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ORIGINAL ARTICLE
Epidemiology and prevention

Intra-individual variability in lipoprotein(a): the value of a repeat measure for reclassifying individuals at intermediate risk

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Aims Lipoprotein(a) [Lp(a)] levels are predominantly genetically determined and repeat measurements are generally considered unlikely to be clinically useful. However, the temporal variation of Lp(a) is not well characterized. Our aim was to determine the intra-individual variability of Lp(a) and whether a repeated measure reclassified Lp(a)-specific cardiovascular risk using the European Atherosclerosis Society (EAS) consensus statement risk categories.

Methods and results This retrospective cohort study analysed initial and repeated serum Lp(a) levels measured using the same methodology from 609 individuals in the Nashville Biosciences database, a de-identified electronic medical records database. Baseline and follow-up paired values were significantly different ($P < 0.05$), with an absolute change of ≥10 mg/dL in 38.1% [95% CI 34.2–42%] and a >25% change in 40.5% [95% CI 36.6–44.3%] of individuals. Although the categories of those whose values were in the EAS low-risk and high-risk categories did not change, 53% of those in the intermediate 'grey-zone' category transitioned to either the low-risk (20%) or high-risk (33%) category. Black individuals exhibited greater variability than White individuals and women exhibited greater variability than men. There was a positive correlation between the baseline Lp(a) levels and the absolute changes in Lp(a), ($r = 0.59$, $P < 0.01$).

Conclusion Temporal-related changes in Lp(a) variability were present in many individuals. A repeat Lp(a) measure may allow more precise Lp(a)-specific cardiovascular risk prediction for individuals whose initial value is in the EAS-defined intermediate 'grey-zone' category. Lp(a) variability should be included in calculating the expected effect sizes in future clinical research studies targeting Lp(a).

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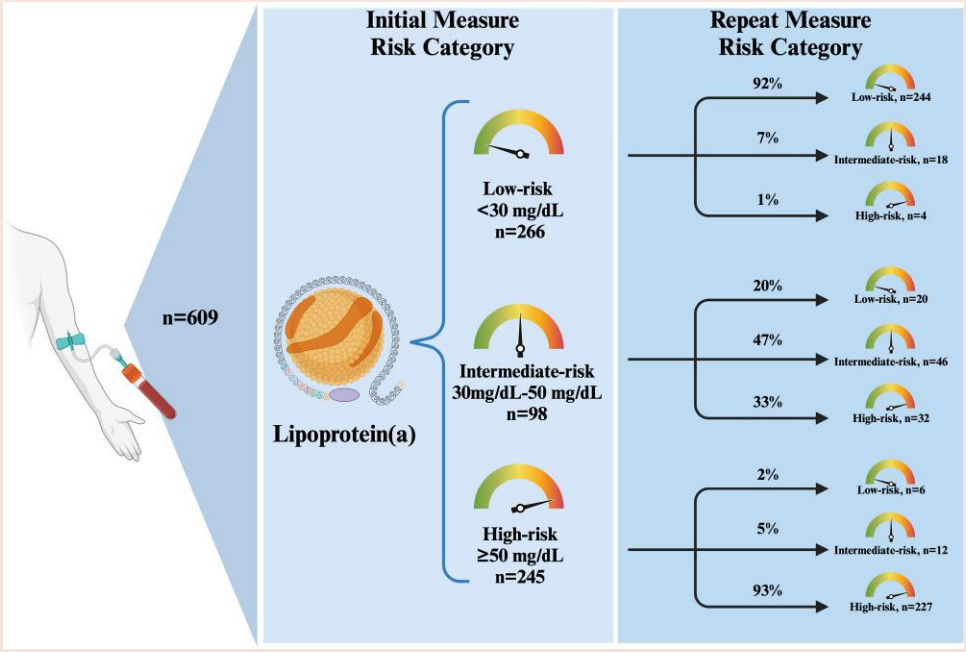
Graphical Abstract



The value of a repeat lipoprotein(a) measure for reclassifying individuals. This study highlights the value of a repeat measure of Lp(a) in risk reclassification using risk stratification categories from the European Atherosclerosis Society (EAS) consensus statement. A repeat Lp(a) measure is not likely to reclassify cardiovascular risk for those with initial Lp(a) levels in the EAS-defined high-risk [≥50 mg/dL (~125 nmol/L)] or low-risk [<30 mg/dL (~75 nmol/L)] groups. However, a repeat measure for those whose values are in the intermediate-risk (30–50 mg/dL) group is likely to transition the person's risk to either the low-risk (20%) or high-risk (33%) category.

Keywords Lipoprotein(a) • Coronary artery disease • Heart disease risk factors

Lay summary

Levels of a cholesterol-carrying particle in the blood called lipoprotein(a), which is associated with increased risk of heart attacks and strokes, may vary over time, and:

- A repeated measure may inform cardiovascular risk particularly in those with an initial value in the intermediate 'grey-zone' risk category of 30–50 mg/dL.
- This information may help when planning future clinical studies aimed at treating Lp(a) in patients with or at risk for cardiovascular disease.

