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Childhood non-HDL Cholesterol and LDL Cholesterol and Adult Atherosclerotic Cardiovascular Events

Running title: Child Non-HDL-C, LDL-C, Atherosclerotic CVD Events

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BACKGROUND

Although low-density lipoprotein cholesterol (LDL-C) remains the primary cholesterol target in clinical practice in children and adults, non-high-density lipoprotein cholesterol (non-HDL-C) has been suggested as a more accurate measure of atherosclerotic cardiovascular disease (ASCVD) risk. We examined the associations of childhood non-HDL-C and LDL-C levels with adult ASCVD events and determined if non-HDL-C has better utility than LDL-C in predicting adult ASCVD events.

METHODS

This prospective cohort study included 21,126 participants from the International Childhood Cardiovascular Cohorts (i3C) Consortium. Proportional-hazards regressions were used to estimate the risk for incident fatal and fatal/nonfatal ASCVD events associated with childhood non-HDL-Cand LDL-C levels (age- and sex-specific z scores; concordant/discordant categories defined by guideline-recommended cut-offs), adjusting for sex, Black race, cohort, age at and calendar year of child measurement, body mass index, and systolic blood pressure. Predictive utility was determined by the C-index.

RESULTS

After an average follow-up of 35 years, 153 fatal ASCVD events occurred in 21,126 participants (mean age at childhood visits, 11.9 years) and 352 fatal/nonfatal ASCVD events occurred in a subset of 11,296 participants who could be evaluated for this outcome. Childhood non-HDL-C and LDL-C levels were each associated with higher risk of fatal and fatal/nonfatal ASCVD events (hazard ratio (95% confidence interval) ranged from 1.27 (1.14-1.41) to 1.35 (1.13-1.60) per unit increase in the risk factor z score). Non-HDL-C had better discriminative utility than LDL-C (difference in C-index =0.0054, 95%CI: 0.0006 to 0.0102 and 0.0038, 0.0008 to 0.0068 for fatal and fatal/nonfatal events, respectively). The discordant group with elevated non-HDL-C and normal LDL-C had a higher risk of ASCVD events compared to the concordant group with normal non-HDL-C and LDL-C (fatal events: hazard ratio =1.90, 95% confidence interval: 0.98-3.70; fatal/nonfatal events: 1.94, 1.23-3.06).

CONCLUSIONS

Childhood non-HDL-C and LDL-C levels are associated with ASCVD events in midlife. Non-HDL-C is better than LDL-C in predicting adult ASCVD events, particularly among individuals who had normal LDL-C but elevated non-HDL-C. These findings suggest that both non-HDL-C and LDL-C are useful in identifying children at higher risk of ASCVD events, but non-HDL-C may provide added prognostic information when it is discordantly higher than corresponding LDL-C and has the practical advantage of being determined without a fasting sample.

Key Words: atherosclerosis; epidemiology; lipoproteins; longitudinal studies; risk assessment; risk factors

Non-standard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
AHA/ACC	American Heart Association/American College of Cardiology
BMI	body mass index
CI	confidence interval
HR	hazard ratio
i3C	International Childhood Cardiovascular Cohorts
ICD	International Classification of Diseases
LDL-C	low-density lipoprotein cholesterol
Non-HDL-C	non-high-density lipoprotein cholesterol
NHLBI	National Heart, Lung, and Blood Institute

Clinical Perspective

What Is New?

• Elevated non-high-density lipoprotein cholesterol (non-HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels in childhood were associated with higher risks of developing atherosclerotic cardiovascular disease (ASCVD) events in a large prospective study of seven cohorts from the International Childhood Cardiovascular Cohorts (i3C) Consortium.

• Childhood non-HDL-C is better than LDL-C as a predictor of adult ASCVD events, especially among individuals who had normal LDL-C but elevated non-HDL-C.

What Are the Clinical Implications?

• By providing direct evidence to link childhood non-HDL-C and LDL-C to the occurrence of clinical ASCVD events in adulthood, our data reinforce the merits of evaluating these markers in childhood.

• Although LDL-C remains the primary cholesterol target in clinical practice in children, elevated non-HDL-C may provide added prognostic information in identifying children at higher risk of ASCVD events and has the practical advantages of no fasting requirement.

INTRODUCTION

Identifying children at potential risk of developing atherosclerotic cardiovascular disease (ASCVD) in adulthood is a central objective for early prevention because childhood ASCVD risk factors (total cholesterol, triglycerides, blood pressure, body mass index, smoking) predict adult risk of fatal and non-fatal ASCVD events[1]. Of the various lipid risk factors, non-high-density lipoprotein cholesterol (non-HDL-C) is considered to have more utility for screening in the assessment of ASCVD risk, even when compared with the primary lipid target for treatment of low-density lipoprotein cholesterol (LDL-C). We previously found child non-HDL-C to be a better predictor of adult dyslipidemia[2] and non-lipid risk factors[2], and is at least as good as LDL-C in predicting arterial injury associated with atherosclerosis[3]. In recognizing the advantages of non-HDL-C (which measures the mass of cholesterol in all atherogenic lipoproteins and can be reliably measured in the non-fasting state), current American Heart Association/American College of Cardiology (AHA/ACC) cholesterol guidelines consider it as a reasonable test for initial screening[4]. Moreover, the recently released Life's Essential 8, aimed at primordial and primary prevention of ASCVD, has updated the metric of interest for blood lipids from total cholesterol to non-HDL-C[5]. However, these recommendations were based on cross-sectional data or ASCVD markers. The National Heart, Lung, and Blood Institute (NHLBI)-sponsored Pediatric CV Risk Reduction Initiative also noted that the lack of data to link childhood ASCVD risk factors to adult ASCVD events is a major research gap that needs to be addressed[6]. To that end, we previously showed that childhood non-HDL-C and LDL-C levels are associated with adult preclinical atherosclerosis[7], but their links to ASCVD events remain unclear.

Therefore, using data from the International Childhood Cardiovascular Cohort (i3C) Consortium, we 1) examined the relationships of childhood non-HDL-C and LDL-C levels with adult ASCVD events; and 2) determined whether non-HDL-C is a stronger predictor than LDL-C in predicting adult risk of ASCVD events.

METHODS

Study design and participants

Anonymized data are available on reasonable request from the i3C Consortium. This prospective study included harmonized data from the seven cohorts (five from the United States and one each from Finland and Australia) collaborating in the i3C Consortium[8]; the study design of the i3C Consortium has been described in detail elsewhere[1]. A total of 42,324 children aged 3–19 years were enrolled across the seven i3C Consortium cohorts in the 1970s and 1980s, of whom, 40,648 had identifying information for follow-up (**Fig. S1** in Supplementary Appendix). The current study included 21,126 participants who had data on both childhood non-HDL-C and LDL-C in addition to other covariates and adult ASCVD events (among whom 11,296 participants could be evaluated for fatal/nonfatal events). Institutional review boards at all participating sites approved the study. All participants' legal guardians provided written informed consent with oral assent from the participant for childhood visits. All participants provided written informed consent for in-person adult visits and gave oral consent under waiver of documentation of consent for the recent follow-up questionnaire.

ASCVD events

Details of how ASCVD events were classified and adjudicated are described elsewhere[1]. From 2015 to 2019, a coordinated study was conducted to locate and survey participants of all i3C Consortium cohorts, and to search national death indexes for those who were unable to be located. The coded causes of death in the International Classification of Diseases (ICD, versions 9 and 10) were used to classify fatal ASCVD events in all the cohorts. Participants of the Finnish cohort were followed for nonfatal ASCVD events through December 31, 2017, using the Finnish national medical registry; the events were classified based on the same version of the ICD that was used to classify deaths. Adult participants of the U.S. and Australian cohorts who had been successfully located completed a health history survey that included information on any ASCVD event that had occurred, and medical records associated with the events were requested for adjudication. The medical records were examined by a physician committee who were blinded to the participant study data, with each reported event classified as a confirmed ASCVD event, not a ASCVD event, or not possible to adjudicate. Nonfatal

ASCVD events included the first adjudicated occurrence of myocardial infarction, stroke, transient ischemic attack, ischemic heart failure, angina, peripheral artery disease, carotid intervention, abdominal aortic aneurysm, or coronary revascularization.

Risk factor assessment

Fasting levels of plasma or serum cholesterol and triglycerides in childhood were measured by means of standard methods as described in previous i3C Consortium publications[1, 7]. Non-HDL-C was calculated as total cholesterol minus high-density lipoprotein cholesterol (HDL-C) (i.e., LDL-C estimated by Friedewald's equation plus triglycerides/5). LDL-C was calculated by Friedewald's equation for participants with serum triglycerides <400 mg/dL[7].

Other measures

Age, sex, race (reported by parents in childhood and updated if the participant was followed up in adulthood), and smoking habits (smoked ≥1 cigarette/day prior to the age of 20 years were considered smokers), were measured by questionnaire. The education levels of the parents were obtained at childhood and adult visits. Standing height and weight were measured, with BMI calculated as weight divided by height squared (kilograms/meters^2). Systolic blood pressure was measured by mercury sphygmomanometers at childhood visits.

