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ORIGINAL RESEARCH ARTICLE

Lipoprotein(a) in Youth and Prediction of Major Cardiovascular Outcomes in Adulthood

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BACKGROUND: Elevated lipoprotein(a) [Lp(a)] is a common risk factor for cardiovascular disease outcomes with unknown mechanisms. 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 9 to 24 years of age were linked to adult ASCVD and carotid intima-media thickness in the YFS (Cardiovascular Risk in Young Finns Study), in which 95 of the original 3596 participants (2.7%) recruited as children have been diagnosed with ASCVD at a median of 47 years of age. Results observed in YFS were replicated with the use of data for White participants from the BHS (Bogalusa Heart Study). In BHS, 587 White individuals had data on youth Lp(a) (measured at 8–17 years of age) and information on adult events, including 15 cases and 572 noncases. Analyses 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 ≈2 times greater risk of developing adult ASCVD compared with nonexposed individuals (hazard ratio, 2.0 [95% CI, 1.4–2.6]). Youth risk factors, including Lp(a), low-density lipoprotein 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 with nonexposed individuals. When also adjusted for low-density lipoprotein 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 with nonexposed individuals. No association was detected between youth Lp(a) and adult carotid artery thickness in either 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-media thickness.

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

Editorial, see p 32

Lipoprotein(a) [Lp(a)] is a lipoprotein particle that was 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

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Clinical Perspective

What Is New?

- Elevated lipoprotein(a) [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 low-density lipoprotein cholesterol levels had ≈4 times greater risk of developing an atherosclerotic cardiovascular outcome during follow-up than the nonexposed 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.

Nonstandard Abbreviations and Acronyms

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

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 in both 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 YFS (Cardiovascular Risk in Young Finns Study) is one of the long-standing cohort studies initiated in the 1970s and 1980s to examine the determinants of cardiovascular disease in children that constitute the International Childhood Cardiovascular Cohort (*i*3C) Consortium.[24,25] During the past 2 decades, the *i*3C cohorts have provided a large evidence base documenting the associations between childhood risk factor exposures and adult preclinical atherosclerotic vascular phenotypes.[26–31] As participants in these cohorts aged, evidence linking childhood risk factors to actual adult ASCVD events emerged. 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 BHS (Bogalusa Heart Study), another *i*3C Consortium cohort. Lp(a) levels were measured in subsets of these cohorts in the mid-1980s with a similar methodology. To provide mechanistic insights, we 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 low-density lipoprotein (LDL) cholesterol, smoking, body mass index, and systolic blood pressure.[26–28]

METHODS

Anonymized data are available on reasonable request from the YFS research group.[33] 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).[34] Children 3, 6, 9, 12, 15, and 18 years of age were chosen from the population register from the 5 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 9 to 24 years of age by radioimmunoassay. Lp(a) levels have been also measured in adulthood, including in year 2001 (n=2281; age, 24–39 years), in year 2007 (n=2204; age, 35–45 years), and in year 2011 (n=2044; age, 39–49 years). Different methods were used in 2001[35] and 2007/2011. Adulthood Lp(a) data were used to impute missing youth Lp(a) values [details of Lp(a) methods are provided in the Supplemental Material].

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 in all follow-up studies. LDL cholesterol was estimated by using the Friedewald formula in individuals with triglycerides <4.0 mmol/L.[36] At all study phases, 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 estimated participant-specific curves for cardiovascular risk factors by mixed-model regression splines.[37] 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 6 to 18 years of age were used here primarily to capture youth exposure. We also conducted sensitivity analyses by using the area-under-the-curve variables that were defined for 6 to 24 years of age and by using single covariate values measured cross-sectionally in the year 1986. All of 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 a mean of 0 and SD of 1. Smoking exposure was queried throughout the follow-up time. Youth smoking status was dichotomized into daily smokers and nonsmokers, defined as current daily smoking (yes/no) at baseline or in any of the follow-up studies when the participants were 12 to 24 years of age. Details of the methods are provided in the Supplemental Material.

