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The Association of Pediatric Low- and High-Density Lipoprotein Cholesterol Dyslipidemia Classifications and Change in Dyslipidemia Status With Carotid Intima-Media Thickness in Adulthood

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

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Objectives This study was designed to determine which of the National Cholesterol Education Program or National Health and Nutrition Examination Survey low- and high-density lipoprotein cholesterol classifications of dyslipidemia status in adolescents is most effective at predicting high common carotid artery intima-media thickness (IMT) in adulthood.

Background Two classifications of pediatric dyslipidemia status have been proposed. No study has assessed which of these is most effective for predicting adolescents who will develop preclinical atherosclerosis in adulthood.

Methods Three population-based, prospective cohort studies collected lipoprotein measurements on 1,711 adolescents age 12 to 18 years who were remeasured as young adults age 29 to 39 years. Lipoproteins in adolescence were classified according to National Cholesterol Education Program and National Health and Nutrition Examination Survey cut points, and high IMT in adulthood was defined as those at or above the age-, sex-, race-, and cohort-specific 90th percentile of IMT.

Results Independent of the classification employed, adolescents with dyslipidemia were at significantly increased risk of having high IMT in adulthood (relative risks from 1.6 to 2.5). Differences in predictive capacity between both classifications were minimal. Overweight or obese adolescents with dyslipidemia had increased carotid IMT (males: 0.11 mm; females: 0.08 mm) in adulthood compared with those who did not have both risk factors. Adolescent dyslipidemia status was more strongly associated with high IMT in adulthood than change in dyslipidemia status.

Conclusions Pediatric dyslipidemia classifications perform equally in the prediction of adolescents who are at increased risk of high IMT in young adulthood. Our data suggest that dyslipidemia screening could be limited to overweight or obese adolescents. (J Am Coll Cardiol 2009;53:860–9) © 2009 by the American College of Cardiology Foundation

Interest in screening children and adolescents for lipid disorders has gained momentum in recent times, with reports from the U.S. Preventive Service Task Force (1), the American Heart Association (2), and others (3–6), outlining challenges with the existing guidelines issued by the National Cholesterol Education Program (NCEP) and

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calling for its revision (7). One area of the existing guidelines outlined for revision includes the lipid and lipoprotein cut points used to assign risk status. Dichotomous cut points for risk stratification aim to define those who are at an increased risk of developing clinically significant atherosclerotic cardiovascular disease (ASCVD), and in whom risk modification will reduce the risk of subsequent complications. Studies that demonstrate this association between proposed pediatric dyslipidemia cut points and clinical outcomes such as myocardial infarction are lacking, due to the long latency of ASCVD. In the absence of "hard" clinical outcomes, noninvasive imaging techniques that have been shown to predict adult ASCVD (such as ultrasound to examine carotid artery intima-media thickness [IMT]) provide a surrogate end point to assess early atherosclerosis (8).

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Two classifications of adolescent dyslipidemia have been circulated. One is a fixed-point classification of dyslipidemias for children and adolescents aged 2 to 19 years that were stipulated by NCEP and are currently used in existing consensus guidelines (6,7). The other is a recently proposed set of age- and sex-specific cut points for adolescents aged 12 to 19 years that were derived from growth curve data of 3 National Health and Nutrition Examination Surveys (NHANES) and linked to established dyslipidemia thresholds for adults (3). We have previously compared the ability of these classifications to predict dyslipidemia in adulthood (9). In this study, we used data from 3 prospective cohort studies commencing in adolescence to: 1) determine which of the NCEP or NHANES adolescent low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) dyslipidemia classifications best predict high common carotid IMT in adulthood; and 2) to assess whether maintaining or changing dyslipidemia status from adolescence to adulthood has an effect on carotid IMT measured in adulthood.

Methods

Following is an abbreviated version of the methodology, for a full description, please see the Online Appendix. Each of the 3 studies described received ethical approval and obtained written informed consent from participants.

Finnish Data: The Cardiovascular Risk in Young Finns Study

Study sample. This study sample is described in detail elsewhere (10). In this study, we included 1,171 subjects (66% of those eligible, 45% male) who were age 12, 15, and 18 years at baseline and who had LDL-C and HDL-C data from 1980 and carotid artery ultrasonography data in 2001.

Clinic measurements. Serum cholesterol and triglyceride concentrations were determined using enzymatic methods (11). HDL-C was analyzed after precipitation of very low-density lipoprotein and LDL-C with dextran sulfate 500,000 (11). Protocols for baseline measures of blood pressure, body mass index (BMI), and cigarette smoking have been described elsewhere (12).

Carotid artery ultrasound studies. B-mode ultrasound studies of the left carotid artery were performed at follow-up using standardized protocols that have been described previously (12). At least 4 measurements of the far wall were taken approximately 10 mm proximal to the bifurcation to derive mean and maximum carotid IMT. The average absolute difference and standard deviation between measurements for 57 participants who underwent repeat ultrasound examinations was 0.05 ± 0.04 mm.

