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Sensitivity and Specificity of Pediatric Lipid Determinations for Adult Lipid Status: Findings From the Princeton Lipid Research Clinics Prevalence Program Follow-up Study

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ABSTRACT

OBJECTIVE. The goal was to determine the diagnostic utility of the National Cholesterol Education Program pediatric guidelines.

METHODS. With the use of pediatric lipid data from the Cincinnati Clinic of the Lipid Research Clinics Prevalence Study and lipid and cardiovascular disease data collected for the same subjects as adults in the Princeton Follow-up Study, the sensitivity and specificity of the National Cholesterol Education Program pediatric guidelines were calculated overall and according to age. Furthermore, whether use of parental cardiovascular disease history during childhood influenced the sensitivity and specificity was assessed.

RESULTS. Overall sensitivities were 43% to 46% and specificities were 82% to 86% for total and low-density lipoprotein cholesterol levels. There was considerable variation in sensitivities according to age, with the lowest sensitivities at ages 14 to 16 years and the highest sensitivities at ages 5 to 10 years and 17 to 19 years. Results were similar whether or not the population was restricted to children with a positive parental history of cardiovascular disease.

CONCLUSIONS. Results of our analyses suggest that the sensitivity and specificity for evaluating total cholesterol or low-density lipoprotein cholesterol levels that are elevated in adulthood are not improved by selecting children with a positive parental history. These data also show the strong role that age (particularly the pubertal years between 10 and 15 years of age) plays in lipid measurements for children and adolescents. Continued prospective and longitudinal studies designed with age as well as other risk parameters are needed to determine the best guidelines for clinical screening in the future.

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Key Words

low-density lipoprotein cholesterol, adolescent, child, sensitivity, specificity, lipoproteins

Abbreviations

NCEP—National Cholesterol Education Program
CVD—cardiovascular disease
LDL—low-density lipoprotein
PFS—Princeton Follow-up Study
LRC—Lipid Research Clinics

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CURRENTLY, CHILDREN AND adolescents are important targets for cardiovascular disease (CVD) risk factor screening. The proportions of pediatricians and all physicians who screen children for serum cholesterol levels are 88% and 76%, respectively; 71% of pediatricians initiate diet therapy first to lower cholesterol levels, and 16% use drug therapy.¹ It is apparent that primary care physicians and specialists are faced increasingly with the responsibility of evaluating the lipid profiles of adolescent patients.

The National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents published screening strategies for the evaluation and treatment of cholesterol abnormalities among children and adolescents.² The guidelines, which were reaffirmed by the American Academy of Pediatrics,³ recommend additional evaluation of all children of parents and grandparents with premature CVD and/or children of parents with elevated total cholesterol levels, defined as total cholesterol levels of ≥ 240 mg/dL (6.21 mmol/L). In addition, the guidelines establish lipid cutoff points, which define elevated levels of total cholesterol (200 mg/dL, 5.17 mmol/L) and low-density lipoprotein (LDL) cholesterol (130 mg/dL, 3.36 mmol/L) among children 2 to 19 years of age. These cutoff points represent the ~ 95 th percentile for these lipids and lead to decisions concerning treatment for pediatric patients depending on family history and the presence of other risk factors. Patients with LDL cholesterol levels of >130 mg/dL are identified for monitoring, >160 mg/dL (4.14 mmol/L) for drug therapy if other CVD risk factors are present, and >190 mg/dL (4.91 mmol/L) for drug therapy even in the absence of other risk indicators.

The purpose of this study was to determine the sensitivity and specificity of the NCEP pediatric cutoff points during childhood and adolescence for adult lipid and CVD status, by applying the cutoff points to persons screened as children in the National Heart, Lung, and Blood Institute Lipid Research Clinics (LRC) Princeton School Study and as adults in the Princeton Follow-up Study (PFS) (1999–2004). Because many of the former students had parents who also participated in the LRC and PFS programs, the utility of parental CVD history as a screening tool could be evaluated. The sensitivity and specificity of the NCEP pediatric cutoff points were determined by using adult outcomes and lipid levels from the PFS. We hypothesized that sensitivity and specificity would vary with the age at which the pediatric lipid determination was made.

