HHS Public Access

Author manuscript

JACC Adv. Author manuscript; available in PMC 2024 March 28.

Published in final edited form as:

JACC Adv. 2024 February ; 3(2): . doi:10.1016/j.jacadv.2023.100800.

Lipoprotein(a) Concentrations Are Independent of Polygenic Score for Coronary Artery Disease

Michael N. Trinh, MD, PhD[a,b,c], **Ashley Pournamdari, MD**[a,d], **Aeron M. Small, MD, MTR**[a,c,e], **Gina M. Peloso, PhD**[f], **Aniruddh P. Patel, MD**[a,c,g], **Pradeep Natarajan, MD, MMSc**[a,c,g,*]

[a]Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA;

[b]Massachusetts General Hospital, Boston, Massachusetts, USA;

[c]Harvard Medical School, Boston, Massachusetts, USA;

[d]David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California, USA;

[e]Brigham and Women's Hospital, Boston, Massachusetts, USA;

[f]Boston University School of Public Health, Boston, Massachusetts, USA;

[g]Massachusetts General Hospital, Boston, Massachusetts, USA.

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein-like particle with an apolipoprotein(a) linked to apolipoprotein B predictive of atherosclerotic cardiovascular disease (ASCVD). As it is currently the most heritable biomarker associated with ASCVD, it is often checked as a marker of high genetic risk among individuals with a paucity of traditional risk factors. Lp(a) levels are now: 1) incorporated into clinical guidelines for cardiovascular risk refinement[1]; and 2) the target of new therapeutics in late-stage clinical development.[2] Moreover, single nucleotide polymorphisms in the gene encoding Lp(a), *LPA*, are very strong predictors of high Lp(a)[3] and are included in a new, multiancestry, genome-wide polygenic score for coronary artery disease (CAD) (CAD GPS_{Mult}).[4] Here, we explored how well high Lp(a) identifies individuals with a high CAD GPS_{Mult}.

The UK Biobank[5] is a prospective observational study of approximately 502,504 adults aged 40 to 69 years between 2006 and 2010. Participants underwent biochemical measurements including Lp(a) (nmol/L at study enrollment using an immunoturbidimetric method on the Beckman Coulter AU5800 platform), physical examination, and recorded their medical histories at the time of study enrollment. Self-reported ethnicities were categorized as mixed, African, European, East Asian, South Asian, and unknown. A recently developed CAD polygenic score, CAD GPS_{Mult}, was constructed using LDPred2, incorporating the weighted

*Massachusetts General Hospital, 185 Cambridge Street, CPZN 3.184, Boston, Massachusetts 02114, USA, pnatarajan@mgh.harvard.edu, @pnatarajanmd.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

effects of >1.2 million single nucleotide polymorphisms from 58 genome-wide association studies for CAD (>222,000 cases and >914,000 controls), other atherosclerotic diseases, and their risk factors from multiancestry cohorts, external to the UK biobank, and calculated in a holdout population of individuals not included in score training.[4] CAD GPS_{Mult} outperforms other published scores for CAD in external validation datasets. The CAD GPS_{Mult} score was residualized for the first 10 principal components of genetic ancestry and then scaled to a mean of 0 and SD of 1 for each ancestral group (ie, African, East Asian, European, and South Asian) for our analysis.

