Association between Lipoprotein(a) and premature atherosclerotic cardiovascular disease: a systematic review and meta-analysis

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Abstract:

Background and aims: High Lipoprotein(a) [Lp(a)] level has been demonstrated as an important risk factor for atherosclerotic cardiovascular diseases (ASCVD) amongst the older populations, whereas its effects in the younger population remain unclear. This study evaluated the associations between Lp(a) and the risk of premature ASCVD.

Method and results: PubMed and Embase were searched for related studies until Nov 12, 2023. 51 studies including 100,540 participants were included. Mean age of patients ranged from 35.3 to 62.3 years. The proportion of male participants ranged from 0% to 100%. The mean follow-up was provided in five studies ranging from one year to 40 years. The definition of elevated Lp(a) varied among studies, such as >30mg/dL, >50mg/dL, the top tertiles, the top quartiles, the top quartiles and so on. Higher Lp(a) was significantly associated with the composite ASCVD (OR: 2.15, 95% CI: 1.53-3.02, P < 0.001), especially for CAD (OR: 2.44, 95%CI: 2.06-2.90, P < 0.001) and PAD (OR: 2.56, 95%CI: 1.56-4.21, P < 0.001). This association remained significant in familial hypercholesterolemia (FH) (OR: 3.11, 95%CI: 1.63-5.96, P < 0.001) and type 2 diabetes mellitus (T2DM) patients (OR: 2.23; 95%CI: 1.54-3.23, P < 0.001). Significant results were observed in South Asians (OR: 3.71, 95%CI: 2.31-5.96, P < 0.001), Caucasians (OR: 3.17, 95%CI: 2.22-4.52, P < 0.001), and patients with baseline low density lipoprotein cholesterol (LDL-C) level ≥ 2.6mmol/L.

Conclusion: Elevated Lp(a) predicts the risk of the composite or individual ASCVD in young, regardless of study design, gender, population characteristics (community or hospitalized), different premature...
definitions, and various Lp(a) measurement approaches. And this association was important in South Asians, Caucasians, FH patients, T2DM patients and patients with baseline LDL-C level \( \geq 2.6 \text{mmol/L} \),

**Word Count: 279**

**Introduction**

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide, with an estimated annual global mortality rate of 17.9 million patients.\(^1\),\(^2\) Although the majority of ASCVD and associated adverse events occur among the elderly, the younger population also remains vulnerable.\(^3\)

The prevalence of ASCVD in those under the age of 60 has been reported to range from seven to 30% depending different domains of ASCVD and geographic regions.\(^1\) ASCVD events in young patients may have an important impact on the patient’s longevity, psychology, and socioeconomics, leading to huge disability-adjusted life lost, as well as heavy healthcare economic burdens on society.\(^3\)

Recently, Lipoprotein(a) [Lp(a)], a low density lipoprotein cholesterol (LDL-c) -like particle, has been demonstrated as a novel risk factor for various cardiovascular outcomes, such as ASCVD and aortic valve stenosis.\(^4\) However, previous studies regarding the association between Lp(a) and ASCVD have mainly focused on the older or general populations.\(^5\) There is a scarcity of evidence on the association between Lp(a) and ASCVD among young patients. The BIOSIGNAL study has observed a significant association between elevated Lp(a) and large artery atherosclerosis stroke amongst individuals aged <60 years.\(^6\) A prospective study of 3596 patients by Raitakari et al. also found that higher Lp(a) was related to
premature ASCVD.\textsuperscript{7} Whereas Cai et al. and Shi et al. reported no significant relationship between Lp(a) and acute myocardial infarction (AMI) at the early age.\textsuperscript{8, 9} 

There was a previous meta-analysis showing that elevated Lp(a) was associated premature CAD.\textsuperscript{2} However, they only included 11 studies with moderate quality, in which the sample size was relatively small. High statistical heterogeneity was also the main limitation of the meta-analysis. In addition, the role of higher Lp(a) in the stroke and peripheral artery disease (PAD) was not been studied. Given the discrepant findings from the existing studies, we conducted a systematic review and meta-analysis to clarify the relationship between Lp(a) and premature ASCVD.

