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Pediatrics 2007;120;S78-S86
DOI: 10.1542/peds.2007-1010G

SUPPLEMENT ARTICLE

Is Family History a Useful Tool for Detecting Children at Risk for Diabetes and Cardiovascular Diseases? A Public Health Perspective

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

Several studies indicate that the risk for type 2 diabetes or cardiovascular disease is detectable in childhood, although these disorders may not emerge until adulthood. In addition, type 2 diabetes and cardiovascular disease seem to share risk factors, including obesity and dyslipidemia, and might even share etiology, which has important implications for screening and prevention strategies for both diseases. Primary prevention, in particular, has gained importance because the results of major randomized, controlled trials strongly suggest that, at least in high-risk adult groups, type 2 diabetes can be prevented or delayed. Furthermore, some intervention studies indicate that the risk factors for diabetes and cardiovascular disease can be reduced in children. A simple way to detect risk for either diabetes or cardiovascular disease is to examine the family history. Numerous studies have shown that adults who have 1 or more first- or second-degree relatives affected with diabetes or cardiovascular disease are at high risk of having or developing these diseases. Currently, there are no overall screening strategies recommended for either diabetes or cardiovascular disease among children and adolescents. The evidence is strong, however, that youth with a positive family history already show signs of increased risk for these conditions. Family history can be part of the approach to screening for children at risk of diabetes and cardiovascular disease and should be part of prevention campaigns aimed at reducing the burden of these diseases and their risk factors in children.

www.pediatrics.org/cgi/doi/10.1542/peds.2007-1010G

doi:10.1542/peds.2007-1010G

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Key Words
family history, diabetes, heart disease, cardiovascular diseases

Abbreviations
CVD— cardiovascular disease
BP— blood pressure
SBP—systolic blood pressure
DBP— diastolic blood pressure
LDL—low-density lipoprotein
HDL— high-density lipoprotein
CHD— coronary heart disease

Accepted for publication May 16, 2007

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275); published in the public domain by the American Academy of Pediatrics

A COMMON ASSUMPTION in the epidemiology of chronic disease is that there will be a long time between exposure and expression of the disease. A challenge to this assumption is the increasing appearance of children with type 2 diabetes or distinctly elevated risk for cardiovascular disease (CVD). Explanations for such accelerated development include increased frequency and intensity of environmental risk factors, greater numbers of genetically susceptible people exposed early to risk factors for chronic disease as a result of urbanization and industrialization, and, most likely, a combination of these circumstances.[1] The appearance of signs of adult chronic diseases in children indicates that genetic factors are important, because the environment has had only a short time to act. However, environmental risk factors are also at work, with drastic deteriorations of diet and physical activity patterns in the past several decades. The foods consumed, the frequency with which we eat, and the amounts we ingest have been affected by major shifts in the way we produce, process, and distribute food. Changes in physical activity have been prompted, mostly, by modifications to our built environment and the technology we have come to depend on in our daily lives.[2]

Distinguishing genetic from environmental causes is difficult in chronic, multifactorial diseases. Fortunately, there is a simple way to explore simultaneously the influence of genetic and environmental factors on a condition: the use of family history. There is no standard operational definition of family history, but having 1 or more first- or second-degree relatives who are affected with a condition is often considered a positive family history for an individual person. In this article we discuss the use of a family history of type 2 diabetes or CVD as both an indicator of risk and a tool for disease prevention in public health practice.

THE BURDEN OF DIABETES AND CVD AND THEIR RISK FACTORS

In the United States there are ~21 million adults (aged >20 years) and 180 000 young people (aged ≤20 years) with diabetes, and there are ~1.5 million new cases of diabetes diagnosed every year.[3] Most adult cases are of type 2 diabetes, and most cases in youth (aged ≤20 years) are type 1. Type 2 diabetes, however, seems to be increasing rapidly among children and adolescents.[4,5]

CVD includes heart disease and stroke, the first and third leading causes of death in the United States.[6] It was estimated recently that some 71 million or 35% of US adults have some form of CVD (ie, heart disease, stroke, heart failure, high blood pressure [BP], and congenital cardiovascular defects).[7] Approximately 10% of adolescents aged 12 to 19 years have total cholesterol concentrations that exceed 200 mg/dL, which an important risk factor for CVD.[7] High BP in children and adolescents is defined as a systolic BP (SBP) and/or a diastolic BP (DBP) at or above the 95th percentile for the youth's age, gender, and height. In youth, a BP between the 90th and 95th percentiles is considered prehypertension (ie, an above-normal BP that is just below the threshold for hypertension); this is associated with an increased risk of developing hypertension.[6] Elevated BP in childhood and adolescence is considered a predictor of elevated BP later in life.[8,9]

