Non-HDL Cholesterol Levels in Childhood and Carotid Intima-Media Thickness in Adulthood

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BACKGROUND: Elevated non–high-density lipoprotein cholesterol (HDL-C) levels are used to identify children at increased cardiovascular risk, but the use of non–HDL-C in childhood to predict atherosclerosis is unclear. We examined whether the National Heart, Lung, and Blood Institute classification of youth non–HDL-C status predicts high common carotid artery intima-media thickness in adulthood.

METHODS: We analyzed data from 4 prospective cohorts among 4582 children aged 3 to 19 years who were remeasured as adults (mean follow-up of 26 years). Non–HDL-C status in youth and adulthood was classified according to cut points of the National Heart, Lung, and Blood Institute and the National Cholesterol Education Program Adult Treatment Panel III. High carotid intima-media thickness (cIMT) in adulthood was defined as at or above the study visit-, age-, sex-, race-, and cohort-specific 90th percentile of intima-media thickness.

RESULTS: In a log-binomial regression analysis adjusted with age at baseline, sex, cohort, length of follow-up, baseline BMI, and systolic blood pressure, children with dyslipidemic non–HDL-C were at increased risk of high cIMT in adulthood (relative risk [RR], 1.29; 95% confidence interval [CI], 1.07–1.55). Compared with the persistent normal group, the persistent dyslipidemia group (RR, 1.80; 95% CI, 1.37–2.37) and incident dyslipidemia (normal to dyslipidemia) groups (RR, 1.45; 95% CI, 1.07–1.96) had increased risk of high cIMT in adulthood, but the risk was attenuated for the resolution (dyslipidemia to normal) group (RR, 1.17; 95% CI, 0.97–1.41).

CONCLUSIONS: Dyslipidemic non–HDL-C levels predict youth at risk for developing high cIMT in adulthood. Those who resolve their non–HDL-C dyslipidemia by adulthood have normalized risk of developing high cIMT in adulthood.

WHAT'S KNOWN ON THIS SUBJECT: Elevated non–high-density lipoprotein cholesterol (HDL-C) levels are used to identify children at increased cardiovascular risk, but the use of non–HDL-C in childhood to predict atherosclerosis is unclear.

WHAT THIS STUDY ADDS: Non–HDL-C levels associate with future risk of preclinical atherosclerosis from the age of 15 years, suggesting a later age for the initial universal lipid screening among the pediatric population than is currently recommended in the National Heart, Lung, and Blood Institute’s expert panel guidelines.

Non–high-density lipoprotein cholesterol (HDL-C) is considered a simpler and more effective screening tool of atherosclerotic cardiovascular disease risk than low-density lipoprotein cholesterol (LDL-C). Estimated LDL-C does not include all classes of atherogenic lipoproteins, may underestimate those with low levels, and requires overnight fasting. Consequently, non–HDL-C is increasingly used and has been specified as a secondary therapy target among patients with the metabolic syndrome or diabetes.

We have previously reported that elevated LDL-C levels in children and adolescents (youth) were associated with high carotid intima-media thickness (cIMT), a marker of preclinical atherosclerosis, in adulthood. For total cholesterol, in our previous analyses it was suggested that measures from those aged ≥12 years, but not in younger children, were associated with adult cIMT. The case for non–HDL-C measurement in youth is further strengthened by data in which it is shown that youth non–HDL-C is a better predictor of adult dyslipidemia, nonlipid risk factors, and cIMT than LDL-C. Moreover, non–HDL-C is independently associated with obesity indices and might provide a more sensitive measure of dyslipidemia than LDL-C among those with overweight or obesity. Recognizing the potential value of non–HDL-C measurement, the 2011 National Heart, Lung, and Blood Institute (NHLBI) expert panel recommended universal (population-wide) screening of nonfasting non–HDL-C levels first at age 9 to 11 years and again at 18 to 21 years to identify youth with dyslipidemia at risk for accelerated atherosclerotic disease.

In contrast to previous guidelines on lipid screening, the NHLBI guidelines were the first to recommend universal versus selected screening for lipid disorders and incorporate cutoffs for non–HDL-C levels, derived from population-based data in the Bogalusa Heart Study. However, these data were cross-sectional, and it is unknown whether the NHLBI cutoffs for non–HDL-C predict future preclinical atherosclerosis.

