Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Measurement of Childhood and Adulthood Factors and Analytic Details

Measurement of Childhood and Adulthood Factors

1.1 Measurement of Non-HDL-C Levels and Covariates

Data were harmonized across the seven cohorts into a single database, managed by the Finland data center housed at the University of Turku, Finland[1]. Because independent protocols, with variable schedules for clinic visits that were conducted at various participant ages, were used for each cohort, not every study measure was assessed in every cohort, in every participant within a cohort, or in every participant at every age[1,2].

Non-HDL-C: For all cohorts, non-HDL-C was calculated as total cholesterol – HDL-C. Fasting levels of plasma or serum cholesterol and HDL-C were measured by means of standard methods (see eTable 1 and details below).

eTable 1. Summary for the Methods of Total Cholesterol and HDL-C in Each Cohort.

Cohort	Total cholesterol	HDL-C
The Cardiovascular Risk in Young Finns Study[3]	Enzymatic methods	Dextran sulfate - magnesium precipitation
The Childhood Determinants of Adult Health Study[4-6]	Enzymatic methods	In 1985: heparin-manganese precipitation In 2004-2006: direct enzymatic method using Olympus AU5400 automated analyzer
The Bogalusa Heart Study[7-11]	Enzymatic methods	Combination of heparin-calcium precipitation and agar–agarose gel electrophoresis procedures
The Minnesota Childhood Cardiovascular Cohorts[12]	Enzymatic methods	Dextran sulfate - magnesium precipitation
The Muscatine Study[13-16]	Enzymatic methods	Heparin-manganese precipitation
The NHLBI Growth and Health Study[17-19]	Enzymatic methods	Heparin-manganese precipitation
The Princeton Lipid Research Study[20-25]	Enzymatic methods	Heparin-manganese precipitation

In *the Cardiovascular Risk in Young Finns* Study at baseline, serum cholesterol was 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 using dextran sulfate 500.000 - magnesium precipitation method[3]. The coefficient of variation for within-assay precision in the Young Finns Study was 2.2% for total cholesterol and 2.3% for HDL-C.

Both the US cohorts and CDAH used chemical and enzymatic procedures meeting the performance requirements of the Lipid Research Clinics (LRC) Program and Lipid Standardization Program of the Centers for Disease Control and Prevention (CDC), which routinely monitors the accuracy of measurements of total cholesterol, triglyceride, and HDL-C concentrations. In *CDAH*, serum total cholesterol was determined according to the LRC Program methods. In childhood (1985) HDL-C was analyzed after precipitation of apolipoprotein B–containing lipoproteins with heparin-manganese[4,5] and in adulthood (2004-

2006) by a direct enzymatic method using Olympus AU5400 automated analyzer[6]. In the *Bogalusa Heart Study*, levels of serum total cholesterol and HDL-C were measured using chemical procedures with a Technicon AutoAnalyzer II (Technicon Instrument Corp, Tarrytown, NY), according to the laboratory 10 manual of the LRC Program[7,8]. Commencing after baseline, these variables were determined by enzymatic procedures using the Abbott VP instrument (Abbott Laboratories, Abbott Park, Ill)[9]. Measurements on CDC–assigned quality control samples showed no consistent bias over time within or between surveys. Serum lipoprotein cholesterols were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures[8,10]. A 10% random sample of the participants was selected daily to assess the reproducibility of all laboratory analyses; intraclass correlation coefficients were 0.96 for total cholesterol levels and 0.94 for HDL cholesterol levels[11]. In the *Minnesota Childhood Cardiovascular Cohorts*, serum lipids were analyzed in the University of Minnesota laboratory with a Cobas FARA. HDL-C was determined after precipitation of non-HDL lipoproteins with a dextran-sulfate magnesium precipitating reagent[12]. In the *Muscatine Study*, the Iowa LRC Laboratory, which participated in the CDC Laboratory standardization program, performed the lipid analyses for the childhood and adult levels. Throughout the study, the samples sent from the center for comparative analyses deviated no more than 3% from the mean of the standards[13]. The blood was analyzed in duplicate for serum cholesterol by a standard AutoAnalyzer (AA-1) technique[14]. HDL-C was analyzed after precipitation of apolipoprotein B–containing lipoproteins with heparin-manganese[15,16]. Duplicate analyses of 215 split samples for cholesterol in the AutoAnalyzer showed an average difference of 3.5 mg/dl with a standard deviation of the difference of 3.5 mg/dl. In the *NHLBI Growth and Health Study (NGHS)*[17], plasma concentrations of total cholesterol and HDL-C in childhood were measured at the NGHS Central Lipid Laboratory at the Department of Lipid Research at Johns Hopkins University Medical Center, which was one of the sites for the CDC Lipid Standardization Program. Total cholesterol and HDL-C were analyzed using the CHOD-PAP method (Boehringer-Mannheim Diagnostics, Somerville, NJ). HDL-C was precipitated with heparin-manganese[18,19]. In young adulthood, lipids were measured using CDC-certified and compliant techniques for lipid measurement (PPD Global Central Laboratory, Highland Heights, KY). For all lipid assessments, technical replicates were assessed to ensure measurement accuracy. In *the Princeton Lipid Research Study*, an original LRC study site, childhood and adult plasma total cholesterol and HDL-C levels were measured in LRC-CDC standardized laboratories[20,21] following the methods of the LRC Laboratory Methods Manual[22]. HDL-C was precipitated with heparin-manganese[23,24]. Interday coefficients of variation for determination of plasma cholesterol in plasma pools containing 158 and 281 mg/dl were 2.0% and 1.2%[25]. Interday coefficients of variation for determination of plasma HDL-C levels in plasma pools containing 50.3 and 43.8 mg/dl were 3.7% and 4.2%, respectively.

