Utility of Currently Recommended Pediatric Dyslipidemia Classifications in Predicting Dyslipidemia in Adulthood

Evidence From the Childhood Determinants of Adult Health (CDAH) Study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study

Costan G. Magnussen, BHM; Olli T. Raitakari, MD, PhD; Russell Thomson, PhD; Markus Juonala, MD, PhD; Dharmendrakumar A. Patel, MD, MPH; Jorma S.A. Viikari, MD, PhD; Jukka Marniemi, PhD; Sathanur R. Srinivasan, PhD; Gerald S. Berenson, MD; Terence Dwyer, MD, MPH; Alison Venn, PhD

Background—New age- and sex-specific lipoprotein cut points developed from National Health and Nutrition Examination Survey (NHANES) data are considered to be a more accurate classification of a high-risk lipoprotein level in adolescents compared with existing cut points established by the National Cholesterol Education Program (NCEP). The aim of this study was to determine which of the NHANES or NCEP adolescent lipoprotein classifications was most effective for predicting abnormal levels in adulthood.

Methods and Results—Adolescent and adult measures of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were collected in 365 Australian, 1185 Finnish, and 273 US subjects participating in 3 population-based prospective cohort studies. Lipoprotein variables in adolescence were classified according to NCEP and NHANES cut points and compared for their ability to predict abnormal levels in adulthood. With the use of diagnostic performance statistics (sensitivity, specificity, positive predictive value, negative predictive value, area under receiver operating characteristic curve) in pooled and cohort-stratified data, the NHANES cut points (compared with NCEP cut points) were more strongly predictive of low high-density lipoprotein cholesterol in adults but less predictive of high total cholesterol, high low-density lipoprotein cholesterol, and high triglyceride levels in adults. We identified heterogeneity in the relative usefulness of each classification between cohorts.

Conclusions—The separate use of NHANES cut points for high-density lipoprotein cholesterol and NCEP cut points for total cholesterol, low-density lipoprotein cholesterol, and triglycerides yielded the most accurate classification of adolescents who developed dyslipidemia in adulthood. (Circulation. 2008;117:32-42.)

Key Words: dyslipidemia ■ epidemiology ■ lipoproteins ■ pediatrics ■ screening

Abnormal lipoprotein levels in children and adolescents have been associated with preclinical atherosclerosis.1–3 Prospective cohort studies have shown that lipoprotein levels not only track strongly from childhood and adolescence to adulthood4–6 but that adverse lipoprotein levels in early life may induce arterial changes that contribute to adult atherosclerosis.7–10 Coupled with data that have found lifestyle and pharmacological intervention in children and adolescents to be effective in modifying lipoprotein levels11–14 and improving markers of atherosclerosis,14–16 these findings provide justification for the development of lipoprotein cut points to identify (1) those at high risk for cardiovascular disease (CVD) later in life and (2) those who may benefit most from intervention.

Editorial p 9

Clinical Perspective p 42

The National Cholesterol Education Program (NCEP) has published a single set of cut points for children and adolescents 2 to 19 years of age that can be used to identify those with abnormal lipoprotein levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides.
tein (HDL) cholesterol, and triglycerides. Although these cut points have been adopted in primary prevention guidelines of the American Heart Association and American Academy of Pediatrics as the basis for identifying children and adolescents at high-risk of CVD, the NCEP cut points do not take into account age- and sex-specific differences in lipoprotein concentrations that have been shown to occur with growth and maturation. As a result, Jolliffe and Janssen have recently proposed new lipoprotein cut points for adolescents 12 to 19 years of age based on combined data from 3 National Health and Nutrition Examination Surveys (NHANES). These cut points were derived with the use of age- and sex-specific growth curves that were linked to adverse adult lipoprotein thresholds established by the NCEP Adult Treatment Panel.

Before the new NHANES cut points can be adopted for use in clinical practice, it is necessary to directly compare the ability of the NCEP and NHANES adolescent lipoprotein classifications to predict dyslipidemia later in life with the use of independent data sets. The aim of this study was to compare the ability of the NCEP and new NHANES adolescent lipoprotein classifications to predict abnormal lipoprotein levels in adulthood with the use of data from 3 different cohort studies. As a secondary aim, we evaluated the effect of different screening strategies on the ability to identify adolescents who would develop dyslipidemia as adults.

