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Universal Versus Targeted Blood Cholesterol Screening Among Youth: The CARDIAC Project

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Universal Versus Targeted Blood Cholesterol Screening Among Youth: The CARDIAC Project

WHAT'S KNOWN ON THIS SUBJECT: Current NCEP guidelines suggest selective screening on the basis of the following criteria: (1) family history of premature cardiovascular disease; (2) parent total cholesterol of >240 mg/dL; and (3) unknown family history.

WHAT THIS STUDY ADDS: Results of this study show that children who possibly warrant pharmacologic treatment would have been missed on the basis of the current NCEP recommendations.

abstract

OBJECTIVES: The goal was to determine the sensitivity and specificity of family history in identifying children with severe or genetic hyperlipidemias in a rural, predominantly white population.

METHODS: A total of 20 266 fifth-grade children in West Virginia, from the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project, who completed a family history and fasting lipid profile were used in analyses. The relationship between hyperlipidemia and family history was determined, and the use of family history to predict the need for pharmacologic treatment among children with dyslipidemia was evaluated.

RESULTS: A total of 71.4% of children met the National Cholesterol Education Program (NCEP) guidelines for cholesterol screening on the basis of positive family history. Of those, 1204 (8.3%) were considered to have dyslipidemia (low-density lipoprotein ≥130 mg/dL), and 1.2% of these children with dyslipidemia warranted possible pharmacologic treatment (low-density lipoprotein ≥160 mg/dL). Of the 28.6% who did not have a positive family history (did not meet NCEP guidelines), 548 (9.5%) had dyslipidemia, 1.7% of whom warranted pharmacologic treatment. Sensitivity and specificity data demonstrated that family history does not provide a strong indication as to whether pharmacologic treatment may be warranted.

CONCLUSIONS: Results indicate that the use of family history to determine the need for cholesterol screening in children would have (1) missed many with moderate dyslipidemia and (2) failed to detect a substantial number with likely genetic dyslipidemias that would require pharmacologic treatment. The use of universal cholesterol screening would identify all children with severe dyslipidemia, allowing for proper intervention and follow-up and leading to the prevention of future atherosclerotic disease. *Pediatrics* 2010;126:260–265

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KEY WORDS

lipids, cardiovascular disease, genetics, children

ABBREVIATIONS

FH—familial hypercholesterolemia
FCH—familial combined hypercholesterolemia
LDL—low-density lipoprotein
CHD—coronary heart disease
NCEP—National Cholesterol Education Program
AAP—American Academy of Pediatrics
CARDIAC—Coronary Artery Risk Detection in Appalachian Communities
FLP—fasting lipid profile
HDL—high-density lipoprotein
CVD—cardiovascular disease
OR—odds ratio
CI—confidence interval

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Epidemiologic studies have documented a strong association between high cholesterol levels (hyperlipidemia) and arteriosclerosis as predisposing adults to heart disease. Hyperlipidemia has long been recognized as a multifactorial condition involving both lifestyle and genetic components. It is commonly known in the medical community that obesity, high dietary intake of saturated fats, inactivity, and tobacco use contribute to abnormal cholesterol levels; however, even in the absence of these adverse factors, familial hyperlipidemia (FH) and familial combined hyperlipidemia (FCH), monogenic autosomal co-dominant disorders caused by mutations in the low-density lipoprotein (LDL) receptor, can result in significantly elevated LDL cholesterol levels.[1]

In both the Muscatine and Bogalusa Heart studies, the greatest single predictor of adult hypercholesterolemia was found to be the blood cholesterol level obtained in childhood.[2,3] In both children and adults, family history of coronary disease was strongly associated with hypercholesterolemia.[2] Children from the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study who died accidentally were submitted to autopsy and evaluated for signs of atherosclerosis. In both studies, fatty streaks and fibrous plaque were observed quantitatively in proportion to the age of the child and the severity of hyperlipidemia.[3,4]

These seminal studies that pointed to the relationship of hyperlipidemia in children and subsequent development of premature coronary heart disease (CHD) led the National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents to propose selective screening recommendations for the pediatric population on the basis of the following criteria:

- screen children and adolescents whose parents or grandparents have documented coronary artery disease before the age of 55 years;
- screen the offspring of a parent who has been found to have a blood cholesterol level of >240 mg/dL; and
- screen children and adolescents for whom family history is unobtainable, particularly those with other risk factors such as hypertension or obesity.

