

Clinical Correlates of Elevated Lipoprotein(a) and Retinal AI-Derived Cardiovascular Risk in Adults with Diabetes and Prediabetes in a Hybrid Care Model

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Abstract

Introduction: Cardiovascular disease (CVD) is a leading global cause of death. Lipoprotein(a) [Lp(a)] is a genetic standalone risk factor for atherosclerotic cardiovascular disease (ASCVD), but its clinical use is limited. This study examines elevated Lp(a) in adults with diabetes and prediabetes within a digital hybrid care model and explores its associations with AI-derived retinal cardiovascular (Reti-CVD) scores.

Methods: A retrospective analysis was performed at Metabolic in Dubai, UAE, on adults aged 18 and older with Lp(a) measurements and relevant demographic, lipid, and clinical data. Participants were divided into two groups based on Lp(a) levels (<30 mg/dL vs. ≥30 mg/dL). Unadjusted lipid profiles were compared using independent t-tests on log-transformed values. Multivariable regression analyses were performed to adjust for statin use. Ordinal logistic regression was used to examine the association between Lp(a) and Reti-CVD risk category (Low, Moderate, High).

Results: Among 233 participants (73% male; mean age 46.8 ± 9.6 years), 32.2% had elevated Lp(a). Total cholesterol and LDL-C levels were higher in the elevated Lp(a) group in unadjusted comparisons (TC: 173.8 vs. 166.0 mg/dL; LDL-C: 109.6 vs. 100.0 mg/dL), though these differences did not reach statistical significance. Multivariable regression showed that there is a directional trend toward higher LDL-C in the ≥ 30 mg/dL Lp(a) group (adjusted geometric mean ratio 1.08, $P = 0.162$). Reti-CVD scores were comparable between groups on both continuous (adjusted $\beta = 0.57$, $P = 0.477$) and ordinal (adjusted OR = 1.14, $P = 0.672$) analysis. Individuals with elevated Lp(a) demonstrated a higher proportion in the moderate risk category (44.0% vs. 33.5%) in unadjusted analysis ($P = 0.195$).

Conclusions: Approximately one-third of adults with diabetes and prediabetes have elevated Lp(a), indicating genetic cardiovascular risk. This study highlights the potential value and support consideration for Lp(a) routine testing.

Keywords: lipoprotein(a); diabetes; prediabetes; cardiovascular risk; AI retinal scan; hybrid care model

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Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide. Traditional risk factors such as low-density lipoprotein cholesterol (LDL-C), hypertension, diabetes, and smoking account for a substantial portion of risk, but residual risk remains unexplained in many patients. In recent years, lipoprotein(a) [Lp(a)] has emerged as a genetically determined, independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis (AVS).^{1,2}

Lp(a) is an LDL-like particle linked to apolipoprotein(a) (apo[a]). The apo(a) moiety is homologous to plasminogen and thus confers prothrombotic and antifibrinolytic properties in addition to atherogenicity.³ Lp(a) also carries oxidized phospholipids, which promote vascular inflammation and plaque vulnerability.⁴ Genetic and Mendelian randomization studies strongly support a causal role of elevated Lp(a) in coronary artery disease (CAD), ischemic stroke, and AVS.^{2,5} Because approximately 90% of Lp(a) variation is genetically determined and levels remain stable over a lifetime, a single measurement may suffice to stratify long-term risk.^{6,7}

In observational cohorts, individuals with extreme Lp(a) values have substantially higher odds of myocardial infarction, CAD, and stroke. In this, extreme Lp(a) levels conferred approximately 2.5-fold higher odds of myocardial infarction and CAD in one large study.⁸ Elevated Lp(a) can justify more aggressive LDL-C lowering (e.g., PCSK9 inhibitors) or closer surveillance even when LDL-C is controlled.³ Moreover, novel antisense oligonucleotides and small interfering RNAs specifically targeting Lp(a) are in advanced clinical development, which may shift the emphasis toward early detection.¹

Despite its recognized role, Lp(a) testing in clinical practice remains rare. In the United States, fewer than 1% of adults had Lp(a) measured over a multi-year span,⁹ and even among patients with established ASCVD, testing is inconsistent.¹⁰ European and Canadian guidelines now recommend at least one lifetime measurement of Lp(a) in adults.¹¹ Additionally, the 2025 Brussels International Declaration further emphasized early detection and routine testing to reclassify and manage high-risk individuals.¹²

Recent advancements in artificial intelligence (AI)-enabled retinal imaging have led to innovative methods for predicting cardiovascular risk.¹³ The Retinal-CVD

(Reti-CVD) score is a non-invasive, AI-derived metric that captures phenotypic changes in the retinal microvasculature and has been proposed as a surrogate marker for systemic cardiovascular risk stratification through predicting the coronary calcium artery score.¹⁴ Unlike genetically determined biomarkers like Lp(a), the Reti-CVD score reflects dynamic vascular phenotypes that are influenced by disease.