Childhood and Adulthood Covariates: Age, sex, race (see below Race and Ethnicity Data Collection and Harmonization), height, weight, and systolic blood pressure (measured by mercury sphygmomanometry) were assessed prospectively at the clinic visits in childhood (age 3-19 years) and adulthood (≥ age 20 years). The education levels of the parents were obtained at childhood and adult visits. The dichotomous childhood smoking variable was based on two sources[26]. First was self-report during childhood, integrated across diverse questions in the different cohorts, as previously described[26]. In this source, minimal smoking during adolescence (or before age 12 in relatively few participants) was coded as nonsmoking because it was observed not to result in adult smoking in most people. Adolescents reporting being former smokers were included as having smoked in childhood. Childhood reports of non-smoking prior to age 15 needed to be validated by a second source (e.g., never smoking

reported in adulthood or self-report of starting smoking after age 20). Not all cohorts included prospective assessment of smoking or saw participants at ages when smoking was more likely (e.g., adolescence). Therefore, the second source was adult recall of starting smoking during ages 15-19 years, available among adult current and former smokers in about half of the participants. Adults indicating never smoking were included as not smoking in adolescence. Information obtained during adulthood in this way was not available for those who died or who were not ever seen in adulthood. Adult smoking was defined by the i3C Heart Health Survey (HHS, 2015-2019) questions asking about daily smoking status (yes/no) during ages twenties and forties[26]. The use of lipid-lowering medications (and the age at which a participant reported their first ever use) was self-report during adulthood, integrated across diverse questions about medications in the different cohorts. Type 2 diabetes was retrospectively reported by questionnaire in the HHS.

Race and Ethnicity Data Collection and Harmonization: The collection of race and ethnicity data varied across the cohorts. While ethnicity data were collected in the most recent follow-up, missing data and lack of Hispanic ethnic diversity led to its exclusion from our analysis. Instead, race data were harmonized using the available information collected historically from each cohort and self-reported information from those contacted at the 2015-19 i3C HHS.

Cohort-specific collection:

- Young Finns Study: Participants were assumed to be non-Hispanic White, as no race or origin data were collected.
- CDAH study: Race was classified based on parent country of origin and language spoken at home self-reported by the participant in childhood, defaulting to non-Hispanic White in the absence of this information.
- US cohorts: Race was generally self-reported by parents during childhood or by participants during adolescence or adulthood. Non-standard race categories were re-coded to standard categories (e.g., Oriental classified as Asian), but mixed race was frequently not captured (e.g., "select one" rather than "select all"). Cohort-specific practices included:
    - Bogalusa Heart Study: Participants self-identified as 'White American' or 'African American'.
    - NGHS: Required participants to have race-concordant families (parents and child were self-reported all White or all Black). Non-standard race categories were re-coded to standard categories (e.g., Oriental classified as Asian), but mixed race was frequently not captured (e.g., "select one" rather than "select all").
    - Muscatine Study: Did not collect race data during childhood, and in those with adult follow-up, race and ethnicity were captured using a single question (race/ethnicity). Those missing self-reported data were assumed to be non-Hispanic White.
    - Princeton: In childhood, questions were asked about place of birth, race and "origin or descent" which captured ethnicity information. At the adult follow-up, ethnicity data were not captured, and race was assessed as "White", "Black" and "Other".
    - Minnesota: In childhood, race and ethnicity were captured in a single question (race/ethnicity), with responses of 'White', 'Black', 'Native American', 'Hispanic' and 'Mixed'.

2015-19 i3C HHS: aimed to harmonize race data across cohorts by collecting a broader and

more standardized range of self-report categories (White, Black/African American, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Other (specify)) and allowing multiple selections. 'More than One Race' was assigned to participants selecting multiple race categories. Reponses specifying 'Other' were reviewed and race and ethnicity categories were updated as possible; those indicating only Hispanic ethnicity were assigned "Unknown" for race if additional information was not available.

Data harmonization for analysis: Race data were categorized into 'Black', 'White', and 'Other', with 'Other' including Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, More than One Race, and Unknown. Due to less than 5% of participants being classified as "Other", we further collapsed the categories to 'Black' and 'non-Black' for analysis. Hispanic ethnicity was missing in 70% of participants, and of those with data, 98% were non-Hispanic, so ethnicity was not included in analysis. The decision to include race in our analysis was guided by our aim to determine the impact of race on our associations, considered alongside social, historical, and cultural influences, on health outcomes without implying any genetic or biological determinants.

1.2. Classification and Adjudication of CVD Events

From 2015 through 2019, we conducted a coordinated study to locate and survey participants of all the i3C Consortium cohorts (HHS) and search national death indexes for the participants who were not located[1,27]. Initial contact was made via a mailed packet. If no response was received after the initial mailing, attempts were made to reach the participant by repeated mailings, phone calls or email. The HHS was completed by direct telephone interviews by site recruiters, paper forms mailed to participants and returned by mail, online survey, and in Bogalusa by participants coming into a dedicated clinic or recruiters going out to find participants in the community. Medical data for Finnish participants were available in a national medical database, including information on all hospital discharges, outpatient visits, and surgical procedures. These data were linked to the existing database of the Finnish cohort by using a national social security number, without the need to locate and recruit participants. These data were found to be highly accurate, based on adjudication of medical records (see below Adjudication of events).

Vital status (CVD or non-CVD death): In all cohorts, vital status was ascertained using searches of the National Death Indices (NDI) or the Finnish national health registries (including the Care Register for Health Care (HILMO) and the national Cause of Death registry). Fatal cardiovascular events were classified according to the coded causes of death in the International Classification of Diseases (ICD), versions 9 and 10. Participants with sufficient identifying information (defined by the NDI search protocol) were submitted for searches extending from their last known contact to the end of 2018; previously known deaths were searched to obtain coded cause of death. All exact matches and any possible matches were examined for validity by requesting death certificates from states, comparing obituaries with known information about participants, and information from families regarding known deaths. Participants with known deaths occurring after 2018 were not yet available in the NDI files and were treated in analyses as "presumed alive." Participants who could not be located for follow-up and were not located in the NDI matches were excluded from the analysis.

Nonfatal CVD events: Finnish participants were followed for nonfatal cardiovascular events through December 31, 2017, with the use of the Finnish national medical registry because

data on all hospitalizations and deaths are registered and cover all participants residing in Finland. This approach available only in Finland is considered the most reliable source. All ICD codes in a record were evaluated, and any meeting the ICD code definition of study endpoints was considered a confirmed event. U.S. and Australian adult participants who had been successfully located reported any cardiovascular event that had occurred, and the i3C Consortium requested consent from the participant to obtain medical records for event adjudication. Another form was used to collect details about the type/location of the medical facility and dates of events.

