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Association of aortic dissection and lipoprotein (a): a meta-analysis

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Background and Aim: Some studies reported a positive relation between aortic dissection (AD) and increased lipoprotein (a) (LP (a)), while other studies reported no association, so the authors aimed to do a meta-analysis to establish the relation between AD and high levels of LP(a).

Methods: PubMed, Scopus, Web of Science, SAGE, EMBASE, Science Direct, and Cochrane Library were searched. The inclusion criteria were any randomized control trials or observational studies that measured the levels of LP(a) in AD patients and healthy controls. The authors excluded case reports, case series, noncontrolled studies, reviews, editorials, and animal studies.

Results: After a search of the literature, four studies were included in the meta-analysis with 678 patients included in the analysis. The pooled analysis showed a statistically significant association between the AD group and increased levels of LP(a), decreased levels of TG, low-density lipoprotein cholesterol, and TC compared with the control group (MD = 11.71, 95% CI = 4.11–19.32, *P*-value = 0.003), (MD = −0,32, 95% CI = −0.48 to −0.16, *P*-value < 0.0001), (MD = −0,21, 95% CI = −0.42 to −0.1, *P*-value = 0.04), (MD = −0,58, 95% CI = −0.62 to −0.54, *P*-value < 0.00001), respectively.

Conclusion: Our study showed that AD is significantly associated with increased levels of LP(a). The significant increase in LP(a) in AD was associated with decreased levels of TG, low-density lipoprotein cholesterol, and TC. Future clinical trials testing Lp (a) targeting medications could be useful in the primary, or secondary prevention of AD in high risk patients.

Keywords: aortic dissection, lipoprotein (a), lipids, meta-analysis

Introduction

Aortic dissection (AD) remains a disease of rapid onset and high mortality, it occurs when the layers of the aortic wall separates, specifically, when the intima is disrupted exposing the middle layer to the blood flow[1–3]. The prevalence of AD varies from 3 to 4 per 100 000 people each year. A number of known risk factors for AD include ageing, aneurysms, hypertension, inflammatory disorders, and smoking. In order to avoid the onset of AD and lower the risk of it, it is crucial to further investigate potential risk factors for the illness[4]. Despite significant advancements in AD diagnosis and care, the disease still has a high death rate.

HIGHLIGHTS

- Some studies reported a positive relation between aortic dissection (AD) and increased lipoprotein (a) (LP(a)), other studies reported no association, so we aimed to do a meta-analysis to establish the relation between AD and high levels of LP(a).
- The pooled analysis showed a statistically significant association between the AD group and increased levels of LP(a), decreased levels of TG, low-density lipoprotein cholesterol, and TC compared with the control group.
- Our study showed that AD is significantly associated with increased levels of LP(a). The significant increase in LP(a) in AD was associated with decreased levels of TG, low-density lipoprotein cholesterol, and TC. Future clinical trials testing Lp (a) targeting medications could be useful in the primary, or secondary prevention of AD in high risk patients.

Sadly, a considerable fraction of aortic-related deaths are caused by AD[5]. This brings up the fact that a large proportion of AD cases are overlooked in the emergency room due to their vague and deceptive presentation. A patient with AD might, for instance, appear with a rapid onset of intense, 'tearing', chest discomfort. As a result, the high early mortality rates and difficult diagnosis of AD make it difficult to determine the precise occurrence of the condition. The reported mortality rate outside of hospitals ranges from 21 to 49%, but when the diagnosis is either

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missed or delayed, the early (within 24 h) fatality rate can increase to 50%[6,7].

Lipoprotein (a) [Lp(a)] is connected to low-density lipoprotein (LDL) not only by its lipid concentration but also by the presence of the protein apoB-100. Each Lp(a) particle also contains an additional glycoprotein called apo(a), which is joined to apoB-100 by a single disulfide link[8–10]. Diet and environment are thought to have less of an impact on plasma Lp(a) levels[11]. However, the LPA gene's polymorphisms, which encode for apo (a), are primarily in charge of controlling the plasma levels of Lp(a)[12]. In patients with early atherosclerotic cardiovascular disease, including coronary artery disease (CAD), and ischemic stroke, increased Lp(a) is now regarded as one of the principal hereditary dyslipidemias. Compared to LDL particles, it also has the potential to sequester into the artery walls[13,14]. Additionally, when examining the cellular and molecular level in more detail, Lp(a) plays a crucial role in stimulating the inflammatory response of the arterial wall, hence raising the risk of vascular injury[15]. This could consequently increase the vessel's susceptibility to aneurysm and dissection growth.

Some studies[16–18] have reported a possible association between AD and elevated levels of Lp(a). On the other hand, two studies[19,20] have contradictorily reported no significant association between AD and elevated levels of Lp(a). Thus, we conducted this meta-analysis to resolve this controversy and evaluate whether AD is related to elevated levels of Lp(a) or not.

