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Lipoprotein (a) in youth and prediction of major cardiovascular outcomes in adulthood

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Conflict of Interest Disclosures
None

Supplemental Materials
Extended Methods
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Supplementary Tables 1–2
Supplementary Figure 1.

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Abstract

Background—Elevated lipoprotein (a) (Lp(a)) is a common risk factor for cardiovascular disease outcomes with unknown mechanism(s). We examined its potential role in identifying youths who are at increased risk of developing adult atherosclerotic cardiovascular disease (ASCVD).

Methods—Lp(a) levels measured in youth at ages 9 to 24 years were linked to adult ASCVD and carotid intima-media thickness in the Cardiovascular Risk in Young Finns Study (YFS), where 95 of the original 3596 participants (2.7%) recruited as children have been diagnosed with ASCVD at median age of 47 years. Results observed in YFS were replicated using data for White participants from the Bogalusa Heart Study (BHS). In BHS, there were 587 White individuals who had data on youth Lp(a) (measured at ages 8–17 years) and information on adult events, including 15 cases and 572 non-cases. Analysis were performed with the use of Cox proportional-hazard regression.

Results—In YFS, those who had been exposed to high Lp(a) level in youth (defined as Lp(a) ≥ 30 mg/dL) had about 2 times greater risk of developing adult ASCVD compared to non-exposed individuals (hazard ratio 2.0, 95%CI 1.4–2.6). Youth risk factors, including Lp(a), LDL-cholesterol, body mass index and smoking, were all independently associated with higher risk. In BHS, in an age and sex-adjusted model, White individuals who had been exposed to high Lp(a) had 2.5 times greater risk (95%CI 0.9–6.8) of developing adult ASCVD compared to non-exposed individuals. When additionally adjusted for LDL-cholesterol and body mass index, the risk associated with high Lp(a) remained unchanged (hazard ratio 2.4, 95%CI 0.8–7.3). In a multivariable model for pooled data, individuals exposed to high Lp(a) had 2.0 times greater risk (95%CI 1.0–3.7) of developing adult ASCVD compared to non-exposed individuals. No association was detected between youth Lp(a) and adult carotid artery thickness in neither cohort or pooled data.

Conclusions—Elevated Lp(a) level identified in youth is a risk factor for adult atherosclerotic cardiovascular outcomes but not for increased carotid intima-thickness.

Keywords

lipoprotein (a); atherosclerosis; longitudinal studies; epidemiology; risk factors; risk prediction

Introduction

Lipoprotein (a) (Lp(a)) is a lipoprotein particle discovered in 1963. Plasma levels of Lp(a) are genetically determined[1] and were first reported to be associated with coronary artery

disease in 1974[2,3]. Recently, there has been renewed interest in Lp(a) because Mendelian randomization studies have established its role as a causal risk factor for coronary heart disease, ischemic stroke, and aortic valve calcification[4–6]. Effective therapeutic interventions to lower Lp(a) levels have been developed[7,8], and ongoing studies will clarify whether lowering Lp(a) levels is safe and can reduce the risk of atherosclerotic cardiovascular disease (ASCVD) outcomes. Lp(a) remains an enigmatic risk factor because it seems to be specifically associated with cardiovascular events but not with the atherosclerotic process[9–14].

The Lp(a) phenotype is fully expressed by the first or second year of life in children[15,16], and the plasma levels show strong tracking over subsequent measurements, both in children and adults[17–21]. Observational studies suggest that elevated Lp(a) levels may be more common in children with arterial ischemic stroke than in control children[22]. Therefore, there has been interest in screening strategies beginning at an early age; however specific recommendations for the assessment of Lp(a) levels in youth are limited[23].