Cardiovascular Disease Outcomes

Between 2015 and 2019, the *i*3C Consortium conducted a coordinated study to locate and survey original cohort participants for fatal and nonfatal 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 ≥1 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 among those whose Lp(a) values had been measured in 1986 at 9 to 24 years of age. This subset included 46 cases and 2409 noncases. Second, we imputed missing year 1986 Lp(a) values for individuals who had participated in later examinations and had at least 1 Lp(a) value available from study years 2001, 2007, or 2011. This subset included 74 cases and 3096 noncases. Last, we imputed missing year 1986 Lp(a) values for all participants. The fully imputed data included 95 cases and 3484 noncases.

Data were imputed with 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% CIs to determine the associations between youth Lp(a) status and adult ASCVD outcomes. We used the procedure mianalyze and the Rubin rule for combining replications (details of the imputations are provided in the Supplemental Material). We report the median of the *P* values from the overall significance tests from the analyses on the imputed data sets.[38] All analyses were conducted accounting for competing risks. We used subdistribution hazard models in which deaths resulting from noncardiovascular causes were considered competing events and handled with the Fine-Gray subdistribution hazard model.[39]

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, which is considered to be 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 also used the continuous natural log-transformed Lp(a) variable to estimate how a 1-SD increase in Lp(a) level is associated with cardiovascular risk. The possibility of a nonlinear 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 3 groups using cut points of 30 mg/dL for Lp(a) and 130 mg/dL (3.36 mmol/L) for LDL cholesterol.[40] Individuals with low Lp(a) and low LDL cholesterol in youth were assigned as the reference group. The reference group was compared with individuals with either high Lp(a) or high LDL cholesterol and with individuals with both high Lp(a) and high LDL cholesterol.

Replication in an Independent Cohort

Replication of the results was performed with the use of data from the BHS, in which Lp(a) measurements were completed during 1985 to 1986 between 8 and 17 years of age.[41] The BHS is a community-based, long-term investigation in Bogalusa, Louisiana, that began in 1973 and focuses on the early natural history and risk factors for cardiovascular disease from childhood. A series of cross-sectional surveys was conducted and repeated every 2 to 3 years, allowing a longitudinal analysis in a cohort setting. Details of the study design and recruitment of participants were described previously[42] and are described briefly in the Supplemental Material. In the 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 the 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 White BHS participants, including 15 cases and 572 noncases (the result observed in the YFS was replicated with the use of data for White participants in the BHS because the YFS included only White participants). Lp(a) was determined

by an ELISA using sheep polyclonal monospecific antibodies against purified human Lp(a) (Biopool AB, Umeå, Sweden).[41] To test the hypothesis that Lp(a) is linked to preclinical vascular damage, we examined the associations between youth Lp(a) and carotid artery intima-media thickness that was measured in both cohorts during adulthood examinations as previously described in detail.[26–28,43] Characteristics of the YFS and BHS participants are shown in Table S1. There were 2455 individuals in the YFS and 587 in the 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 the cut point of 30 mg/dL are shown in Table S2.

RESULTS

In the YFS, by the end of 2018, 95 individuals (2.7%) had been diagnosed with ≥1 cardiovascular outcomes. The mean age of the participants was 48.4 years (range, 41–56 years). The median age at cardiovascular diagnoses was 47 years (range, 31–56 years). Most diagnoses were coronary artery disease (n=58, 61%). The noncoronary 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 a high Lp(a) level in youth had ≈2 times greater risk of developing adult ASCVD outcome compared with nonexposed individuals: There were 8 cases (3.2%) among those exposed to high Lp(a) [defined as Lp(a) ≥30 mg/dL; n=247] and 38 cases (1.7%) among those not exposed (n=2208). When Lp(a) was modeled as a continuous variable, the risk increased ≈30% per 1-SD increase in Lp(a) level. These effects were similarly seen in nonimputed 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% CI, 1.3–2.9]) and noncoronary atherosclerotic outcomes (hazard ratio, 1.8 [95% CI, 0.8–2.8]).

We found no evidence for a nonlinear relation between Lp(a) and cardiovascular outcomes; the *P* value for the second-order interaction term for log-Lp(a)×log-Lp(a) in the Cox proportional hazard was nonsignificant (*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).

