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Long-term tracking and population characteristics of lipoprotein (a) in the Cardiovascular Risk in Young Finns Study

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ABSTRACT

Background and aims: Lipoprotein (a) (Lp(a)) is a causal risk factor for cardiovascular diseases and its levels are under strict genetic control. Therefore, it is hypothesized that the concentration of Lp(a) remains stable throughout life. Finns have lower Lp(a) levels than central Europeans, but it is unknown whether there are differences within Finland, especially between the eastern and western parts of the country with known genetic duality and persistent differences in cardiovascular disease rates. We have examined the long-term stability of Lp (a) levels over 25 years in the Cardiovascular Risk in Young Finns Study (YFS), and the characteristics of individuals with different Lp(a) levels, including their geographical origin within Finland.

Methods: In YFS, the first large baseline examination was conducted in 1980 (baseline age, 3–18 years). Several follow-ups during the past 40 years have been conducted to investigate the determinants of cardiometabolic health. Lp(a) levels have been measured in study years 1986 (N = 2464, ages 9–24 years), 2001 (N = 2281, ages 24–39 years), 2007 (N = 2204, ages 35–45 years) and 2011 (N = 2044, ages 39–49 years). Tracking of Lp(a) was estimated by calculating Spearman's rank order correlations between the study years, and by cross-tabulating how many individuals diagnosed with either elevated or non-elevated Lp(a) levels in 1986, 2001 and 2007 remained in the same category in the latest follow-up in 2011.

Results: Spearman's correlation coefficients varied between r = 0.84–0.96. Most individuals (87–94%) who had a high Lp(a) level (>30 mg/dl) in any of the previous study years had a high level also in 2011. On average, the median Lp(a) levels were consistently ~20% higher in the individuals originating from eastern Finland compared to those from western Finland, but there were no differences in the distribution of known genetic determinants between eastern and western Finns that would have explained the observed difference.

Conclusions: These data confirm that Lp(a) levels remain very stable over the life-course. In line with the genetic duality between eastern and western parts of Finland, we observed about 20% higher Lp(a) levels in individuals originating from eastern Finland compared to those originating from western Finland.

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1. Introduction

Lipoprotein (a) (Lp(a)) is a lipoprotein synthetized by the liver and composed of one molecule of LDL like particle containing apolipoprotein-B and one of apolipoprotein(a) linked by a disulfide bridge [1]. Lp(a) levels are genetically determined and many-fold differences have been reported between ethnicities [2]. The physiological role of Lp(a) is unknown, but elevated Lp(a) levels associate with increased risk of atherosclerotic cardiovascular disease outcomes, such as coronary heart disease, myocardial infarction, ischemic stroke, and aortic valve calcification [3–5]. Recently, there has been renewed interest in Lp(a) because it appears to be a causal risk factor and independent of other lipid markers [6]. The causal role of Lp(a) in the etiology of these outcomes has been demonstrated in genetic studies applying the Mendelian randomization technique (reviewed in Refs. [1,3,7]). Therapeutic interventions to lower Lp(a) levels have been developed, but it is still unknown whether Lp(a) lowering leads to clinical benefits [8]. New compounds with the potential to lower Lp(a) very effectively include RNA-based approaches [9]. An antisense oligonucleotide that inhibits the production of apolipoprotein(a) in hepatocytes, the major source of plasma Lp(a), has been shown to induce up to 80% reductions in the levels of Lp(a) in patients with cardiovascular disease [10]. Ongoing studies will clarify whether lowering Lp(a) levels is safe and can reduce the risk of atherosclerotic cardiovascular outcomes. Distribution of Lp(a) is often highly skewed and large proportion of individuals have very low or nearly undetectable levels of Lp(a). Several population studies have linked low concentrations of Lp(a) with increased risk of type 2 diabetes [11], and there is evidence that low Lp(a) levels correlate with increased risk of fatty liver disease [12]. The mechanisms behind these associations are unclear.

Finns have about 50% lower Lp(a) levels compared to Central Europeans [13,14]. This is partly explained by the differences in the distributions of certain *LPA* gene variants and Lp(a) isoforms [14]. However, the distribution of Lp(a) levels according to the geographic origin within Finland is unknown. The question is relevant because previous studies have documented pronounced genetic differences between individuals originating from north-eastern and south-western parts of Finland [15–17] that are larger than between some nations in Europe [18]. Finland is also characterized with distinct regional differences in cardiovascular event rates, which are more frequent in the north-eastern compared to the south-western parts of the country [19]. Due to reductions in the levels of smoking, serum total cholesterol and blood pressure, there has been marked improvement in cardiovascular health in the whole country during the past decades and narrowing of the regional differences. According to the latest national statistics (updated in 2018), the incidence of coronary heart disease was about 1.5 times greater in the north-eastern as compared to the south-western parts of the country (National Institute for Health and Welfare, https://thl.fi), and reasons for this difference are not completely understood.

The European Society of Cardiology and the European Atherosclerosis Society recommend universal Lp(a) testing of all adults, at least once during their lifetime [20]. This is based on the current understanding that the levels remain largely stable throughout life because they are under strong genetic control. The stability or tracking of Lp(a) levels have previously been studied, both in children and adults [21–25]. These earlier results have shown that Lp(a) levels are stable, at least up to five years [24]. Nevertheless, the natural variability of Lp(a) levels over the life-course has not been studied in detail. For example, it is unknown how well Lp(a) measurements done in adolescence and young adulthood predict values decades later in mid-adulthood.

The present analyses was undertaken to examine the serially measured Lp(a) levels in the ongoing Cardiovascular Risk in Young Finns Study cohort (YFS) [26]. We examined the long-term stability of Lp(a) levels over 25 years, and the characteristics of individuals with different Lp(a) levels, including their geographical origin within Finland.