METHODS

Study Group

The subjects for the PFS were drawn from the Cincinnati Clinic of the LRC Prevalence Study (1972–1978). The LRC Prevalence Study was a multistage National Heart,

Lung, and Blood Institute survey of lipid levels and other CVD risk factors in 10 US and Canadian communities, plus Israel and the former Soviet Union.⁴ The Cincinnati LRC Prevalence Study studied students in grades 1 to 12 of the public and parochial schools in the Princeton School District.^{5–8} Briefly, the participating student population of the district was 73% white/27% black and 52.3% male/47.7% female. After an initial visit, at which total cholesterol and triglyceride levels were measured, a sample of the participants were recalled ~ 6 weeks later for a second visit, at which complete fasting lipid profiles were measured and the participant's family history of CVD was documented.⁶ At a third visit,⁸ all consenting first-degree relatives of selected index cases had the same data collected as at visit 2.

The purpose of the PFS was to assess 30-year changes in the familial associations of CVD risk factors. The PFS targeted former students and parents from LRC study visit 3 families, plus participants seen at LRC study visit 2 who had first-degree family members seen at visit 2. The study protocol was approved by the Children's Hospital institutional review board, and all participants gave signed informed consent. We restricted the analysis sample to PFS subjects who were 5 to 19 years of age at the LRC study visit and who underwent total cholesterol and/or LDL cholesterol measurement at the LRC study visit (total cholesterol, $n = 897$; LDL cholesterol, $n = 844$).

Clinical Measures

In both the LRC study and the PFS, data were collected with standard protocols.⁹ In each study, fasting blood samples were drawn into vacuum tubes containing ethylenediaminetetraacetic acid, kept on wet ice (LRC study) or cold packs (PFS), and delivered to the laboratory within 3 hours for processing; lipid profiles were measured in LRC Centers for Disease Control and Prevention-standardized laboratories. LDL cholesterol levels were calculated with the Friedewald formula but were measured through direct determination for all participants with triglyceride levels of >400 mg/dL in the LRC study or >350 mg/dL in the PFS. Direct LDL cholesterol quantification at the LRC has been described elsewhere⁶ and at the PFS was performed on the Hitachi 704 using the LDL-Plus package insert from Roche Diagnostics Corporation (Indianapolis, IN).

Statistical Analyses

Age was calculated as the age, in years, at the LRC study visit at which lipid levels were measured. Because there were few children at the ends of the age distribution, children who were 5 to 8 years of age were grouped, as were children who were 17, 18, and 19 years of age. Many subjects in this analysis had >1 lipid measurement as children in the LRC study. We used the visit 2 measurement if one was available or the visit 3 measure-

ments if there was no visit 2 measurement. If the subject had no visit 2 or visit 3 lipid measurements, then we used the total cholesterol measurement from visit 1. Therefore, there are fewer LDL cholesterol measurements than total cholesterol measurements in this analysis.

According to the NCEP pediatric guidelines, total cholesterol levels of ≥ 200 mg/dL (5.17 mmol/L) and LDL cholesterol levels of ≥ 130 mg/dL (3.36 mmol/L) defined elevated total cholesterol and LDL cholesterol levels, respectively.² Total cholesterol levels of 170 to 199 mg/dL and LDL cholesterol levels of 110 to 129 mg/dL are considered borderline by NCEP² but were not considered positive for elevated lipid status in this analysis. Each subject's lipid status (normal or elevated) as an adult in the PFS was the first outcome evaluated and was defined with the NCEP adult cutoff points for elevated total cholesterol levels (240 mg/dL, 6.21 mmol/L) and LDL cholesterol levels (160 mg/dL, 4.14 mmol/L).¹⁰ Subjects with total cholesterol (or LDL cholesterol) levels above the cutoff points in both the LRC study and the PFS were classified as having true-positive results, whereas those with levels above the cutoff point in the LRC study but not in the PFS were classified as having false-positive results. Similarly, subjects with levels below the cutoff values as children and adults were classified as having true-negative results, whereas those with levels below the cutoff values as children but above the cutoff values as adults were classified as having false-negative results. With the use of childhood lipid status as a predictor, the sensitivity (true-positive results divided by the sum of true-positive and false-negative results) and specificity (true-negative results divided by the sum of true-negative and false-positive results) of the NCEP pediatric cutoff values were estimated and reported as percentages. Use of lipid-lowering medication as an adult was counted as an indicator of elevated lipid levels in the PFS. The calculations were made for all subjects and for separate age groups.