Abbreviations and Acronyms

ASCVD = atherosclerotic cardiovascular disease
AUC = area under the receiver-operator characteristic curve
BMI = body mass index
HDL-C = high-density lipoprotein cholesterol
IMT = intima-media thickness
LDL-C = low-density lipoprotein cholesterol
NCEP = National Cholesterol Education Program
NHANES = National Health and Nutrition Examination Survey

U.S. Data: The Bogalusa Heart Study

Study sample. This study sample has been described in detail elsewhere (13). For this study, 254 participants (17% of those eligible from the 1984 to 1985 survey, 44% male, 30% African American) age 12 to 17 years at baseline who had LDL-C and HDL-C measures from baseline (1984 to 1985) and carotid artery ultrasound at follow-up (2001 to 2002) were included.

Clinic measurements. In 1984 to 1985, serum cholesterol and triglyceride levels were measured with a Technicon Auto Analyzer II (Technicon Instrument Corp., Tarrytown, New York), according to the laboratory manual of the Lipid Research Clinics program (14). In 2001 to 2002, serum cholesterol and triglycerides levels were determined by enzymatic procedures. Serum lipoprotein cholesterol levels were analyzed using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (15). Baseline measures of blood pressure, BMI, and cigarette smoking have been described in detail previously (16).

Carotid artery ultrasound studies. B-mode ultrasound examinations were performed according to protocols previously described (17). Maximum IMT measurements were taken from both left and right common carotid, carotid bifurcation, and internal carotid segments according to strict protocols (18). The average absolute difference and standard deviation between measurements for 75 participants who underwent repeat ultrasound examinations was 0.05 ± 0.03 mm.

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Australian Data: The CDAH (Childhood Determinants of Adult Health) Study

Study sample. This study sample has been described in detail elsewhere (9,19). In this study, we include data from 286 participants (26% of those eligible from baseline, 50% male) aged 12 and 15 years at baseline who had LDL-C and HDL-C data from 1985 and carotid artery ultrasound measures at follow-up (2004 to 2006).

Clinic measurements. In 1985, serum total cholesterol and triglycerides were determined according to the Lipids Research Clinic Program (14), and HDL-C analyzed following precipitation of apolipoprotein-B–containing lipoproteins with heparin-manganese (19). In the period from 2004 to 2006, serum total cholesterol, triglyceride, and HDL-C concentrations were determined enzymatically (9). The LDL-C concentration was calculated using the Friedewald formula (20). Baseline measurements of blood pressure, BMI, and smoking habits were collected according to protocols presented elsewhere (19).

Carotid artery ultrasound studies. B-mode ultrasound studies of the carotid artery were performed using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, California) ultrasound machine with a 7.0-MHz linear-array transducer by a single technician. We have previously demonstrated that vascular measurements derived from this machine compare well with those from a clinic-based machine (21). The ultrasound technician followed carotid artery imaging protocols described by the Cardiovascular Risk in Young Finns study (12). Six measurements of the common carotid far wall were taken approximately 10 mm before the border of the carotid bulb to derive mean and maximum carotid IMT. The average absolute difference and standard deviation between measurements for 30 participants who had replicate maximum IMT measurements was 0.02 ± 0.04 mm.

Classification of Dyslipidemia Status in Adolescence and Adulthood

The NCEP (7) and NHANES (3) pediatric cut points were used to assign adolescent LDL-C and HDL-C status (Online Tables 1A and 1B). At follow-up, NCEP adult treatment panel guidelines were used to classify participants as nondyslipidemic (<4.14 mmol/l; <160 mg/dl) or dyslipidemic (≥4.14 mmol/l; ≥160 mg/dl) LDL-C status, and nondyslipidemic (≥1.036 mmol/l; ≥40 mg/dl) or dyslipidemic (<1.036 mmol/l; <40 mg/dl) HDL-C status (22).

Carotid IMT Measurements and Classification of High Carotid IMT in Adulthood

For the analyses, we chose the most consistent IMT measurement across the 3 study sites, which incorporated the maximum measurement at the far wall of the left common carotid artery (Online Table 2, Online Fig. 1). Although no consensus clinical definition of high carotid IMT currently exists for young adults, we defined high IMT in adulthood as a maximum IMT ≥90th percentile for age-, sex-, race- (Bogalusa), and cohort-specific values. The specific values used to denote high IMT are provided in Online Table 3.

Statistical Analyses

Comparisons between baseline characteristics of participants and nonparticipants at follow-up within each cohort were performed using logistic regression.

Comparison of NCEP versus NHANES adolescent dyslipidemia classifications. Logarithmic-binomial regression was used to estimate the relative risk of high IMT at follow-up for various baseline lipoprotein classifications (23). Estimates were adjusted for age at baseline, sex, race (for the Bogalusa data only), and length of follow-up. We adjusted for length of follow-up to account for within-cohort differences observed between length of follow-up and risk of high IMT in both the CDAH and Bogalusa studies. For pooled estimates, we additionally adjusted for cohort to account for differences in lipoprotein determination methods between the 3 cohorts. We also considered baseline BMI status (normal weight vs. overweight/obese in adolescence) (24) as a potential confounding variable in these analyses. The analyses for NCEP and NHANES HDL-C classifications were stratified by BMI status due to effect modification.

The ability of each adolescent LDL-C and HDL-C classification to predict high IMT in adulthood was assessed using sensitivity, specificity, positive predictive value, negative predictive value, and area under receiver-operator characteristic curves (AUC). Tests for significant differences between AUC were calculated using the DeLong algorithm (25). This method assumes the correct null distribution when there are only 3 classification levels (i.e., normal-, borderline-, and high-risk groups), as is the case here. Analyses were stratified by BMI status owing to effect modification.