Introduction

The successful management of risk factors such as hypertension and dyslipidaemia have decreased atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality.[1,2] However, the presence of other, 'residual' risks that are not adequately addressed is one of the main reasons ASCVD remains one of the leading causes of deaths and significant life-long disability worldwide.[1,2] Lipoprotein(a) [Lp(a)] has emerged as one of the more important residual risks.[3] Elevated serum levels are present in over 20% of the general population, and epidemiologic, Mendelian randomisation, and genome-wide association data all support a causal role.[4,5]

In practice, the effectiveness of a medical intervention directed to a specific risk factor is often assessed by the change in the risk factor following the initiation, or changing the dose, of the intervention. An important pre-requisite for this evaluation is an understanding of the inherent intra-individual variability of that measure and for that reason the result of at least one repeat measure, for example of blood pressure, is often incorporated into clinical decisions when optimizing personalized preventive care.[6]

Although there is significant racial and ethnic heterogeneity in Lp(a) levels, concentrations are believed to be largely genetically determined and therefore not expected to exhibit significant 'intra-individual' variability.[4,7] The UK Biobank study of predominantly White participants for whom two or more Lp(a) measures separated by a median of 4.42 (3.69–4.93) years used a change of 25 nmol/L or more to define variability. Only 12.8% of the participants had such a change[8] and current guidelines do not recommend repeat Lp(a) measurement as it is thought that doing so would not meaningfully improve risk prediction.[9]

However, there are studies that suggest factors beyond genetics impact Lp(a) levels. In a longitudinal study in children, De Boer *et al.* reported a change in Lp(a) levels of at least 20% between two measurements in a majority of the 967 children studied.[10] Additionally, in the dose-finding phase one and phase two studies of pelacarsen, a hepatocyte-directed antisense oligonucleotide targeting the mRNA transcribed from the *LPA* gene, 21 of the 52 placebo assigned patients had ≥25% variation in Lp(a) within a 6-month period.[11] The *LPA* gene contains an interleukin 6 response element, which can up-regulate apolipoprotein(a) [apo(a)] expression.[12] Lp(a) levels are also influenced by hepatic and kidney function, indicating non-genetic influences related to Lp(a) production and/or catabolism.[4,13,14]

There are two units, mg/dL and nmol/L, for reporting Lp(a) results. Although there is no straightforward conversion factor,[15] it is common

to multiply the mg/dL values by 2.5 to estimate the nmol/L values, as was used in the European Atherosclerosis Society (EAS) consensus statement.[9] In their statement on Lp(a), the EAS emphasized the relationship of Lp(a) concentrations with the risk of major cardiovascular events as a continuum of risk, and also suggested clinically useful categories to determine cardiovascular risk, with ≥50 mg/dL (~125 nmol/L) indicative of high risk, < 30 mg/dL (~75 nmol/L) indicative of low risk, and values between 30 and 50 mg/dL constituting a 'grey-zone' of risk.[9] An update to the 2019 National Lipid Association Scientific Statement on use of Lp(a) in clinical practice was recently published and adopted the same risk stratification thresholds.[16] The experts of the Polish Cardiac Society and the Polish Lipid Association also noted the uncertainty regarding the Lp(a) associated risk for those whose values are within this 'grey-zone'.[17]

For this analysis, we accessed the Nashville Biosciences database through the American Heart Association's Precision Medicine Platform and queried it to define intra-individual variability over 1.07 (0.5–2.1) years in 609 individuals for whom two Lp(a) levels were available using the same methodology. We calculated the intra-individual variability in the entire cohort and assessed the variability within sex- and race-based cohorts. We also calculated the number of individuals whose Lp(a) levels transitioned from one EAS risk category to another. As kidney and hepatic function are reported to impact variability,[13,14] we also separately report the results in those without a diagnosis of kidney or hepatic dysfunction.

Methods

Data source and design

The dataset used for this study was accessed through the American Heart Association's Precision Medicine Platform (https://precision.heart.org/), which was obtained from the Vanderbilt University Medical Center's BioVU. The Vanderbilt University Medical Center Institutional Review Board has classified the use of these data as non-human subject research.[18] A retrospective cohort study was conducted. Lp(a) data were clinically obtained between 2011 and 2022 at Vanderbilt University Medical Center facilities using the MedTestDx's immunoturbidimetric assay for all measures and data from individuals with two Lp(a) values were analysed. If patients had more than two measurements in the studied period, we included the first and the most recent Lp(a) measurements.

Statistical methods

Categorical variables are presented as counts (%) and compared using Fisher's exact test. Continuous variables are presented as mean ± standard deviation or median (Q1–Q3), were tested for normality using the Shapiro–Wilk test, and compared using parametric and non-parametric tests where appropriate. The Spearman's Rank correlation coefficient was used to assess the relationship between two variables. The significance level was set at $P < 0.05$ and the statistical analysis was performed using the RStudio Server 2022.07.01.