2. Patients and methods

The YFS is a prospective multicenter study from Finland initiated in the late 70s. The first large baseline examination was conducted in 1980 (baseline age, 3–18 years) [26]. Children (N = 4320) aged 3, 6, 9, 12, 15, and 18 years were haphazardously chosen from the population register from the 5 Finnish university cities and their surrounding rural communities. One aim of the YFS was to examine regional differences in the distribution of risk factors. Therefore, an equal number of participants were recruited from the south-western Finland (cities of Turku, Tampere and Helsinki, and rural communities in their vicinity) and north-eastern parts of the country (cities of Kuopio and Oulu, and rural communities in their vicinity) [27,28]. In addition to the participants' birth origin, we assessed the effect of family origin by categorizing the study population according to their grandparents' birthplace [29].

Several follow-ups during the past 40 years have been conducted to investigate the determinants of cardiometabolic health. Lp(a) levels have been measured in study years 1986 (N = 2464, ages 9–24 years), 2001 (N = 2281, ages 24–39 years), 2007 (N = 2204, ages 35–45 years) and 2011 (N = 2044, ages 39–49 years).

2.1. Assessment of Lp(a)

In 1986, Lp(a) was assessed by radioimmunoassay, according to the same principles as described for an immunoenzymatic assay using research kits from Pharmacia Diagnostics, Uppsala, Sweden [30]. The detection limit for Lp(a) was 3.0 mg/dL. Thirty-five percent of the values were under the detection limit in 1986.

Year 2001 plasma samples were stored at −70 °C, and assessed in 2015 by using a sandwich ELISA method described by Kronenberg et al. [31] with minor modifications. The same samples were used to determine apolipoprotein(a) isoforms by western blot [31] in the same laboratory (Institute of Genetic Epidemiology, Medical University of Innsbruck, Austria).

In 2007 and 2011, Lp(a) was measured using an immunoturbidimetric method (Lp(a)-HA reagent, Wako Chemicals GmbH, Germany) on an AU400 instrument (Olympus, Japan). The detection limit for this method is 1.0 mg/dl [32].

2.2. Definition of Lp(a) groups

At least one Lp(a) measurement was available for 3181 participants (there were 1209, 805, 575, 592 individuals with 4, 3, 2 and 1 measurements, respectively). The study population was categorized in four groups according to their Lp(a) level: 1) always less than 5 mg/dL (N = 1028, 32.3%); 2) 5-<30 mg/dL in one or more occasions (N = 1649, 51.8%); 3) 30-<50 mg/dL in one or more occasions (N = 314, 9.9%); and 4) ≥50 mg/dL in one or more occasions (N = 190, 6.0%). The cut-points 30 and 50 mg/dL were chosen because Lp(a) levels above these cut-points are considered being in the atherothrombotic range [33–35]. The mean and median Lp(a) levels in each study year across the Lp(a) groups are shown in Table 1. The distribution of Lp(a) is skewed in the YFS population, as shown in the histogram displaying the maximum values of each individual (Fig. 1.)

2.3. Genotyping

Lp(a) levels are mainly determined by the *LPA* gene locus, modifying genes outside the *LPA* locus include *APOE* and *PCSK9*. Especially, the APOE2 [36] genotype and the *PCSK9* loss-of-function mutation R46L (rs11591147) have been associated with lower Lp(a) concentrations [37]. Therefore, we used genome-wide genotyping data for evaluation of known *LPA* variants, including SNPs rs3798220, rs783147, rs143431368, rs41272114 and rs10455872, as well as *PCSK9* rs11591147 (loss-of-function mutation R46L) [14]. The genotyping and related quality control was done by using Illumina 670K Custom array in

Table 1
Geometric mean, mean (median) Lp(a) levels in the Lp(a) groups.

	<5 mg/dL	5-<30 mg/dL	30-<50 md/dL	≥50 mg/dL
Prevalence % (N)	32.3% (1028)	51.8% (1649)	9.9% (314)	6.0% (190)
Lp(a) levels:				
Year 1986 (ages 9 to 24)	2.9, 3.0 (2.8)	7.1, 8.8 (6.8)	25.8, 28.1 (29.3)	46.9, 51.3 (51.8)
Year 2001 (ages 24 to 39)	1.7, 2.1 (1.8)	7.9, 9.7 (7.9)	29.3, 31.0 (31.4)	52.6, 54.9 (52.1)
Year 2007 (ages 30 to 45)	1.9, 2.2 (2.0)	9.5, 11.2 (9.1)	31,7, 33.3 (33.6)	57.1, 60.1 (58.7)
Year 2011 (ages 34 to 49)	2.3, 2.6 (2.5)	10.0, 11.6 (9.8)	33.0, 34.4 (34.1)	58.0, 60.9 (59.3)

Lp(a) measurements were available for N = 2464 for study year 1986, N = 2281 for study year 2001, N = 2204 for study year 2007 and N = 2044 for study year 2011. At least one Lp(a) measurement was available for 3181 participants. The study population was categorized in four groups according to their Lp(a) level: 1) always less than 5 mg/dL; 2) 5-<30 mg/dL in one or more occasions; 3) 30-<50 mg/dL in one or more occasions; and 4) ≥50 mg/dL in one or more occasions.
In the whole population, the geometric means (95% confidence intervals) for Lp(a) were 6.8 mg/dL (6.5–7.0), 6.5 mg/dL (6.1–6.8), 7.6 mg/dL (7.2–8.0) and 8.4 mg/dL (8.0–8.8), for study years 1986, 2001, 2007 and 2011, respectively. Analysis of variance of log-transformed Lp(a) values between study years indicated that all pairwise comparisons differed at the level $p < 0.005$. The only exception was the pairwise comparison between study years 1986 and 2001 that differed at the level of $p = 0.15$.

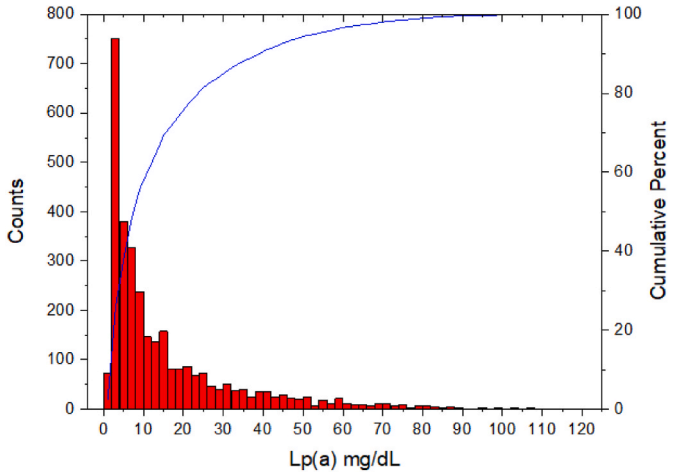

Fig. 1. Distribution of Lp(a) values in 3181 participants.
The maximum Lp(a) value for each individual is used.