**Methods**

This study used data from 3 population-based, prospective cohort studies conducted in Australia, Finland, and the United States. Each study was approved by local ethics committees, and informed consent was obtained from all participants before entry into the study.

**Australian Data (Childhood Determinants of Adult Health Study)**

**Study Sample**

The Childhood Determinants of Adult Health (CDAH) study was established to examine childhood predictors of adult cardiovascular disease and diabetes mellitus. Baseline data were collected in 1985 on a representative sample of 8498 school children 7 to 15 years of age as part of the Australian Schools Health and Fitness Survey. Extensive lifestyle and biological risk variables were measured, including lipoproteins on a subsample (n = 1919) of children 9, 12, and 15 years of age. Sampling procedures and methods of data collection for the Australian Schools Health and Fitness Survey have been described in detail elsewhere. In 2004–2006, a total of 3170 participants (61%) from the original cohort provided data to the follow-up study. Of these, 2410 participants were reexamined at 34 field-work clinics across Australia. In this study, we analyzed data from 365 participants (35% of those eligible from baseline, 49% male) aged 12 and 15 years at baseline who had lipoprotein data available in 1980 and 2001 and who were aged 12, 15, and 18 years at baseline (in 1980).

**Measures**

Venous blood samples were collected at baseline and follow-up from the antecubital vein after an overnight fast. In 1985, the Lipid Research Clinics procedures for blood sampling and analysis were followed. In 2004–2006, total cholesterol and triglycerides were determined with the use of a Technicon Auto Analyzer II (Technicon Instrument Corp, Tarrytown, NY), and HDL cholesterol was analyzed after precipitation of apoprotein-B–containing lipoproteins with heparin-manganese. In 2004–2006, total cholesterol, triglyceride, and HDL cholesterol concentrations were determined enzymatically with the use of an Olympus AU5400 automated analyzer (Olympus Optical, Tokyo, Japan). LDL cholesterol concentration was determined indirectly by the Friedewald formula.

**Finnish Data (Cardiovascular Risk in Young Finns Study)**

**Study Sample**

The Cardiovascular Risk in Young Finns Study is an ongoing epidemiological study of atherosclerosis risk factors and precursors from childhood to adulthood. In 1980, 3596 children and adolescents aged 3, 6, 9, 12, 15, and 18 years participated in the first cross-sectional study. The study was performed in all 5 Finnish university cities with medical schools (Helsinki, Kuopio, Oulu, Tampere, Turku) and their rural surroundings. Study subjects were chosen randomly from national population registers from these areas. Details of the study design have been presented elsewhere. The most recent follow-up study was performed between September 2001 and January 2002, when 2283 subjects from the original cohort (63%) participated in the study. In the present analysis, we included 1185 subjects (66% of those eligible from baseline, 45% male) with lipoprotein data available in 1980 and 2001 and who were aged 12, 15, and 18 years at baseline (in 1980).

**Measures**

All serum lipid determinations were performed on fasting samples in duplicate in the same laboratory. In 2001, serum cholesterol and triglyceride concentrations were determined enzymatically (Olympus System Reagent, Olympus Diagnostica, Hamburg, Germany) in a clinical chemistry analyzer (AU400, Olympus Optical, Mishima, Japan). HDL cholesterol was analyzed after precipitation of very low-density lipoprotein and LDL cholesterol was calculated by the Friedewald formula. Details of the methods in earlier studies have been published previously. Because of changes in determination methods and kits during study years, lipoprotein levels from 1980 were corrected to those in 2001 with the use of correction factor equations.