Defining Lipoprotein(a) variability

Variability can be defined as the absolute change and as a relative, percent change from the first to the second value. In the UK Biobank study, a change of at least 25 nmol/L, roughly equivalent to 10 mg/dL, was used to define values that were not stable.[8] In the study examining variability in participants enrolled in the placebo arms of the IONIS-APO(a)Rx and IONIS-APO(a)-LRx clinical trials, a change of >25% was used to evaluate temporal variability.[11]

For those with lower initial values, e.g. 16 mg/dL, a change to 24 mg/dL would result in a large 50% relative change but which would, nevertheless, not be clinically significant, whereas for those with higher initial values, e.g. 100 mg/dL an absolute change to 150 mg/dL would also result in the same 50% relative change but indicate a significant change in risk assessment. Therefore, we are reporting results as both an absolute change of at least 10 mg/dL (roughly equivalent to the 25 nmol/L used in the UK Biobank study) and a relative change of 25%, used in the placebo arms of the above-referenced clinical trials.

International statistical classification of diseases and related health problems (ICD) codes

ICD 9 and 10 codes definitions were used to identify kidney and hepatic comorbidities.

The following ICD 10 codes were used: N18*, K70-76*

The following ICD 9 codes were used: 585*, 571*

Results

Baseline characteristics

In this dataset, there are 609 individuals with baseline and follow-up Lp(a) values. Baseline characteristics are summarized in *Table 1*. Median age was 52.5 (37.1–62.8) years, 45% were women, 80.3% were White patients, 13.3% were Black patients, 1.6% were Asian patients, and 4.8% were other/unknown patients. In terms of relevant comorbidities, 24.1% had chronic kidney disease, and 13.5% had liver disease. The median time between the two Lp(a) measures was 1.07 (0.5–2.1) years.

From the 609 patients in the total cohort, 177 patients had either chronic kidney disease, or liver disease, or both. These 177 patients were excluded from a subgroup analysis that included only individuals with no kidney or liver disease. In this subgroup, median age was 50 (28.3–61.5) years, 49.8% were women, 82.9% were White patients, 9% were Black patients, 1.9% were Asian patients, and 6.2% were other/unknown patients.

Lipoprotein(a) variability in total cohort

The Lp(a) values were not normally distributed, and the results are presented as medians and quartiles and compared using non-parametric tests. Although initial median Lp(a) [37 (13–75) mg/dL] and follow-up [36 (12–79) mg/dL] levels did not differ, there was a significant difference between the paired values ($P < 0.05$), with 38.1% [95% CI 34.2–42%] changing by ≥10 mg/dL, and 40.5% [95% CI 36.6–44.3%] changing by >25% (*Table 2*). There was a positive correlation between the baseline Lp(a) value and the absolute change in Lp(a), Spearman's rank correlation coefficient ($r = 0.59$, $P < 0.01$, *Figure 1A*).

Results are stratified by sex and race in *Table 2*. The initial median Lp(a) level was higher in women [47 (17–81) mg/dL] than in men [31 (11–66) mg/dL, $P < 0.01$] and the median absolute change in Lp(a) in women [8 (3–17) mg/dL] was also higher than in men [5 (2–12.25), $P = 0.01$]. A change of ≥10 mg/dL was present in 44.0% of the women and 33.3% of the men ($P < 0.01$). The relative change in Lp(a) was not different between men [18.75% (5.6–36.6%)] and women [20.3% (8.8–37.5%), $P = 0.58$]. The median age of women was 51.3 (31.7–63.0) years, which is similar to the mean age for menopause in the USA and Europe.[19,20] The initial median Lp(a) level was higher in women older than 51 years [51.5 (20–85.3)] than in women younger than 51 years [43 (13–74), $P < 0.01$], and there were no statistically significant differences in the changes in Lp(a) (*Table 3*). The initial median Lp(a) level was higher in Black individuals [44 (28–97) mg/dL] than in White individuals [36 (12–72) mg/dL, $P < 0.01$] and the median absolute change in Lp(a) in Black individuals [10 (5–17) mg/dL] was also higher than in White individuals [6 (2–14) mg/dL, $P < 0.01$]. A change of ≥10 mg/dL was present in 53.1% of Black individuals and in 35.8% of White individuals ($P < 0.01$).