Adjudication of events: Adjudication of de-identified medical records was conducted by physicians blinded to participant identity, including cohort. If the same diagnosis was arrived at by two MD adjudicators, coding separately, that diagnosis was accepted as the final diagnosis entered into the final database. In the event of a disagreement, the case was discussed by the adjudication committee (composed of all adjudicators and the chair and co-chair of the committee), with disagreements settled by the committee. In the final year of the project, in order to speed up the adjudication process, only a single MD adjudicated each case. This was supported by analyses that showed near total agreement between the doubly adjudicated cases. A random sample of singly adjudicated cases weighted towards the more difficult to adjudicate endpoints of congestive heart failure and transient ischemic attack were continually sampled and agreement was 90%. Nonfatal events in the Finnish cohort were assessed through record linkage with the Finnish national health registry, using the ICD codes. The validity of these diagnoses was determined through review of 10 medical records using the same procedure as above, with 100% agreement between the registry diagnosis and determination of diagnosis via the adjudication of medical records.

Analytic Details

2.1. Generation of childhood and adulthood non-HDL-C z score

In this study, there were 29,026 visits for non-HDL-C measurements, with 2 to 14 visits per participant (eTable 2). Because of age-related developmental changes, childhood non-HDL-C levels at each visit were standardized as age- and sex-specific z scores within the i3C Consortium via $\frac{\text{measured value} - \text{mean value}}{\text{standard deviation}}$ within each age (six age groups: 3-5.99, 6-8.99, 9-11.99, 12-14.99, 15-17.99, and 18-19.99 years) and sex stratum. The resulting z scores for each participant were then averaged across their childhood measurements (obtained between age 3 to 19 years; 1-8 visits per participant, median number of visits=3) to obtain a single mean z score per person for analysis. For consistency with childhood risk factors and z-scores, a single mean z score for adult non-HDL-C measurements between age 20-40 was generated using the same approach (1-6 visits per participant, median number of visits=2), within each age (seven 3-year adult age groups: 20-22.99, 23-25.99, 26-28.99, 29-31.99, 32-34.99, 35-37.99, and 38-39.99 years) and sex stratum. For all analyses, only risk factors measured prior to any reported cardiovascular event were included. A single mean z score per person was also generated for childhood and adulthood BMI and systolic blood pressure using the same approach for all analyses.

eTable 2. The Distribution of the Number of non-HDL-C Measures in Childhood and Adulthood.

	Child		Adult	
No. of measures	Frequency	Percent	Frequency	Percent
1	1213	23.69	1645	32.12
2	1045	20.41	1508	29.45
3	1462	28.55	1213	23.69
4	738	14.41	585	11.42
5	462	9.02	165	3.22
6	125	2.44	5	0.10
7	64	1.25	0	0
8	12	0.23	0	0
Total No. of participants	5121	100	5121	100

2.2. Analyses of Childhood non-HDL-C z-score with Adult non-HDL-C z-score

We examined associations with adult cardiovascular events based on the childhood and adult non-HDL-C z score alone, as well as two parameterizations of models considering both child and adult non-HDL-C z scores: a) child z score and adult z score as separate terms (equation 1) and b) child z score and change in z scores between childhood and adulthood (adult minus child; equation 2). Algebraically, the terms can be substituted and rearranged into the equivalencies shown in equations 3 and 4, with the two models presenting identical likelihood but somewhat different interpretations.

$Parameterization\ A$: $Z = \beta_{1a}(child) + \beta_{2a}(adult)$ **(1)**

$Parameterization\ B$: $Z = \beta_{1b}(child) + \beta_{2b}(adult - child)$, $which\ simplifies\ to$:

$$Z = (\beta_{1b} - \beta_{2b})(child) + \beta_{2b}(adult) \quad \textbf{(2)}$$

$$\beta_{2b} = \beta_{2a} \quad \textbf{(3)}$$

$$\beta_{1b} = \beta_{1a} + \beta_{2b} \quad \textbf{(4)}$$

The first model lends itself to interpretation as mutual adjustment (independence of the adult and child terms), while the interpretation of the second model frames adult z score as a function of childhood z score, consistent with a preventive perspective and a lifecourse approach[27,28]. The first model provides information about the etiological association, that is, whether childhood exposure is independently associated with CVD risk, and vice versa. However, this perspective is "retrospective", viewing the contribution of child non-HDL-C as supplementary once adult levels are established. In comparison, the second model provides a forward-looking assessment of risk. That is, "knowing childhood non-HDL-C, does change from childhood to adulthood matter?". This model also provides information about the importance of the assessment of childhood non-HDL-C in identifying high-risk individuals, and whether this risk could be offset by improving non-HDL-C levels from childhood to adulthood.

2.3. Prediction and Reclassification

We estimated the change in C-index and the category-free net reclassification improvement (NRI) for time to event outcome[29,30] to compare the utility of two pairs of models in risk prediction and reclassification for incident CVD events. To estimate NRI, age 50 was set as the time to determine event/non-event as this ensures both a sufficient length of follow-up and a large proportion of participants contributing to the time at risk for this estimation (over a half of the participants had been followed up until age 50). Confidence intervals for NRIs were calculated by the percentile bootstrap method. The first pair of models estimated the incremental value of childhood non-HDL-C z score plus adult non-HDL-C z score vs. adult

non-HDL-C z score alone (Comparison 1). The second pair of models estimated the incremental value of childhood non-HDL-C z score plus change in non-HDL-C z score vs. change in non-HDL-C z score alone (Comparison 2). All comparisons included sex, cohort, Black race, mean age at and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure.