The Cardiovascular Risk in Young Finns Study (YFS) is one of the long-standing cohort studies that were initiated in the 1970s and 1980s to examine the determinants of cardiovascular disease in children, and that constitute the International Childhood Cardiovascular Cohort (*i*3C) Consortium[24,25]. During the past two decades, the *i*3C cohorts have provided a large evidence base documenting the associations between childhood risk factor exposures and adult pre-clinical atherosclerotic vascular phenotypes[26–31]. As participants in these cohorts became older, the evidence linking childhood risk factors to actual adult ASCVD events began to emerge. By pooling data, the *i*3C Consortium recently demonstrated that traditional risk factors, including youth body mass index, serum total cholesterol and triglycerides, systolic blood pressure and smoking were directly associated with adult cardiovascular events[32]. However, whether Lp(a) levels measured in youth predict adult-onset cardiovascular events is not known. To examine this question, we investigated whether Lp(a) levels measured in children, adolescents and young adults were associated with adult-onset ASCVD events in the YFS with replication in the Bogalusa Heart Study (BHS), another *i*3C Consortium cohort. Lp(a) levels were measured in subsets of these cohorts in the mid 80’s using a similar methodology. To provide mechanistic insights, we have also examined the association between youth Lp(a) and adult carotid intima-media thickness - a vascular phenotype that is strongly associated with conventional youth risk factors, including LDL-cholesterol, smoking, body mass index and systolic blood pressure[26–28].

Methods

Anonymized data are available upon reasonable request from the YFS research group (https://youngfinnsstudy.utu.fi/). The YFS is a prospective multicenter study from Finland initiated in the late 1970s. The first large baseline examination was conducted in 1980 (baseline age, 3–18 years, N=3596)[33]. Children aged 3, 6, 9, 12, 15, and 18 years were chosen from the population register from the five Finnish university cities with medical schools (Helsinki, Kuopio, Oulu, Tampere, and Turku). Several follow-ups during the past 40 years have been conducted to investigate the determinants of cardiometabolic health. The

study was approved by local ethics committees. All participants provided written informed consent.

Assessment of youth Lp(a)

In 1986, youth Lp(a) was measured in 2464 participants at ages 9–24 years by radioimmunoassay. Lp(a) levels have been also measured in adulthood, including in year 2001 (N=2281, ages 24–39 years), in year 2007 (N=2204, ages 35–45 years) and in year 2011 (N=2044, ages 39–49 years). Different methods were used in 2001[34] and 2007/11. Adulthood Lp(a) data were utilized to impute missing youth Lp(a) values (details of Lp(a) methods are provided in the Supplemental Materials).

Other variables

In the present analyses, we have used conventional risk variables, including serum LDL-cholesterol, body mass index, smoking and systolic blood pressure, as covariates in multivariable models. Standard methods were used for measuring serum total-cholesterol, high-density lipoprotein cholesterol, and triglycerides at baseline and all follow-up studies. LDL-cholesterol was estimated by using Friedewald's formula in individuals with triglycerides less than 4.0 mmol/L[35]. At all study phases, the participants' weight and height were measured and body mass index was calculated. To use all available repeatedly measured exposure data for LDL-cholesterol, body mass index, and systolic blood pressure, we have estimated participant-specific curves for cardiovascular risk factors by mixed model regression splines[36]. The area under the curve for continuous risk variables was evaluated to indicate a long-term burden of each measured attribute. The area under the curve variables defined for ages 6 to 18 were used here primarily to capture youth exposure. We also conducted sensitivity analyses by using the area under curve variables that were defined for ages 6 to 24 years, and by using single covariate values measured cross-sectionally in year 1986. All these analyses gave similar results pertaining the association between Lp(a) and cardiovascular events. For interpretability, the continuous covariates were standardized resulting in variables with mean 0 and standard deviation 1. Smoking exposure was queried throughout the follow-up time. Youth smoking status was dichotomized into daily smokers and non-smokers, defined as current daily smoking (yes/no) at baseline or at any of the follow-up studies when the participants were age 12 to 24 years. Details of the methods are provided in the Supplemental Materials.

Cardiovascular disease outcomes

Between 2015–2019, the *i*3C Consortium conducted a coordinated study to locate and survey original cohort participants for fatal and non-fatal cardiovascular events. The details of the protocols have been previously published[32]. In Finland, linkages to national registries, including the Care Register for Health Care and the National Death Index, were used to ascertain ASCVD outcomes, including coronary artery disease, atherosclerotic cerebrovascular disease and peripheral artery disease. All Finnish citizens are covered in the registry data, thus the diagnoses were available for 3579 participants (17 individuals declined the use of their registry data). By study year 2018, 95 individuals had been diagnosed with one or more events and were included in this analysis. The outcomes included both thrombotic events and confirmed diagnoses without a thrombotic event.