Lipoprotein(a) risk category transitions in total cohort

Baseline and follow-up Lp(a) values were categorized using the EAS risk categories. At baseline, there were 266 values in the low-risk category (<30 mg/dL), 98 in the 'grey-zone' category (between 30 and 50 mg/

Table 1 Characteristics of the total cohort and of those without kidney and liver disease

	Total cohort	Without kidney and liver disease
Number of individuals	609	432
Age in years, median (Q1–Q3)	52.5 (37.1–62.8)	50 (28.3–61.5)
Men, *n* (%)	336 (55)	217 (50.2)
Women, *n* (%)	273 (45)	215 (49.8)
Race		
White, *n* (%)	489 (80.3)	358 (82.9)
Black, *n* (%)	81 (13.3)	39 (9)
Asian, *n* (%)	10 (1.6)	8 (1.9)
Other/unknown, *n* (%)	29 (4.8)	27 (6.2)
Comorbidities		
Chronic kidney disease[a], *n* (%)	147 (24.1)	0 (0)
Liver disease[a], *n* (%)	82 (13.5)	0 (0)
Lipid-lowering therapy		
Statin[b], *n* (%)	507 (83.3)	333 (77.1)
Niacin[b], *n* (%)	95 (15.6)	71 (16.4)
PCSK9 inhibitor[b], *n* (%)	178 (29.2)	128 (29.6)
Never exposed to any lipid-lowering agent	91 (14.9)	88 (20.4)

[a]Comorbidities are based on ICD 9 and 10 codes definitions.
[b]Lipid-lowering therapy data were limited to 'exposure' and does not include the duration and dose of therapies.

Table 2 Lipoprotein(a) values in the total cohort

	Initial lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) ≥ 10 mg/dL, *n* (%)	Relative change in lipoprotein(a) > 25%, *n* (%)
Total cohort (*n* = 609)	37 (13–75)	6 (2–14)	232 (38.1)	247 (40.5)
Men (*n* = 336)	31 (11–66)[a]	5 (2–12.25)[b]	112 (33.3)[c]	137 (40.8)
Women (*n* = 273)	47 (17–81)[a]	8 (3–17)[b]	120 (44)[c]	110 (40.3)
Black individuals (*n* = 81)	44 (28–97)[a]	10 (5–17)[d]	43 (53.1)[c]	33 (40.7)
White individuals (*n* = 489)	36 (12–72)[a]	6 (2–14)[d]	175 (35.8)[c]	201 (41.1)

Initial and absolute changes in lipoprotein(a), and proportion of individuals with absolute changes ≥10 mg/dL, and relative changes >25% in the total cohort and stratified by sex and race.
[a]$P < 0.01$ for initial lipoprotein(a) in men vs. women and in Black individuals vs. White individuals.
[b]$P = 0.01$ for absolute lipoprotein(a) change in men vs. in women.
[c]$P < 0.01$ for proportion of men vs. women and for Black individuals vs. White individuals with lipoprotein(a) change of ≥10 mg/dL.
[d]$P < 0.01$ for absolute lipoprotein(a) change in Black individuals vs. White individuals.

dL), and 245 in the high-risk category (≥50 mg/dL). Only 8% of those with values in the low-risk category transitioned to either the 'grey-zone' (7%) or high-risk (1%) category, and only 7% of those with values in the high-risk category transitioned to either the 'grey-zone' (5%) or low-risk (2%) category. However, 53% of those with values in the 'grey-zone' transitioned to either the low-risk (20%) or high-risk (33%) category. In summary, those starting with values in the high-risk and low-risk groups stayed in their categories on repeat testing, while values in a large proportion of individuals in the 'grey-zone' underwent a significant transition to a different risk category. The proportion of patients in the low-risk category who were not on any lipid-lowering therapy was 14.7%. This is not different from the 19.7% of patients in the grey-zone category who were not on any lipid-lowering therapy ($P = 0.33$), or the 13.5% of those in the high-risk category who were not on any lipid-lowering therapy ($P = 0.71$).

Lipoprotein(a) variability in individuals with no kidney or liver disease

The results were very similar in the subgroup of individuals with no kidney or liver disease ($n = 432$). The median baseline and follow-up Lp(a) values were 38.5 (14–73) mg/dL and 38.5 (13–75.3) mg/dL, respectively ($P = 0.07$), with 38% [95% CI 33.4–42.5%] changing by ≥10 mg/dL and 40.3% [95% CI 35.7–44.9%] changing by >25% (*Table 4*). There was also a positive correlation between the baseline Lp(a) value and the absolute change in Lp(a), Spearman's rank correlation coefficient $r = 0.59$, $P < 0.01$ (*Figure 1B*).