A major public health concern is that diabetes and CVD share risk factors. In the pediatric age group, both overweight (BMI ≥ 95th percentile according to age and gender) and impaired glucose metabolism are now relatively common and have been increasing among both children and adolescents. A recent report estimated that among US children aged 2 to 19 years, 17.1% are overweight, and another 16.5% are at risk of overweight.[10] In addition, among adolescents, 1 in 10 boys and 1 in 25 girls have impaired fasting glucose; these figures double among overweight adolescents.[11] Compared with their peers with normal fasting glucose, adolescents with impaired fasting glucose have an unfavorable cardiovascular profile, with significantly higher levels of glycohemoglobin, total and low-density lipoprotein (LDL) cholesterol levels, fasting triglyceride levels, SBP, and fasting insulin, as well as lower concentrations of high-density lipoprotein (HDL) cholesterol.[11]

FAMILY HISTORY AS AN INDEPENDENT RISK FACTOR FOR TYPE 2 DIABETES AND CVD

Numerous epidemiologic studies have shown that people with 1 or more first-degree relatives who are affected with diabetes are 2 to 6 times as likely to have the disease compared with people who have no affected relatives.[12] Some studies have suggested that the contribution of family history to this excess risk is actually independent of that conferred by other common risk factors. For example, in a recent study that tested the effectiveness of the screening guidelines from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus using a US national sample, having at least 1 first-degree relative with diabetes doubled a person's risk of having undiagnosed diabetes even after adjusting for age, ethnicity, BMI, hypertension, HDL-cholesterol level, high triglyceride level, and gestational diabetes.[13]

In support of the consistent epidemiologic findings about family history, a wide range of metabolic studies have reported early signs of abnormalities among otherwise healthy people who have a family history of diabetes. Persons with a positive family history of diabetes, including children, might show early signs of defective insulin actions,[14–18] glucose intolerance,[19,20] lipid abnormalities, high BP, large weight gains,[21] reduced β-cell function,[20,22] impaired endothelial function,[23] and altered energy (mitochondrial) metabolism.[24–27]

The epidemiologic evidence for the familial aggregation of CVD is also strong. For example, a US study

found that 14% of the families had a positive family history of coronary heart disease (CHD), but this group contained 72% of the cases of early CHD (at <55 years of age). Similarly, 11% of the families had a positive family history for stroke, but 86% of the cases of early stroke (at <55 years of age) occurred in this group.[28] Researchers from the Framingham Study, who used prospective data and consistently validated CVD events in parents, offspring, and siblings, reported that having CVD in at least 1 parent doubled the 8-year risk of CVD among men and increased (albeit nonsignificantly) the risk among women by 70%. The excess risk was independent of other risk factors such as age, ratio of total/HDL-cholesterol level, SBP, antihypertensive therapy, diabetes, BMI, and current smoking status.[29] Furthermore, having at least 1 sibling with CVD was associated with an increased risk independent of the usual risk factors and the premature occurrence of CVD in the parents.[30]

Although family history has been found to contribute independently to the risk of both diabetes and CVD, it is rarely used quantitatively to assess such risk. When it is, family history is mostly used to rank subgroups within a population according to the excess prevalence in 1 group relative to another (relative risk).[31] More often, family history is used in concert with other well-known risk factors to predict disease in individual people in a given period (absolute risk). Guidelines from the American Diabetes Association,[32] the American Heart Association,[33] and the National Cholesterol Education Program[34] include family history as a factor that should be considered to assess risk and make decisions about treatment. In addition, in several major studies, family history has shown significant contributions to risk scores even after accounting for other well-established risk factors.[35–38]

Because diabetes and CVD share risk factors such as obesity and dyslipidemia and might even share etiology,[39,40] people with a family history of diabetes show increased risk for CVD.[41–44] Conversely, people with a family history of CVD might show early signs of insulin resistance and impaired glucose metabolism and, ultimately, risk of diabetes.[45–47] This sharing of risk factors, and possibly of etiology, has important implications regarding joint screening and prevention strategies for the 2 diseases.