Statistical methods

First, we examined the association between youth Lp(a) and adult ASCVD amongst those whose Lp(a) values had been measured in 1986 at ages 9 to 24 years. This subset included 46 cases and 2409 non-cases. Secondly, we imputed missing year 1986 Lp(a) values for individuals who had participated in later examinations and had at least one Lp(a) value available from study years 2001, 2007 and/or 2011. This subset included 74 cases and 3096 non-cases. Finally, we imputed missing year 1986 Lp(a) values for all participants. The fully imputed data included 95 cases and 3484 non-cases.

Data were imputed using the Statistical Analyses System procedure MI (chained equations with fully conditional specification) and 20 replications of Cox proportional hazards regression to calculate hazard ratios and 95% confidence intervals to determine the associations between youth Lp(a) status and adult ASCVD outcomes. We used the procedure mianalyze and Rubin's rule for combining replications (details of the imputations are provided in the Supplemental Materials). We report the median of the p-values from the overall significance tests from the analyses on the imputed datasets[37]. All analyses were conducted accounting for competing risks. We used subdistribution hazard models where deaths from non-cardiovascular causes were considered as competing events and handled using Fine-Gray subdistribution hazard model[38].

To study the associations of youth Lp(a) with adult ASCVD, we classified Lp(a) into a binary variable using a cut-point of 30 mg/dL. Approximately 10% of the YFS participants have Lp(a) values above this cut-point that is considered being in the range of increased cardiovascular disease risk[5]. In sensitivity analyses, we examined other cut-points (10–50 mg/dL) for Lp(a), and additionally used the continuous natural log-transformed Lp(a) variable to estimate how a one standard deviation increase in Lp(a) level is associated with cardiovascular risk. The possibility of a non-linear relation between Lp(a) and cardiovascular outcomes was tested by including the second-order interaction term for log-Lp(a)*log-Lp(a) in the Cox proportional hazard model.

To test whether exposure to high Lp(a) was associated with higher risk when simultaneously controlled with youth LDL-cholesterol, body mass index, systolic blood pressure, and smoking, in addition to age and sex, we constructed multivariable models using fully imputed data.

To examine the additive effects of Lp(a) and LDL-cholesterol, we categorized the study population into three groups using cut-points of 30 mg/dL for Lp(a) and 130 mg/dL (3.36 mmol/L) for LDL-cholesterol[39]. Individuals with low Lp(a) and low LDL-cholesterol in youth were assigned as the reference group. The reference group was compared to individuals with either high Lp(a) or high LDL-cholesterol, and to individuals with both high Lp(a) and high LDL-cholesterol.

Replication in an independent cohort

Replication of the results was performed using data from the BHS, where Lp(a) measurements were completed during 1985–86 between ages 8 and 17 years[40]. The BHS is a community-based, long-term investigation in Bogalusa, Louisiana, begun in 1973,

focusing on the early natural history and risk factors for cardiovascular disease from childhood. A series of cross-sectional surveys was conducted, repeated every 2–3 years, allowing a longitudinal analysis in a cohort setting. The details of the study design and recruitment of participants were described previously[41], and briefly described in the Supplemental Materials. In BHS, successfully located adult participants self-reported cardiovascular events, and medical records were requested for adjudication of self-reports. Medical records were reviewed by a physician committee blinded to participant study data. National death index was searched for participants not located[32]. The BHS has been approved by local Institutional Review Board, and all participants provided written informed consent. Data on youth Lp(a) levels and verified ASCVD events were available for 587 BHS White participants, including 15 cases and 572 non-cases (the result observed in the YFS was replicated using data for White participants in the BHS because the YFS included only White participants). Lp(a) was determined by an enzyme-linked immunosorbent assay using sheep polyclonal monospecific antibodies against purified human Lp(a) (Biopool AB, Umeå, Sweden)[40]. To test the hypothesis that Lp(a) is linked to pre-clinical vascular damage, we examined the associations between youth Lp(a) and carotid artery intima-media thickness that has been measured in both cohorts during adulthood examinations as previously described in detail[26–28,42]. The characteristics of YFS and BHS participants are shown in the Supplemental Materials (Table S1). There were 2455 individuals in YFS and 587 in BHS with data on youth Lp(a) and adult cardiovascular events. The numbers of individuals with composite cardiovascular outcome and each specific component diagnoses stratified by youth Lp(a) level using cut-point of 30 mg/dL are shown in Table S2.