Sanger Institute (UK) as previously described in detail [38]. Genotype imputation was performed using population-specific Sequencing Initiative Suomi as reference panel. APOE isoform genotypes were determined using TaqMan SNP assays for rs7412 and rs429358 as previously described [39].

2.4. Laboratory analyses

Venous blood samples were drawn after an overnight fast during the physical examination in each study year. Separated plasma or serum was frozen in aliquots at −70 °C and measured within weeks or months after the examination. Serum total cholesterol, triglycerides and glucose were measured using enzymatic methods. HDL-cholesterol was determined with the cholesterol reagent after precipitation of very low and low density lipoproteins. LDL-cholesterol was estimated using the Friedewald's equation [40]. Serum apolipoprotein-B and apolipoprotein-A1 concentrations were analyzed immunoturbidimetrically (Orion Diagnostica, Finland) on an AU400 analyzer (Olympus, Japan). Serum insulin was measured by an immunoassay and glycated hemoglobin in whole blood immunoturbidimetrically on an ARCHITECT ci8200 analyzer (Abbott Laboratories, Illinois, USA). Serum creatinine was measured photometrically (Creatinine reagent, Olympus, Ireland) on an AU400 analyzer (Olympus, Japan), and values were used to estimate glomerular filtration rate with the CKD-EPI formula.

2.5. Vascular phenotypes and liver fat

Vascular ultrasound measurements were done in 2001 and 2007 using Siemens Sequoia 512 ultrasound mainframes (Acuson, Mountain View, CA) equipped with 13.0 MHz linear array transducer as previously described in detail [41–43]. Carotid artery intima-media thickness was measured on far wall of the left common carotid artery and scanned for the presence of local plaques. To measure arterial elasticity, the left common carotid diameter was measured 10 mm proximal to the carotid bifurcation at least twice during end diastole and end systole. Ultrasound and concomitant brachial blood pressure measurements were used to calculate the carotid distensibility. To assess brachial artery flow-mediated endothelial-dependent dilation, the left brachial artery diameter was measured both at rest and during reactive hyperemia.

Liver fat was estimated with the similar ultrasound mainframes in 2011. The liver fat was scanned using 4.0 MHz adult abdominal transducers. A trained sonographer graded the liver fat status from the ultrasonographic images using five widely accepted criteria for fatty liver: (1) the liver-to-kidney contrast, (2) parenchymal brightness, (3) deep beam attenuation, (4) brightness of the vessel walls, and (5) visibility of the neck of the gallbladder. A binary outcome variable (normal liver versus fatty liver) was constructed based on the sonographer's clinical judgment of the image data.

2.6. Cardiovascular disease outcomes and type 2 diabetes

Linkages to national registries, including the Care Register for Health Care and the National Death Index, were used to ascertain atherosclerotic cardiovascular outcomes, including coronary artery disease, atherosclerotic cerebrovascular disease and peripheral artery disease. For all deaths, and registry-based cardiovascular events, all ICD-9 and ICD-10 codes in a record were evaluated, and any meeting the ICD code definition of study endpoints was considered a confirmed event, as previously detailed [44]. 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). Seventy individuals with data on Lp(a) concentration had been diagnosed with one or more cardiovascular event and were included in this analysis.

Participants were classified as having type 2 diabetes if they: (1) had a fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL); (2) or had a glycated hemoglobin level of ≥6.5% (48 mmol/mol); (3) or reported or were identified from the national Drug Imbursement Registry of receiving oral hypoglycemic agents and/or insulin injections and did not have type 1 diabetes mellitus; or (4) reported a history of physician-diagnosed type 2 diabetes. Diabetes status was available for 2774 participants, 111 individuals with data on Lp(a) phenotype had been diagnosed with type 2 diabetes phenotype and were included in this analysis.

2.7. Other variables

Height and weight were measured. Body mass index was calculated using the formula: weight [kg]/(height [m]) [2]. Blood pressure was

Table 2
Characteristic of the study population according to the Lp(a) groups[a].