EVIDENCE THAT DIABETES AND CVD START EARLY IN LIFE

Several studies have highlighted the presence of insulin resistance and CVD risk factors among children. For example, the Bogalusa Heart Study, in a series of cross-sectional studies, demonstrated conclusively that cardiovascular risk factors are detectable in childhood and that signs of adult heart disease, including atherosclerotic lesions, are evident as early as the second and third decades of life.[48–50] Other studies that have demonstrated the presence and development of risk factors in children and adolescents include the Pathobiological Determinants of Atherosclerosis in Youth Study,[51] the Muscatine Study,[52] Project HeartBeat!,[53] and the Cardiovascular Risk in Young Finns Study.[54] A different line of argument, which began with detailed geographic studies in the United Kingdom and Wales, is that infants who are malnourished during their fetal life and early infancy are more susceptible to CVD and diabetes as adults.[55,56]

EVIDENCE THAT TYPE 2 DIABETES AND CVD ARE PREVENTABLE

Results of 3 major randomized, controlled trials from China,[57] Finland,[58] and the United States[59] indicate that, at least in high-risk adult groups, the incidence of type 2 diabetes can be significantly reduced with lifestyle interventions involving diet, exercise, or a combination of both. In the study from the United States, the reduction in risk was similar across all racial/ethnic groups and was significant in all age and BMI subgroups.

In the pediatric population, there have been some attempts to lessen the risk factors for diabetes in children from high-risk groups. For example, the Bienestar Health Program is a school-based intervention that was designed to reduce the risk of diabetes in preadolescent Mexican Americans.[60,61] This 7- to 8-month program used 50 training sessions with 3 major messages: decrease dietary intake of saturated fat, increase dietary intake of fiber, and increase physical activity. At the end of the program, children in the intervention group had decreased blood glucose concentrations and increased fitness and intake of dietary fiber when compared with the control group. There were no differences between the control and intervention groups regarding the percentage of total body fat and intake of saturated fat.

In adults, reducing or controlling risk factors for heart disease and stroke can reduce the risk of cardiovascular deaths and events. For example, studies conducted in Veterans Administration hospitals in the 1960s demonstrated that lowering DBP by medication resulted in fewer cases of stroke, cardiac failure, and worsening hypertension.[62,63] More recently, an average reduction of 12 to 13 mm Hg in SBP over 4 years of follow-up was reported to be associated with reductions of 21% in CHD, 37% in stroke, 25% in total cardiovascular mortality, and 13% in all-cause mortality.[64] Others have estimated that a 10% reduction in serum cholesterol concentrations may reduce the incidence of coronary events by 30%.[65]

With regard to the prevention of CVD in children, the evidence from well-designed school-based interventions indicates that health-related knowledge, attitudes, and behaviors in children can be changed significantly and positively in a relatively short time.[66–69] In addition, several randomized, controlled trials have shown that risk factors in children and adolescents can be modified outside the school setting. Overall, these changes are usu-

ally modest, but they might prove to be of importance when translated to the general population of pediatric age and to high-risk children in particular.[70] For example, in a 3-year intervention, the Child and Adolescent Trial for Cardiovascular Health demonstrated that the percentage of calories from fat could be significantly reduced in school lunches (from 38.7% to 31.9%) and that the amount of vigorous physical activity could be significantly increased during physical education classes (from 37% to 52%). However, total cholesterol level, SBP and DBP, and BMI did not differ significantly between those in the intervention and control schools at the end of the study.[71,72]

As an example of an investigation in a non–school setting, the Dietary Intervention Study in Children was a randomized, controlled trial in children aged 8 to 10 years with elevated LDL-cholesterol levels.[73] The children were recruited from schools, a health maintenance organization, and several pediatric practices. The dietary intervention, which followed recommendations of the National Cholesterol Education Program, reduced the percentage of energy intake from total fat from 33.4% to 28.5% during the intervention, and this percentage remained virtually unchanged at a later follow-up (5 years later). Meanwhile, LDL-cholesterol levels decreased from 130.6 to 109.8 mg/dL and then increased to 114.1 mg/dL 5 years later.