Methods

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Supplemental Digital Content 1, http://links.lww.com/MS9/A89 and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines[21], Supplemental Digital Content 2, http://links.lww.com/MS9/A90.

Study design

A meta-analysis was done aiming to evaluate the possible association between AD and high levels of lipoprotein A.

Search strategy

We located suitable observational studies or randomized control trials using the search keywords ((‘Lipoprotein (a)’ OR ‘lipoprotein A’ OR ‘LPA’) AND (‘aortic dissection’ OR ‘aortic dissecting’ OR ‘dissecting’)) in PubMed, Scopus, Web of Science, SAGE, EMBASE , Science Direct, and the Cochrane Library from inception to 14 September 2022.

Eligibility criteria

We included randomized control trials and observational studies (Cross sectional, Prospective or Retrospective cohorts and Case—control studies) that measured the levels of lipoprotein A in AD patients and healthy controls.

Exclusion criteria

We excluded animal studies, case reports, case series, non-controlled studies, reviews, and editorials.

Study selection process

Two independent authors revised the titles and/or abstracts of the searched papers to determine suitable studies. Then, the two authors revised the full texts of the retrieved reports independently. Any conflicts between authors were solved by the first author.

Data extraction

Two independent authors used an Excel sheet to extract the following data: the first author's name, year of publication, study design, country of the study, results, conclusion, number of patients in each group, age, sex, smoking, kidney functions, comorbidities, and outcomes. Additionally, data was retrieved to assess the quality. Two authors performed data extraction and any conflicts were solved by the first author.

Quality assessment

Newcastle–Ottawa scale tool was used to perform the quality assessment because all the included publications were observational studies. Each study was given a score and ranked as good, fair, or poor quality.

Data analysis

The data were analyzed using RevMan software, version 5.4. Sensitivity analysis (leave-one-out test and subgroup analysis) was used. If no heterogeneity was observed, results were presented in a fixed effect model and a random effect model if significant heterogeneity was observed. Results were considered significant if the *P*-value was less than 0.05.

Results

Summary of studies

After a search of the literature, 1361 studies resulted and then became 481 eligible for title and abstract screening after duplicates were removed. Of the 481, 453 were irrelevant and 28 studies were eligible for full-text screening. Finally, four studies[16–18,20] were included in the meta-analysis after full-text screening, as shown in the PRISMA in (Fig. 1), summary of the included studies are shown in Table 1.

Level of LP(a), level of TG, level of low-density lipoprotein cholesterol (LDL-C), HDL-C, and level of TC were compared between the AD group and the control group in 4, 2, 2, 2, and 2 studies, respectively. Subgroup analysis on the level of LP(a) was done according to age. The age subgroup was divided into two subgroups; (more than 60 years) or (less than 60 years).

The overall quality was high in the four included studies, details of the quality assessment for each study are shown in supplementary material, Supplemental Digital Content 3, http://links.lww.com/MS9/A91.

A total number of 678 patients were included in the study, 311 patients in the AD group, and 367 patients in the control group. Other baseline data are shown in Table 2.

Outcomes

Level of lipoprotein (a)

A statistically significant association was observed between the AD group and increased levels of LP(a) (MD = 11.71, 95%

CI = 4.11–19.32, *P*-value = 0.003). We observed a significant heterogeneity among studies ($P < 0.00001$, $I^2 = 99\%$) that was not solved by the leave-one-out test, Fig. 2.

Age subgroup analysis

A statistically significant association was observed between the AD group and increased levels of LP(a) in the subgroup of less than 60 years (MD = 15.87, 95% CI = 1.04–30.69, *P*-value = 0.04). We observed a significant heterogeneity among studies ($P < 0.00001$, $I^2 = 99\%$) that was not solved by leave-one-out test, Fig. 3.

The pooled analysis showed no significant difference between the AD group and the control group in the subgroup of more than 60 years (MD = 0.00, 95% CI = – 0.76–0.76, *P*-value = 1.00), Fig. 3.

Level of TG

A statistically significant association was observed between the AD group and decreased levels of TG (MD = – 0,32, 95% CI = – 0.48 to –0.16, *P*-value < 0.0001).We observed a moderate heterogeneity between the two studies ($P = 0.08$, $I^2 = 68\%$), Fig. 4.

Level of LDL-C

A statistically significant association was observed between the AD group and decreased levels of LDL-C (MD = – 0,21, 95% CI = – 0.42 to –0.1, *P*-value = 0.04). We observed a moderate heterogeneity between the two studies ($P = 0.07$, $I^2 = 70\%$), Fig. 5.