Using data from 4 population-based prospective cohorts beginning in youth with follow-up into adulthood, we examined if the NHLBI classification of youth non–HDL-C status is associated with adult cIMT. We also compared associations for LDL-C and examined whether resolution of elevated youth non–HDL-C status by adulthood reduces the risk of developing high cIMT.

**METHODS**

**Study Sample**

The study sample was drawn from 4 prospective cohorts in the i3C Consortium. These were the Bogalusa Heart Study (LA), the Insulin Study (Minneapolis), the Cardiovascular Risk in Young Finns Study (YFS) (Finland), and the Childhood Determinants of Adult Health (CDAH) Study (Australia). Study characteristics and methods have been previously described. Although loss to follow-up varied by cohort, previous analyses have suggested the representativeness of the cohorts has largely been maintained. In total, 4582 participants with non–HDL-C data from their first study visit in youth when aged 3 to 19 years and longitudinal ultrasound data from adulthood when aged 19 to 51 years were included. Local ethics committees reviewed and approved the individual cohort studies that we analyzed, and participants in those studies (or their legal guardians) provided written informed consent. The present analysis conformed to the Declaration of Helsinki.

**Risk Factor Assessment**

In the YFS at baseline, serum cholesterol and triglycerides were measured using fully enzymatic Boehringer CHOD-PAP kits with an OLLI 3000 analyzer. Subsequently, an Olympus System reagent analyzer in a clinical chemistry analyzer (AU400; Olympus) was used. Serum HDL-C was measured by the dextran sulfate 500 000 method. In CDAH, serum total cholesterol and triglycerides were determined according to the Lipid Research Clinics Program, and HDL-C was analyzed after precipitation of apolipoprotein B–containing lipoproteins with heparin-manganese. In the Bogalusa Heart Study, HDL-C and triglycerides were measured by using chemical procedures with a Technicon Auto Analyzer II (Technicon Instrument Corp), according to the Lipid Research Clinics Program. Serum concentrations of LDL-C and HDL-C were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures. In the Insulin Study, serum lipids were analyzed in the University of Minnesota laboratory with a Cobas FARA. HDL-C was determined after precipitation of non–high-density lipoproteins with a dextran-sulfate magnesium precipitating reagent. Triglycerides were determined with a standard glycerol blanked enzymatic triglyceride method. For all cohorts, non–HDL-C was calculated as total cholesterol – HDL-C, and LDL-C was calculated using the Friedewald formula. The coefficient of variation for within-assay precision in the YFS was 2.2% for total cholesterol,
2.3% for HDL-C, and 3.8% for serum triglycerides. Both of the US cohorts and CDAH used chemical and enzymatic procedures meeting the performance requirements of the Lipid Clinics Program and Lipid Standardization Program of the Centers for Disease Control and Prevention, which routinely monitors the accuracy of measurements of total cholesterol, triglyceride, and HDL-C concentrations. Height and weight were measured and used to calculate BMI as weight (kilograms)/(height [meters])². Cole’s international BMI cutoffs²⁰ were used to denote weight status. Systolic blood pressure at baseline was measured by using a standard mercury sphygmomanometer.³¹ Youth smoking habits were assessed by questionnaire. Those who had smoked ≥1 cigarette per day in youth (<20 years old) were considered smokers.

**Ultrasound Measurements**
B-mode ultrasound studies of the left common carotid artery were performed at follow-up examinations by using standardized protocols in each study. Details of the ultrasound data, protocols, and reproducibility have been described elsewhere.⁷,³²

