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Differential associations of lipoprotein(a) level with cerebral large artery and small vessel diseases

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ABSTRACT

Background and purpose Cerebral large artery and small vessel diseases are related to different pathogenetic mechanisms and have different risk factor profile. Lipoprotein(a) (Lp(a)) was shown to promote atherosclerosis but data was limited on its association with cerebral small vessel diseases (cSVD). The objective of this study was to assess the associations of Lp(a) level with the two types of cerebrovascular diseases.

Methods Community-dwelling subjects aged 50–75 years from the baseline survey of The PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events study were included. Lp(a) concentrations was measured and categorised into three groups according to the tertiles. Eligible participants were scanned by a 3.0T MRI scanner and assessed for intracranial atherosclerosis and cSVD burden based on four imaging markers.

Results This study included 3059 subjects. The average age of the participants was 61.2±6.7 years, and 53.5% (1636) were female. Compared with the first tertile, subjects with the second and third tertiles of Lp(a) concentrations were associated with an increased odds of presence of intracranial plaque (18.7% vs 15.4%, adj.OR 1.37, 95% CI 1.08 to 1.75; 18.9% vs 15.4%, adj.OR 1.34, 95% CI 1.05 to 1.72). Similar associations were observed for intracranial atherosclerotic burden. Whereas, subjects with the third tertile of Lp(a) level had a decreased odds of presence of cSVD (25.9% vs 31.7%, adj.OR 0.74, 95% CI 0.60 to 0.92) and lower cSVD burden (adj.cOR 0.76, 95% CI 0.62 to 0.94).

Conclusions In this study, Lp(a) concentrations were positively associated with presence and burden of intracranial atherosclerosis, but was inversely associated with cSVD.

Trial registration number NCT03178448.

INTRODUCTION

Cerebrovascular diseases, including both cerebral large artery and small vessel diseases, were shown to be contribute to impairment of cognition and brain health.[1] Although structurally connected,[2] cerebral large artery and small vessel diseases are related to different pathogenetic mechanisms.[3] Previous studies showed that these two types of cerebrovascular diseases may have different risk factor profile.[4 5]

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Lipoprotein(a) (Lp(a)) may promote atherosclerotic cardiovascular diseases, but the association between Lp(a) and cerebral small vessel diseases is uncertain.

WHAT THIS STUDY ADDS

⇒ We demonstrate that elevated Lp(a) level is positively associated with presence and burden of intracranial atherosclerosis, but is inversely associated with cerebral small vessel diseases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Further investigation may be required for optimal level of Lp(a) in clinical practice and underlying mechanisms of double-sided role of Lp(a) level on cerebral arteries.

Lipoprotein(a) (Lp(a)) contains apolipoprotein B100 and glycoprotein apolipoprotein(a).[6] Lp(a) was shown to be proatherogenic and may promote atherosclerotic cardiovascular diseases.[7–11] Previous studies also have demonstrated that high Lp(a) level was related to carotid atherosclerosis,[12 13] atherothrombotic stroke[14] and ischaemic stroke.[7 8 15 16] In contrast, few study investigated the association of Lp(a) level with cerebral small vessel diseases (cSVD). Some previous small-scale studies found lower Lp(a) level in patients with cSVD but with inconclusive results.[14 17 18] A recent Mendelian randomisation study demonstrated an inverse association of Lp(a) level with small vessel stroke.[19] This indicates that there may be differential relationships of Lp(a) concentrations with cerebral large artery and small vessel diseases. However, the relationships of Lp(a) level with cerebral large artery and small vessel diseases have not been well elucidated.

In this cross-sectional study, we comprehensively investigated the associations of Lp(a) concentrations with cerebral large artery and

small vessel diseases in a community population in south-eastern China.

METHODS
Study design and participants
We derived data from the PRECISE (The PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events) study. The design and baseline data of PRECISE have been previously published.[20] In brief, PRECISE is a community-based cohort study recruited community-dwelling adults aged 50–75 years from 6 villages and 4 communities of Lishui city in southeastern China. These selected sites were all living communities (living with general population instead of people with same sort of work) with stable populations. All the eligible subjects in these villages and communities without contraindications for MRI and CT angiography (CTA) scanning were recruited and subjects were excluded only when they still refused after being reached at home by at least 3 attempts over 3 days. The baseline data collection of PRECISE was performed from May 2017 to September 2019 and enrolled 3067 participants. Participants in this study had similar baseline characteristics as samples of nationwide survey in China.[20]