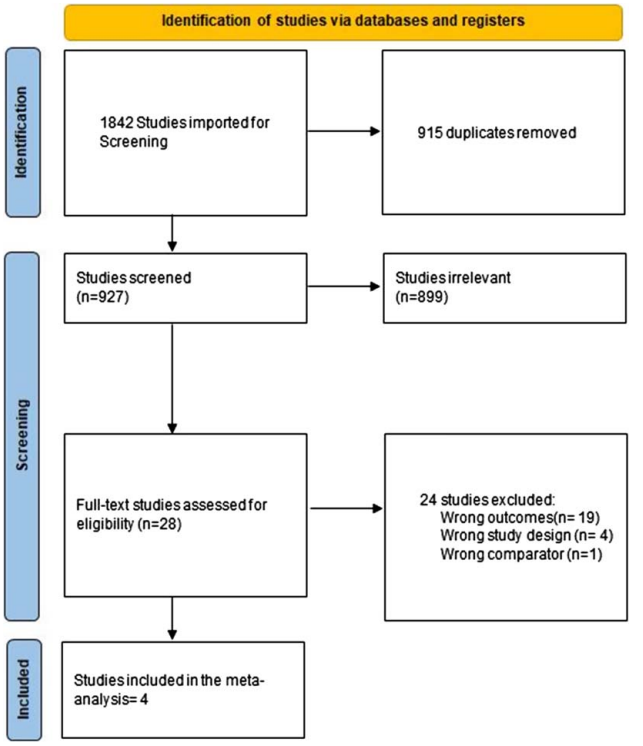

Figure 1. PRISMA flow diagram.

Level of HDL-C

The pooled analysis showed no significant difference between the AD group and control (MD = 0.04, 95% CI = – 0.12–0.19, *P*-value = 0.65), we observed a significant heterogeneity between the 2 studies ($P = 0.02$, $I^2 = 82\%$), Fig. 6.

Level of TC

A statistically significant association was observed between AD group and decreased levels of TC (MD = – 0,58, 95% CI = – 0.62 to –0.54, *P*-value < 0.00001). We observed no heterogeneity between the two studies ($P = 0.45$, $I^2 = 0\%$), Fig. 7.

Discussion

A statistically significant association was revealed by our analysis between the AD group and increased levels of LP(a) when compared with the control group. In a similar manner, subgroup analysis for age revealed a statistically significant correlation between higher levels of LP(a) in the AD group in comparison to the control group, especially in patients younger than 60 years of age, but not older than 60 years. On the other hand, the analysis revealed a statistically significant correlation between the AD group and decreased levels of TG, LDL-C, and TC when compared with the control group.

Therefore, as compared to the control group, our study found that the significantly lower levels of TG, LDL-C, and TC in AD patients are associated with the significantly increased Lp(a). This conclusion was entirely based on the results of two studies, Chen *et al.* and Yang *et al.*[16,18].

Yang *et al.*[18], supposed that AD patients exhibited decreased median values of TG, TC, HDL, and LDL cholesterol when compared to the control group. Additionally, Chen *et al.*[16] reported that when TG levels were examined, it was found that AD patients had lower TG levels than healthy controls.

Our results are consistent with Yang *et al.*[18], which evaluated that high levels of Lp(a) are substantially linked to AD independent of other cardiovascular risk factors. Similarly, after adjustment was done, age, sex, CAD, dyslipidemia, or diabetes mellitus were not significantly different between the two groups. As proposed by Genest Jr *et al.*[14] , the unique assembly of Lp(a) permits it to stimulate atherosclerosis, which can precipitate cardiovascular events[22]. According to this study's findings and the role of Lp(a), a number of medications, including PCSK9 inhibitors[23], have been shown to lower Lp(a) levels, which lowers the risk of cardiovascular events linked to Lp(a). In consequence of the complex association between renal disease, Lp(a), and cardiovascular risk and also the ability of the renal function to influence Lp(a) plasma levels[16], this study excluded folks with a medical history of kidney-related diseases. Moreover, a prospective study has revealed that black people have higher amounts of Lp(a) than white people, suggesting that Lp(a) levels vary by race[24]. As a result, the cardiovascular risk associated with Lp(a) may vary according on race or ethnicity[25–27]. Since that LDL-C is known to have a pro-atherogenic effect, Yang *et al.* verified the relationship between AD and LDL-C. It was hypothesized that the median LDL-C levels in the control group were marginally higher than those in the AD group. But further research is required to prove the association between atherosclerosis and the emergence of AD. Future large cohort studies or Mendelian randomization

Table 1

Summary of the included studies.