Despite the fundamentally different origins of Lp(a) and Reti-CVD, genetic and phenotypic risk markers may provide complementary information when used alongside each other. However, limited evidence exists regarding their relationship. Therefore, the present study integrates these two complementary domains of risk assessment, aiming to determine the prevalence and clinical correlates of Lp(a) and examine the association between Lp(a) and Reti-CVD scores.

Methodology

Study design and setting

This study is a retrospective, observational cross-sectional analysis conducted at Metabolic (GluCare.-health), a digitally enabled outpatient clinic located in Dubai, United Arab Emirates. The study incorporated laboratory data from patients who visited the clinic between January 2024 and September 2025 and underwent Lp(a) testing as part of their cardiovascular risk evaluation.

Study population

Individuals aged 18 years and older who visited Metabolic and had recorded Lp(a) measurements were considered for inclusion. Participants were eligible if they had accessible demographic information, lipid profiles, and a clinical diagnosis of prediabetes or diabetes. In the analyses concerning Reti-CVD, only patients who had a completed retinal scan were taken into account. Reti-CVD scanning was conducted only in those with no prior history of ASCVD.

Data collection

Demographic variables collected included age, sex, and ethnicity. Clinical diagnoses were obtained from electronic medical records (EMR) and classified as either diabetes or prediabetes using the ADA diagnostic criteria, where those who had a hemoglobin A1c (HbA1c) between 5.7%–6.4% or fasting blood glucose of more than 100 mg/dL were in the prediabetes cohort.¹⁵ While those who had an HbA1c value of

$\geq 6.5\%$ were in the diabetes cohort.¹⁵ Additionally, information regarding statin therapy at the time of Lp(a) testing was recorded to indicate whether there was an active prescription for any statin use.

Blood samples were collected as part of standard clinical practice following established protocols. The concentration of Lp(a) was assessed using a standardized immunoassay technique called immunoturbidimetry, which detects the turbidity caused by the agglutination of Lp(a) particles when they react with anti-Lp(a) antibodies and is expressed in mg/dL.¹⁶ Although Lp(a) levels are often divided into 3 categories (normal, elevated, and highly elevated),¹⁷ in this paper, patients were divided into two groups: normal (<30 mg/dL) and elevated (≥ 30 mg/dL). This approach was taken to ensure adequate statistical power, reduce small subgroup sizes, and improve comparison reliability, given the cohort's moderate size. Those with Lp(a) levels above normal ranges (≥ 30 mg/dL) were grouped into one category, as they are associated with increased cardiovascular risk.¹⁸ A standard lipid profile, which included total cholesterol, LDL-Cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides, was determined using enzymatic assays.

AI retinal CVD

A group of patients received a Reti-CVD scan during their standard cardiovascular risk evaluation. Fundus images were obtained using the FDA-cleared and CE-Marked 3D OCT-1 Maestro2 multimodal OCT system (Topcon Corporation). The images were then assessed using AI-based software (Dr. Noon); the software's algorithm assessed the retinal images, which uses a confirmed deep learning model that estimates the percentage of 5-year cardiovascular risk by predicting the probability of coronary artery calcium.¹⁷ In the pivotal validation study, the model demonstrated good discrimination for cardiovascular risk prediction and was evaluated across multiple international cohorts, including individuals with diabetes.¹⁷ However, the validation dataset was primarily derived from a non-Middle Eastern population, and therefore its generalizability to this region remains uncertain.

The model generates a continuous risk score that is stratified into three categories for clinical interpretation: low (<31), moderate (31–40), and high (≥ 41) risk. These thresholds are empirically derived from the distribution of risk scores in the original validation cohorts and their corresponding associations with cardiovascular outcomes, although they should

be interpreted as risk stratification aids rather than diagnostic cut-offs.

Statistical analysis

Participants were categorized based on Lp(a) levels into two groups (<30 mg/dL and ≥ 30 mg/dL). Descriptive statistics were summarized as mean $\pm$ SD or median and interquartile range (IQR) as appropriate. All lipid parameters were logarithmically transformed ($\log_{10}$) prior to analysis to correct for skewness. The transformed lipid parameters were compared between the two Lp(a) levels using independent sample *t*-test. The unadjusted association between Lp(a) category and Reti-CVD risk classification was assessed using the chi-square test.

