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Authors

Vazirian, Fatemeh
Sadeghi, Masoumeh
Kelesidis, Theodoros
et al.

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Predictive value of lipoprotein(a) in coronary artery calcification among asymptomatic cardiovascular disease subjects: A systematic review and meta-analysis

Fatemeh Vazirian[a,1], **Masoumeh Sadeghi**[b,1], **Theodoros Kelesidis**[c], **Matthew J. Budoff**[d], **Zahra Zandi**[e], **Sara Samadi**[f,*,2], **Amir Hooshang Mohammadpour**[f,g,**,2]

[a]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

[b]Department of Epidemiology, Faculty of Health, Mashhad University of Medical Sciences, Mashhad, Iran

[c]Department of Medicine, Division of Infectious Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[d]Department of Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA

[e]Department of Cardiovascular Disease, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[f]Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

[g]Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Aims: Studies have indicated inconsistent results regarding the association between plasma levels of Lipoprotein(a) [Lp(a)] and coronary artery calcification (CAC). We performed a systematic review and meta-analysis to investigate the association between elevated levels of Lp(a) and risk of CAC in populations free of cardiovascular disease (CVD) symptoms.

Data synthesis: PubMed, Web of Science, Embase, and Scopus were searched up to July 2022 and the methodological quality was assessed using Newcastle–Ottawa Scale (NOS) scale. Random-effects meta-analysis was used to estimate pooled odds ratio (OR) and 95% confidence

[*]Corresponding author. Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. samadi.srh@gmail.com (S. Samadi). [**]Corresponding author. Department of Clinical Pharmacy, School of Pharmacy; Mashhad University of Medical Sciences, Mashhad, Iran. MohamadpoorAH@mums.ac.ir (A.H. Mohammadpour).

[1]Equally contributed as the first author.

[2]Equally contributed as the corresponding author.

Authors' contribution

Fatemeh Vazirian: Conceptualization, Methodology, Investigation, Writing – original draft. Masoumeh Sadeghi: Formal analysis, Writing – review & editing, Software. Theodoros Kelesidis: Conceptualization, Investigation, Writing – review & editing. Matthew J. Budoff: Writing – review & editing, Validation. Zahra Zandi: Writingeoriginal draft, Conceptualization. Sara Samadi: Conceptualization, Methodology, Writinge-review & editing, Supervision. Amir Hooshang Mohammadpour: Writing – review & editing.

Declaration of competing interest

The authors declared no personal or financial conflicts of interest.

interval. Out of 298 studies, data from 8 cross-sectional (n = 18,668) and 4 cohort (n = 15,355) studies were used in meta-analysis. Cohort studies demonstrated a positive significant association between Lp(a) and CAC, so that individuals with Lp(a)≥30–50 exposed to about 60% risk of CAC incidence compared to those with lower Lp(a) concentrations in asymptomatic CVD subjects (OR, 1.58; 95% CI, 1.38–1.80; I^2, 0.0%; P, 0.483); Subgroup analysis showed that a cut-off level for Lp(a) measurement could not statistically affect the association, but race significantly affected the relationship between Lp(a) and CAC (OR,1.60; 95% CI, 1.41–1.81). Analyses also revealed that both men and women with higher Lp(a) concentrations are at the same risk for increased CAC.

Conclusions: Blood Lp(a) level was significantly associated with CAC incidence in asymptomatic populations with CVD, indicating that measuring Lp(a) may be a useful biomarker for diagnosing subclinical atherosclerosis in individuals at higher risk of CAC score.

Keywords

lipoprotein(a); CAC; atherosclerosis; cardiovascular disease; meta-analysis

1. Introduction

Atherosclerotic cardiovascular disease (CVD) such as ischemic heart disease (IHD) is the main global cause of mortality worldwide and is estimated to contribute to more than 23.6 million deaths by the year 2030 [1]. Moreover, ischemic heart disease (IHD) caused by atherosclerosis has the most attribution role in occurrence of CVD. Meanwhile, general population with asymptomatic condition showed almost 50% of CVD deaths [2]. Coronary artery calcification (CAC) has a recognized role in assessing the risk of atherosclerotic cardiovascular disease (CVD) and serves as an independent predictive value for future cardiovascular events [3]. Moreover, computed tomography (CT) scanning that is commonly used for CAC measurement, is relatively costly and exposes subjects to radiation, which increases their risk of cancer [4,5]. Therefore, identifying practical biomarkers that predict increased CAC can facilitate risk stratification of people with subclinical atherosclerosis who are at risk for CVD.

Lipoprotein(a) (Lp(a)) is the aggregation of low-density lipoprotein (LDL)-like particles bound to apolipoprotein B100 molecule in plasma [6,7]. Lp(a) contributes to the calcification process through multiple pathways [8,9,10]. *In vitro* studies demonstrated that Lp(a) can facilitate calcium precipitation in the arterial endothelium by inducing the chondro-osteogenic differentiation in vascular smooth muscle cells (VSMC) [11]. In addition, Lp(a) may act as a favorable carrier for pro-inflammatory factors like oxidized lipids and autotaxin, an endothelial enzyme responsible for inducing the inflammatory response (Fig. 1) [12–14]. Emerging evidence suggests that Lp(a) can trigger the release of pro-calcific proteins, bone morphogenetic protein 2 (BMP2) and osteopontin (OPN), by activating Notch 1 signaling pathway which leads to osteogenic trans-differentiation of VSMCs and vascular calcification [15,16]. In accordance with these findings, it was reported that patients with CAC, had elevated levels of OPN and Notch1 [15]. Thus, blood levels of Lp(a) can potentially be a useful blood biomarker that predicts an increased risk of CAC.