Change in dyslipidemia status and high IMT in adulthood. A change variable was created that divided participants into 4 categories depending on their lipoprotein status at both time points. Participants were classified as "persistent nondyslipidemia," "nondyslipidemia to dyslipidemia," "dyslipidemia to nondyslipidemia," and "persistent dyslipidemia." Their adolescent lipoprotein status was determined using what we judged to be the best performing LDL-C and HDL-C pediatric dyslipidemia classifications for predicting adult IMT, ascertained from the above-mentioned comparison analyses. Logarithmic-binomial regression was used to estimate the relative risk of high carotid IMT in adulthood depending on the change variable. These analyses were performed for pooled data only and are presented adjusted for age at baseline, sex, cohort, and length of follow-up in Model 1,

and with additional adjustments for BMI at baseline, systolic blood pressure at baseline, and smoking status at baseline in Model 2. Interaction between the model variables was tested; no significant interactions were found.

To complement the categorical analyses, we also examined the effect of change in the continuous lipoprotein levels on the continuous outcome measure of IMT using linear regression. We adopted the life-course analysis approach described by De Stavola et al. (26), with the adolescent lipoprotein variable and change in the lipoprotein variable (derived as the difference between adult and adolescent lipoprotein levels) used as predictor variables. The regression coefficient for the adolescent lipoprotein variable quantifies the total effect, that is, the sum of direct and indirect (mediated via adult lipoprotein levels due to tracking) (27) effects of adolescent LDL-C or HDL-C on IMT, whereas the regression coefficient for change in lipoprotein levels quantifies the additional gain from increasing or decreasing lipoprotein levels by 1 mmol/l between adolescence and adulthood relative to participants with the same adolescent lipoprotein level, but whose lipoprotein level was unchanged. Multivariable models were specified, including adolescent LDL-C and change in LDL-C, and adolescent HDL-C and change in HDL-C. All models were adjusted for age at baseline, sex, cohort, length of follow-up, baseline BMI, baseline systolic blood pressure, and baseline smoking status. The assumption of linearity in the regression models of the continuous predictor variables was checked using the method of fractional polynomials (28). The analyses are presented stratified by adolescent BMI status due to effect modification. The distribution of IMT values were right-skewed; however, for ease of interpretation and

Table 1 Mean Values for Adolescent and Adult Characteristics in Those With and Without IMT ≥90th Percentile in Adulthood in Cohorts From Finland, the U.S., and Australia

	Males		Females		
Cohort	IMT <90th Percentile	IMT ≥90th Percentile	IMT <90th Percentile	IMT ≥90th Percentile	All
Young Finns					
Adolescence					
n	469	54	566	82	1,171
Age, yrs	15.0 ± 2.4	14.8 ± 2.4	14.8 ± 2.4	15.0 ± 2.5	14.9 ± 2.4
LDL-C, mmol/l	3.22 ± 0.78	3.49 ± 0.84	3.34 ± 0.79	3.39 ± 0.79	3.30 ± 0.79
HDL-C, mmol/l	1.50 ± 0.31	1.49 ± 0.33	1.59 ± 0.29	1.57 ± 0.29	1.55 ± 0.30
Adulthood					
Age, yrs	36.0 ± 2.4	35.8 ± 2.4	35.8 ± 2.4	36.0 ± 2.5	35.9 ± 2.4
LDL-C, mmol/l	3.63 ± 0.92	3.84 ± 0.83	3.25 ± 0.78	3.35 ± 0.80	3.43 ± 0.87
HDL-C, mmol/l	1.18 ± 0.28	1.15 ± 0.31	1.40 ± 0.30	1.37 ± 0.31	1.30 ± 0.31
IMT, mm	0.64 ± 0.08	0.87 ± 0.11	0.61 ± 0.07	0.79 ± 0.06	0.65 ± 0.10
Bogalusa					
Adolescence					
n	98	13	128	15	254
Age, yrs	14.8 ± 1.6	14.9 ± 1.9	14.8 ± 1.5	14.7 ± 1.3	15.3 ± 1.5
LDL-C, mmol/l	2.39 ± 0.72	2.62 ± 0.67	2.48 ± 0.61	2.76 ± 0.67	2.47 ± 0.66
HDL-C, mmol/l	1.44 ± 0.52	1.17 ± 0.54	1.56 ± 0.49	1.32 ± 0.39	1.48 ± 0.51
Adulthood					
Age, yrs	31.8 ± 1.5	32.2 ± 1.6	31.9 ± 1.5	31.9 ± 1.2	32.4 ± 1.4
LDL-C, mmol/l	3.21 ± 0.81	3.50 ± 0.66	3.03 ± 0.89	3.39 ± 0.83	3.15 ± 0.85
HDL-C, mmol/l	1.09 ± 0.27	1.15 ± 0.37	1.28 ± 0.35	1.22 ± 0.49	1.20 ± 0.34
IMT, mm	0.73 ± 0.11	1.06 ± 0.11	0.67 ± 0.09	0.92 ± 0.08	0.73 ± 0.14
CDAH					
Adolescence					
n	119	24	131	12	286
Age, yrs	13.4 ± 1.5	13.1 ± 1.5	13.4 ± 1.5	13.3 ± 1.5	13.4 ± 1.5
LDL-C, mmol/l	2.61 ± 0.56	2.73 ± 0.67	2.67 ± 0.63	3.58 ± 1.58	2.69 ± 0.69
HDL-C, mmol/l	1.38 ± 0.26	1.45 ± 0.35	1.50 ± 0.28	1.36 ± 0.38	1.44 ± 0.29
Adulthood					
Age, yrs	33.4 ± 1.7	32.9 ± 1.6	33.4 ± 1.6	32.9 ± 1.8	33.3 ± 1.7
LDL-C, mmol/l	3.21 ± 0.71	3.26 ± 0.75	2.79 ± 0.80	3.96 ± 2.17	3.05 ± 0.90
HDL-C, mmol/l	1.27 ± 0.29	1.33 ± 0.30	1.57 ± 0.36	1.57 ± 0.33	1.43 ± 0.36
IMT, mm	0.60 ± 0.08	0.80 ± 0.08	0.59 ± 0.07	0.78 ± 0.05	0.62 ± 0.10