Weight loss in overweight adolescents has been found to be associated with a decrease in BP.[74] A meta-analysis of 12 randomized trials suggested that increased physical activity resulted in a small but not statistically significant decrease in BP.[75]

SCREENING STRATEGIES FOR DIABETES AND CVD

No overall screening strategies have been recommended for either diabetes or CVD among children and adolescents. The American Diabetes Association recommends that children should be tested every 2 years for diabetes if they are overweight (BMI $\geq$ 85th percentile according to age and gender) and have any 2 of the following 3 risk factors: (1) a positive family history of type 2 diabetes (first- or second-degree relatives); (2) belong to a minority racial/ethnic group (black, Hispanic, Native American, Asian American, Pacific Islander); or (3) have signs of insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome). Testing should start at 10 years of age or at the onset of puberty if that comes before age 10.[32]

In its guidelines for the primary prevention of CVD beginning in childhood, the American Heart Association includes general assessment of diet, tobacco use, physical activity, family history, height, weight, and BP. The existence of first-degree relatives with conditions or diseases such as obesity, hypertension, dyslipidemia, diabetes, and premature CVD (age of onset: $<$55 years in men and $<$65 years in women) should be assessed. Family history should be taken into account in decisions to screen and treat children for high cholesterol levels and other risk factors.[33,76,77]

The US Preventive Services Task Force has concluded that it is not known whether routine screening for high BP or overweight in children and adolescents can reduce their risk of CVD. Even so, the task force has acknowledged that BMI is a reasonable indicator of overweight and risk of overweight in children and adolescents, and overweight children and adolescents are likely to become obese adults. Unfortunately, effective interventions that produce long-lasting weight loss among children and adolescents have not been reported. Accordingly, the potential harms or benefits of routinely screening for overweight among children and adolescents remain unknown.[78]

It is paradoxical that as the evidence accumulates that certain factors in childhood contribute to the later development of some important chronic diseases such as diabetes and CVD, there is a virtual lack of data on detecting and reversing the risk factors and early signs of these diseases in children. In truth, however, the difficulties of determining how to proceed are not trivial. First, the association between the presence of risk factors in children and their health outcomes as adults must be established with certainty. Second, early interventions to reduce risk factors in children must be proven safe and effective in both short- and long-term scenarios. Finally, issues such as the cost and selection of the best screening strategy must be addressed.

IMPORTANCE OF FAMILY HISTORY IN ASSESSING RISK

Familial health risk does not remain constant throughout life. It changes as families grow, as family members age and increase their exposure to the environment, and as the status of their health evolves. Accordingly, a person's family history needs to be updated regularly, which might make this history an excellent tool for increasing awareness of risk among people as they age. Family history assessment is probably not as useful when the risk of those persons compared is too low or high according to risk factors other than family history. For example, in the selection of participants for the Diabetes Prevention Program, a family history of diabetes did not increase the yield of high-risk participants.[79] Among persons whose risk factors are intermediate, however, family history could play a role in discriminating levels of risk. More importantly, health risks are more likely to be reversible for those in this group.

Findings from family history studies may lead not only to an understanding of how inherited factors interact with the environment to cause disease in some families but also to assessing how this interaction works in the population at large. Long-term follow-up of persons at high familial risk may help us understand the natural course of some diseases and identify the life stages at

which people would benefit the most from interventions such as screening, early detection, prevention, and genetic counseling. Although it is possible that just a modest proportion of all cases of a disease in the population emerge from people who are genetically susceptible, such as those with a strong family history, this is still an important group, because it might be the first to show, at a population level, the effects of adverse environmental changes. An example of the application of these principles is the identification of several gene variants associated with diabetes and CVD in studies in which family history was an important criterion for selecting high-risk persons.[80,81]

Incidentally, those who are assessing for cases of diabetes and CVD in families should know that the pattern of inheritance of these diseases is not always complex. For example, maturity-onset diabetes of the young is inherited as an autosomal-dominant trait.[82] There are many other examples of rare cases in which a well-defined genetic component has been identified. In a recent search of the Online Mendelian Inheritance in Man database, a large catalog of human genes and genetic disorders, a total of 2592 entries were reviewed for common chronic conditions related to cancer, diabetes, and CVD.[83] In all, 188 entries for these diseases were reported in >1 family and displayed a discernible pattern of inheritance, mostly autosomal dominant. Of those entries, a subgroup of 156 referred to CVD or diabetes; interestingly, 74 of them included combinations of at least 2 traits from 1 or both diseases.[83]

FAMILY HISTORY AS A SCREENING TOOL

Screening is the systematic search for precursors or preclinical signs of a condition in apparently healthy people and entails health risks and costs. For example, it might increase the cost and length of treatments; it might also cause unnecessary anxiety among those who are wrongly assigned to high-risk categories or give a false sense of security to those who are wrongly assigned to low-risk categories. Therefore, the World Health Organization has issued criteria[84] to screen for a condition: the condition must be of public health importance, the diagnostic tests must be safe and reliable, adequate treatments or interventions must be available, and finding, diagnosing, and treating people with the condition should be affordable. Diabetes and CVD meet most of the World Health Organization criteria. It is not clear, however, what the best strategy or combination of strategies might be to provide routine screening for diabetes or CVD (whole population, high-risk persons, opportunistic) and how cost-effective these strategies might be.