Baseline characteristics collection
Data collection for all participants was conducted at Lishui Hospital via face-to-face clinical interviews and medical examinations. Data collection was performed by trained research coordinators with standardised questionnaires.[20] Baseline demographics, medical history and medication use were collected at the baseline survey. Those participants who smoked one cigarette per day or more on average during the last month was considered as current smokers.[21] Blood pressure was measured three times in seated position after resting for 5 min and the mean of the second and third measurements was recorded. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure≥90 mm Hg, self-reported previously diagnosed hypertension or current on antihypertensive treatment.[22] For participants without history of diabetes, the oral glucose tolerance test was conducted. Diabetes was defined as fasting glucose ≥7.0 mmol/L, 2-hour postload glucose ≥11.1 mmol/L, haemoglobin A1c≥6.5%, self-reported previously diagnosed diabetes or current on antidiabetic treatment.[23]

Fasting blood samples were collected at baseline survey. Lp(a) level was tested by immunoturbidimetric method with an Abbott C16000 analyzer (Abbott Laboratories, Chicago, USA). Lp(a) concentrations were further categorised into three groups according to the tertiles.

MRI acquisition and assessment
Eligible subjects without contraindications for MRI were scanned by a 3.0T scanner (Ingenia 3.0T, Philips, Best, The Netherlands) at baseline survey. Imaging data were collected and central adjudicated at the Imaging Research Centre at Beijing Tiantan Hospital by well-trained and experienced personnel who were blinded to clinical information. Images with poor quality or technical failures were excluded from analysis.

The presence of intracranial atherosclerotic plaque as well as degree of arterial stenosis were analysed by two raters (YD and HL). The presence of intracranial atherosclerotic plaque was defined as eccentric wall thickening on 3D-TOF MRA or black-blood T1w vessel wall images.[24] Detectable plaques in each arterial segment of distal internal carotid, middle cerebral (M1 and M2), anterior cerebral (A1 and A2), posterior cerebral (P1 and P2), basilar and vertebral arteries (V4) was recorded. Lumen stenosis was assessed according to the Warfarin-Aspirin Symptomatic Intracranial Disease Trial criteria.[25] The atherosclerotic lesions for each arterial segment were graded as 0–3 score for no stenosis, stenosis <50%, 50%–99% and occlusion. The degree of atherosclerotic burden was measured by summing the total score of the involved vessels and further categorised into scores of 0, 1, 2–3 and ≥4, respectively.[26] The inter-rater reproducibility was studied by replicating the assessment of all participants by the two raters. Inconsistencies were determined by another senior neurologist (JJ). Good reproducibility was found for the presence of plaque and artery stenosis with kappa coefficient of 0.97 and 0.79, respectively.

Four neuroimaging markers of cSVD, that is, white matter hyperintensity (WMH), lacunes, cerebral microbleeds (CMBs) and enlarged perivascular spaces (EPVS), were graded by trained raters according to the STandards for ReportIng Vascular changes on nEuroimaging criteria.[27] WMH was defined as hyperintense on T2-weighted and fluid-attenuated inversionrecovery (FLAIR) sequences and evaluated according to the Fazekas scale.[28] Lacunes were defined as lesion in the subcortical, basal ganglia or brainstem, with diameter of 3–15 mm and cerebrospinal fluid signal density on T2 and FLAIR sequences without increased signal on DWI. CMBs were defined as circular, hypodense foci within brain parenchyma on SWI sequences, up to 10 mm in diameter.[29] EPVSs were defined as <3 mm in diameter, cerebrospinal fluid-isointense lesions along the penetrating arteries on all sequences. The total cSVD burden was rated as 0–4 scores, by allocating 1 point to confluent WMH (ie, periventricular WMH of Fazekas scale 3 or deep WMH of Fazekas scale 2–3), presence of lacunes, CMBs and basal ganglia PVS >10.[30] Imaging assessment was assessed by two readers who were trained and blinded to subjects' characteristics. Inconsistencies were determined by another reader (YY). Good interobserver reproducibility was found for each cSVD marker between raters (kappa=0.80 for lacune, 0.82 for WMH, 0.90 for EPVS and 0.80 for CMB, respectively).

Statistical analysis
Categorical variables are presented as frequency with proportion and continuous variables as the mean±SD as appropriate. Comparison of baseline characteristics

among Lp(a) tertile groups were performed by analysis of variance and χ^2 test as appropriate.