**Exposure and Outcome Definitions**
In youth, non–HDL-C status was defined as normal if <3.10 mmol/L (<120 mg/dL), elevated if 3.10 to <3.75 mmol/L (120–<145 mg/dL), and dyslipidemia if ≥3.75 mmol/L (≥145 mg/dL), and LDL-C status was defined as normal if <2.85 mmol/L (<110 mg/dL), elevated if 2.85 to <3.36 mmol/L (110–<130 mg/dL), and dyslipidemia if ≥3.36 mmol/L (≥130 mg/dL) according to cut points from the NHLBI expert panel.¹⁴ Non–HDL-C status in adulthood was defined as normal if <4.91 mmol/L (<190 mg/dL) and dyslipidemia if ≥4.91 mmol/L (≥190 mg/dL), and LDL-C was defined as normal if <4.14 mmol/L (<160 mg/dL) and dyslipidemia if ≥4.14 mmol/L (≥160 mg/dL). Change in non–HDL-C and LDL-C status between youth and adulthood was defined as persistent dyslipidemia (dyslipidemia at both time points), incident dyslipidemia (normal to dyslipidemia), resolution (dyslipidemia to normal), and persistent normal (normal at both time points). The latest available measurement of cIMT was used, and high cIMT in adulthood was defined as at or above the follow-up year-, age-, sex-, race-, and cohort-specific 90th percentile. Because there was a small number of participants in some categories after stratification by age, sex, race, cohort, and follow-up years (in which the proportion of high-risk cIMT ranged between 10% and 20%), the combined average rate for the pooled data was higher than the expected 10%.

**Statistical Analysis**
Univariable and/or multivariable modified Poisson regression models (using a robust error variance) were used to estimate the relative risk (RR) and 95% confidence intervals (CIs) for the association of youth lipids and changes in their status between youth and adulthood with adult risk of having high cIMT. Because weight status is thought to influence the predictive use of non–HDL-C versus LDL-C, we performed a sensitivity analysis stratified by Cole BMI weight categories.³⁰ There were significant interactions between youth non–HDL-C and LDL-C status with cohort and youth age but not sex. Therefore, we also conducted multivariable modified Poisson regression models for associations between youth non–HDL-C and LDL-C status and adult risk of high intima-media thickness (IMT) stratified by cohort and youth age groups (3–8, 9–11, 12–14, 15–17, and 18+ years). Youth age groups were based on current risk screening age windows used by the NHLBI in which universal screening occurs from age 9 to 11 years and again at 18+ years.¹⁴ All multivariable analyses were adjusted for age, BMI, and systolic blood pressure at baseline, sex, cohort, and length of follow-up. Logistic regression models (all covariates adjusted above were included in the model) were used to obtain area under receiver-operating curve (AUC) values to estimate and compare the predictive use of youth non–HDL-C and LDL-C on adult risk of having high IMT. All analyses were re-run after additional adjustment for youth smoking or exclusion of those individuals having lipid-lowering medication (n = 155, all in adulthood: 112 from Bogalusa Heart Study, 2 from CDAH, and 41 from YFS), and risk ratios remained essentially similar in these analyses. As a sensitivity analysis, funnel plots were generated for the association of non–HDL-C or LDL-C status in youth with carotid artery IMT ≥90th percentile in adulthood. Analyses were performed in Stata version 15.1 (Stata Corp, College Station, TX). A 2-tailed P value <.05 was considered statistically significant.

**RESULTS**
Characteristics are shown in Supplemental Table 6. Youth characteristics among those who had elevated non–HDL-C or LDL-C are presented in Table 1. Of those with elevated youth non–HDL-C levels, 2335 (94%) also had elevated youth LDL-C levels. Moreover, 150 participants had elevated youth non–HDL-C but not elevated LDL-C levels, and 70 had elevated youth LDL-C but not elevated non–HDL-C levels. A total of 47% of those with elevated youth non–HDL-C levels had elevated levels as adults, compared with 57% of those with
TABLE 1 Characteristics Among Those With Elevated non–HDL-C and LDL-C in Youth

