 5-year CHD mortality in men and 57% in women in families with FH.[35]

Other single-gene disorders (e.g., hypertension from glucocorticoid-remediable aldosteronism and Liddle syndrome) can also fit the FH paradigm. Dietary and medication responses may also be greater in persons with other genotypes less strongly associated with increased risk for CVD.[36–39] Results from three different randomized, controlled hypertension clinical trials have demonstrated the beneficial impact of intervention among persons at highest risk.[40–42] These studies demonstrated that persons with the angiotensinogen gene variant, which is associated with salt sensitivity and increased risk of hypertension, experience the greatest blood pressure reduction through dietary salt reduction[40]; weight loss[40]; salt reduction with potassium, magnesium, and calcium supplementation[41]; and high fruit/vegetable and low-fat diets.[42]

Even in the absence of a specific "high-risk" genotype, persons at increased risk of CVD because of their genetic makeup may realize the greatest benefit from intervention. In this setting, family history can be an effective surrogate for the underlying genes and their environmental interactions. For example, quitting smoking is projected to decrease CHD to a greater extent in men with a positive family history of CHD compared with men without a positive family history.[43] These results suggest that intervening even on mild-risk factor levels in families with positive family histories may have more preventive benefit than expected because both the main and interactive effects of these risk factors are removed.

All family members share the same positive family history as a risk factor, but they often share other risk factors as well. Interventions such as dietary modification or weight control may be more effective when delivered to the family than to the individual because of the built-in support mechanisms of the family. For example, guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure encourage involving family members in the treatment of hypertension.[44]

Cost-Effectiveness Considerations

Family history can be inexpensively collected from the entire population to educate families about risk factors and family history, promote healthy lifestyles, and identify the subset of persons at highest risk of CVD. The cost of identifying an unaffected relative in a high-risk family was $4.60 in a study that used optical scanning sheets to collect family history.[45] In the absence of actual data, we estimate the cost of an Internet-based, family-history collection program to range from $1 to $3 per family (approximately $5 per high-risk family) if administered through school systems. If such a program were made accessible to the general population, the cost would probably be substantially <$1, because the need for personnel to recruit and interact with schoolteachers would be eliminated. This cost would cover collecting and reporting family history information on every participating family in the population and identifying high-risk families for targeted intervention. Participating families would bear no direct costs for family history collection, and subsequent costs for actual risk factor evaluation would be limited to the high-risk family members. The collection and analysis of family history using the Internet will become even more effective as a greater number of people gain access to the Internet. School-based family history programs that provide such access can help overcome the access drawback of the Internet.

In contrast, traditional population screening programs for CVD risk factors are much more expensive. For example, in the MRFIT study, measuring smoking, blood pressure, and cholesterol risk factors cost an estimated $100 per person.[46]

Several studies have compared the costs of different screening and intervention programs. In North Karelia, Finland, the cost of community screening for blood pressure and cholesterol was an estimated $25.50 per person, whereas the cost of a community education program was only $3.75 per person.[47] The cost-effectiveness of a screening program also depends on the relative costs and benefits of alternative interventions for persons found to be at increased risk. For example, one analysis estimated that a population approach designed to reduce CHD deaths by 28% by lowering cholesterol levels would cost $20 per person per year; the same effect could be achieved by using cholesterol-lowering drugs to treat persons with cholesterol levels in the top 20% at an approximate cost of $400 per person per year.[48]

The cost per year-of-life saved by statin treatment has been estimated for both primary and secondary CHD.[49] The cost of primary intervention was analyzed further by comparing persons who had a single elevated risk factor (cholesterol) with persons who had multiple risk factors. Secondary prevention was the least expensive per year-of-life saved, and primary prevention for persons with only one risk factor was most expensive. However, the cost of primary prevention in persons with multiple risk factors was only slightly higher than that of secondary prevention. Because family history identifies families with multiple risk factors, which have contributed to increased prevalence of disease in the family, using a family history approach to direct treatment to high-risk families could be very cost-effective.

Potential Public Health Value of Family History Evaluation

Family history evaluation with subsequent feedback to participating family members has great potential for educating and motivating entire populations about their familial health risks and increasing awareness about the importance of preventive health practices. Many families are unaware of their family history and risk for CVD until they start contacting relatives and putting the data together to see the complete picture. Even if a family is found to be at average population risk, this information can be used to reinforce the importance of risk factor control for everyone. Internet links to more comprehensive population advice written for the public as part of a family history program would provide the potential for greater understanding of how to reduce risks. In addition, families who become aware of disease in their families, as opposed to risk factors, are likely to be more motivated to heed the population advice given. Further research in these areas is needed.

Using a school-based approach to family risk assessment provides an opportunity to teach young people to adopt lifelong healthy habits. Enhancing the family's awareness of their shared disease risk provides an opportunity to promote family-based changes in lifestyle, enhanced by family support mechanisms, family education, and family referral, which can translate into decreased long-term health risk and improved quality of life. Some studies have demonstrated behavior change in families that are made aware of their increased risk of certain diseases[50,51]; however, not all studies have found a positive effect.[52] High-risk families may require extra help to reduce their risk. Using family history to identify a subset of the population for more intensive intervention can make this additional intervention more feasible. By drawing the attention of all participating families to standard guidelines for risk reduction, a family history program does not supplant but rather enhances population-wide prevention efforts.

Family history effectively bridges clinical medicine with public health by focusing risk assessment and intervention at a level between the extremes of "one at a time" and "one size fits all."[53,54] Although physicians are trained to ask their patients about family history, few physicians use this information to guide prevention

recommendations for patients or their family members.[15,54] Combining family history information with clinical assessment could change the clinical threshold for instituting more intensive intervention or treatment. Asking patients to complete a family history questionnaire in advance and to bring it to their medical appointment offers several advantages: giving patients time to obtain information from family members, saving time during the visit, and prompting physicians to discuss family history with their patients. Making the questionnaire available to patients on a computer[55] or on the Internet could provide additional benefits by collecting family history more consistently and storing the information in a format that is easy to retrieve and update as family history changes over time.

Summary

Screening the general population for family history combines the benefits of population-wide education with more intensive screening directed only to a defined high-risk subset of the population. This approach is relatively inexpensive and efficient because most CVD events, especially those that occur at an early age, are concentrated in a relatively limited number of families. Assessing family history also serves to remind families with average population risk of the general health recommendations that they should follow to reduce their risk of CVD. High-risk families can be directed to health education and health promotion services at the community level (including school and family) and to more intensive counseling to reduce the risk of CVD in family members. Persons at high risk can be reassured that, in most cases, specific lifestyle changes and preventive therapies are available to help reduce their risk. Family history assessment provides a starting point for family-based intervention (e.g., improved diet or increased physical activity), which can be very effective if it draws on the inherent social support found in most families. New strategies to collect family history (e.g., on the Internet) may further reduce the costs and substantially increase the effectiveness of family history as a tool for preventive medicine and public health.

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