Statistical analysis

Exposure calculations/definitions: Childhood non-HDL-C and LDL-C levels were normalized to z scores within the i3C Consortium, using age- and sex-specific mean values and standard deviations; participants were stratified into six age groups: 3-5, 6-8, 9-11, 12-14, 15-17, and 18-19 years. A single mean z score for each participant was generated by averaging all z scores across the participant's childhood measurements when multiple measurements were taken (54% of participants had at least two measures). Childhood non-HDL-C and LDL-C levels were also categorized according to cut-offs from the NHLBI expert panel[6]: LDL-C: < 110 mg/dL, 110 to <130 mg/dL, and ≥130 mg/dL; non-

HDL-C: < 120 mg/dL, 120 to <145 mg/dL, and 145 mg/dL. These cut-offs were also used to assign the population into four concordant and discordant groups: 1) LDL-C <110 mg/dL and non-HDL-C <120 mg/dL (reference group); 2) LDL-C ≥110 mg/dL and non-HDL-C <120 mg/dL; 3) LDL-C <110 mg/dL and non-HDL-C ≥120 mg/dL; 4) LDL-C ≥110 mg/dL and non-HDL-C ≥120 mg/dL. Likewise, in sensitivity analysis, participants were divided into groups using higher NHLBI cut-offs (130 mg/dL for LDL-C and 145 mg/dL for non-HDL-C) and 75th percentiles (117 mg/dL for LDL-C and 130 mg/dL for non-HDL-C). We also applied a higher and clinically relevant cut-off to define discordance and to assess the robustness of the findings: 190 mg/dL for LDL-C corresponding to probable familial hypercholestorolemia[9]; cut-off for non-HDL-C (≥208 mg/dL) was identified using equivalent population percentiles from the i3C Consortium cohorts corresponding to this LDL-C value.

All analyses were performed for fatal and fatal/nonfatal ASCVD events separately as done in a previous i3C Consortium publication[1]. We estimated hazard ratios (HRs) for the association of z scores and categories of childhood non-HDL-C and LDL-C levels with adult ASCVD events using Fine-Gray subdistribution hazards regressions, with adult age as the time axis (the age at the end of follow-up or the age when the outcome or competing event occurred, whichever came first) and non-cardiovascular mortality as a competing risk. We compared z score-related HRs for non-HDL-C and LDL-C using two independent-sample t-test based on bootstrapped estimates (n=100). Analyses were adjusted for cohort, sex, Black race, mean age at and mean visit year of childhood measurement, and childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure. The proportionality assumption was checked by including interactions of the exposure and time (log(time)). Nonlinear associations between childhood exposures (z scores) and adult ASCVD events were examined using restricted cubic splines, using four knots (at the 5th, 35th, 65th and 95th percentiles) as recommended[10]. Nonlinearity was tested by comparing the log-likelihood of the new model with that of the linear model.

Harrell C-statistics were estimated to compare the overall predictive utility of childhood non-HDL-C vs. LDL-C on adult risk of ASCVD events. We acknowledge that conventional epidemiological methods of predictive analysis (such as C-statistics) examine if a new marker improves the overall

predictive power of a model that includes established predictors of an event, which substantially underestimate the importance of modifiable causes given the predominant role of non-modifiable causes (e.g., age and sex)[11]. Thus, C-statistics often underestimate important differences in risk prediction between highly correlated modifiable factors (e.g., non-HDL-C vs. LDL-C in our case). Thus, we also performed discordance analysis[11] to examine whether non-HDL-C predicts ASCVD risk more accurately than LDL-C when they are discordant (discordance defined as described above).

We also examined for differences by childhood age (continuous), sex, and race (Black vs. non-Black) through interaction (i.e., including a product term of the exposure, for example, non-HDL-C z score with sex) and stratification analysis by these variables. Childhood age groups (<9, 9-11, 12-16, 17-19 years) were constructed according to current lipid screening age windows recommended by the NHLBI for universal screening from age 9–11 years and again at 17-21 years[6]. Cohort-specific analysis was performed for two of the seven cohorts (Bogalusa and Young Finns), where sufficient ASCVD events allowed for meaningful analyses. Because childhood smoking and parental education did not exist for more than half of the participants, sensitivity analyses using reduced datasets with the addition of these two variables were performed. Moreover, we repeated the analyses for the association of childhood exposures with adult ASCVD events using the first available observation of these exposures in childhood. Analyses were performed in Stata version 16.0 (Stata Corp, College Station, TX). A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

Among 38,589 participants with ASCVD event data, 21,126 who had at least one childhood measurement of both non-HDL-C and LDL-C and non-missing covariates were included in the analysis of fatal ASCVD events. A subset of 11,296 participants who could be evaluated for fatal/nonfatal ASCVD events were included in the analysis of fatal/nonfatal ASCVD events (**Figure S1**). After an average follow-up of 35 years, 153 fatal ASCVD events occurred among 21,126 participants (49.0% male and 23.9% Black; mean [±standard deviation] age at child visits, 11.9±3.3 years) and 352 fatal/nonfatal ASCVD events occurred among the subset of 11,296 participants (**Table**

1). There were 13243 (62.7%) participants with normal LDL-C and non-HDL-C, 311 (1.5%) with elevated LDL-C but normal non-HDL-C, 970 (4.6%) with normal LDL-C but elevated non-HDL-C, and 6062 (31.2%) with elevated LDL-C and non-HDL-C. The mean age at ASCVD diagnoses was 44.9 years and the mean age at follow-up of participants who did not have ASCVD events was 45.8 years.

Childhood non-HDL-C and LDL-C levels were associated with higher risk of fatal and fatal/nonfatal ASCVD events (HRs ranged from 1.27 to 1.35 per unit increase in the risk factor z score) (**Figure 1** and **Table S1**); the associations for non-HDL-C were stronger than those for LDL-C ($p<0.001$). When classified according to NHLBI cut-offs, child non-HDL-C and LDL-C categories were associated with adult ASCVD events in relation to increasing levels of the risk factors (**Table S1**, **Figure 1**, **Figure 2**). There was no clear evidence of nonlinear associations between childhood non-HDL-C and LDL-C levels with fatal or fatal/nonfatal ASCVD events (**Figure S2**).

Non-HDL-C had better predictive utility for ASCVD events than LDL-C when cohort was added to the model (**Table 2**); these differences remained significant when baseline age and visit year, sex, race, body mass index, and systolic blood pressure were also included in the model (difference in C-index = 0.0054, 95%CI: 0.0006 to 0.0102 for fatal event and 0.0038, 0.0008 to 0.0068 for fatal/nonfatal event). The discordant elevated non-HDL-C and normal LDL-C group had a higher risk of ASCVD events compared to the concordant normal group (HR =1.90, 95%CI: 0.98 to 3.70 for fatal events and 1.94, 1.23 to 3.06 for fatal/nonfatal events) (**Figure 3**, **Table S2**). The number of participants with normal non-HDL-C and elevated LDL-C was too low to evaluate the association with ASCVD events (only two events among 114 to 311 individuals). When 75^{th} percentiles or higher cut-offs were used to define the status of these markers, similar patterns of associations from discordance analyses were found (**Table S3**).

Significant interactions were observed among these markers in childhood with sex for fatal ASCVD events ($p<0.05$). Females had much stronger associations with fatal ASCVD events than males (**Table S4**). There were no interactions with age or race (**Table S5** and **S6**), though stratification analysis

suggested that non-Black (mostly White) participants had stronger associations between the markers with ASCVD events than Black individuals (**Table S6**). Cohort-specific analysis yielded similar results in the Bogalusa Heart and Cardiovascular Risk in Young Finns studies (**Table S7**). In sensitivity analysis with additional adjustment for parental education and child smoking, the associations of non-HDL-C and LDL-C with ASCVD events remained similar for fatal/nonfatal events but were largely reduced for fatal events (**Table S8**). Sensitivity analysis using the first available measurement in childhood for non-HDL-C and LDL-C showed reduced associations with ASCVD events (**Table S9**).

DISCUSSION

This large prospective cohort study, with a mean follow-up of 35 years, showed that childhood non-HDL-C and LDL-C levels are associated with incident ASCVD events in midlife. The magnitude of the associations is clinically important, especially among those with very high levels. For example, each 3-SD increase (approximately 90-100 mg/dL) in non-HDL-C and LDL-C levels is estimated to more than double the risks of ASCVD events, leading to 110% to 146% higher increase in risk. Moreover, childhood non-HDL-C is better than LDL-C in predicting adult ASCVD events, particularly among individuals who had normal LDL-C but elevated non-HDL-C. These findings suggest that both non-HDL-C and LDL-C are useful in identifying children at higher risk of ASCVD events, but non-HDL-C may provide added prognostic information when it is discordantly higher than corresponding LDL-C and has the practical advantage of being determined without a fasting sample.