Several meta-analysis and epidemiological studies have reported that elevated blood level of Lp(a) is a contributing genetic factor in acute coronary syndrome, myocardial infraction, heart failure, and peripheral atherosclerosis and is associated with an increased calcification process [17–21]. Presently, various lipid disorder guidelines suggested assessing Lp(a) in the general population, highlighting the important role of Lp(a) in the enhanced risk of CVD development [22,23]. However, routine lipid measurement panels in clinical settings do not include the assessment of Lp(a) levels for therapeutic intervention. Thus, stronger evidence is required to determine the impact of Lp(a) on cardiovascular health [24]. Various studies have presented inconclusive results regarding the potential association between Lp(a) and the occurrence of CAC in asymptomatic CVD subjects [25–27]. This meta-analysis aimed to establish clinical evidence on the association between Lp(a) and coronary artery calcium score in asymptomatic CVD subjects to identify individuals with subclinical atherosclerosis who may be at increased risk of developing cardiovascular events. Furthermore, we assessed the effect of confounding variables, such as gender, race, and Lp(a) cut-off levels, on the contribution of Lp(a) in occurrence of CAC.

2. Materials

Our report was conducted in accordance with the recommendations of the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guideline for retrieving observational studies and presenting the systematic review and meta-analyses. The protocol of the current systematic review was recorded in the international PROSPERO (prospective register of systematic reviews), registration number: CRD42022350297.

2.1. Search strategy and selection criteria

The included studies were retrieved from four databases comprising of Pubmed, Embase, Web of Science, and Scopus until July 2022. To achieve more sensitivity and specificity, both Medical Subject Headings (MESH) and non-MESH words were used to retrieve the studies. The keywords were included as (“Coronary Artery Disease”[Mesh] OR “Coronary Arteriosclerosis” OR “Atherosclerosis”[Mesh] OR “Myocardial Ischemia”[Mesh] OR “Ischemic Heart Disease” OR “Myocardial Infarction”[-Mesh] OR “Coronary Heart Disease”) AND (“‘Lipoprotein(a)”[Mesh] OR “Lipoprotein Lp(a)” OR “Lp(a)” OR “Lipoprotein a” OR “Lipoprotein (a)”) AND (“Coronary Artery calcification” OR “Coronary Artery calcification score” OR “Coronary Artery calcium score” OR “Calcific Coronary Artery Disease” OR “calcific coronary disease” OR “CAC score”). In addition, we employed Emtree words, which included “Lipoprotein A” AND “coronary artery calcification” AND “coronary artery disease” OR “atherosclerosis” OR “heart muscle ischemia” OR “heart infarction” OR “ischemic heart disease”. Meanwhile, we manually investigated Google Scholar and the references of included articles to determine any overlooked related records.

Our search was restricted to human observational studies including cohort, case-control and cross-sectional studies investigating the relationship between Lp(a) and CAC among asymptomatic CVD patients. The outcome of the study was coronary artery calcification that is measured by electron beam tomography. To eliminate heterogeneity between the studies,

we attempted to pool results from the studies that have the same methodology and setting. We excluded case reports, animal studies, conference abstracts, review articles, genetic studies, editorials, information articles for patients and clinical guidelines. The search was not restricted to language and time. The titles and abstracts of the retrieved studies were independently screened by two authors, and the inconsistency was resolved by a third author. The description of the selection process is presented in Fig. 2.

2.2. Data abstraction and quality assessments

The data extraction was based on author's last name, year, country, age, study design, study population and number of participants, risk estimates (odds ratios; OR, relative risk; RR) with their confidence intervals (CI), covariates adjustment, and method of Lp(a) measurement. The data was extracted by two investigators, and the inconsistency was resolved by the interfering of a third author. The quality assessment was based on New Castle Ottawa scale (NOS) which evaluates type of study, covariates adjustment, performance, clinical evidence, analysis, and validity of results.

2.3. Statistical analysis

All statistical analyses were performed via Stata version 11.2 software (Stata Corp., College Station, TX, USA). In case of determining the multivariable adjusted OR and corresponding 95% CI, we created forest plot for visual inspection across studies and the lowest and highest of Lp(a) categories were compared. Our meta-analysis used Logarithm of the odds ratio and the standard error and for calculating the estimation of pooled OR with its corresponding 95% CI, we performed Der-Simonian and Laird method. Also, Heterogeneity between studies could be identified by I^2 statistic (I^2 = 0% shows no heterogeneity and $I^2 \geq$ 50% shows the substantial heterogeneity).

Cochran's Q statistic was applied in order to analyze the heterogeneity and we used sensitivity analysis for assessing the robustness of the findings on the analysis. Moreover, we performed subgroup analyses in studies having different Lp(a) level cut-off and racial diversity to find the source of heterogeneity within the included studies. Our meta-analysis could not apply Egger's regression asymmetry test and Begg's adjusted rank correlation test and report publication bias regarding to the limited included studies. Furthermore, for evaluating simulation, the trimand-fill method was carried out. The significance association was identified by level under 0.05 for all tests, while in the heterogeneity test the significant relationship was not considered as similar as other tests and all the statistical tests were two-tailed.

3. Results

3.1. Results of the literature search

Our review screened four databases (Scopus, PubMed, Web of Science, and Embase) and identified 298 records. After applying eligibility criteria, 111 articles were excluded, and 167 duplicate studies were removed. In addition, 10% of the references in the included studies were reviewed to find any overlooked literatures. Out of remaining 20 included

studies in this systematic review, 6 were prospective cohorts, and 14 were cross-sectional studies.

3.2. General characteristics of included studies

In the eligible studies both men and women were investigated, except for one study that only recruited asymptomatic CVD men subjects, and Lp(a) was measured by Immunoturbidimetric assay by majority of the studies. Among the included studies, five were conducted in Asia, nine in United States, and five in Europe. The detailed characteristics of the studies are provided in Table 1. Most of the studies rated as good in the quality assessment. Eleven studies reported OR [15,25,27–35], three studies reported β that CAC was measured as a quantitative variable [9,36,37], and two studies reported RR [26,38] for the association between Lp(a) and CAC in subjects with CVD history. Regarding the reported data and studies population, our meta-analysis included 12 studies, 4 cohorts [26,31,32,35] and 8 cross-sectional studies [25,27–30,33,34,38], to estimate the relationship of Lp(a) with CAC among asymptomatic CVD subjects (Table 2). As seen in studies, 9 articles have shown significant positive association between Lp(a) and CAC in asymptomatic CVD patients [25,26,28,30–35], while 3 cross-sectional studies demonstrated no statistically significant relationship between Lp(a) level and abnormal coronary artery calcium score [27,29,38]. In our meta-analysis, 15,355 human individuals were recruited in the 4 included cohort studies with mean follow-up duration of 6.5 years and the 8 cross-sectional studies involved 18,668 subjects.