We used multivariable binary logistic regression to examine the relationships between Lp(a) concentrations and the presence of intracranial atherosclerotic plaque and cSVD using the first tertile as the reference. For each model, ORs with their 95% CIs were calculated. We used multivariable ordinal logistic regression to examine the associations between the Lp(a) level and a shift in the direction of a higher intracranial atherosclerotic or cSVD burden using the first tertile as the reference. Common ORs with their 95% CIs were evaluated. For each dependent variable, two adjusted regression models were conducted. We only adjusted for age and sex in the first model. Then, in model 2, we further adjusted for body mass index, histories of hypertension, diabetes and atrial fibrillation, current smoking, current drinking, total cholesterol, low density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, antihypertensive, antidiabetic, lipid-lowering and anticoagulant agents use.

To assess the pattern and magnitude of relationship between Lp(a) level and presence of intracranial atherosclerotic plaque, cSVD, the intracranial atherosclerotic and cSVD burden, a binary or ordinal logistic regression model with restricted cubic splines for Lp(a) concentrations was performed. Lp(a) level of 40 mg/L (33rd percentile) was set as the reference.

Data related to the analysis are available to researchers on request by contacting the corresponding author. A two-sided p<0.05 was considered to be statistically significant. All analyses were performed with SAS software V.9.4 (SAS Institute).

RESULTS
Baseline characteristics
The PRECISE study enrolled 3067 community-dwelling adults at baseline. After excluding 6 subjects with missing or poor quality of MR images to assess cSVD or intracranial atherosclerosis and 2 subjects without Lp(a) data, a total of 3059 subjects were included in this analysis (figure 1).

Baseline demographics of the included participants according to tertiles of Lp(a) concentrations are shown in table 1. The average age was 61.2±6.7 years, and 53.5% (1636) were female. Participants with high Lp(a) concentrations were less likely to be current drinker or have history of diabetes, with lower fasting plasma glucose level but higher lipid level.

Association of Lp(a) concentrations with intracranial plaque and cSVD
Among all the 3059 included subjects, 541 (17.7%) participants had intracranial atherosclerotic plaque, among whom 304 (9.9%), 200 (6.5%) and 37 (1.2%) had intracranial atherosclerotic burden score of 1, 2–3 and ≥4, respectively. There were 933 (30.5%) participants
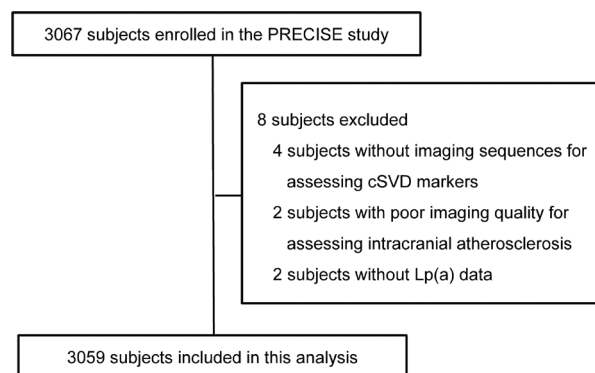

Figure 1 Flow chart of the participant selection. CSVD, cerebral small vessel disease; Lp(a), lipoprotein(a); PRECISE, PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events.

having at least one of the four cSVD neuroimaging markers (16.6%, 5.6%, 10.2% and 9.8% had presence of confluent WMH, lacunes, CMBs and BG-PVS >10), among whom 678 (22.2%), 176 (5.8%) and 79 (2.6%) had cSVD burden score of 1, 2 and 3–4, respectively.

Distribution of intracranial atherosclerotic and cSVD burden by tertiles of Lp(a) concentrations are presented in figure 2. Compared with the first tertile, subjects with the second and third tertiles of Lp(a) concentrations were associated with an increased odds of presence of intracranial atherosclerotic plaque (18.7% vs 15.4%, adj. OR 1.37, 95% CI 1.08 to 1.75; 18.9% vs 15.4%, adj.OR 1.34, 95% CI 1.05 to 1.72) (figure 3). Similar associations were observed for intracranial atherosclerotic burden (T2 vs T1: adj.cOR 1.36, 95% CI 1.07 to 1.73; T3 vs T1: adj.cOR 1.36, 95% CI 1.06 to 1.73). Whereas, compared with the first tertile, subjects with the third tertile of Lp(a) level were associated with a decreased odds of presence of cSVD (25.9% vs 31.7%, adj.OR 0.74, 95% CI 0.60 to 0.92) and lower cSVD burden (adj.cOR 0.76, 95% CI 0.62 to 0.94). The third tertile of Lp(a) level was numerically associated with a reduced odds of presence of confluent WMH, lacunes and BG-PVS >10 although all were not significant (figure 4).