It was initially projected that ~25% of all US children would meet guidelines for blood cholesterol screening.[5] Selective screening on the basis of family history rather than universal screening was recommended because of several concerns, including the implications of labeling children with a diagnosis of hyperlipidemia, the possibility of overuse of cholesterol-lowering medications, and the cost of universal screening.[6]

The American Academy of Pediatrics (AAP), Committee on Nutrition issued a policy statement in 1998 that encouraged the selective screening of children and adolescents with a significant family history of coronary disease and/or elevated parental blood cholesterol levels.[7] Although it was acknowledged that some children with hyperlipidemia would be missed by selective screening, the committee predicted that those children would have only modest elevations that were responsive to lifestyle changes. In fact, the most recent AAP clinical report on "Lipid Screening and Cardiovascular Health in Childhood," published in 2008, acknowledged that selective screening may have missed between 30% and 60% of children with hypercholesterolemia.[8] Still, blood cholesterol screening in children and adolescents remains a targeted approach, primarily because of the lack of compelling evidence to justify universal screening of youth.[8]

Since 2000, the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project has offered universal screening to fifth-grade children statewide in West Virginia public schools. The CARDIAC Project uses a universal approach because of the high prevalence of heart disease in West Virginia and the alarming prevalence of youth obesity. As part of the comprehensive design, family history of heart disease and hyperlipidemia is documented for all children. Retrospective analysis provides the opportunity to analyze the relationship of family history, both positive and negative, to cholesterol values in >10 000 children. Because family history was recorded among all participants for whom there was informed consent, we were able to examine its relationship to hyperlipidemia; therefore, the goal of this study was to determine the sensitivity and specificity of family history in identifying children with severe or genetic hyperlipidemias in this rural, predominantly white population.

METHODS

The CARDIAC project was developed in 1998 as a means to identify children and families at risk for coronary artery disease. Fifth-grade children who were enrolled in the public school system received an information packet and were invited to participate in the CARDIAC Project. The information packet included an explanation of the project and the procedures to take place on screening day, parental consent/child assent forms, and a parental self-report family history questionnaire. The study protocol was approved by the West Virginia University institutional review board.

Screenings were conducted first thing in the morning within the school setting by trained health professionals and health science students. This study included 20 266 West Virginia

TABLE 1 Questions Relating to CVD From Family History Questionnaire

Does either parent have high blood cholesterol?	○ Yes	○ No	○ Don't Know
Is there a history of early heart disease in your child's family, parents and/or grandparents (younger than age 55)?			
Heart attack requiring hospitalization?	○ Yes	○ No	○ Don't know
Coronary bypass (open heart) surgery?	○ Yes	○ No	○ Don't know
Coronary angioplasty/heart catheterization?	○ Yes	○ No	○ Don't know
Died from heart disease?	○ Yes	○ No	○ Don't know
If yes, at what age? ____			

fifth-grade children who had a fasting lipid profile (FLP) and completed the family history questionnaire between September 2003 and April 2008. The questions that pertained to family history are presented in Table 1. Children with incomplete data were excluded from analyses. Of these, 93.3% were white and 53.6% were female. The mean age was 10.93 years (SD: 1.87 years). A fasting blood sample was collected to determine total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. LDL cholesterol was calculated by using the Friedewald equation.[9]

Etiologic Classification

Premature CHD was defined as coronary disease that occurred before age 55, evidenced by (1) a myocardial infarction ("heart attack") that required hospitalization, (2) coronary bypass surgery, (3) coronary angioplasty and/or stent placement, (4) or death that resulted from CHD event.

The NCEP Expert Panel for Children and Adolescents (1991) and the AAP (2008) recommended that consideration be given to pharmacologic treatment of hyperlipidemia when the child is at least 8 years of age and an adequate period of dietary restriction (at least 6 months) has not achieved therapeutic goals. Drug therapy should be considered when

- LDL cholesterol remains ≥190 mg/dL;
- LDL cholesterol remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) before 55 years of age, or ≥2 other risk factors for CVD are present after rigorous attempts at lifestyle modification; and
- LDL is ≥130 mg/dL in the presence of diabetes.

Statistical Analysis

All analyses were conducted with SPSS 16.0 (SPSS, Inc, Chicago, IL). We explored the sample composition by collecting a series of descriptive statistics on participant gender (0, male; 1, female), race/ethnicity, and age. The frequency and percentage of children in the sample who met family history, hyperlipidemia, and criteria for cholesterol-lowering medications were calculated and are presented in Fig 1.