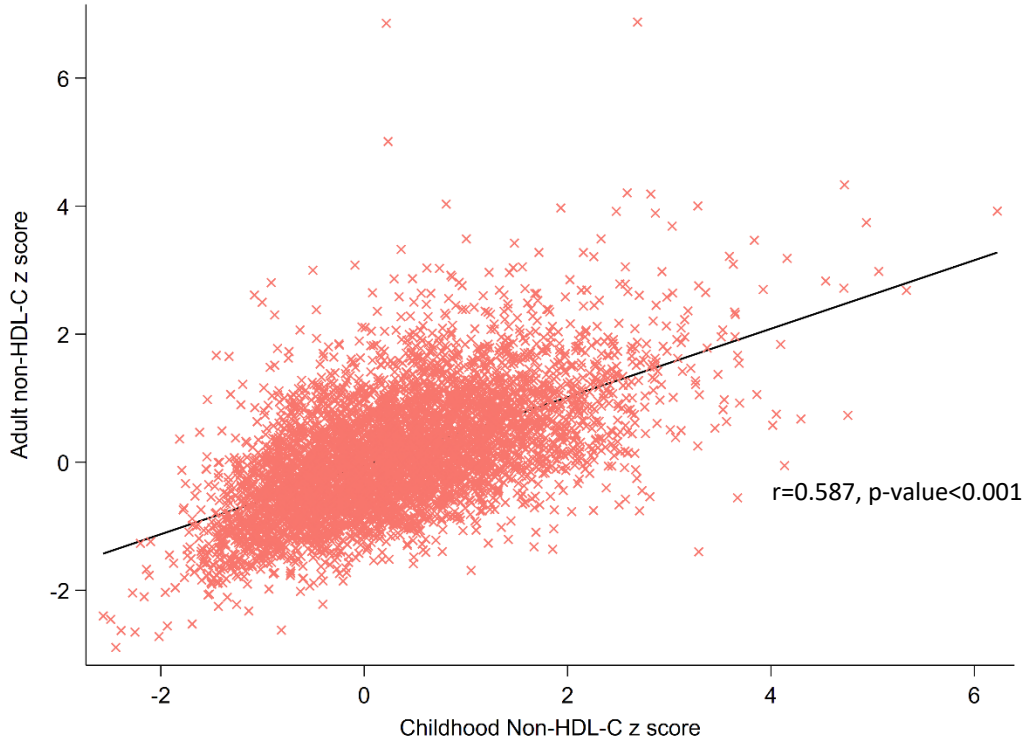
2.4. Selection of Measures to Define Childhood and Adulthood Dyslipidemia Status

In our primary analysis, the average of all available measures at each age period was used for each person because this may reduce measurement error due to intraindividual variations over time and therefore the attenuation of the associations[31]. It is also possible that the cumulative averages, which reflect long-term exposure level, are more relevant etiologically than either the most remote (baseline) or the most recent exposure level[31]. Moreover, the choice of a single measure would be also arbitrary, because within person variance may also differ between persons[32]. However, to assess the influence of the issue of different number of measures across studies, individuals, and ages, we performed sensitivity analysis that used a single measure approach to define dyslipidemia status at each age period. This includes a) the maximum value at each age period; b) the first available childhood measure and the first adulthood measure; and c) the first available childhood measure and the last available adulthood measure.

2.5. Selection Bias

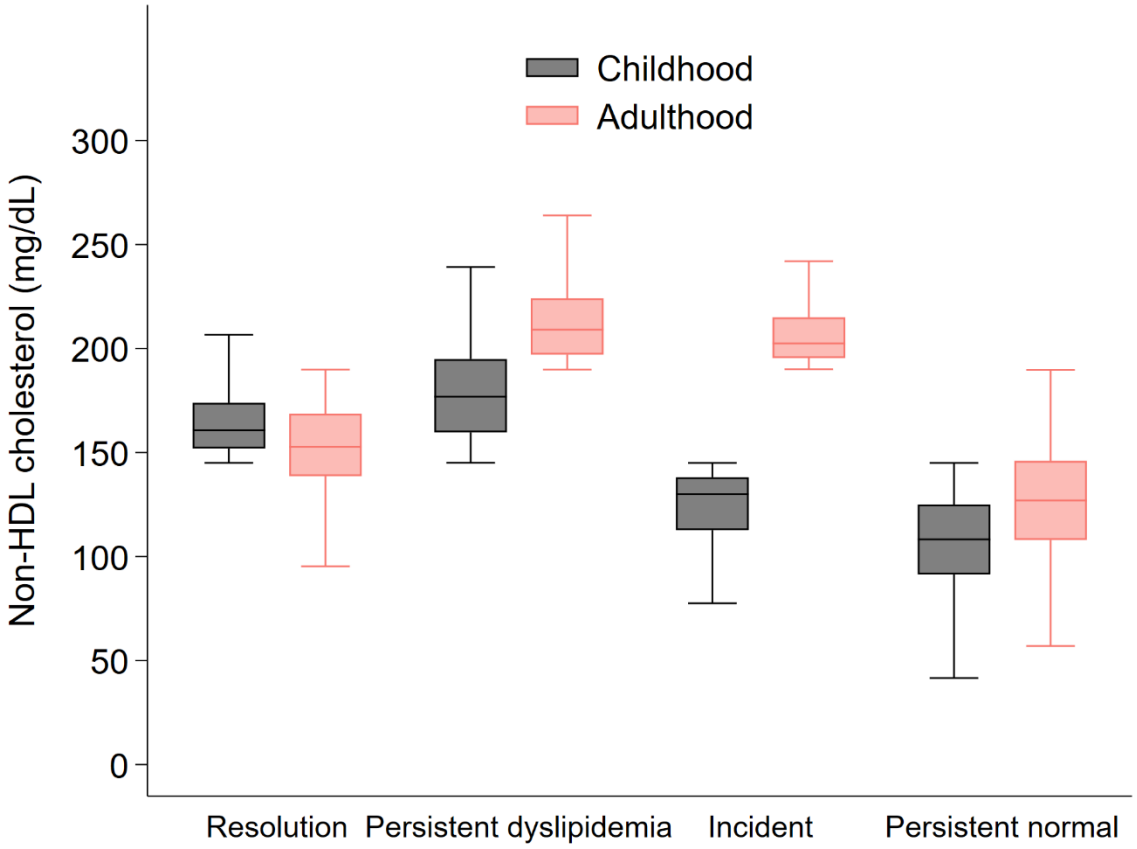
We applied a combination of multiple imputation[35] and inverse probability weighting to adjust for the impact of selection bias[36] since the distribution of missingness predictors differ between complete cases and incomplete cases and individuals with missing data tend to have missing values on many variables (including the exposure)[37]. Firstly, all missing baseline variables (race, smoking, mean age at and calendar year of childhood non-HDL-C measurements, BMI, and systolic blood pressure) were imputed by multiple imputation using chained equations. Secondly, the imputed data for baseline variables were used to predict the probability of being included. The probability of being included in analysis was estimated using logistic regression with baseline variables as predictors (age, visit year, sex, Black race, study cohort, and smoking; BMI and systolic blood pressure were not significant predictors and not included), based on 40,648 participants (the sampling frame). Lastly, all complete cases were weighted by the inverse of their probability of being included in analysis. Weight truncation was applied to deal with large weights since the Hinkley's method suggested that the large weights may be poorly estimated[37]. In weight truncation, a maximum weight is chosen and all weights greater than this are set equal to it. A maximum value of 10 was used in the analysis[37]. Moreover, a higher maximum value of 20 was also used to assess sensitivity of results to the choice of maximum weight and the results remained similar (data not shown).

eFigure 1. The Correlation Between Childhood and Adulthood Non-HDL-C Z Score.