In the study cohort (n = 249,971), the mean age was 57.0 ± 8.1 years, and 135,806 (54.3%) werewomen. To assess the relationship between Lp(a) levels and CAD GPS_{Mult}, we assessed the proportion of individuals at or above the 90th percentile of CAD GPS_{Mult} according to bins of Lp(a) levels at increments of 50 nmol/L. We found a positive, albeit modest association ($P < 2.2 \times 10^{-16}$ by chi-squared test) across the Lp(a) bins: 18.8% from 0 to 50 nmol/L, 21.6% between 50 and 100 nmol/L, 23.4% between 100 and 150 nmol/L, and 25.2% >150 nmol/L (Figure 1A). We further assessed mean levels of Lp(a) in patients from the UK Biobank separated into deciles of the scaled CAD GPS_{Mult} score and observed a positive but weak association across different ancestries (mean concentrations of Lp(a) in top vs bottom deciles of CAD GPS_{Mult} [*P* value by Welch 2-sample t-test]: Overall, 51.4 vs 38.9 [$P < 2.2 \times 10^{-16}$]; European, 50.9 vs 38.1 [$P < 2.2 \times 10^{-16}$]; African, 77.3 vs 69.5 [$P = 0.004$]; East Asian, 42.9 vs 29.7 [$P = 0.007$]; and South Asian, 46.2 vs 43.0 [$P = 0.13$] [Figure 1B]).

Higher CAD GPS_{Mult} is modestly enriched among individuals with elevated Lp(a). Despite the enrichment of higher CAD GPS_{Mult} among those with increased Lp(a), Lp(a) is not a suitable screening approach to identify high CAD GPS_{Mult} levels and is generally not a marker for high CAD GPS_{Mult}. These data provide additional evidence, and now in multiple ancestry groups, that there is a positive but weak association between Lp(a) and the newly published CAD GPS_{Mult}, which incorporates discovery data from multiancestry CAD GWASs as well as CAD-related trait GWASs to boost prediction. Interestingly, when we used Cox proportional hazards regression models to predict incidence of CAD, there was modest synergy (combined area under the curve of the receiver operating characteristic, 0.756; multivariate HR/SD for polygenic risk score 1.71 [95% CI: 1.67–1.74]; multivariate HR/50 nmol/L Lp(a) 1.13 [95% CI: 1.11–1.15]) in combining CAD GPS_{Mult} with serum Lp(a) levels (Lp(a) alone area under the curve of the receiver operating characteristic, 0.737; HR: 50 nmol/L of Lp(a) 1.17 [95% CI: 1.15–1.19]).

These results should be interpreted within the context of the previously described[3] generalizability limitations of polygenic risk scores, the UK Biobank, the relationship of genetic variants with Lp(a) concentrations and risk of ASCVD, and the available immunoassay for Lp(a) measurement, which is not fully isoform-insensitive.

In conclusion, while Lp(a) is a highly heritable biomarker for ASCVD, it remains a modest contributor to CAD polygenic risk and is therefore not clinically reliable to identify high CAD GPS_{Mult}.

Acknowledgments

This work was supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (to Dr Patel); grants R01HL1427 (to Dr Natarajan), R01HL148565 (to Dr Natarajan), R01HL148050 (to Dr Natarajan), K08HL168238 (to Dr Patel) from the National Heart, Lung, and Blood Institute; and grant 1U01HG011719 from the National Human Genome Research Institute (to Drs Patel and Natarajan). Dr Natarajan has received research grants from Allelica, Apple, Amgen, Boston Scientific, Genentech/Roche, and Novartis; personal fees from Allelica, Apple, AstraZeneca, Blackstone Life Sciences, Foresite Labs, Genentech/Roche, GV, HeartFlow, Magnet Biomedicine, and Novartis; scientific advisory board membership of Esperion Therapeutics, Preciseli, and TenSixteen Bio; scientific cofounder of TenSixteen Bio; equity in Preciseli and TenSixteen Bio; and spousal employment at Vertex Pharmaceuticals, all unrelated to the present work. All other authors have reported that they have no relationship relevant to the contents of this paper to disclose. The authors thank all the participants and staff of the UK Biobank study. This analysis of data from the UK Biobank was approved by the Mass General Brigham institutional review board and was performed under UK Biobank application #7089.