Using a binary or ordinal logistic regression with restricted cubic spline for Lp(a) concentrations, we found that subjects with elevated Lp(a) concentrations had higher odds of presence of intracranial plaque and higher intracranial atherosclerotic burden, but lower odds of presence of cSVD and lower cSVD burden (figure 5).

DISCUSSION
In the cross-sectional baseline study of a population-based cohort, we observed differential associations of Lp(a) level with cerebral large artery and small vessel diseases. We found that higher Lp(a) concentrations was related to a higher odds of presence of intracranial plaque and higher intracranial atherosclerotic burden, but a lower odds of presence of cSVD and lower cSVD burden.

Table 1 Baseline demographic and clinical characteristics according to tertiles of Lp(a) level

Characteristics	Total (n=3059)	Tertiles of the lp(a) level			P value
		T1 (n=1002)	T2 (n=1027)	T3 (n=1030)	
Age, years	61.2±6.7	61.2±6.8	61.1±6.5	61.3±6.7	0.95
Female sex, n (%)	1636 (53.5)	513 (51.2)	546 (53.2)	577 (56.0)	0.09
BMI, kg/m^2	23.8±3.0	23.9±3.2	23.7±2.9	23.7±3.1	0.17
Current smoker, n (%)	626 (20.5)	221 (22.1)	207 (20.2)	198 (19.2)	0.27
Current drinker, n (%)	573 (18.7)	217 (21.7)	174 (16.9)	182 (17.7)	0.01
Medical history, n(%)					
Hypertension	1316 (43.0)	444 (44.3)	430 (41.9)	442 (42.9)	0.54
Diabetes mellitus	660 (21.6)	269 (26.8)	203 (19.8)	188 (18.3)	<0.001
Dyslipidaemia	613 (20.0)	201 (20.1)	190 (18.5)	222 (21.6)	0.22
Stroke	87 (2.8)	24 (2.4)	34 (3.3)	29 (2.8)	0.46
Coronary artery disease	13 (0.4)	2 (0.2)	8 (0.8)	3 (0.3)	0.10
Atrial fibrillation	26 (0.8)	8 (0.8)	12 (1.2)	6 (0.6)	0.34
SBP, mmHg	129.3±16.3	129.3±16.3	129.0±16.6	129.5±16.2	0.66
DBP, mmHg	75.2±9.0	75.2±9.2	75.2±9.1	75.3±8.9	0.72
Fasting plasma glucose, mmol/L	5.96±1.58	6.09±1.66	5.98±1.78	5.81±1.25	<0.001
TC, mmol/L	5.28±0.99	5.09±0.98	5.28±0.95	5.47±1.01	<0.001
LDL-C, mmol/L	2.78±0.79	2.60±0.81	2.77±0.75	2.96±0.79	<0.001
HDL-C, mmol/L	1.37±0.34	1.33±0.35	1.36±0.32	1.40±0.34	<0.001
Medication use, n(%)					
Antihypertensive	820 (26.8)	264 (26.3)	266 (25.9)	290 (28.2)	0.47
Antidiabetic	273 (8.9)	107 (10.7)	89 (8.7)	77 (7.5)	0.04
Lipid lowering	120 (3.9)	40 (4.0)	33 (3.2)	47 (4.6)	0.29
Anticoagulants	4 (0.1)	1 (0.1)	3 (0.3)	0 (0.0)	0.18
Imaging markers, n(%)					
Intracranial plaque	541 (17.7)	154 (15.4)	192 (18.7)	195 (18.9)	0.06
Cerebral small vessel diseases	933 (30.5)	318 (31.7)	348 (33.9)	267 (25.9)	<0.001
Confluent WMH	509 (16.6)	177 (17.7)	183 (17.8)	149 (14.5)	0.07
Lacune	170 (5.6)	58 (5.8)	67 (6.5)	45 (4.4)	0.10
Cerebral microbleeds	313 (10.2)	90 (9.0)	121 (11.8)	102 (9.9)	0.10
BG-PVS >10	300 (9.8)	111 (11.1)	99 (9.6)	90 (8.7)	0.20

P value tests difference of baseline characteristics among Lp(a) tertile groups by analysis of variance for continuous variables and $\chi 2$ test for categorical variables. Tertiles of Lp(a): T1, <40 mg/L; T2, 40–105 mg/L; T3, ≥106 mg/L.
BG-PVS, basal ganglia-enlarged perivascular spaces; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SBP, systolic blood pressure; T, tertile; TC, total cholesterol; WMH, white matter hyperintensity.