\section*{Methods}

\subsection*{Study design and search strategy}

The meta-analysis was performed according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses statement.\textsuperscript{10} The study protocol was registered in the PROSPERO database on Nov 12, 2023 (registration number: CRD42023476725). PubMed and EMBASE were searched from their inception through 26 October, 2023. We used both controlled MeSH terms and free-text terms related to premature ASCVD and Lp(a) to identify related studies, with no language restrictions. The detailed search algorithm is presented in Supplementary material. References listed in the identified studies were scrutinized for relevant studies. Trial eligibility was confirmed by two independent reviewers (X.T. and N.Z.) and discrepancies were resolved by a third author (T.L.).
Outcome and selection criteria

The outcome was the occurrence of any ASCVD at the age less than 65. ASCVD in this study included CAD, stroke and PAD. A study was eligible if the following criteria were fulfilled: (1) observational studies conducted in humans; (2) investigating the associations between blood Lp(a) level and premature ASCVD; (3) blood Lp(a) level was reported as a continuous (e.g. per one unit or per one SD increase of Lp(a) or log [Lp(a)]), or categorical variable (e.g. tertile, quartile, quintile or specific thresholds); (4) reported the composite ASCVD or at least one individual outcome. The exclusion criteria were (1) comments, reviews or animal studies; (2) studies not investigated Lp(a) level; (3) age of onset was ineligible (4) outcomes with interest were not reported; (5) helpful OR/RR/HR were not provided.

Data extraction

Two reviewers (X.T. and N.Z.) independently performed data extraction. Pre-specified forms were used for data collection to include the following items: (1) publication details: first author, publication year, country, and study design; (2) baseline characteristics: sample size, age of onset, duration of follow-up, and outcome-related variables; (3) Lp(a) measurements. Conflicts between investigators were resolved by discussion, and if necessary, through consultation with a third reviewer (T.L.).

Quality assessment

Quality of cohort studies and case-control studies were assessed by Newcastle-Ottawa Quality Assessment Scale (NOS) from the following three aspects: (1) selection of patients, (2) comparability of groups, and (3) ascertainment of exposure or outcomes. Varying from 0 to nine stars, the studies
were graded as high if they met ≥ eight criteria, medium if they met five-seven criteria, and poor if they met < five criteria. Quality assessment of cross-sectional studies were performed using American Agency for Health care Research and Quality (AHRQ) criterion with eleven items. The AHRQ varied from 0 to 11 stars, which indicated that studies were graded as poor quality if they met < five criteria, fair if they met five-seven criteria, and good if they met ≥ eight criteria.

Statistical analysis

Hazard ratio (HR), risk ratio (RR) odds ratio (OR) and corresponding 95% confidence interval (CI) were extracted from the fully adjusted models to evaluate the of association between Lp(a) and outcomes. When results of multivariable analysis were not available, those from univariable analysis were used. If HR/RR/OR was not reported, events number in the case and control groups was applied to calculate the unadjusted risk estimates. The HR/RR value in Cox proportional hazards model was equated to the OR value. Pooled effects were summarized as OR (95% CI) using the inverse variance method. Heterogeneity was assessed by using the Cochrane Q statistic and I² statistic. For the Q test, P-value < 0.1 was considered statistically significant. I² < 50% was considered as no heterogeneity, < 70% as moderate heterogeneity, otherwise was high. If I² value > 50%, the random-effects model was used; otherwise, the fixed-effects model was used. The ORs are scaled per one unit or SD change of Lp(a) or log \[\text{Lp(a)}\] for continuous variable, and compared with the lowest quantile for categorical variable. Lp(a) could be reported in the mass concentration method (mg/dL) and the molar concentration method and no fixed value was used as a conversion factor between the two units. However, to calculate the data of different units, levels above 72 nmol/L were considered consistent with
traditional thresholds for elevated Lp(a) above 30 mg/dL, 110nmol/L for 50mg/dL and 450nmol/L for 180mg/dL. When the definition of elevated Lp(a) was the top tertile (compared to the bottom tertile) the top quartile (compared to the bottom quartile) and the top quintile (compared to the bottom quintile), the difference of unit did not affect data merging.27

Subgroup analyses were performed according to study design, gender, race (Caucasian, South Asian and Chinese), population characteristic (community population and hospitalization population), baseline LDL-c level (<100mg/dL (2.6mmol/L), 100-130mg/dL (2.6-3.4mmol/L), 130-160mg/dL (3.4-4.1mmol/L) and ≥160mg/dL (4.1mmol/L), 28 definition of the “premature” (50 years and 60 years)14, categorization approaches of Lp(a) [tertile, quartile, quintile or specific cut-off such as 30 mg/dL (72nmol/L) and 50 mg/dL (110nmol/L)] and Lp(a) measurements [enzyme linked immunosorbent assay (ELISA), immunoturbidimetric method and immunoradiometric assay (IRMA)]. Due to the limited number of studies that reported continuous variables, subgroup analyses were mainly conducted using categorical variables. To evaluate the impact of each study on the overall effect size, a one-study removed sensitivity analysis was performed. Funnel plots used to assess possible publication bias. Statistical significance was defined as p values <0.05. Statistical analyses were performed with the Review Manger, version 5.4 (RevMan; The Cochrane Collaboration, Oxford, UK).