REFERENCES

1. Arnett DK, Blumenthal RSL, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2019;74:e177–e232. [PubMed: 30894318]
2. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med. 2020;382:244–255. [PubMed: 31893580]
3. Trinder M, Uddin MM, Finneran P, et al. Clinical utility of lipoprotein(a) and LPA genetic risk score in risk prediction of incident atherosclerotic cardiovascular disease. JAMA Cardiol. 2021;6:287–295.
4. Patel AP, Wang M, Ruan Y, et al. Polygenic score informed by genome-wide association studies of multiple ancestries and related traits improves risk prediction for coronary artery disease. Nat Med. 2023;29:1793–1803. [PubMed: 37414900]
5. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562:203–209. [PubMed: 30305743]

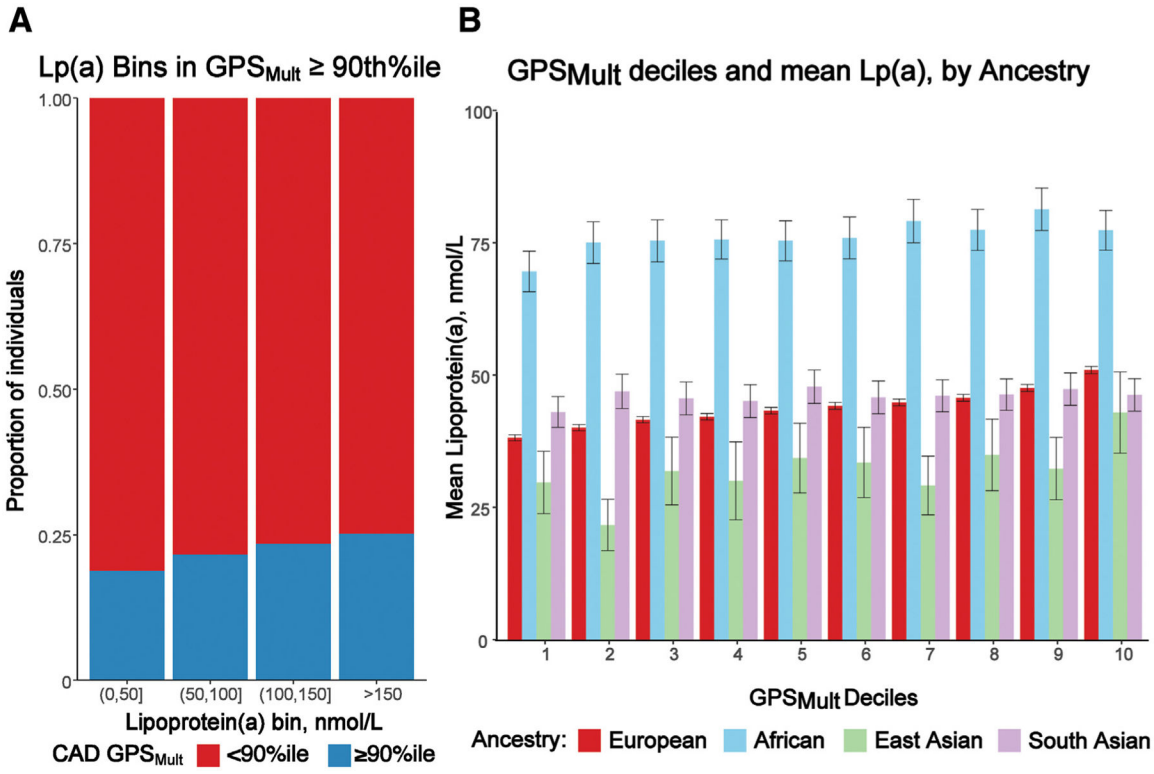

FIGURE 1.

Comparison of CAD GPS_{Mult} and Lipoprotein(a) Distributions

(A) The proportion of individuals at or above the 90th percentile of GPS_{Mult}, grouped by measured lipoprotein(a). (B) Mean levels of lipoprotein(a) (nmol/L) in study cohort, grouped by genetic ancestry across deciles of the GPS_{Mult}. 95% CI shown. CAD = coronary artery disease.