<table>
<thead>
<tr>
<th>Elevated non–HDL-C in Youth</th>
<th>Elevated LDL-C in Youth</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>2485 (54)</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>1079 (43)</td>
</tr>
<tr>
<td>Mean age in y. (SD)</td>
<td>10.7 (4.6)</td>
</tr>
<tr>
<td>Mean non–HDL-C, mmol/L (SD)</td>
<td>3.98 (0.88)</td>
</tr>
<tr>
<td>Mean LDL-C, mmol/L (SD)</td>
<td>3.64 (0.88)</td>
</tr>
<tr>
<td>Mean total cholesterol, mmol/L (SD)</td>
<td>5.50 (0.77)</td>
</tr>
<tr>
<td>Mean HDL-C, mmol/L (SD)</td>
<td>1.52 (0.36)</td>
</tr>
<tr>
<td>Mean triglycerides, mmol/L (SD)</td>
<td>0.77 (0.41)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>18.1 (3.5)</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg (SD)</td>
<td>110.9 (12.4)</td>
</tr>
</tbody>
</table>

TABLE 2 RR and 95% CIs From Pooled Data for the Association of non–HDL-C or LDL-C with Adult cIMT

<table>
<thead>
<tr>
<th>non–HDL-C</th>
<th>Elevated non–HDL-C</th>
<th>Elevated LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Normal</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Elevated</td>
<td>1.08 (0.89–1.31)</td>
<td>1.05 (0.87–1.28)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.35 (1.12–1.63)</td>
<td>1.29 (1.07–1.55)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Normal</td>
<td>1.05 (0.84–1.27)</td>
<td>1.03 (0.84–1.27)</td>
</tr>
<tr>
<td>Elevated</td>
<td>1.30 (1.08–1.57)</td>
<td>1.26 (1.04–1.51)</td>
</tr>
</tbody>
</table>

To convert non–HDL-C, LDL-C, and total cholesterol from mmol/L to mg/dL, multiply values by 38.67. To convert triglycerides from mmol/L to mg/dL, multiply values by 88.57.

a Percent of the total number of study participants (N = 4582).
b Percent of the number of participants with elevated youth non–HDL-C in youth (n = 2485) or LDL-C in youth (n = 2405).

elevated youth LDL-C levels having elevated levels as adults (Table 1).

Pooled RR and their 95% CIs for high adult cIMT according to non–HDL-C and LDL-C status in youth are shown in Table 2. Compared with those classified as not having dyslipidemia, youth with non–HDL-C dyslipidemia or LDL-C dyslipidemia were at increased risk of high cIMT in adulthood. Additional adjustment for youth BMI and systolic blood pressure (model 2, Table 2) did not appreciably change the effect estimates. The AUC was comparable between non–HDL-C and LDL-C models, with AUC of 0.622 and 0.620, respectively (P > .5). The AUC was similar between non–HDL-C and LDL-C when stratified by BMI status (normal weight: non–HDL-C AUC of 0.630 versus LDL-C AUC of 0.628, P > .5; overweight or obese: non–HDL-C AUC of 0.552 versus LDL-C AUC of 0.549, P > .5). A sensitivity analysis using funnel plots showed an asymmetry in the scatter of small studies, with more studies showing a lower-magnitude association between youth non–HDL-C or LDL-C with adult risk of cIMT (Supplemental Fig 1). In an additional pooled analysis based on 3 smaller cohorts (ie, excluding the Young Finns data), youth non–HDL-C dyslipidemia or LDL-C dyslipidemia was not associated with the risk of high cIMT in adulthood (Supplemental Table 7).

Age-stratified results for the association between youth non–HDL-C and LDL-C status with adult high cIMT are shown in Table 3. Those with dyslipidemia aged 15 to 17 years had significantly increased risk of adult high cIMT, as did those aged 18 years or over with elevated non–HDL-C or LDL-C status.

Table 4 shows results for adult high cIMT by youth non–HDL-C and LDL-C status, stratified by cohort. Within each cohort, associations were similar for both elevated and dyslipidemia non–HDL-C and LDL-C classifications. Between each cohort, there was large heterogeneity in effect estimates for elevated and dyslipidemia status in both non–HDL-C and LDL-C, with only participants in the YFS showing a consistent and graded increase in risk for adult high cIMT on the basis of youth non–HDL-C or LDL-C status.

Table 5 shows the pooled RR and their 95% CIs for high adult cIMT according to youth and adult non–HDL-C and LDL-C status. Compared with the persistent normal non–HDL-C group, those with persistent or incident non–HDL-C dyslipidemia had increased risk of high cIMT in adulthood; increased but weaker associations were observed for resolution and incident non–HDL-C dyslipidemia groups. On the basis of LDL-C classification in youth and adulthood, only those with persistent dyslipidemia had significantly increased risk of high adult cIMT compared with the normal LDL group (Table 5). We observed similar risk estimates after further adjustment for youth BMI and systolic blood pressure (model 2, Table 5).
DISCUSSION

These longitudinal data suggest that youth non–HDL-C levels are associated with high cIMT, in adulthood. In age-stratified analyses, this relationship was similar using either LDL-C or non–HDL-C. We have previously reported that elevated youth LDL-C levels and total cholesterol were associated with high cIMT in adulthood. For LDL-C we observed that only persistent dyslipidemia was related to higher cIMT. For total cholesterol, our previous analyses suggested that the measures in those aged $\leq$ 12 years, but not in younger children, were associated with high adult cIMT. The present data for non–HDL-C are in line with these observations but provide additional information that non–HDL-C levels in youth, especially among those aged $\geq$ 15 years, are among those related to higher cIMT.

We have previously reported that youth non–HDL-C levels are associated with higher cIMT in adulthood. In age-stratified analyses performed on all participants, this relationship was similar using either LDL-C or non–HDL-C. For total cholesterol, we observed that only persistent dyslipidemia was related to higher cIMT. For total cholesterol, we observed that only persistent dyslipidemia was related to higher cIMT. For total cholesterol, we observed that only persistent dyslipidemia was related to higher cIMT.

### TABLE 3

<table>
<thead>
<tr>
<th>Youth Age Group, y</th>
<th>n Out of N</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>n Out of N</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>n Out of N</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>n Out of N</th>
<th>%</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Non–HDL-C</td>
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</tr>
<tr>
<td>Normal</td>
<td>117 out of 633</td>
<td>18.5</td>
<td>Reference</td>
<td>54 out of 392</td>
<td>13.8</td>
<td>Reference</td>
<td>77 out of 627</td>
<td>12.3</td>
<td>Reference</td>
<td>47 out of 342</td>
<td>13.7</td>
<td>Reference</td>
</tr>
<tr>
<td>Elevated</td>
<td>45 out of 371</td>
<td>12.1</td>
<td>0.89 (0.65–1.24)</td>
<td>28 out of 238</td>
<td>11.8</td>
<td>0.95 (0.61–1.49)</td>
<td>31 out of 240</td>
<td>12.9</td>
<td>1.27 (0.85–1.95)</td>
<td>25 out of 191</td>
<td>13.1</td>
<td>1.11 (0.70–1.75)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>68 out of 477</td>
<td>14.3</td>
<td>1.10 (0.80–1.52)</td>
<td>45 out of 290</td>
<td>16.1</td>
<td>1.42 (0.92–2.20)</td>
<td>34 out of 263</td>
<td>12.9</td>
<td>1.36 (0.91–2.03)</td>
<td>32 out of 177</td>
<td>18.1</td>
<td>1.72 (1.08–2.72)</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Normal</td>
<td>116 out of 628</td>
<td>18.4</td>
<td>Reference</td>
<td>56 out of 398</td>
<td>14.1</td>
<td>Reference</td>
<td>86 out of 673</td>
<td>12.8</td>
<td>Reference</td>
<td>49 out of 359</td>
<td>13.7</td>
<td>Reference</td>
</tr>
<tr>
<td>Elevated</td>
<td>34 out of 298</td>
<td>11.5</td>
<td>0.84 (0.59–1.21)</td>
<td>25 out of 188</td>
<td>13.3</td>
<td>1.05 (0.66–1.67)</td>
<td>21 out of 190</td>
<td>11.1</td>
<td>1.04 (0.66–1.67)</td>
<td>20 out of 169</td>
<td>11.8</td>
<td>1.08 (0.66–1.77)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>80 out of 558</td>
<td>14.4</td>
<td>1.15 (0.85–1.57)</td>
<td>48 out of 324</td>
<td>14.2</td>
<td>1.24 (0.80–1.92)</td>
<td>35 out of 287</td>
<td>13.1</td>
<td>1.33 (0.90–2.03)</td>
<td>35 out of 182</td>
<td>19.2</td>
<td>1.97 (1.24–3.15)</td>
</tr>
</tbody>
</table>

All analyses were adjusted for age, BMI, and systolic blood pressure at baseline, sex, cohort, and length of follow-up.