Results

Study selection and study characteristics

Initially, a total of 2496 and 2489 records were identified through PubMed and Embase, 51 studies were finally included in the meta-analysis. A flow diagram of the data search and study selection is
shown in Figure 1. The baseline characteristics of the included studies are summarized in Table 1. A total of 51 studies including 100,540 individuals were studied, of which sixteen were cross-sectional studies, nine were prospective cohort studies, twenty-six were retrospective studies. The proportion of male participants ranged from 0% to 100%. The mean follow-up was provided in five studies ranging from one year to 40 years. Nineteen studies included hospital-based patients and others included community-based patients. Quality assessment indicated that all of included studies were graded as high or medium quality.

Association between Lp(a) and premature ASCVD

Lp(a) and overall ASCVD among overall population

A total of three studies reporting the association between Lp(a) and composite ASCVD, which suggested that compared to lower Lp(a), elevated Lp(a) level was associated with significant higher risks of composite ASCVD events among individuals at an early age (OR: 2.15, 95% CI: 1.53-3.02, P < 0.001) (Fig 2A). In addition, after pooling 49 studies focusing on individual ASCVD events, the association between increased Lp(a) level and overall ASCVD remained significant when analyzed as a categorical variable (OR: 2.35, 95% CI: 2.01-2.74, P< 0.001) (Figure 2B) or continuous variable as per one SD increase of the log Lp(a) (OR: 1.36, 95% CI: 1.14-1.61, P < 0.001) (Figure 2C), but not for other forms of continuous variable (Supplemental material, Figure S2)

Lp(a) and overall ASCVD among specific populations
In addition, the aggregated data of 3 studies showed that significant prognostic value of Lp (a) level for premature ASCVD was significant in familial hypercholesterolemia (FH) patients (OR: 3.11, 95%CI: 1.63-5.96, P < 0.001) (Fig 3A). A total of 2 studies focusing on patients with type 2 diabetes mellitus, the pooled results of these 2 studies suggested a significant association between elevated Lp(a) with premature ASCVD events among T2DM population (OR: 2.23; 95%CI: 1.54-3.23, P < 0.001) (Fig 3B), in relation to those with lower Lp(a). Funnel plot showed little publication bias (Supplementary material online, Figure S1).

**Lp(a) and individual ASCVD**

As for the individual ASCVD events, there was a positive association between Lp(a) levels with risk of premature CAD (OR: 2.44, 95%CI: 2.06-2.90, P < 0.001) and PAD (OR: 2.56, 95%CI: 1.56-4.21, P < 0.001), but not for stroke (OR: 1.25, 95%CI: 0.87-1.81, P = 0.06) (Fig 3C). When further classified premature CAD into subcategories, the association remained significant between elevated Lp(a) level and increased risk of angiographically-proven CAD (OR: 3.36, 95%CI: 2.09-5.40, P < 0.001), stable angina and ACS (OR: 2.95, 95%CI: 2.15-4.04, P < 0.001), ACS only (OR: 2.70, 95%CI: 1.92-3.81, P < 0.001), as well as MI (OR: 1.88, 95%CI: 1.53-2.32, P < 0.001) (Fig 3D).

**Subgroup analyses**

The results of subgroup analysis were reported in Table 2. In subgroup analysis according to study design, elevated Lp(a) was associated with significantly increased risk of premature ASCVD in cross-sectional studies (OR: 2.09, 95%CI: 1.59-2.75, P < 0.001), retrospective studies (OR: 2.84, 95%CI: 2.31-3.50, P < 0.001) and prospective studies (OR: 1.73, 95%CI: 1.40-2.13, P < 0.001) (Supplementary material online).
material online, Figure 3). In addition, the association between Lp(a) and premature ASCVD was significant both in male (OR: 2.31, 95%CI: 1.80-2.97, P < 0.001) and female patients (OR: 2.34, 95%CI: 1.53-3.58, P < 0.001) (Supplementary material online, Figure 4). As for race, elevated Lp(a) could predict premature ASCVD in South Asians (OR: 3.71, 95%CI: 2.31-5.96, P < 0.001) and white patients (OR: 3.17, 95%CI: 2.22-4.52, P < 0.001), but not in Chinese (OR: 1.20, 95%CI: 0.99-1.45, P = 0.06) (Supplementary material online, Figure S5). In subgroup analysis by population characteristics, the significant association between higher Lp(a) and increased risk of premature ASCVD was noted both among community population (OR: 2.34, 95%CI: 1.93-2.84, P < 0.001) and hospitalized patients (OR: 2.37, 95%CI: 1.78-3.15, P < 0.001) (Supplementary material online, Figure S6).

