

Elevated Lipoprotein(a) prevalence and association with family history of premature cardiovascular disease in general population with moderate cardiovascular risk and increased LDL cholesterol

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ABSTRACT

Background: Elevated Lipoprotein(a) [Lp(a)] is independently associated with increased cardiovascular disease (CVD) risk. There are discrepancies regarding its epidemiology due to great variability in different populations. This study aimed to evaluate the prevalence of elevated Lp(a) in people with moderate CVD risk and increased LDL-c and to determine the association between family history of premature CVD and elevated Lp(a).

Methods: Random subjects from the CESCAS population-based study of people with moderate CVD risk (Framingham score 10–20 %) and LDL-c ≥ 130 mg/dL, were selected to evaluate Lp(a) by immunoturbidimetry independent of the Isoforms variability. The association between family history of premature CVD and elevated Lp(a) was evaluated using multivariate logistic regression models. Elevated Lp(a) was defined as Lp(a) ≥ 125 nmol/L.

Results: Lp(a) was evaluated in 484 samples; men = 39.5 %, median age = 57 years (Q1-Q3: 50–63), mean CVD risk = 14.4 % (SE: 0.2), family history of premature CVD = 11.2 %, Lp(a) median of 21 nmol/L (Q1-Q3: 9–42 nmol/L), high Lp(a) = 6.1 % (95 % CI = 3.8–9.6). Association between family history of premature CVD and elevated Lp(a) in total population: OR 1.31 (95 % CI = 0.4, 4.2) $p = 0.642$; in subgroup of people with LDL-c ≥ 160 mg%, OR 4.24 (95 % CI = 1.2, 15.1) $p = 0.026$.

Conclusions: In general population with moderate CVD risk and elevated LDL-c from the Southern Cone of Latin America, less than one over ten people had elevated Lp(a). Family history of premature CVD was significantly associated with the presence of elevated Lp(a) in people with LDL-c ≥ 160 mg/dL.

1. Introduction

Lipoprotein(a) [Lp(a)] is one of the atherogenic particles included in the non-HDL fraction of circulating lipoproteins. Lp(a) is characterized by having in its structure an LDL particle attached to an apoprotein(a) that presents heterogeneity in size [1–3]. Both observational and genetic

studies have widely described the association between elevated levels of Lp(a) and the development of atherosclerotic cardiovascular disease (CVD) and aortic valve stenosis [2,4–6]. It is known that plasma Lp(a) values are 90 % genetically determined and their levels are not associated with traditional cardiovascular risk factors [1]. Although the pathophysiological mechanisms that lead to cardiovascular damage

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have not been fully described so far, it has been proposed that Lp(a) does not only actively promote cholesterol accumulation in the intima of vessels and aortic valves inducing a pro-oxidative and inflammatory context, but it also participates in processes of inhibition of plasma fibrinolysis [2,7]. Although its causal role in CVD is independent of other CVD risk factors, it has been described that the risk of CVD is even more pronounced when LDL cholesterol (LDL-c) values are higher [8,9].

Standardization problems linked to Lp(a) measurement methods, general population ethnic variations and the absence of a global consensus regarding populations cut-off values are some of Lp(a) current issues in clinical practice [6]. Some of the evidence suggests a concentration greater than 125 nmol/L as a cut-off point for elevated Lp(a) but there is significant variability in current recommendations incorporated into clinical practice guidelines in relation to the preferred target group for Lp(a) evaluation and clinical management in case of elevated values [5,10–12].

High prevalence of elevated Lp(a), and its potential role in population CVD stratification improvement suggest a significant utility of Lp(a) for a better classification of people with moderate CVD risk or family history of premature CVD [2]. Currently, in the Southern Cone of Latin America there is limited available data from population-based epidemiology of this emerging CVD risk factor. Using population-based data from the CESCAS study, the aims of this study were to assess the prevalence of elevated Lp(a) in people with moderate CVD risk and increased LDL-c, and to determine the association between family history of premature CVD and elevated Lp(a).