The exact confidence intervals for the estimates of sensitivity and specificity were calculated on the basis of binomial probabilities, because of the small sample size of the age groups.¹¹ Positive and negative predictive values were also calculated. The positive predictive value was calculated as true-positive results divided by (true-positive results plus false-positive results), and the negative predictive value was calculated as true-negative results divided by (false-negative results plus true-negative results). Some of the analyses were also conducted according to gender and race.

Myocardial infarction, stroke, coronary bypass grafting, and angioplasty or other vascular surgery constituted CVD for these analyses. The second outcome evaluated was positive CVD history, reported by the subject at the PFS. Parental CVD history, to mimic NCEP screening, was determined with the parents' report if they also

participated in the PFS or with the subject's report if the parents did not participate. Parental CVD events at ≤ 55 years of age were considered to be premature for this analysis.² A parent who had total cholesterol levels of ≥ 240 mg/dL in the LRC study also indicated a positive parental history, in keeping with the NCEP pediatric guidelines. All analyses were performed with SAS 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

Subjects in this study were 28 to 48 years of age at the time of the PFS. Figure 1A illustrates the relationship between the LRC study LDL cholesterol values (childhood) and the PFS LDL cholesterol values (adult). The graph is divided into 4 quadrants, defined by the NCEP cutoff points of 130 mg/dL (child) and 160 mg/dL (adult). Thirty-four of the subjects in this analysis reported taking lipid-lowering medication as adults and therefore demonstrated artificially low adult lipid levels. For this analysis, they were classified as having elevated adult lipid levels and accordingly were counted as having true-positive or false-negative results. Data for total cholesterol levels were similar (Fig 1B). When percentages of false-negative results were computed for each age (data not shown), they averaged 8.5% for LDL cholesterol levels and 5.5% for total cholesterol levels at ages 5 to 14. There was a jump at age 15 and 16 to 16.5% for LDL cholesterol levels and to 13.5% (age 15) and 16.3% (age 16) for total cholesterol levels. A marked decrease in false-negative results occurred at age 17 for both lipids.

The lowest mean childhood LDL cholesterol and total cholesterol levels occurred consistently at 14 to 16 years of age, regardless of adult lipid status (Table 1). The differences in mean childhood lipid levels between subjects with and without elevated lipid levels as adults were generally less at ages 15 and 16 than at other ages. When these means were calculated according to gender or race (data not shown), the patterns were less consistent, probably because of the small population in each of the 10 age groups. Female ($n = 486$) and white ($n = 638$) subjects tended to follow the pattern of the entire population ($n = 898$), but male ($n = 412$) and black ($n = 260$) subjects did not show a consistent pattern.

The overall sensitivity for elevated LDL cholesterol levels in this population was 43.1% (95% confidence interval: 34.8%–51.6%), and the specificity was 86.1% (95% confidence interval: 83.4%–88.6%). The positive predictive value was 39%, and the negative predictive value was 88%. For elevated total cholesterol levels, the sensitivity was 44.2% (95% confidence interval: 35.1%–53.5%) and the specificity was 84.8% (95% confidence interval: 82.1%–87.3%). The positive predictive value was 31%, and the negative predictive value was 91%.

When the complete NCEP guidelines were applied and the analysis was restricted to children of parents

FIGURE 1

A, Childhood LDL cholesterol (LDL-C) levels in the LRC study, compared with adult LDL cholesterol levels in the PFS. Reference lines represent NCEP cutoff points for elevated LDL cholesterol levels. B, Adult total cholesterol levels in the LRC study, compared with adult LDL cholesterol levels in the PFS. Reference lines represent NCEP cutoff points for elevated total cholesterol levels.