**US Data (Bogalusa Heart Study)**

**Study Sample**

The Bogalusa Heart Study is a biracial community-based investigation of the early natural history of CVD. The study cohort was derived from individuals who participated in the 1984–1985 cross-sectional survey of 2666 children and in the 2001–2002 cross-sectional survey of 1203 young adults. For this study, 273 participants (18% of those eligible from baseline, 44% male, 29% black) aged 12 to 17 years at baseline who had fasting lipid and lipoprotein data available from both baseline (1984–1985) and follow-up (2001–2002) surveys were selected.

**Measures**

Standardized protocols were used by trained observers in all examinations. In 1984–1985, cholesterol and triglyceride levels were measured with a Technicon Auto Analyzer II (Technicon Instrument Corp, Tarrytown, NY), according to the laboratory manual of the Lipid Research Clinics program. In 2001–2002, cholesterol and triglyceride levels were determined by enzymatic procedures with a Hitachi 912 Automatic Analyzer (Roche Diagnostics, Indianapolis, Ind). Lipoprotein cholesterol levels were analyzed with a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.

**Classification of Lipoprotein Status in Adolescence and Adulthood**

Status of lipoprotein variables in adolescents was defined according to NCEP and NHANES classifications (Table 1 in the online-only Data Supplement). In adulthood, NCEP Adult Treatment Panel guidelines for total cholesterol (≥6.22 mmol/L; ≥240 mg/dL), LDL
cholesterol ($\geq 4.14$ mmol/L; $\geq 160$ mg/dL), HDL cholesterol ($< 1.036$ mmol/L; $< 40$ mg/dL), and triglycerides ($\geq 2.26$ mmol/L; $\geq 200$ mg/dL) were used to identify those at high risk (ie, those with substantially increased risk of CVD).24

Statistical Analyses
Two CDAH participants (1 male), 5 Young Finns participants (all male), and 7 Bogalusa participants (3 males) were currently taking lipid-lowering medications at follow-up and were removed from the analyses. Including or excluding these participants in the analyses made no difference to the final results presented.

Descriptive Analyses
Descriptive statistics were used to summarize participant characteristics at baseline and follow-up for each cohort. Continuous variables were expressed as mean±SD, and dichotomous variables were presented as proportions.

Prediction of Abnormal Lipoprotein Levels in Adulthood

Relative Risks
Log-binomial regression was used to examine associations between baseline lipoprotein classifications and the development of abnormal levels at follow-up. Relative risks and 95% confidence intervals (CIs) were calculated for cohort-stratified and pooled data. Estimates were adjusted for age at baseline, sex, and change in body mass index (body mass index=weight in kilograms divided by height in meters squared) rank between adolescence and adulthood. Analyses of Bogalusa data were additionally adjusted for race; pooled estimates were additionally adjusted for cohort and length of follow-up. Interactions between cohort and adolescent lipoprotein classifications were added to each pooled model and examined for significance. Significant interactions were present between cohort and NCEP HDL cut points and between cohort and NHANES HDL cut points. These data are considered in Results. Body mass index data were not available for 44 Australian, 8 Finnish, and 2 US participants at follow-up. Hence, log-binomial analyses were performed on reduced sample sizes of up to 319 CDAH, 1172 Young Finns, and 264 Bogalusa participants.

Direct Comparisons of NCEP Versus NHANES Classifications
The ability of each adolescent lipoprotein classification to predict abnormal adult levels was assessed with the use of diagnostic performance statistics, including the following: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under receiver operating characteristic curves (AUC). Sensitivity was calculated as true positives/(true positives+false negatives), specificity as true negatives/(true negatives+false positives), PPV as true positives/(true positives+false positives), and NPV as true negatives/(false negatives+false negatives). Tests for significant differences of sensitivity and specificity between NCEP and NHANES adolescent cut points were performed with the use of the McNemar test.37 CIs for sensitivity and specificity were calculated with the use of the binomial distribution. The AUC has a range of 0 to 1; a value of 0.5 represents no discrimination, and a value of 1 indicates perfect discrimination. Tests for significant differences between AUC for each adolescent lipoprotein classification were calculated with the DeLong algorithm.38 This method assumes the correct null distribution when there are only 3 classification levels, as is the case here (confirmed through simulation; data not shown).

