

# Lipoprotein(a): Levels and Reference Intervals Among People in Saudi Arabia

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**Purpose:** Blood Lp(a) concentration is recognized as an independent risk factor for cardiovascular disease (CVD). Population-based lipoprotein(a) (Lp[a]) research in Saudi Arabia is rare. Thus, the primary goal of this pilot study was to identify age- and sex-specific reference ranges for Lp(a) levels, in addition to the associations between Lp(a) levels and other atherosclerotic markers in Saudi individuals.

**Patients and methods:** A five-year retrospective study of Lp(a) and lipid markers in Saudi patients was conducted using the Al-Borg diagnostics database (2015–2020). The population sample consisted of 361 Saudi individuals aged 18–93 years (162 males, 199 females). An immunoturbidimetric technique was used to determine Lp(a) concentration.

**Results:** The mean and median Lp(a) levels in the study population were 35 nmol/L and 50 nmol/L, respectively. Sex and age did not influence Lp(a) values. Lp(a) values showed a minor correlation with other atherosclerotic markers when the Pearson correlation coefficient was used. In Saudi Arabia, the distribution of Lp(a) concentrations is skewed to the left, favoring lower values.

**Conclusion:** Lp(a) levels in individuals residing in Saudi Arabia were comparable to those observed in other ethnic groups. Additionally, standardizing Lp(a) measurements according to sex and age may enhance broader applicability and facilitate comparisons across different populations. However, larger studies are required to provide more comprehensive data for comparison.

**Keywords:** lipoprotein(a), lipids, cardiovascular disease, reference range, reference interval, Saudi Arabia

## Introduction

Kåre Berg, a Norwegian scientist, first discovered lipoprotein(a) [Lp(a)], as known as “Lp little a”, approximately six decades ago.<sup>1</sup> Presumed to be a genetic variant of low-density lipoprotein (LDL),<sup>2</sup> a mysterious class of cholesterol-carrying lipoproteins observed in plasma. A distinct unit of apolipoprotein (apo) B-100 (apo-B100) is linked to a distinct unit of a protein designated apolipoprotein(a) [apo(a)] to form the Lp(a) protein moiety.<sup>1</sup> Apo(a) is a polymorphic glycoprotein with a portion that is rich in carbohydrates whose mRNA is nearly exclusively formed in the liver.<sup>3</sup> Lp(a) possesses a cholesterol-carrying lipoprotein unit indistinguishable from LDL in terms of composition and molecular characteristics.<sup>1</sup> Because Lp(a) and LDL are physiologically separate due to the existence of apo(a), the unique characteristics of Lp(a), such as its mass and compactness heterogeneity, are almost entirely mediated by apo(a).<sup>4</sup> The observation that apo(a) has a structural resemblance to plasminogen (PLG), an important enzyme in fibrinolysis, establishes a possible connection between Lp(a) and thrombosis.<sup>5</sup> The LPA gene, which originates from the replication and modification of the kringle (K) domains of the PLG gene, regulates the plasma Lp(a) concentration.<sup>5</sup>

In contrast to LDL-C, which follows a normal Gaussian distribution in the population, Lp(a) levels are skewed toward lower values in the majority of populations studied to date,<sup>6</sup> such that the majority of individuals have low Lp(a) levels and the tail of individuals exhibits high Lp(a) levels and a correspondingly high cardiovascular disease (CVD) risk. Although Lp(a) levels in the atherothrombotic range interval are broadly acknowledged as > 30–50 mg/dL or > 75–125 nmol/L, additional studies are required to fully comprehend the importance of Lp(a) in CVD, including the Lp(a) risk cutoffs for CVD, to define population risk among ethnic communities.<sup>1</sup> Moreover, numerous cohort studies conducted in diverse populations and ethnic groups have shown an inverse link between low Lp(a) concentrations and increased risk of type 2 diabetes (T2D), indicating that the relationship is causal.<sup>7,8</sup> Over the entire range of Lp(a) levels, this association generally appeared to be nonlinear, with a significant increase in risk occurring only for very low concentrations of Lp(a), plateauing at moderate and high Lp(a) levels.<sup>9</sup> Low Lp(a) concentrations or those below 4 mg/dL (10 nmol/L), which correspond to the lowest quintile of the population, were demonstrated by Mora et al<sup>10,11</sup> to be associated with an elevated risk of T2D. This was significantly more obvious for the population's 2.5% with the lowest Lp(a) values. A population-based prospective Bruneck study also found that each standard deviation decrease in Lp(a) concentration was associated with a 12% increase in the incidence of type 2 diabetes. Their subsequent meta-analysis of four prospective cohort studies showed that those with the lowest Lp(a) concentrations had a higher risk of developing T2D, with the highest risk observed when Lp(a) was less than 7 mg/dL.<sup>11</sup>