2. Methods

2.1. Study participants and data collection

The design and sampling methods of the CESCAS population-based study were described in previous publications [13,14]. Its main objective is to generate epidemiological information on cardiovascular disease and risk factors in the general population of the Southern Cone of Latin America. Between December 2010 and December 2012, 7,524 adults (3,165 men and 4,359 women) aged 35–74 were included in the study. The sample came from a representative multi-stage sample of the general population of four cities in the Southern Cone of Latin America: Bariloche and Marcos Paz (Argentina), Temuco (Chile) and Pando-Barros Blanco (Uruguay). Trained personnel collected CESCAS study baseline data during a home visit and a clinical visit. A fasting blood sample was obtained for measurements of lipids and lipoproteins, creatinine, and glucose. Blood glucose, total cholesterol, HDL cholesterol, triglycerides, and creatinine were evaluated via standard methods. The LDL-c concentration was calculated using the Friedewald equation in case the triglycerides were less than 400 mg/dL [15]. In addition, sera samples were processed and stored in ultra-freezers at -80°C in a central laboratory for later measurements. Blood pressure measures were evaluated with the participant in a sitting position after 5 min of rest using a standard aneroid sphygmomanometer, and the average of three readings was used for the analysis.

This study complies with the ethical principles of the 1975 Declaration of Helsinki and was carried out following the guidelines for the protection of the rights of people who voluntarily participate in research studies. All participants signed a written informed consent authorizing the future use of the stored samples for research purposes. The protocol was approved by the ethics committees of all participating centers in Argentina, Chile and Uruguay.

2.2. Lp(a) assessment and definitions

For the purposes of this study, during 2019 a random sample of 1000 participants free of previous CVD with moderate 10-year cardiovascular risk was selected. CVD risk was estimated using the Framingham risk score (FRS) [16], moderate risk was considered if its value was between

10 % and 20 %.

From this sample, Lp(a) was evaluated in all participants with LDL-c ≥ 130 mg/dL ($n = 484$). The determinations were performed by the Lipids and Atherosclerosis Laboratory of the University of Buenos Aires, using the stored sera samples. Automated immunoturbidimetry method was used in COBAS INTEGRA systems (ROCHE), with polyclonal anti-Lp(a) antibodies and reference material -Preciset Lp(a) Gen2 calibrator set-consisting of five calibrators based on stabilized and lyophilized pool of human plasmas, with traceability to SRM2B, IFCC/WHO, independent of apo(a) size. Values were expressed in nanomoles per liter (nmol/L). The Preci Control Lp(a) Gen.2 control set contains two lyophilized controls in human plasma matrix. All procedures were done under good quality control, applying external quality control Lipid Program (RIQAS), accredited according to ISO 17043. Elevated Lp(a) was defined as Lp(a) ≥ 125 nmol/L.

Family history of CVD was defined as the occurrence of acute myocardial infarction (AMI) or sudden death (SD) in a first-degree relative man before the age of 55 years or woman before the age of 65, or the history of stroke before age 50 in a first-degree relative.

Hypertension (HT) was defined as mean systolic blood pressure ≥ 140 mmHg and/or mean diastolic blood pressure ≥ 90 mmHg and/or current use of anti-hypertensive medication. Diabetes (DB) was defined as blood glucose ≥ 126 mg/dL and/or self-report of a personal history of diabetes and/or current treatment with insulin or oral hypoglycemic agents. According to LDL-c values, LDL-c levels were defined as moderate LDL-c (130–159 mg/dL) and high LDL-c (≥ 160 mg/dL).

2.3. Statistical analysis

Distribution of Lp(a) values was analyzed as a continuous (nmol/L) and categorical variable [elevated Lp(a)]. Results were analyzed by sex and LDL-c level. Proportions were weighted on the basis of the population distribution of the four cities in terms of gender and age. Confidence Intervals (CI) were calculated using standard errors that take into account the complex survey design. The association between family history of premature CVD and elevated Lp(a) was evaluated using multivariate logistic regression models; odds ratios (OR) with 95 % CI were calculated. For these estimates, the multi-stage design of a complex sample was also considered. Regarding LDL-c levels, three models were analyzed: one for the total population, one for the group of people with moderately elevated LDL-c, and one for the group with high LDL-c. Sex, age, DB and HT were included as adjustment variables in the models.