Results

In the YFS, by the end of year 2018, 95 individuals (2.7%) had been diagnosed with one or more cardiovascular outcomes. The mean age of the participants was 48.4 years (range 41 to 56 years). The median age at cardiovascular diagnoses was 47 years (range 31 to 56 years). Most diagnoses were coronary artery disease (N=58, 61%). The non-coronary diagnoses (N=37, 39%) included ischemic stroke, peripheral artery disease, transient ischemic attack or temporary stroke, blocked carotid artery and abdominal aneurysm[32].

The age- and sex-adjusted hazard ratios of adult ASCVD outcomes associated youth Lp(a) levels are shown in Table 1. Individuals who had been exposed to high Lp(a) level in youth had about 2 times greater risk of developing adult ASCVD outcome compared to non-exposed individuals: there were 8 (3.2%) cases among those exposed to high Lp(a) (defined as Lp(a) ≥ 30 mg/dL, N=247) and 38 (1.7%) cases among those non-exposed (N=2208). When Lp(a) was modelled as a continuous variable, the risk increased about 30% per one standard deviation increase in Lp(a) level. These effects were similarly seen in non-imputed data, partially imputed data and fully imputed data.

In sensitivity analyses, high Lp(a) exposure was similarly associated with the risk of coronary heart disease outcomes (hazard ratio 2.1, 95% 1.3–2.9) and non-coronary atherosclerotic outcomes (hazard ratio 1.8, 95% 0.8–2.8).

We found no evidence for a non-linear relation between Lp(a) and cardiovascular outcomes, as the p-value for the second-order interaction term for log-Lp(a)*log-Lp(a) in the Cox proportional hazard was non-significant (p=0.48). In addition, when different cut-points were used to define high-risk youth Lp(a) level, the risk increased linearly above the cut-point of 20 mg/dL (Figure S1 under section Assessing non-linearity in Supplemental Materials).

In the multivariable model, high Lp(a) (RR=1.77), LDL-cholesterol, body mass index and smoking, were all independently associated with higher risk (Table 2). Every standard deviation increase in youth LDL-cholesterol level and body mass index was associated with 26% and 25% increase in cardiovascular risk, respectively. Furthermore, the association between youth Lp(a) and adult cardiovascular events did not materially change after excluding individuals with high LDL-cholesterol levels (please see Table S3).

Individuals exposed to high Lp(a) and high LDL-cholesterol levels in youth had about 4 times greater risk of developing a cardiovascular outcome during the follow-up than the non-exposed reference group (Table 3). Individuals exposed to either high Lp(a) or high LDL-cholesterol level had about 2.5 times greater risk compared to the non-exposed reference group.

Replication in the BHS data

In BHS, there were 587 White individuals who had data on both Lp(a) and events, including 15 cases and 572 non-cases. There were 7 (4.7%) cases among those exposed to high Lp(a) (defined as Lp(a) ≥ 30 mg/dL, N=150) and 8 (1.8%) cases among those non-exposed (N=437).

In Black individuals, the number of cases with Lp(a) data was too low to determine the association between Lp(a) and cardiovascular events. There were 437 Black individuals who had data on both Lp(a) and cardiovascular events, including 12 cases and 425 non-cases. There were only 2 (1.2%) cases among those exposed to high Lp(a) (defined as Lp(a) ≥ 30 mg/dL, N=167) and 10 (3.7%) cases among those non-exposed (N=270).

In age and sex-adjusted model, White individuals who had been exposed to high Lp(a) had 2.5 times greater risk (95%CI 0.9–6.9, p=0.089) of developing a cardiovascular outcome compared to non-exposed individuals. When additionally adjusted for LDL-cholesterol and body mass index, the risk associated with high Lp(a) remained unchanged (hazard ratio 2.4, 95% 0.8–7.3).

Analyses in pooled data

In further analyses, we pooled YFS (non-imputed) and BHS datasets (White individuals). The pooled data included 2981 non-cases and 61 cases. There were 15 (3.8%) cases among those exposed to high Lp(a) (defined as Lp(a) ≥ 30 mg/dL, N=397) and 46 (1.5%) cases among those non-exposed (N=2645).