	<5 mg/dL	5-<30 mg/dL	30-<50 mg/dL	≥50 mg/dL	*p*-value[b]
Prevalence % (N)	32.3% (1028)	51.8% (1649)	9.9% (314)	6.0% (190)	
Age	41.1	41.3	41.7	41.5	
Males (%)	48%	48%	48%	46%	
Body mass index (kg/m2)	26.4 (5.2)	26.5 (4.8)	27.1 (5.8)	26.8 (5.0)	0.12
Apolipoprotein B (g/L)	1.05 (0.30)	1.04 (0.28)	1.10 (0.30)	1.14 (0.29)	2.85E-04
Apolipoprotein A1 (g/L)	1.59 (0.24)	1.59 (0.24)	1.60 (0.25)	1.61 (0.22)	0.36
Total cholesterol (mmol/L)	5.14 (0.94)	5.14 (0.94)	5.36 (0.99)	5.52 (0.98)	3.10E-06
LDL-cholesterol (mmol/L)	3.20 (0.81)	3.23 (0.82)	3.44 (0.84)	3.60 (0.89)	1.70E-08
HDL-cholesterol (mmol/L)	1.33 (0.34)	1.32 (0.34)	1.33 (0.33)	1.31 (0.29)	0.45
Triglycerides (mmol/L)	1.37 (1.23)	1.32 (1.32)	1.28 (0.76)	1.39 (0.97)	0.51
Systolic blood pressure (mmHg)	119 (14)	119 (14)	120 (14)	117 (13)	0.76
Education years	15.5 (3.7)	15.2 (3.5)	15.4 (3.6)	15.6 (3.4)	0.83
Daily smoking	14%	16%	13%	15%	
Alcohol drinks per day	0.8 (1.2)	0.8 (1.1)	0.9 (1.3)	0.8 (1.0)	0.35
Physical activity index	9.0 (1.8)	9.0 (1.9)	9.2 (2.0)	9.0 (1.9)	0.24
Dietscore[c]	13.7 (4.4)	13.5 (4.3)	13.8 (4.3)	14.4 (3.9)	0.10
Statin use	1.6%	2.4%	2.5%	5.8%	0.01
Hypertension medication	10.2%	9.4%	13.0%	11.8%	0.40
Birth origin (eastern Finland)	45%	50%	54%	49%	0.01
GFR ml/min	95 (13)	95 (12)	96 (13)	93 (12)	0.20
Isoform 1 (nKIV)[d]	31.6 (6.5)	29.8 (5.3)	24.0 (4.8)	20.6 (2.7)	<1.00E-14
LMW isoform carriers (%)	5.3%	6.8%	49.3%	87.9%	<1.00E-14
LPA rs3798220 (C allele)	1.3%	0.3%	1.6%	29.9%	<1.00E-14
LPA rs783147 (C allele)	63.8%	85.4%	87.3%	93.6%	<1.00E-14
LPA rs143431368 (C allele)	10.9%	3.4%	3.5%	0.6%	9.55E-11
LPA rs41272114 (T allele)	18.6%	5.3%	4.3%	4.4%	<1.00E-14
LPA rs10455872 (G allele)	1.1%	1.6%	37.4%	37.5%	<1.00E-14
PCSK9 R46L carriers[e]	8.8%	5.7%	10.4%	6.8%	0.64
APOE2 carriers	9.7%	8.3%	8.4%	6.4%	0.16
APOE4 carriers	37.3%	35.3%	34.2%	39.0%	0.80

The phenotype characteristics are from the study year in 2011, except for the Lp(a) isoforms that have been measured in samples collected in year 2001. GFR = Estimated glomerular filtration rate by the CKD-EPI formula.
LWM indicates low molecular weight isoform carriers, defined as those with ≤22 Kringle IV repeats.
KIV=Kringle IV.

[a] Based on the available data, the number of individuals varies between the Lp(a) groups; <5 mg/dL N = 505–1028; 5-<30 mg/dL N = 937–1649; 30-<50 mg/dL N = 165–314; ≥50 mg/dL N = 118-190.

[b] *p*-values are from age and sex adjusted linear or logistic regression models testing the trend across the 4 Lp(a) groups.

[c] Dietscore indicates the healthiness of the diet as recommended by dietary guidelines (range 1–27).

[d] Shorter isoform present.

[e] rs11591147: loss-of-function mutation, all carriers were heterozygous.

measured using a random zero sphygmomanometer. The average of three measurements was used in the analysis. Smoking habits, alcohol intake, physical activity, use of medications, and socioeconomic status (years of education in this report) were inquired with the use of questionnaires. Participants were asked to report their alcohol consumption of cans or bottles (1/3 l) of beer, glasses (12 cl) of wine and shots (4 cl) of strong alcohol per week. These data were used to calculate the intake of standard drinks (14 g of alcohol) per day. Diet was assessed by a validated 128-item food frequency questionnaire and a diet index (range 1–27) was calculated to estimate how well the diet reflects healthiness as recommended by guidelines. Healthy items included whole grain products, fruits and vegetables (excluding potatoes), fish, and nuts. Unhealthy items included red meat, soft drinks (with sugar), fried potatoes, sweet deserts and pastry products and candy.

2.8. Statistical methods

Standard statistical analyses were performed using Statistical Analysis System (SAS, version 9). We compared characteristics across the Lp (a) groups using linear or logistic regression. Relative risks and 95% confidence intervals were calculated using Poisson regression to determine the associations between Lp(a) status and selected outcomes. Spearman's non-parametric correlation coefficients were calculated to study the tracking of Lp(a) levels between study years. Because of the skewed distribution of Lp(a) non-parametric median test was used when comparing Lp(a) distributions at different study years between individuals originating from eastern and western Finland. Additionally, the distributions of geometric means were compared using parametric regression. The effects of age and sex, as well as geographical origin, on longitudinal log-transformed Lp(a) levels were studied with a linear mixed-effects model for repeated measures using compound symmetry covariance structure.

3. Results

The characteristics of the study population according to the four Lp (a) groups are shown in Table 2. The groups were similar in terms of age, sex, body mass index, years of education, smoking status, alcohol intake, physical activity, healthiness of diet, estimated glomerular filtration rate, blood pressure and antihypertensive medication use. The use of statin medication was more prevalent (5.8%) in the highest Lp(a) group than in the other groups (1.6–2.5%).

Serum apolipoprotein-B, total cholesterol and LDL-cholesterol were directly related to the Lp(a) group, while the distributions of apolipoprotein A-1, HDL-cholesterol and triglycerides were similar across the groups.

The median size of the smaller isoform (isoform 1) decreased linearly across the Lp(a) groups. At the same time, the prevalence of low molecular weight isoform carriers (≤22 Kringle IV repeats) increased across the Lp(a) groups, being 5.3% in the low (<5 mg/dL) and 87.9% in the

Table 3
Spearman's correlations coefficients between the Lp(a) measurements from different study years.

Study year	1986		2001		2007	
	Females	Males	Females	Males	Females	Males
1986						
2001	0.88	0.84				
2007	0.88	0.86	0.93	0.93		
2011	0.88	0.85	0.93	0.92	0.96	0.96
	Age group 1	Age group 2	Age group 1	Age group 2	Age group 1	Age group 2
1986						
2001	0.88	0.85				
2007	0.88	0.87	0.92	0.93		
2011	0.88	0.85	0.92	0.93	0.95	0.96

Age group 1, individuals aged 9, 12 and 15 years of age in 1986 (birth years 1977, 1974 and 1971). Age group 2, individuals aged 18, 21 and 24 years of age in 1986 (birth years 1968, 1965 and 1962).

high (≥50 mg/dl) group.