3.3. Association of Lp(a) with CAC among asymptomatic CVD subjects

Fig. 3A indicates the forest plot of the association between Lp(a) levels and CAC incidence. Given the data in cross-sectional studies, we estimated the pooled odds ratio for coronary artery calcium score by 1.08 (95% CI, 1.02e1.13) among asymptomatic CVD subjects with elevated Lp(a) levels and there was a high degree of between-study heterogeneity (I^2 = 90.6%; P = 0.00) [25,27–30,33,34,38]. In case of finding the possible source of heterogeneity between the studies, we used a sub-group meta-analysis for the contribution of Lp(a) in CAC incidence. A subset of studies reported the odds ratio separately for Lp(a) different cut-off levels (Lp(a) ≥50 [25,28,29,38] and 20< Lp(a)> 38 [27,30,33,34]). The subgroup analysis based on Lp(a) cut-off levels indicated that the relationship between CAC and Lp(a) is statistically independent from Lp(a) cut-off threshold, however a significant effect size for the 20< Lp(a)> 38 was estimated (OR,1.96; 95% CI, 0.98–3.95; I^2,92.8%; p,0.000)) (OR,1.01; 95% CI, 0.99–1.03; I^2,62.2%; p,0.032) (Fig. 3B). In addition, the sensitivity analysis was carried out for evaluating the impact of each included study via removing every single study at a time and the robustness of the meta-analysis was confirmed.

Moreover, considering the data of the 4 cohort studies, comparing the top versus the bottom tertile of baseline Lp(a) levels, the pooled odds ratio for CAC incidence was 1.58 (95% CI, 1.38e1.80) and there was no significant heterogeneity between the studies (I^2,0.0%; p,0.483) (Fig. 4) [26,31,32,35]. In addition, the sensitivity analysis was performed for cohort studies and the robustness of the meta-analysis model was confirmed.

Regarding the race and sex difference among the included studies, subgroup analysis was performed. The 2021 study conducted by Garg et al., which recruited a multiethnic population, revealed that race could potentially impact the contribution of Lp(a) in CAC by up to 67% [26]. The pooled OR for the white population in the included studies demonstrated the significant association between CAC and Lp(a) (OR,1.66; 95% CI,1.41–1.96; I^2,0.0%; p,0.869) [31,35]. Considering Asian individuals, the cohort study of Cho.et al., among 2611 subjects reported that Asian asymptomatic CVD subjects with high concentration of Lp(a) had a 33% higher risk of CAC incidence [32]. In addition, a recent cohort study, which recruited 2083 individuals, investigated the impact of black race on CAC. The study revealed that black subjects with elevated Lp(a) levels were found to have the highest risk of CAC burden when compared to individuals of other ethnicities (OR, 2.44; 95% CI, 1.13–5.27) [35]. Our visual summary of the data from various studies suggests that race may be a potential contributing factor in the relationship between Lp(a) and CAC (OR, 1.60; 95% CI, 1.41–1.81, I^2,0.0%; p,0.601). These findings are consistent with the results from the 2021 cohort study conducted by Garg et al. [26] (Fig. 5A). When conducting a subgroup analysis based on gender among the cohort studies, the association between CAC burden and Lp(a) was similar in both men and women participants (OR for CAC in men,1.71;95% CI,1.32e2.22) (OR for CAC in women,1.70;95% CI,1.38e2.10) [31,35] (Fig. 5B).

4. Discussion

Our meta-analysis, which relied on cohort studies, found that elevated blood level of Lp(a) in asymptomatic CVD individuals are associated with a 58% higher risk of abnormal coronary artery calcification score. This estimated risk aligns with the pooled OR derived from the cross-sectional studies (OR,1.08; 95% CI, 1.02–11.13). Despites variations in the characteristics of the studies included in our analysis, such as differences in female to male ratio, Lp(a) levels, mean age, ethnic diversity, and length of follow-up, our findings demonstrate a consistent and significant positive association between Lp(a) and CAC.

Taking a clinical perspective, our findings suggested that Lp(a) concentration should be considered as an influential factor in determining CAC burden. Specifically, the data of our analysis demonstrated that the plasma level of Lp(a) between 20 and 38 mg/dl was a better predictor of subclinical CAC compared to individuals with plasma Lp(a)≥50 mg/dl. Traditionally, two cut-off points for Lp(a) level, 30 mg/dl and 50 mg/dl, have been applied in the studies to identify individuals with subclinical CVD risk factors, however in light of our findings, applying the lower cut-off point could indicate more accurate results when stratifying the risk of CAC. In agreement with the result of this meta-analysis, in a young population aged 2–17 years with family history for premature CVD, Lp(a) > 30 mg/dl represented the higher likelihood of cardiovascular incidence [39]. Moreover, findings of Australian Research Integrity Committee (ARIC) study indicated that Lp(a) cut-off of 30 mg/dl was independently associated with the odds of CVD, stroke, and CHD risk in both black and white individuals that were followed for 20 years (n = 13,318) [40].