The 2011 Integrated Guidelines (sponsored by NHLBI and endorsed by the American Academy of Pediatrics) and the AHA/ACC guidelines recommended pediatric screening for dyslipidemia[4, 6, 12] because identifying and correcting dyslipidemia in childhood might reduce the risk of ASCVD in adulthood. Our previous analysis, which focused on traditional risk factors showed that childhood total cholesterol and triglycerides are associated with adult ASCVD events[1]. Non-HDL-C includes the mass of cholesterol in all atherogenic (i.e., ApoB containing) particles and recent AHA/ACC cholesterol guidelines consider non-HDL-C a reasonable target for initial screening[4]. In contrast, total

cholesterol includes HDL-C, which is not causally associated with ASCVD based on Mendelian randomization studies[13, 14]. However, non-HDL-C and LDL-C and their guideline-suggested cut-offs have not been examined in children as predictors for ASCVD events. To that end, our findings provide epidemiological basis for pediatric screening and control of dyslipidemia by directly linking these markers in childhood to clinical ASCVD outcomes.

LDL-C, a major form of atherogenic cholesterol, is widely used to screen for dyslipidemia and is the primary target of lipid lowering treatment. In comparison, non-HDL-C is an emerging marker for ASCVD risk with evidence among middle-aged and older adults suggesting non-HDL-C had better predictive utility or stronger associations than LDL-C for the risk of coronary heart disease[15] and ischemic stroke[16]. Our analysis extended these findings into childhood, showing that both LDL-C and non-HDL-C have their roles in predicting adult ASCVD events, although non-HDL-C may add prognostic information, especially among those with normal LDL-C but elevated non-HDL-C. Although the proportion of children with discordant non-HDL-C and LDL-C levels is relatively small, this would have considerable impact if lipid screening is applied to the overall pediatric population. In line with our findings, two large cohort studies in adults identified a slightly higher proportion of participants discordantly high non-HDL-C but low LDL-C (8%-11.6%) and these people had higher risk of incident coronary events[17], myocardial infarction, all-cause mortality[18].

The 2011 Integrated Guidelines recommended universal screening of non-HDL-C levels as the initial stage to identify children at current or future risk for ASCVD[6] on the basis of lipid levels, a practice considered reasonable by AHA/ACC[4]. Our study contributes to this approach by highlighting the unique prognostic value of non-HDL-C. Importantly, children with normal LDL-C but elevated non-HDL-C appear more likely to have metabolic syndrome, as indicated by a higher prevalence of high BMI and blood pressure. This observation aligns with the European Society of Cardiology/European Atherosclerosis Society's 2019 guidelines on dyslipidemia management. These guidelines note that LDL-C might not fully reflect the total concentration of ApoB-containing lipoproteins in individuals with conditions such as metabolic syndrome, elevated triglycerides, diabetes mellitus, obesity, or very

low LDL-C levels. Therefore, they recommended including non-HDL-C or ApoB in routine lipid analysis for cardiovascular risk assessment among these populations[19]. Moreover, the ability to calculate non-HDL-C in a non-fasting state adds to its utility. By underscoring the value of both non-HDL-C and LDL-C in assessing ASCVD risk, especially given the low rates of lipid screening in children[20-23], our findings support the continuation of non-HDL-C as the preferred initial step in lipid screening, and provide insights into its potential added benefits.

It is noteworthy that more than half of the ASCVD events occurred in children with normal non-HDL-C and LDL-C, emphasizing the importance of global CV risk assessment beyond lipid screening. Indeed, several traditional ASCVD risk factors in childhood such as total cholesterol, triglycerides, blood pressure, body mass index, and smoking have been directly associated with adult ASCVD events[1]. Recommended as a risk enhancer in adults[24], our recent findings indicate that lipoprotein(a) in childhood is associated with ASCVD events, independent of traditional risk factors[25]. These findings suggest a multifactorial public health strategy is necessary to minimize the risk of future ASCVD events.

Females appeared to have stronger associations between these markers and ASCVD events compared with males. Likewise, non-Black (mainly White) individuals appeared to have stronger associations compared with Black individuals though our study was not designed to be powered to detect race differences. These findings may help refine the targeted population for preventive interventions, though the mechanisms underlying the observed sex and race divergence in the associations are unclear. Previous data from the Bogalusa Heart Study also showed that child LDL-C was associated with adult carotid intima media thickness in white males and females and Black females, but not Black males[26]. In contrast to our findings, recent Mendelian randomization analysis has shown a stronger association of genetically determined LDL-C levels with ASCVD risk in males than females[27], but this finding may not generalize to childhood as genetic associations are likely to vary by age[28]. We did not find an interaction with age and our results support the initial screening to start as early as in ages 9 to 11 or later until age 20 if an earlier screening is missed, though the

associations were somewhat weaker during ages of 12 to 16. This differs from our previous i3C study using carotid intima media thickness as the outcome that suggested initial screening from a later age of 15 years[7]. This could be explained by the fact of carotid intima media thickness being a predictor of ASCVD risk and the younger age in the adult follow-up and the much smaller sample size of that study[7]. This also highlights the importance of the current study that used ASCVD events.

This study benefited from the large sample and a long follow-up of more than three decades that allowed us to directly link childhood risk factors with adult incident ASCVD events; and the rigorous adjudication of ASCVD outcomes. There were some limitations. First, while some participants were lost to follow-up, we employed multiple imputation that confirmed no appreciable influence on the associations of childhood risk factors, including total cholesterol and triglycerides, with adult ASCVD events[1]. Second, as ApoB was only measured in a subsample of two of the seven i3C cohorts, we cannot rule out the possibility that ApoB levels will have better predictive utility compared to non-HDL-C, which warrants further investigation. Third, we had a limited number of participants with probable familial hypercholesterolemia due primarily to the low prevalence; thus, the discordance analysis based on this cut-off warrants further investigation. Lastly, this study had a small proportion of non-White individuals, and the results may not generalize to other ethnic groups.

This prospective study demonstrated that childhood non-HDL-C and LDL-C levels were associated with incident ASCVD events in midlife. Moreover, childhood non-HDL-C appeared to be better than LDL-C in identifying children at increased CVD risk in adulthood, especially among those with normal LDL-C but elevated non-HDL-C. These findings suggest that both non-HDL-C and LDL-C are useful in identifying children at higher risk of ASCVD events, but non-HDL-C may provide added prognostic information when it is discordantly higher than corresponding LDL-C and has the practical advantage of being determined without a fasting sample.

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Disclosures

None.

Supplemental Materials

Figure S1-2

Table S1-9

REFERENCES

1. Jacobs DR, Jr., Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, Kartiosuo N, Lehtimäki T, Magnussen CG, Viikari JSA, Zhang N, Bazzano LA, Burns TL, Prineas RJ, Steinberger J, Urbina EM, Venn AJ, Raitakari OT and Dwyer T. Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events. *N Engl J Med*. 2022;386:1877-1888.
2. Srinivasan SR, Frontini MG, Xu J and Berenson GS. Utility of childhood non-high-density lipoprotein cholesterol levels in predicting adult dyslipidemia and other cardiovascular risks: the Bogalusa Heart Study. *Pediatrics*. 2006;118:201-6.
3. Frontini MG, Srinivasan SR, Xu J, Tang R, Bond MG and Berenson GS. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. *Pediatrics*. 2008;121:924-9.
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS and Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082-e1143.
5. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, Rosamond W and American Heart A. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. *Circulation*. 2022;146:e18-e43.
6. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128 Suppl 5:S213-56.
7. Juonala M, Wu F, Sinaiko A, Woo JG, Urbina EM, Jacobs D, Steinberger J, Prineas R, Koskinen J, Sabin MA, Burgner DP, Burns TL, Bazzano L, Venn A, Viikari JSA, Hutri-Kähönen N, Daniels SR, Dwyer T, Raitakari OT and Magnussen CG. Non-HDL Cholesterol Levels in Childhood and Carotid Intima-Media Thickness in Adulthood. *Pediatrics*. 2020;145.
8. Sinaiko AR, Jacobs DR, Jr., Woo JG, Bazzano L, Burns T, Hu T, Juonala M, Prineas R, Raitakari O, Steinberger J, Urbina E, Venn A, Jaquish C and Dwyer T. The International Childhood Cardiovascular Cohort (i3C) consortium outcomes study of childhood cardiovascular risk factors and adult cardiovascular morbidity and mortality: Design and recruitment. *Contemp Clin Trials*. 2018;69:55-64.
9. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Boren J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Steinhagen-Thiessen E, Stroes ES, Taskinen MR, Tybjaerg-Hansen A, Wiklund O and European Atherosclerosis Society Consensus P. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36:2425-37.
10. Desquilbet L and Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med*. 2010;29:1037-57.
11. Sniderman AD, Pencina M and Thanassoulis G. ApoB. *Circ Res*. 2019;124:1425-1427.
12. de Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, Mietus-Snyder M, Mitsnefes MM, Peterson AL, St-Pierre J, Urbina EM, Zachariah JP and Zaidi AN. Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139:e603-e634.
13. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Holm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M,

Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, Konig IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schafer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D and Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572-80.

14. Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G and Holmes MV. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: A multivariable Mendelian randomisation analysis. *PLoS Med*. 2020;17:e1003062.

15. Arsenault BJ, Rana JS, Stroes ES, Despres JP, Shah PK, Kastelein JJ, Wareham NJ, Boekholdt SM and Khaw KT. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. *J Am Coll Cardiol*. 2009;55:35-41.

16. Johannesen CDL, Mortensen MB, Langsted A and Nordestgaard BG. ApoB and Non-HDL Cholesterol Versus LDL Cholesterol for Ischemic Stroke Risk. *Ann Neurol*. 2022;92:379-389.

17. Mora S, Buring JE and Ridker PM. Discordance of Low-Density Lipoprotein (LDL) Cholesterol With Alternative LDL-Related Measures and Future Coronary Events. *Circulation*. 2014;129:553-561.

18. Johannesen CDL, Mortensen MB, Langsted A and Nordestgaard BG. Apolipoprotein B and Non-HDL Cholesterol Better Reflect Residual Risk Than LDL Cholesterol in Statin-Treated Patients. *J Am Coll Cardiol*. 2021;77:1439-1450.

19. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O and Group ESCSD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111-188.

20. Berger JH, Chen F, Faerber JA, O'Byrne ML and Brothers JA. Adherence with lipid screening guidelines in standard- and high-risk children and adolescents. *Am Heart J*. 2021;232:39-46.

21. Smith AJ, Turner EL and Kinra S. Universal Cholesterol Screening in Childhood: A Systematic Review. *Acad Pediatr*. 2016;16:716-725.

22. Valle CW, Binns HJ, Quadri-Sheriff M, Benuck I and Patel A. Physicians' Lack of Adherence to National Heart, Lung, and Blood Institute Guidelines for Pediatric Lipid Screening. *Clin Pediatr (Phila)*. 2015;54:1200-5.

23. de Ferranti SD, Rodday AM, Parsons SK, Cull WL, O'Connor KG, Daniels SR and Leslie LK. Cholesterol Screening and Treatment Practices and Preferences: A Survey of United States Pediatricians. *J Pediatr*. 2017;185:99-105 e2.

24. Wilson DP, Koschinsky ML and Moriarty PM. Expert position statements: comparison of recommendations for the care of adults and youth with elevated lipoprotein(a). *Current Opinion in Endocrinology, Diabetes and Obesity*. 2021;28:159-173.

25. Raitakari O, Kartiosuo N, Pahkala K, Hutri-Kahonen N, Bazzano LA, Chen W, Urbina EM, Jacobs DR, Jr., Sinaiko A, Steinberger J, Burns T, Daniels SR, Venn A, Woo JG, Dwyer T, Juonala M and

Viikari J. Lipoprotein(a) in Youth and Prediction of Major Cardiovascular Outcomes in Adulthood. *Circulation*. 2022.
26. Li S, Chen W, Srinivasan SR, Tang R, Bond MG and Berenson GS. Race (black-white) and gender divergences in the relationship of childhood cardiovascular risk factors to carotid artery intima-media thickness in adulthood: the Bogalusa Heart Study. *Atherosclerosis*. 2007;194:421-5.
27. Cupido AJ, Asselbergs FW, Schmidt AF and Hovingh GK. Low-Density Lipoprotein Cholesterol Attributable Cardiovascular Disease Risk Is Sex Specific. *J Am Heart Assoc*. 2022;11:e024248.
28. Labrecque JA and Swanson SA. Interpretation and Potential Biases of Mendelian Randomization Estimates With Time-Varying Exposures. *American Journal of Epidemiology*. 2018;188:231-238.

Table 1. Baseline Characteristics of Participants and Cardiovascular Outcomes According to Categories of Concordant and Discordant Values of Childhood non-HDL-C versus LDL-C

Characteristic	LDL-C <110 Non-HDL-C <120	LDL-C ≥110 Non-HDL-C <120	LDL-C <110 Non-HDL-C ≥120	LDL-C ≥110 Non-HDL-C ≥120	Overall population
No. of participants (%)	13243 (62.7)	311 (1.5)	970 (4.6)	6062 (31.2)	21126
Age, years	9.9 (3.6)	8.7 (3.4)	10.5 (3.7)	10.1 (4.0)	10.0 (3.7)
Female sex, n (%)	6430 (48.6)	155 (49.8)	507 (52.3)	3683 (55.8)	10775 (51.0)
Race, n (%)					
Black	3576 (27.0)	112 (36.0)	128 (13.2)	1291 (19.6)	5107 (24.2)
White or others	9667 (73.0)	199 (74.0)	842 (86.8)	5311 (80.4)	16019 (75.8)
Cohorts (country), n (%)					
Bogalusa Heart Study (U.S.)	8385 (63.3)	250 (80.4)	428 (44.1)	2459 (37.3)	11522 (54.5)
Childhood Determinants of Adult Health (Australia)	898 (6.83)	13 (4.2)	96 (9.9)	597 (9.0)	1604 (7.6)
Minnesota Childhood Cardiovascular Cohorts (U.S)	395 (3.0)	0 (0)	51 (5.3)	92 (1.4)	538 (2.6)
Muscatine Study (U.S.)	1178 (8.9)	0 (0)	113 (11.7)	259 (3.9)	1550 (7.3)
NHLBI Growth and Health Study (U.S.)	494 (3.7)	2 (0.6)	43 (4.4)	218 (3.3)	757 (3.6)
Princeton Lipid Research Study (U.S.)	934 (7.1)	32 (10.3)	75 (7.7)	599 (9.1)	1640 (7.8)
Cardiovascular Risk in Young Finns Study (Finland)	959 (7.2)	14 (4.5)	164 (16.9)	2378 (36.0)	3515 (16.4)
BMI, kg/m^2	17.5 (3.2)	17.0 (3.0)	19.1 (4.3)	18.2 (3.8)	17.8 (3.5)
Smokers, n (%)	3323 (38.1)	55 (38.2)	269 (40.6)	1802 (38.0)	5449 (38.2)
Systolic blood pressure, mmHg	100.8 (11.4)	98.0 (10.1)	104.9 (12.3)	105.6 (13.2)	102.4 (12.2)
Parental education level					
Less than high school degree	1582 (21.2)	34 (15.7)	159 (26.2)	1844 (37.4)	3619 (27.3)
High school degree	2286 (30.6)	67 (30.9)	144 (23.7)	988 (20.2)	3485 (26.3)
Higher than high school degree but no college degree	689 (22.6)	55 (25.3)	148 (24.3)	1076 (21.8)	2968 (22.4)
College degree or higher	1921 (25.7)	61 (28.1)	157 (25.8)	1027 (20.8)	3166 (24.0)
LDL-C, mg/dL *	84.5 (14.7)	112.6 (2.3)	105.0 (5.0)	133.9 (21.5)	101.3 (28.1)
Non-HDL-C, mg/dL *	93.8 (15.9)	117.0 (2.2)	125.6 (5.9)	147.7 (23.2)	112.4 (30.7)
Fatal ASCVD events, no./total no. (%)	96/13243 (0.72)	2/311 (0.64)	10/970 (1.03)	45/6602 (0.68)	153/21126 (0.72)
Fatal/nonfatal ASCVD events, no./total no. (%)	193/6306 (3.06)	2/114 (1.75)	22/540 (4.07)	135/4336 (3.11)	352/11296 (3.12)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; NHLBI, National Heart, Lung and Blood Institute; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol. Values are mean (standard deviation) unless otherwise stated. To convert non–HDL-C and LDL-C from mg/dL to mmol/L, divide values by 38.67. * Individual mean (if the participant had multiple measurements) of the measurements across childhood (3-19 years).

Table 2. Comparisons of Utilities Between Childhood Non-HDL-C and LDL-C Levels in Predicting Adult Atherosclerotic Cardiovascular Disease Events

		LDL-C	Non-HDL-C	Non-HDL-C vs. LDL-C
		C-index (95% CI)	C-index (95% CI)	Difference in C-index (95% CI)
Fatal event	Model 1	0.6676 (0.6206 to 0.7147)	0.6770 (0.6306 to 0.7235)	0.0094 (0.0006 to 0.0182)
Fatal event	Model 2	0.7406 (0.6992 to 0.7821)	0.7460 (0.7054 to 0.7867)	0.0054 (0.0006 to 0.0102)
Fatal/nonfatal event	Model 1	0.6600 (0.6282 to 0.6917)	0.6677 (0.6364 to 0.6989)	0.0077 (0.0025 to 0.0129)
Fatal/nonfatal event	Model 2	0.7191 (0.6896 to 0.7485)	0.7229 (0.6937 to 0.7521)	0.0038 (0.0008 to 0.0068)

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Model 1 included cohort.