Results in this cohort are stratified by sex and race in *Table 4*. The initial median Lp(a) level was higher in women [50 (19–79) mg/dL] than in men [32 (10–60) mg/dL, $P < 0.01$], the median absolute change in Lp(a) in women [8 (3–17) mg/dL] was also higher than in men [4 (2–

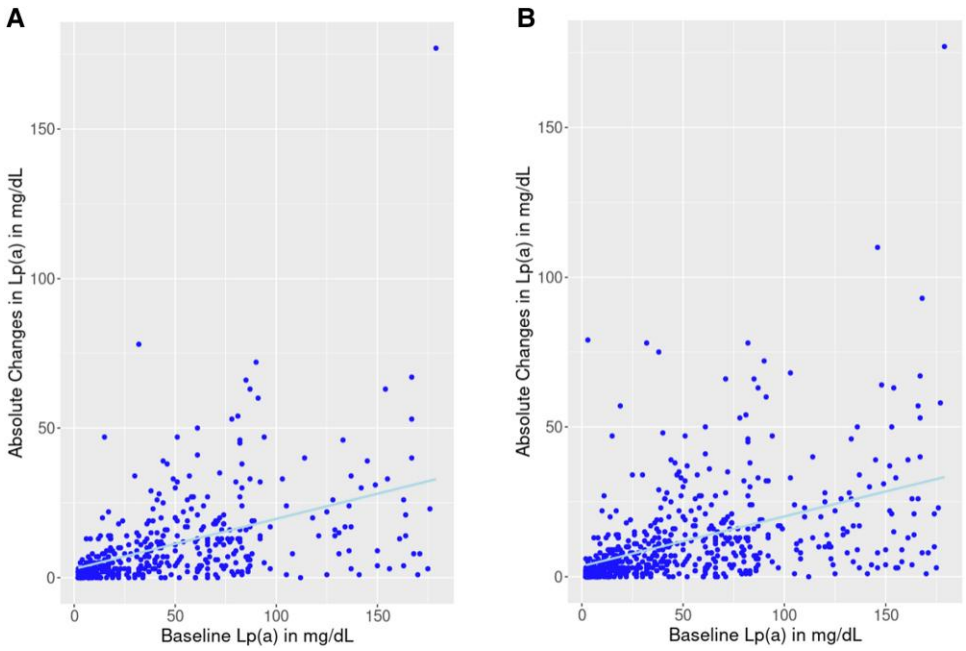


Figure 1 Plot showing correlation between baseline lipoprotein(a) levels and the absolute change in lipoprotein(a). Absolute changes in lipoprotein(a) are plotted against baseline lipoprotein(a) values. There is a positive correlation, i.e. the greater the baseline value the greater the absolute change in lipoprotein(a). (*A*) Total cohort, $n = 609$, Spearman's rank correlation coefficient $r = 0.59$, $P < 0.01$. (*B*) Subgroup with no kidney or liver disease, $n = 432$, $r = 0.57$, $P < 0.01$.

Table 3 Lipoprotein(a) values in women stratified by their median age

	Initial lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) ≥ 10 mg/dL, *n* (%)	Relative change in lipoprotein(a) > 25%, *n* (%)
Women ≤ 51 years ($n = 133$)	43 (13–74)[a]	8 (2–17)	60 (45%)	56 (42%)
Women > 51 years ($n = 140$)	51.5 (20–85.3)[a]	8 (2–17)	60 (43%)	54 (38.6%)

Initial and absolute changes in lipoprotein(a), and proportion of individuals with absolute changes ≥10 mg/dL, and relative changes >25% in the subgroups of women younger and older than 51 years.
[a]$P < 0.01$ for initial lipoprotein(a) in women ≤51 years vs. >51 years.

12), $P = 0.01$], and the proportion of women whose Lp(a) values that changed by ≥10 mg/dL, 44.7%, was larger than the 31.3% of men whose Lp(a) values changed by ≥10 mg/dL ($P < 0.01$). The initial median Lp(a) level was higher in Black individuals [50 (34–77.5) mg/dL] than in White individuals [37(13–71.75) mg/dL, $P = 0.01$], and the median absolute change in Lp(a) in Black individuals [12 (5–18) mg/dL] was also higher than in White individuals [5 (2–14) mg/dL, $P = 0.01$].

Lipoprotein(a) risk category transitions in individuals with no kidney or liver disease

Regarding the EAS risk categories, there were 178 values in the low-risk category, 76 values in the intermediate 'grey-zone' category, and 178 values in the high-risk category at baseline. Only 7.3% of the individuals whose values were in the low-risk category transitioned to either the 'grey-zone' (6.7%) or high-risk (0.6%) category, and only 8% of those whose values were in the high-risk category transitioned to either the 'grey-zone' (5%) or low-risk (3%) category. However, 48.7% of those whose values were in the 'grey-zone' category transitioned to the low-risk (18.4%) or high-risk (30.3%) category. In summary, those whose values were in the high-risk and low-risk groups stayed in their categories on repeat testing, while a large proportion of those whose values were in the intermediate 'grey-zone' category underwent a significant transition to a different risk category (*Figure 2*).