References	Study design	Country of the study	Study arms	Results	Conclusion
Yang [18]	case–control study	China	case = patients with AD, control = without AD	Patients with AD had greater median Lp(a) concentrations than non-AD people (152.50 vs. 81.75 mg/l). Lp(a) was associated with AD in a multivariate logistic regression analysis (odds ratio, 8.03; 95% CI, 2.85–22.62), comparing those with Lp(a) quartile 4 with those with Lp(a) quartile 1. Stratified analysis showed that this relationship was observed in both men and women, as well as in older and younger individuals.	High levels of Lp(a) are strongly associated with AD, independent of other cardiovascular risk factors.
Schillinger 2002[20]	case–control study	Austria	case = patients with AA caused by AD, control = without AA	Median Lp(a) levels of patients with AAA and TAA and of control subjects were 18.9 mg/dl (interquartile range [IQR], <9.6–40.5), less than 9.6 mg/dl (IQR, <9.6–16.7), and less than 9.6 mg/dl (IQR, <9.6–16.3), respectively. Lp(a) was positively associated with the extent of atherosclerosis in patients and control subjects ($P < .0001$). Lp(a) levels of patients with AAA were significantly higher compared with patients with TAA ($P < .0001$) and control subjects ($P < .0001$). Multivariate analysis confirmed an independent association between Lp(a) and AAA (P .009). No significant differences of lipoprotein (a) were found between patients with TAA and control subjects (P .3).	The Lp(a) serum level, an indicator of atherosclerosis, is significantly elevated in patients with abdominal aneurysms independently of cardiovascular risk factors and the extent of atherosclerosis. Patients with TAAs caused by dissection have Lp(a) levels comparable with healthy individuals.
Chen 2008 [16]	case–control study	China	case = patients with AD, control = without AD	Patients with aortic dissection had significantly higher Lp(a) serum levels (median, 17.6 mg/dl; range, 6.4–88.7 mg/dl) compared to healthy individuals (median, 12.4 mg/dl; range, 4.9–26.4 mg/dl) ($P = 0.005$). The Lp(a) concentration in nonsmoking patients with aortic dissection (median, 19.1 mg/dl, range, 10.5–88.7 mg/dl) significantly surpassed that of the smoking patients with aortic dissection of comparable age (median, 10.7 mg/dl; range, 6.4–22.1 mg/dl) ($P < 0.0001$). Multivariate analysis confirmed an independent association between Lp(a) and aortic dissection in the nonsmoking population ($P = 0.001$).	Serum Lp(a) level is significantly elevated in nonsmoking patients with aortic dissection independently of other cardiovascular risk factors. Therefore, determination of Lp(a) levels may be important in identifying subjects at risk of aortic dissection among nonsmokers.
Wen 2009 [17]	case–control study	China	case = patients with AD, control = without AD	Serum MMP-9, LP(a) and hsCRP levels were significantly higher in the three groups of patients than in the healthy controls, with no significant fluctuation within 24 h of admission in any group. Mean serum MMP-9 levels in patients with acute pancreatitis (768 (95% CI: 651–885) ng/ml within 1 h; 708 (95% CI: 677–740) ng/ml at 24 h) were significantly higher than in patients with other acute abdomen (244 (95% CI: 182–266) ng/ml within 1 h; 259 (95% CI: 219–299) ng/ml at 24 h) and lower than in patients with AAD (1052 (95% CI: 921 1183) ng/ml at 1 h; 1107 (95% CI: 973–1241) ng/ml at 24 h) (all P,0.05). No significant difference was detected in serum LP(a) and hsCRP levels among the three groups of patients.	Patients with AAD who have abdominal pain have significantly higher serum MMP-9 levels than patients with surgical acute abdomen.

Table 2

Baseline characteristics.

	Number of patients in each group		Age (M) ± SD		Sex (*n*)				Smoking		Kidney function		Comorbidities	
					Intervention		Control							
References	Intervention	Control	Intervention	Control	female	male	female	Male	Intervention	Control	Intervention	Control	Intervention	Control
Yang[18]	200	200	53.83 ± 12.10	52.74 ± 11.71	24%	76%	24%	76%	32.50%	5%	NA	NA	Hypertension(%) = 77.50 , Dyslipidemia(%) = 53.50 ,CAD (%) = 2 ,CVD(%) = 5 ,DM(%) = 4	Hypertension (%) = 77.50 , Dyslipidemia (%) = 53.50 ,CAD (%) = 2 ,CVD(%) = 5 , DM(%) = 4
Schillinger[20]	AAA = 75 , TAA = 39	43	(AAA) = 72 ± 9 (TAA) = 64.67 ± 13.3	68.3 ±567	(AAA) = 39%, (TAA) = 75%	(AAA) = 61%, (TAA) = 25%	70%	30%	(AAA) = 33% , (TAA) = 11%	0	NA	NA	(AAA):Arterial hypertension = 42%,Hyperlipidemia = 50%, Cerebrovascular disease = 57%,CAD = 39%,PAD = 39%,Diabetes mellitus = 15%(TAA):Arterial hypertension = 29%,Hyperlipidemia = 6%, Cerebrovascular disease = 12%,CAD = 8%,PAD = 5%,Diabetes mellitus = 1%	Arterial hypertension = 0,Hyperlipidemia = 0, Cerebrovascular disease = 0,CAD = 0,PAD = 0, Diabetes mellitus = 0
Chen[16]	52	104	59 ± 11	60 ± 9	12	40	24	80	23 (44%)	32 (31%)	Uric acid (μmol/l) 321 ± 110 , Creatinine (μmol/l) 140 ± 86	Uric acid (μmol/l) = 309 ± 92 , Creatinine (μmol/l) = 88 ± 11	History of hypertension = 22 (42%) , Hyperlipidaemia = 9 (17%),CAD = 2 (4%),CVD = 2 (4%),COPD = 3 (6%), DM = 5 (10%)	History of hypertension = 14 (14%)) , Hyperlipidaemia = 21 (20%),CAD = 0), CVD = 0),COPD = 0, DM = 9 (9%)
Wen[17]	20	20	50 (4)	48 (9)	3	17	4	16	16	4	Cr (mmol/l) = 87 (25)	Cr (mmol/l) = 104 (30)	Cases of hypertension (n) = 15	Cases of hypertension (n) = 0