The distribution of known genetic determinants of Lp(a) showed that the studied *LPA* variants, including rs3798220, rs783147, rs143431368, rs41272114 and rs10455872, were strongly associated with Lp(a) levels.

3.1. Tracking of Lp(a)

Tracking of Lp(a) was estimated by calculating Spearman's rank order correlations between the study years. To study the effects of age and sex, we calculated the correlation coefficients separately for males and females, as well as for younger and older participants (individuals aged <18 vs. ≥18 years in 1986) (Table 3). Spearman's correlation coefficients varied between r = 0.84–0.96 indicating strong tracking of Lp(a) levels between the study years similarly in both sexes and age groups. The tracking correlation coefficients were also identical in those originating from eastern and western Finland and in those with ≤22 or >22 Kringle IV repeats (data not shown).

The tracking of Lp(a) was additionally analyzed by cross-tabulating how many individuals diagnosed with either elevated or non-elevated Lp(a) levels in 1986, 2001 and 2007 remained in the same category in the latest follow-up in 2011 (Table 4). Most individuals (87–94%) who had a high Lp(a) level (>30 mg/dl) in any of the previous study years had a high level also in 2011. Conversely, only a minority of individuals (3–6%) with a low Lp(a) level (<30 mg/dL) in previous examinations had a high level in 2011.

3.2. Regional differences between eastern and western Finland

The geographical origin at birth (western vs. eastern) differed between the Lp(a) groups: individuals with eastern origin were under-represented in the low Lp(a) group (<5 mg/dL) and over-represented in the high group (30–50 mg/dL) (Table 2).

A comparison of Lp(a) levels measured at different time points according to the geographical origin at birth is shown in Table 5. In every study year, the participants originating from eastern Finland had higher Lp(a) levels compared to those originating from western Finland. On average, the median Lp(a) levels were consistently ~20% higher and the geometric Lp(a) means were ~10% higher in the individuals originating from eastern Finland compared to those from western Finland.

All individual Lp(a) measurements (total of 14,384 data points from 3181 participants) obtained at different ages in individuals originating from eastern and western Finland are shown in Fig. 2. Median Lp(a) levels increased by age in both groups and were systematically higher across all ages in participants originating from eastern Finland compared to participants from western Finland.

The Lp(a) levels according to the participants' grandparents birth place are shown in Fig. 3. In every study year, the highest median Lp(a) levels were observed in individuals with all four grandparents originating from eastern Finland.

The median size of the smaller isoform (isoform 1) and the prevalence of low molecular weight isoform carriers (≤22 Kringle IV repeats) were similar in the participants originating from eastern and western Finland. In addition, there were no differences in the distribution of known genetic determinants between eastern and western Finns that would have explained the observed difference in Lp(a) phenotype distribution (data not shown).

3.3. Vascular phenotypes and cardiovascular events

The distribution of vascular phenotypes and cardiovascular events are shown in Table 6. Mean carotid artery intima-media thickness, carotid distensibility, brachial artery endothelium-dependent dilation, and the prevalence of carotid plaques were similar across the Lp(a) groups. On the other hand, the prevalence of cardiovascular events increased linearly across the Lp(a) groups. When low Lp(a) (<5 mg/dL) was treated as the reference group, the age and sex adjusted relative risk for a cardiovascular event was 1.8 (95% confidence interval 0.8 to 4.9) times greater in the Lp(a) group 30–50 mg/dL ($p = 0.16$), and 3.4 (95% confidence interval 1.6 to 7.5) times greater in the highest Lp(a) ≥50 mg/dL group ($p = 0.002$).

Table 4
Number of individuals detected with either elevated (≥30 mg/dL) or non-elevated (<30 mg/dL) Lp(a) levels during the follow-up remaining in the same category in the last examination.

	Lp(a) ≥30 mg/dL in 2011	Lp(a) < 30 mg/dL in 2011
Lp(a) ≥30 mg/dL in 1986	136 (94%)	9 (6%)
Lp(a) ≥30 mg/dL in 2001	180 (87%)	26 (13%)
Lp(a) ≥30 mg/dL in 2007	226 (89%)	29 (11%)
Lp(a) < 30 mg/dL in 1986	90 (6%)	1307 (94%)
Lp(a) < 30 mg/dL in 2001	69 (5%)	1413 (95%)
Lp(a) < 30 mg/dL in 2007	44 (3%)	1482 (97%)

No. individuals with data: 1986 and 2011 (N = 1542), 2001 and 2011 (N = 1688), 2007 and 2011 (N = 1781).

Table 5
Lipoprotein(a) (mg/dL) levels in participants originating from eastern and western parts of Finland.

Study year	Eastern origin	Median	IQ range	GM	Western origin	Median	IQ range	GM	%diff in median	%diff in GM	*p*-value[a]	*p*-value[b]
	Mean				Mean							
1986	11.5	5.3	2.8–14.3	7.0	11.2	4.5	2.8–13.5	6.5	18%	7.7%	0.007	0.052
2001	13.0	6.8	2.9–16.9	6.7	11.9	5.7	2.7–14.1	6.2	19%	9.7%	0.003	0.065
2007	15.1	8.6	3.5–20.4	8.0	13.5	6.8	3.2–17.0	7.2	27%	11.9%	0.001	0.028
2011	15.6	9.0	4.0–20.9	9.0	14.2	7.4	3.6–17.9	8.0	22%	12.4%	0.002	0.018

IQ = interquartile; GM = geometric mean.
Number of individuals in comparisons: eastern origin 961-1181; western origin 1083-1283.
[a] Comparison of median: non-parametric two-sample median test.
[b] Comparison of GM: parametric test of log-transformed values.