3. Results

The Fig. 1 shows the sample selection process for this study: from the 7,524 participants in the CESCAS study, 1669 had moderate CV risk. Then, from a random sample of 1000 participants from this last group, Lp(a) was analyzed in all participants with LDL-c ≥ 130 mg/dL (484 participants).

Table 1 includes general characteristics of the studied population. Of the 484 individuals, 39.5 % were men, median age was 57 years (Q1-Q3: 50–63), mean 10-year CVD risk was 14.4 (SE: 0.2) and 11.2 % reported history of family premature CVD. Regarding to LDL-c, 55.2 % belonged to participants within the moderate LDL-c level and 44.8 % to the high LDL-c level. In the first group, the LDL-c median value was 142.4 mg/dL (Q1-Q3: 136–149.6 mg/dL); while in the high LDL-c group the median value observed was 175.8 mg/dL (Q1-Q3: 167–188.6 mg/dL) with a maximum observed value of 240.4 mg/dL.

The histogram in Fig. 2 shows the frequency of Lp(a) values. Globally, mean value for Lp(a) serum concentration was 36.7 nmol/L (SE: 2.1), median of 21 nmol/L (Q1-Q3: 9–42 nmol/L). By sex, there were no significant differences in the observed means: men 34.8 nmol/L (SE: 3.6) and women 38.9 (SE: 2.9), $p = 0.383$. Overall prevalence of elevated Lp(a) (values ≥ 125 nmol/L) was 6.1 % (95 % CI = 3.8, 9.6); in men 5.8 % (95 % CI = 2.7, 12.0) and women 6.4 % (95 % CI = 3.6, 11.1), $p = 0.812$.