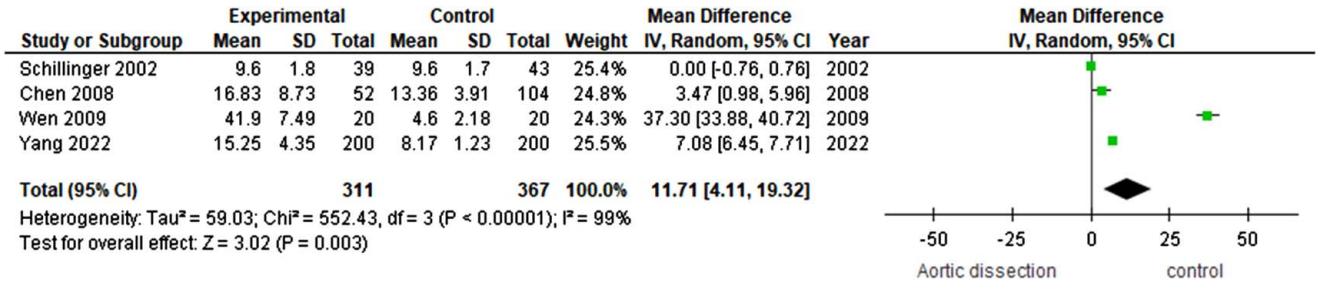

Figure 2. Forest plot of level of lipoprotein (a) outcome.

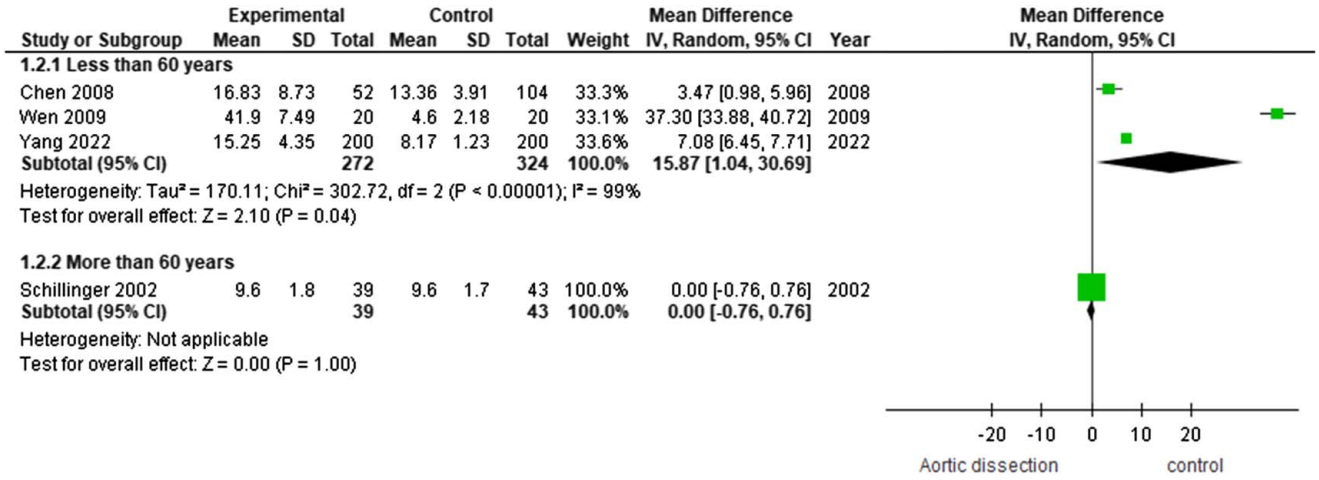

Figure 3. Forest plot of level of lipoprotein (a) age subgroup.