In an age-, sex-, and cohort-adjusted model, individuals who had been exposed to high Lp(a) had 2.6 times greater risk (95% CI 1.5–4.6, p=0.009) of developing adult ASCVD compared to non-exposed individuals.

In a multivariable model adjusted for LDL-cholesterol and body mass index, in addition to age, sex and cohort, individuals exposed to high Lp(a) had 2.0 times greater risk (95%CI 1.0–3.7, p=0.04) of developing adult ASCVD compared to non-exposed individuals. In the multivariable model, every standard deviation increase in youth LDL-cholesterol was associated with a 34% increase in risk (95%CI, 1.0–1.8, p=0.05).

Lp(a) and carotid intima-media thickness/plaques

Finally, to provide mechanistic insights of links between elevated Lp(a) and ASCVD events, we examined the associations between youth Lp(a) and carotid artery intima-media thickness (and carotid plaques in YFS). There were 1979 individuals in the YFS and 252 individuals in the BHS with data on both youth Lp(a) and carotid artery intima-media thickness measured at the mean age of 33–34 years. In a multivariable model for pooled data, youth LDL-cholesterol and body mass index were strongly associated with carotid artery intima-media thickness (both p<10E-14), whereas no association was detected between Lp(a) and carotid artery thickness (p=0.73 when Lp(a) was modelled as a binary variable using cut-point of 30 mg/dL and p=0.61 when Lp(a) was modelled as a continuous log-transformed variable). Similarly, when the cohorts were analysed separately, no association was observed between elevated Lp(a) and carotid artery intima-media thickness. Furthermore, no association was seen between elevated Lp(a) and distinct carotid artery plaques[43] that were detected in 64 YFS participants: 7 individuals (3.5%) had a plaque in the high Lp(a) group (7/203); and 57 individuals (3.2%) in the low Lp(a) group (57/1776). Information on carotid artery plaques was not available in the BHS data.

Discussion

We examined whether Lp(a) measured in youth would help to identify individuals at increased risk for adult ASCVD. In the YFS, the Lp(a) level was first measured in 1986 when the participants were aged 9 to 24 years. We found that individuals with high Lp(a) level in youth (defined as Lp(a) ≥ 30 mg/dL) had about 2 times greater risk of developing ASCVD compared to individuals with low Lp(a). This result was replicated in data from the BHS where Lp(a) were measured using similar methodology in serum samples collected in 1984–85 in children aged 8–17 years of age[40].

In the YFS data, high Lp(a) was similarly associated with coronary heart disease events and non-coronary atherosclerotic cardiovascular events, and these associations were not attenuated when simultaneously controlled for youth LDL-cholesterol, body mass index, systolic blood pressure and smoking. In multivariable models, the effects of elevated Lp(a) and LDL-cholesterol were additive: individuals exposed to both high Lp(a) and high LDL-cholesterol levels in youth had about 4 times greater risk of developing a cardiovascular outcome during the follow-up than the non-exposed reference group. The link between youth Lp(a) and subsequent ASCVD was anticipated given that Lp(a) is a

causal cardiovascular risk factor[4–6] and because its levels are established at a very young age, and remain stable over a lifetime irrespective of lifestyle changes[15].

The European Society of Cardiology and the European Atherosclerosis Society recommend universal screening of Lp(a) in all adults at least once during their lifetime[44]. As such, there has been growing interest in screening beginning at an early age, but specific recommendations for the assessment of Lp(a) levels in youth are limited, and universal screening is not recommended. The National Lipid Association recommends measuring Lp(a) in individuals under the age of 20 years with familial hypercholesterolemia, with family history of first-degree relatives with premature atherosclerotic cardiovascular disease, with an unknown cause of ischemic stroke, or with a parent or sibling found to have an elevated Lp(a) level[45]. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommends measuring Lp(a) in youth with an ischemic or hemorrhagic stroke or youth with a parental history of cardiovascular disease not explained by classical risk factors[39]. One reason why the guidelines do not recommend measuring Lp(a) as part of routine lipid screening is the lack of knowledge of whether elevated Lp(a) levels detected at a young age predict cardiovascular outcomes later on in adulthood. The data from the YFS and BHS reported herein suggest that an elevated Lp(a) level identified at young age is a sign of substantially increased future risk for early-onset ASCVD.