The correlation coefficient is superimposed on the figure, along with a trend line estimated with the use of simple linear regression. Childhood non-HDL-C levels at each visit were standardized as age- and sex-specific z scores within each age and sex stratum. The mean of resulting z scores across their childhood measurements for each participant was then calculated to obtain a single mean z score for analysis (see eMethod 2 for details). The same approach was applied to obtain adult non-HDL-C z score.

eFigure 2. Medians of Childhood and Adulthood Non-HDL-C Levels According to Change in Non-HDL-C Status Between Childhood and Adulthood.



Lower and upper limits of boxes indicate interquartile range; horizontal lines inside boxes indicate the median values. The lines extending from the boxes indicate the 5th and 95th percentiles. Non-HDL-C cutoffs to define dyslipidemia were: 145 mg/dL in childhood and 190 mg/dL in adulthood; to convert non–HDL-C from mg/dL to mmol/L, divide values by 38.67. The change in non-HDL-C status between childhood and adulthood was defined as: resolution (dyslipidemia to non-dyslipidemia), persistent dyslipidemia (dyslipidemia in both childhood and adulthood), incident dyslipidemia (non-dyslipidemia to dyslipidemia), and persistent normal (non-dyslipidemia in both childhood and adulthood).

eTable 3. Characteristics of Participants According to Adult Cardiovascular Outcomes.

Characteristic	Incident CVD events [a] (N =5,121)	
	Yes	No
No. of participants (%)	147 (3.0)	4974 (97.0)
Age at the first visit for non-HDL-C measurement, median (IQR), y	12.3 (10.0-14.4)	10.3 (7.0-13.7)
Sex, No. (%)		
Men	84 (57.2)	1974 (39.7)
Women	63 (42.8)	3000 (60.3)
Race, No. (%) [b]		
American Indian or Alaskan Native	0 (0)	3 (0.1)
Black or African American	43 (29.3)	729 (14.6)
Native Hawaiian or Pacific Islander	0 (0)	1 (0)
White	104 (70.7)	4223 (84.9)
More than one race	0 (0)	18 (0.4)
Cohorts (country), No. (%)		
Bogalusa Heart Study (U.S.)	92 (62.5)	1681 (33.8)
Minnesota Childhood Cardiovascular Cohorts (U.S.)	1 (0.7)	93 (1.9)
Muscatine Study (U.S.)	2 (1.4)	92 (1.9)
NHLBI Growth and Health Study (U.S.)	0 (0)	256 (5.1)
Princeton Lipid Research Study (U.S.)	15 (10.2)	237 (4.7)
Cardiovascular Risk in Young Finns Study (Finland)	37 (25.2)	2615 (52.6)
Childhood Factors		
Mean age at childhood visits, median (IQR), y [c]	14.8 (12.5-16.4)	13.5 (11.0-15.7)
Mean calendar year of childhood visits, median (IQR) [c]	1976.5 (1974.5-1980.0)	1981.5 (1977.5-1983.0)
Parental education level, No. (%) [total no. =4421]		
Less than high school degree	38 (33.3)	1701 (39.5)
High school degree	37 (32.5)	742 (17.2)
Higher than high school degree but no college degree	19 (16.7)	1043 (24.2)
College degree or higher	20 (17.5)	821 (19.1)
Smoked cigarettes, No. (%)	85 (57.8)	2057 (41.4)
BMI, mean (SD), kg/m^2	19.8 (4.44)	18.0 (3.3)
Systolic blood pressure, mean (SD), mmHg	110 (14)	107 (13)
Non-HDL-C, mean (SD), mg/dL [d]	121.6 (38.0)	122.0 (33.8)
Adulthood Factors		
Mean age at adulthood visits, median (IQR), y [c]	30.6 (28.0-35.4)	29.9 (27.2-33.0)
Mean calendar year of adulthood visits, median (IQR) [c]	1993.5 (1989.7-1999.0)	1999.0 (1992.0-2004.0)
Age at the end of follow-up, median (IQR), y [e]	48.6 (44.5-51.5)	49.4 (43.9-53.2)
Type 2 diabetes, No. (%) [total no. =4131]	23 (23.7)	268 (6.6)
Lipid medications, No. (%) [total no. =5034]	21 (14.7)	232 (4.7)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; IQR, interquartile range; NHLBI, National Heart, Lung and Blood Institute; non-HDL-C, non-high-density lipoprotein cholesterol; SD, standard deviation.

[a] Incident CVD included the first occurrence of adjudicated myocardial infarction, stroke, transient ischemic attack, ischemic heart failure, angina, peripheral artery disease, carotid intervention, abdominal aortic aneurysm, or coronary revascularization, and CVD deaths.

[b] Collection of race was based on self-reported data from various sources and harmonized to the categories shown. See eMethod 1 for a complete description.

[c] The mean age at childhood or adulthood visits was the mean age of the participant across all available childhood (age 3-19) visits or adulthood (age 20-40) visits for non-HDL-C measurements. The mean calendar year of childhood or adulthood visits was the mean calendar year across all available childhood (age 3-19) visits or adulthood (age 20-40) visits for non-HDL-C measurements by the participant. Mean age at childhood visits is larger than

age at the first visit for non-HDL-C measurement because most individuals had multiple measurements from different ages.
[d] Individual mean (if the participant had multiple measurements) of the measurements across childhood (3-19.99 years). To convert non–HDL-C from mg/dL to mmol/L, divide values by 38.67.
[e] Age at time of the event, the non-CVD deaths, or the end of follow-up (whichever came first).

eTable 4. C-Index and Category-Free Net Reclassification Index for the Additive Predictive Value of Childhood Non-HDL-C in Addition to Adult Non-HDL-C or the Change in Non-HDL-C From Childhood to Adulthood.

	C-index or change in C-index (95% CI)	Net Reclassification Index (95% CI)
Model Comparison 1		
Change in non-HDL-C z score (reference)	0.7649 (0.7231 to 0.8067)	Reference
Childhood z score and change in z score	0.0165 (0.0090 to 0.0239)	0.495 (0.283 to 0.688)
Model Comparison 2		
Adulthood non-HDL-C z score (reference)	0.7800 (0.7377 to 0.8224)	Reference
Child z score and adult z score	0.0013 (-0.0005 to 0.0031)	0.123 (-0.1120 to 0.444)

CI, confidence interval. All models included cohort, sex, Black race, child smoking and mean age at and calendar year of childhood measurement, childhood mean age- and sex-specified z scores for BMI and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood. Childhood non-HDL-C levels at each visit were standardized as age- and sex-specific z scores within each age and sex stratum. The mean of resulting z scores across their childhood measurements for each participant was then calculated to obtain a single mean z score for analysis (see eMethod 2 for details). The same approach was applied to obtain adult non-HDL-C z score. Change in z score was calculated by subtracting the participant's childhood mean z score from adult mean z score.

eTable 5. Hazard Ratios for Adult Cardiovascular Events According to Adult Non-HDL-C Category Within Each Child Risk Category.