As for the baseline LDL-c level, the association between elevated Lp(a) level and increased risk of premature ASCVD was relationship was significant among patients with baseline LDL-c level of 100-130mg/dL (2.6-3.4mmol/L) (OR: 2.09, 95%CI: 1.56-2.79, P < 0.001), 130-160mg/dL (3.4-4.1mmol/L) (OR: 2.70, 95%CI: 1.92-3.88, P < 0.001) and ≥160mg/dL (4.1mmol/L) (OR: 4.38, 95%CI: 2.57-7.46, P < 0.001), but not in <100mg/dL (2.6mmol/L) (OR: 3.02; 95%CI: 0.65-14.00, P = 0.16) (Supplementary material online, Figure S7). And the information of the treatment was reported in Supplement Material Table 1. In subgroup analysis according to different definition of “premature”, increased level of Lp(a) was associated with significant higher risk of ASCVD among patients younger than 50 years (OR: 2.72; 95%CI: 2.16-3.41, P < 0.001), or younger than 60 years (OR: 2.40, 95%CI: 2.00-2.89, P < 0.001) (Supplementary material online, Figure S8).
Subgroup analysis based on different cut-off levels indicated that the association between increased Lp(a) and premature ASCVD was significant when taking Lp(a) ≥30 mg/dL (72nmol/L) (OR: 2.19, 95%CI: 1.75-2.74, P < 0.001), Lp(a) ≥50mg/dL (110nmol/L) (OR: 2.98, 95%CI: 1.94-4.58, P < 0.001), top quartiles OR: 2.39, 95%CI: 1.55-3.68, P < 0.001), or top tertiles (OR: 2.22, 95%CI: 1.15-4.29, P = 0.02) as exposed, but not for top quintiles (OR: 1.47, 95%CI: 0.78-2.76, P = 0.23) (Supplementary material online, Figure S9). And the data of absolute value was reported in Supplement Material Table 2.

To examine the potential influence of technique of Lp(a) measurements, further subgroup analysis was conducted, which revealed a pooled estimated OR of 1.86 (95%CI: 1.50-2.31, P < 0.001) for immunoturbidimetric method, 2.93 (95%CI: 2.15-3.98, P = 0.02) for IRMA, and 4.32 for ELISA (95%CI: 2.78-6.73, P < 0.001) (Supplementary material online, Figure S10).

Heterogeneity and Sensitivity analyses

There was no significant heterogeneity in analyses of Lp(a) and overall ASCVD, whereas high heterogeneity was observed in analyses of Lp(a) and individual ASCVD. After excluding Li et al.,29 in which the important confounding factor of FH was ignored, the I² decreased to moderate from high, suggesting the unadjusted confounders could have contributed to the heterogeneity observed (Supplementary material online, Figure S11). And subgroups stratified by study design, Lp(a) measurement approaches, baseline LDL-c level, definition of "premature", gender and race showed a substantial decline of heterogeneity, indicating the potential origins of heterogeneity (Supplementary material online, Figure S3~S10). And Longenecker et al is confounded due to dialysis and chronic kidney diseases (CKD)30. When excluded the study, the result of the composite ASCVD remained
significant. (Supplementary material online, Figure S12) In addition, only Arnold et al.\textsuperscript{6} discussed the secondary prevention, while others discussed the primary prevention. After excluding the study, the result of the individual ASCVD remained significant. (Supplementary material online, Figure S13)

**Discussion**

This comprehensive meta-analysis evaluated the associations between elevated Lp(a) and the risk of premature ASCVD, the main findings are the followings: (1) elevated Lp(a) is significantly associated with higher risk of composite premature ASCVD, especially for CAD and PAD, and amongst patients with FH and T2DM; (3) the association between Lp(a) and premature ASCVD was significant regardless of study design, gender, population characteristics (community or hospitalized), different premature definitions, and various Lp(a) measurement approaches.

Lp(a) is a LDL-c-like particle derived in liver, which is covalently bound to apolipoprotein (apo) B100 by apo(a).\textsuperscript{31} It’s the major carrier of oxidized phospholipid and promotes atherosclerotic plaque development through the pro-inflammatory, pro-thrombotic and anti-fibrinolytic effects.\textsuperscript{26, 31-36} In our meta-analysis, we found that genetically determined high Lp(a) is an independent predictor of premature ASCVD.