To address potential confounding, multivariable regression analyses were performed. For each log-transformed lipid parameter and the continuous Reti-CVD score, multivariable linear regression was used with adjustment for age, sex, statin use (yes/no), and primary diagnosis (diabetes vs. prediabetes). Regression coefficients (β) and 95% confidence intervals (CIs) are reported; for lipid outcomes, β coefficients were back-transformed to geometric mean ratios ($\text{GMR} = 10^{\beta}$) to aid clinical interpretation. For the Reti-CVD ordinal outcome (Low/Moderate/High), ordinal logistic regression under the proportional odds model was used with the same covariate set, with results reported as odds ratios (ORs) with 95% CIs. A binary logistic regression comparing $\geq$ Moderate vs. Low Reti-CVD risk category was additionally performed as a sensitivity analysis. To further characterize the role of statin therapy, stratified analyses of lipid parameters and Reti-CVD score by Lp(a) group were performed separately within statin users and non-users. A two-sided *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS version 29 (Armonk, NY, USA) and verified independently using Stata (StataCorp, College Station, TX, USA).

Results

Study population

Among the 233 participants, 158 (67.8%) had Lp(a) < 30 mg/dL and 75 (32.2%) had Lp(a) ≥ 30 mg/dL. The mean age of the total participants was 46.82 ± 9.61 years, with comparable mean ages between the two groups. Males constituted the majority of the cohort (73.0%), and a similar sex distribution was observed between Lp(a) categories. Most participants

Table 1. Characteristics of the Study Population by Lp(a) Category

Characteristic	Total n (%)	Lp(a) <30 n (%)	Lp(a) ≥30 n (%)
Number of patients	233 (100%)	158 (67.8%)	75 (32.2%)
Age (years), mean ± SD	46.82 ± 9.61	47.42 ± 9.04	45.57 ± 10.66
Sex, Male	170 (73.0%)	118 (69.4%)	52 (30.6%)
Sex, Female	63 (27.0%)	40 (63.5%)	23 (36.5%)
Ethnicity, Asian	104 (44.6%)	71 (68.3%)	33 (31.7%)
Ethnicity, Black	6 (2.6%)	4 (66.7%)	2 (33.3%)
Ethnicity, Middle Eastern	68 (29.2%)	46 (67.6%)	22 (32.4%)
Ethnicity, White	46 (19.7%)	30 (65.2%)	16 (34.8%)
Ethnicity, Other	9 (3.9%)	7 (77.8%)	2 (22.2%)
Prediabetes	35 (15.0%)	22 (62.9%)	13 (37.1%)
Diabetes	198 (85.0%)	136 (68.7%)	62 (31.3%)
Statin therapy, No	102 (43.8%)	63 (61.8%)	39 (38.2%)
Statin therapy, Yes	131 (56.2%)	95 (72.5%)	36 (27.5%)

Values are frequencies (%) unless otherwise stated.
SD, standard deviation.

were of Asian ethnicity (44.6%), followed by Middle Eastern (29.2%) and White (19.7%). The majority of participants had diabetes (85.0%), while 15.0% had pre-diabetes; proportions were comparable across Lp(a) categories. More than half of the participants were receiving statin therapy (56.2%). Statin use was more frequent in the Lp(a) < 30 mg/dL group (72.5%) compared with the Lp(a) ≥ 30 mg/dL group (27.5%) (Table 1).

Unadjusted lipid comparisons

Total cholesterol levels were higher in the Lp(a) ≥ 30 mg/dL group compared with the Lp(a) < 30 mg/dL group [173.8 (162.2–186.2) vs. 166.0 (158.5–173.8) mg/dL, $P = 0.290$]. Similarly, LDL-C tended to be higher in the Lp(a) ≥ 30 mg/dL group [109.6 (107.2–120.2) vs. 100.0 (91.2–100.0) mg/dL, $P = 0.104$]. HDL-C levels were comparable between groups ($P = 0.381$). Triglyceride levels were lower in the Lp(a) ≥ 30 mg/dL group [123.0 (107.2–141.3) vs. 141.3 (125.9–154.9) mg/dL, $P = 0.164$] (Table 2).

Multivariable-Adjusted lipid analyses

After adjusting for age, sex, statin use, and diabetes status in multivariable linear regression ($n = 228$ with complete lipid data), no lipid parameter showed a

statistically significant independent association with elevated Lp(a) (Tables 3). For LDL-C, the adjusted β coefficient for Lp(a) ≥ 30 mg/dL was 0.035 (95% CI –0.014, 0.084; $P = 0.162$), corresponding to a GMR of 1.08, indicating a directional trend toward approximately 8% higher geometric mean LDL-C in the Lp(a) ≥ 30 mg/dL group. For total cholesterol, the adjusted GMR was 1.03 ($P = 0.482$). HDL-C (GMR 1.01, $P = 0.666$) and triglycerides (GMR 0.89, $P = 0.199$) showed no meaningful association. Diabetes diagnosis was independently and strongly associated with lower triglyceride ($\beta = -0.111$, $P < 0.001$) and lower LDL-C ($\beta = -0.168$, $P < 0.001$). Female sex was independently associated with higher TC, LDL-C, and HDL-C (all $P < 0.05$).