Statistics are mean ± SD. To convert LDL-C and HDL-C to mg/dl, multiply values by 38.67.
CDAH = Childhood Determinants of Adult Health Study; HDL-C = high-density lipoprotein cholesterol; IMT = intima-media thickness; LDL-C = low-density lipoprotein cholesterol.

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comparability with previous studies in young adults, we used nontransformed IMT values. Using logarithmic-transformed IMT values made little difference to the results presented.

Results

Characteristics of participants and nonparticipants. Nonparticipation in those eligible for follow-up measures (34% Young Finns, 82% Bogalusa, 67% CDAH) was more likely in males and those of younger age in each cohort and more likely in African Americans in the Bogalusa cohort. There were no statistically or clinically significant differences in LDL-C or HDL-C levels or LDL-C or HDL-C dyslipidemia status between participants and nonparticipants in any of the 3 cohorts (data not shown).

Adolescent and adult characteristics by carotid IMT status. Mean values for key baseline and follow-up variables are displayed in Table 1 for males and females in each cohort who had IMT ≥90th percentile and IMT <90th percentile (see Online Table 3 for values in milligrams per deciliter). Across each sex and cohort, those with high IMT at follow-up tended to have higher LDL-C levels during adolescence and adulthood. Bogalusa participants and females in the CDAH study with high IMT had lower HDL-C levels during adolescence but not at follow-up.

Comparison of NCEP versus NHANES cut points. The prevalence of adolescent LDL-C dyslipidemia was 32.3% for NCEP or 19.6% for NHANES cut points. High-density lipoprotein cholesterol dyslipidemia was prevalent in 2.5% of adolescents using NCEP cut points or 6.1% of adolescents using NHANES cut points. Pooled data showed that the risk of having high IMT in adulthood was significantly higher in those with borderline- and high-risk LDL-C levels in adolescence compared with those with normal levels using NHANES cut points (Fig. 1A). Use of NCEP LDL-C cut points showed only those with high-risk levels in adolescence had significantly increased risk of high IMT in adulthood compared with those classified as normal, although the borderline-risk group showed a nonsignificant trend toward increased risk (Fig. 1A). A graded increase in the risk of having high IMT in adulthood was observed when moving from normal, to borderline-risk, to high-risk groups for NCEP and NHANES LDL-C cut points (Fig. 1A).

Normal-weight adolescents with NCEP classified high-risk (low) HDL-C were at significantly increased risk of having IMT ≥90th percentile at follow-up (Fig. 1B). There was no increased risk of having high IMT at follow-up for normal-weight adolescents classified as borderline-risk HDL-C levels using either classification or for those with high-risk HDL-C levels according to NHANES cut points (Fig. 1B). For overweight or obese adolescents, the risk of high IMT in adulthood was significantly increased in those with borderline- or high-risk HDL-C levels compared with