However, owing to its probable involvement in tumor angiogenesis, a crucial stage in the growth and metastasis of malignancies, the role of Lp(a) in tumors has recently drawn increasing interest.<sup>12</sup> However, experimental trials have also identified anti-angiogenic and anti-tumor effects.<sup>13</sup>

Population-based research is required to develop precise Lp(a) indices for identifying relative risks for the prevention or management of CVD. To the best of our knowledge, no study has focused on the serum Lp(a) concentration reference ranges in the Saudi population. This study aimed to develop Lp(a) concentration-stratified reference ranges for individuals living in Saudi Arabia for use in future research and/or comprehension of preventative and treatment strategies for CVD based on Lp(a). In addition, this study aimed to examine the relationship between Lp(a) levels and diabetes-related biological markers in the blood, including fasting blood glucose and glycosylated hemoglobin A1c (HbA1c).

## Methods

### Study Population

This retrospective study was conducted at Al Borg Diagnostics Laboratories, Kingdom of Saudi Arabia, one of the largest referral laboratories in Saudi Arabia, between 2015 and 2020, based on laboratory records. Al-Borg Diagnostics analyzed the Lp(a) levels of individuals who visited private practice clinics and underwent Lp(a) testing. Lp(a) concentrations were measured in a Saudi population stratified by age and sex. The data were anonymized before analysis. This study was conducted in accordance with the Declaration of Helsinki and the Institutional Review Board of Al-Borg Diagnostics (No03/22) approved all operations involving human subjects. The Biomedical Ethics Unit waived the requirement for consent for participation because of the retrospective nature of the investigation and the absence of participant identities. The laboratory results of 361 participants (2015–2020) were obtained from the database. The sexes were separated, and age groupings were established. We included young individuals ( $\geq 18$  years), young adults (19–39 years), adults (40–59 years), and older adults (60 years).

### Blood Sample

Fasting blood samples were collected and immediately processed for total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), apolipoprotein B (Apo-B), Lp(a), C-reactive protein, and glucose levels. The LDL-C levels were calculated using the Friedewald equation. All measurements were performed by Al-Borg Diagnostics using a standard enzymatic colorimetric procedure. Lp(a) concentration was measured using an immunoturbidimetric assay. For the analysis, the Lp(a) results were divided into low ( $< 75$  nmol/L) and high ( $\geq 75$  nmol/L) concentrations.<sup>14</sup> A cut-off point of  $< 75$  nmol/L (300 mg/L) represented the 80th percentile of Lp(a) in our cohort.

## Statistics

In the descriptive statistical analysis, the mean value and standard deviation (SD) of continuous variables (fasting blood sugar [FBS], T-cholesterol, TG, HDL-C, LDL-C, and apoB) were estimated. The mean (Geometric Mean), Median, SD, Variance, Kurtosis, Skewness, and 10th–90th percentiles were used to describe the Lp(a) distribution. Student's *t*-test was used to examine the statistical significance between sexes. Statistical significance between age groups was examined using a one-way analysis of variance (ANOVA) and the multiple comparison method developed by Scheffe. Two-tailed *P*-values were reported, and those less than 0.01 were considered statistically significant. Correlation coefficients were computed to assess the relationship between Lp(a) levels and other atherogenic factors. This analysis was performed using the Pearson's correlation technique. The RStudio software suite was used for all statistical analyses (RStudio 2022.07.2+576 for macOS; RStudio Inc., Boston, MA, USA).

## Results

The mean age  $\pm$  SD of the studied population was  $50.59 \pm 16.48$  years. Table 1 represents the age and sex distribution of the participants. There were several differences between the sexes in the study population (Table 2). The mean  $\pm$  SD of total cholesterol (TC) was  $182.2 \pm 53.2$  mg/dl and  $207.7 \pm 36.6$  mg/dl ( $P < 0.001$ ) in men and women, respectively. The mean  $\pm$  SD of low-density lipoprotein (LDL-C) was  $113.8 \pm 44.7$  mg/dl and  $128.5 \pm 34.6$  mg/dl ( $P < 0.05$ ) in men and women, respectively. HDL, non-HDL, and LDL/HDL ratios were significantly higher in women than in men ( $P < 0.01$ ,  $P < 0.05$ , and  $P < 0.05$ , respectively). TG, apo-B, FBS, and HbA1c levels were similar in men and women, while Lp(a) and log-Lp (a) levels were significantly lower in men than in women ( $P < 0.01$ ) (Table 2).

