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Comparing the predictive value of genetic determinants and measured plasma levels of Lipoprotein(a) in cardiovascular risk assessment: evidence from a large-scale UK Biobank study

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ABSTRACT

Introduction: Lipoprotein(a) [Lp(a)] is a genetically influenced lipoprotein causally associated with atherosclerotic cardiovascular disease risk. This study compares the predictive value of genetically determined versus directly measured Lp(a) levels for major coronary events (MCE).

Methods: From UK Biobank data, participants with complete genetic and plasma Lp(a) data, including LPA variants rs3798220 and rs10455872, were selected. Cox proportional hazards models were employed to estimate the risk of MCE, associated with both Lp(a) genetic score (0, 1, or ≥2 minor alleles) and measured Lp(a) levels.

Results: Among 410,194 participants (mean age 57.25, 54% females), both Lp(a) genetic score and measured levels were independently associated with a stepwise increase in MCE risk. Within each genetic score group, increasing measured Lp(a) quintiles were associated with higher MCE. However, for individuals with similar measured Lp(a), MCE risk did not differ by genetic score.

Conclusions: Directly measured Lp(a) levels offer superior cardiovascular risk prediction, supporting the practice of measuring Lp(a) levels at least once in adulthood.

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality worldwide. Lipoprotein(a) [Lp(a)] is a lipoprotein subclass that has gained significant attention due to its strong association with an increased risk of ASCVD [1-3]. The concentration of plasma Lp(a) is primarily genetically determined, with 70–90% of its variability attributed to differences in the number of repeats in the DNA sequence encoding kringle IV type 2 (KIV-2), with the *LPA* gene playing a pivotal role [1]. Despite its strong genetic basis, Lp(a) levels vary widely among individuals, influencing cardiovascular risk assessment. While genetic variants associated with Lp(a) identifies predisposition, direct plasma Lp(a) measurement is gaining clinical relevance despite certain limitations [4]. Given its established causal role in cardiovascular diseases, it is crucial to determine whether genetic assessment or direct measurement provides a more accurate prediction of cardiovascular risk. By comparing the cumulative lifetime risk of major coronary events (MCE) based on genetic variants and measured plasma levels of Lp(a), we aim to identify the most effective approach for cardiovascular risk stratification, ultimately guiding clinical decision-making and improving patient outcomes.

Methods

This was a prospective observational cohort study based on data from the UK Biobank, a large, population-based biomedical database and research resource. Participants with complete genetic and principal component data who self-identified as being of white ancestry were evaluated. Only subjects genotyped for the *LPA* gene with available measured plasma levels of Lp(a) were included.

We used the number of inherited minor alleles of genetic variants rs3798220 (Ile4399→Met) and rs10455872 (intronic A/G polymorphism) to calculate a genetic score for each participant, with the reference group defined as participants with no copies of either mi-

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nor allele (Lp(a) score equal to 0), the second group defined as participants with one minor allele (Lp(a) score equal to 1), and the third group defined as participants with at least two minor alleles (Lp(a) score equal to 2).

Plasma Lp(a) concentration was measured in nmol/L at study enrolment using an immunoturbidimetric method on the Beckman Coulter AU5800 platform (Randox Bioscience, UK) [5]. The primary outcome for the study was major coronary events (MCE), defined as the first occurrence of either a fatal or non-fatal myocardial infarction (MI), or coronary revascularization. Cox proportional hazards models adjusted for age, sex, and the first 10 principal components of ancestry were used, with age as the time scale (hazard ratio [HR] and 95% confidence interval [95% CI]) to evaluated the effect of Lp(a) on MCE risk. Cumulative lifetime risk of MCE was plotted, using Kaplan-Meier curves.

All analyses were performed using Stata (version 17; StataCorp). A 2-tailed p-value less than 0.05 was considered statistically significant.

Results

A total of 410,194 participants were included in the study, with a mean (SD) age at enrolment of 57.25 (8.03) years; 54% were of female sex. The median [IQR] Lp(a) level in the overall population was 18.70 [7.40–72.90] nmol/L. Despite the same genetic determinants, participants exhibited substantial variability in measured Lp(a) levels: among individuals with an Lp(a) score of 0 (N=334,182), the median Lp(a) concentration was 13.56 [6.20–35.00] nmol/L, increasing to 146.3 [104.80–200.20] nmol/L for those with a score of 1 (N=72,087) and to 261.80 [190.21–336.00] nmol/L for those with a score of 2 (N=3,925). Notably, only 5.55% of individuals with an Lp(a) score of 0 had measured Lp(a) levels exceeding the cut-off of 125 nmol/L (which is considered elevated [2]), with this proportion increasing to 63.04% for those with a score of 1 and to 90.80% for those with a score of 2.

A clear stepwise increase in the risk of MCE was observed with rising genetic Lp(a) score. Compared to individuals with an Lp(a) score of 0, those with a score of 1 had a hazard ratio (HR) of 1.47 (95% CI 1.42–1.53, p <0.001), while those with a score of 2 had an even higher risk, with an HR of 1.86 (95% CI 1.67–2.08, p <0.001). We than stratified participants within each genetic score group into quintiles based on their measured plasma levels of Lp(a). Using the lowest quintile as the reference, we found a progressive increase in MCE risk from the first to the highest quintile within the same genetic score value (HR from 0.96 [95% CI 0.91–1.01] to 1.41 [95% CI 1.35–1.48] for Lp(a) score of 0; HR from 1.11 [95% CI 0.99–1.23] to 2.34 [95% CI 2.13–2.57] for Lp(a) score of 1; HR from 0.98 [95% CI 0.67–1.44] to 1.63 [95% CI 1.15–2.31] for Lp(a) score of 2).