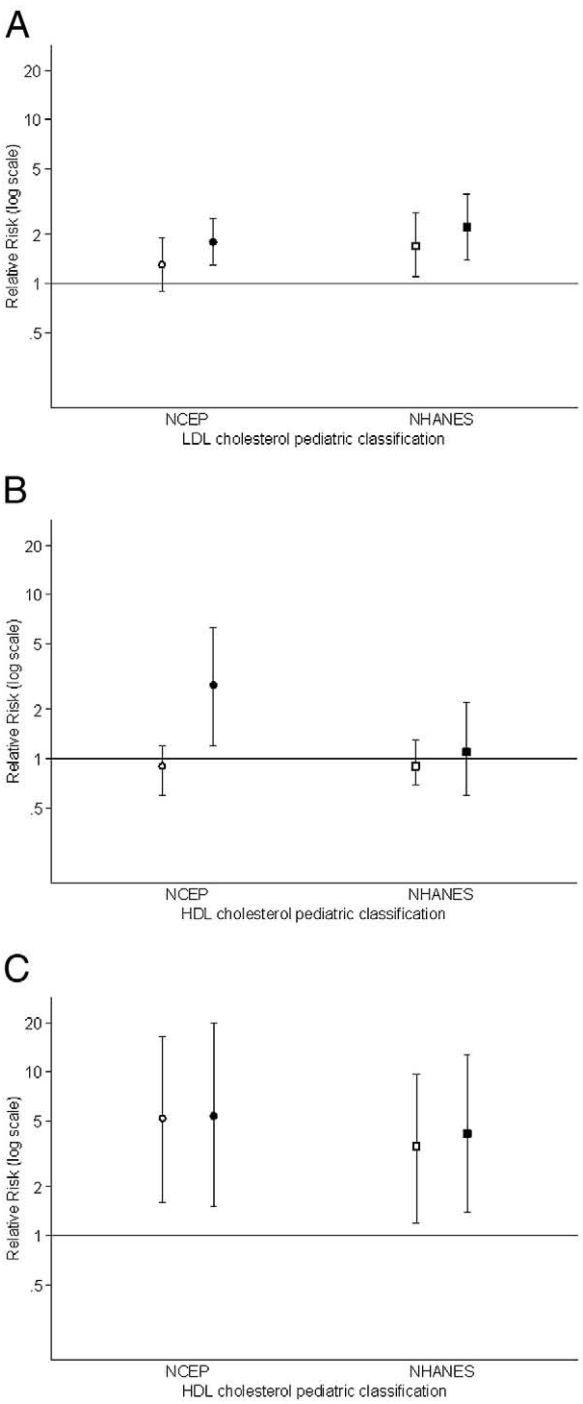

Figure 1 **Relative Risks for High IMT in Adulthood According to NCEP and NHANES Cut Points**

Relative risks for high IMT (≥90th percentile) in adulthood according to NCEP and NHANES for **(A)** LDL cholesterol dyslipidemia status, **(B)** HDL cholesterol dyslipidemia status in normal-weight adolescents, and **(C)** HDL cholesterol dyslipidemia status in overweight/obese adolescents. Relative risks and 95% confidence intervals adjusted for age, sex, cohort, and length of follow-up. HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program; NHANES = National Health and Nutrition Examination Survey.

Table 2 Sensitivity, Specificity, PPV, NPV, and AUC Data of NCEP and NHANES Classifications for Adolescent Borderline- and High-Risk Lipoprotein Variable Cut Points to Predict High Carotid IMT in Adulthood

		Dyslipidemia Status in Adolescence									
		Borderline Risk				High Risk					
Lipoprotein Variable	Classification	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	AUC*	p Value†
Normal weight											
LDL cholesterol	NCEP	64.8‡	44.0	12.2	91.3	38.9‡	68.7	12.9	90.4	0.55	
	NHANES	50.6	56.6‡	12.2	90.6	23.5	80.7‡	12.7	89.8	0.55	0.73
HDL cholesterol	NCEP	53.7	43.9	10.3	88.8	3.1	98.8‡	22.7	89.5	0.49	
	NHANES	52.5	47.0‡	10.6	89.2	4.9	95.4	11.4	89.4	0.49	0.69
Overweight/obese											
LDL cholesterol	NCEP	63.2‡	52.0	24.7	84.9	50.0‡	70.4	29.7	84.9	0.60	
	NHANES	55.3	59.2‡	25.3	84.1	34.2	85.5‡	37.1	83.4	0.63	0.33
HDL cholesterol	NCEP	92.1	30.5	24.6	94.0	15.8	90.3‡	28.6	81.3	0.62	
	NHANES	89.5	30.5	24.1	92.2	26.3	83.8	28.6	82.2	0.62	0.88

Sensitivity = true positives/(true positives + false negatives) × 100. Specificity = true negatives/(true negatives + false positives) × 100. PPV = true positives/(true positives + false positives) × 100. NPV = true negatives/(true negatives + false negatives) × 100. *Normal-, borderline-, and high-risk included in AUC analyses as 3 groups. †Test for difference between AUCs. ‡McNemar test for difference between sensitivities and specificities.

AUC = area under the receiver-operator characteristic curve; NCEP = National Cholesterol Education Program; NHANES = National Health and Nutrition Examination Survey; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

those who had normal levels using either pediatric classification (Fig. 1C). The relative risks were similar for overweight or obese adolescents with borderline- or high-risk HDL-C levels. When data where not stratified by BMI status, only those with high-risk HDL-C were at significantly increased risk of having high IMT at follow-up (NCEP: relative risk [RR]: 2.5, 95% confidence interval [CI]: 1.4 to 4.6; NHANES: RR: 1.6, 95% CI: 1.0 to 2.7).

Diagnostic performance statistics comparing NCEP and NHANES classifications are presented in Table 2. The NCEP high-risk LDL-C cut points were more sensitive but less specific than the NHANES cut points. Although this trend in sensitivity and specificity was consistent across cohorts, heterogeneity in the point estimates between cohorts was observed (data not shown). False positives were high for both LDL-C classifications in normal weight adolescents with 87% of those with high levels not developing high IMT in young adulthood. Sensitivity, positive predictive value, and AUC values increased when borderline- and high-risk HDL-C cut points were applied to overweight or obese adolescents (Table 2), but remained low overall. The diagnostic performance characteristics were similar for both classifications of adolescent HDL-C. We note that AUC using other age-, sex-, and cohort-specific cut points of IMT (70th, 75th, 80th, 85th, 90th, and 95th percentiles) in our data did not appreciably modify the results presented (data not shown). Diagnostic statistics of adolescents with other risk factors including hypertension and cigarette smoking in addition to the NCEP dyslipidemia cut points are displayed in Table 3. The addition of hypertension to the LDL-C cut points improved the prediction of those with high IMT in adulthood (29). The prediction was comparable to those who were overweight and did not improve further when either hypertension or