Lipoprotein(a) variability by lipid-lowering therapy exposure

Lipoprotein(a) variability in those exposed to lipid-lowering therapies was also calculated. The initial median Lp(a) level was higher in those exposed to niacin or a PCSK9 (proprotein convertase subtilisin/kexin type 9) antibody [57 (21–92) mg/dL] than in those not exposed [26.5 (11–64) mg/dL, $P < 0.01$] and the median absolute change in Lp(a) was also higher in those exposed [9 (3–21) mg/dL] than in those

Table 4 Lipoprotein(a) values in individuals with no kidney or liver disease

	Initial lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) ≥ 10 mg/dL, *n* (%)	Relative change in lipoprotein(a) > 25%, *n* (%)
Individuals with no kidney or liver disease ($n = 432$)	38.5 (14–73)	6 (2–14)	164 (38)	174 (40.3)
Men ($n = 217$)	32 (10–60)[a]	4 (2–12)[b]	68 (31.3)[c]	85 (39.2)
Women ($n = 215$)	50 (19–79)[a]	8 (3–17)[b]	96 (44.7)[c]	89 (41.4)
Black individuals ($n = 39$)	50 (34–77.5)[a]	12 (5–18)[d]	15 (38.5)	13 (33.3)
White individuals ($n = 358$)	37 (13–71.75)[a]	5 (2–14)[d]	126 (35.2)	149 (41.6)

Initial and absolute changes in lipoprotein(a), and proportions of individuals with absolute changes ≥10 mg/dL, and relative changes >25% in the subgroup with no kidney and no liver disease and stratified by sex and race.
[a]$P < 0.01$ for initial lipoprotein(a) in men vs. women and in Black individuals vs. White individuals.
[b]$P = 0.01$ for absolute lipoprotein(a) change in men vs. in women.
[c]$P < 0.01$ for proportion of men vs. women with lipoprotein(a) change of ≥10 mg/dL.
[d]$P < 0.01$ for absolute lipoprotein(a) change in Black individuals vs. White individuals.

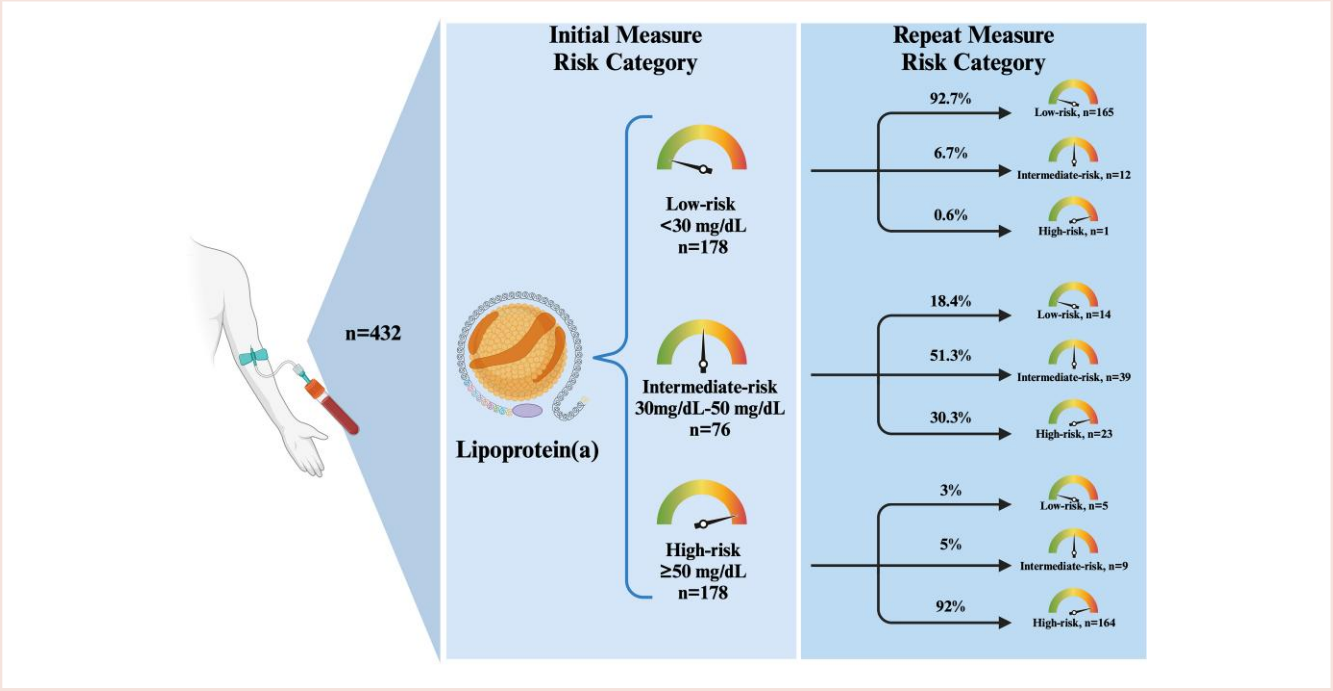


Figure 2 Subgroup analysis for those with no kidney or liver disease. Similar to the findings seen in the total cohort, a repeat lipoprotein(a) measure is not likely to reclassify cardiovascular risk for those with no kidney or liver disease and with initial lipoprotein(a) levels in the EAS-defined high-risk [≥50 mg/dL (~125 nmol/L)] or low-risk [<30 mg/dL (~75 nmol/L)] groups. However, a repeat measure for those whose values are in the intermediate-risk (30–50 mg/dL) group is likely to transition the person's risk to either the low-risk (20%) or high-risk (33%) category.

not exposed [5 (2–12), $P < 0.01$]. A change of ≥10 mg/dL was present in 48.5% in those exposed to niacin or a PCSK9 antibody and 31.8% of those not exposed ($P < 0.01$, *Table 5*).