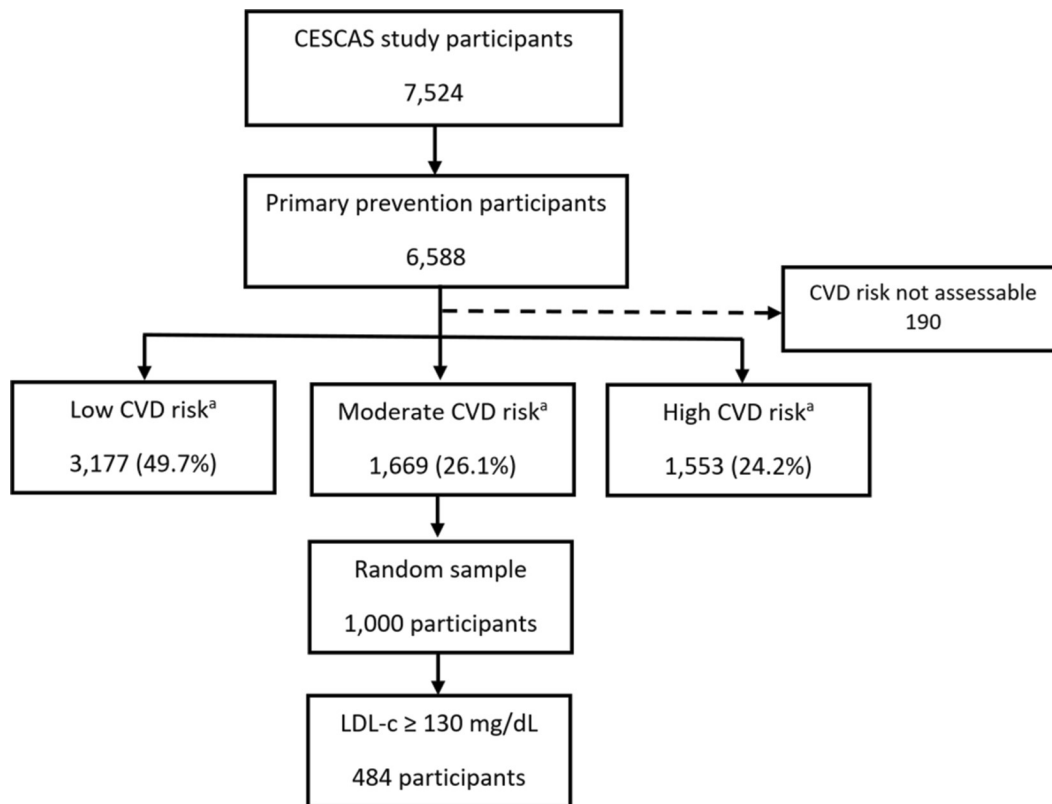


Fig. 1. Study population selection. ^a 10-year Cardiovascular Disease (CVD) risk evaluated by Framingham risk equation: low CVD risk (<10 %), moderate risk (10–20 %) y high risk (≥20 %).

Table 1
Study population characteristics.

	Total population (N = 484)	LDL-c 130–159 mg/dL (n = 267)	LDL-c ≥ 160 mg/dL (n = 217)
Male, %	39.5	44.2	33.6
Median age, (Q1-Q3)	57 (50–63)	57 (50–63)	57 (50–63)
Mean CVD risk, (SE)	14.4 (0.2)	14.3 (0.2)	14.6 (0.3)
Family history of premature CVD, %	11.2	10.3	12.4
Hypertension, %	49.7	51.3	47.4
Current smoker, %	40.2	42.8	36.3
Diabetes, %	8.9	9.3	8.4

Abbreviations and definitions: LDL-c: LDL-cholesterol; Q1-Q3: quartil 1 - quartil 3; SE: standard error; CVD risk estimated by the Framingham equation; Family history of premature CVD: AMI / sudden death in a primary relative under 55 years of age in men and 65 years in women, stroke before age 50 years; Hypertension: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, and/or self-reported use of anti-hypertensive medication; Diabetes: fasting blood glucose ≥ 126 mg/dL or self-reported diabetes or receiving hypoglycemic medication.

The prevalence of elevated Lp(a) was also analyzed by LDL-c stratum without finding a statistically significant difference: LDL-c 130–159 mg/dL: 5.7 % (95 % CI = 2.8, 11.3), LDL-c ≥ 160 mg/dL: 6.7 % (95 % CI = 3.7, 11.8), $p = 0.733$.

Finally, **Table 2** includes models that analyzed the association between family history of premature CVD and elevated Lp(a): the first model includes the overall population and the second model includes people with high LDL-c levels (above 160 mg/dL). In the first model, no significant association was found: OR 1.32 (95 % CI = 0.41, 4.26), $p = 0.641$. However, in the second model a statistically significant association was found between having a family history of premature CVD and having elevated Lp(a): OR 4.24 (95 % CI = 1.2, 15.1), $p = 0.026$. In the

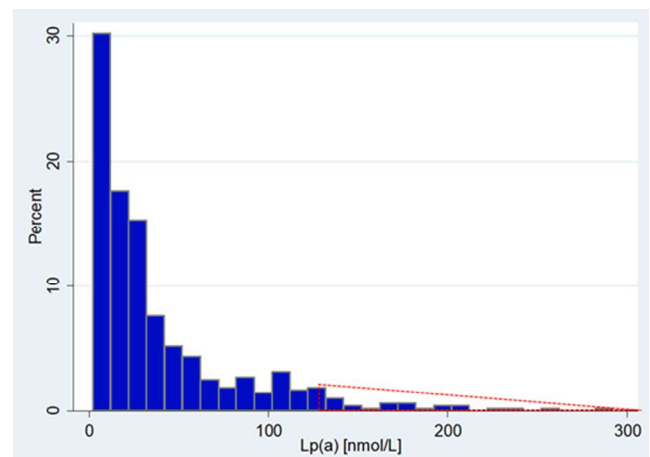


Fig. 2. Lp(a) values frequency^a. ^a Selected area represents proportion of participants with elevated Lp(a).

high LDL-c level group, the prevalence of elevated Lp(a) among those who did not report a family history of premature CVD was 5 %, while it was 18.1 % among those with a family history of premature CVD. This association could not be evaluated in individuals with moderate LDL-c level since there were no individuals in this subgroup with a family history of premature CVD and elevated Lp(a).