* The age when non–HDL-C or LDL-C levels were first measured in youth.
* Number of participants with high IMT out of all participants.
* Statistical significance, $P < 0.05$. 

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plots), longer follow-up time, higher childhood lipid levels in the YFS (highest in the world in 1970s33), providing larger lifetime lipid exposure, and differences in lipid measurement and IMT methodology across the cohorts.

The 2011 NHLBI Expert Panel Guidelines14 were the first to suggest universal lipid screening in youth, initially at age 9 to 11 years and again at 18 to 21 years, using non–HDL-C as the preferred lipid measure. We observed that youth non–HDL-C measurements are comparable to LDL-C in predicting preclinical atherosclerosis. However, there is still limited evidence on population-based interventions in youth to reduce cIMT over the long-term. Screening using non–HDL-C comes with the benefit of not requiring the measurement of triglycerides to calculate LDL-C and the subsequent advantage of not requiring patients to provide a fasting sample. Concerning the optimal age for lipid screening, our observational data suggest that neither non–HDL-C nor LDL-C levels at the age of 9 to 11 years are associated with subsequent cIMT because associations only became evident from age 15 years onwards. However, our findings need to be interpreted with caution because effect estimates were inconsistent across ages. In pooled estimates, elevated lipids significantly related with later cIMT only among those aged 18 to 19 years and dyslipidemic levels only among 15- to 17-year-olds.

For preventive interventions, our findings that the adverse effects of youth dyslipidemia are attenuated if lipid status is improved or normalized by adulthood are encouraging. These data indicate there is a window for change in late adolescence and young adulthood in which individual- and public health–focused programs might have long-term preventive effects. In addition, because the effect of elevated childhood non–HDL-C was not completely attenuated or reversed in the resolution group, primordial prevention will continue to be an important goal. We have shown in these cohorts that although lipid levels track, or persist, well from youth to adulthood,34 those able to change from high risk in youth to normal risk in adulthood coincide with healthful lifestyle changes, such as lower gains in fatness and improvements in cardiorespiratory fitness relative to their peers, not smoking, and upward mobility in education.35-38 Higher gains in BMI from youth to adulthood have been associated with more adverse adult lipid levels irrespective of genetic susceptibility.39 Indeed, the genetic effect on life-course lipid levels tends to persist, or slightly

TABLE 4 RR and 95% CIs for the Association of non–HDL-C and LDL-C Status in Youth With Carotid Artery IMT ≥90th Percentile in Adulthood by Cohorts (n = 4382)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Non–HDL-C</th>
<th>n Out of N</th>
<th>%</th>
<th>Model 1 (95% CI)</th>
<th>Model 2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>48 out of 234</td>
<td>20.5</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>177 out of 1068</td>
<td>16.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
<td>11 out of 74</td>
<td>14.9</td>
<td>0.71 (0.41–1.22)</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>Normal</td>
<td>51 out of 248</td>
<td>20.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>178 out of 1075</td>
<td>16.6</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
<td>12 out of 77</td>
<td>15.6</td>
<td>0.75 (0.44–1.35)</td>
<td></td>
</tr>
</tbody>
</table>

All analyses were adjusted for age, BMI, and systolic blood pressure at baseline, sex, cohort, and length of follow-up.

TABLE 5 RR and 95% CIs From Pooled Data for the Association of Change in non–HDL-C or LDL-C Status Between Youth and Adulthood With Carotid Artery IMT ≥90th Percentile in Adulthood (n = 4582)