Non-HDL-C groups	No. of event/total no. (Rate/1000 person-y)	HR (95% CI)
Child <120 mg/dL		
Adult <150 mg/dL	56/2167 (2.75)	Reference
Adult 150-190 mg/dL	18/383 (4.51)	1.50 (0.82 to 2.76)
Adult ≥ 190 mg/dL	4/50 (7.41)	2.90 (0.96 to 8.78)
p for trend		0.04
Child 120-145 mg/dL		
Adult <150 mg/dL	17/812 (2.67)	Reference
Adult 150-190 mg/dL	11/412 (2.92)	0.99 (0.35 to 2.84)
Adult ≥ 190 mg/dL	5/108 (5.27)	1.56 (0.43 to 5.72)
p for trend		0.62
Child ≥ 145 mg/dL		
Adult <150 mg/dL	5/418 (1.64)	Reference
Adult 150-190 mg/dL	8/519 (1.89)	0.74 (0.14 to 3.90)
Adult ≥ 190 mg/dL	23/252 (10.20)	5.30 (1.10 to 25.60)
p for trend		0.009

Abbreviation: HR, hazard ratio; CI, confidence interval. Cohort-stratified cause-specific hazard models were used, and analyses were weighted by the inverse of the probability of being included in analysis and adjusted for sex, black race, mean age at and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood. Childhood/adulthood individual mean of non-HDL-C for each participant was used to classify different risk status. Non-HDL-C cutoffs: ≥ 120 mg/dL and ≥ 150 mg/dL, respectively, were used to define childhood and adulthood elevated levels; 145 mg/dL and 190 mg/dL, respectively, to define childhood and adulthood dyslipidemia. To convert non-HDL-C from mg/dL to mmol/L, divide values by 38.67.

eTable 6. Hazard Ratios for Adult Cardiovascular Events According to Change in Non-HDL-C Status Between Childhood and Adulthood by Sex, Age, or Race.

	SEX				
	Male		**Female**		
Change in non-HDL-C status	No. of event/total no. (Rate/1000 person-y)	HR (95% CI)	No. of event/total no. (Rate/1000 person-y)	HR (95% CI)	p-value *
Resolution	7/301 (2.89)	0.78 (0.23 to 2.74)	6/636 (1.23)	1.39 (0.46 to 4.16)	0.99
Persistent dyslipidemia	16/153 (12.10)	4.34 (1.87 to 10.06)	7/99 (7.52)	7.23 (3.06 to 17.24)	0.46
Incident dyslipidemia	5/101 (5.28)	1.77 (0.60 to 5.22)	4/57 (7.38)	2.92 (1.11 to 7.72)	0.41
Persistent normal	56/1503 (3.94)	Reference	46/2271 (2.27)	Reference	
	AGE				
	3-11.99 years		**12-19.99 years**		
Resolution	0/377 (0)	NA	13/560 (2.17)	1.45 (0.61 to 3.42)	0.90
Persistent dyslipidemia	4/81 (11.49)	6.20 (1.88 to 20.47)	19/171 (9.97)	5.03 (2.41 to 10.52)	0.94
Incident dyslipidemia	6/62 (15.53)	6.56 (2.13 to 20.22)	3/96 (2.72)	0.44 (0.12 to 1.58)	0.001
Persistent normal	18/1198 (2.75)	Reference	84/2576 (3.01)	Reference	
	RACE				
	Black		**Non-Black**		
Resolution	1/37 (3.47)	0.59 (0.08 to 4.49)	12/900 (1.71)	1.39 (0.59 to 3.30)	0.47
Persistent dyslipidemia	2/15 (15.86)	1.74 (0.30 to 10.09)	21/237 (9.87)	7.14 (3.96 to 12.89)	0.18
Incident dyslipidemia	2/18 (9.10)	1.50 (0.39 to 5.71)	7/140 (5.51)	2.47 (0.99 to 6.18)	0.81
Persistent normal	38/702 (6.23)	Reference	64/3072 (2.26)	Reference	

HR, hazard ratio; CI, confidence interval; NA, not available. Cohort-stratified cause-specific hazard models were used, and analyses were weighted by the inverse of the probability of being included in analysis and adjusted for sex (not for analysis by sex), Black race (not for analysis by race), mean age at (not for analysis by age groups) and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood. * P value for interaction.
Childhood/adulthood individual mean of non-HDL-C for each participant was used to classify different risk status. Non-HDL-C cutoffs to define dyslipidemia were: 145 mg/dL in childhood and 190 mg/dL in adulthood; to convert non–HDL-C from mg/dL to mmol/L, divide values by 38.67. The four groups were defined as: resolution (dyslipidemia in childhood to non-dyslipidemia in adulthood), incident dyslipidemia (non-dyslipidemia in childhood, dyslipidemia in adulthood), persistent dyslipidemia (dyslipidemia in both childhood and adulthood), and persistent normal (non-dyslipidemia in both childhood and adulthood).

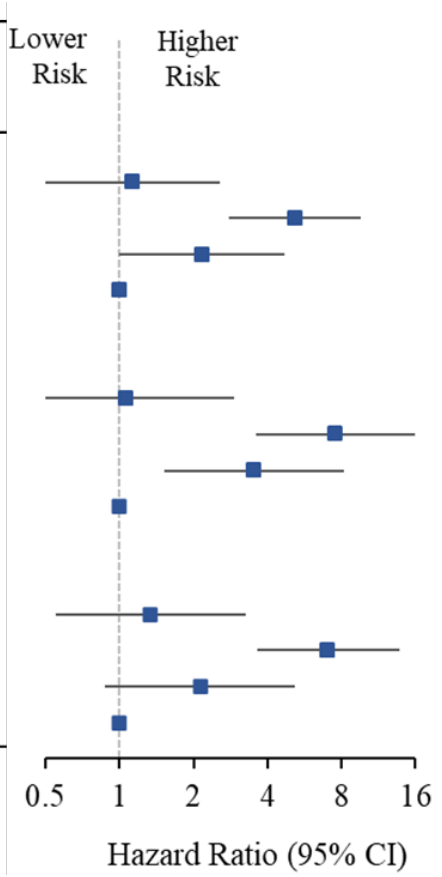
eTable 7. Cohort-Specific Hazard Ratios for Adult Cardiovascular Events According to Change in Non-HDL-C Status Between Childhood and Adulthood.