There were no statistically significant Lp(a) differences between those exposed and those not exposed to a statin (*Table 6*).

Discussion

This study evaluated the intra-individual variability in Lp(a) results from 609 individuals from the Nashville Biosciences database who had two values obtained between 2011 and 2022 and measured using the same MedTestDx's immunoturbidimetric assay. Lipoprotein(a) levels were presented using mg/dL units and changed by ≥10 mg/dL, roughly comparable to 25 nmol/L, in 38.1% [95% CI 34.2–42%] of the individuals. Levels and the changes were greater in women than in men and in Black individuals than in White individuals. The initial Lp(a) in women older than 51 years was higher than in those younger than 51 years, the average age of menopause in the USA and Europe,[19,20] but the variability in the two age groups did not differ. Although the categories of those whose values were in the EAS low-risk and high-risk categories did not change, 53% of those in the

Table 5 Subgroup analysis for those exposed to niacin or a PCSK9-modulating therapy vs. those non-exposed

	Initial lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) ≥ 10 mg/dL, *n* (%)	Relative change in lipoprotein(a) > 25%, *n* (%)
Niacin or PCSK9i (*n* = 229)	57 (21–92)[a]	9 (3–21)[b]	111 (48.5)[c]	94 (41)
No niacin or PCSK9i (*n* = 380)	26.5 (11–64)[a]	5 (2–12)[b]	121 (31.8)[c]	153 (40.3)

[a]$P < 0.01$ for initial lipoprotein(a) for niacin or PCSK9i vs. no niacin or PCSK9i.
[b]$P < 0.01$ for absolute lipoprotein(a) for niacin or PCSK9i vs. no niacin or PCSK9i.
[c]$P < 0.01$ for proportion for niacin or PCSK9i vs. no niacin or PCSK9i with lipoprotein(a) change of ≥10 mg/dL.

Table 6 Subgroup analysis for those exposed to statin vs. those non-exposed

	Initial lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) (mg/dL), median (Q1–Q3)	Absolute change in lipoprotein(a) ≥ 10 mg/dL, *n* (%)	Relative change in lipoprotein(a) > 25%, *n* (%)
Statin (*n* = 507)	37 (14–78)	6 (2–15)	197 (38.9)	211 (41.6)
No statin (*n* = 102)	39.5 (11.5–70)	6 (1–13)	35 (34.3)	36 (35.3)

intermediate 'grey-zone' category transitioned to either the low-risk (20%) or high-risk (33%) category.

The low-density lipoprotein (LDL)-like moiety in Lp(a) promotes atherogenesis in a manner similar to LDL. The contribution of Lp(a) to ASCVD risk, however, is greater than that of LDL[21,22] and may do so because (i) it is the preferred carrier of proinflammatory oxidized phospholipids that contribute to vascular inflammation[7,23,24]; (ii) its apo(a) moiety resembles plasminogen, resulting in decreased plasminogen activation to plasmin thus limiting fibrinolysis[25]; and (iii) it activates platelets, which results in platelet aggregation and the release proinflammatory cytokines.[25,26]

Lipoprotein(a) variability was also explored in recent studies. In contrast to the Nashville Biosciences database, all of the participants in the OCEAN(a) dose-finding study had known ASCVD and an initial Lp(a) of >150 nmol/L (~ > 60 mg/dL). The mean initial Lp(a) was 246 (200–343) nmol/L and there was a mean intra-individual difference of 22 nmol/L over 72 weeks of follow-up.[27] Variability was also examined in a study of 775 patients attending a lipid clinic in Greece.[28] The median initial Lp(a) was 10.7 (4.4–27.8) mg/dL and over a median follow-up of 0.6 [0.3–1.7] years, the median intra-individual variation was 13% [5–23%] with 32% of the patients reclassified to a higher Lp(a) risk category and 28% to a lower Lp(a) risk category.[28] Lipoprotein(a) variability was also assessed in 2740 children, with a mean age of 10.1 (±3.6) years at the time of the initial measurement referred to a paediatric lipid clinic in Amsterdam with a diagnosis of inherited dyslipidaemia and two-thirds with proven heterozygous familial hyperlipidaemia.[10] Over mean 4.2 (±3.24) years of follow-up, 66% had a change of at least 20% between the two measurements.[10]