4. Discussion

4.1. Main findings

To our knowledge, this study evaluated the epidemiology of Lp(a) in

Table 2
Association of family history of premature CVD and elevated Lp(a).

	Total population		LDL-c \geq 160 mg/dL	
	OR (CI 95 %)	p	OR (CI 95 %)	p
Male	0.47 (0.12–1.7)	0.257	0.43 (0.05–3.4)	0.421
Age (years)	0.92 (0.84–1.01)	0.101	0.99 (0.91–1.1)	0.940
Family history of premature CVD	1.32 (0.41–4.25)	0.642	4.24 (1.2–15.1)	0.026
Diabetes	1.67 (0.43–6.37)	0.452	1.93 (0.18–20.6)	0.582
Hypertension	1.03 (0.32–3.32)	0.572	0.93 (0.18–4.9)	0.935

the general population with moderate CV risk and increased LDL-c in the Southern Cone of Latin America for the first time. The prevalence of elevated Lp(a) in the studied population was less than 1 in 10 people (6.1 %). In the high LDL-c group, the prevalence of elevated Lp(a) among those with a family history of premature CVD was almost 2 out of 10 people (18.1 %) and the odds of having elevated Lp(a) in this subgroup was more than 4 times as high as those who did not have the antecedent.

4.2. Existing literature

The observed prevalence of high Lp(a) was lower than prevalence described in other populations such as 20 % in the Copenhagen General Population Study [11]. However, the observed median in this study of 21 nmol/L was similar to the one reported in 2017 by seven prospective population-based cohorts across Europe that evaluate Lp(a) in more than 52,000 participants: 8.7 mg/dL (~21 nmol/L) [17]. In addition, a study conducted in more than 450,000 of the UK Biobank reported a Lp(a) median of 19.6 nmol/L [18].

Additionally, regarding to Lp(a) distribution in this study, it is important to high light that the CESCAS study includes cities as Temuco (La Araucanía region) in Chile and Bariloche (province of Rio Negro) in Argentina that are located in areas where there is a higher proportion of native population, in whom there is no information about Lp(a) epidemiology. Based on information of the 2010 national census in Argentina, 7.1 % of the population of the province of Rio Negro reported native population origins [19]. On the other hand, in the 2017 national census in Chile reported that 34.3 % of the people in the La Araucanía region belonged to native population origins [20].

This study offers population-based information about a subgroup of people with higher CVD risk that could potentially benefit from more aggressive preventive interventions. A publication by Afshar M. et al. in 2020 [9] studied the association between LDL-c levels \geq 135 mg/dL and Lp(a) \geq 100 nmol/L and the risk of CVD. This study, using information from the Framingham cohort, concluded that individuals with LDL-c and Lp(a) above these cut-off points belonged to a group at higher risk of cardiovascular disease. Also, a recent publication from Nurmohamed et al. in 2021 analyzed the association between very high level of Lp(a) and CVD risk. This cross-sectional case-control study found that the OR for atherosclerotic cardiovascular disease (ASCVD) among those adults with Lp(a) > 99th percentile was 2.6 compared to people with Lp(a) \leq 20th percentile. Moreover, the incorporation of the Lp(a) into ASCVD risk algorithms led to a reclassification of one-third of the population with very high Lp(a) in primary prevention [21]. These observations support the potential utility of Lp(a) to better stratify people with increased LDL-c. In addition, recent evidence confirms the additive effect of Lp(a) levels and family history of CVD to optimize risk reclassification [22]. Precisely, family history of CVD is a recommendation for the measurement of Lp(a) in the latest 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of dyslipidemia [23].