About 90% of the Lp(a) concentration is inherited and primarily determined by the LPA gene singly, so it shows more pronounced effect in younger patients, who are less affected by environmental risk factors accumulating with age.\textsuperscript{37} It’s found that Lp(a) was a persuasive predictor of the composite ASCVD in young but not in old.\textsuperscript{30} For the individual ASCVD, the significant correlation was also observed in patients <60 years but not in those >60 years in the studies by Arnold et al.\textsuperscript{6} and Hanif et al.\textsuperscript{38}. Rallidis
et al.\textsuperscript{39} further found that a ten mg/dL increase in Lp(a) was associated with four percent of higher risk of acute coronary syndrome in patients <45 years and two percent of higher risk in patients of 45-60 years. All studies above agreed that the correlation decreased with increasing age. So far, there has been only one similar meta-analysis focusing on the impact of high Lp(a) on premature CAD. It’s reported that Lp(a) concentration increased significantly in patients with premature CAD (SMD: 0.97, 95%CI: 0.52-1.42, $P < 0.001$, $I^2 = 98\%$) compared to controls. But the results remained controversial because of relatively small case-control studies of moderate quality and high statistical heterogeneity.\textsuperscript{40} Compared with the previously published meta analyses, our study has several strengths. Firstly, all observational studies meeting the criteria were included, so the impact of elevated Lp(a) on premature ASCVD in cohort studies and cross-sectional studies could be analyzed. Secondly, most included studies were assessed as high quality, thus the reliability of the results was guaranteed. Thirdly, we performed sensitivity analysis and subgroup analysis to reduce the heterogeneity. Fourthly, the influence of high Lp(a) on composite ASCVD, stroke and PAD was reported, which was absent in the previous study. It’s worth noting that the correlation is not significant for ischemic stroke. Ischemic strokes are caused by several pathologies, including atherosclerotic vascular disease in large arteries, arteriolar disease in small arteries, and embolic disease caused by aorta or carotid arteries atherosclerosis and heart disease, such as atrial fibrillation.\textsuperscript{41}Lp(a) levels of large artery atherosclerosis (LAA) stroke were significantly higher than those of the other stroke mechanisms. A two-sample Mendelian randomization analyses reported that reduction of Lp(a) levels were associated with lower risks for LAA
stroke, but not for any IS, cardioembolic stroke, or small vessel stroke. Arnold also found that elevated Lp(a) was independently associated with (LAA) ischemic stroke aetiology but not with non LAA ischemic stroke. However, some of the included studies reporting premature ischemic stroke neither identified the classification nor indicated evident arteriosclerotic disease in patients. It is possible that only LAA stroke is associated with elevated Lp(a) in young patients due to its machine of proatherosclerotic effect. We need more study with high quantity to determine the association for different subtypes of ischemic stroke in young patients and specific mechanisms should be clarified to evaluate the correlation between elevated Lp(a) and premature ischemic stroke.

FH is an inherited metabolic disease characterized by high levels of circulating LDL-c, and is relatively prevalent in premature ASCVD patients. The current meta-analysis confirmed strong correlation between elevated Lp(a) and premature ASCVD in FH patients compared with general population. Elevated Lp(a) is the key factor for risk stratification in the management of FH. Some guidelines suggested that Lp(a) should be incorporated into the genetic cascade testing of FH to identify family members in high risk. A research team at Fuwai Hospital found that in older patients comorbid with T2DM, the ASCVD risk associated with Lp(a) might further increase. And in this study, increased Lp(a) level is also a risk factor for premature ASCVD in T2DM patients. As for dialysis patients with CKD, in whom the Lp(a) was higher than others, the significant association between Lp(a) and premature ASCVD was revealed by Longenecker et al. Whether this finding applied to CKD patients at the early age remained to be confirmed, for the existing studies focusing on young people with CKD and dialysis were limited and the subgroup analysis failed. Arnold et al. reported significant relation between higher Lp(a) and recurrence
Although Lp(a) concentration is predominantly determined by genetics, gender exerts an important influence. Therefore, subgroup analysis based on gender was conducted. There was an agreement that Lp(a) could predict ASCVD in men, but the prognostic value in women remained controversial. A Mendelian randomization study showed that correlation existed in both men and women, while Wild et al. reported only in men. We found that men could benefit from Lp(a) testing. As for women, although we reached a positive conclusion, significant heterogeneity might raise some question. The inconsistent findings might be due to various estrogen levels of women included in different studies and research for women stratified by menstruation and estrogen replacement treatment is needed in the future to explore the influence on women.