Reti-CVD score and category

Figure 1 represents the distribution of cardiovascular risk categories classified using Reti-CVD scanning across the Lp(a) levels. In the low Reti-CVD category, a similar proportion was observed in both Lp(a) groups (48.7% for Lp(a) < 30 mg/dL vs. 45.3% for Lp(a) ≥ 30 mg/dL). Individuals with elevated Lp(a) levels (≥30 mg/dL) showed a higher proportion in the moderate risk category compared with those with Lp(a) < 30 mg/dL (44.0% vs. 33.5%), indicating a cluster towards higher Lp(a) levels in moderate risk groups, in parallel with higher LDL-C and total cholesterol, but neither HDL-C nor triglyceride levels. The overall association between Lp(a) category and Reti-CVD risk classification was not statistically significant (chi-square $P = 0.195$).

Lipid parameters did not differ significantly across Reti-CVD risk categories in unadjusted comparisons (Figure 2), with total cholesterol ($P = 0.205$), LDL-C ($P = 0.179$), and triglycerides ($P = 0.435$) showing no meaningful gradient; HDL-C showed a borderline trend toward lower levels in the high-risk group ($P = 0.078$).

Table 2. Unadjusted Comparison of Lipid Parameters and Reti-CVD Score by Lp(a) Category

Parameter	Lp(a) <30 median (IQR)	Lp(a) ≥30 median (IQR)	P value*
Total Cholesterol (mg/dL)	166.0 (158.5, 173.8)	173.8 (162.2, 186.2)	0.290
LDL-C (mg/dL)	100.0 (91.2, 100.0)	109.6 (107.2, 120.2)	0.104
HDL-C (mg/dL)	46.8 (44.7, 49.0)	47.9 (44.7, 51.3)	0.381
Triglycerides (mg/dL)	141.3 (125.9, 154.9)	123.0 (107.2, 141.3)	0.164
Reti-CVD Score, mean ± SD	31.7 ± 8.72	30.92 ± 9.19	0.519 [†]
Reti-CVD Risk %, Median (IQR)	64 (41, 81)	61 (42, 80)	—

* P values from independent samples t -test on $\log_{10}$ -transformed values.

[†] t -test on continuous score.

Table 3. Multivariable Regression Analyses: association of Lp(a) Category with Lipid Outcomes and Reti-CVD