Lp(a) concentrations in the study population are presented in (Figure 1). Lp(a) concentration stratified by age and sex is represented in (Figure 2). The Lp(a) distribution statistics, partitioned by sex, are also shown in Table 3. The median

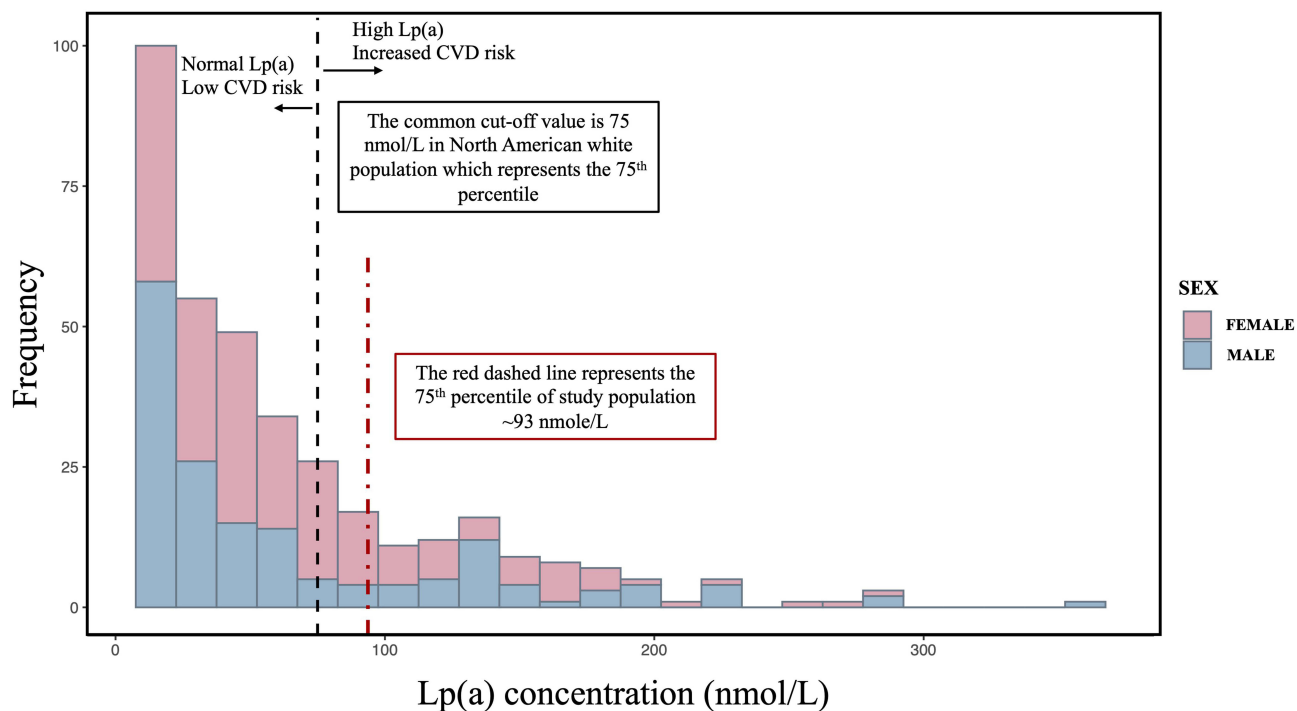
**Table 1** Subject Distribution by Age (in Years) and Sex

Age category	Total (N=361)		Males (N=162)		Females (N=199)	
	N	%	N	%	N	%
<20	9	2.49	2	1.23	7	3.51
20–40	97	26.86	44	27.16	53	26.63
40–60	148	40.99	68	41.97	80	40.20
$\geq 60$	107	29.63	48	29.62	59	29.64
M $\pm$ SD	$50.59 \pm 16.48$		$50.17 \pm 16.92$		$51.12 \pm 15.97$	