We studied the impact of ethnicity on the contribution of Lp(a) in CAC incidence. Race is a causal factor influencing the Lp(a) distribution in the population and had a crucial impact

on the association between Lp(a) and CAC, accounting for up to 60% of the observed effect (OR, 1.60; 95% CI,1.41e1.81). In agreement with our finding, a large cohort study recruiting a population of Multi-Ethnic Study of Atherosclerosis (MESA) in 2021 indicated that the risk of CAC progression among the multi-ethnic population with elevated Lp(a) level is about 67% higher compared to those with lower Lp(a) concentration [26]. In addition, the evidence of our study suggests that black individuals are more susceptible to the risk of CAC comparing to white populations. Consistent evidence from multiple population-based cohort studies has established same results, demonstrating that Lp(a) distribution vary significantly across black and white populations. For instance, findings of Coronary Artery Risk Development in Young Adults (CARDIA) study among 4215 black and white participants indicated that the median Lp(a) levels in black adults was about three-fold higher than white subjects [41]. Among the participants of the MESA cohort study, Guan and colleagues, reported that the black-white differences in plasma Lp(a) level was significant and black subjects had elevated Lp(a) concentration comparing to white individuals [42]. Taken together, there is an obvious race difference in plasma Lp(a) level that can influence cardiovascular risk stratification at the clinical level. Given the highest median Lp(a) concentration in black individuals, preventive therapy for cardiovascular events and Lp(a) lowering medication should be applied at early adulthood ages.

Following the recognition of the gender's influence on the association between Lp(a) and CAC burden, our pooled OR from the included cohort studies (n = 6039) demonstrated similar risk of CAC incidence between men and women [31,35]. In agreement with our findings, several population-based cohort studies reported the same median Lp(a) concentrations between genders [41,43], suggesting that sex may not be a significant factor to consider in the contribution of Lp(a) to CAC risk stratification. Our findings were consistent to the result of a recent ARIC study, which indicated that there was no significant difference in the association between Lp(a) and CAC in either men or women having elevated Lp(a) level [35].

As indicated by a recent population-based cohort study recruiting 5975 asymptomatic CVD subjects, Lp(a) ≥ 30 (mg/dl) concentration was a predictive marker for absolute increase in CAC volume (β, 3.21; 95% CI, 0.56e5.87) [9]. Additionally, data obtained from The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study in 2022 demonstrated that Lp(a) could predict CAC density progression among 285 subjects free of CVD symptoms (β, 0.81; 95% CI, 0.08–1.54; p, 0.03) [36]. Consistent with the significant association between CAC and Lp(a), the analysis on the data of a large occupational cohort study among 14,583 individuals without CVD symptoms indicated that elevated level of Lp(a) were associated with increased the risk of CAC score by 23% and the contribution of Lp(a) in CAC was independent of multiple CVD risk factors [44]. Our findings were consistent with the growing body of evidence on this topic [45,46]. A study in 2022 recruiting 7201 asymptomatic subjects undergoing coronary computed tomographic angiography (CCTA) demonstrated that higher concentration of Lp(a) was significantly associated with the extent of coronary atherosclerosis, suggesting the potential appliance of Lp(a) measurement in the evaluation of subclinical coronary atherosclerosis [47]. Considering the clinical relevance of higher Lp(a) concentration in risk stratification for subclinical atherosclerosis, the potential causality of plasma Lp(a)

with mitral and aortic valve calcification was investigated in a recent study among 12,006 individuals, which indicated that a 10-fold elevated Lp(a) levels was associated with a 26% enhanced risk of valve calcification [48]. Lp(a) has been emerged as a robust independent genetic determinant of the absolute risk of CVD in multiple studies. For instance, the investigation of the UK Biobank dataset among 112,338 subjects demonstrated that decreased levels of Lp(a) can lower the likelihood of coronary heart disease by 29%, suggesting pharmacological intervention aimed at lowering circulating Lp(a) can influence the development of atherosclerosis-related diseases [49]. Furthermore, in a 2019 study conducted in Copenhagen, the long-term association of Lp(a) with cardiovascular mortality was examined in a cohort of 69,764 individuals with a lengthy follow-up period. The results demonstrated that subjects with Lp(a) concentration >69 mg/dl had enhanced risk of cardiovascular mortality (hazard ratio (HR),1.32;95% CI, 1.12–1.56) [50].

Despite the promising results indicating the independent role of Lp(a) in determining CAC burden, a few studies reported contradictory findings. The study of Jug et al., showed that Lp(a) was a predictor of CAC among population having dyslipidemia, but Lp(a) was not associated with CAC among asymptomatic CVD subjects without any risk factors [51]. In accordance with the previous study, Lp(a) was not associated with increased CAC prevalence among 886 South Asian asymptomatic subjects with mean age of 55.4 [27]. Moreover, within 1288 asymptomatic CVD individuals in the Dallas heart study, CAC could not be predicted by Lp(a) levels in asymptomatic black and white subjects [52]. However, Lp(a) concentration among white population with cardiovascular risk factors including high LDL and triglycerides was associated with increased likelihood of coronary calcium incidence [52]. Nevertheless, the casual and longitudinal relationship between Lp(a) and CAC could not be addressed by these cross-sectional studies.

Given the essential function of Lp(a) in the process of CAC development, the significant influence of Lp(a) in determining CAC could be elucidated. Lp(a) serves as a preferable carrier for pro-inflammatory factors like oxidized lipids, which can induce stress oxidative response in endothelial cells and promote the chondro-osteogenic differentiation in VSMCs. These events result in calcium precipitation in arterial endothelium driving the development of CAC [12–14]. Recently, the direct role of Lp(a) in mediating the VSMC trans-differentiation through Notch1 signaling pathway was demonstrated [53]. Notch1 interaction with BMP2 and NF-κB pathway can trigger vascular calcification [15]. It was indicated that BMP2 concentration is elevated during atherosclerosis and BMP2 can directly increase the osteogenic differentiation by activating Smad1/5/9, which are signal transducers that contribute to the overexpression of Msx2 [16,54–57]. Msx2 plays a role in upregulation of Wnt3a and Wnt5a in the arterial endothelium, which can result in increased influx of calcium in the cells [57,58]. BMP2-Msx2-Wnt pathway stimulate the overproduction of OPN, either by inducing NF-κB pathway or by directly activating Notch1. This leads to the osteogenic overexpression and the trans differentiation of VSMC into osteoblast-like cell, ultimately leading to CAC occurrence [15,59,60].

There are several strengths of our study. We estimated the pooled odds ratio based on different subgroups, including Lp(a) cut-off, study design, gender, and race to provide more comprehensive results for the association of circulating Lp(a) in CAC prevalence.