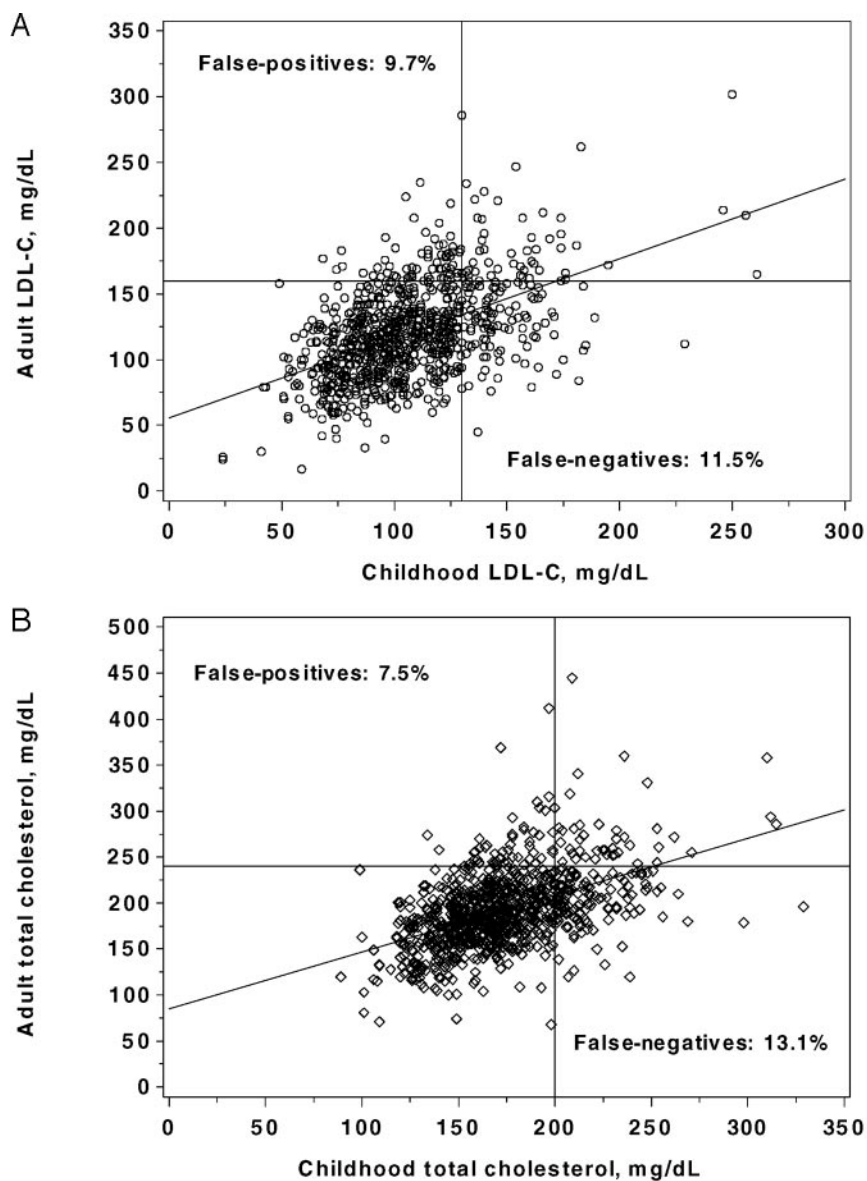


TABLE 1 Mean and SD of Childhood LDL Cholesterol and Total Cholesterol Levels at the Cincinnati Clinic of the LRC Prevalence Study According to Age and Lipid Status in the PFS