Therapeutic interventions to lower Lp(a) levels have been developed, and ongoing studies will clarify whether lowering Lp(a) levels is safe and leads to clinical benefits[46]. It is unlikely, however, that the newly developed pharmaceuticals would have a major role in the treatment of most children and adolescents with elevated Lp(a) levels. Analogously, pharmaceutical therapies using statins to lower LDL-cholesterol are only reserved for special high-risk pediatric populations, such as children with familial hypercholesterolemia[47]. Thus, even if in theory, effective pharmaceutical lowering of causal risk factors initiated in early life would likely lead to the substantial reduction of cardiovascular diseases, such a strategy is not feasible due to potential ethical and health issues related to the long-term use of pharmaceuticals targeted at healthy children. Therefore, the interventions to prevent risk factors for cardiovascular disease beginning in childhood in larger population segments need to concentrate on intervening on diet and lifestyle. The evidence from existing prevention programs indicate that lifestyle and dietary counselling actions have the potential to promote cardiovascular health beginning from childhood[31,48]. Although Lp(a) levels cannot be modified by lifestyle or diet, the guidelines note that if an elevated level of Lp(a) is detected in youth, it is important to emphasize early and lifelong adoption of a heart-healthy lifestyle by the child and family members[45].

Mechanisms relating Lp(a) to ASCVD are unknown. The LDL-like particle containing apolipoprotein B may enter the arterial wall and initiate the formation of atherosclerotic lesions[49]. In addition, the presence of oxidized phospholipids on apolipoprotein (a) has been suggested to constitute a potential mechanism leading to atherosclerosis[46]. Furthermore, given its homology to plasminogen, apolipoprotein (a) has been suggested to contribute to cardiovascular diseases by promoting thrombosis[50]. It has also been suggested that the accumulation of Lp(a) at sites of vascular injury could be a primary mechanism causing

cardiovascular events given the capacity of Lp(a) to bind fibrin or glycosaminoglycans[5]. We previously examined in detail the association of Lp(a) with early vascular phenotypes, including carotid artery intima-media thickness and brachial artery endothelial function in the YFS using conventional and Mendelian randomization analysis, and found no support for early vascular effects of increased Lp(a) levels[10]. In the present analyses, we re-analyzed the YFS data together with the BHS data, and specifically examined the links between youth exposure to high Lp(a) levels and carotid artery intima-media thickness measured in adulthood. In the pooled data, we could demonstrate the very well-documented[26,27] strong link between youth LDL-cholesterol and adult carotid artery intima-media thickness, but found virtually no association between elevated Lp(a) and carotid artery intima-media thickness. Other studies have also failed to demonstrate a link between Lp(a) and indicators of pre-clinical atherosclerosis[9,11]. In fact, referring to Lp(a) as an atherogenic lipoprotein has been criticized, because such labelling gives a false impression that its atherogenicity would be well documented[51]. For example, Klein et al.[12] observed that high Lp(a) was an independent predictor of carotid artery occlusion, but not of carotid plaque area. Similarly, in the Bruneck study, high Lp(a) was associated with the risk of advanced carotid atherosclerosis (incident carotid stenosis), but not with incident early carotid atherosclerosis[52]. Most recently, Mehta et al.[14] reported that high Lp(a) level and high coronary calcium score were both independently associated with cardiovascular outcomes in the participants of the Multi-Ethnic Study of Atherosclerosis, but found no direct association between Lp(a) and coronary calcium score. Together, these observations suggest the importance of other potential pathological mechanisms of Lp(a), such as antifibrinolytic and pro-inflammatory properties, rather than the initiation of atherosclerosis. This may have important clinical implications for those with elevated Lp(a) indicating the need to focus on the prevention of thrombosis. In line with this hypothesis, patients with elevated Lp(a) have been reported to benefit from prolonged antiplatelet therapy after coronary intervention procedures[53].