Table 3 Sensitivity, Specificity, PPV, NPV, and AUC Data for Combining NCEP High-Risk Lipoprotein Variable Cut Points to Other Risk Factors Present in Adolescence to Predict High Carotid IMT in Adulthood

Lipoprotein Variable	Screening Strategy	N*	Sensitivity	Specificity	PPV	NPV	AUC
LDL cholesterol							
	Universal	1,707	41.0	68.9	14.9	89.8	0.56
	Overweight† + NCEP cut points	190	50.0	70.4	29.7	84.9	0.60
	Hypertension‡ + NCEP cut points	355	45.3	71.2	21.6	88.1	0.61
	Smoking§ + NCEP cut points	218	30.3	79.5	20.8	86.5	0.54
	Overweight† or hypertension‡ + NCEP cut points	491	43.4	71.6	21.9	87.4	0.60
HDL cholesterol							
	Universal	1,710	5.5	97.8	25.6	88.7	0.53
	Overweight† + NCEP cut points	192	15.8	90.3	28.6	81.3	0.62
	Hypertension‡ + NCEP cut points	355	7.6	99.3	66.7	86.0	0.54
	Smoking§ + NCEP cut points	218	9.1	96.8	33.3	85.6	0.52

*Refers to the total number of participants that would be screened. †Overweight or obese determined according to International Obesity Task Force body mass index cut points for pediatrics (24). ‡Hypertension defined according to pediatric cut points from the National High Blood Pressure Education Program (29). §Participants were classified as smokers at baseline if they indicated regular cigarette smoking on a weekly basis or more often. Family history was considered but not included in these analyses owing to divergence in the definitions of positive history among the 3 cohorts. Previously, we found family history in Young Finns did not appreciably add to the prediction of adolescents with adulthood dyslipidemia (9).

Abbreviations as in Tables 1 and 2.

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Table 4 Relative Risks From Pooled Data for the Effect of Change in LDL-C and Change in HDL-C Status Between Adolescence and Adulthood on Carotid Artery IMT ≥90th Percentile

	Model 1				Model 2			
Lipoprotein Status in Adolescence and Adulthood	n/N*	%	RR	95% CI	n/N*†	%	RR	95% CI
LDL-C								
Persistent nondyslipidemia	127/1,206	10.5	1.0	Ref	121/1,148	10.5	1.0	Ref
Nondyslipidemia to dyslipidemia	19/143	13.3	1.3	0.8–2.1	16/136	11.8	1.2	0.8–1.9
Dyslipidemia to nondyslipidemia	25/205	12.2	1.2	0.8–1.9	23/191	12.0	1.2	0.7–1.9
Persistent dyslipidemia	25/124	20.2	2.1	1.4–3.1	24/117	20.5	2.0	1.4–3.0
HDL-C								
Persistent nondyslipidemia	143/1,303	11.0	1.0	Ref	135/1,234	10.9	1.0	Ref
Nondyslipidemia to dyslipidemia	45/358	12.6	1.2	0.9–1.7	41/338	12.1	1.2	0.8–1.6
Dyslipidemia to nondyslipidemia	4/16	25.0	2.6	1.0–6.5	4/15	26.7	2.8	1.1–6.9
Persistent dyslipidemia	7/27	25.9	2.6	1.3–5.2	7/27	25.9	2.1	1.1–4.3

Model 1 was adjusted for age at baseline, sex, cohort, and length of follow-up. Model 2 was additionally adjusted for baseline body mass index, baseline smoking status, and baseline systolic blood pressure. *Number of participants with high IMT/all participants. †Sample sizes differ between Models 1 and 2 owing to missing baseline data on smoking and/or systolic blood pressure in some participants. CI = confidence interval; Ref = reference group; RR = relative risk; other abbreviations as in Table 1.

overweight status was combined with the LDL-C cut points.

Effect of change in dyslipidemia status on high IMT. For the analyses of change in lipoprotein status between adolescence and adulthood, we used the NHANES classification to assign adolescent LDL-C dyslipidemia status and the NCEP classification to assign adolescent HDL-C dyslipidemia status. In Table 4, we present pooled relative risks of having a high IMT in young adulthood according to LDL-C and HDL-C dyslipidemia status during adolescence and adulthood. A change in LDL-C status from nondyslipidemia to dyslipidemia or dyslipidemia to nondyslipidemia did not significantly increase the risk of high IMT compared with those who remained normal at both times. Those with LDL-C dyslipidemia at both times had significantly increased risk of high IMT in adulthood than those with persistently normal levels. Analysis of continuous data showed that participants with higher baseline levels of LDL-C had higher IMT as adults (regression coefficient for a 1 standard deviation [SD] increase: 0.014, $p < 0.001$). There was some evidence that those who increased LDL-C levels between adolescence and adulthood had higher IMT at follow-up, but this effect was not statistically significant (regression coefficient for a 1 SD increase: 0.005, $p = 0.08$).

