EDITORIAL COMMENT

Can Lipid and Lipoprotein Concentrations in Childhood Predict Adult Atherosclerosis?*

Stephen R. Daniels, MD, PhD, FACC
Denver, Colorado

Since the initial publication of the recommendations of the National Cholesterol Education Program (NCEP) Pediatric Panel in 1992, there has been intense interest in and concern about the identification and treatment of lipid and lipoprotein abnormalities in children and adolescents (1). Some of the most important questions concerning screening have been the following: 1) How useful are pediatric lipid and lipoprotein concentrations for the prediction of adult outcomes? 2) What adult outcomes are most important and which have data available to address them? 3) If screening is to be implemented, would it be better to use a universal or targeted strategy? 4) Is it acceptable to use a single set of cut points for lipids and lipoproteins across all ages in the pediatric age group?

In a previous publication (2) and this issue of the Journal (3), Magnussen et al. attempt to provide answers to some of these questions. Magnussen et al. (3) have used data from 3 large cohort studies—the Cardiovascular Risk in Young Finns Study (Finland), the Bogalusa Heart Study (U.S.), and the Childhood Determinants of Adult Health Study (Australia)—all of which have followed subjects from childhood into young adulthood. In a previous analysis (2), they evaluated the ability of lipid and lipoprotein levels in childhood to predict levels in adulthood. This addresses the issue of tracking, or the extent to which patients are likely to maintain their percentile rank compared with peers over time. They found that with a mean follow-up of 20.2 years there was a progressive and substantial relative risk of adult dyslipidemia associated with borderline or high risk levels in adolescence. However, there were important differences across the cohorts. For example, 77.8% of Finnish adults with abnormal total cholesterol levels would have been identified in childhood with the use of the NCEP high-risk cut point. However, only 42.9% of Americans and 27.8% of Australians would have been identified using the same approach. The investigators were unable to provide a clear recommendation regarding whether universal or targeted screening would be optimal based on these results (2). They noted that despite tracking, approximately 60% of adolescents identified as high risk would not have elevated levels of lipids and lipoproteins in adulthood with the use of either a universal or targeted strategy. However, universal screening in adolescence has reasonable sensitivity with identification of 75% of those affected in adulthood. Interestingly, neither the single cut point across childhood and adolescence approach recommended by the NCEP (1) nor the percentile by age approach, based on distributions from the National Health and Nutrition Examination Survey (NHANES), suggested by Jolliffe and Janssen (4), proved clearly better for prediction. This was somewhat surprising because lipid and lipoprotein levels change substantially during childhood and adolescence, and one might anticipate that a percentile by age approach would be better.

In this issue of the Journal, Magnussen et al. (3) go further in providing more useful information on childhood lipid screening. For this study, the outcome was carotid intima-media thickness (IMT). This is a more important end point because it reflects actual structural change in the carotid artery, which is associated with the atherosclerotic process, and it is associated with cardiovascular outcomes. The design of this study is similar to the previous study and uses the same 3 cohorts. Lipid and lipoprotein measurements were made during the teenage years and ultrasound measurements of the carotid IMT were made in the early-to-mid 1930s. The most important findings are that measurements of low- and high-density lipoprotein cholesterol in adolescence were important predictors of adult carotid IMT. In fact, those with a low level of high-density lipoprotein cholesterol during childhood had higher carotid IMT irrespective of their adult levels. They also found that overweight and obese adolescents with dyslipidemia had substantially higher carotid IMT in adulthood. This emphasizes that from an epidemiologic perspective, lipid and lipoprotein levels in adolescence are important, and they are particularly important in conjunction with obesity.

Magnussen et al. (3) also found that there was no difference between the NCEP single cut point and the NHANES percentile-based cut points in predicting carotid IMT in adulthood. This is similar to the result in prediction of adult lipid and lipoprotein levels and argues in favor of the NCEP approach because it is simple and easier to use. Despite the associations between adolescent levels of lipids and lipoproteins and adult carotid IMT, lipid and lipoprotein levels in adolescence were far from perfect clinical predictors. Sensitivity was modest and specificity

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Department of Pediatrics, University of Colorado, Denver School of Medicine, Denver, Colorado. Dr. Daniels has consulted for Abbott Laboratories and Merck/Schering-Plough.
was low resulting in a low positive predictive value, but acceptable negative predictive value. This means that a dyslipidemic value in adolescence results in a high proportion of false negatives. However, a normal adolescent value for lipids and lipoproteins makes elevated carotid IMT in adulthood unlikely. The inclusion of overweight and hypertension in adolescence improved the prediction of elevated carotid IMT in adulthood, but prediction remained low overall.

There are some limitations with this study. Nonparticipation of those eligible for follow-up ranged from 34% to 82% across the 3 cohorts. The 3 studies used different protocols for measurement of carotid IMT and different methods of lipoprotein determinations. These limitations are often inherent in the type of combined analysis performed for this study, but they do limit the inferences that can be made.

Although there remains an imperfect base of evidence to determine the optimal strategy for screening for lipids and lipoproteins, the work of Magnussen et al. (2,3) begins to provide needed information. Based on their work, it appears that there are clear epidemiologic associations between lipid and lipoprotein levels in the pediatric age range and adult outcomes including lipid levels (2) and carotid IMT (3). It also appears clear that the single set of cut points recommended by the original NCEP pediatric panel work as well overall as percentile-based cut points. How to best develop a screening strategy for children and adolescents is less clear. Screening in adolescents has a low positive predictive value, but a good negative predictive value. It is not known whether screening at a different age or with a different lipid measure such as non-density lipoprotein cholesterol would have different results. The question of whether a universal or a targeted screening program is superior will require additional information. The current NCEP pediatric screening guidelines are based on a family history of premature cardiovascular disease, or dyslipidemia or the presence of other risk factors such as obesity, diabetes, or hypertension. The results of Magnussen et al. (3) support the concept that prediction of adult carotid IMT improves somewhat with the inclusion of additional risk factors such as obesity or hypertension. It remains unknown if a combination of variables could improve the performance of targeted screening.

Implementation of a screening program requires information on the ability to have a positive impact on the outcome once an abnormality is detected and on the problem of individuals who will be false positives and false negatives. Assessment of a screening program also requires evaluation of costs associated with screening and potential benefits related to identification and treatment of the identified abnormality. A screening program must also have a high level of acceptability to those being screened. Unfortunately, there is a smaller evidence base regarding these issues for lipid screening in children and the study by Magnussen et al. (3) does not address them. This is 1 reason why the U.S. Preventive Services Task Force found insufficient evidence to recommend for or against screening for lipids and lipoproteins in children and adolescents (5).

Some progress is being made in developing the evidence base needed for making recommendations regarding lipid and lipoprotein screening in the pediatric population. However, a substantially greater base of information is needed that will require additional investigation. Until the base of evidence deepens, clinical and public health recommendations will have to be based on less than optimal evidence.

Reprint requests and correspondence: Dr. Stephen R. Daniels, University of Colorado at Denver and Health Science Center, Department of Pediatrics, 13123 East 16th Avenue, B065, Aurora, Colorado 80045. E-mail: daniels.stephen@tchden.org.

REFERENCES


Key Words: pediatrics • dyslipidemia • carotid atherosclerosis • epidemiology • screening.