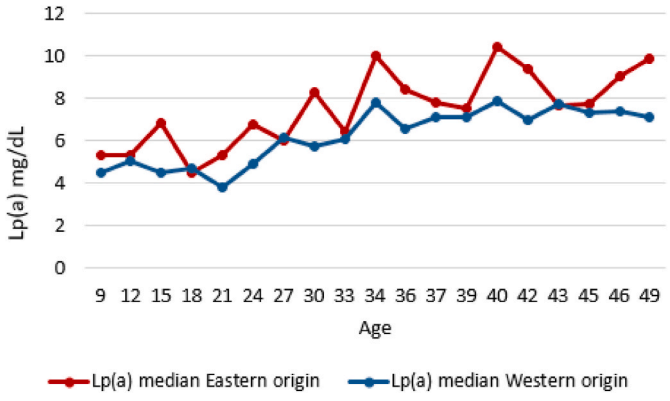

Fig. 2. Median Lp(a) levels by age and geographical origin based on 14,384 Lp (a) measurements from 3181 participants from study years 1986 (ages 9 to 24), 2001 (ages 24 to 39), 2007 (ages 30 to 45) and 2011 (ages 34 to 49). Longitudinal mixed model indicated increased trend by age ($p < 0.0001$) and higher level in individuals originating from Eastern Finland ($p = 0.023$), but no difference between the sexes (data not shown, $p = 0.82$).

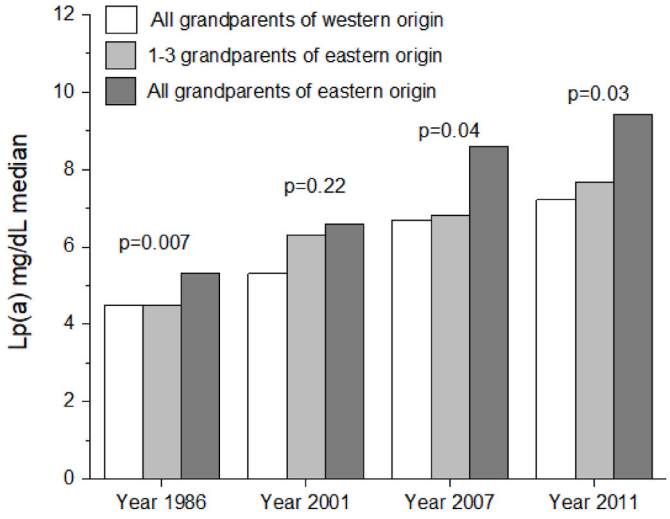

Fig. 3. Median Lp(a) levels in study participants categorized according to their grandparents' birth place (eastern or western Finland).

3.4. Type 2 diabetes, insulin, glucose and fatty liver

The prevalence of type 2 diabetes and fatty liver across the Lp(a) groups, as well as mean glucose and insulin values, are shown in Table 7. The prevalence of type 2 diabetes decreased across the Lp(a) groups. When low Lp(a) (<5 mg/dL) was treated as the reference group, the age, sex and statin use adjusted relative risk for type 2 diabetes was 0.66 (95% confidence interval 0.45 to 0.95) in the three higher Lp(a) groups combined ($p = 0.025$). Low Lp(a) was also associated with the prevalence of fatty liver. When low Lp(a) (<5 mg/dL) is treated as the reference group, the age, sex and statin use adjusted relative risk for fatty liver was 0.82 (95% confidence interval 0.69 to 0.99) in the three higher Lp(a) groups combined ($p = 0.039$).

4. Discussion

We report data on serial Lp(a) measurements in the longitudinal YFS cohort spanning across a time period of 25 years from youth to mid-adulthood. Our results confirm the assumption that Lp(a) levels are stable over the life-course [20]. We found strong tracking of Lp(a) between subsequent study years in both males and females: the rank-order correlations ranged between r = 0.85 (25-year tracking) and r = 0.96 (4-year tracking). In addition, most individuals (87–94%) who had high Lp(a) level (≥30 mg/dL) in one time-point, had a high level also in the latest study year in 2011. The European Society of Cardiology and European Atherosclerosis Society as well as the Canadian Cardiovascular Society [45] recommend universal Lp(a) testing of all adults, at least once during their lifetime [20]. Our data support this notion that one measurement during the life is adequate to identify individuals at risk. This is in line with a recent investigation of repeated measurements in more than 15,000 participants of the UK Biobank which showed that a single measurement of Lp(a) is efficient to inform about the coronary artery disease risk [25]. Furthermore, we found that tracking was strong already from childhood and adolescence suggesting that measurements done in early life may reliably reflect the Lp(a) levels later in mid-adulthood. The long-term tracking correlations for Lp(a) are noticeably stronger than we have previously reported e.g. for the LDL-cholesterol levels and body mass index that are in the order of r = 0.4–0.6 [46]. Thus, our results may have implications for informing Lp (a) screening strategies as a part of pediatric preventive cardiology programs, where the recommendations are currently limited [47]. Our data extend previous reports that have examined the stability of Lp(a) over shorter time periods. In infants, Wilcken et al. [21] reported that Lp (a) levels at 3–5 days and 8.5 months were highly correlated (r = 0.73). Similarly, Routi et al. [48] found a strong correlation between Lp(a) levels at 7 and 36 months of age (r = 0.88) in 430 children participating in the STRIP Study. In middle-aged adult population of the UK Biopank, the 4-year tracking of Lp(a) was r = 0.96[25]. Strong tracking reflects the fact that Lp(a) levels are genetically determined and not much influenced by extrinsic factors. In line, we found no associations with life-style factors, including smoking, alcohol intake, diet or physical activity. On the contrary, the several known variants of the LPA gene were strongly associated with the Lp(a) phenotype.

About 20–30% of the global population are affected by Lp(a) levels >30–50 mg/dL that are considered as being in the atherothrombotic range [33–35]. We found that about 16% of the YFS population had Lp (a) levels exceeding 30 mg/dL. This is in line with previous studies observing that Finns have lower Lp(a) levels than Central Europeans partly due to genetic differences [13,14]. Here, we specifically

Table 6
Vascular phenotypes and cardiovascular events in the cohort participants according to their Lp(a) levels.