	Bogalusa Heart Study	
Change in non-HDL-C status	No. of event/total no. (Rate/1000 person-y)	HR (95% CI)
Resolution	2/59 (3.80)	0.53 (0.10 to 2.82)
Persistent dyslipidemia	6/30 (25.33)	3.30 (1.16 to 9.36)
Incident dyslipidemia	7/79 (8.59)	2.30 (0.96 to 5.51)
Persistent normal	77/1605 (4.60)	Reference
	Young Finns Study	
Resolution	8/817 (1.29)	1.09 (0.45 to 2.63)
Persistent dyslipidemia	11/200 (6.18)	3.90 (1.73 to 8.75)
Incident dyslipidemia	1/57 (2.20)	1.67 (0.21 to 12.94)
Persistent normal	17/1578 (1.28)	Reference

HR, hazard ratio; CI, confidence interval. Cause-specific hazard models were used and analyses were weighted by the inverse of the probability of being included in analysis and adjusted for sex, Black race, mean age at and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood. Childhood/adulthood individual mean of non-HDL-C for each participant was used to classify different risk status. Non-HDL-C cutoffs to define dyslipidemia were: 145 mg/dL in childhood and 190 mg/dL in adulthood; to convert non–HDL-C from mg/dL to mmol/L, divide values by 38.67. The four groups were defined as: resolution (dyslipidemia in childhood to non-dyslipidemia in adulthood), incident dyslipidemia (non-dyslipidemia in childhood, dyslipidemia in adulthood), persistent dyslipidemia (dyslipidemia in both childhood and adulthood), and persistent normal (non-dyslipidemia in both childhood and adulthood).

eFigure 3. Hazard Ratios for Adult Cardiovascular Events According to Change in Non-HDL-C Status Between Childhood and Adulthood – Sensitivity Analyses.

Change in non-HDL-C status [a]	No. of event/total no. (Rate/1000 person-y)	Unadjusted incidence rate difference, per 1000 person-y (95% CI)	Hazard Ratio (95% CI)
Model 1 [b]			
Resolution	13/937 (1.78)	-1.18 (-2.30 to -0.05)	1.13 (0.50 to 2.56)
Persistent dyslipidemia	23/252 (10.20)	7.25 (3.04 to 11.46)	5.17 (2.80 to 9.56)
Incident dyslipidemia	9/158 (6.04)	3.08 (-0.91 to 7.07)	2.17 (1.00 to 4.69)
Persistent normal	102/3774 (2.96)	0 [Reference]	1 [Reference]
Model 1 plus adult lipid-lowering medications and type 2 diabetes			
Resolution	8/682 (1.51)	-0.59 (-1.76 to 0.58)	1.06 (0.39 to 2.93)
Persistent dyslipidemia	18/178 (10.97)	8.87 (3.78 to 13.96)	7.56 (3.58 to 15.95)
Incident dyslipidemia	8/132 (6.33)	4.23 (-0.18 to 8.65)	3.54 (1.53 to 8.19)
Persistent normal	61/3131 (2.10)	0 [Reference]	1 [Reference]
Model 1 excluding participants using lipid-lowering medications			
Resolution	11/872 (1.69)	-1.03 (-2.18 to 0.12)	1.34 (0.55 to 3.27)
Persistent dyslipidemia	17/206 (9.82)	7.10 (2.40 to 11.81)	7.06 (3.62 to 13.77)
Incident dyslipidemia	7/132 (5.87)	3.15 (-1.24 to 7.53)	2.13 (0.87 to 5.19)
Persistent normal	87/3571 (2.72)	0 [Reference]	1 [Reference]



Abbreviations: HR, hazard ratio; CI, confidence interval. See the Figure 2 footnote for conditions included in the incident CVD event. There were 147 incident CVD events (N=5121 participants; incidence rate=3.23 per 1000 person-y). [a] Childhood/adulthood individual mean of non-HDL-C levels for each participant was used to classify different risk status. Non-HDL-C cutoffs to define dyslipidemia were: 145 mg/dL in childhood and 190 mg/dL in adulthood; to convert non-HDL-C from mg/dL to mmol/L, divide values by 38.67. The four groups were defined

as: resolution (dyslipidemia in childhood to non-dyslipidemia in adulthood), persistent dyslipidemia (dyslipidemia in both childhood and adulthood), incident dyslipidemia (non-dyslipidemia in childhood, dyslipidemia in adulthood), and persistent normal (non-dyslipidemia in both childhood and adulthood). [b] Cohort-stratified cause-specific hazard models were used; Model 1 is the same as the model in Figure 3 (landmark analysis weighted by the inverse of the probability of being included in analysis; see eMethod 1), adjusted for sex, Black race, mean age at and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood.

eTable 8. Characteristics of Participants Included vs. Excluded From the Analysis.

Characteristic	Included	Excluded
No. of participants [a]	5121	35527
Age at baseline (first visit), mean (SD), years	10.7 (4.2)	10.2 (3.4)
Female sex, No. (%)	3063 (60)	17364 (49)
Race, No. (%)		
Black	772 (15)	5182 (18)
White or others [b]	5407 (85)	23807 (82)
Cohorts (country), No. (%)		
Bogalusa Heart Study (U.S.)	1773 (34.6)	10189 (28.7)
Childhood Determinants of Adult Health (Australia)	0 (0)	8494 (23.9)
Minnesota Childhood Cardiovascular Cohorts (U.S)	94 (1.8)	1984 (5.5)
Muscatine Study (U.S.)	94 (1.8)	11283 (31.8)
NHLBI Growth and Health Study (U.S.)	256 (5)	614 (1.7)
Princeton Lipid Research Study (U.S.)	252 (5)	2021 (5.7)
Cardiovascular Risk in Young Finns Study (Finland)	2652 (51.8)	942 (2.7)
Childhood Factors		
Body mass index, mean (SD), kg/m^2	18.0 (3.4)	18.0 (3.5)
Smoked cigarettes, No. (%)	2142 (42)	7297 (36)
Systolic blood pressure, mean (SD), mmHg	108 (13)	104 (13)
Parental education level, No. (%)		
Less than high school degree	1739 (39)	2733 (22)
High school degree	779 (18)	3593 (28)
Higher than high school degree but no college degree	1062 (24)	2937 (23)
College degree or higher	841 (19)	3394 (27)

Abbreviations: NHLBI, National Heart, Lung and Blood Institute.