We statistically evaluated the relationship between hyperlipidemia and family history by using χ^2 analyses. Statistical significance was interpreted at $P < .05$. Cramer's V was used to determine effect size. Then the use of family history to predict the need for pharmacologic treatment among children with dyslipidemia was statistically evaluated by using χ^2 tests (first to assess whether an association exists), odds ratios (ORs; as compared with those without a positive family history), and

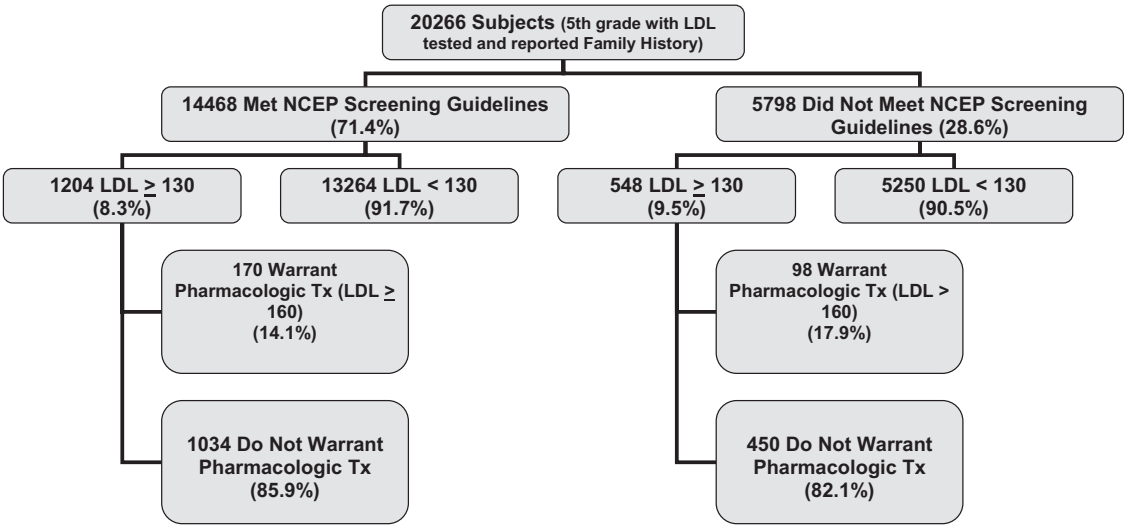

FIGURE 1
Universal versus selective screening: testing current NCEP guidelines.

sensitivity and specificity. Odds ratios different from 1 (as assessed with the 95% confidence interval [CI]) was considered significant. Specificity and sensitivity >0.70 were considered satisfactory.

RESULTS

First, we compared the number of children in our study who would have met the original NCEP selective screening guidelines on the basis of a positive family history with the total number of children screened. On the basis of positive family history alone, 71.4% (14 468 of 20 266) met the initial NCEP guidelines for selective blood cholesterol screening. Only 1.2% (170 of 14 468) of those with a positive family history had an LDL level of ≥160 mg/dL and warranted consideration of pharmacologic treatment; however, a similar percentage, 1.7% (98 of 5798) of those without positive family history met pharmacologic treatment consideration. A total of 268 children (1.3% of the entire sample) met the criteria for possible pharmacologic intervention (LDL ≥160 mg/dL). Of those, 63.4% (170 of the 268) had an LDL level of ≥160 mg/dL and a positive family history; 36.6% (98 of 268) did not have a positive family history (Fig 1).

Having a positive family history and having hyperlipidemia (defined as having LDL ≥130 mg/dL) were significantly related (Pearson χ^2 [N = 20 266] = 6.69, P = .01); however, the effect size was small (Cramer's V = .02). A significant relationship was found between a positive family history and meeting the criteria for pharmacologic treatment (defined as having LDL ≥160 mg/dL [Pearson χ^2 (N = 20 266) = 8.42, P = .004]), but, again, Cramer's V = .02 indicated a small effect size. The OR (0.692 [95% CI: 0.54–0.89]), specificity (0.63; [95% CI: 0.57–0.69]), and sensitivity (0.29; [95% CI: 0.28–0.29]) indicated that using family history for preliminary screening does not provide a good test as to whether the child needs subsequent pharmacologic treatment.

When looking at children who were identified as having dyslipidemia, positive family history was related to meeting criteria for pharmacologic treatment (Pearson χ^2 [N = 1752] = 4.12, P = .04). The effect size was still small (Cramer's V = .05), and even among these children with dyslipidemia, the OR (0.76 [95% CI: 0.58–0.99]), specificity (0.30 [95% CI: 0.28–0.33]), and sensitivity (0.63; [95% CI: 0.57–0.69]) indicated that using family history does not provide strong indication as to whether pharmacologic treatment is warranted.