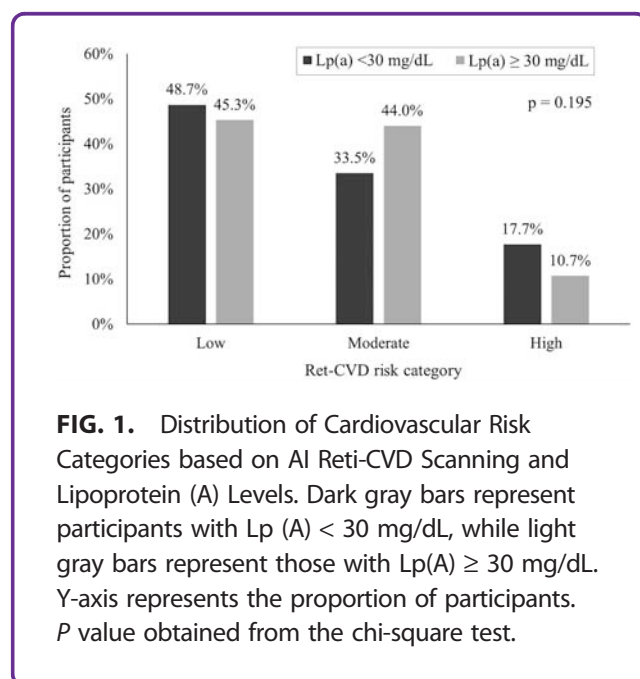
Multivariable linear regression — Log-transformed lipid outcomes				
Predictor	β coefficient	95% CI	P value	GMR
Outcome: Log ₁₀ total cholesterol ($n = 228$, $R^2 = 0.183$)				
Lp(a) ≥ 30 mg/dL	0.012	(−0.021, 0.045)	0.482	1.027
Age (per year)	−0.002	(−0.003, −0.000)	0.037	0.996
Female sex	0.062	(0.029, 0.095)	<0.001	1.153
Statin use	0.017	(−0.013, 0.048)	0.264	1.041
Diabetes	−0.111	(−0.155, −0.067)	<0.001	0.774
Outcome: Log ₁₀ LDL-C ($n = 228$, $R^2 = 0.158$)				
Lp(a) ≥ 30 mg/dL	0.035	(−0.014, 0.084)	0.162	1.084
Age (per year)	−0.003	(−0.006, −0.000)	0.024	0.993
Female sex	0.066	(0.014, 0.119)	0.014	1.165
Statin use	0.025	(−0.023, 0.074)	0.308	1.060
Diabetes	−0.168	(−0.228, −0.107)	<0.001	0.679
Outcome: Log ₁₀ HDL-C ($n = 228$, $R^2 = 0.222$)				
Lp(a) ≥ 30 mg/dL	0.006	(−0.022, 0.035)	0.666	1.014
Age (per year)	−0.001	(−0.002, 0.001)	0.527	0.999
Female sex	0.119	(0.088, 0.150)	<0.001	1.315
Statin use	−0.008	(−0.036, 0.020)	0.558	0.981
Diabetes	−0.022	(−0.061, 0.016)	0.273	0.951
Outcome: Log ₁₀ Triglycerides ($n = 227$, $R^2 = 0.032$)				
Lp(a) ≥ 30 mg/dL	−0.049	(−0.125, 0.026)	0.199	0.892
Age (per year)	−0.000	(−0.004, 0.003)	0.953	1.000
Female sex	−0.077	(−0.156, 0.003)	0.059	0.838
Statin use	−0.001	(−0.074, 0.072)	0.969	0.997
Diabetes	0.060	(−0.034, 0.155)	0.211	1.149
Multivariable regression — Reti-CVD outcomes				
Predictor	β /or	95% CI	P value	Model
Linear regression: Reti-CVD continuous score (β , $n = 233$, $R^2 = 0.537$)				
Lp(a) ≥ 30 mg/dL	0.572	(−1.009, 2.152)	0.477	Linear
Age (per year)	0.668	(0.584, 0.752)	<0.001	Linear
Female sex	−4.667	(−6.708, −2.626)	<0.001	Linear
Statin use	−1.445	(−3.127, 0.236)	0.092	Linear
Diabetes	1.214	(−1.119, 3.547)	0.306	Linear
Ordinal logistic regression: Reti-CVD category Low/Moderate/High (OR, $n = 233$, Pseudo $R^2 = 0.259$)				
Lp(a) ≥ 30 mg/dL	1.138	(0.626, 2.069)	0.672	Ordinal
Age (per year)	1.201	(1.153, 1.251)	<0.001	Ordinal
Female sex	0.247	(0.119, 0.515)	<0.001	Ordinal
Statin use	0.838	(0.471, 1.490)	0.547	Ordinal
Diabetes	1.899	(0.784, 4.595)	0.155	Ordinal
Binary logistic: $\geq$ Moderate vs Low Reti-CVD risk (OR, $n = 233$, sensitivity)				
Lp(a) ≥ 30 mg/dL	2.157	(0.987, 4.713)	0.054	Logistic
Age (per year)	1.265	(1.186, 1.349)	<0.001	Logistic
Female sex	0.246	(0.104, 0.584)	0.001	Logistic
Statin use	0.940	(0.463, 1.908)	0.863	Logistic
Diabetes	2.386	(0.895, 6.359)	0.082	Logistic

β : unstandardized regression coefficient (log₁₀ scale). GMR, geometric mean ratio (10^{β}); GMR > 1 indicates higher geometric mean in the elevated Lp(a) group. Each sub-panel is a separate regression model adjusted for age, sex, statin use, and diabetes status. Robust standard errors used throughout.

Linear regression, β coefficients for continuous Reti-CVD score. Ordinal logistic (primary): OR under proportional odds assumption. Binary logistic (sensitivity): OR for $\geq$ Moderate vs. Low. All models adjusted for age, sex, statin use, and diabetes status.

In multivariable-adjusted analyses, Lp(a) status showed no independent association with the continuous Reti-CVD score ($\beta = 0.57$, 95% CI −1.01 to 2.15, $P = 0.477$; $R^2 = 0.537$). Ordinal logistic regression, used as the primary model for the three-category Reti-CVD outcome, confirmed no significant association

(OR 1.14, 95% CI 0.63–2.07, $P = 0.672$). However, age and female sex were the dominant determinants of Reti-CVD score and category in all adjusted models (both $P < 0.001$). In a sensitivity binary logistic regression comparing $\geq$ Moderate vs. Low Reti-CVD risk, elevated Lp(a) was associated with an approximately two-



fold higher odds (OR 2.16, 95% CI 0.99–4.71, $P = 0.054$) (Tables 3).

Stratified analysis by statin use

In stratified analyses within statin users ($n = 131$), no lipid parameter differed significantly between Lp(a) groups (all $P > 0.55$). Among statin non-users ($n = 102$), directional trends toward higher triglycerides ($P = 0.066$), higher LDL-C ($P = 0.069$), and lower triglycerides ($P = 0.068$) in the elevated Lp(a) group were observed, consistent with the adjusted model ($n = 39$ with Lp(a) ≥ 30 mg/dL) (Table 4).