Limitations

First, the Lp(a) measurements done in the 1980s in the YFS and BHS used a similar but not identical immunoassay method that has been calibrated in milligrams per deciliter of total Lp(a) mass. This assay calibration assumes that the mass of the individual Lp(a) components is constant in all individuals. At present, this is considered inaccurate because of the extreme size variability of apolipoprotein(a). It is currently recommended that Lp(a) concentrations should be measured using isoform-insensitive assays reported in nanomoles per liter[54]. A simple conversion from mg/dL to nanomoles per liter is not adequate because the Lp(a) mass does not reflect accurately the number of Lp(a) particles, and hence not reported here. Furthermore, in YFS, the methods for adult measurements that were used in the imputations were not identical across the study years. It has been reported that the levels of commercially available immunoassays may vary by as much as 32%[55]. Therefore, direct comparisons of the levels between cohorts (YFS vs. BHS), or between the study years in YFS may not be possible. For example, our observation suggesting a direct correlation with aging in the YFS (Table S1) could be biased if the levels between subsequent study years are not comparable. However, in YFS, the mean levels of Lp(a) do not substantially differ

between the study years (11.38–14.71 mg/dL), and importantly, the repeated Lp(a) values showed strong tracking. The Spearman's rank order correlation coefficients between study years varied between r=0.86–0.96. Thus, despite potential heterogeneity in the absolute levels, the rank order of individuals based on their Lp(a) levels remains similar in different study years. This gives reassurance that the imputed estimations of the missing year 1986 Lp(a) values in those individuals with at least one measured Lp(a) value can be considered reliable. Second, we calculated LDL-cholesterol using the Friedewald's formula that does not take into account the presence of Lp(a), which is associated with LDL-cholesterol. It has previously been estimated that the cholesterol content of Lp(a) is about 30%[56]. However, it was recently demonstrated that actually the percent of cholesterol carried by lipoprotein(a) ranges from 6% to 57% among individuals[57], and that the use of historical 30% value should be discontinued for estimating corrected LDL-cholesterol because of the high likelihood of error at the individual level[57]. Therefore, we have not made any attempt to correct the LDL-cholesterol values reported here for the Lp(a)-cholesterol. Third, the YFS and BHS were the only i3C cohorts with the available data to link Lp(a) levels measured in youth to adult-onset ASCVD. The number of cases with verified ASCVD is still limited in these cohorts as the participants are now reaching only into their 50s and 60s, a time when incident events are beginning to increase. In both cohorts, the risk estimates associated with high youth Lp(a) levels were numerically consistent, although the association did not reach the conventional level of statistical significance in the BHS cohort. Despite limited data, however, the consistency of our findings from two cohorts with the previous evidence from Mendelian randomization studies makes a strong case for inferring that Lp(a) in youth is materially associated with the risk of future ASCVD. Fourth, in the BHS data, the association between high Lp(a) and ASCVD was only seen in White participants. In Black individuals, the number of cases in the Lp(a) strata were too low to make meaningful assessments. However, the Multi-Ethnic Study of Atherosclerosis has demonstrated that elevated Lp(a) is a strong risk factor for coronary heart disease also in Black individuals[14]. Both BHS and the National Health and Nutrition Examination Survey has demonstrated that Lp(a) levels are on average higher in Black as compared to White children[40,58]. Finally, the ultrasound techniques used in this study do not provide information about atherosclerotic plaque characteristics that may mediate the adverse effects of Lp(a), such as necrotic core composition, fibrous cap characteristics, and intraplaque hemorrhage. Detailed imaging studies are needed to reveal the exact mechanisms how Lp(a) contributes to cardiovascular events.

In summary, these data from the YFS and BHS demonstrate that elevated Lp(a) identified in young White individuals is related to higher future risk for early-onset ASCVD. Complete lack of association with carotid artery intima-media thickness, and carotid plaques in YSF, which are strongly related to other youth risk markers, such as LDL-cholesterol and body mass index, may suggest that elevated Lp(a) levels do not confer cardiovascular risk by contributing to early pre-clinical vasculopathy.

Supplementary Material

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Non-standard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
BHS	the Bogalusa Heart Study
***i*3C**	International Childhood Cardiovascular Cohort
Lp(a)	lipoprotein (a)
YFS	the Cardiovascular Risk in Young Finns Study

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Clinical Perspective

What is new?

- Elevated Lp(a) (≥30 mg/dL) identified in youth was related to higher future risk for early-onset atherosclerotic cardiovascular disease in White participants of the Young Finns and Bogalusa Heart studies.
- Individuals exposed to both high Lp(a) and high LDL-cholesterol levels had about 4 times greater risk of developing an atherosclerotic cardiovascular outcome during the follow-up than the non-exposed reference group.