For HDL-C, the relative risk of having a high IMT in adulthood was significantly increased for participants who had low (dyslipidemic) levels in adolescence irrespective of their adult levels (Table 4). The relative risk of high IMT in the nondyslipidemia to dyslipidemia group was similar to that of the persistent nondyslipidemia group. Only a small number of participants moved from dyslipidemia to nondyslipidemia, so the data for this group should be interpreted with caution. Analyses of continuous data showed evidence that higher HDL-C levels in overweight or obese adolescents were associated with lower IMT in adulthood (regression coefficient for a 1 SD increase: −0.011, $p = 0.01$), whereas change in HDL-C between adolescence and adulthood was not. In normal-weight adolescents, analyses of continuous data showed no association between baseline or change in HDL-C levels and IMT in adulthood. In multivariable analyses that included adolescent and change variables for LDL-C and HDL-C in the model, baseline lipoprotein levels were generally stronger predictors of IMT than changes in levels between adolescence and adulthood (Fig. 2).

Based on this model, we predicted the level of IMT at 35 years of age for normal-weight and overweight or obese adolescents, with normal and dyslipidemic levels of LDL-C and HDL-C at age 15 years (Fig. 3). The difference in IMT at age 35 years for normal-weight adolescents with and without dyslipidemia was minimal. IMT at age 35 years for those who were overweight or obese as adolescents and did not have dyslipidemia were comparable with IMT for normal-weight adolescents. Overweight or obese adolescents with dyslipidemia had markedly higher IMT at age 35 years than the other groups (Fig. 3).

Discussion

In this study, we sought to determine whether 2 classifications of pediatric dyslipidemia (NCEP vs. NHANES) predicted IMT in adulthood and which of these would be most effective in identifying adolescents at high risk of increased IMT as adults. We found that both dyslipidemia cut points were able to predict those with high IMT in adulthood, but our data did not provide a clear indication of which LDL-C and HDL-C cut points should be preferred by those who wish to identify adolescents with lipid disorders. Given that there were no substantial differences in the diagnostic performance of the classifications, the simplicity in applying the fixed NCEP cut points may offer an advantage over the age- and sex-specific NHANES cut points in a clinical or research setting. Importantly, users of either classification need to be mindful that most adolescents identified with dyslipidemic LDL-C and HDL-C levels will not be at or above the 90th percentile for carotid

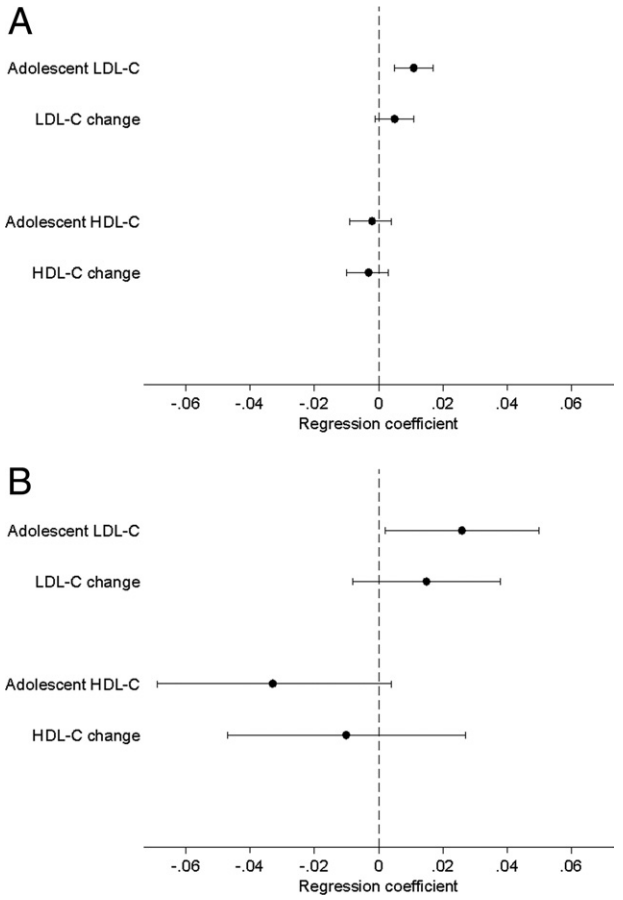

Figure 2 **Regression Coefficients for Associations of Adolescent LDL-C and HDL-C, and Change in LDL-C and HDL-C With Carotid IMT in Adulthood**

Regression coefficients for associations of adolescent LDL-C, change in LDL-C between adolescence and adulthood, adolescent HDL-C, and change in HDL-C with carotid IMT in adulthood for **(A)** normal-weight and **(B)** overweight or obese adolescents. Regression coefficients and their 95% confidence intervals are adjusted for age at baseline, sex, cohort, length of follow-up, systolic blood pressure at baseline, and smoking status at baseline. Regression coefficients expressed in millimeters for 1 standard deviation change in the continuous variables. Adolescent LDL-C, HDL-C, and change in LDL-C and HDL-C variables were included in the same multivariable model. HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; other abbreviations as in Figure 1.

IMT in early adulthood and most individuals with high IMT will not be identified by using lipoprotein levels in adolescence. Discrimination was considerably better for overweight or obese adolescents compared with their normal-weight peers, which does support targeted, rather than universal (whole- or random-population), screening strategies endorsed in current guidelines (2,6,7).