	<5 mg/dL	5-<30 mg/dL	30-<50 mg/dL	≥50 mg/dL	*p*-value
No. with ultrasound data	795	1373	276	169	
Carotid IMT, mm, mean (SD)	0.602 (0.090)	0.603 (0.086)	0.606 (0.088)	0.620 (0.094)	0.09
Carotid plaque, No of cases (%)	30 (3.3%)	45 (3.4%)	7 (2.8%)	6 (4.6%)	0.84
Brachial FMD, %, mean (SD)	8.6 (4.0)	8.5 (3.9)	8.1 (4.0)	8.8 (3.9)	0.88
Carotid distensibility, %/10 mmHg mean (SD)	2.07 (0.67)	2.02 (0.64)	2.02 (0.66)	2.02 (0.58)	0.34
No. with event data	1026	1641	341	190	
Cardiovascular events, No of cases (%)	15 (1.5%)	36 (2.2%)	9 (2.9%)	10 (5.3%)	0.003

p-values are from age and sex adjusted linear (continuous outcomes) or logistic (binary outcomes) regression models testing the trend across the 4 Lp(a) groups. Ultrasound data are the mean values of measurements done in study years 2001 and 2007.
IMT = intima-media thickness; FMD = flow-mediated dilation.

Table 7
Diabetes, glucose, insulin and fatty liver in the cohort participants according to their Lp(a) levels[a].

	<5 mg/dL	5-<30 mg/dL	30-<50 mg/dL	≥50 mg/dL	*p*-value[b]
Type 2 diabetes, %	5.1%	3.5%	4.9%	1.7%	0.03
Fasting glucose, mmol/L	5.4 (1.0)	5.4 (1.0)	5.3 (0.5)	5.3 (0.5)	0.06
HbA1C, mmol/mol	36.8 (5.4)	36.8 (5.7)	36.7 (3.6)	36.2 (2.8)	0.28
Insulin, mU/L	10.4 (15.2)	10.1. (14.9)	8.9 (6.7)	9.5 (6.6)	0.52
HOMA-IR	3.0 (9.6)	2.7 (6.0)	2.1 (1.8)	2.3 (1.8)	0.39
Fatty liver, %	21.6%	18.3%	16.0%	17.0%	0.03

HOMA-IR = homeostasis model assessment–insulin resistance; HbA1C = glycated hemoglobin fraction in whole blood.
[a] Based on the available data, the number of individuals varies between the Lp(a) groups; <5 mg/dL N = 574–839; 5-<30 mg/dL N = 1107–1461; 30-<50 mg/dL N = 212–285; ≥50 mg/dL N = 140–177.
[b] *p*-values are from age, sex and statin use adjusted linear (continuous outcomes) or logistic (binary outcomes) regression models testing the trend across the 4 Lp(a) groups.

investigated the differences in the distribution of Lp(a) within Finland according to participants' geographic birth place. The YFS was launched in 1980 to study risk factor levels in Finnish children and adolescents. One of the original key study aims was to provide insights to the observed excess cardiovascular disease risk that exists amongst those born in eastern compared to western parts of Finland and has been evident since the 1960s [49]. Among the YFS cohort, we have previously observed higher total cholesterol, lower HDL-cholesterol and higher triglycerides levels in individuals originating from eastern Finland compared to those originating from western Finland. These differences were pronounced in the 1980's when the participants were children and adolescents [27], but non-detectable in the latest survey in 2011 in mid-adulthood [28]. In the present analyses, we found ~20% higher median and ~10% higher geometric mean for Lp(a) in individuals originating from eastern Finland compared to those originating from western Finland. Unlike we have observed for other lipoproteins, the differences in Lp(a) levels have remained relatively constant during the follow-up. Earlier studies have documented genetic duality in Finland evidenced by pronounced differences between eastern and western Finns observed in the Y-chromosomal and autosomal variation, as well as regional enrichment of several monogenic diseases [15,16,18,50]. However, we could not demonstrate differences between eastern and western participants in the distributions of genetic variants that are known to influence Lp(a) levels. This suggests that there may exist yet undiscovered genetic factors that explain the difference. Whether the difference in Lp(a) distributions contributes to the regional differences in cardiovascular morbidity and mortality needs to be examined in a larger sample.

Lp(a) is thought to be causally associated with atherosclerotic cardiovascular disease outcomes through potentially proatherogenic, proinflammatory, and antifibrinolytic mechanisms [51]. The LDL-like particle containing apolipoprotein-B may enter arterial wall and initiate molecular responses that lead to the formation of atherosclerotic lesions [52,53]. In addition, the apolipoprotein(a) has properties that might accentuate its atherogenic potential, especially the presence of oxidized phospholipids on apolipoprotein(a) has been suggested to constitute a key mechanism leading to atherosclerosis [8]. Furthermore, given its homology to plasminogen, apolipoprotein(a) might contribute to cardiovascular diseases by promoting thrombosis [1]. In the current analyses, we found that individuals with high Lp(a) levels did not differ from those with low levels in respect of pre-clinical vascular phenotypes, including carotid artery intima-media thickness, carotid plaques, carotid artery elasticity or brachial artery endothelium-dependent flow--mediated vasodilation. We have previously examined in detail the association of Lp(a) with early arterial injury in this cohort by using both conventional and Mendelian randomization analysis, and found no support for causal effects of increased Lp(a) levels [54]. However, in the present analyses, we were able to link Lp(a) levels to cardiovascular events. Seventy individuals had experienced a cardiovascular event at a relatively young age confirmed by the national health registries and had information on Lp(a) levels. The role of Lp(a) in causing cardiovascular disease outcomes is indisputable, and this effect is also seen in our study with very limited power due to small number of cases. Compared to individuals with low Lp(a) levels (<5 mg/dL), the relative risk of a cardiovascular event was about 3 times greater in individuals with high Lp(a) level (≥50 mg/dL). Therefore, our data are in line with notion that elevated Lp(a) levels increase the risk of cardiovascular events and suggest that measuring Lp(a) could help identifying individuals at risk. However, at the same time these data do not give support for the hypothesis that Lp(a) would have role in the development of pre-clinical phenotypes. Other studies have also failed to demonstrate a robust link between Lp(a) and indicators of pre-clinical atherosclerosis [55,56]. In addition, Klein et al. [57] have demonstrated in a relatively large patient population that high Lp(a) is an independent predictor of carotid stenosis and occlusion, but not of carotid plaque area. Similarly, in the Bruneck study, high Lp(a) was not associated with incident early carotid atherosclerosis but was associated with the risk of advanced carotid atherosclerosis (incident carotid stenosis) [58]. Together, these observations suggest that other potential pathological mechanisms of Lp(a), such as thrombosis and inflammation, may play a more important role

than the initiation of atherosclerosis.