DISCUSSION

Our data indicate that using family history to selectively determine the need for cholesterol screening would have (1) missed many children with moderate hyperlipidemia and (2) failed to detect a substantial number of children who likely have FH or FCH and require pharmacologic treatment. The total number of children in our study who met the NCEP selective screening guidelines was nearly threefold greater than projected from the original Lipid Research Clinics data of several decades ago.[5]

This substantial difference in those who met the NCEP guidelines for screening may be related to the high prevalence of coronary artery disease in West Virginia.[10] The CARDIAC Project includes family history data for both parents and grandparents. Inclusion of grandparents in the family history may have increased the number with a positive family history. Even with the disproportionate amount of positive family history, the CARDIAC Project estimates that one-third of children who would have met the criteria for pharmacologic intervention would have been missed if screening were based on having a positive family history. Our findings in this study are similar to those reported by Griffith et al[11] in a study conducted of 100 children at Children's Memorial Hospital in Chicago.

According to a study conducted by Williams et al[12] that validated the criteria for diagnosing genetic hyperlipidemias, a child with an LDL value of ≥160 mg/dL and a first-degree relative with FH has a 90% chance of having FH himself or herself. In this study, one-third of children with LDL ≥160 mg/dL did not report having a positive family history. In agreement with Dennison et al,[13] we found several explanations as to why children with severe hyperlipidemia have negative family histories. First, the mean age of our children was 10.93 years. At this age, children may have parents and grandparents who are still too young to have experienced premature CVD. In addition, many adults (parents and grandparents) have never had an FLP because of the high proportion of uninsured families without primary care providers in West Virginia; therefore, they cannot accurately report family histories that are positive for hyperlipidemia. According to the National Kids Count Program Data from 2007,[14] 29% of children in West Virginia live in single-family homes. In some cases, this may result in an incomplete or absent family history of the noncustodial parent. It is therefore prudent to implement universal screening in the pediatric population independent of family history.

When the original NCEP guidelines were written, recommendations for medical treatment of children with levels of LDL ≥160 mg/dL were proposed only when there was a positive family

history of premature heart disease or ≥2 additional CVD risk factors that were unresponsive to lifestyle modification were present. An isolated value of LDL ≥160 mg/dL is not an indication for pharmacologic therapy but does indicate the need for continued medical follow-up. Committee members advocated selective screening, in part, because of their concerns about labeling young children with the diagnosis of hyperlipidemia, overusing cholesterol-lowering medication, and the safety of statin medications in children; however, these concerns have not been proved to be valid.[15–17] In fact, the use of statin medication in children with severely elevated blood cholesterol levels has had positive results in returning levels to normal with minimal adverse effects.[18,19]

The CARDIAC Project attempts to address issues related to accuracy of family history by offering parents of children who have participated in the project the opportunity to receive a free FLP. This cascade approach has resulted in screening of ~2500 parents in the past 10 years. Of these parents screened, 8.5% had an LDL level of ≥160 mg/dL. Rather than relying on known family history to determine which children are offered FLPs, the CARDIAC Project attempts to provide families with an increased awareness and knowledge of their cardiac risk through reverse cholesterol screening.

CONCLUSIONS

Analysis of our CARDIAC blood cholesterol screening data reveals that if cholesterol testing had been limited to those with a family history of premature CVD or premature hyperlipidemia, then one-third of children who met criteria for pharmacologic treatment would have been missed. The current epidemic of obesity in the United States and the association of high BMI with dyslipidemia (the clustering of moderately elevated total cholesterol, low HDL, and high triglycerides) has prompted some practitioners to screen obese children with FLPs. Although it is true that LDL goes up modestly with increasing weight, it generally does not reach levels that are appropriate for medication. Often the child may have low HDL cholesterol and elevated triglycerides suggestive of metabolic syndrome/insulin resistance.

Universal cholesterol screening in the pediatric population will allow early diagnosis and appropriate treatment of children with significant dyslipidemia secondary to genetic and/or adverse lifestyle factors, hopefully preventing arterial disease. In addition, the added and undeniable benefit of identifying and screening parents and other first-degree relatives as a result of finding elevated LDL levels in their children could lead to the prevention of premature cardiac events in adults that may have otherwise gone undiagnosed.

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