Repeat measures of Lp(a) in UK Biobank participants suggested that levels are generally stable,[8] and current guidelines do not recommend repeat measurements as it was thought they would not improve risk prediction.[9] Potential reasons for the differences in the intra-individual variability in the UK Biobank and Nashville Biosciences databases include the higher median baseline values in the Nashville Biosciences data (37 mg/dL, or ~92.5 nmol/L, compared with 19.5 nmol/L in UK Biobank), a larger representation of Black individuals (13.3% vs. 0.4% in UK Biobank) who have higher Lp(a) levels than other racial groups,[29] a wider age distribution [52.5 (37.1–62.8) vs. 58.2 ± 7.4 years], and a shorter time interval between the two measures [1.07 (0.5–2.1) years vs. 4.42 (3.69–4.93) years].

Navigating the management of individuals placed in the intermediate-risk category for developing ASCVD poses a challenge for healthcare providers as decisions regarding preventive measures and choices of therapy are less straightforward. The American College of Cardiology/American Heart Association Cholesterol and Primary Prevention of Cardiovascular Disease guidelines recommend the use of Lp(a) measures as a risk-enhancing factor.[4] In this study, the values of 53% of those whose Lp(a) values were in the EAS-defined intermediate 'grey-zone' category transitioned to either the high-risk or the low-risk category, indicating that a repeat measurement may improve Lp(a)-specific cardiovascular risk stratification for those individuals and inform a more personalized ASCVD prevention and treatment strategy. One reason the grey-zone values undergo significant transition is the narrow 30–50 mg/dL window of the category. It is not unusual for 'borderline' categories to encompass a narrower window than the 'definite yes' and 'definite no' categories. With a narrow window, an Lp(a) change for those initially in a narrow window would be more likely to transition to another category than a similar change for those initially in a category with a wider window. There is also more of an opportunity for change in a 'middle' category, with two opportunities, i.e. to go to a higher or to a lower category. If one is initially in the high-risk or the low-risk category, higher, or lower, respectively, subsequent value would not transition to a different category.

RNA-targeted Lp(a) therapeutics, which specifically target the hepatic synthesis of apo(a), significantly decrease Lp(a) levels: pelacarsen, a single-stranded antisense oligonucleotide, decreases Lp(a) by up to 80%,[30] while the small interfering RNA drugs olpasiran and SLN360 decrease Lp(a) by up to 95%[31] and 98%,[32] respectively. Phase 3 outcome studies for pelacarsen (NCT04023552) and olpasiran (NCT04270760) are currently ongoing using Lp(a) concentrations of ≥70 mg/dL (~175 nmol/L) and ≥200 nmol/L, respectively, to determine eligibility. Our results provide data regarding the expected variability in the placebo groups of future studies in those with lower initial Lp(a) levels and therefore may help to inform the effect size, and thus design, of those studies.

Study limitations

First, this is a retrospective study of individuals with more than one Lp(a) value measured clinically and is thus subject to selection bias. Second, data collected from medical records may be incomplete and/or inaccurate. Third, the information available on lipid-lowering therapy is limited to 'exposure' and does not include detailed duration and dose of therapies. Fourth, comorbidities were defined by ICD code definitions. Fifth, Lp(a) values in this database are reported in mass concentrations (mg/dL) and the number of particles, reported as nmol/L may better define cardiovascular risk.[15] Sixth, there is a disproportionate representation of Black to White patients, which might lead to an overestimation or underestimation of the effect sizes for the race differences we reported.

Conclusions

Lipoprotein(a) temporal variability was present in many individuals and was greater in Black individuals than in White individuals and in women than in men. This variability should be considered when assessing serum Lp(a) outcomes of targeted interventions in the clinical setting and the expected temporal variation in the placebo groups of future Lp(a) clinical research studies. A second measure of Lp(a) is not likely to impact Lp(a)-specific cardiovascular risk for those whose initial values are in either the low-risk (<30 mg/dL) or high-risk (≥50 mg/dL) categories. However, a second measure should be considered for those whose values are in the intermediate-risk (30–50 mg/dL) category as it is likely to result in a transition to either the high- or low-risk category and therefore allow better ASCVD risk stratification.

Lead author biography

Dr Tarek Harb holds a medical degree from the American University of Beirut, Lebanon. Soon after graduating, he joined Johns Hopkins University to work with his mentors Drs Thorsten M. Leucker and Gary Gerstenblith as a post-doctoral research fellow in the Division of Cardiology. He works on multiple projects related to lipoprotein(a), coronary vascular function, and vascular inflammation.

Authors' contribution

T.H., E.Z., R.S.B., G.G., and T.M.L. contributed to the conception and design of the work. T.H., G.G., and T.M.L. contributed to the acquisition, analysis, and interpretation of the data for the work and drafted the work. T.H., E.Z., R.S.B., G.G., and T.M.L. reviewed the work critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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