Family history has the potential to become a screening tool to identify people at increased risk of chronic diseases such as diabetes and CVD, but several conditions will need to be met. First, family history should be a demonstrable, independent risk factor for the diseases. Second, the methodology used to determine risk according to family history must be valid and reliable. Third, people must be aware of the disease status of their relatives and willing to report it. Finally, the time and resources required to collect and interpret the data on family history should be comparable to those needed for alternative screening tools.

Family history is an independent risk factor for diabetes and CVD, but the tools and methodologies for collecting and assessing familial risk for these and other chronic diseases are not well developed.[85,86] Family history of diabetes and major CVD events are reported fairly accurately, because each has a good case definition, both are serious enough to be of concern to relatives, and there is little stigma associated with them.[12,28,87] Even so, diabetes, in particular, is likely to be underreported; approximately one third of the people with diabetes have not had it diagnosed.[88]

In addition to primary care, schools and national or state surveys are settings in which family history could be used as a screening tool to identify children who are at increased risk of chronic diseases. For example, there are states in which BMI is a required measurement for schoolchildren, and parents are notified of the weight status of their children.[89] If family history of diabetes and CVD is collected from overweight children, it may be possible to identify a subgroup of children who, because of their greater risk, would benefit the most from personalized and family-based efforts at prevention. As for surveys, Hariri et al[90] recently used a national survey to compare obesity and self-reported family history of diabetes as screening tools to identify adults with undiagnosed diabetes. The authors found that a positive family history identified 73% of all respondents with diabetes, compared with obesity, which identified only 40%. In addition, the 2 risk factors combined had a larger positive predictive value for diabetes than family history or obesity alone.

Other features to be considered when collecting family history of diabetes and CVD include early age at disease onset; presence of related conditions (hypercholesterolemia and CHD); the existence of 2 or more closely related affected relatives; and a history of 2 or more generations with affected relatives. Algorithms for stratifying risk that incorporate these features of family history to rank individual people are being evaluated in adult populations.[91–93] Algorithms to predict the risk of chronic conditions in susceptible children may have to be modified to account for the potentially prolonged period between exposure and outcomes. Ideally, the algorithm should identify children at increased risk who would benefit the most from early preventive measures and children at very high risk, who may be referred to a specialist.

Even if family history is properly validated as a screening tool, it would still need to face the question of

clinical utility; how does this tool influence early detection and the prevention of disease in populations? Will parents be more motivated to engage their children in healthy behaviors if they are aware of the familial risk of disease? Will adolescents make healthier choices for themselves if they know about a preventable disease that "runs in the family?" There are some indications that the answer to these questions is affirmative. We note that family-based lifestyle interventions with parents as coaches may be more effective than individual approaches.[94]

Several ethical and legal issues need to be considered before family history can be used as a screening tool in children. For example, what are the consequences of labeling children at risk for diseases that will not emerge for years to come? How will the labeling affect their present and future medical insurability? Is there a potential for fatalism, impairment of self-image, depression, or blame associated with assessment of familial risk? These issues have been examined in more detail for single-gene disorders than for common chronic diseases.[95,96] Legal issues associated with collecting family histories include informed consent, ownership of the data, obligation to disclose, and requirements for reporting. These vary with the setting, but clinical settings already have guidelines and regulations (eg, Health Insurance Portability and Accountability Act regulations) that protect medical information.

If family history improves the risk assessment for both diabetes and CVD, and if the evidence shows that screening and early behavioral changes help prevent these diseases, clinicians and parents may be more receptive to considering family history as a legitimate risk factor in children and start intervening earlier rather than later.

CONCLUSIONS

Diabetes and CVD are common and costly health problems, the public health impact of which could be eradicated or greatly ameliorated by early detection and interventions in the population at risk. The evidence is clear that type 2 diabetes and CVD start early in life and that both can be prevented or delayed, at least among adult, high-risk men and women. In addition, family history has been found to be an established, independent risk factor for both diseases as well as for some precursors of these diseases. A next step that would not add much expense would be to make family history part of mass-awareness strategies and prevention campaigns aimed at reducing the burden of diabetes and CVD and their risk factors. Much research needs to be done, however, on the most effective ways to incorporate family history in those strategies and campaigns, particularly for children and young adults.

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Pediatrics 2007;120;S78-S86
DOI: 10.1542/peds.2007-1010G