Age, y	Childhood LDL Cholesterol Level, mg/dL						Childhood Total Cholesterol Level, mg/dL					
	Nonelevated Adult LDL Cholesterol Level (<160 mg/dL, 4.14 mmol/L)			Elevated Adult LDL Cholesterol Level (\geq 160 mg/dL, 4.14 mmol/L)			Nonelevated Adult Total Cholesterol Level (<240 mg/dL, 6.21 mmol/L)			Elevated Adult Total Cholesterol Level (\geq 240 mg/dL, 6.21 mmol/L)		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
5–8	105.5	26.1	109	144.5	37.8	20	174.0	27.5	125	213.2	45.8	17
9	99.2	23.2	51	156.8	41.7	13	169.8	28.4	55	219.9	43.8	14
10	102.8	24.3	60	140.6	27.0	7	173.2	30.0	66	198.0	39.0	4
11	105.7	29.2	67	123.3	25.2	11	170.0	29.6	75	203.6	29.4	8
12	101.1	26.8	72	129.3	32.8	16	167.8	28.2	84	206.5	37.2	11
13	105.2	29.8	64	135.0	39.1	17	172.7	30.8	77	206.8	45.0	10
14	94.4	22.3	60	128.5	32.4	8	156.8	26.6	66	196.7	39.0	6
15	96.3	23.7	67	114.8	20.2	18	160.2	26.8	71	184.6	23.0	18
16	97.0	24.2	62	114.7	22.5	17	164.9	26.4	64	179.6	22.6	16
17–19	103.5	27.3	88	139.5	35.2	17	173.9	35.1	94	195.1	18.6	16

with premature CVD and/or total cholesterol levels of ≥ 240 mg/dL (6.21 mmol/L), the test sensitivity and specificity were not much affected. The sensitivity for elevated LDL cholesterol levels was 46.2% (95% confidence interval: 34.8%–57.8%) and the specificity was 84.4% (95% confidence interval: 79.8%–88.4%). The positive predictive value was 44%, and the negative predictive value was 86%. For elevated total cholesterol levels, the sensitivity was 45.5% (95% confidence interval: 33.1%–58.2%) and the specificity was 81.7% (95% confidence interval: 77.1%–85.7%). The positive predictive value was 33%, and the negative predictive value was 88%. We did not refine this analysis according to age because of the smaller number of subjects (LDL cholesterol, $n = 373$; total cholesterol, $n = 399$).

Because the overall sensitivity and specificity of LDL cholesterol and total cholesterol levels for those with parental CVD were similar to those of the larger PFS population, we examined the sensitivity and specificity for the entire population according to age. The sensitivities for each age group ranged from highs of 69% (LDL cholesterol) and 63% (total cholesterol) to lows of 22% (LDL cholesterol) and 18% (total cholesterol) (Fig 2A). The lowest sensitivities occurred at ages 14 to 16. The highest sensitivities occurred at ages 5 to 10 for LDL cholesterol and ages 5 to 11 for total cholesterol. There seemed to be an increase in the sensitivity by ages 17 to 19. The specificities were high (Fig 2B), consistent with the overall specificity, ranging from 77% to 96% for both LDL cholesterol and total cholesterol. The pattern