Besides gender, ethnicity also have an impact on Lp(a) level, so we performed subgroup analysis for different races. Not only differ in Lp(a) concentration, patients among different races also show various population-attributable risk of elevated Lp(a) for MI in the populations of all ages, ranging from 0% in Africans to 9.5% in South Asians, and modest in Caucasians (4.6%). Our meta-analysis showed significantly increased risk for premature ASCVD in Caucasians and South Asians with high Lp(a). South Asians and Caucasians could benefit from Lp(a) testing. In the review by Li et al. summarizing recent research regarding to Lp(a)-related studies in the Chinese population, it is recommended to test Lp(a) at least once in a lifetime. However, this study draws the opposite conclusion in young Chinese population, suggesting the necessity varied among Chinese in different age stratification. To present meaningful data on this topic, we look forward to large studies which analyzed Lp(a) levels progressively for each decade.
of life to determine the parts of Chinese population in need of Lp(a) testing. For the data about African-
Caribbean patients was too little to conduct a meta-analysis, more studies are needed to provide
sufficient information.

It’s found that high variability of Lp(a) levels could be considered an independent risk factor for
increased post percutaneous coronary intervention (PCI) C-reactive protein (CRP) level. And the result
of subgroup analysis of patients under 65 years remained consistent. In FH patients, Cao et al. found
that high visit to visit variability of Lp(a) levels were associated with major adverse cardiovascular
events (MACE). The repeated process of dissolution and crystallization of the cholesterol within
coronary plaques caused by the variability of lipid might impair the plaque stability, thereby leading to
plaque rupture and cardiovascular events. Whereas a large, observational study found that difference
between follow-up and baseline lipoprotein(a) molar concentration was not significantly associated
with incident CAD. No consensus has been reached on this issue. In our meta-analysis, given the lack
of related data in the original articles, we could not further investigate the association between Lp(a)
variability with premature ASCVD. More study are needed to clarify the relationship between high
variability of Lp(a) levels and cardiovascular disease.

Cumulative Lp(a) exposure, incorporating both the Lp(a) concentration and exposure duration into a
single risk parameter, was an important predictive factor in the secondary prevention. And Wang et al.
found that higher level of cumulative Lp(a) exposure was related with poorer prognosis among
individuals with prediabetes and T2DM. Due to the stability of Lp(a) level during the lifespan, in the
individuals with higher Lp(a) level in the early age, high cumulative Lp(a) exposure tended to be
reached faster, which explained the relationship between elevated Lp(a) and premature ASCVD from another perspective.

Premature ASCVD occurred more often in patients with elevated Lp(a) compared to those without when the baseline LDL-c $\geq 100\text{mg/dL}$ (2.6mmol/L). It’s considered that Lp(a) contributed to a residual risk of ASCVD even at relatively low baseline LDL-c concentration of 100-130mg/dL (2.6-3.4mmol/L). However, when the threshold dropped further to 55mg/dL (1.4mmol/L), which was the LDL-c control target of patients with ASCVD recommended by the 2019 ESC/EAS guideline, the correlation no longer existed in older population. The mechanism of this unique association was not yet clear. It’s found that the degradation of Lp(a) was partly mediated by the LDL receptors. And high levels of LDL-c might occupy the receptors, competitively inhibiting the catabolism of Lp(a) and enhancing the biological effect of Lp(a).

Patients with very low LDL-c levels tended to have high levels of activity of LDL receptors and a strong metabolic capacity for Lp(a). Although Lp(a) levels were high, they could be metabolized quickly and the biological effects were weakened. In adults at the early age, those with LDL-c below the cut-off of 2.6mmol/L would not suffer from more often ASCVD for elevated Lp(a) according to the meta-analysis, providing a reference threshold for the prevention of early-onset ASCVD. The patients with combination of LDL-c $\geq 100\text{mg/dL}$ (2.6 mmol/L) and Lp(a) elevations should be considered as the vulnerable ones and need to further reduce their LDL-c levels below 100mg/dL (2.6 mmol/L). For only two study focused on patients with baseline LDL-c $< 100\text{mg/dL}$ (2.6mmol/L), further studies were needed to clarify the LDL-c control target for young patients with high Lp(a).
Moreover, it's seemed that the association between Lp (a) levels and ASCVD events follows a linear pattern. Whether the results are significant might be related to the increased doses of Lp(a) in the exposed group compared to the control group. And Lp(a) is often termed as a categorical variable through setting a threshold directly, which is more convenient in clinical practice. The risk of premature ASCVD is considered moderate at the level of 30-50mg/dL (72nmol/L-110nmol/L), high above 50mg/dL (110nmol/L) and very high above 180mg/dL (450nmol/L). In this meta-analysis, significant association was observed when the “high Lp(a)” were defined according to commonly used thresholds, 30mg/dL (72nmol/L) and 50mg/dL (110nmol/L). Among included studies, none reported outcomes in patients with Lp(a) level >180mg/dL, and we could not conduct a subgroup analysis focusing on these patients in very high risk, which is one of the limitations of our study. Moreover, exploring the prognostic effects of very high levels of Lp(a) in patients with prior ASCVD may be of little significance. Berman et al. conducted a retrospective cohort study, found that there was a plateau around 70 percent in risk for patients with prior ASCVD when analyzing the association between Lp(a) and ASCVD, whereas there was a linear association between Lp(a) and risk among patients without ASCVD. For this situation, they explained that in the patients with baseline ASCVD, which already had higher absolute risk of CVD events and were treated with optimal preventive therapies usually, extremely elevated Lp(a) (above the 90th percentile) might have less effect on the future ASCVD risk. The threshold for risk assessment was 53mg/dL (112nmol/L) in secondary prevention, while the threshold was 102mg/dL (216 nmol/L) in primary prevention, suggesting that elevated Lp(a) should be defined differently for different populations for optimal risk prediction and clinical management.
However, it’s strange that people with top quintile Lp(a) didn’t show higher risk of premature ASCVD, but people with top quartile and tertile did. The study from Shi et al. should be rebuked for it focused on Chinese people, in whom the association was not significant. Moreover, due to the small total number of included studies, the result of the subgroup analysis was less reliable.