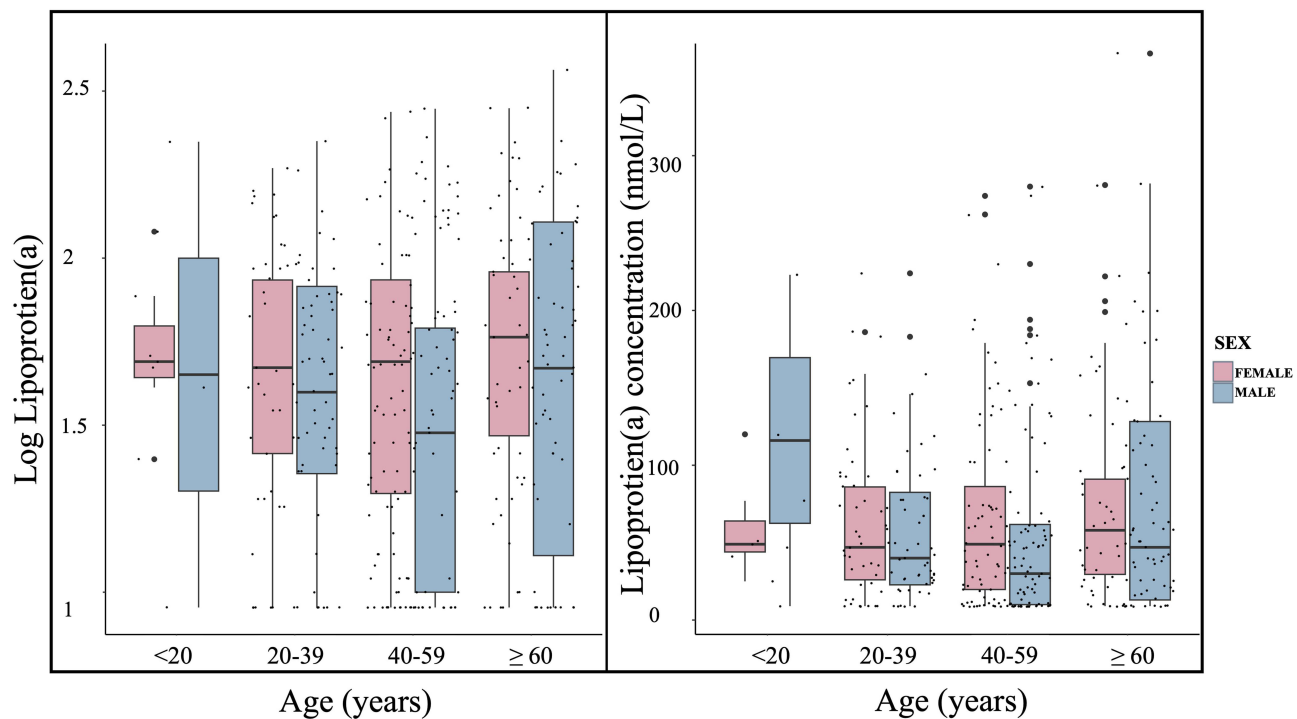
**Table 2** Mean  $\pm$  S.D. of the Other Atherosclerotic Markers

Variables	Total N	Total	Males	Females	P-Value
Age (years)	361	$50.6 \pm 16.5$	$50.2 \pm 16.9$	$51.1 \pm 15.9$	0.65
Total Cholesterol (mg/dl)	223	$197.2 \pm 45.9$	$182.2 \pm 53.2$	$207.7 \pm 36.6$	<0.001
LDL-C (mg/dl)	361	$122.4 \pm 39.7$	$113.8 \pm 44.7$	$128.5 \pm 34.6$	<0.05
HDL-C (mg/dl)	361	$56.5 \pm 15.4$	$49.9 \pm 16.7$	$61.1 \pm 12.5$	<0.001
TG (mg/dl)	224	96 (352.9)	99 (352.9)	95 (253)	0.64
Non-HDL (mg/dl)	222	$140.73 \pm 42.2$	$136.3 \pm 44$	$146.1 \pm 49.9$	<0.05
LDL/HDL	361	$2.3 \pm 1.1$	$2.52 \pm 1.4$	$2.2 \pm 0.7$	<0.05
ApoB (mg/dl)	225	$2.9 \pm 16.5$	$1.0 \pm 0.3$	$1.0 \pm 0.2$	0.69
Lp(a) nmol/L*	361	47 (357)	35 (1.6)	50 (227)	<0.05
Log Lp(a)	361	$1.6 \pm 0.4$	$1.56 \pm 0.5$	$1.66 \pm 0.3$	<0.05
FBG	361	$98.4 \pm 32.48$	$95.5 \pm 41.4$	$102.7 \pm 41.4$	0.07
HbA1c	361	$5.57 \pm 1.18$	$5.76 \pm 1.48$	$5.44 \pm 0.92$	0.06

Notes: (\*) Lp(a) levels represented by median due to non-Gaussian (skewed) distribution.