A review by Ward N. et al. in 2019 [1] showed different types of discrepancies in Lp(a) assessment and management recommendations in current clinical practice guidelines. Population subgroups for which the evaluation of this risk marker is recommended is not universally defined. The 2019 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemias have suggested that Lp(a) plasma levels should be measured at least once in a person's life for risk stratification [24]. However, other guidelines proposed a variety of subgroups of targets as people with moderate risk, increased LDL-c or people with a family history of premature CVD. In addition, Lp(a) ethnic variations influence the cut-off points proposed by the guidelines. For example, a universal cut point level of 100 nmol/L has been recommended by the National Lipid Association while other guidelines such as the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) suggest that a level of 125 nmol/L or higher should be considered as elevated CVD risk [1]. In addition to this, cut-off points are sometimes expressed in mg/dL from methods susceptible to size variations in the different isoforms of the particle [1,2,4]. To date, there is no specific treatment for people with elevated Lp(a) - although there are molecules currently under study [25] - and there is variability in recommended clinical behaviors in case of elevated Lp(a). Lipoprotein apheresis has been proposed as a possible treatment option; however, high cost, availability and patient burden have to be considered for this option [1,4]. As well, PCSK9 inhibitors can be used to lower Lp(a) in very high risk patients; however further studies about its cost-effectiveness are needed [1,4]. Finally, noteworthy Lp(a) is not currently considered in any of the risk prediction equations usually used in daily practice [1,4].

4.3. Implications for clinical practice

Considering current published information, decisions on Lp(a) evaluation in daily practice should be based on the identification of specific population subgroups taking into account ethnicity, comorbidity, family history and cardiovascular risk [6,8]. At this point, it should be noted that in the absence of certain conditions (i.e. acute infections or renal disease) Lp(a) values are considered stable throughout a person's life, therefore a single measurement in a selected population sub-group would help improve risk stratification [4].

Based on the observations of this study, a simple question in daily clinical practice such as family history of premature CVD could help to the identification of sub-group of people with higher risk. Family history of CVD is extremely important for the comprehensive risk management of individuals. Nevertheless, not only is there insufficient registry of this background in medical records [26], but there is also a significant variability in its definition [27]. Therefore, more future research is required to improve this important usual aspect of practice linked to the identification of groups that would benefit from Lp(a) assessment.

4.4. Strengths and limitations

This study has important strengths. In first place, data that come from a complex sample with representativeness of the general population of four cities in the Southern Cone of Latin America. In addition, it has to be highlighted that determination of Lp(a) in this study was carried out through an internationally recommended standardized method, which is independent of particle size variations (practically not influenced by lipoprotein size isoforms) and it is standardized with the reference materials of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [28]. Accurate determination of Lp(a) levels has a significant difficulty due to the complexity of the particle. In its structure, it contains an LDL particle bound to apo(a) and this last one shows significant heterogeneity of isoforms of different sizes as a consequence of mutations in the LPA gene, which finally determines the circulating levels of this lipoprotein [3,4]. Size polymorphism of apo(a) is established by the number of repetitions of Kringle IV type 2 of the

apo(a). Therefore, to achieve reliable results, it is essential to have a validated and standardized method such as the one implemented in this study, which is insensitive to variations in Lp(a) size. Hence, the expression of the results in nmol/l makes them independent of the mass (mg/dL) that is affected by the concentration of the different components of the particle.

On the other hand, the following limitations need to be mentioned. Family history of premature CVD was evaluated by participants' self-report, as it is usually assessed in daily clinical practice. Moreover, in the moderately elevated LDL-c group, the association between family history of premature CVD and elevated Lp(a) could not be evaluated since no people with both conditions were found in the sample. Male rate observed in this study was lower than that for women, however this proportion is close to the one described in the total population in the CESCAS study (around 42 %), where the overall response rate to participate in the study was 73.4 % [14]. Higher women participation rate was observed also in other population-based studies [29,30]. Finally, it has to be mentioned that the sera samples used in this study have been analyzed after a long term of storage, however its influence in Lp(a) assessment it is not well known.

4.5. Conclusions

This study described the epidemiology of Lp(a) in the general population with moderate CVD risk and elevated LDL-c in the Southern Cone of Latin America. Less than one over ten people had elevated Lp(a) and family history of premature CVD was significantly associated with the presence of elevated Lp(a) in people with LDL-c \geq 160 mg/dL. Increasing local and regional scientific evidence about this emerging lipid risk factor, strongly contribute to the development of specific evidence-based recommendations for improving cardiovascular risk stratification in population subgroups.

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6. Data statement

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

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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