In the multivariable model, high Lp(a) (hazard ratio, 1.77), LDL cholesterol, body mass index, and smoking were all independently associated with higher risk (Table 2). Every 1-SD 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 (Table S3).

Table 1. Age- and Sex-Adjusted Hazard Ratios of Cardiovascular Events in Midadulthood in Relation to Youth Lp(a) Level in the Young Finns Study

Data sets	Hazard ratio (95% CI)	*P* value
Nonimputed 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 1-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 1-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 1-SD change	1.25 (1.03–1.47)	0.030

Participants were 9 to 24 years of age in 1986 when Lp(a) measurements were introduced. Nonimputed data include 46 cases and 2409 noncases. Partly imputed data (20 data sets) include 74 cases and 3097 noncases. Fully imputed data (20 data sets) include 95 cases and 3484 noncases. Lp(a) indicates lipoprotein(a).

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

Replication in the BHS Data

In the BHS, 587 White individuals had data on both Lp(a) and events, including 15 cases and 572 noncases. There were 7 cases (4.7%) among those exposed to high Lp(a) [defined as Lp(a) ≥30 mg/dL; n=150] and 8 cases (1.8%) among those not exposed (n=437).

In Black individuals, the number of cases with Lp(a) data was too small 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 noncases. There were only 2 cases (1.2%) among those exposed to high Lp(a) [defined as Lp(a) ≥30 mg/dL; n=167] and 10 cases (3.7%) among those not exposed (n=270).

Table 2. Multivariable Model of Youth Risk Variables Predicting Cardiovascular Events Based on Fully Imputed Data Including 95 Cardiovascular Cases and 3483 Noncases in the Young Finns Study

Variable	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 also adjusted for age and sex. LDL cholesterol and body mass index represent average values between 6 and 18 years of age and are modeled as standardized continuous variables (hazard ratios indicate change per 1 SD). For LDL cholesterol, 1 SD equals 26 mg/dL (0.66 mmol/L); for body mass index, 1 SD equals 2.4 kg/m^2; and for systolic blood pressure, 1 SD equals 6.4 mm Hg. . Pooled estimates are based on 20 imputed data sets. LDL indicates low-density lipoprotein; and Lp(a), lipoprotein(a).

In the 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 with nonexposed 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]).

Analyses in Pooled Data

In further analyses, we pooled the YFS (nonimputed) and BHS data sets (White individuals). The pooled data included 2981 noncases and 61 cases. There were 15 cases (3.8%) among those exposed to high Lp(a) [defined as Lp(a) ≥30 mg/dL; n=397] and 46 cases (1.5%) among those not 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 with nonexposed 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 with nonexposed individuals. In the multivariable model, every 1-SD 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

Last, to provide mechanistic insights into 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 a mean of 33 to 34 years of age. 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 modeled as a binary variable using a cut point of 30 mg/dL and *P*=0.61 when Lp(a) was modeled as a continuous log-transformed variable]. Similarly, when the cohorts were analyzed 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[44] that were detected in 64 YFS participants: 7 individuals (3.5%) in the high Lp(a) group (7 of 203) and 57 individuals (3.2%) in the low Lp(a) group (57 of 1776) had plaque. Information on carotid artery plaque was not available in the BHS data.

Table 3. Youth Lp(a) and LDL Cholesterol Values Predicting Cardiovascular Events Occurring in Midadulthood in the Young Finns Study

Lipid status in youth*	Hazard ratio (95% CI)†	*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

Average number of cardiovascular cases and noncases in the imputed data sets: low Lp(a) and low LDL cholesterol, n=19 of 1684; high Lp(a) or high LDL cholesterol, n=61 of 1581; and high Lp(a) and high LDL cholesterol, n=15 of 219. Cut points used: Lp(a) ≥30 mg/dL and LDL cholesterol ≥130 mg/dL (3.36 mmol/L). Models are also adjusted for age and sex. LDL indicates low-density lipoprotein; and Lp(a), lipoprotein(a).

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

†Compared with reference.