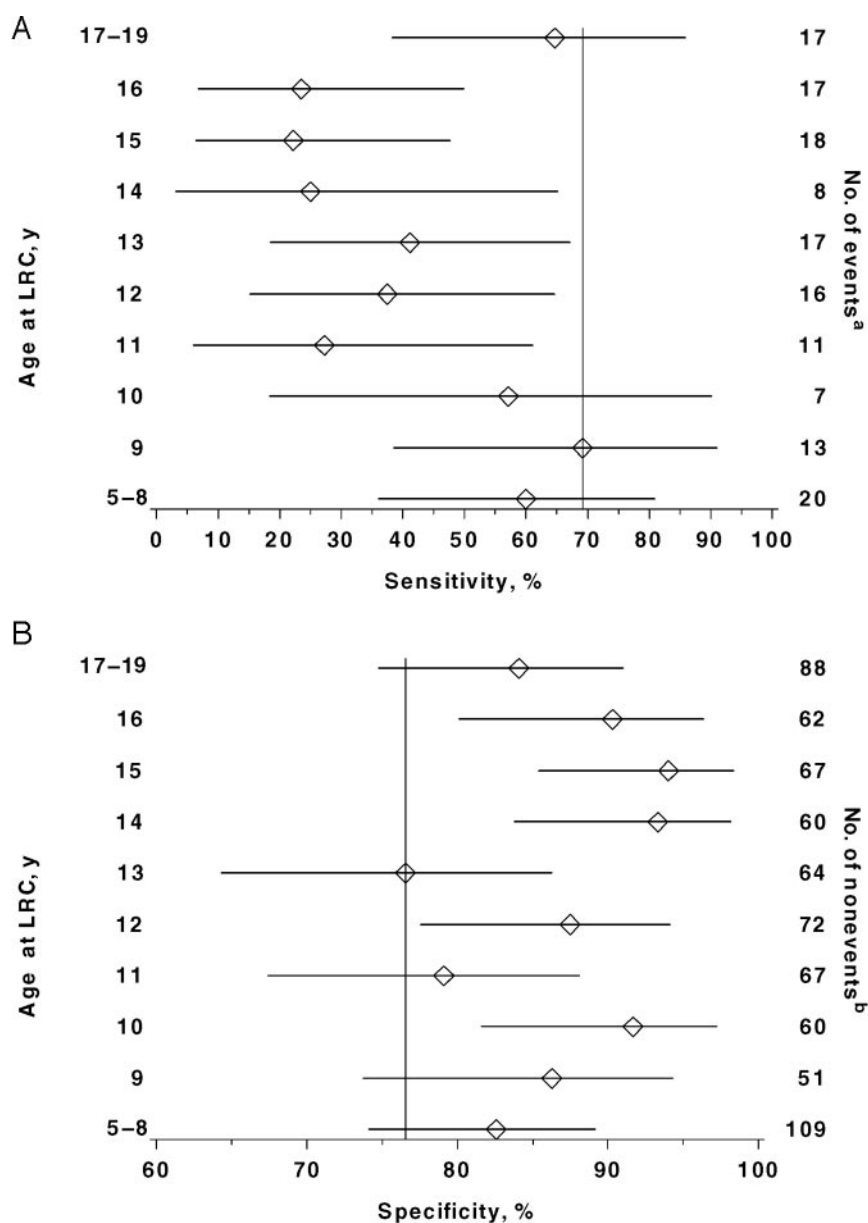


FIGURE 2

A, Sensitivity and 95% confidence intervals for childhood LDL cholesterol levels, according to age at the time of the LRC study. Diamonds indicate point estimates. B, Specificity and 95% confidence intervals for childhood LDL cholesterol levels, according to age at the time of the LRC study. Diamonds indicate point estimates. ^aAn event is the occurrence of elevated LDL cholesterol level at the adult (PRS) visit. ^bA nonevent is no occurrence of elevated LDL cholesterol level at the adult (PRS) visit.

of decrease in the sensitivities of LDL cholesterol levels at ages 14 to 16 was apparent in the confidence intervals as well as the point estimates. The specificities showed less variation than the sensitivities. The pattern for total cholesterol levels was similar to that for LDL cholesterol levels (Fig 3).

White subjects tended to follow the same trends in sensitivity according to age as did the entire population (data not shown). These sensitivities were low and dipped at ages 14 to 16. The specificities were all high. There was much less consistency in the results for black subjects, male subjects, and female subjects because of the small numbers in each age group, with the number of events (ie, elevated lipid levels as adults) all being <13.

The sensitivity of childhood lipid levels for predict-

ing adult CVD outcomes was lower than that for predicting adult lipid status, but the specificity was not much different. The sensitivity of childhood LDL cholesterol levels in predicting adult CVD was 10.5% (95% confidence interval: 1.3%–33.1%), and the specificity was 81.0% (95% confidence interval: 78.1%–83.6%). The sensitivity of childhood total cholesterol levels in predicting adult CVD was 20% (95% confidence interval: 5.7%–43.7%), and the specificity was 81.0% (95% confidence interval: 78.2%–83.5%). The number of adult CVD events (LDL cholesterol, $n = 19$; total cholesterol, $n = 20$) made it impossible to perform this analysis according to age. When the analysis was restricted to children with parental CVD or elevated cholesterol levels, the sensitivities increased to 11.1% for LDL cholesterol (95% confidence interval: 0.3%–48.3%) and 30%