**Figure 1** This schematic representation shows the Lp(a) distribution in the study. The dashed red line represents the 75th percentile of the study population at approximately 93 nmol/L. The common cut-off value is 75 nmol/L in North American White population which represents also the 75th percentile which represent the cutoff value between high and low levels.



**Figure 2** Lp(a) concentrations (nmol/L) stratified by age and sex (Right). Lp(a) concentrations (Log-Lp[a]) stratified by age and sex (left).

**Table 3** Lp(a) Distribution Statistics Partitioned by Gender

	Females		Males	
	Lp(a) nmol/L	Log Lp(a)	Lp(a) nmol/L	Log Lp(a)
N	199	199	162	162
Mean	65.49	1.67	63.56	1.57
Sd	54.1	0.38	66.77	0.47
Median	50	1.7	35	1.54
Min	9	0.95	9	0.95
Max	281	2.45	366	2.56
Range	272	1.49	357	1.61
Skew	1.48	-0.27	1.63	0.11
Kurtosis	2.3	-0.69	2.74	-1.24

**Table 4** Distribution of Lp(a) (Nmol/L) Classification

Age	N	Geometric Mean	Log Lp(a) Mean	10%	25%	50% (median)	75%	90%
Total	361	41.8 ± 2.6	1.6 ± 0.4	9	20	47	93	153
<20	9	50.7 ± 2.4	1.7 ± 0.4	21.8	41.0	49.0	77.0	140.6
20–39	97	42.2 ± 2.4	1.6 ± 0.3	9.0	24.0	45.0	86.0	124.6
40–59	148	36.9 ± 2.8	1.5 ± 0.4	9.0	13.0	40.0	73.2	148.6
≥60	107	48.4 ± 2.7	1.7 ± 0.4	9.0	23.5	51.0	111.5	173.6
Males	162	36.8 ± 1.6	1.5 ± 0.4	9.0	11.0	35.0	96.5	152.3
<20	2	44.8 ± 1.6	1.6 ± 0.9	30.4	62.5	116.0	169.5	201.6
20–39	44	39.2 ± 1.6	1.6 ± 0.4	9.0	22.75	40.0	82.5	133.7
40–59	68	31.0 ± 1.5	1.5 ± 0.5	9.0	10.0	30.0	61.7	136.6
≥60	48	44.0 ± 1.6	1.6 ± 0.5	9.00	13.0	47.0	128.2	184.0
Females	199	46.3 ± 2.4	1.5 ± 0.4	10.8	26.0	50.0	87.5	150.6
<20	7	52.6 ± 1.6	1.7 ± 0.2	34.6	44.0	49.0	64.0	94.2
20–39	53	44.8 ± 2.3	1.6 ± 0.3	13.8	26.0	47.0	86.0	113.0
40–59	80	42.7 ± 2.6	1.6 ± 0.4	9.9	19.7	49.0	86.25	150.3
≥60	59	52.4 ± 2.3	1.7 ± 0.4	18.6	29.5	58.0	91.0	161.6

(interquartile range) Lp(a) level was 47 (20–93) nmol/L. Median (IQR) Lp(a) levels were higher in women (50, 26–87.5 nmol/L) than in men (35, 11–97.6 nmol/L,  $P < 0.0001$ ).

Overall geometric mean ± SD concentration of Lp(a) was 41.8 ± 2.6 nmol/L in Saudi Arabian adults, 36.8 ± 1.6 nmol/L and 46.3 ± 2.4 nmol/L in men and women, respectively. The Lp(a) concentration was significantly higher in women than in men ( $P < 0.01$ ). Geometric mean ± SD levels of Lp(a) by age group were 50.7 ± 2.4 nmol/L for < 20 years, 42.2 ± 2.4 nmol/L for 20–39 years, 36.9 ± 2.8 nmol/L for 40–59 years, and 48.4 ± 2.7 nmol/L for ≥ 60 years. Lp(a) concentration, by age group, tended to grow with age and in both sexes, although not in a statistically significant way. The range of Lp(a) was 93–9 nmol/L, and its distribution was highly skewed towards lower levels across both sexes (Figure 1).