What are the clinical implications?

- These data suggest that Lp(a) measured in youth would help to identify individuals at higher risk for future atherosclerotic cardiovascular disease.
- Although Lp(a) levels cannot be modified by lifestyle or diet, if an elevated level of Lp(a) is detected in youth, it is important to emphasize lifelong adoption of a heart-healthy lifestyle.

Table 1.

Age and sex adjusted hazard ratios of cardiovascular events in mid-adulthood in relation to youth* Lp(a) level in the Young Finns Study.

Datasets	Hazard Ratio (95%)	P-value
Non-imputed data		
Binary Lp(a)		
Lp(a) < 30 mg/dL		
Lp(a) ≥ 30 mg/dL	2.06 (0.96–4.42)	0.064
Continuous $\log_e$-Lp(a)		
Per SD change	1.35 (1.03–1.77)	0.032
Partly imputed data		
Binary Lp(a)		
Lp(a) < 30 mg/dL		
Lp(a) ≥ 30 mg/dL	2.32 (1.75–2.89)	0.003
Continuous $\log_e$-Lp(a)		
Per SD change	1.31 (1.09–1.53)	0.016
Fully imputed data		
Binary Lp(a)		
Lp(a) < 30 mg/dL		
Lp(a) ≥ 30 mg/dL	1.96 (1.35–2.57)	0.011
Continuous $\log_e$-Lp(a)		
Per SD change	1.25 (1.03–1.47)	0.030

* The participants were aged 9 to 24 years in 1986 when Lp(a) measurements were introduced.

Non-imputed data include 46 cases and 2409 non-cases.

Partly imputed data (20 datasets) include 74 cases and 3097 non-cases.

Fully imputed data (20 datasets) include 95 cases and 3484 non-cases.

Table 2.

Multivariable model of youth risk variables predicting cardiovascular events based on fully imputed data including 95 cardiovascular cases and 3483 non-cases in the Young Finns Study.

	Hazard Ratio	P-value
Lp(a) < 30 mg/dL vs. ≥ 30 mg/dL	1.77 (1.17–2.37)	0.035
LDL-cholesterol	1.26 (1.06–1.47)	0.025
Body mass index	1.25 (1.06–1.43)	0.022
Smoking (no vs. yes)	1.58 (1.16–2.00)	0.033
Systolic blood pressure	1.13 (0.86–1.40)	0.36

Models were additionally adjusted for age and sex. LDL-cholesterol and body mass index represent average values between ages 6–18 years and are modelled as standardized continuous variables (risk ratios indicate change per one standard deviation). For LDL-cholesterol one standard deviation equals 26 mg/dL (0.66 mmol/L); for body mass index one standard deviation equals 2.4 kg/m^2; for systolic blood pressure one standard deviation equals 6.4 mmHg.

Pooled estimates are based on 20 imputed datasets.

Table 3.

Youth Lp(a) and LDL-cholesterol values predicting cardiovascular events occurring in mid-adulthood in the Young Finns Study.

Lipid status in youth*	Hazard Ratio (95% confidence interval) †	p-value
Low Lp(a) and low LDL-cholesterol	reference	
High Lp(a) or high LDL-cholesterol	2.45 (1.89–3.00)	0.001
Both high Lp(a) and high LDL-cholesterol	4.30 (3.30–5.30)	0.00004

*Lp(a) level in 1986 when participants were aged 9 to 24 years. LDL-cholesterol status is an estimate of the cumulative exposure to LDL-cholesterol in childhood between ages 6 and 18 years. This is calculated for each individual based on the modelling of serial LDL-cholesterol measurements taken in study years 1980, 1983, 1986, 1989, 1992, 2001, 2007 and 2011.

†compared to reference.

Average number of cardiovascular cases and non-cases in the imputed datasets:

Low Lp(a) and low LDL-cholesterol (N=19/1684)

High Lp(a) or high LDL-cholesterol (N=61/1581)

High Lp(a) and high LDL-cholesterol (N=15/219)

Cut-points used: Lp(a) ≥ 30 mg/dL and LDL-c ≥ 130 mg/dL (3.36 mmol/L)

Models are additionally adjusted for age and sex.