Single adolescent measures of LDL-C and HDL-C in this study were stronger predictors of adult IMT than change between adolescence and adulthood. Although a beneficial change in lipoprotein levels did show trends toward lower IMT in adulthood, particularly for those who were overweight or obese as adolescents, the magnitude of this effect was smaller than for the baseline measure. Moreover, based on our predictive modeling (Fig. 3), the degree of IMT difference at age 35 years between overweight or obese 15 year olds with LDL-C dyslipidemia and HDL-C dyslipidemia compared with normal-weight 15 year olds with normal LDL-C and HDL-C levels was clinically significant (8) (males: 0.11 mm; females: 0.08 mm) and more than would be expected from measurement error alone.

Taken together, our and others' data (12,30,31) clearly show the importance of adolescent lipid levels as a predictor of pre-clinical atherosclerosis and provide some epidemiological rationale for recent recommendations for pediatric lipid screening released in July 2008 (6). However, the efficacy of screening for dyslipidemia in a general population using NCEP or NHANES classifications as a way to identify adolescents at risk of ASCVD has considerable limitations (as indicated), particularly for clinic use. For normal-weight adolescents, population-wide primary prevention programs that target LDL-C levels, such as those used in the DISC (Dietary Intervention Study in Children) and STRIP (Special Turku Coronary Risk Factor Intervention Project for Children) studies (32,33), and maintenance of healthy weight may be most practical. Lipid screening in the general pediatric population could be limited to adolescents who have other CVD risk factors such as obesity or hypertension to further stratify the risk of this group.

Study limitations. This study has a number of potential limitations. First, there was heterogeneity in the IMT location and ultrasound protocols between cohorts. Even though we attempted to take this heterogeneity into account by defining high IMT according to age-, sex-, race- (Bogalusa), and cohort-specific values, we note that attempts by future investigators to merge imaging studies for statistical

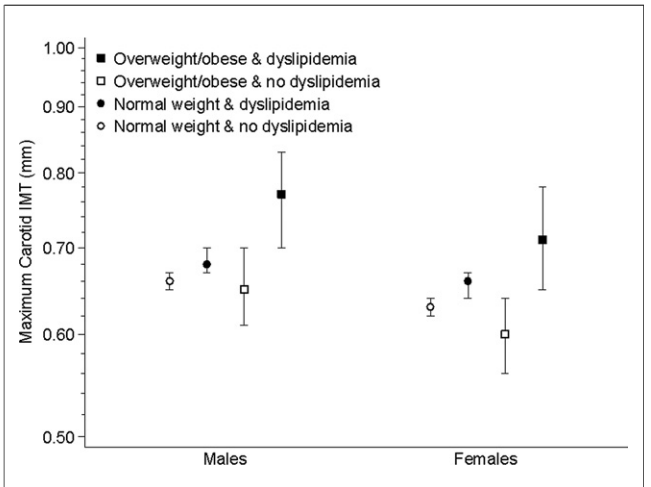

Figure 3 **Least Square Means of Carotid IMT at Age 35 Years for Males and Females by BMI Status and Dyslipidemia Status at Age 15 Years**

Least square means are adjusted for length of follow-up, cohort, change in LDL-C, change in HDL-C, baseline smoking status, and baseline systolic blood pressure. Abbreviations as in Figures 1 and 2.

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power will have this limitation unless calls for method standardization are heeded (8). Second, 1 explanation for the poor diagnostic performance of the dyslipidemia classifications in this study may have been due to differing methods of lipoprotein determination between NCEP/NHANES samples and our cohorts. Lipoprotein levels, particularly HDL-C, have been shown to differ depending on which methodology is used (34). Third, because we only had data from 2 time points, we were unable to account for multiple changes that may have occurred in the intervening period or the timing of these changes. Moreover, use of only 1 lipoprotein measurement at each time point may have contributed to misclassification of some participants (27), which would likely lead to an underestimate of the prediction estimates in this study (35). Fourth, we were unable to account for the potential role of pubertal status as a confounding variable, because data were not available for all cohorts. We performed sensitivity analyses with Young Finns data to adjust for pubertal status. The coefficients were generally unchanged from those analyses where age adjustment was used. Fifth, poorer image quality in ultrasound scans (assessed subjectively in the Young Finns and CDAH studies) was associated with higher BMI ($r = 0.11$) and could bias carotid IMT readings in overweight or obese individuals. Sensitivity analyses adjusting for image quality yielded similar results to those presented. Finally, our data are from population-based cohorts and may not be generalizable to other higher-risk patients, such as those with diabetes mellitus or a strong family history of premature CVD.

Conclusions

Our data indicate that dyslipidemic lipoprotein levels in adolescence are associated with an increased risk of high IMT in young adulthood; that the predictive capacity of both NCEP and NHANES cut points are similar and could be applied for lipid screening with equal success; that adolescent lipid levels are more strongly associated with high IMT in adulthood than change in lipid levels; and that dyslipidemia in the presence of overweight or obesity places affected adolescents at substantially higher risk of increased IMT as adults compared with those who do not have both risk factors. These data underscore the importance of both population-wide and individualized prevention programs to improve pediatric dyslipidemia-related causes of early atherosclerosis.

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

APPENDIX

For the supplementary methods section and accompanying tables and figure, please see the online version of this article.