The geometric mean concentration of Lp(a) partitioned by age group in the men were; 36.8 ± 1.6 nmol/L for < 20 years, 39.2 ± 1.6 nmol/L for 20–39 years, 31.0 ± 1.5 nmol/L for 40–59 years, and 44.0 ± 1.6 nmol/L for ≥ 60 years. The mean concentration of Lp(a) subdivided by age categories in women were; 52.6 ± 1.6 nmol/L for < 20 years, 44.8 ± 2.3 nmol/L for 20–39 years, 42.7 ± 2.6 nmol/L for 40–59 years, and 52.4 ± 2.3 nmol/L for ≥ 60 years. The percentile values of Lp(a) were 9 nmol/L for 10th percentile, 20 nmol/L for 25th percentile, 47 nmol/L for 50th percentile, 93 nmol/L for 75th percentile, and 153 nmol/L for 90th percentile (Table 4 and Figure 2).

**Table 5** Distribution of Lp(a) (Nmol/L) Classification

Lp(a) category	Total (N=361)		Males (N=162)		Females (N=199)	
	N	%	N	%	N	%
<75 nmol/L	245	67.9	116	71.6	138	69.4
≥75 nmol/L	102	32.1	46	28.4	61	30.6

**Table 6** Association Between Lp(a) and Important Atherosclerotic Markers by Sex\*

	Age	HbA1c	FBS	Non-HDL-C
Total	0.023	0.037	0.021	-0.003
Males	0.021	0.031	0.032	-0.013
Females	0.034	0.044	0.029	-0.007

Note: (\*) P-value <0.05.

The proportion of the high level (high-risk) group ( $\geq 75$  nmol/L of Lp(a)) in the studied population was 32.1%, 28.4% and 30.6% in men and women, respectively. Moreover, 28% of men and 30.6% of women in this study were considered under high risk owing to high Lp(a) levels (Table 5).

Pearson's Correlations for Lp(a) levels and important atherogenic risk factors were estimated in the study population. Lp(a) failed to significantly correlate with age ( $r = 0.023$ ,  $P > 0.05$ ), non-HDL-C ( $r = -0.003$ ,  $P > 0.05$ ), and HbA1c ( $r = 0.037$ ,  $P > 0.05$ ). An inverse relationship was found with TG ( $r = -0.083$ ,  $P < 0.001$ ). Lp(a) levels did not significantly correlate with FBS levels ( $r = 0.021$ ,  $P > 0.05$ ). Furthermore, the correlation between Lp(a) levels and the aforementioned risk factors did not reach statistical significance after we stratified the study population by gender (Table 6).

## Discussion

In this pilot study, we evaluated serum and plasma Lp(a) levels in adults referred to Al-Borg Diagnostics in Saudi Arabia. Antifibrinolytic and atherogenic properties have been associated with Lp(a).<sup>15</sup> Therefore, the serum Lp(a) concentration is a valuable CVD risk factor.<sup>15</sup> Lp(a) serum concentration in the laboratory can be measured using immunoturbidimetry, immunonephelometry, single-radical immunodiffusion, and ELISA.<sup>14</sup> This work determined serum Lp(a) concentration using an immunoturbidimetric test and an automated analyzer.

In this research, the geometric mean SD concentration of Lp(a) in Saudi adults was  $41.8 \pm 2.6$  nmol/L, with a range of 20–9 nmol/L. The 10th, 25th, 50th, 75th, and 90th percentiles of Lp(a) level were 9, 20, 47, 93, and 153 nmol/L, respectively. The geometric mean  $\pm$  SD concentration of Lp(a) in men and women was  $36.8 \pm 1.6$  nmol/L and  $46.3 \pm 2.4$  nmol/L, respectively. Women often have higher Lp(a) concentrations than men. In both sexes, age-specific Lp(a) concentrations tended to increase.