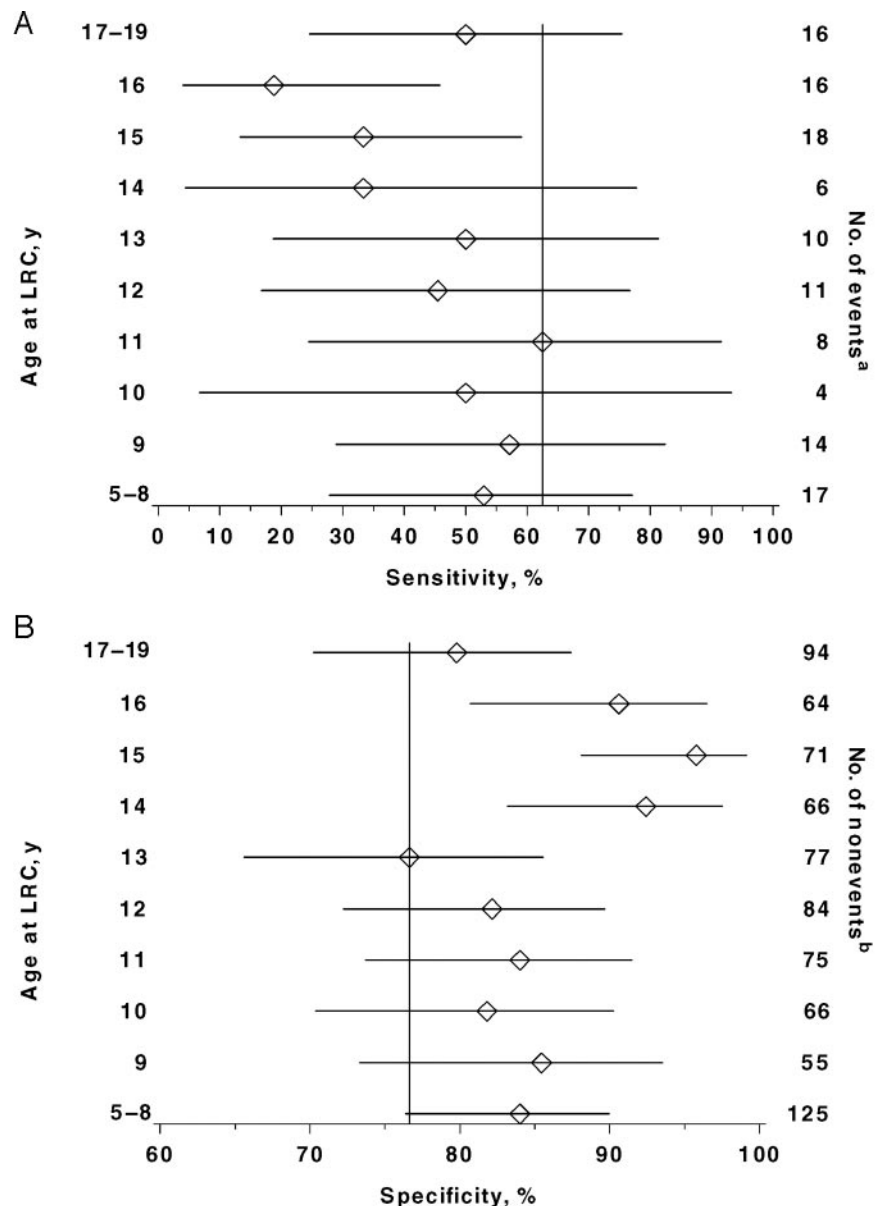


FIGURE 3
 A, Sensitivity and 95% confidence intervals for childhood total cholesterol levels, according to age at the time of the LRC study. Diamonds indicate point estimates. B, Specificity and 95% confidence intervals for childhood total cholesterol levels, according to age at the time of the LRC study. Diamonds indicate point estimates. ^aAn event is the occurrence of elevated total cholesterol level at the adult (PRS) visit. ^bA nonevent is no occurrence of elevated total cholesterol level at the adult (PRS) visit.

for total cholesterol (95% confidence interval: 6.7%–65.2%); the specificities for both lipids decreased to 77% (95% confidence intervals: 73%–82%).