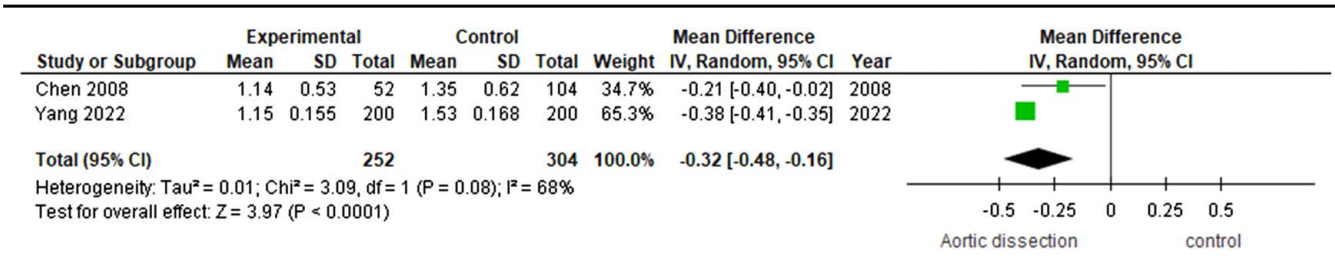

Figure 4. Forest plot of level of TG outcome.

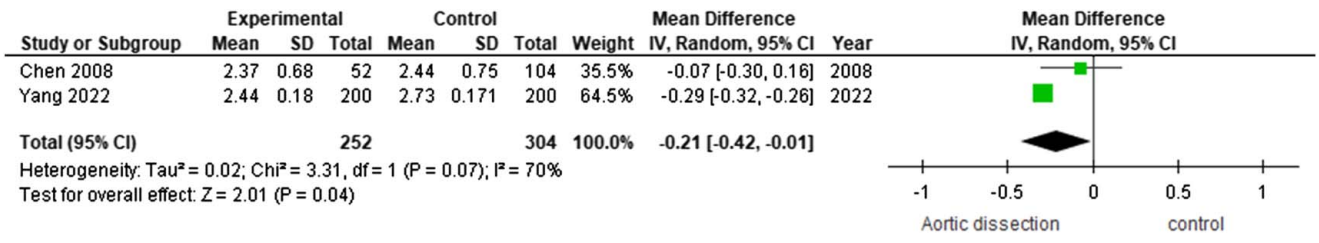

Figure 5. Forest plot of level of LDL-C outcome.

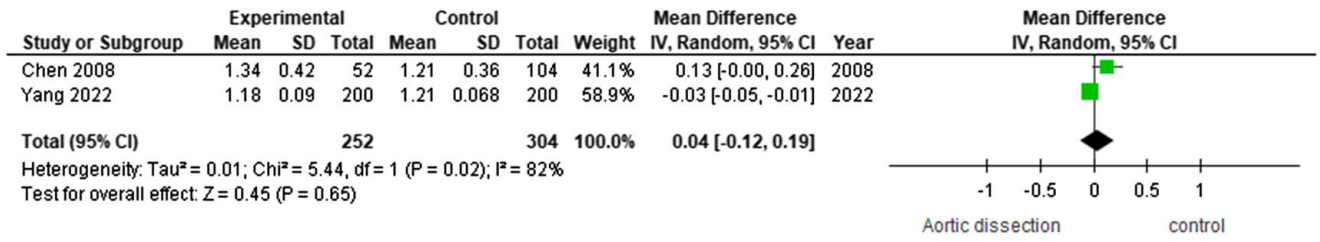

Figure 6. Forest plot of level of HDL-C outcome.

studies are required because this study's primary limitation is the limited evidence it provides. In addition, some variables—like body mass index and homocysteine—were excluded from this study as there was insufficient data for some participants. Studies of Lp(a) and AD among various races are also required since more limitations were found as a result of the influence of race on serum Lp(a) concentrations. Finally, not all AD patients had their Lp(a)concentrations following an overnight fast due to the intricacy of the disease.

Similarly, Wen[17], showed that serum LP(a) levels were greater in patients with acute aortic dissection (AAD) than in control persons. However, because Lp(a) is regarded as a protein during the acute phase response, it is typically raised in a number of disorders such as acute onset surgical trauma, severe infection, and cardiovascular disease (CVD). Nevertheless, the fact that this study was a case–control study presents a significant limitation. As a result, precise sensitivity and specificity estimates cannot be determined. Therefore, more investigation is required to evaluate the diagnostic efficacy of a clinically related cohort of individuals with abdominal pain possibly associated to AAD.