Mendelian randomisation and observational studies have shown that elevated Lp(a) concentrations are proatherogenic and contribute to atherosclerotic cardiovascular/cerebrovascular disease.[7–11 15 16] However, previous studies on cerebrovascular diseases mostly included all ischaemic stroke regardless of aetiological subtypes,[7 8 15 16] and study on the relationship of Lp(a) level with specific subtype of ischaemic stroke, intracranial atherosclerosis or cSVD is limited. It was reported that apolipoprotein(a) genetic sequence variants (*LPA*) of rs10455872 and rs3798220 were only correlated to large artery stroke but not significant for small vessel stroke.[31] Previous two-sample Mendelian randomisation study showed that Lp(a) level was positively associated with large artery stroke but inversely associated with small vessel stroke and Alzheimer disease.[19] Another study observed a positive correlation between Lp(a) level and the extent of intracranial stenoses identified on transcranial Doppler in 166 first-ever TIA or patients who had a stroke.[32] Previous studies showed a high Lp(a) level in large artery stroke but low Lp(a) level in small vessel stroke, suggesting that Lp(a) may promote atherothrombotic stroke but not
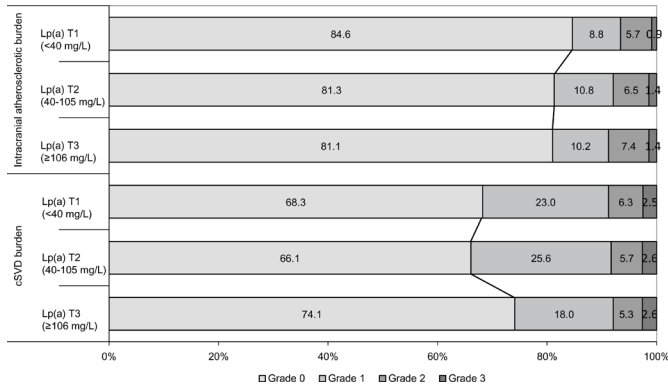
Figure 2 Distribution of intracranial atherosclerotic and cSVD burden by tertiles of Lp(a) level. Grades 0–4 indicate intracranial atherosclerotic burden score of 0, 1, 2–3 and ≥4, or total cSVD burden score of 0, 1, 2, 3–4, respectively. cSVD, cerebral small vessel disease; Lp(a), lipoprotein(a); T, tertile.

Figure 4 Forest plots for the association between Lp(a) level and cSVD imaging markers. The plots showed the OR and their 95% CIs. BG-PVS, basal ganglia-enlarged perivascular spaces; CMBs, cerebral microbleeds; cSVD, cerebral small vessel disease; Lp(a), lipoprotein(a); T, tertile; WHM, white matter hyperintensities.

small vessel stroke.[14 18 33] Another study also observed an insignificant lower Lp(a) in patients with cSVD than those without cSVD.[17] Few study focused on the association of Lp(a) with WMH, although some,[34] but not all,[35] studies showed that dyslipidaemia was associated with presence and progression of WMH. However, the sample size of these studies[14 17 18 33 34] was relatively small and most based on hospitalised patients rather than representative community population. Consistent with the previous studies,[19 31] the current study adds the cross-sectional evidence of distinct relationships of Lp(a) level with

intracranial atherosclerosis (positive association) and cSVD (inverse association) in a large-scale community-based population with advanced MRI imaging test. We also observed a trend of reduced odds of presence of neuroimaging markers of cSVD like BG-PVS, WMH and lacunes in those with high Lp(a) level. The different directions of association between the second and third tertiles of Lp(a) for lacunes and WMH, and overall insignificance for the association of individual neuroimaging markers of cSVD may possibly be due to the small sample size for each neuroimaging marker.