We found that low levels of Lp(a) were associated with increased risk of type 2 diabetes. This observation is in line with several previous population-based studies that reported a similar association [11]. The Bruneck population-based prospective study suggested a 12% higher risk of type 2 diabetes with each standard deviation lower Lp(a) concentration. Subsequent meta-analysis of four prospective cohort studies found that the risk of type 2 diabetes was higher in those with the lowest Lp(a) concentration, with the highest risk in those with a Lp(a) less than 7 mg/dL [59]. The mechanisms through which Lp(a) might be inversely associated with diabetes risk are not yet clear. One large Mendelian randomization study found that low Lp(a) level alone was not associated with type 2 diabetes, but a causal association for large lipoprotein(a) isoform could not be excluded [60]. Low Lp(a) level is also a risk factor for fatty liver disease. Inverse correlation between fatty liver disease and Lp(a) levels was reported in a large Korean study of over 22,000 participants [12]. In addition, recent studies have found that in patients with fatty liver disease, low Lp(a) levels correlate with the degree of fibrosis [61,62]. In the present analyses, we observed the highest prevalence of fatty liver in individuals with constantly low (<5 mg/dL) Lp(a) levels. The mechanism explaining the inverse association between fatty liver disease and Lp(a) is unclear, but it has been suggested that the decrease in liver function may influence the expression of apolipoprotein (a) in the liver [62]. Ongoing trials will clarify whether effective Lp (a) lowering agents will increase the risk of type 2 diabetes and fatty liver disease.

The effects of statin treatment on circulating Lp(a) levels have been evaluated with conflicting results. One meta-analysis suggested that statins may increase Lp(a) levels by 10–20% [63], while another systematic review and meta-analyses reached a different conclusion that statin therapy does not lead to clinically important differences in Lp(a) concentration [64]. The reason for these dissimilarities are unclear. We observed the highest prevalence of statin use (~6%) in the high Lp(a) group (≥50 mg/dL) compared to other groups (~2%) but due to low number of statin users were are unable to provide insights about the causality. Recent study based on the UK Biobank data showed that statin usage was associated with a significant increase in Lp(a) only among those with initially high levels [25].

4.1. Limitations

In the present study, the Lp(a) concentration was measured using the same immunoturbidimetric methodology in study years 2007 and 2011 [32]. However, different methods were used to analyze samples collected in 1986 [30] and 2001 [31]. Scharnagl et al. [65] recently compared commercially available immunoassays. They concluded that current assays are differently calibrated, and found that their biases differed across clinically relevant concentration range in a non-linear manner. Therefore, direct comparisons between the study years may not be possible in our study, and our observation suggesting a direct correlation with aging could be biased if the levels between subsequent study years are not comparable. Conflicting results have been published regarding the effect of age, and the issue of to what extent age per se influences Lp(a) levels remains unresolved [2].

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% [66]. However, Yeang et al. recently demonstrated that actually the percent of cholesterol carried by lipoprotein(a) ranges from 6% to 57% among individuals [67]. Therefore, the investigators suggested that the historical 30% value should be discontinued in clinical studies for estimating corrected LDL-cholesterol because of the high likelihood of error at the individual level [67]. Therefore, we have not made attempt to correct the LDL-cholesterol values reported here for the Lp(a)-cholesterol.

We found no evidence that Lp(a) would contribute to the development of pre-clinical vasculopathy. The lack of an association may reflect insufficient exposure time, as the vascular phenotypes were measured in young adulthood. Furthermore, the ultrasound techniques used herein do not provide detailed information about important vascular characteristics that may mediate the adverse effects of Lp(a) and make atherosclerotic lesions vulnerable, such as necrotic core size, fibrous cap thickness, inflammatory activity, and the presence of intraplaque hemorrhage. Therefore, more detailed imaging studies are needed to reveal the exact mechanisms how Lp(a) contributes to cardiovascular events.

In summary, the data from the ongoing YFS confirm that Lp(a) levels are highly genetically determined and remain very stable over the lifecourse. In line with the genetic duality between eastern and western parts of Finland, we observed about 20% higher Lp(a) levels in individuals originating from eastern Finland compared to those originating from western Finland. We were able to replicate previous observations, as we found that high Lp(a) levels associate with increased risk of cardiovascular events, and that low levels associate with increased risk of type 2 diabetes and fatty liver.

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Based on the available data, the number of individuals varies between the categories; all grandparents from western origin (N = 288–330); 1–3 grandparents from eastern origin (N = 521–653); all grandparents from eastern origin N = 781–888).

CRediT authorship contribution statement

Olli Raitakari: Funding acquisition, Study idea, data collection, funding, data analyses, writing the manuscript. **Annukka Kivelä:** Study idea, commenting the manuscript. **Katja Pahkala:** Funding acquisition, Data collection, funding, data analyses, commenting the manuscript. **Suvi Rovio:** Funding acquisition, Data collection, funding, data analyses, commenting the manuscript. **Juha Mykkänen:** Data collection, data analyses, commenting the manuscript. **Ari Ahola-Olli:** Data collection, genetic data analyses, commenting the manuscript. **Britt-Marie Loo:** Data collection, Lp(a) methods, commenting the manuscript. **Leo-Pekka Lyytikäinen:** Data collection, genetic data analyses, commenting the manuscript. **Terho Lehtimäki:** Data collection, genetic data analyses, funding, commenting the manuscript. **Mika Kähönen:** Data collection, funding, commenting the manuscript. **Markus Juonala:** Data collection, funding, commenting the manuscript. **Tapani Rönnemaa:** Funding acquisition, Data collection, funding, commenting the manuscript. **Claudia Lamina:** Data collection, Lp(a) methods, commenting the manuscript. **Florian Kronenberg:** Data collection, Lp (a) methods, commenting the manuscript. **Jorma Viikari:** Funding acquisition, Data collection, funding, commenting the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Olli Raitakari has received consultations fees from Novartis Inc.

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