DISCUSSION

The current pediatric recommendations for lipid screening among children use a 2-step approach.^{2,3} The first step is to identify children with a family history of premature CVD or elevated total cholesterol levels. The next step is to identify children with elevated lipid levels. This approach was chosen to minimize the false-positive values and to limit treatment of children with diet or medication to those who would qualify for treatment as adults. The results of our analyses suggest that the sensitivity and specificity for evaluating total cholesterol or LDL cholesterol levels that are elevated in adulthood are not improved by selecting children with a positive family history. The differences in overall sensitivity between the NCEP 2-step approach and analysis of the entire PFS population were 3% for LDL cholesterol and 1% for total cholesterol, whereas the differences in overall specificity were 2% for LDL cholesterol and 3% for total cholesterol. In addition, the positive predictive values (the probability of adult elevated LDL cholesterol levels given childhood elevated LDL cholesterol levels) were comparable for the NCEP and full-population approaches (44% and 39%, respectively). These comparable outcomes illustrate the limited benefits of targeted screening. Our data suggest that universal pediatric screening for lipid levels provides comparable prediction of adult values to a more-focused screening of children with family histories of heart disease. Indeed, a universal screening approach would have the advantage of not requiring the frequent updating of family history and could identify many who remain outside physicians' protocols for preventive therapy. However, the medical implications of treating children necessitate identification of individuals at particularly high vascular risk and not just those with hyperlipidemia. Furthermore, the direct and indirect costs of the screening program are relevant variables.

More-critical elements in the evaluation of a pediatric population are the well-known total cholesterol and LDL cholesterol level changes that occur concurrently with the maturational changes during puberty.^{8,12,13} In the PFS data reported here, the lowest childhood total cholesterol and LDL cholesterol levels occurred between the ages of 14 and 16. We found that, if lipid levels were measured at age 15, only 22% of the children who would have elevated LDL cholesterol levels as adults would be identified. In contrast, if lipid levels were measured at age 9, then 69% of the children who would have elevated LDL cholesterol levels as adults would be identified. This marked variation in sensitivities according to age suggests another limitation of the lipid-predicting value of the current guidelines. Because

children present to physicians at various ages, age-blinded screening can lead to misinterpretation of observed elevated serum LDL cholesterol values.

Although there is often clinical value in using cutoff points to determine low-risk and high-risk groups, risk groups should be defined according to known predictive factors.^{14,15} NCEP adult guidelines were constructed with known risk factors related to actual CVD events.^{10,14} Because the NCEP pediatric recommendations are based on less-direct evidence^{3,16} (ie, lack of longitudinal data and CVD events), it is not surprising that the sensitivity for lipid measurements in any population of children would be low. The longitudinal data available from this study could be helpful for developing new pediatric guidelines for lipid screening in the future.

The strength of this study lies in the measurement of lipid values in childhood and adulthood for the same subjects. This study evaluated LDL cholesterol levels, in addition to total cholesterol levels, and the impact of age, unlike an earlier analysis of the Muscatine Study.¹⁷ Limitations include the fact that the small number of CVD events at this time does not allow a definitive interpretation of the relationship between childhood lipid levels and resulting adult CVD, because the oldest subject was 48 years of age at the time of follow-up assessment. Unfortunately, the sample size was too small to allow any meaningful conclusions about race and gender.

Additional follow-up of this population as it ages would allow a more-conclusive analysis of the relationship between childhood lipid levels and CVD events later in life. With the use of this study and, it is hoped, other studies designed to evaluate the risk of elevated childhood lipid levels, the appropriate lipid-screening algorithm could be developed for clinical use. Continued prospective and longitudinal studies designed with age as well as other risk parameters are needed to determine the best guidelines for pediatric clinical screening in the future. This should be the aim of the NCEP.

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Gordon ME. *N Engl J Med*. 354;16, April 20, 2006

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