The findings of the meta-analysis could be clinically relevant. The patients with higher Lp(a) might suffer from ASCVD earlier, so the Lp(a) testing for reclassification in people who are borderline between moderate and high-risk and the preventive measures to lower Lp(a) should be taken in time, especially in males, females, Caucasians, South Asians, FH patients and T2DM patients. It’s recommended in the guideline that measurement of Lp(a) is a routine at least once in a lifetime. Young patients with higher Lp(a) levels should be given earlier appointment for decisive tests like CT angiography or invasive angiography, regardless of their history of T2DM or FH. For the approach to reducing Lp(a) level, existing data have indicated that intensification of treatment, such as the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evolocumab and alirocumab could reduce Lp(a) levels by about 20% to 30%, providing great risk reduction for cardiovascular risk. In addition, lipoprotein apheresis could lower Lp(a) immediately. Novel drugs under development such as RNA-targeting therapy was still in the early development stage. Moreover, a more aggressive management of lifestyle modifications and reduction of elevated LDL-c levels, especially with statins, due to the synergistic effects of Lp(a) and LDL-c, was needed.

Limitation

Several potential limitations should be noted in our meta-analysis. Firstly, only articles published on
PubMed and Embase were included, which might lead to missing articles that were not indexed in these search engines. Secondly, in consideration of the characteristics of the included studies, Lp(a) concentration was analyzed as a continuous (per one unit or per one SD increase of Lp(a) or log [Lp(a)]) and categorical variable (tertile, quartile, quintile or specific thresholds), resulting in failure of pooling all relative studies together. Thirdly, most studies included in our studies were retrospective studies and cross-sectional studies, which might have more recall bias. Fourthly, publication bias in meta-analyses was examined by checking for asymmetry in a funnel plot, which was determined subjectively. Fifthly, in subgroup analyses based on races, we failed to provide data about other races such as data for the lack of information. Finally, certain analysis contained only two or three studies, which were relatively few, and more studies were needed to increase the reliability of the results.

Conclusion

Our meta-analysis supports that elevated Lp(a) concentration, which is genetically determined, can predict both composite and individual ASCVD in young patients. The presence of high Lp(a) concentration indicates prospective evaluation and validation as a clinical risk factor in premature ASCVD in Caucasians, South Asians, FH population and patients with the baseline LDL-c level ≥100mg/dL (2.6mmol/L).

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Figure legends

Fig 1. Flow diagram of the study selection process.

Fig 2. Meta-analysis of elevated Lp(a) and the risk of the composite ASCVD at the early age (A). Meta-analysis of elevated Lp(a) and the risk of the individual ASCVD at the early age for categorical variables (B), and continuous variable as per one SD increase of the log Lp(a) (C).

Abbreviations: ASCVD: Arteriosclerotic cardiovascular disease; CI: Confidence interval; Lp(a): Lipoprotein(a); OR: Odds ratio; SE: standard error;

Fig 3. Further analysis of elevated Lp(a) and the risk of overall ASCVD at the early age for in FH patients (A) and in T2DM patients (B) when analyzed as categories. meta-analysis of elevated Lp(a) and the risk of individual ASCVD at the early age (C) and further analysis classifying premature CAD into subcategories (D).