Model 2 included cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

z scores for LDL-C and non-HDL-C were used in all models: visit-specific measurements were centered at the i3C Consortium's age- and sex-specific mean, and divided by the corresponding standard deviation (ranged from 31 to 37 mg/dL for non-HDL-C and 28 to 34 mg/dL for LDL-C for each stratum by age and sex); childhood z score for each participant was calculated as the mean of each participant's z scores across childhood.

Figure Legend

Figure 1. Hazard Ratios for Adult ASCVD Events According to Child LDL-C and non-HDL-C Levels or Status. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol. All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure. Childhood individual mean of non-HDL-C and LDL-C for each participant was used to assign participants into different categories. Visit-specific measurements were centered at the i3C Consortium's age- and sex-specific mean, and divided by the corresponding standard deviation (ranged from 31 to 37 mg/dL for non-HDL-C and 28 to 34 mg/dL for LDL-C for each stratum by age and sex); childhood z score for each participant was calculated as the mean of all a participant's z scores across childhood.

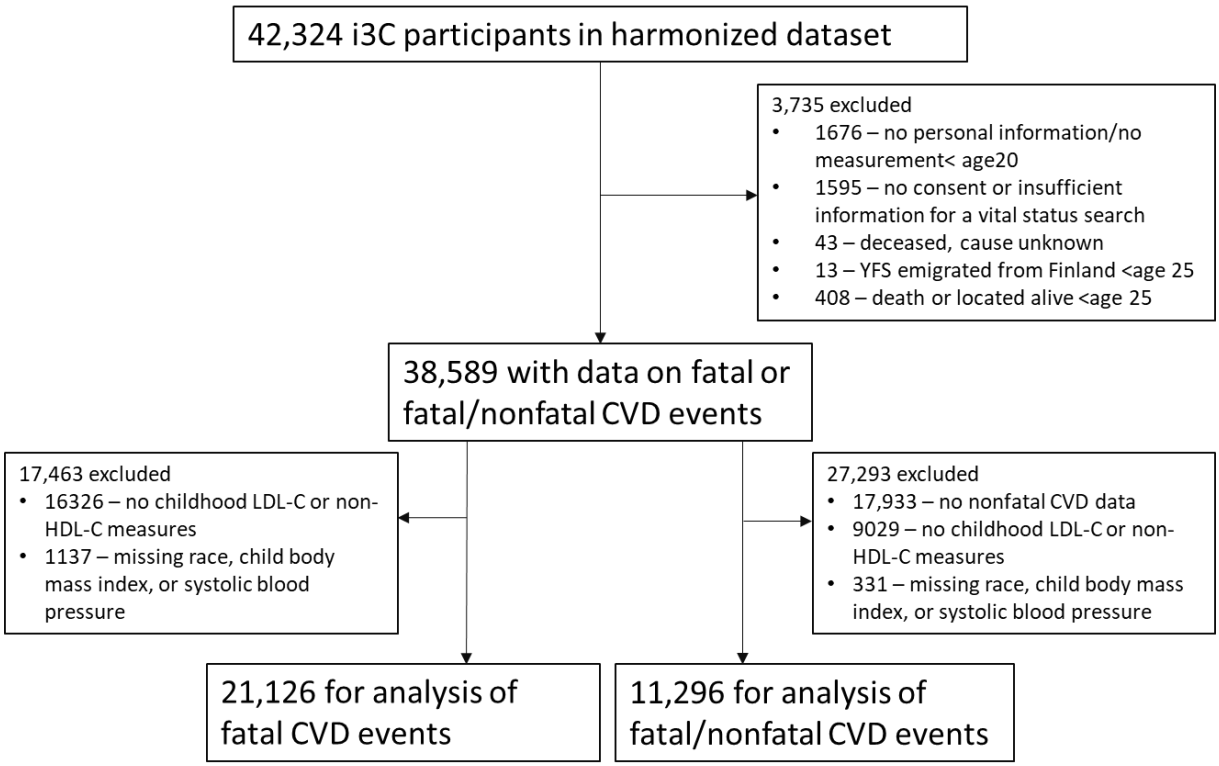
Figure 2. Cumulative Risk of ASCVD Events According to Childhood LDL-C and non-HDL-C categories. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol. All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure. Childhood individual mean of non-HDL-C and LDL-C for each participant was used to assign participants into different categories.

Figure 3. Hazard Ratios for Adult ASCVD Events According to Discordant Versus Concordant Categories of Childhood non-HDL-C with LDL-C. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; NA, not available (due to small number of cases and participants). n/N, number of events/number of participants. All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

SUPPLEMENTAL MATERIAL

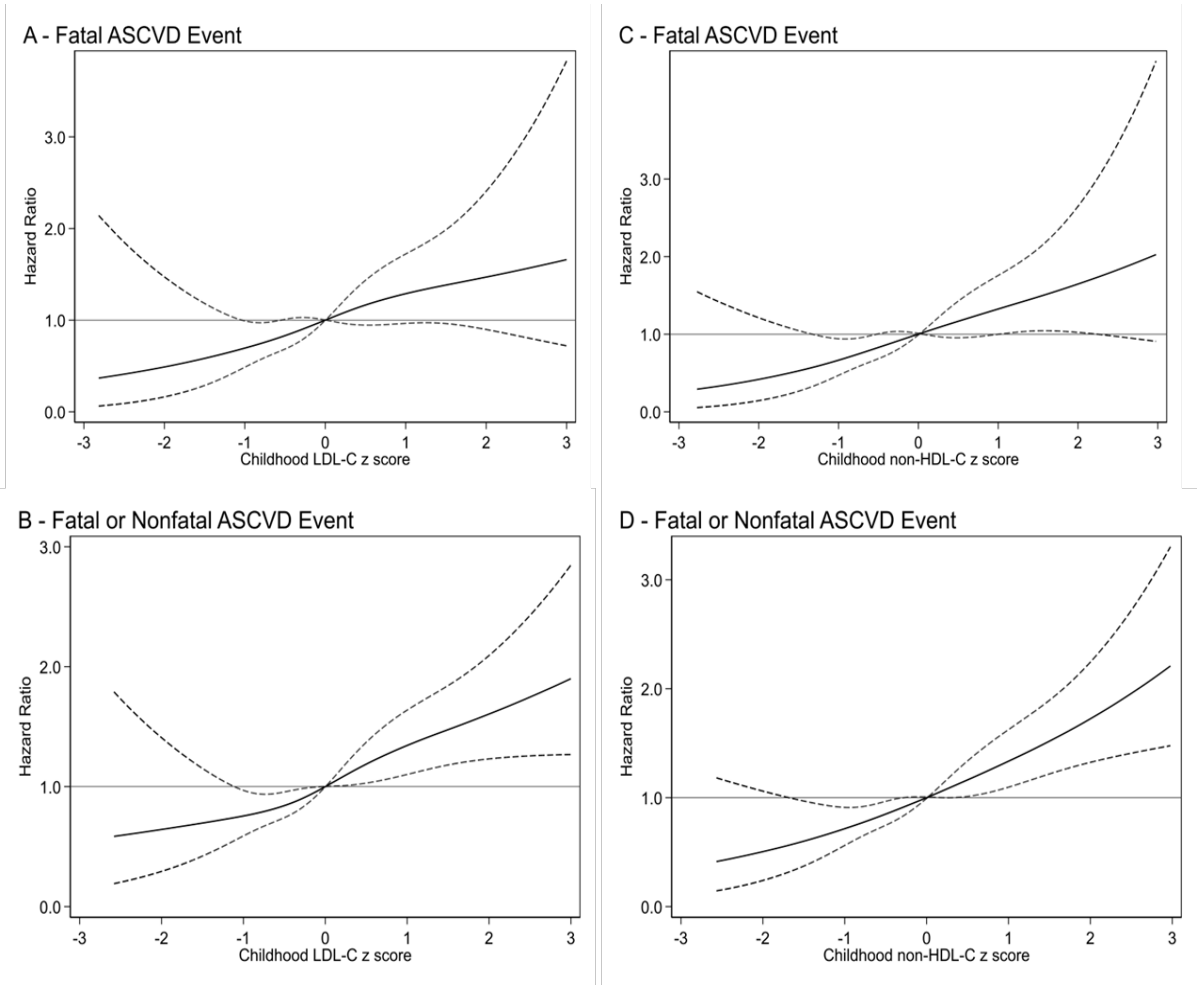
Contents

Figure S1. Flow of study participants



Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Figure S2. Nonlinear Analysis for Association of Child LDL-C and Non-HDL-C Levels with Adult ASCVD Events