[a] Number of participants with available data on the variables varied and ranged from 17078 (parental education) to 40648 (age, sex, cohort). Others include American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or those who had more than one race.

eTable 9. Hazard Ratios for Adult Cardiovascular Events According to Change in Non-HDL-C Status Between Childhood and Adulthood – With or Without Further Adjustment of Parental Education.

	Adjustment for parental education	
Change in non-HDL-C status	No. of event/total no. (Rate/1000 person-y)	HR (95% CI)
Resolution	12/842 (1.85)	1.11 (0.46 to 2.68)
Persistent dyslipidemia	21/207 (10.53)	5.65 (2.84 to 11.24)
Incident dyslipidemia	9/118 (7.17)	2.91 (1.31 to 6.47)
Persistent normal	72/3028 (2.62)	Reference
	No adjustment for parental education (including only those with available data on parental education)	
Resolution	12/842 (1.85)	1.11 (0.46 to 2.68)
Persistent dyslipidemia	21/207 (10.53)	5.66 (2.85 to 11.25)
Incident dyslipidemia	9/118 (7.17)	2.88 (1.30 to 6.38)
Persistent normal	72/3028 (2.62)	Reference

HR, hazard ratio; CI, confidence interval. Cohort-stratified cause-specific hazard models were used, and analyses were weighted by the inverse of the probability of being included in analysis and adjusted for sex, cohort, Black race, mean age at and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood. Childhood/adulthood individual mean of non-HDL-C for each participant was used to classify different risk status. Non-HDL-C cutoffs to define dyslipidemia were: 145 mg/dL in childhood and 190 mg/dL in adulthood; to convert non–HDL-C from mg/dL to mmol/L, divide values by 38.67. The four groups were defined as: resolution (dyslipidemia in childhood to non-dyslipidemia in adulthood), incident dyslipidemia (non-dyslipidemia in childhood, dyslipidemia in adulthood), persistent dyslipidemia (dyslipidemia in both childhood and adulthood), and persistent normal (non-dyslipidemia in both childhood and adulthood).

eTable 10. Hazard Ratios for Adult Cardiovascular Events According to Change in Non-HDL-C Status Between Childhood and Adulthood – Based on Different Choices of Single Value of Childhood and Adulthood Non-HDL-C Measurements.

Change in non-HDL-C status	No. of event/total no. (Rate/1000 person-y)	HR (95% CI)
Child maximum value + adult maximum value		
Resolution	16/1283 (1.70)	1.07 (0.53 to 2.15)
Persistent dyslipidemia	34/514 (7.69)	4.25 (2.48 to 7.27)
Incident dyslipidemia	15/277 (4.76)	1.76 (0.95 to 3.27)
Persistent normal	82/3047 (2.87)	Reference
Child first measure + adult first measure		
Resolution	13/1114 (1.54)	1.11 (0.51 to 2.42)
Persistent dyslipidemia	24/263 (10.85)	5.14 (2.75 to 9.64)
Incident dyslipidemia	9/157 (6.08)	2.28 (1.08 to 4.81)
Persistent normal	101/3587 (3.03)	Reference
Child first measure + adult last measure		
Resolution	14/1080 (1.76)	1.28 (0.60 to 2.72)
Persistent dyslipidemia	23/297 (8.48)	4.91 (2.58 to 9.32)
Incident dyslipidemia	17/259 (6.07)	2.23 (1.25 to 3.98)
Persistent normal	93/3485 (2.90)	Reference

HR, hazard ratio; CI, confidence interval. Cohort-stratified cause-specific hazard models were used, and analyses were weighted by the inverse of the probability of being included in analysis and adjusted for sex, Black race, age at and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood.

Childhood/adulthood individual mean of non-HDL-C for each participant was used to classify different risk status. Non-HDL-C cutoffs to define dyslipidemia were: 145 mg/dL in childhood and 190 mg/dL in adulthood; to convert non–HDL-C from mg/dL to mmol/L, divide values by 38.67. The four groups were defined as: resolution (dyslipidemia in childhood to non-dyslipidemia in adulthood), incident dyslipidemia (non-dyslipidemia in childhood, dyslipidemia in adulthood), persistent dyslipidemia (dyslipidemia in both childhood and adulthood), and persistent normal (non-dyslipidemia in both childhood and adulthood).

eTable 11. Hazard Ratios for Adult Cardiovascular Events According to Change in Non-HDL-C Status Between Childhood and Adulthood Using Cohort-Stratified Fine-Gray Subdistribution Hazard Models.

Change in non-HDL-C status	No. of event/total no. (Rate/1000 person-y)	HR (95% CI)
Resolution	13/937 (1.78)	1.11 (0.48 to 2.56)
Persistent dyslipidemia	23/252 (10.20)	5.77 (3.10 to 10.73)
Incident dyslipidemia	9/158 (6.04)	2.07 (0.94 to 4.56)
Persistent normal	102/3774 (2.96)	Reference

HR, hazard ratio; CI, confidence interval. Cohort-stratified cause-specific hazard models were used, and analyses were weighted by the inverse of the probability of being included in analysis and adjusted for sex, Black race, mean age at and calendar year of childhood measurement, childhood smoking and mean age- and sex-specified z scores for body mass index and systolic blood pressure, adult smoking, and change in z scores for BMI and systolic blood pressure between childhood and adulthood.

Childhood/adulthood individual mean of non-HDL-C for each participant was used to classify different risk status. Non-HDL-C cutoffs to define dyslipidemia were: 145 mg/dL in childhood and 190 mg/dL in adulthood; to convert non–HDL-C from mg/dL to mmol/L, divide values by 38.67. The four groups were defined as: resolution (dyslipidemia in childhood to non-dyslipidemia in adulthood), incident dyslipidemia (non-dyslipidemia in childhood, dyslipidemia in adulthood), persistent dyslipidemia (dyslipidemia in both childhood and adulthood), and persistent normal (non-dyslipidemia in both childhood and adulthood).

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