Likewise, Chen *et al.*[16], determined that serum Lp (a) levels were considerably higher in AD patients. Again, there were no obvious differences in Lp(a) levels between patients with and without complications from AD, as well as between those who passed away within three days of presentation and those who survived hospital discharge. Additionally, the study showed that, regardless of other traditional atherosclerotic risk factors, the blood Lp(a) concentration of the nonsmoking AD patients was considerably higher than that of the smoking AD patients and healthy controls. This study was unable to fully explain the mechanism of Lp(a) in AD due to the controversial etiologic significance of atherosclerosis in AD[28], Despite being a risk factor for atherosclerosis, Lp(a) was found to have an independent relationship with AD in the current investigation. Smoking was also linked to greater levels of very-low- and LDL (VLDL + LDL), cholesterol, and lower levels of HDL-C, which was another intriguing finding[29]. Such unfavorable lipoprotein modifications can partially explain smokers' higher likelihood of developing CVD. In contrast, Chen *et al.* found that nonsmoking AD patients had much higher Lp(a) concentrations than smoking AD patients. Additionally, similar results have been documented for pregnant women who smoke and do not smoke[30]. But further research is still needed to determine the underlying cause of the elevated Lp(a) in nonsmoking AD patients. Additionally, the study reported that the levels of TG were lower in patients with AD than in healthy controls.

Chen *et al.*, revealed certain limitations, primarily the very small patient population, which may have an impact on the outcomes. The study also examined biomarkers in distinct patient populations. Therefore, it is impossible to conclusively determine a causal link between Lp(a) and AD using these records. Last but not least, longitudinal studies with a sizable population free of AD are required to ascertain whether a high Lp(a) is a predictor of the onset of AD. Since AD has a high mortality rate and some patients may need significant surgery, the natural course of Lp(a) in AD would be of considerable interest but is challenging to measure due to the results of Lp(a) measurements.

Contradictory to our results, Schillinger *et al.*[20], showed no apparent differences in serum levels of LP(a) between the AD group and the control group.

Additionally, the study observed no significant changes in the levels of the LP(a) serum between individuals with abdominal aortic aneurysms (AAA) dissection and those without it, as well as between those who had dissection of the ascending and descending thoracic aorta. However, regardless of atherosclerotic risk factors and the degree of atherosclerosis, patients with AAA had significantly higher serum LP(a) levels, whereas patients with thoracic aortic disease had levels that were equal to those of healthy people. No significant age or gender gaps between these groups of paired samples were found after adjusting the groups.

The study discovered that serum levels of LP(a), which are involved in both tissue synthesis and tissue repair, were substantially correlated with atherosclerosis in both patients and control people. It was therefore hypothesized to play a role in the

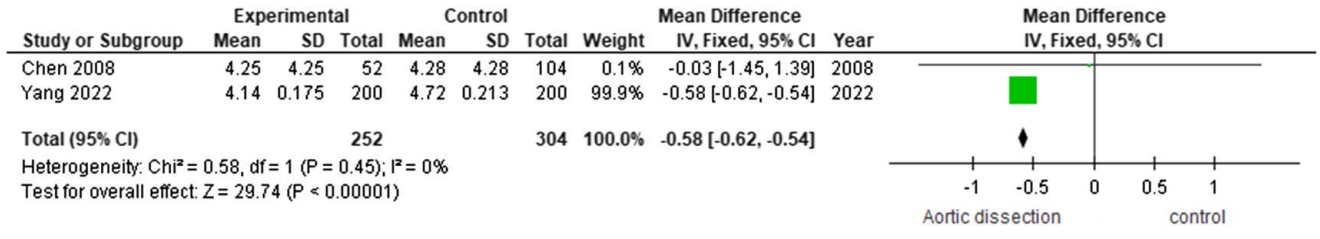

Figure 7. Forest plot of level of TC outcome.

development of thrombi and reinforcement of the aortic wall in patients with aortic aneurysms[31], which may account for its elevation, particularly in patients with abdominal aneurysms where mural thrombus formation is frequently seen. However, patients with intracranial aneurysms without clinically significant atheromatous disease also had elevated lipoprotein(a) levels[32,33]. As a result, the physiologic function of LP(a) is still not entirely known.

The results also revealed that LP(a) is not connected to the growth of TAAs brought on by dissection. AD in these patients is brought on by mechanisms other than atherosclerosis and aberrant lipoproteins, which then causes aneurysmal dilation. However, there were no variations in LP(a) levels between individuals with and without dissecting membranes in those with abdominal aneurysms. Furthermore, rather than being the trigger for the beginning of aortic dilation, dissection of the abdominal aorta may develop as a side effect of the aneurysmal process. The kidney is one of the primary sites of Lp(a) catabolism, which was also underlined in this investigation. Fragments of LP(a) were found in the urine, according to Schillinger *et al.* Because of this, any decline in kidney function enables these fragments to accumulate in the plasma, which will cause its plasma levels to rise and produce misleading implications and outcomes[34,35].