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

We used restricted cubic splines to consider nonlinear association of childhood LDL-C and non-HDL-C levels with adult ASCVD events (see methods in main text for details). Solid line indicates the association across LDL-C and non-HDL-C values, relative to the chosen reference group of an individual with a value of zero (corresponding 95% confidence intervals demonstrated by dotted lines). All analyses were adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

Table S1. Hazard Ratios (HRs) for Adult ASCVD Events According to Child LDL-C and non-HDL-C Levels or Status

		Fatal event		Fatal/nonfatal event
LDL-C	n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)
z Score *	153/21,126 (0.72)	**1.28 (1.08-1.52)**	352/11,296 (3.12)	**1.27 (1.14-1.41)**
Categories				
<110 mg/dL	106/14,213 (0.75)	Reference	215/6,846 (3.14)	Reference
110-130 mg/dL	26/3,945 (0.66)	1.26 (0.81-1.97)	63/2,348 (2.68)	1.18 (0.88-1.60)
≥130 mg/dL	21/2,968 (0.71)	1.58 (0.94-2.65)	74/2,102 (3.52)	**1.72 (1.27-2.33)**
Non-HDL-C				
z Score *	153/21,126 (0.72)	**1.35 (1.13-1.60)**	352/11,296 (3.12)	**1.33 (1.19-1.48)**
Categories				
<120 mg/dL	98/13,554 (0.72)	Reference	195/6,420 (3.04)	Reference
120-145 mg/dL	29/4,669 (0.62)	1.30 (0.85-2.00)	79/2,800 (2.82)	**1.41 (1.07-1.86)**
≥145 mg/dL	26/2,903 (0.90)	**2.15 (1.31-3.54)**	78/2,076 (3.76)	**2.01 (1.48-2.74)**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

Bold denotes statistical significance, $p<0.05$.

Childhood individual mean of non-HDL-C and LDL-C for each participant was used to classify different risk status.

* Visit-specific measurements were centered at the i3C Consortium's age- and sex-specific mean, and divided by the corresponding standard deviation; childhood z Score for each person was calculated as the mean of all of that person's z Scores across childhood.

Table S2. Hazard Ratios (95% Confidence Intervals) for Adult ASCVD Events According to Discordant Versus Concordant Categories of Childhood Non-HDL-C with LDL-C

	Fatal event		Fatal/nonfatal event	
Non-HDL-C vs. LDL-C	n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)
<120 mg/dL & <110 mg/dL	96/13243 (0.72)	Reference	193/6306 (3.06)	Reference
<120 mg/dL & ≥110 mg/dL	2/311 (0.64)	NA	2/114 (1.75)	NA
≥120 mg/dL & <110 mg/dL	10/970 (1.03)	1.90 (0.98-3.70)	22/540 (4.07)	**1.94 (1.23-3.06)**
≥120 mg/dL & ≥110 mg/dL	45/6602 (0.68)	**1.49 (1.01 -2.20)**	135/4336 (3.11)	**1.54 (1.19-1.97)**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; NA, not available (due to small number of cases and participants). n/N, number of events/number of participants.

All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

Table S3. Hazard Ratios (95% Confidence Intervals) for Adult ASCVD Events According to Discordant Versus Concordant Categories of Childhood Non-HDL-C with LDL-C Using Different Cut-offs

	Fatal event		Fatal/nonfatal event	
Non-HDL-C vs. LDL-C	n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)
<75th percentile & <75th percentile [#]	111/15315 (0.72)	Reference	225/7474 (3.01)	Reference
<75th percentile & ≥75th percentile	4/542 (0.74)	1.32 (0.48-3.65)	8/268 (2.99)	1.21 (0.59-2.50)
≥75th percentile & <75th percentile	6/536 (1.12)	2.05 (0.87-4.83)	13/315 (4.13)	**2.01 (1.13-3.58)**
≥75th percentile & ≥75th percentile	32/4733 (0.68)	1.50 (0.97-2.30)	106/3239 (3.27)	**1.62 (1.24-2.12)**
Non-HDL-C vs. LDL-C				
<145 mg/dL & <130 mg/dL	126/17833 (0.71)	Reference	269/9001 (2.99)	Reference
<145 mg/dL & ≥130 mg/dL	1/390 (0.26)	NA	5/219 (2.28)	1.09 (0.45-2.64)
≥145 mg/dL & <130 mg/dL	6/325 (1.85)	**3.01 (1.28-7.36)**	9/193 (4.66)	1.89 (0.94-3.83)
≥145 mg/dL & ≥130 mg/dL	20/2578 (0.78)	**1.75 (1.04-2.95)**	69/1883 (3.66)	**1.75 (1.29-2.35)**
Non-HDL-C vs. LDL-C				
<208 mg/dL & <190 mg/dL *	148/20953 (0.71)	Reference	342/11162 (3.06)	Reference
<208 mg/dL & ≥190 mg/dL	0/25 (0)	NA	0/18 (0)	NA
≥208 mg/dL & <190 mg/dL	1/24 (4.17)	7.29 (0.87-61.17)	4/20 (20.0)	**7.66 (2.45-23.96)**
≥208 mg/dL & ≥190 mg/dL	4/124 (3.23)	**5.54 (2.00-15.36)**	6/96 (6.25)	2.27 (0.98-5.27)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; NA, not available (due to small number of cases and participants).

n/N, number of events/number of participants.

All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

* These were cut-offs to define probable familial hypercholesterolemia by LDL-C and non-HDL-C (percentage equivalents derived from the i3C data corresponding to 190 mg/dL for LDL-C).

[#] 75th percentiles were 117 mg/dL for LDL-C and 130 mg/dL for non-HDL-C. To convert LDL-C or non–HDL-C from mg/dL to mmol/L, divide values by 38.67.

Table S4. Sex-specific Hazard Ratios for Adult ASCVD Events According to Childhood LDL-C and non-HDL-C Levels or Status

	Fatal event		Fatal/nonfatal event	
	Males	Females	Males	Females
LDL-C	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
z Score	1.17 (0.92-1.48)	**1.60 (1.32-1.94)**	**1.23 (1.06-1.41)**	**1.35 (1.17-1.56)**
Categories				
<110 mg/dL	Reference	Reference	Reference	Reference
110-130 mg/dL	0.75 (0.40-1.41)	**3.18 (1.56-6.48)**	0.90 (0.60-1.36)	**1.67 (1.07 -2.62)**
≥130 mg/dL	1.16 (0.60-2.26)	**3.11 (1.34-7.21)**	**1.47 (1.01-2.15)**	**2.15 (1.30-3.56)**
Non-HDL-C				
z Score	1.20 (0.95-1.51)	**1.74 (1.42-2.13)**	**1.27 (1.09-1.47)**	**1.44 (1.25-1.66)**
Categories				
<120 mg/dL	Reference	Reference	Reference	Reference
120-145 mg/dL	0.73 (0.39-1.36)	**3.69 (1.88-7.22)**	1.01 (0.69-1.48)	**2.17 (1.42-3.33)**
≥145 mg/dL	1.65 (0.88-3.11)	**4.36 (1.91-9.95)**	**1.71 (1.16-2.52)**	**2.60 (1.57-4.31)**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

All analyses adjusted for cohort, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z Scores for body mass index and systolic blood pressure.

Bold denotes statistical significance, $p<0.05$.

Childhood individual mean of non-HDL-C and LDL-C for each participant was used to assign participants into different categories.

Table S5. Age-specific Hazard Ratios for Adult ASCVD Events According to Childhood LDL-C and non-HDL-C Levels or Status

	Age categories							
	<9 years	9-11 years	12-16 years	17-19 years	<9 years	9-11 years	12-16 years	17-19 years
	Fatal event				Fatal/nonfatal event			
LDL-C	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
z Score	1.27 (0.94-1.71)	1.16 (0.89-1.51)	1.12 (0.93-1.35)	**1.30 (1.03-1.63)**	1.21 (0.99-1.49)	**1.31 (1.13-1.51)**	**1.18 (1.05-1.33)**	**1.27 (1.11-1.46)**
Categories								
<110 mg/dL	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
110-130 mg/dL	**2.26 (1.09-4.70)**	**1.91 (1.01 -3.63)**	0.89 (0.50-1.60)	**2.45 (1.20-5.15)**	**2.00 (1.15-3.50)**	**1.78 (1.14-2.78)**	1.15 (0.82-1.62)	**1.92 (1.19 -3.09)**
≥130 mg/dL	0.82 (0.17-3.98)	1.11 (0.46-2.68)	1.38 (0.73-2.59)	1.90 (0.85-4.28)	1.46 (0.69-3.08)	**1.92 (1.17-3.17)**	**1.68 (1.17-2.40)**	**1.93 (1.19-3.01)**
Non-HDL-C								
z Score	1.27 (0.95-1.69)	1.18 (0.91-1.53)	1.18 (0.98-1.42)	**1.33 (1.06-1.67)**	1.19 (0.97-1.46)	**1.34 (1.16-1.55)**	**1.25 (1.11-1.42)**	**1.30 (1.13 -1.50)**
Categories								
<120 mg/dL	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
120-145 mg/dL	2.03 (0.91-4.54)	1.42 (0.74-2.75)	1.17 (0.72-1.92)	**2.89 (1.45-5.77)**	**2.13 (1.22-3.70)**	**1.66 (1.08-2.56)**	1.26 (0.92-1.73)	**2.18 (1.38-3.43)**
>145 mg/dL	1.52 (0.47-5.00)	1.62 (0.71-3.69)	1.58 (0.85-2.94)	2.04 (0.93-4.47)	1.63 (0.77-3.46)	**2.42 (1.47-3.99)**	**1.82 (1.26-2.63)**	**1.91 (1.19-3.06)**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z Scores for body mass index and systolic blood pressure.