The variability in levels among different demographic groups is one of the most distinguishing characteristics of Lp(a).<sup>16</sup> Although considerable knowledge has been gained regarding the genetic variability of apo(a) between populations, the underlying mechanisms of this variation remain largely unresolved. The Lp(a) distribution in our study was highly skewed toward low levels. The geometric mean concentration of Lp(a) was  $41.8 \pm 2.6$  nmol/L in Saudi adults, while the geometric mean concentration of Lp(a) was  $36.8 \pm 1.6$  nmol/L and  $46.3 \pm 2.4$  nmol/L in men and women, respectively. Early population studies examining the association between Lp(a) level and coronary artery disease (CAD) risk were conducted primarily in European populations.<sup>17</sup> Nonetheless, some investigators have observed considerable variations in Lp(a) concentrations and distributions.<sup>18</sup> Black individuals have a mean Lp(a) concentration that is  $75 \pm 6.72$  nmol/L,<sup>19</sup> which is twice as high as that in White individuals with a mean of  $< 30 \pm 5.5$  nmol/L.<sup>11,12</sup> Beyond Black and White individuals, a heterogeneous distribution of Lp(a) concentration was observed among Asian ethnicities, with



significantly increased Lp(a) concentrations in Indians compared to Chinese, a conclusion validated by thorough studies.<sup>18</sup>

Studies have used cutoffs ranging from 75 nmol/L to 125 nmol/L (30 mg/dL to 50 mg/dL, using a conversion factor of  $\text{nmol/L} \times 0.4167 = \text{mg/dL}$ ) to define the Lp(a)-driven risk and outcomes of established and developing treatments.<sup>20</sup> In Canada and the United States, an Lp(a) concentration of 75 nmol/L (30 mg/dL), which approximates the 75th percentile in Caucasian communities, is commonly used as the cut-off value.<sup>21</sup> The European Cardiology and Atherosclerosis Society (EAS) endorses screening for elevated Lp(a) levels in individuals at moderate or high risk of CVD and sets an acceptable Lp(a) level of 125 nmol/L (50 mg/dL).<sup>22</sup> Moreover, they imply that the Lp(a) risk is substantial when the concentrations are over the 80th percentile.<sup>23</sup>

In this study, Lp(a) levels  $\geq 75$  nmol/L accounted for 28.4% and 30.6% of men and women, respectively. An important study<sup>24</sup> reports Lp(a) levels  $\geq 75$  nmol/L in 25% of Asian Indians, Kim et al reports Lp(a) levels  $\geq 75$  nmol/L accounted for ~22% in the South Korean population (47.6 nmol/L), while levels in Caucasians were lower at 17%. However, it is unclear whether absolute cutoffs, risk percentiles, or ethnicity-specific cutoffs improve the recognition of high-risk individuals for clinical risk prediction. Future research is required to examine the associations between genetic polymorphisms, apo(a) isoforms, and Lp(a) concentrations and major adverse CVD events in different racial groups.

This study did not correlate Lp(a) levels with non-HDL-C, HbA1c, serum, or plasma glucose levels. The statistical results may have been affected because few Lp(a) measurements had concurrent lipid, HbA1c, or glucose measurements. Therefore, it is important to consider and validate the relationship between Lp(a) levels and serum biomarkers of high blood sugar levels and CVD with additional research.

Several limitations must be addressed when interpreting the data. First, the small sample size is an important limitation. Second, the study was conducted retrospectively, which may have created bias regarding the accuracy and completeness of the data extracted from medical records. Third, one of the main limitations of this study was the absence of clinical data, such as thorough records of coexisting illnesses including diabetes, prescription histories, physical examinations, and other laboratory tests related to CVD and illness severity. For instance, a recent report hypothesized that Coronavirus disease 2019 (COVID-19) could cause various CVDs by increasing Lp(a) levels.<sup>25</sup> Future research is required to clarify the potential impact of elevated Lp(a) levels as an acute-phase reactant in COVID-19, which may contribute to CVD and could be missed when reporting the data. Finally, we acknowledge the possibility of a selection bias because the participants underwent Lp(a) testing, which may have indicated a greater risk profile.

## Conclusion

The average Lp(a) concentration in our pilot research population was  $41.8 \pm 2.6$  nmol/L, ranging from 20 to 9 nmol/L. Our findings indicated that women exhibited a higher concentration of Lp(a) than men. We suggest the establishment of population reference ranges for Lp(a) specifically for the Saudi population. To examine the chronological connection between Lp(a) and the risk, onset, and consequences of DM in different medical scenarios, we suggest conducting prospective population-based research.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; drafting, revising, or critically reviewing the article. All authors approved the final version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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