We also discovered that the case–control study design has some limitations, most notably that the data cannot establish a causal link between LP(a) and AAA. In order to determine whether increased LP(a) is predictive concerning the development of AAA, this topic must be investigated in longitudinal studies with several individuals who do not yet develop AAA.

Correspondingly, Sbarouni *et al.*[19], examined serum Lp(a) levels in patients with AAD, chronic aneurysms, and controls and found no significant differences. Potential interactions with other risk factors known to exist, such as diabetes, hypercholesterolemia, or the presence of other illnesses that also affect Lp(a). Additionally, it showed that patients with AAA had greater levels of Lp(a) than did controls, and there is evidence that Lp(a) is elevated in nonsmokers with AD[16,20,36,37]. However, there was no evident change in serum levels of Lp(a) when the study adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, and cigarette smoking. Although the actual pathogenic function of Lp(a) has not yet been determined, its proteolytic and inflammatory characteristics have been identified as contributing to the rupture of the aortic wall.

Further confirming the possible role of Lp(a) as a risk factor for vascular disease is also the lack of sensitivity to environmental influences[38].

Future implications

Regular follow-up and Lp(a) plasma level monitoring in CVD patients must be done. Recent developments in clinical and genetic studies have demonstrated the primary role of Lp(a) in the pathogenesis of CVD. Furthermore, despite good LDL-C management, several mendelian randomization studies have shown that Lp(a) concentrations are responsible for a variety of CVDs, including CAD, calcified aortic valve disease, stroke, and heart failure. Since apolipoprotein (apo) B100 is covalently bonded to apoA in Lp(a). Therefore, it possesses both apoB (derived from LDL) and apoA atherothrombotic characteristics (thromboinflammatory aspects). Additionally, we acknowledge that traditional pharmacological treatments like statins, niacin, and cholesteryl ester transfer protein have not been able to significantly lower Lp(a) levels; however, new therapeutic approaches, like proprotein convertase subtilisin-kexin type 9 inhibitors or antisesnse oligonucleotide technology, are currently being developed and have recently demonstrated encouraging results in effectively lowering Lp(a) levels[39].

In addition to the importance of Lp(a) as a biomarker for various CVDs, we should also pay attention to the dangerous complications of AD. Chen *et al.*, showed that many cases of acute AD die in the hospital due to complications like pulmonary embolism, (contained) rupture, heart failure, and also renal dysfunction. Future clinical trials testing Lp(a) targeting medications could be beneficial in the primary or secondary prevention of AD in patients at high risk.

Strengths and limitations

The general quality was good in all the studies included in our analysis. Our study included a good sample size, as 678 patients were included in our analysis. Some studies[16,18–20] used a multivariate analysis to account for confounding factors. For instance, adjusting for the conventional cardiovascular risk variables of age, sex, blood pressure, the existence of hypertension, diabetes mellitus, smoking, and serum lipids (TC, TG, LDL-C, and HDL-C). Detecting a significant heterogeneity in most of the outcomes is one of the primary limitations of our analysis, which neither the leave-one-out test nor the subgroup analysis were able to resolve.

Moreover, all the studies were observational, not randomized clinical trials. Thus, to more thoroughly assess the connection between Lp(a) and AD development, prospective multicenter studies with bigger sample sizes and longer follow-up durations are required.

Conclusion

A statistically significant association was revealed by our analysis between the AD group and increased levels of lipoprotein(a) when compared to the control group, especially in individuals under 60, but not in those who are beyond 60 years old. Contrarily, a statistically significant association between the AD group and decreased levels of TG, LDL-C, and TC was shown on comparison with the control group. Thus, our study paves the way for the evolution of further medications for AD. Thus, future clinical trials testing Lp(a) targeting medications could be beneficial in the primary or secondary prevention of AD in patients at high risk.

Also, more randomized multicenter studies are warranted to support our findings concerning the role of Lp(a) in the pathogenesis for AD.

Ethics approval and consent to participate

Not applicable as it is meta-analysis study.

Consent for publication

Not applicable as it is meta-analysis study.

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None.

Authors contribution

K.R.M.: supervision, analysis, and writing; R.H.E.: writing; S.R.: screening, data extraction, and quality assessment; N.T.: screening and data extraction; S.R. and P.C.: writing; M.M.: screening and writing; J.S.: screening and reviewing the final draft.

Conflicts of interests disclosure

None.

Research registration unique identifying number (UIN)

1. Name of the registry: We did not register the protocol for this systematic review.
2. Unique Identifying number or registration ID: Not applicable.
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Availability of data and material

Data and material are available within the manuscript.

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