Abbreviations: ASCVD: Arteriosclerotic cardiovascular disease; CAD: Coronary artery disease; CI: Confidence interval; FH: familial hypercholesterolemia; Lp(a): Lipoprotein(a); OR: Odds ratio; PAD: Peripheral arterial disease; SE: standard error; T2DM: Type 2 diabetes mellitus
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Editorial Board Member of Cardio-Oncology (SCI)

Editorial Board Member of PACE

Editorial Board Member of BMC Cardiovascular Disorders

Editorial Board Member of Journal of Clinical Medicine
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Abbreviations: ACS: Acute coronary syndrome; ASCVD: Arteriosclerotic cardiovascular disease; CAD: Coronary artery disease; CHD: Coronary heart disease; ELISA: Enzyme linked immunosorbent assay; HR: Hazard ratio; IMA: Immunoradiometric assay; LDL-c: Low density lipoprotein-cholesterol; MI: Myocardial infarction; NA: Not available; OR: Odds ratio; PAOD: Peripheral arterial occlusive disease; PVD: Peripheral vascular disease.
Table 2. Subgroup analysis of the association between elevated Lp(a) and the risk of premature ASCVD for categorical variables.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of studies</th>
<th>Meta-analysis</th>
<th>Heterogeneity</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>OR 95% CI</td>
<td>P value  I² (%)</td>
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<tr>
<td>Study design</td>
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<tr>
<td>Prospective</td>
<td>9</td>
<td>1.73 1.40-2.13</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Retrospective</td>
<td>26</td>
<td>2.84 2.31-3.50</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>15</td>
<td>2.09 1.59-2.75</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Female</td>
<td>12</td>
<td>2.34 1.53-3.58</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Male</td>
<td>10</td>
<td>2.31 1.80-2.97</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Race</td>
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<tr>
<td>Caucasians</td>
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<td>3.17 2.22-4.52</td>
<td>P &lt; 0.001</td>
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<tr>
<td>South Asians</td>
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<td>3.71 2.31-5.96</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Chinese</td>
<td>4</td>
<td>1.20 0.92-1.45</td>
<td>P = 0.06</td>
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<td>Population characteristics</td>
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<td>Community population</td>
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<td>2.34 1.93-2.84</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Hospitalized patients</td>
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<td>2.37 1.78-3.15</td>
<td>P &lt; 0.001</td>
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<td>Baseline LDL-c level</td>
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<tr>
<td>&lt; 2.6mmol/L</td>
<td>2</td>
<td>3.02 0.65-14.00</td>
<td>P = 0.16</td>
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<tr>
<td>2.6-3.4mmol/L</td>
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<td>2.09 1.56-2.79</td>
<td>P &lt; 0.001</td>
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<tr>
<td>3.4-4.1mmol/L</td>
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<td>2.70 1.92-3.80</td>
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<td>≥ 4.1mmol/L</td>
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<td>4.38 2.57-7.46</td>
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<td>Definition of &quot;premature&quot;</td>
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<td>60 years</td>
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<td>2.40 2.00-2.89</td>
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<td>50 years</td>
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<td>2.72 2.16-3.41</td>
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<td>Different cut-off levels of Lp(a)</td>
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<td>Immunoturbidimetric method</td>
<td>IRMA</td>
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<tr>
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<td>2.93</td>
<td>1.86</td>
<td>3.41</td>
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<td>2.15-3.98</td>
<td>1.50-2.31</td>
<td>1.80-6.48</td>
<td>1.95</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
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<td>48</td>
<td>69</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P = 0.02</td>
<td>P = 0.001</td>
<td>P = 0.75</td>
<td>P = 0.75</td>
</tr>
</tbody>
</table>

1 Abbreviations: ACS: Acute coronary syndrome; ASCVD: Atherosclerotic cardiovascular diseases; CAD: Coronary artery diseases; CI: Confidence interval; ELISA: Enzyme linked immunosorbent assay; IRMA: Immunoradiometric assay; Lp(a): Lipoprotein(a); LDL-c: Low density lipoprotein-cholesterol; MI: Myocardial infarction OR: Odds ratio
Figure 1

2496 and 2389 records identified through PubMed and Embase → 1016 duplicates removed

3869 records after duplicates removed → 3472 records excluded from titles and abstracts

397 full-text articles for further screened

332 full-text articles excluded
- Review article (n=1)
- Comments (n=7)
- Full-text unavailable (n=16)
- Age of onset ineligible (n=212)
- Duplicate data (n=2)
- Unclear referent group (n=1)
- Insufficient data (n=5)
- No outcomes with interest (n=42)
- Absence of helpful HR/RR/OR (n=60)

51 full-text articles for further screened

168x168 mm (x DPI)
### Figure 2

112x171 mm (x DPI)
Elevated Lipoprotein(a) is associated with higher risk of premature ASCVD