Discussion

This study included patients diagnosed with diabetes and prediabetes who attended a digitally enabled clinic in Dubai. Approximately one-third of these patients had elevated Lp(a) levels (≥30 mg/dL). This prevalence is consistent with previously reported estimates from the UAE and the broader Gulf region, where elevated Lp(a) has been observed in 15%–30% of individuals tested.^{19,20} Our findings contribute to this regional evidence by specifically focusing on metabolically high-risk individuals, highlighting the significant burden of genetically mediated lipid risk among those with impaired glucose metabolism.

The demographic and clinical characteristics of patients with elevated Lp(a) levels (≥30 mg/dL) were similar to those with lower levels, including age, sex

distribution, ethnicity, and diabetes status. This aligns with the recognized genetic determination of Lp(a), which remains relatively stable over the lifespan and is largely independent of lifestyle or glycemic control.^{21,22} The absence of demographic differences suggests that elevated Lp(a) may go unnoticed unless specifically tested, especially in individuals with traditional cardiometabolic risk factors.

In unadjusted analyses, participants with elevated Lp(a) (≥30 mg/dL) showed numerically higher total cholesterol and LDL-C, consistent with the known structural contribution of Lp(a) to measured LDL-C concentrations.^{23,24} This observation is biologically plausible since Lp(a) has a similar structure to LDL particles and contributes to measured LDL-C concentrations.^{23,24} These findings strengthen the notion that patients exhibiting elevated levels of Lp(a) may continue to experience residual atherosclerotic risk, even when their LDL-C levels appear to be within acceptable ranges. This phenomenon, characterized by an ongoing risk for cardiovascular issues despite seemingly well-managed LDL-C levels, has been thoroughly explored and documented in earlier research studies.^{25–27}

Triglyceride levels were found to be lower in the elevated Lp(a) group in unadjusted analysis, consistent with prior epidemiological and genetic data reporting an inverse relationship between Lp(a) and triglyceride concentrations.^{28,29} This inverse correlation may reflect the independent hepatic synthesis pathway of Lp(a), which is not dependent on triglyceride-rich lipoprotein metabolism.²⁸ This emphasizes that conventional lipid profiles may not fully capture Lp(a)-related cardiovascular risk, particularly in patients with diabetes, where triglycerides are often elevated due to insulin resistance.³⁰ The findings may also be influenced by differences in the use of lipid-lowering therapies. In this cohort, only statin medication use was captured, and information on other triglyceride-lowering agents was not collected. Therefore, it is possible that residual confounding from unmeasured lipid-lowering treatments still exists but cannot be excluded.

Statin use was substantially more prevalent in the Lp(a) < 30 mg/dL group (72.5% vs. 27.5%). This finding may indicate a bias in treatment selection, clinicians focusing on LDL reduction, or varying referral patterns, not captured in the present analysis. Statins are known to have minimal or modestly increasing effects on Lp(a) levels, which is genetically-determined