Furthermore, Lp(a) and CAC values stated in included studies were measured with various methods and instruments. Likewise, Lp(a) and CAC measures with different cut points have been reported. In this meta-analysis, we attempted to pool results from studies using consistent Lp(a) and CAC cut-off points. As a limitation to our study, most of the included studies were cross-sectional and thus causal relationships of Lp(a) and CAC incidence cannot be identified. Moreover, our meta-analysis included the data of four eligible cohort studies having different duration of follow-ups and one of them applied a different method for Lp(a) measurement. The data of our study suggests that lifelong elevated levels of Lp(a) might lead to an increase in CAC progression, ultimately leading to cardiovascular events.

In conclusion, elevated Lp(a) level is an independent marker for identifying CVD asymptomatic individuals who are at risk of CAC incidence. The impact of Lp(a) lowering therapies should be investigated in prospective studies to gain a better understanding of CAC risk assessment in different racial and ethnic subgroups. Moreover, given the crucial role of elevated Lp(a) in relation to CAC, Lp(a) lowering agents could be a novel and promising therapeutic strategy for CVD primary prevention.

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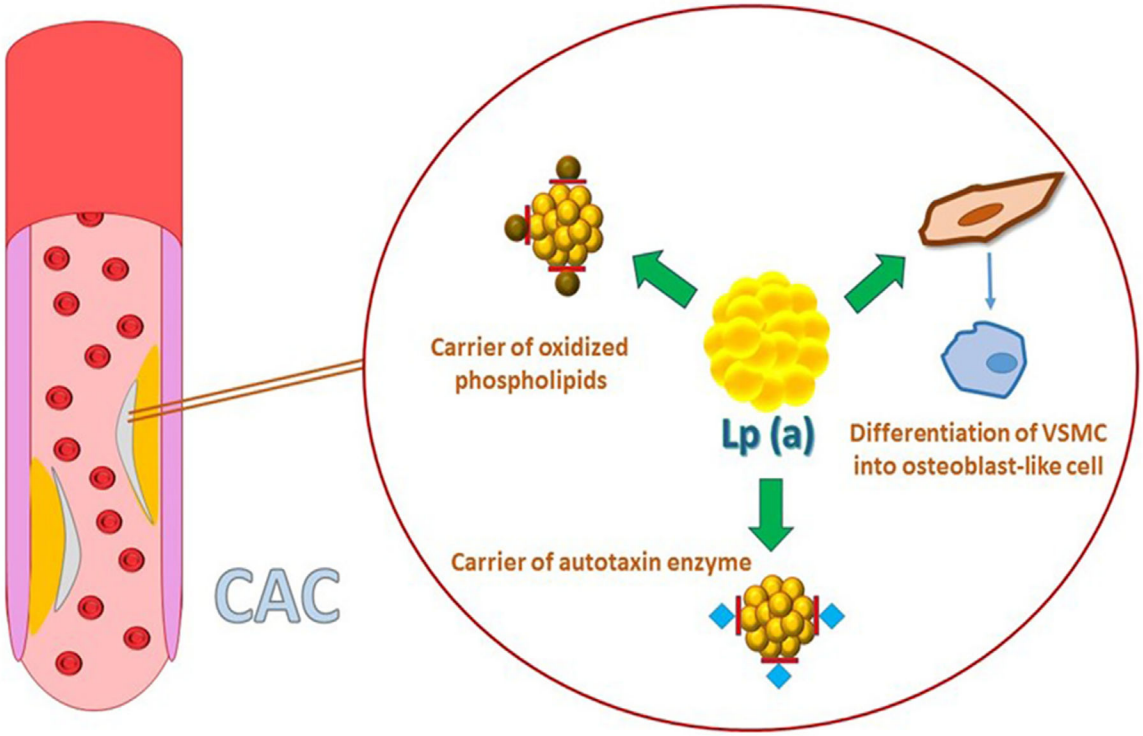

Figure 1.

Lp(a) can play different roles in CAC incidence. (1) Facilitating the osteogenic differentiation in VSMC which can further induce calcium precipitation in the arterial. (2) Be a preferable carrier for oxidized phospholipids that can induce oxidative stress in the endothelium of arterials that activates atherosclerosis process. (3) Activating the inflammatory response, leading to plaque formation in the arterials by inducing autotaxin enzyme.