Bold denotes statistical significance, $p<0.05$.

Childhood individual mean of non-HDL-C and LDL-C for each participant was used to assign participants into different categories.

Table S6. Race-specific Hazard Ratios for Adult ASCVD Events According to Childhood LDL-C and non-HDL-C Levels or Status

	Fatal event		Fatal/nonfatal event	
	Black	non-Black	Black	non-Black
LDL-C	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
z Score	1.13 (0.85-1.51)	**1.35 (1.09-1.67)**	1.09 (0.86-1.37)	**1.32 (1.18-1.48)**
Categories				
<110 mg/dL	Reference	Reference	Reference	Reference
110-130 mg/dL	1.28 (0.61-2.68)	1.26 (0.72-2.20)	1.22 (0.69-2.15)	1.15 (0.81-1.63)
≥130 mg/dL	1.35 (0.55-3.34)	1.65 (0.87-3.14)	1.35 (0.67-2.72)	**1.78 (1.26-2.50)**
Non-HDL-C				
z Score	1.15 (0.87-1.52)	**1.45 (1.17-1.79)**	1.08 (0.86-1.37)	**1.40 (1.25-1.58)**
Categories				
<120 mg/dL	Reference	Reference	Reference	Reference
120-145 mg/dL	1.13 (0.53-2.43)	1.40 (0.83-2.38)	1.25 (0.70-2.21)	**1.45 (1.05-2.00)**
≥145 mg/dL	1.61 (0.65-3.99)	**2.48 (1.35-4.55)**	1.39 (0.66-2.95)	**2.15 (1.53-3.03)**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

All analyses adjusted for sex, cohort, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

Bold denotes statistical significance, $p<0.05$.

Childhood individual mean of non-HDL-C and LDL-C for each participant was used to assign participants into different categories.

Table S7. Cohort-specific Hazard Ratios for Adult ASCVD Events According to Childhood LDL-C and non-HDL-C Levels or Status

	Bogalusa Heart Study		**Young Finns Study**	
	Fatal event	Fatal/nonfatal event	Fatal event *	Fatal/nonfatal event
LDL-C	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
z Score	**1.35 (1.10-1.65)**	**1.32 (1.13-1.54)**	1.33 (0.87-2.02)	**1.29 (1.07-1.55)**
Categories				
<110 mg/dL	Reference	Reference	Reference	Reference
110-130 mg/dL	1.36 (0.80-2.32)	1.15 (0.75-1.76)	1.80 (0.31-10.54)	1.23 (0.63-2.40)
≥130 mg/dL	1.50 (0.73-3.12)	1.64 (0.96-2.79)	2.25 (0.46-10.93)	**1.83 (1.03-3.24)**
Non-HDL-C				
z Score	**1.39 (1.13-1.70)**	**1.35 (1.15-1.58)**	1.40 (0.95-2.06)	**1.36 (1.12-1.65)**
Categories				
<120 mg/dL	Reference	Reference	Reference	Reference
120-145 mg/dL	1.38 (0.83-2.29)	1.42 (0.96-2.09)	0.92 (0.13-6.48)	1.38 (0.69-2.77)
≥145 mg/dL	**2.29 (1.19-4.39)**	**2.03 (1.22-3.39)**	2.33 (0.50-10.75)	**2.16 (1.16-4.04)**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

All analyses adjusted for sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

Bold denotes statistical significance, $p<0.05$.

Childhood individual mean of non-HDL-C and LDL-C for each participant was used to assign participants into different categories.

* Calendar year of childhood measurement of non-HDL-C was not adjusted because convergence was not achieved due to zero fatal events in many categories of the covariate.

Table S8. Hazard Ratios for Adult ASCVD Events According to Childhood LDL-C and non-HDL-C Levels or Status – Sensitivity Analysis with Additional Adjustment for Parental Education and Child Smoking

	Fatal event		Fatal/nonfatal event	
LDL-C	n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)
z Score	44/9487 (0.46)	1.16 (0.88-1.54)	186/7590 (2.45)	**1.30 (1.13-1.49)**
Categories				
<110 mg/dL	27/5620 (0.48)	Reference	99/4138 (2.39)	Reference
110-130 mg/dL	8/2041 (0.39)	1.30 (0.56-3.01)	34/1777 (1.91)	1.14 (0.75-1.72)
≥130 mg/dL	9/1826 (0.49)	1.37 (0.59-3.17)	53/1675 (3.16)	**1.92 (1.29-2.86)**
Non-HDL-C				
z Score	44/9487 (0.46)	1.17 (0.87-1.56)	186/7590 (2.45)	**1.33 (1.15-1.54)**
Categories				
<120 mg/dL	25/5320 (0.47)	Reference	88/3889 (2.26)	Reference
120-145 mg/dL	9/2397 (0.38)	1.31 (0.57-3.00)	44/2073 (2.12)	1.41 (0.95-2.10)
≥145 mg/dL	10/1770 (0.56)	1.70 (0.74-3.91)	54/1628 (3.32)	**2.27 (1.52-3.40)**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Childhood individual mean of non-HDL-C and LDL-C for each participant was used to assign participants into different categories.

All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z Scores for body mass index and systolic blood pressure, parental education and child smoking.

Bold denotes statistical significance, $p<0.05$.

Table S9. Hazard Ratios for Adult ASCVD Events According to Childhood First Available Measurement of LDL-C and non-HDL-C Levels or Status

	Fatal event		Fatal/nonfatal event	
LDL-C	n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)
z Score *	153/21126 (0.72)	**1.24 (1.05-1.47)**	352/11296 (3.12)	**1.21 (1.09-1.34)**
Categories				
<110 mg/dL	103/13929 (0.74)	Reference	209/6555 (3.19)	Reference
110-130 mg/dL	28/3713 (0.75)	1.50 (0.97-2.32)	62/2196 (2.82)	1.30 (0.96-1.76)
≥130 mg/dL	22/3484 (0.63)	1.55 (0.93-2.60)	81/2545 (3.18)	**1.70 (1.25-2.30)**
Non-HDL-C				
z Score *	153/21126 (0.72)	**1.29 (1.10-1.52)**	352/11296 (3.12)	**1.24 (1.12-1.38)**
Categories				
<120 mg/dL	98/13424 (0.73)	Reference	194/6238 (3.11)	Reference
120-145 mg/dL	27/4491 (0.60)	1.26 (0.81-1.96)	78/2719 (2.87)	**1.40 (1.06 -1.85)**
≥145 mg/dL	28/3211 (0.87)	**2.18 (1.34-3.56)**	80/2339 (3.42)	**1.85 (1.35-2.52)**

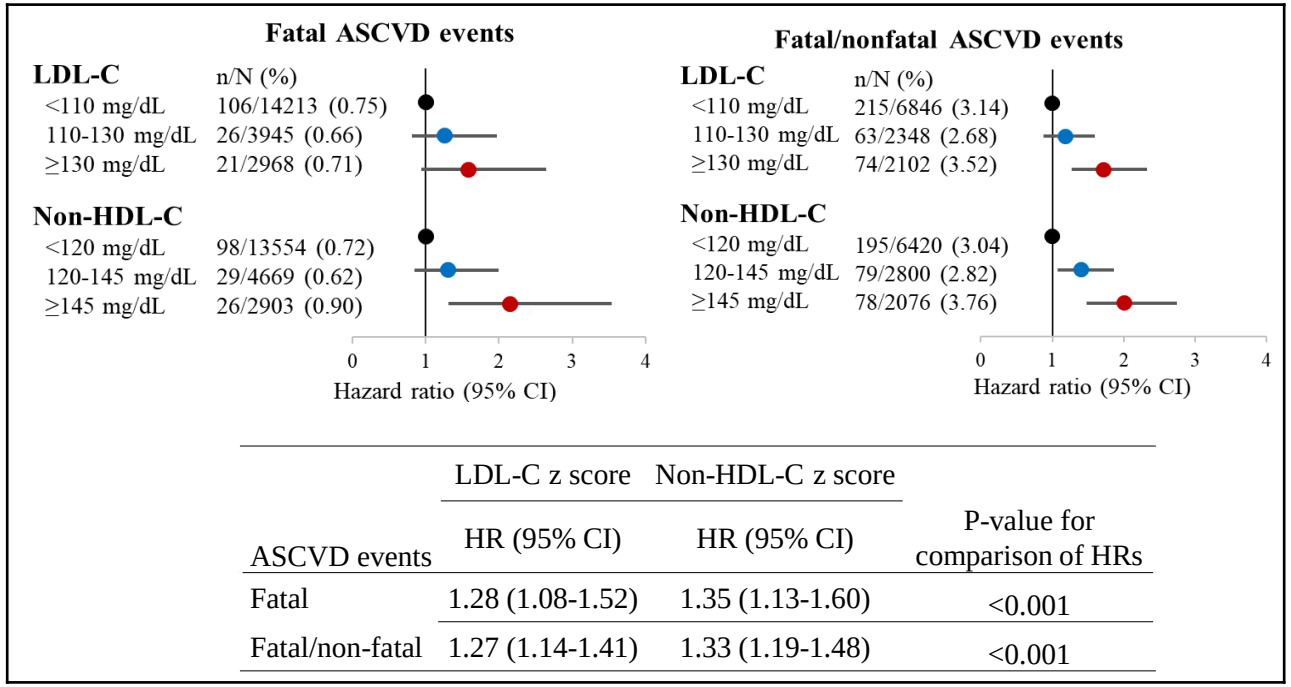
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