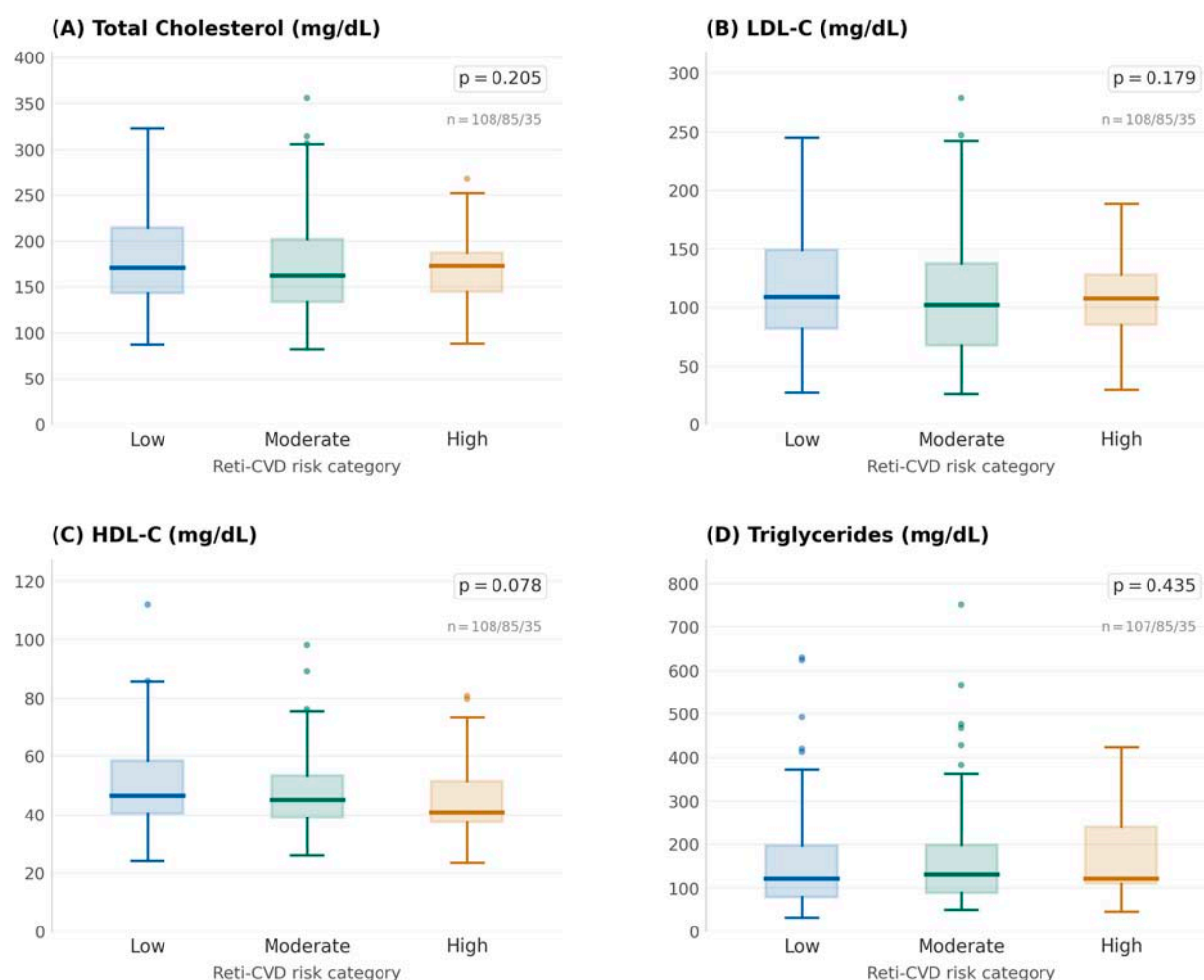


FIG. 2. Comparison of Lipid Profile Parameters Across Reti-CVD Risk Categories. Box-and-whisker plots depicting the distribution of **(A)** Total Cholesterol, **(B)** LowDensity Lipoprotein Cholesterol (LDL-C), **(C)** High-Density Lipoprotein Cholesterol (HDL-C), and **(D)** Triglycerides across Reti-CVD risk categories (Low, Moderate, and High). The boxes represent the interquartile range (IQR), the horizontal line within each box denotes the median, the cross (×) denotes the mean value, and the individual dots represent outliers. P values were obtained from one-way analysis of variance (ANOVA).

and independent of hepatic LDL receptor-mediated clearance, the primary pathway targeted by statins.³¹ This further reinforces the importance of routine Lp(a) measurement to identify residual cardiovascular risk beyond statin therapy. Such assessment may help guide consideration for additional therapies, including PCSK9 inhibitors, which have been shown to reduce Lp(a) by an average of 27%.^{32,33}

In the multivariable-adjusted models, no lipid parameter showed a statistically significant independent association with Lp(a) category. Nevertheless, the

direction of effect remained consistent, with LDL-C trending to be higher in participants in the elevated Lp(a) group (adjusted GMR 1.08, $P = 0.162$). Stratified analyses restricted to statin non-users showed numerically stronger and borderline statistical significance for LDL-C ($P = 0.069$), suggesting that the relationship between LDL-C and Lp(a) may be partially attenuated by lipid-lowering therapy.

The use of AI-driven retinal cardiovascular risk assessment added a novel perspective to this analysis. In multivariable-adjusted models, Lp(a) category was

Table 4. Stratified Unadjusted Comparisons by Statin Use

Parameter	Statin users Lp(a) < 30	Statin users Lp(a) ≥ 30	<i>p</i>	Non-users Lp(a) < 30	Non-users Lp(a) ≥ 30	<i>P</i>
Log ₁₀ TC	2.229	2.223	0.845	2.210	2.256	0.066
Log ₁₀ LDL-C	2.003	2.026	0.558	1.984	2.055	0.069
Log ₁₀ HDL-C	1.665	1.654	0.633	1.671	1.709	0.110
Log ₁₀ TG	2.136	2.128	0.878	2.158	2.055	0.068
Reti-CVD score	31.5 ± 8.4	31.9 ± 8.0	0.772	32.0 ± 9.2	30.0 ± 10.2	0.311

Values are means of log₁₀-transformed lipid parameters (independent samples t-test). Statin users *n* = 131 (Lp(a) < 30: *n* = 95, Lp(a) ≥ 30: *n* = 36); Non-users *n* = 102 (Lp(a) < 30: *n* = 63, Lp(a) ≥ 30: *n* = 39).