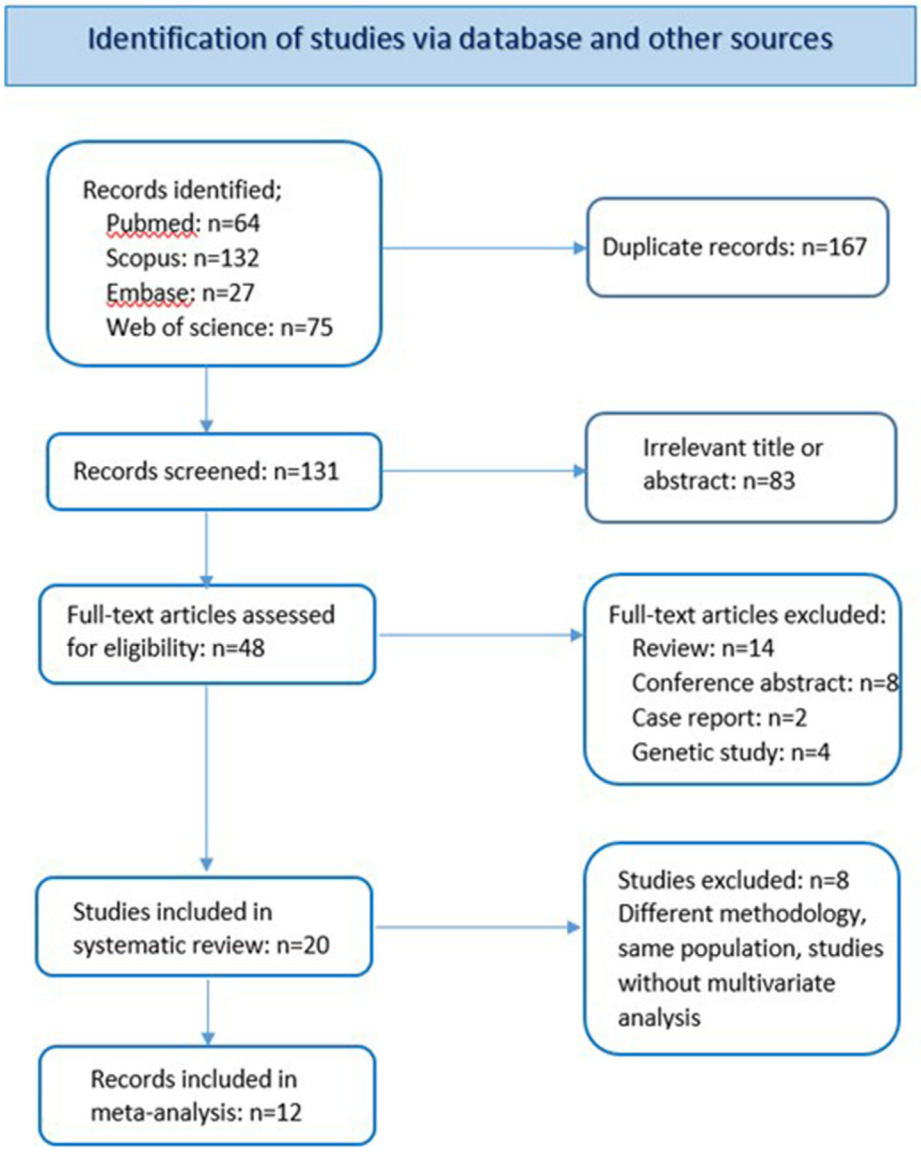

Figure 2.
Study selection flowchart.

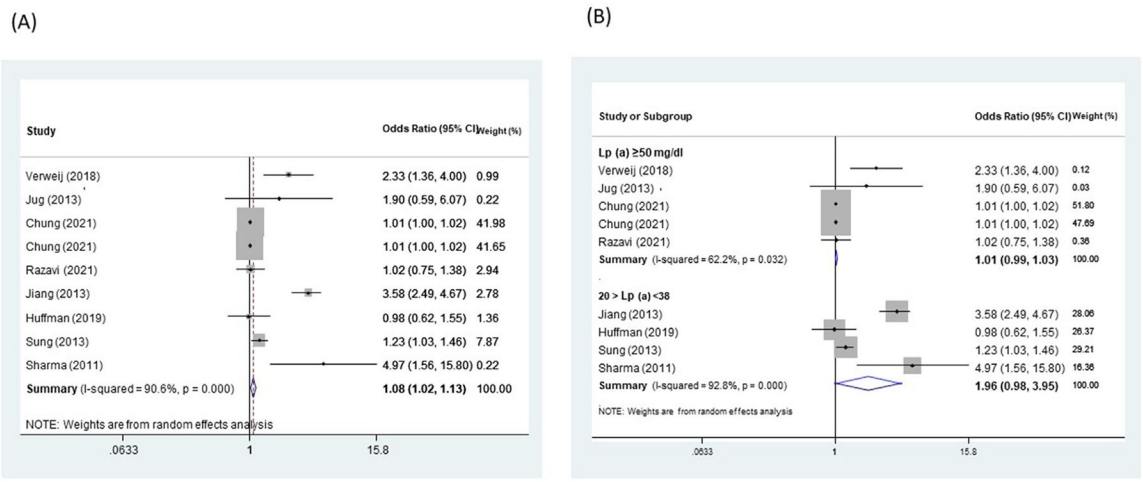

Figure 3.

A) Forest plot of cross-sectional studies investigating the association between Lp(a) and CAC incidence. Diamond represents the summary odds ratio (pooled OR) estimate and its width shows corresponding 95% CI with random effects estimate. B) Subgroup analysis for the association of Lp(a) and CAC based on two different Lp(a) cut-off points (Lp(a) ≥ 50 and 20< Lp(a)> 38) among the cross-sectional studies.