Figure 3 Association of intracranial plaque and cSVD with Lp(a) level. *Model 1 adjusted for age and sex. †Model 2 adjusted for age, sex, body mass index, histories of hypertension, diabetes and atrial fibrillation, current smoking, current drinking, TC, LDLC, HDLC, antihypertensive, antidiabetic, lipid-lowering and anticoagulant agents use. ‡OR and 95% CI for the presence of intracranial plaque and cSVD by binary logistic regression, whereas COR and 95% CI for intracranial atherosclerotic burden and cSVD burden by ordinal logistic regression. §The degree of intracranial atherosclerotic burden was graded as scores of 0, 1, 2–3 and ≥4, respectively. ‖The degree of cSVD burden was graded as scores of 0, 1, 2 and 3–4, respectively. COR, common OR; cSVD, cerebral small vessel disease; HDLC, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LDLC, low-density lipoprotein cholesterol; Ref., reference; T, tertile; TC, total cholesterol.
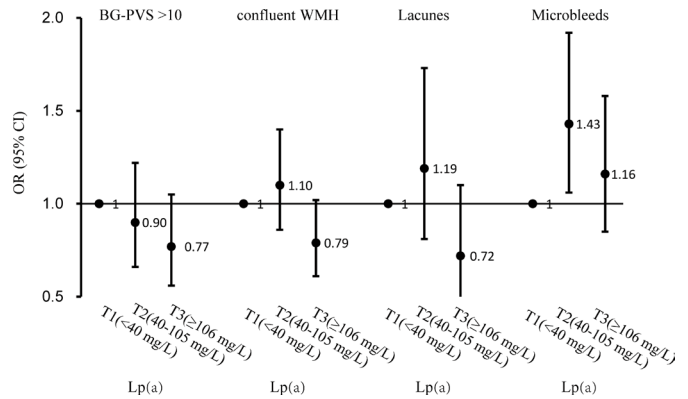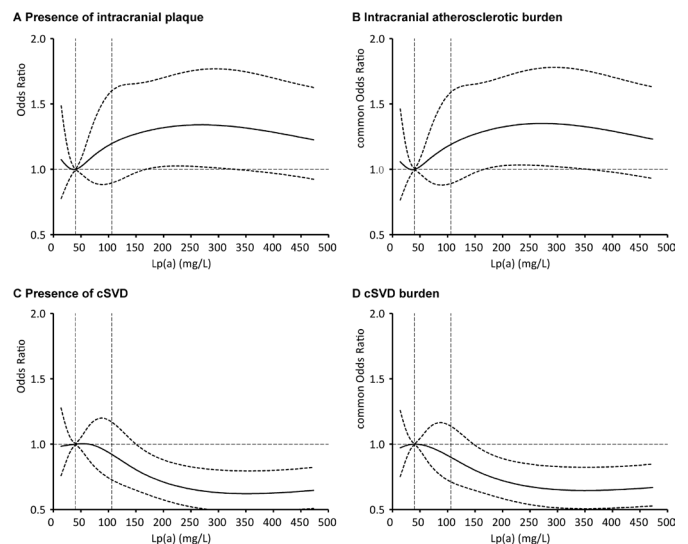

Figure 5 ORs/ common ORs of intracranial plaque and cSVD according to Lp(a) level. (A) Presence of intracranial plaque; (B) intracranial atherosclerotic burden; (C) presence of cSVD; (D) cSVD burden. Lp(a) level of 40 mg/L (33rd percentile) was set as reference. Data were fitted using a binary or ordinal logistic regression with restricted cubic spline. cSVD, cerebral small vessel disease; Lp(a), lipoprotein(a).

Lp(a) is composed of apolipoprotein B100 and apolipoprotein(a).[6] Lp(a) has shown to be proinflammatory, proatherogenic, prothrombotic, and antifibrinolytic potential, and promote atherosclerosis.[6] Recent studies demonstrated that elevated (Lp(a)) concentrations was correlated to greater degree of carotid artery stenosis and plaque progression.[12 13] Our study further demonstrated that elevated Lp(a) was associated with high odds of presence and burden of intracranial atherosclerosis. Whereas, the underlying mechanism that elevated Lp(a) level was correlated with lower risk of cSVD is poorly understood. Potential explanations may reveal this inverse association. First, high LDL cholesterol level was reported to be correlated with a reduced WMH volume.[35] Lp(a) may have similar mechanism as LDL cholesterol since Lp(a) and LDL cholesterol both contain apolipoprotein B100. Second, previous study showed that Lp(a) was present in cerebrospinal fluid and correlated with serum Lp(a) level.[36] Lipoproteins, such as ApoA-I, may take part in the regulation of cholesterol metabolism in cerebrospinal fluid.[37] It is suspected that Lp(a) may contribute to lipoprotein metabolism in the brain and glioneurovascular unit maintenance.[38] Third, apolipoprotein(a), primary determiner of the plasma Lp(a) level, may modify ApoE isoform metabolism, which is a key player in lipid metabolism.[39] Previous study showed that APOE ε2 and APOE ε4 were associated with MRI markers of cSVD.[40] Nevertheless, more researches are warranted to further elucidate the mechanisms for the inverse associations between Lp(a) level and cSVD.