All analyses adjusted for cohort, sex, Black race, mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for body mass index and systolic blood pressure.

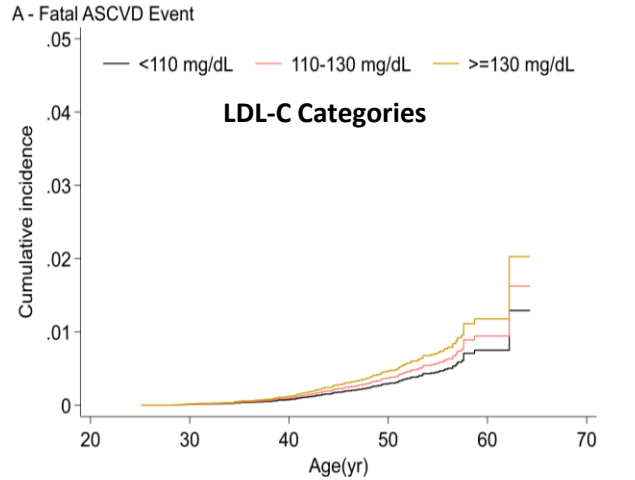
Bold denotes statistical significance, $p<0.05$.

Childhood first available measurement of non-HDL-C and LDL-C for each participant was used to assign participants into different categories.

* The first available measurement in childhood for each person was centered at the i3C Consortium's age- and sex-specific mean, and divided by the corresponding standard deviation.

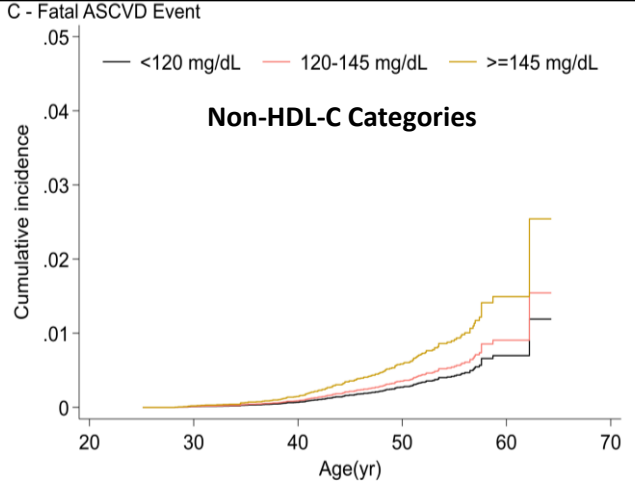


	LDL-C z score	Non-HDL-C z score	
ASCVD events	HR (95% CI)	HR (95% CI)	P-value for comparison of HRs
Fatal	1.28 (1.08-1.52)	1.35 (1.13-1.60)	<0.001
Fatal/non-fatal	1.27 (1.14-1.41)	1.33 (1.19-1.48)	<0.001



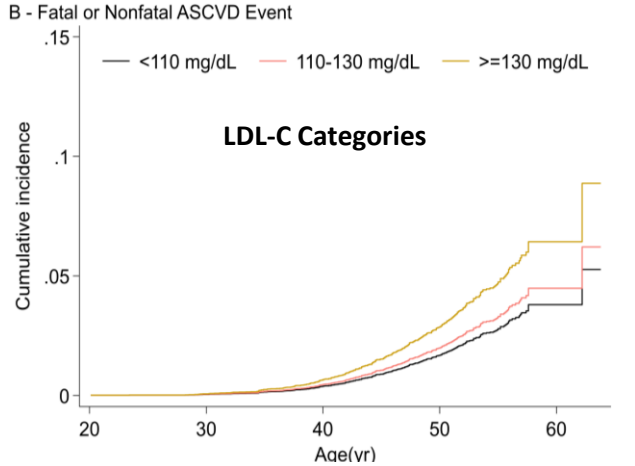
No. at Risk

Age (yr)	25	30	35	40	45	50	55	60
<110 mg/dL	14213	13938	12885	11421	8503	5270	2355	232
110-130 mg/dL	3945	3861	3520	3027	1991	1257	514	61
>=130 mg/dL	2968	2915	2713	2424	1567	1053	396	42
Total	21126	20714	19118	16872	12061	7580	3265	335



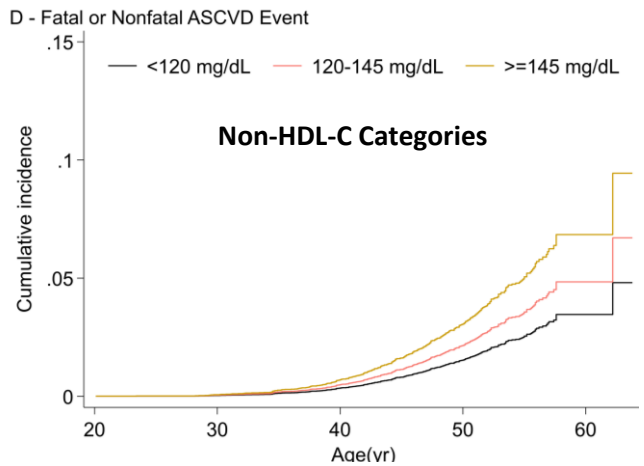
No. at Risk

Age (yr)	25	30	35	40	45	50	55	60
<120 mg/dL	13554	13292	12322	10926	8122	5028	2240	213
120-145 mg/dL	4669	4565	4163	3584	2392	1517	633	82
>=145 mg/dL	2903	2857	2633	2362	1547	1035	392	40
Total	21126	20714	19118	16872	12061	7580	3265	335



No. at Risk

Age (yr)	25	30	35	40	45	50	55	60
<110 mg/dL	6845	6649	6041	5417	3992	2221	854	73
110-130 mg/dL	2347	2285	2083	1870	1250	637	280	28
>=130 mg/dL	2102	2059	1941	1812	1150	581	269	18
Total	11294	10993	10065	9099	6392	3439	1403	119

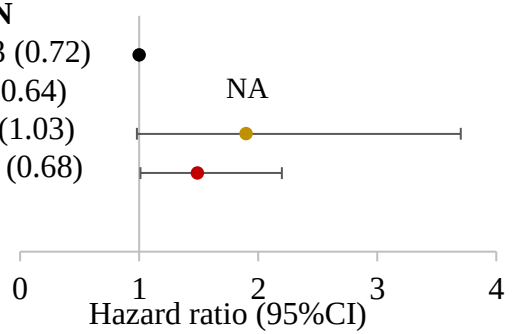


No. at Risk

Age (yr)	25	30	35	40	45	50	55	60
<120 mg/dL	6420	6237	5685	5085	3735	2085	812	68
120-145 mg/dL	2798	2721	2483	2231	1512	780	322	34
>=145 mg/dL	2076	2035	1897	1783	1145	574	269	17
Total	11294	10993	10065	9099	6392	3439	1403	119

Fatal ASCVD events

Non-HDL-C	vs.	LDL-C	n/N
<120 mg/dL		<110 mg/dL *(reference)*	96/13243 (0.72)
<120 mg/dL		≥110 mg/dL	2/311 (0.64)
≥120 mg/dL		<110 mg/dL	10/970 (1.03)
≥120 mg/dL		≥110 mg/dL	45/6602 (0.68)



Fatal/non-fatal ASCVD events

Non-HDL-C	vs.	LDL-C	n/N (%)
<120 mg/dL		<110 mg/dL *(reference)*	193/6306 (3.06)
<120 mg/dL		≥110 mg/dL	2/114 (1.75)
≥120 mg/dL		<110 mg/dL	22/540 (4.07)
≥120 mg/dL		≥110 mg/dL	135/4336 (3.11)