<table>
<thead>
<tr>
<th>Status</th>
<th>n Out of N</th>
<th>%</th>
<th>Model 1 (95% CI)</th>
<th>Model 2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non–HDL-C</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Persistent normal</td>
<td>411 out of 3056</td>
<td>13.5</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Incident dyslipidemia</td>
<td>39 out of 200</td>
<td>19.5</td>
<td>1.45 (1.07–1.98)</td>
<td>1.47 (1.09–1.98)</td>
</tr>
<tr>
<td>Resolution</td>
<td>147 out of 1082</td>
<td>13.6</td>
<td>1.21 (1.00–1.46)</td>
<td>1.17 (0.97–1.41)</td>
</tr>
<tr>
<td>Persistent dyslipidemia</td>
<td>50 out of 244</td>
<td>20.5</td>
<td>1.80 (1.37–2.37)</td>
<td>1.74 (1.53–2.28)</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Persistent normal</td>
<td>400 out of 2900</td>
<td>13.8</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Incident dyslipidemia</td>
<td>36 out of 222</td>
<td>16.2</td>
<td>1.14 (0.83–1.56)</td>
<td>1.15 (0.84–1.58)</td>
</tr>
<tr>
<td>Resolution</td>
<td>161 out of 1189</td>
<td>13.5</td>
<td>1.20 (0.99–1.45)</td>
<td>1.16 (0.96–1.40)</td>
</tr>
<tr>
<td>Persistent dyslipidemia</td>
<td>50 out of 271</td>
<td>18.5</td>
<td>1.80 (1.21–2.60)</td>
<td>1.55 (1.18–2.04)</td>
</tr>
</tbody>
</table>

Model 1 is adjusted for age at baseline, sex, cohort, and length of follow-up. Model 2 includes model 1 covariates plus baseline BMI and systolic blood pressure.

a Number of participants with high IMT out of all participants.

b Statistical significance, P < .05.
Weaken, with age, suggesting greater importance of lifestyle factors at different life stages. We have also shown evidence of an infant-onset dietary counseling intervention aimed primarily at improving fat quality in the diet but also promoting intake of fruit, vegetables, and whole grains to associate with a higher likelihood of achieving dietary guidelines and reduced lipid levels even into adulthood. These data provide insight on lifestyle and environmental factors that could be targeted at individual or population-wide prevention.

The main strength of this study is the use of pooled data on youth risk factors and adult CIMT from 4 international longitudinal cohorts. The study also has some limitations. First, because the study cohorts are composed of relatively young adults at follow-up, we were not able to study associations with cardiovascular events. Instead, we have used CIMT as a surrogate endpoint with the risk stratification groupings, not based on absolute risk of cardiovascular events (as in adult risk score algorithms) but on high CIMT (defined as ≥ 90th percentile). However, in older adults, CIMT has been shown to predict subsequent cardiovascular disease events. Second, study participants were predominantly white, and the results may not be generalizable to other ethnicities. Third, observational studies are prone to bias when trying to establish causality. Finally, concerning the possible confounding factors, most cohorts did not have data available on some possible childhood confounders, such as socioeconomic factors.

CONCLUSIONS

In our analysis, we show that elevated non–HDL-C levels in youth are related to high CIMT in adulthood. In age-stratified analyses, a significant association was observed if non–HDL-C levels were measured at the age of 15 to 19 years. The predictive use of youth non–HDL-C and LDL-C were similar. It is also demonstrated in the data that individuals with normal non–HDL-C in youth but elevated non–HDL-C in adulthood had high CIMT, whereas those with dyslipidemia in youth but normal non–HDL-C as adults had the proportion of high CIMT comparable to those who never had dyslipidemia.

**ABBREVIATIONS**

AUC: area under receiver-operating curve  
CDAH: Childhood Determinants of Adult Health  
CI: confidence interval  
CIMT: carotid intima-media thickness  
HDL-C: high-density lipoprotein cholesterol  
IMT: intima-media thickness  
LDL-C: low-density lipoprotein cholesterol  
NHLBI: National Heart, Lung, and Blood Institute  
RR: relative risk  
YFS: Young Finns Study

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Drs Juonala, Wu, and Magnussen conceptualized and designed the study, analyzed the data, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Sinaiko, Woo, Urbina, Jacobs, Steinberger, Prineas, Burns, Bazzano, Venn, Viikari, Nutri-Kindren, Daniels, Dwyer, and Raitakari designed and executed data collection, collected data, and critically reviewed and revised the manuscript for important intellectual content; all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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