The strength of the study is comprehensive assessment of intracranial atherosclerosis and cSVD through advanced imaging techniques in a large-scale community-based population. The participants in this study had similar demographic characteristics as does nationwide survey in China.[20] This enables extrapolation of the findings to the general population. Inclusion of both cerebral large artery and small vessel diseases may help comprehensive assessment of the influence of Lp(a) level on the cerebral arteries. This study demonstrated that elevated Lp(a) level may be deleterious for cerebral large arteries but protective for cerebral small vessels. Considering the potential double-sided role of Lp(a), further investigation may be warranted on the optimal level of Lp(a) in clinical practice.

Several limitations should be considered in this study. First, this study is a cross-sectional analysis of a baseline survey of the PRECISE cohort and, therefore, cannot yet investigate the association for progression of intracranial atherosclerosis and cSVD. Longitudinal follow-up data of the cohort may provide us with an opportunity to investigate disease progression. Potential unmeasured confounders and reverse causation may exist in an observational study. Second, selection bias may still exist as the study population was all recruited from the Lishui city. Finally, the participants in this cohort were restricted to Chinese elderly adults. Further large-scale investigation is required before extrapolation of the findings to other populations.

CONCLUSIONS

In this community-based population, we observed differential associations of Lp(a) level with cerebral large artery and small vessel diseases. We found that elevated Lp(a) concentrations was positively associated with presence and burden of intracranial atherosclerosis, but was inversely associated with cSVD. This suggests that elevated Lp(a) concentrations may be deteriorating for cerebral large arteries but protective for cerebral small vessels. The clinical relevance and underlying mechanisms of the double-sided role of Lp(a) level on cerebral arteries requires further investigation.