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 9 to 24 years of age. We found that individuals with high Lp(a) level in youth [defined as Lp(a) ≥30 mg/dL] had ≈2 times greater risk of developing ASCVD compared with individuals with low Lp(a). This result was replicated in data from the BHS in which Lp(a) was measured with a similar methodology in serum samples collected in 1984 to 1985 in children 8 to 17 years of age.[41]

In the YFS data, high Lp(a) was similarly associated with coronary heart disease events and noncoronary 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 ≈4 times greater risk of developing a cardiovascular outcome during follow-up than the nonexposed 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 the lifetime regardless 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.[45] Therefore, 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 <20 years of age with familial hypercholesterolemia, with a family history of first-degree relatives with premature ASCVD, with an unknown cause of ischemic stroke, or with a parent or sibling found to have an elevated Lp(a) level.[46] 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 classic risk factors.[40] 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 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.[47] 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 reserved for special high-risk pediatric populations such as children with familial hypercholesterolemia.[48] Thus, even if, in theory, effective pharmaceutical lowering of causal risk factors initiated in early life would likely lead to a substantial reduction of cardiovascular diseases, such a strategy is not feasible because of the potential ethical and health issues related to the long-term use of pharmaceuticals targeted at healthy children. Therefore, interventions to prevent risk factors for cardiovascular disease beginning in childhood in larger population segments need to concentrate on intervening on diet and lifestyle. Evidence from existing prevention programs indicates that lifestyle and dietary counseling actions have the potential to promote cardiovascular health beginning from childhood.[31,49] 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.[46]

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.[50] In addition, the presence of oxidized phospholipids on apolipoprotein(a) has been suggested to constitute a potential mechanism leading to atherosclerosis.[47] Furthermore, given its homology to plasminogen, apolipoprotein(a) has been suggested to contribute to cardiovascular diseases by promoting thrombosis.[51] 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 we found no support for early vascular effects of increased Lp(a) levels.[10] In the present analyses, we reanalyzed 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 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 preclinical atherosclerosis.[9,11] Therefore, referring Lp(a) as an atherogenic lipoprotein has been criticized because such labeling gives a false impression that its atherogenicity would be well documented.[52] 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.[53] Most recently, Mehta et al[14] reported that both high Lp(a) level and high coronary calcium score were independently associated with cardiovascular outcomes in the participants of the Multi-Ethnic Study of Atherosclerosis, but they 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 proinflammatory 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.[54]

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 with isoform-insensitive assays reported in nanomoles per liter.[55] A simple conversion from milligrams per deciliter to nanomoles per liter is not adequate because the Lp(a) mass does not accurately reflect the number of Lp(a) particles and hence is not reported here. Furthermore, in the YFS, methods for adult measurements 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%.[56] Therefore, direct comparisons of the levels between cohorts (YFS versus BHS) or between study years in the 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 the YFS, the mean levels of Lp(a) do not differ substantially between the study years (11.38–14.71 mg/dL), and it is important to note that the repeated Lp(a) values showed strong tracking. The Spearman rank-order correlation coefficients between study years varied between r=0.86 and r=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 1 measured Lp(a) value can be considered reliable. Second, we calculated LDL cholesterol using the Friedewald formula, which 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 ≈30%.[57] However, it was recently demonstrated that the percent of cholesterol carried by lipoprotein(a) actually ranges from 6% to 57% among individuals[58] and that the use of the historical 30% value should be discontinued for estimating corrected LDL cholesterol because of the high likelihood of error at the individual level.[58] Therefore, we have not made any attempt to correct the LDL cholesterol values reported here for Lp(a) cholesterol. Third, the YFS and BHS were the only *i*3C cohorts with 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 because the participants are now reaching 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 2 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 seen only in White participants. In Black individuals, the number of cases in the Lp(a) strata was too small 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 the BHS and the National Health and Nutrition Examination Survey have demonstrated that Lp(a) levels are on average higher in Black than in White children.[41,59] Last, 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 by which Lp(a) contributes to cardiovascular events.

Conclusions

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 the 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 preclinical vasculopathy.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Extended Methods

Extended Results

Tables S1 and S2

Figure S1

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