not independently associated with either the continuous Reti-CVD score ($\beta = 0.57$, $P = 0.477$) or the ordinal Reti-CVD risk category (OR 1.14, $P = 0.672$). While sensitivity analyses identified a borderline increase in the odds of moderate or high retinal risk among participants with elevated Lp(a), this finding did not reach statistical significance and should be interpreted cautiously. This could be attributed to the fundamental biological differences between the two measures, where it is not yet established whether Reti-CVD algorithms are expected to fully capture the vascular consequence of elevated Lp(a). Although Lp(a) is associated with ASCVD, its effect may be mediated primarily through large-vessel atherosclerotic processes that develop over decades and may not be reflected in retinal microvascular features that are detected by Reti-CVD.¹ Consequently, the lack of association may not be interpreted as evidence against the relevance of Lp(a), but rather as an indication that genetically mediated risk and Reti-CVD may provide complementary information.

Age and female sex were the dominant predictors of Reti-CVD score in all models, which is consistent with prior evidence showing that retinal deep-learning algorithm captures age and sex-related biological features and that these variables contribute substantially to Reti-CVD risk assessment.^{34–36} A borderline, non-significant trend toward higher odds of moderate or greater Reti-CVD risk in the elevated Lp(a) group (OR 2.16, 95% CI 0.99–4.71, $P = 0.054$) was identified in a binary logistic sensitivity analysis, but this finding was sensitive to model specification and should not be over-interpreted.

These findings emphasize the importance of measuring Lp(a) in individuals with prediabetes and diabetes, who are already at increased risk for accelerated atherosclerosis. Although elevated Lp(a) was not significantly associated with Reti-CVD in the present study, the absence of statistical significance should not diminish its established clinical relevance.

Mendelian randomization studies have demonstrated that Lp(a) is a causal risk factor for ASCVD.⁵ Additionally, the prevalence of elevated Lp(a), approximately one-third in this high-risk cohort, represents a substantial genetic risk burden that would remain undetected without systematic testing. As novel Lp(a)-lowering therapies continue to advance through clinical development and international guidelines increasingly recommending at least one lifetime Lp(a) measurement^{11,12} These findings are particularly relevant to clinical practice in the Middle East, where cardiovascular risk is high, and lipid management often falls short of guideline targets.³⁷

Strengths and Limitations

This study has several strengths, as it is one of the first from the Middle East to evaluate the prevalence of elevated Lp(a) in adults with diabetes and prediabetes and to use an AI-derived retinal cardiovascular risk assessment tool within a digitally enabled hybrid care model. It incorporated detailed clinical, lipid, and retinal imaging data and used multivariable regression analyses to address confounding factors such as age, sex, diabetes status, and statin use. Sensitivity and stratified analyses further supported the robustness of the findings despite disparities in statin therapy.

However, there are notable limitations. The single-center, cross-sectional retrospective design limits causal inference and the assessment of long-term cardiovascular implications, therefore, limits the generalizability of the results. Additionally, Lp(a) testing was part of routine risk assessment rather than systematic screening, potentially introducing selection bias. The sample size, especially in subgroup analyses, may also limit the detection of modest associations. Lastly, while Reti-CVD has shown promise as an AI tool for cardiovascular risk assessment, further validation in Middle Eastern populations is needed, along with investigations into the relationship between genetically

mediated risk factors like Lp(a) and retinal AI-derived risk signatures in larger prospective cohorts.

Conclusion

In a cohort of adults with diabetes and prediabetes receiving care in a digitally enabled hybrid model, approximately one-third had elevated Lp(a) levels, indicating significant genetic cardiovascular risk. Directional trends in LDL-C remained consistent with expected biological effects. These findings demonstrate that elevated Lp(a) is common among adults with diabetes and prediabetes and underscore its potential value as an additional risk stratification marker beyond conventional lipid parameters.

Authors' Contributions

J.A. conceptualized the study, coordinated data analysis, and led article writing. I.R. and M.M. contributed to conceptualizing the study and clinical oversight. H.Z. contributed with methodological design and article revision. G.P. was responsible for statistical analysis and figure/table generation. M.G.I. was responsible for the revision of the analysis. A.A. and A.H. contributed to article revisions. I.A. supervised the project and provided critical review of the final draft. All authors read and approved the final article.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Statement of Ethics

This study was reviewed and approved by the Dubai Scientific Research Ethics Committee under the Dubai Health Authority (DHA) (Approval number: DSREC-02/2025_09). The requirement for written informed consent was waived due to the retrospective nature of the study and use of de-identified data.

Author Disclosure Statement

J.A., I.R., M.M., H.Z., M.G.I., A.A., A.H., and I.A. are all affiliated with the metabolic clinic (GluCare.health). I.H. and A.H. are co-founders of the metabolic clinic. The authors declare no other competing interests.

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