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REFERENCES

1 Pan Y, Li H, Wardlaw JM, *et al*. A new dawn of preventing dementia by preventing cerebrovascular diseases. *BMJ* 2020;371:m3692.
2 Del Brutto OH, Mera RM, Del Brutto VJ, *et al*. Cerebral small vessel disease score and atherosclerosis burden - A population study in community-dwelling older adults. *Clin Neurol Neurosurg* 2020;194:105795.
3 Khan U, Porteous L, Hassan A, *et al*. Risk factor profile of cerebral small vessel disease and its subtypes. *J Neurol Neurosurg Psychiatry* 2007;78:702–6.
4 Feng C, Bai X, Xu Y, *et al*. Hyperhomocysteinemia associates with small vessel disease more closely than large vessel disease. *Int J Med Sci* 2013;10:408–12.
5 Shu M-J, Zhai F-F, Zhang D-D, *et al*. Metabolic syndrome, intracranial arterial stenosis and cerebral small vessel disease in community-dwelling populations. *Stroke Vasc Neurol* 2021;6:589–94.
6 Kotani K, Serban M-C, Penson P, *et al*. Evidence-based assessment of lipoprotein(a) as a risk biomarker for cardiovascular diseases - Some answers and still many questions. *Crit Rev Clin Lab Sci* 2016;53:370–8.
7 Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, *et al*. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009;302:412–23.
8 Larsson SC, Gill D, Mason AM, *et al*. Lipoprotein(a) in Alzheimer, Atherosclerotic, Cerebrovascular, Thrombotic, and Valvular Disease: Mendelian Randomization Investigation. *Circulation* 2020;141:1826–8.
9 Burgess S, Ference BA, Staley JR, *et al*. Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis. *JAMA Cardiol* 2018;3:619–27.
10 Saleheen D, Haycock PC, Zhao W, *et al*. Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis. *Lancet Diabetes Endocrinol* 2017;5:524–33.
11 Trinder M, Uddin MM, Finneran P, *et al*. Clinical Utility of Lipoprotein(a) and *LPA* Genetic Risk Score in Risk Prediction of Incident Atherosclerotic Cardiovascular Disease. *JAMA Cardiol* 2021;6:287–95.
12 Steffen BT, Thanassoulis G, Duprez D, *et al*. Race-Based Differences in Lipoprotein(a)-Associated Risk of Carotid Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2019;39:523–9.
13 van Dam-Nolen DHK, van Dijk AC, Crombag GAJC, *et al*. Lipoprotein(a) levels and atherosclerotic plaque characteristics in the carotid artery: The Plaque at RISK (PARISK) study. *Atherosclerosis* 2021;329:22–9.
14 Cerrato P, Imperiale D, Fornengo P, *et al*. Higher lipoprotein (a) levels in atherothrombotic than lacunar ischemic cerebrovascular disease. *Neurology* 2002;58:653–5.
15 Arora P, Kalra R, Callas PW, *et al*. Lipoprotein(a) and Risk of Ischemic Stroke in the REGARDS Study. *Arterioscler Thromb Vasc Biol* 2019;39:810–8.
16 Langsted A, Nordestgaard BG, Kamstrup PR. Elevated Lipoprotein(a) and Risk of Ischemic Stroke. *J Am Coll Cardiol* 2019;74:54–66.
17 Yu X, Yu Y, Wei C, *et al*. Association between small dense low-density lipoprotein cholesterol and neuroimaging markers of cerebral small vessel disease in middle-aged and elderly Chinese populations. *BMC Neurol* 2021;21:436.
18 Iskra T, Turaj W, Słowik A, *et al*. [Lipoprotein (a) in stroke patients with large and small vessel disease]. *Przegl Lek* 2002;59:877–80.
19 Pan Y, Li H, Wang Y, *et al*. Causal Effect of Lp(a) [Lipoprotein(a)] Level on Ischemic Stroke and Alzheimer Disease: A Mendelian Randomization Study. *Stroke* 2019;50:3532–9.
20 Pan Y, Jing J, Cai X, *et al*. PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events (PRECISE)-a population-based prospective cohort study: rationale, design and baseline participant characteristics. *Stroke Vasc Neurol* 2021;6:e000411–51.
21 Xu L, Schooling CM, Chan WM, *et al*. Smoking and hemorrhagic stroke mortality in a prospective cohort study of older Chinese. *Stroke* 2013;44:2144–9.
22 Wang Z, Chen Z, Zhang L, *et al*. Status of hypertension in China: results from the China hypertension survey, 2012-2015. *Circulation* 2018;137:2344–56.
23 Wang L, Gao P, Zhang M, *et al*. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. *JAMA* 2017;317:2515–23.
24 Qiao Y, Guallar E, Suri FK, *et al*. Mr imaging measures of intracranial atherosclerosis in a population-based study. *Radiology* 2016;280:860–8.
25 Samuels OB, Joseph GJ, Lynn MJ, *et al*. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol* 2000;21:643–6.
26 Sun P, Liu L, Pan Y, *et al*. Intracranial atherosclerosis burden and stroke recurrence for symptomatic intracranial artery stenosis (sICAS). *Aging Dis* 2018;9:1096–102.
27 Wardlaw JM, Smith EE, Biessels GJ, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12:822–38.
28 Fazekas F, Chawluk JB, Alavi A, *et al*. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987;149:351–6.
29 Greenberg SM, Vernooij MW, Cordonnier C, *et al*. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol* 2009;8:165–74.
30 Staals J, Makin SDJ, Doubal FN, *et al*. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology* 2014;83:1228–34.
31 Helgadottir A, Gretarsdottir S, Thorleifsson G, *et al*. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. *J Am Coll Cardiol* 2012;60:722–9.
32 Arenillas JF, Molina CA, Chacón P, *et al*. High lipoprotein (a), diabetes, and the extent of symptomatic intracranial atherosclerosis. *Neurology* 2004;63:27–32.
33 Yuan B-B, Luo G-G, Gao J-X, *et al*. Variance of serum lipid levels in stroke subtypes. *Clin Lab* 2015;61:1509–14.
34 Shu Z, Xu Y, Shao Y, *et al*. Radiomics from magnetic resonance imaging may be used to predict the progression of white matter hyperintensities and identify associated risk factors. *Eur Radiol* 2020;30:3046–58.
35 Schilling S, Tzourio C, Dufouil C, *et al*. Plasma lipids and cerebral small vessel disease. *Neurology* 2014;83:1844–52.
36 Pepe G, Chimienti G, Liuzzi GM, *et al*. Lipoprotein(a) in the cerebrospinal fluid of neurological patients with blood-cerebrospinal fluid barrier dysfunction. *Clin Chem* 2006;52:2043–8.
37 Saczynski JS, White L, Peila RL, *et al*. The relation between apolipoprotein A-I and dementia: the Honolulu-Asia aging study. *Am J Epidemiol* 2007;165:985–92.
38 Kunutsor SK, Khan H, Nyyssönen K, *et al*. Is lipoprotein (a) protective of dementia? *Eur J Epidemiol* 2016;31:1149–52.
39 IWAMOTO T, WATANABE D, UMAHARA T, *et al*. Dual inverse effects of lipoprotein(a) on the dementia process in Japanese late-onset Alzheimer's disease. *Psychogeriatrics* 2004;4:64–71.
40 Schilling S, DeStefano AL, Sachdev PS, *et al*. Apoe genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. *Neurology* 2013;81:292–300.