When the lifetime risk of MCE was assessed across different genetic determinants (using individuals with an Lp(a) score of 0 as the reference group) in subjects matched for similar median Lp(a) plasma concentrations (**Figure 1**), the risk was found to be comparable.

Discussion

This large-scale study provides critical insights into the predictive value of Lp(a) in assessing the risk of MCE and the comparative utility of Lp(a) genetic determinants versus directly measured concentrations in clinical practice. Our findings demonstrate that, despite the strong genetic basis of Lp(a) variability, measured Lp(a) levels offer superior predictive value for cardiovascular risk assessment.

Specifically, measured Lp(a) concentrations showed a stronger association with MCE compared to genetic Lp(a) score, indicating that direct measurement provides a more accurate risk stratification tool. This finding is particularly relevant because Lp(a) levels are stable over a lifetime, requiring only a single measurement in adulthood to offer a reliable estimate of long-term cardiovascular risk [6]. Additionally, Lp(a) measurement is more accessible and cost-effective than genetic testing, making it a practical option for routine clinical use. However, genetic testing retains its value in specific scenarios, particularly for identifying individuals with a familial predisposition to elevated Lp(a) levels, which may be useful when measured Lp(a) values are borderline or inconclusive.

This study has several limitations. First, the observational nature of the analysis precludes definitive conclusions about causality. Although extensive adjustments were made, residual confounding cannot be ruled out. Second, the study population included only individ-

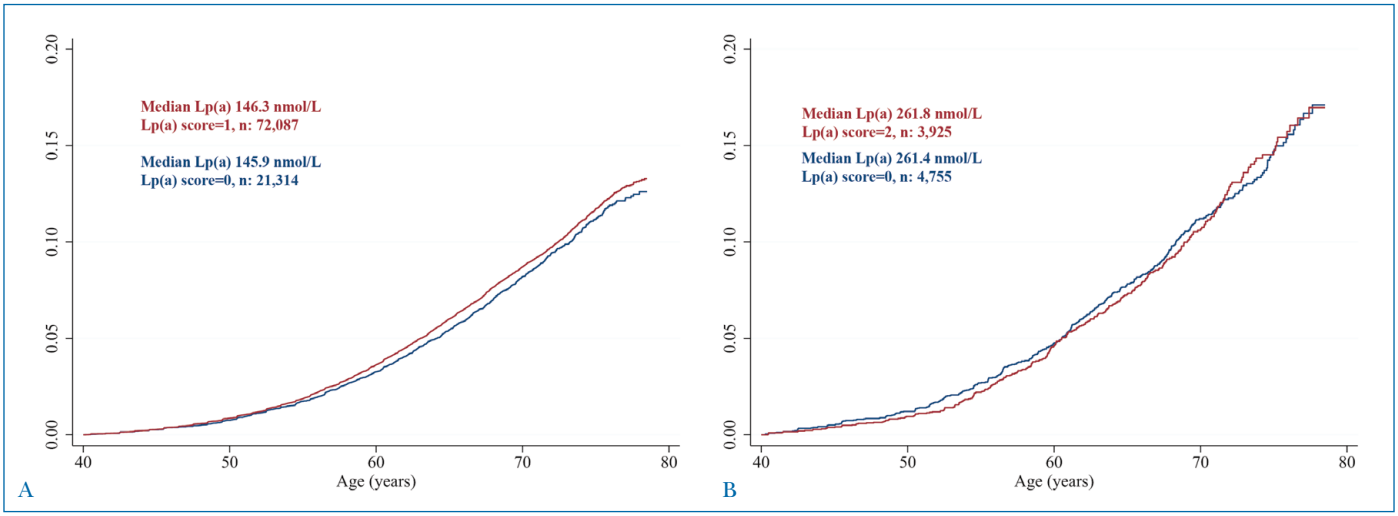

Figure 1 | **Survival curves showing the lifetime risk of major coronary events by Lp(a) score values among participants with comparable median Lp(a) concentrations.**
Panel A compares the lifetime risk for subjects with Lp(a) score of 1 to those with Lp(a) score of 0. Panel B compares the lifetime risk for subjects with Lp(a) score of 2 to those with Lp(a) score of 0.

uals of white ancestry, limiting the generalizability of the findings to other ethnic groups, especially considering that Lp(a) levels and their genetic determinants vary across populations. Third, Lp(a) was measured only once at baseline, although its lifelong stability mitigates this limitation. Finally, genetic scoring was limited to two well-established *LPA* variants, and additional *loci* may contribute to Lp(a) variability and associated risk, which were not captured in this analysis.

In conclusion, our study strongly supports prioritizing direct Lp(a) measurement for cardiovascular risk assessment, even when genetic data are available. When Lp(a) levels are unknown, clinical testing should be the first-line approach, given its greater predictive accuracy, simplicity, and cost-effectiveness in guiding preventive and therapeutic strategies.

Author contributions

E.O., F.G., and A.L.C. were responsible for the study concept and design. A.L.C was responsible for study management and data collection. E.O., F.G., and M.C. provided methodological and statistical knowledge and performed the analysis. A.L.C. and M.C. contributed to the interpretation of the results. E.O., and F.G. wrote the article. A.L.C. and M.C. critically revised for important intellectual content and approved the final article.

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Conflict of interest

All authors declare no support from any organization for the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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Ethical statement

Ethical approval was not required for this study.

Data Sharing Statement

The data that support the findings of this study are available on reasonable request from the corresponding author, F.G.

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