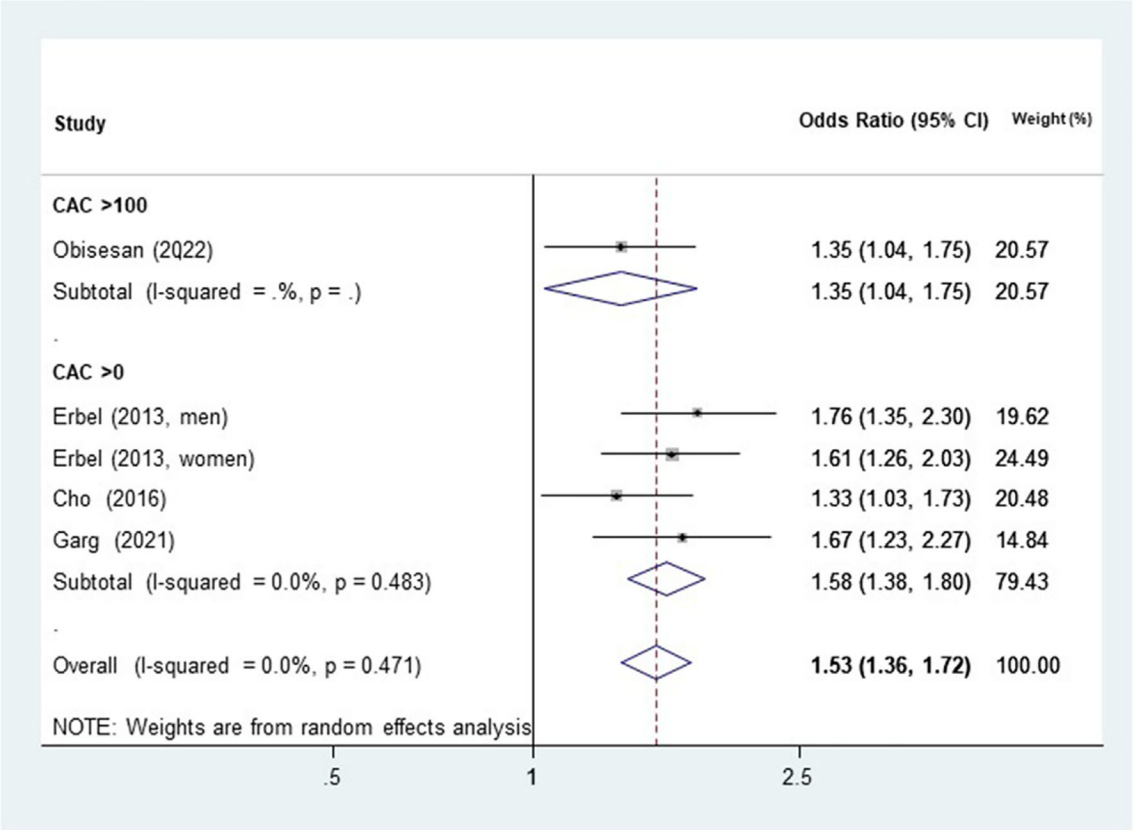

Figure 4.

Forest plot of cohort studies that investigated the association between Lp(a) and CAC using random effects meta-analysis. Diamond represents the summary odds ratio (pooled OR) estimate and its width shows corresponding 95% CI with random effects estimate.

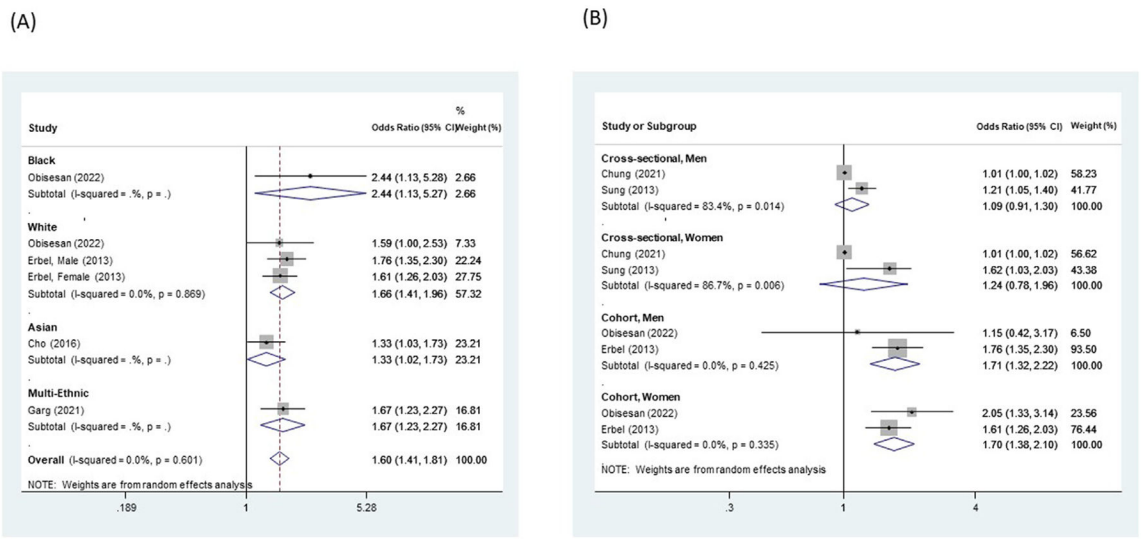

Figure 5.

A) Subgroup analysis for the association of Lp(a) and CAC based on race across the studies. B) Subgroup analysis for the contribution of Lp(a) in CAC incidence based on gender across the cross-sectional and cohort studies.

Table 1

Characteristics of the studies discussing the association between lipoprotein(a) and CAC burden.

Author (year)	Population	Type of study	Country	Age (Mean ± SD)	n	Effect size (OR/β/RR)	Lp(a) assay	Quality
Verweij et al.(2018) [1]	Asymptomatic CVD subjects	Cross-sectional	Netherland	44.85 ± 12.4	937	OR = 2.33[1.36–4]	ELISA	Good
Ong et al.(2021) [2]	Asymptomatic CVD subjects (MESA)	Cohort	USA	61.7 ± 10.1	5975	B = 0.83[−0.51, 2.17], p = 0.23	ITMA	Good
Kutkienė et al. (2019)	Asymptomatic CVD subjects	Cross-sectional	Lithuania	49.15 ± 8.01	213	-	-	Good
Jug et al.(2013) [3]	Asymptomatic CVD subjects	Cross-sectional	USA	50.3 ± 10	410	OR = 1.90[0.59–6.17]	Vertical autoprofile II method	Moderate
Jiang et al.(2013) [5]	Asymptomatic CVD subjects	Cross-sectional	China	35–80 *	302	OR = 3.58[2.497–4.678]	Electro immunodiffusion	Good
Guerra et al.(2005) [6]	Asymptomatic CVD subjects (Dallas Heart Study)	Cross-sectional	USA	52.25 ± 5.75	1288	-	Sandwich ELISA	Good
Erbel et al.(2013) [9]	Asymptomatic CVD subjects	Cross-sectional	Germany	59.45 ± 7.75	3956	Men: OR = 1.76[1.35–2.30], p = 0.0001 Women: OR = 1.61[1.28–2.03], p = 0.001	ITMA	Good
Chironi et al. (2002) [10]	Asymptomatic CVD men	Cohort	France	51.3 ± 7.7	55	-	ITMA	Moderate
Cassidy et al. (2004) [11]	Asymptomatic CVD subjects	Cross-sectional	USA	56.8 ± 9.4	616	-	ITMA	Good
Cho et al. (2016) [12]	Asymptomatic CVD subjects	Cohort	Korea	41 ± 5.7	2611	OR = 1.33[1.027–1.730]	ITMA	Good
Huffman et al. (2019) [13]	Asymptomatic CVD subjects South Asian MASALA cohort)	Cross-sectional	USA	55.4 ± 9.4	886	OR = 0.98[0.62–1.55]	Particle-enhanced immunonephelometry	Good
Sharma et al. (2011) [14]	Asymptomatic CVD subjects	Cross-sectional	USA. Indonesia	56 ± 10.3	104	OR = 4.97[1.56–15.88]	Kits by Daiichi Sankyo (Tokyo, Japan)	Moderate
Sung et al. (2013) [15]	Asymptomatic CVD subjects occupational cohort)	Cross-sectional	South Korea	42.12 ± 7	14,583	OR = 1.23[1.03–1.46], p = 0.02	ITMA	Good
Garg et al. (2021) [16]	Asymptomatic CVD subjects	Cohort	USA	62 ± 10.3	6705	RR = 1.67[1.23–2.27]	ITMA	Good
Chung et al. (2021) [17]	Asymptomatic CVD subjects	Cross-sectional	Korea	57.05 ± 8.99	1313	Men: OR = 1.010 [1.004–1.016], p = 0.001 Women:	Commercial kit (Lip(a) Daiichi Pure)	Good