Point estimates for pooled data are presented in Results, with cohort-stratified data presented graphically. Log-binomial regression analyses and diagnostic performance statistics were calculated twice for each data set: the first with the use of NCEP cut points and the second with the use of NHANES cut points. All analyses were performed with the use of STATA version 9.2 (STATA Corp, College Station, Tex), and statistical significance was inferred as a 2-tailed $P \leq 0.05$. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
To determine whether those participants analyzed in this study were representative of the original eligible cohorts, we compared baseline characteristics between participants and those lost to follow-up. Those lost to follow-up were more likely to be younger and male in all cohorts and black in the Bogalusa cohort (all $P<0.05$), but no significant differences were present between participants and nonparticipants in any of the 3 cohorts in total cholesterol, LDL cholesterol, HDL cholesterol, or triglyceride levels in age- and sex-adjusted analyses (data not shown).

Adolescent and Adulthood Levels
Adolescent and adult levels of lipoprotein variables and the proportion of adults classified with lipid disorders in each study cohort are displayed in Table I (see Table II in the online-only Data Supplement for values in mg/dL). The proportions of adolescents within normal-, borderline-, and high-risk categories according to NCEP and NHANES lipoprotein variable classifications are provided in Table III in the online-only Data Supplement. With the exception of HDL cholesterol, females tended to have a worse lipoprotein profile in adolescence compared with their male counterparts, but this trend was reversed in adulthood. Compared with adult women, a higher proportion of adult men were classified as having abnormal levels of LDL cholesterol, HDL cholesterol, and triglycerides across all cohorts. The data do not allow direct comparisons of Australian, Finnish, and US participants owing to dissimilar age distributions between cohorts and differences in lipoprotein measurement methods.

Prediction of Abnormal Levels of Lipoprotein Variables in Adulthood

Relative Risks
Adjusted relative risks for developing abnormal lipoprotein levels in adulthood across NCEP and NHANES lipoprotein cut points are shown in Figure 1 (cohort-stratified and pooled data) and Table IV in the online-only Data Supplement (pooled data point estimates). The pooled data showed that the risk of developing an abnormal condition in adulthood was significantly higher in those adolescents with borderline- and high-risk levels compared with those with normal levels for all lipoprotein variables. Moreover, a graded increase in the risk of developing abnormal levels in adulthood was observed when moving from the normal, to borderline-risk, to high-risk groups. With the exception of the NHANES high-triglyceride threshold in the CDAH cohort (which had no adolescent cases develop the risk factor in adulthood), stratified analyses indicated similar relative risk patterns for borderline- and high-risk classified adolescents in each cohort. Interaction terms between cohort and both NCEP and NHANES HDL cholesterol cut points were significant, suggesting that the relationship between adolescent risk status and the development of
abnormal HDL cholesterol levels as adults differed between cohorts. We have included the pooled estimates for HDL cholesterol for completeness; however, in light of the significant interaction, the pooled estimates should be interpreted with caution. Instead, interpretations are best made with the relative risks stratified by cohort (Figure 1). In cohort-stratified analyses, it is evident that the relative risks for HDL cholesterol in the Bogalusa data were substantially lower than estimates from CDAH and Young Finns data (Figure 1); race-stratified data indicated that the HDL cholesterol classifications predicted abnormal levels in adulthood for blacks but not whites (data not shown).

**Direct Comparisons of NCEP Versus NHANES Classifications**

Diagnostic performance statistics of NCEP and NHANES adolescent cut points in the pooled data are presented in Table 2. Cohort-stratified and pooled data for sensitivity and specificity of high-risk cut points are presented in Figure 2. Where sample sizes permitted, sex-, age-, or race-stratified (Bogalusa) analyses were comparable with
Figure 1. Relative risks and 95% CIs of developing abnormal lipoprotein variable levels in adulthood according to borderline- and high-risk lipoprotein status in adolescence with the use of NCEP and NHANES classifications. Estimates were adjusted for age at baseline, sex, and change in body mass index rank between adolescence and adulthood; Bogalusa analyses were additionally adjusted for race; estimates from pooled data were additionally adjusted for cohort and length of follow-up. Adolescents classified as normal were used as the referent group. All \( P \leq 0.01 \) (analysis for trend) unless otherwise noted.
the final results presented (data not shown). Borderline- and high-risk NCEP cut points for total cholesterol were considerably more sensitive than the corresponding NHANES cut points, with modest to high trade-offs in specificity. Although this trend was consistent across each cohort, substantial heterogeneity existed in the sensitivity point estimates and CIs between studies (Figure 2). Of those adults with abnormal total cholesterol levels, 32.3% would not be identified in adolescence with the high-risk NCEP cut point, and 60.6% would not be identified in adolescence with the equivalent NHANES cut point. The proportion classified as high risk during adolescence that did not develop the risk factor in adulthood (false-positives) was 72.4% for NCEP and 68.7% for NHANES classifications.

The NCEP borderline- and high-risk LDL cholesterol cut points were more sensitive and less specific than the NHANES cut points (Table 2, Figure 2). The trade-off in sensitivity gain and specificity loss between both classifications was particularly noticeable at the high-risk cut point. The NHANES high-risk cut point did not identify 35.0%. A small improvement in PPV was observed when concentrations as opposed to the NCEP cut point, which did not identify 55.4% of those adults with an abnormal LDL cholesterol concentration as opposed to the NCEP cut point, which did not identify 35.0%. A small improvement in PPV was observed when concentrations were compared. We observed considerable heterogeneity in sensitivities when cohort-stratified plots were compared.

For HDL cholesterol, the best combination of diagnostic performance statistics was produced when concentrations were classified by the NHANES borderline- and high-risk cut points (Table 2, Figure 2). Even though sensitivity of the NHANES high-risk cut point was higher than the corresponding NCEP cut point, both classifications performed relatively poorly, ie, 83.3% and 93.3% of the adults with low HDL cholesterol would not be identified with the use of the NHANES and NCEP high-risk cut point, respectively. The PPV for the high-risk NCEP cut point was higher than the NHANES cut point. Evaluation of AUC indicated that NHANES cut points were significantly better at predicting low HDL in adulthood than NCEP cut points. Increased sensitivity of the high-risk cut point and gains in specificity at the borderline-risk cut point for NHANES compared with NCEP classifications is likely to explain these differences.

The NCEP classification for triglycerides was a better predictor of high triglycerides in adulthood compared with the NHANES classification. For both borderline- and high-risk cut points, gains in sensitivity were relatively large compared with modest trade-offs in specificity (Table 2, Figure 2). In practical terms, however, the sensitivities of both classifications were poor. The classifications did not identify 86.0% (NCEP) and 97.7% (NHANES) of adults with a high triglyceride level. Significantly higher AUC is a reflection of increased sensitivity across all NCEP cut points.

### Additional Analyses: Evaluation of Different Screening Strategies

We evaluated whether different screening strategies had an effect on the ability to identify adolescents who would develop associated dyslipidemia as adults. In these analyses, we considered the existing NCEP pediatric screening algorithm that uses positive family history as a criterion before children and adolescents are subject to lipoprotein analysis. The Young Finns cohort was chosen for these analyses to maximize sample numbers and take advantage of comprehensive data on family history of premature coronary heart disease available from the 2001 follow-up survey. To identify adolescent Finns who may develop high-risk levels as adults, the following screening strategies were employed: (1) universal (whole- or random-population) screening employing the best-performing high-risk cut points from earlier analyses; (2) positive family history of coronary heart disease and lipoprotein levels exceeding best-performing high-risk cut points; (3) overweight or obesity according to International...
Figure 2. Sensitivity, specificity, and 95% CIs for predicting abnormal lipoprotein variable levels in adulthood for adolescents classified as high risk with the use of NCEP and NHANES cut points.
Obesity Task Force criteria and lipoprotein levels exceeding best-performing high-risk cut points; and (4) positive family history of coronary heart disease or overweight-obesity and lipoprotein levels exceeding best-performing high-risk cut points. Sensitivity, specificity, PPV, NPV, and AUC for different screening strategies are presented in Table 3. Additional illustrations and data comparing false-positive and false-negative rates and the proportion identified/not identified and degree of overlap between screening strategies are presented in the online-only Data Supplement. Because results for total cholesterol and LDL cholesterol and results for HDL cholesterol and triglycerides were similar, we focus on LDL cholesterol and HDL cholesterol results herein.

Adding positive family history and/or overweight-obesity status to the NCEP high-risk cut point only marginally improved the identification of adolescent Young Finns who would develop abnormal LDL cholesterol levels as adults compared with universal screening. Forty-three participants (20%) with high LDL cholesterol levels at follow-up were not identified by any of the screening strategies (Figure I in the online-only Data Supplement). Universal screening alone identified 75% of participants with high LDL cholesterol levels at follow-up but at a high trade-off in false-positives (66.2%). The absolute numbers of participants identified with the use of family history, overweight-obesity, or family history/overweight-obesity were considerably lower than universal screening, but false-positive proportions remained high (58.5%, 66.7%, 62.6%, respectively; Figure II in the online-only Data Supplement). We observed improvements in sensitivity, specificity, and PPV when NHANES HDL cholesterol high-risk cut points were combined with family history, overweight-obesity status, or family history/overweight-obesity compared with universal screening. Regardless of the adolescent screening strategy employed, most adults (71%) with low HDL cholesterol levels were not identified at baseline (Figure III in the online-only Data Supplement). Selective screening of HDL cholesterol in those with family history, overweight-obesity, or family history/overweight-obesity identified fewer total cases but at a considerably lower proportion of false-positives compared with universal screening (Figure II in the online-only Data Supplement). Interestingly, screening adolescents by positive family history or overweight-obesity, or family history/overweight-obesity identified more total and unique at-risk individuals compared with universal HDL cholesterol screening (Figure III in the online-only Data Supplement).

**Discussion**

Age- and sex-specific lipoprotein cut points developed from NHANES data have been proposed to provide a more accurate classification of high-risk lipoprotein levels in adolescents compared with the current NCEP classification. However, there have been no studies to assess whether the NHANES cut points improve the prediction of those individuals who will develop associated dyslipidemia in adulthood. In this study, we examined data from 1809 participants in 3 prospective cohort studies who had...
lipoprotein variables collected during adolescence and again in adulthood with a mean follow-up of 20.2 years. After adjustment for potential confounding variables, our pooled and cohort-stratified data show a progressive and substantial increase in the relative risk of adolescents with borderline- or high-risk lipoprotein levels, whether defined according to NCEP or NHANES cut points, to develop associated dyslipidemia 15 to 20 years later. These findings are consistent with reports that have shown that lipoprotein levels maintain rank order (track) from adolescence to adulthood and emphasize the usefulness of evaluating lipoprotein variables to identify adolescents who may benefit from intervention. The present study directly compared differences in the predictive capacity of the NCEP and NHANES lipoprotein variable cut points. The new NHANES cut points for HDL cholesterol offered a better prediction of those adolescents most likely to develop abnormal levels in adulthood, whereas the predictions for total cholesterol, LDL cholesterol, and triglycerides were poorer than those achieved with the NCEP classification. These results are surprising given that the new NHANES cut points recognize age and sex shifts during adolescence and are linked to evidence- and health-based adult NCEP Adult Treatment Panel thresholds. In interpreting these data, we need to take into account the populations examined in this study and to consider the practical implementation of these findings to revision of pediatric cut points in a likely update to the guidelines.39

Because the cohorts used in this study collected baseline data in the early to mid 1980s, it is necessary to consider secular trends in lipoprotein data over this time in consideration of the performance of both NCEP and NHANES cut points. Secular trend data from the Young Finns cohort have showed modest decreases in total cholesterol and LDL cholesterol, more substantial decreases in HDL cholesterol, and increases in triglyceride levels in both adolescents and young adults since 1980. Moreover, when the source populations for each adolescent classification are examined, it is evident that levels of total cholesterol, LDL cholesterol, and HDL cholesterol were lower and triglyceride levels were higher in the NHANES studies than in the Lipid Research Clinics Prevalence Study, from which the NCEP cut points were derived. This trend is consistent when adolescent lipoprotein variable levels in CDAH, Young Finns, and Bogalusa cohorts are compared with levels from NHANES. This is not surprising given that baseline data were collected before the more recent obesity epidemic, whereas the NHANES data were collected during this period. It is possible that the observed gains in predictive power of the NCEP cut points in our data could be attributed to the period when the cut points were developed (reflecting the population distribution at the time). We cannot discount that the NHANES cut points may provide a more accurate classification of today’s adolescents. Prospective studies of the type used in this study, with periods of follow-up that span adolescence and early adulthood, will always be subject to this limitation.

Heterogeneity between cohort data was apparent. Although comparisons of NCEP versus NHANES cut points showed similar patterns within cohorts, the relative value of the cut points in each population differed considerably. Discrepancies in the sensitivity and specificity of high-risk cut points were evident between studies when each classification was considered separately (Figure 2), particularly for total cholesterol and LDL cholesterol. For example, in adults with abnormal total cholesterol levels, 27.8% of Australians, 77.8% of Finns, and 42.9% of Americans would have been identified in childhood with the use of the NCEP high-risk cut point. The value of these cut points for screening should be considered in different population settings. For example, the efficacy of universal screening with the use of the NCEP total cholesterol cut points in a Finnish population would be different from that in an Australian population. We do not believe that selection bias explains these differences because baseline lipoprotein variables for participants and nonparticipants at follow-up were similar in each cohort.

Noticeable differences in lipoprotein levels were apparent between countries in our data, which may partly explain the degree of heterogeneity observed. Because different methods were used for lipoprotein determination, it would be erroneous to conclude that these necessarily reflect population differences. For example, several studies have shown that HDL cholesterol levels vary depending on the method of determination.42–44 Using standardized methods for lipid determination, Knuiman et al demonstrated between-country differences in total cholesterol and HDL cholesterol concentrations in 7- to 8-year-old boys from 16 countries and differences in HDL cholesterol concentrations in 33- to 48-year-old men from 13 countries.46 The heterogeneity observed in this study is likely a function of both actual differences and methodological differences. It is reassuring that the best-performing classifications for each lipoprotein variable were consistent between cohorts despite differences in laboratory methodology for lipoprotein variable determination.

The existing pediatric guidelines recommend targeted lipoprotein screening in children and adolescents with a positive family history of premature CHD or high total cholesterol levels (≥6.2 mmol/L; 240 mg/dL), with a recent update recommending screening children who are overweight or obese.39 From our screening data in the Young Finns cohort, we are unable to provide a clear recommendation on the best screening approach (universal versus selective) for clinical use in adolescents. For example, universal screening and selective screening for total cholesterol and LDL cholesterol are not acceptable with rates of false-positives that suggest that ≈60% of adolescents identified as having high-risk levels would not have abnormal levels in early adulthood. However, universal screening comes with the benefit of identifying 75% of those affected in adulthood. Neither universal nor selective screening for HDL cholesterol or triglycerides was efficient in identifying those adolescents who developed abnormal levels as adults. Although selective HDL cholesterol screening reduced the false-positive rate compared with universal screening, the strategies were inefficient at identifying adolescents who developed low HDL cholesterol levels as adults. This is highlighted by the fact that using overweight or obesity status or positive family history alone to indicate an adolescent’s risk identified more total cases than any form of HDL cholesterol screening. In consideration of these
findings with current pediatric recommendations that endorse a selective screening approach, clinicians need to observe that a substantial number of adolescents with LDL cholesterol abnormalities will not have high-risk levels in early adulthood and that most individuals who develop low HDL cholesterol levels as adults will not be identified in adolescence.

Several limitations are evident in this study. First, misclassification of lipoprotein status may have occurred by using a single lipoprotein measurement at baseline and follow-up. Nevertheless, the results were largely unchanged when repeat adolescent measures were considered for Young Finns (data not shown). Second, owing to the low number of blacks in our data, we advocate caution in the application of conclusions from this study to biracial populations until more data are available. Third, this study used lipoprotein risk status in adulthood as the outcome of interest and did not establish whether the 2 adolescent classifications predict clinically relevant end points such as the presence and progression of atherosclerosis or CVD events. Fourth, we applied cut points derived from, and intended for, US populations to Australian and Finnish data. Although our data suggest that the adolescent cut points could be generalized to other populations of European ancestry, applying them without consideration of possible country- or region-specific differences may not be optimal. Finally, our measure of family history of prematurity CHD in the Young Finns cohort was acquired at follow-up and not during baseline examination.

Our findings suggest that the separate use of NHANES cut points for HDL cholesterol and NCEP cut points for total cholesterol, LDL cholesterol, and triglycerides provided the most accurate classification of normal-, borderline-, and high-risk lipoprotein levels in adolescents.

Acknowledgments

We gratefully acknowledge the contributions of data collection teams across all 3 study centers. Above all, we thank the children and adults who participated in these studies. We also thank Dr Seana Paul for valuable feedback on the final manuscript.

Sources of Funding

The CDAH study was financially supported by the National Health and Medical Research Council (project grant 211316) and the Heart Foundation (award GOOH 0578). The Cardiovascular Risk in Young Finns study was financially supported by the Academy of Finland (grants 117941, 77841, 210283), the Social Insurance Institution of Finland, the Turku University Foundation, Special Federal Grants for the Turku University Central Hospital, the Juho Vainio Foundation, the Finnish Foundation of Cardiovascular Research, and the Finnish Cultural Foundation. The Bogalus Heart Study was financially supported by National Institutes of Health grants AG-16592 from the National Institute of Aging and HL-38844 from the National Heart, Lung, and Blood Institute.

Disclosures

Dr Raitakari has received research grants from the Academy of Finland. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Good prospective evidence exists that children and adolescents with abnormal lipid and lipoprotein levels are not only at risk of becoming adults with abnormal levels but that exposure to adverse levels in early life may induce arterial changes that facilitate atherosclerosis. Because of this evidence, there has been a resurgent interest in screening children and adolescents for dyslipidemias to identify those at high risk for cardiovascular disease later in life and those who may benefit from early intervention. Although 2 groups (the National Cholesterol Education Program and Jolliffe and Janssen [Circulation. 2006;114:1056–1062]) have proposed pediatric cut points for normal, borderline, and high-risk lipoprotein levels, no study has assessed which of these classifications is most effective for predicting those adolescents who will develop abnormal levels in adulthood. On the basis of pooled data from 3 prospective cohort studies from Australia, Finland, and the United States, our results suggest that clinicians wishing to identify lipid disorders in adolescents would likely improve risk stratification by the separate adoption of cut points for high-density lipoprotein cholesterol stipulated by Jolliffe and Janssen and National Cholesterol Education Program–stipulated cut points for total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Our data also suggest that clinicians employing current pediatric guidelines for targeted lipoprotein screening in children and adolescents with a positive family history of premature coronary heart disease or who are overweight or obese need to consider that a substantial number of those adolescents identified with high total cholesterol or low-density lipoprotein cholesterol levels will not have high-risk levels in early adulthood and that most individuals who develop abnormal high-density lipoprotein cholesterol or triglyceride levels as adults will not be identified in adolescence.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
Utility of Currently Recommended Pediatric Dyslipidemia Classifications in Predicting Dyslipidemia in Adulthood: Evidence From the Childhood Determinants of Adult Health (CDAH) Study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study

Costan G. Magnussen, Olli T. Raitakari, Russell Thomson, Markus Juonala, Dharmendrakumar A. Patel, Jorma S.A. Viikari, Jukka Marniemi, Sathanur R. Srinivasan, Gerald S. Berenson, Terence Dwyer and Alison Venn

_Circulation_. 2008;117:32-42; originally published online December 10, 2007; doi: 10.1161/CIRCULATIONAHA.107.718981

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/117/1/32

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2007/12/10/CIRCULATIONAHA.107.718981.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/