Author (year)	Population	Type of study	Country	Age (Mean ± SD)	n	Effect size (OR/β/RR)	Lp(a) assay	Quality
						OR = 1.007[0.996–1.018], p = 0.23		
Obisesan et al.(2022) [18]	Asymptomatic CVD subjects	Cohort	USA	59.2 ± 4.3	2083	Lp(a) > 50 OR = 1.35[1.04–1.75]	Automated assay by Denka Seiken Co (Tokyo, Japan)	Good
Pechlivanis et al. (2020) [19]	Asymptomatic CVD subjects	Cross-sectional	Germany	59 ± 7.7	3639	Log transformed Lp(a) levels: B = 0.11[0.04–0.18], 0.002 Lp(a) > 54.3 vs Lp(a) < 54.3: B = 0.23[0.005–0.45], 0.05	Particle-enhanced immunonephelometry	Good
Razavi et al. (2021) [21]	Without clinical ASCVD(MESA)	Cross-sectional	-	72.1 ± 7.6	325	Lp(a) < 50 PR = 1.02 [0.75–1.38]	ITMA	Good
Bhatia et al. (2022) [22]	Asymptomatic CVD subjects MASALA)	cohort	USA	58.5 ± 9	387	Lp(a) and baseline CAC volume: B = 0.36[−1.10 – 1.83] n = 285 Lp(a) and CAC incidence: B = −0.87[−2.18 −0.45] n = 102	Particle-enhanced immunonephelometry	Good

Abbreviations: T2DM, type 2 diabetes; CVD, cardiovascular disease; CAC, coronary artery calcification; ITMA, immunoturbidimetric assay; MESA, multi-ethnic study of atherosclerosis; MASALA, mediators of atherosclerosis in south Asians living in America; RCT, randomized clinical trial; GENOVA, genomic medicine at VA study; OR, odds ratio; RR, relative risk; PR, prevalence ratio.

*Participants aged 35–80 years. Mean ± SD was not stated

Table 2

Data of covariates adjustment in the included studies for the meta-analysis.

Author (year)	Risk ratio (95% CI)	Adjustment
Verweij et al. (2018)	OR = 2.33 (1.36–4)	Age, sex, BMI, systolic blood pressure, DM, and LDL levels.
Jug et al. (2013)	OR = 1.90 (0.59–6.17)	Age, sex, ethnicity/race, arterial hypertension, DM, BMI, and smoking.
Jiang et al. (2013)	OR = 3.588 (2.497–4.678)	Systolic blood pressure, and total cholesterol.
Erbel et al. (2013)	Men: OR = 1.76 (1.35–2.30) Women: OR = 1.61 (1.28–2.03)	Age, hypertension, obesity, diabetes, ever smoking.
Cho et al. (2016)	OR = 1.333 (1.027–1.730)	Age, sex, BMI, fasting blood glucose, ALT, LDL levels, triglyceride and systolic blood pressure, current smoking, alcohol drinking history and moderate exercise.
Huffman et al. (2019)	OR = 0.98 (0.62–1.55)	Age, sex, smoking, systolic and diastolic blood pressure, hypertension medication, total cholesterol, HDL levels and diabetes status.
Sharma et al. (2011)	OR = 4.97 (1.56–15.88)	Age, sex, diabetes,hypertension, dyslipidemia, smoking, family history of CAD, total cholesterol, HDL levels, LDL levels, triglycerides.
Sung et al. (2013)	OR = 1.23 (1.03–1.46)	Age, sex, alcohol, smoking status, exercise, prior CVA, prior CHD, prior diabetes, prior hypertension, systolic blood pressure, waist circumference, glucose, triglyceride, HDL levels, LDL levels, insulin, ferritin and history of treatment with lipid lowering agent.
Garg et al. (2021)	RR = 1.67 (1.23–2.27)	Age, sex, race, education, and clinic site, cigarette smoking, BMI, diabetes, hypertension, family history of CHD, total cholesterol, HDL levels, eGFR, hs-CRP, statin use, and aspirin use.
Chung et al. (2021)	Men: OR = 1.010 (1.004–1.016) Women: OR = 1.007 (0.996–1.018)	Smoking, hypertension, DM, LDL levels, and BMI (sex and age specific analysis).
Obisesan et al. (2022)	OR = 1.35 (1.04–1.75)	Age, race, sex, education level, smoking status, alcohol drinking status, BMI, systolic blood pressure, diabetes, antihypertensive medication use, HDL, triglycerides, and lipid powering therapy
Razavi et al. (2021)	IRR = 1.02 (0.75–1.38)	Age, sex, race, total cholesterol/HDL cholesterol ratio, fasting blood glucose, serum triglycerides, blood pressure, smoking status, lipid-lowering, glucose-lowering, and blood-pressure lowering medication.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; LDL, low-density lipoprotein; ALT, Alanine transaminase; HDL, high-density lipoprotein; CAD, coronary artery disease; CVA, cerebrovascular accident; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein.