Association between lipoprotein(a) concentration and the risk of stroke in the Chinese Han population: a retrospective case-control study

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Background: Lipoprotein(a) [Lp(a)] is a risk factor of coronary heart disease, however, its effects on stroke are less well-defined.

Methods: We performed a single-center, retrospective case-control study in 1,953 and 196 ischemic stroke and hemorrhagic stroke in-hospital patients, respectively. Controls were healthy individuals that were matched for sex and age (±5 years) for the ischemic (1:1 ratio) and hemorrhagic (1:2 ratio) stroke. Lp(a) concentration was measured using the latex agglutination turbidimetric method. Logarithmic transformation and quartile categorization were applied to adjust for the skewed distribution of Lp(a). Conditional logistic regression models were used to assess the association between Lp(a) and stroke risk.

Results: Median Lp(a) concentration was higher in stroke patients when compared with controls (12.2 *vs.* 8.60 mg/dL) and hemorrhagic strokes (14.40 *vs.* 13.40 mg/dL). The conditional multivariate analysis revealed a positive association between Lp(a) and ischemic stroke (OR =2.03, 2.36, and 2.03 for quartiles 2, 3 and 4, respectively, *vs.* quartile 1; P<0.001). In addition, elevated Lp(a) was also significantly associated with increased hemorrhagic stroke risk, after adjusted for potential covariates (OR =1.93, 3.24, and 2.19 for quartile 2, 3 and 4 respectively *vs.* quartile 1, P<0.05). The stratified analyses for ischemic and hemorrhagic stroke revealed significant association between elevated log-transformed Lp(a) and ischemic stroke in men. Furthermore, there was a trend towards a higher stroke risk for younger patients compared with older patients.

Conclusions: Elevated serum Lp(a) is significantly positively correlated with ischemic and hemorrhagic stroke risk in the Chinese Han population, especially among men and younger patients.

Keywords: Lipoprotein(a) [Lp(a)]; ischemic stroke; hemorrhagic stroke; case-control study

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Introduction

Stroke has become the second leading cause of disease burden worldwide and the first leading cause of disability among Chinese populations (1). Chinese populations have a higher overall incidence of stroke and greater proportion of hemorrhagic stroke than Caucasian populations. Despite a greater incidence of ischemic stroke, hemorrhagic stroke contributes to a similar number of deaths in China (2). Conventional risk factors include hypertension, diabetes, and smoking; however, approximately 25% of all ischemic strokes lack a clear cause (3). Therefore, it is important to identify other potential stroke risk factors.

Lipoprotein (a) [Lp(a)] is formed from a low-density lipoprotein (LDL)-like particle and the glycoprotein, apolipoprotein(a) [apo(a)], linked to apolipoprotein B in the LDL by a single disulphide bond (4). Lp(a) plays a role in atherogenic and pro-thrombotic/anti-fibrinolytic processes (5,6). In addition, studies have reported roles in inflammatory responses, binding of oxidized phospholipids, and vascular remodeling (7).

A causal association between elevated Lp(a) and increased risk of myocardial infarction has been proved (8); however, there are conflicting reports regarding the relationship between stroke risk and Lp(a) concentration. Several meta-analyses with large samples have shown that Lp(a) is a risk factor for ischemic stroke (9-11). However, a systematic literature review with 16 prospective studies found no significant effect of Lp(a) on stroke risk (12). Additionally, the concentration of serum Lp(a) is determined by genetic factors primarily and differs substantially across ethnicities. Few studies have assessed the effects of Lp(a) on stroke in Asian populations. Moreover, previous studies have used unclassified stroke or ischemic stroke patients only; fewer studies have assessed the effect of Lp(a) on hemorrhagic stroke. Therefore, we sought to detect the association between Lp(a) and ischemic or hemorrhagic stroke risk in this case-control study in the Chinese Han population.

Methods

Study participates

This was a retrospective case-control study assessing the relationship between serum Lp(a) and ischemic and hemorrhagic stroke risk in the Chinese Han population. Cases were extracted from administrative data from the Peking Union Medical College Hospital (PUMCH), a national comprehensive hospital. Patients >18 years old were eligible for inclusion if they had been diagnosed with ischemic (International Classification of Diseases, 10th edition (ICD-10, code I63) or hemorrhagic stroke (ICD-10; codes I61, I62) between January 1, 2009 and December 31, 2018. Patients with transient ischemic attack were excluded.

All diagnostic information and laboratory data were obtained from discharge files and the hospital's electronic laboratory database. Exclusion criteria were non-Han nationality, malignant tumor with ≤5 years remission, chronic liver disease (>3-fold transaminase elevation), chronic kidney disease (serum creatinine, ≥152.5 μmol/L), and systemic autoimmune disease. For patients with multiple hospitalizations, we included records during hospitalization for the first stroke diagnosis only. Eligible healthy individuals without stroke history were selected from the health examination center of PUMCH during the same period with the same exclusion criteria. Control participants were selected and matched by age (±5 years) and gender for the ischemic stroke (1:1 ratio) and hemorrhagic (1:2 ratio) group, respectively. The study protocol was approved by the Ethics Committee of the PUMCH who waived the requirement for informed consent because this study used anonymized data in a retrospective analysis.

Hypertension was defined as the use of antihypertensive drugs or with a diagnosis in the medical records. Diabetes (DM) was diagnosed when the percentage of hemoglobin A1c (HbA1c%) was >6.5%, use of glucose-lowering drugs, or with a diagnosis in the medical records. Coronary atherosclerotic heart disease (CAD) refers to those with a record of coronary atherosclerotic stenosis or occlusion, or coronary stent implantation. Hyperlipidemia was defined as LDL >4.1 mmol/L, HDL <1.0 mmol/L, or the use of lipid-lowering medication (13).

Lp(a) measurement

Lp(a) and other plasma biochemical parameters were analyzed in the Department of Laboratory Medicine at PUMCH and archived data were identified using computer retrieval. Blood samples were obtained after a 12-hour overnight fast and centrifuged at 3,500 r/min for 15 min after standing for 30 min. The concentration of serum Lp(a) was measured using the latex agglutination turbidimetric method with mouse monoclonal anti-Lp(a) antibody (Beckman AU5800 automatic biochemistry, Sekisui Medical Company, Tokyo, Japan). The detection range was 0–100 mg/dL with a normal value of below 30 mg/dL. The intra- and inter-assay coefficients of variation (CV) were

below 5.0% and 10%, respectively. Triglyceride (TG), total cholesterol (TC), LDL cholesterol (LDL-c), and homocysteine (HCY) were measured using an enzymatic method. High density lipoprotein cholesterol (HDL-c) was determined by direct methods. Hypersensitive C-reactive protein (hsCRP) was detected using immune turbidimetric analysis. All plasma biochemical parameters were assayed by an automatic biochemistry analyzer (AU5800, Beckman Coulter, Brea, CA).

Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous normally distributed variables and median with interquartile ranges for skewed distributed variables. Student's *t*-test was applied to compare normally distributed variables or skewed distributed variables after logarithm transformation, and Pearson's χ^2 test was applied for categorical comparisons. A common logarithm (Lg) transformation was applied for the skewed distribution of Lp(a). Further, analysis was undertaken to assess the relationship between quartiles of Lg-transformed Lp(a) levels and stroke risk. Univariate and multivariate conditional logistic regression models for matched case-control data were used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CI) of Lg-transformed Lp(a) as a categorical variable. We adjusted for diabetes, hyperlipidemia, and hypersensitive CRP. In addition, we also adjusted for variables that changed the matched odds ratio by at least 10% when added to this model. Interaction and stratified analyses were conducted by age (<55 and ≥55 years) and sex. A two-tailed P value of <0.05 was considered significant. All statistical analyses were performed with R software, EmpowerStats (X&Y Solutions, Boston, MA) and SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Clinical characteristics

Among the 464,567 hospitalizations in the study cohort, we enrolled 2,296 and 205 ischemic and hemorrhagic stroke patients, respectively, based on the inclusion and exclusion criteria (*Figure S1*). We randomly selected 1,953 and 392 age- and sex-matched healthy controls for the ischemic and hemorrhagic groups, respectively. The characteristics of the controls are presented in *Table 1*. The ischemic group had a higher mean age and higher proportion of males compared with the hemorrhagic group. The proportions of DM and CAD were higher in the ischemic group. The median Lp(a) concentration in the two groups was similar (*Table S1*). Cases and controls were similar in age, sex and BMI in the ischemic group. There was a greater burden of hypertension, diabetes, cardiovascular disease, and hyperlipidemia, in ischemic stroke cases compared with controls. In addition, data showed lower median HDL, LDL, total cholesterol, and triglyceride levels and higher homocysteine levels in ischemic stroke cases when compared with controls. A similar distribution was found in the hemorrhagic group, except that the hemorrhagic cases showed lower CAD ratios and higher triglyceride levels when compared with controls.

Lp(a) and ischemic stroke risk

The median concentration of Lp(a) was 12.2 and 8.60 mg/dL in the ischemic stroke and control groups, respectively (*Table 1*). We used conditional logistic regression models to assess whether Lp(a) was independently associated with ischemic stroke (*Table 2*). After adjustment for hypertension, diabetes, hyperlipidemia, and hsCRP, we found that lg-transformed Lp(a) was significantly associated with ischemic stroke with odd radios (ORs) and 95% confidence intervals (CI) for lg-transformed Lp(a) quartiles 4, 3, and 2 (*vs.* quartile 1 as a reference) of 2.03 (1.61, 2.57), 2.36 (1.85, 2.99) and 2.03 (1.60, 2.59), respectively. After further adjustment for BMI, cardiovascular disease, and homocysteine on Model 2, the relationship persisted (all P values for the log-transformed Lp(a) quartiles 2, 3, and 4 *vs.* quartile 1 were <0.001). In the stratified analysis, we found a significant association between elevated Lg-transformed Lp(a) and ischemic stroke in men. No statistically significant association was found in women in the Model adjusted for hypertension, hyperlipidemia, and hsCRP; and there was a significant interaction (P=0.006). Interestingly, younger patients (<55 years) showed greater increased risk than older patients for ischemic stroke in the multivariable analysis, and no significant differences for interactions were detected (*Figure 1*).

Lp(a) and hemorrhagic stroke risk

There was a higher median Lp(a) concentration in the hemorrhagic group (14.40 mg/dL) compared with the control group (13.40 mg/dL; *Table 1*). The association between log-transformed Lp(a) and hemorrhagic stroke

Table 1 Baseline characteristics of ischemic and hemorrhagic stroke cases and controls after age and sex matching

Characteristics	Ischemic stroke		Hemorrhagic stroke	
	Cases (n=1,953)	Controls (n=1,953)	Cases (n=196)	Controls (n=392)
Age, years	62.38±11.82	59.97±11.07	57.90±13.78	57.91±13.76
Male, %	64.98	64.98	55.61	55.61
BMI, kg/m^2	25.21±3.67	25.22±3.24	24.46±3.64	24.74±3.29
Hypertension, %	69.53	44.08	60.2	40.6
DM, %	39.99	18.23	22.45	15.31
CAD, %	23.70	18.23	12.8	17.34
Hyperlipidemia, %	68.00	33.29	62.76	30.61
TC, mmol/L	4.09 (3.41, 4.92)	4.82 (4.17, 5.49)	4.2 (3.77, 5.28)	4.82 (4.27, 5.41)
TG, mmol/L	1.29 (0.92, 1.82)	1.34 (0.97, 1.92)	1.42 (0.96, 2.10)	1.28 (0.99, 1.73)
HDL-c, mmol/L	0.99 (0.84, 1.19)	1.20 (1.01, 1.43)	1.00 (0.80, 1.22)	1.23 (1.03, 1.45)
LDL-c, mmol/L	2.41 (1.83, 3.07)	3.07 (2.48, 3.63)	2.71 (2.16, 3.37)	3.08 (2.56, 3.57)
Lp(a), mg/dL	12.20 (5.80, 24.80)	8.60 (3.70, 21.30)	14.40 (11.75, 18.45)	13.40 (11.30, 16.10)
HCY, μmol/L	14.20 (11.40, 18.65)	13.30 (11.50, 15.67)	13.05 (7.25, 25.33)	9.70 (3.98, 24.00)
hsCRP, mg/dL	1.74 (0.68, 4.75)	0.80 (0.44, 1.66)	3.26 (1.10, 14.71)	0.77 (0.40, 1.58)

Continuous variables presented as mean ± standard deviation or median (Q1, Q3).

Table 2 Odd ratios (95% confidence intervals) for ischemic stroke and lg-transformed Lp(a) concentration

Group	Unadjusted model		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.91 (1.58, 2.30)	<0.001	2.03 (1.61, 2.57)	<0.001	1.74 (1.30, 2.33)	<0.001
Quartile 3	2.34 (1.93, 2.82)	<0.001	2.36 (1.85, 2.99)	<0.001	1.98 (1.47, 2.68)	<0.001
Quartile 4	2.02 (1.67, 2.45)	<0.001	2.03 (1.60, 2.59)	<0.001	1.88 (1.40, 2.53)	<0.001

Model 1: adjusted for hypertension, diabetes, hyperlipidemia, hypersensitive C-reactive protein. Model 2: adjusted for body mass index, diabetes, hypertension, cardiovascular disease, hyperlipidemia, hypersensitive C-reactive protein, homocysteine. The 25th, 50th, and 75th percentile cut-off points for corresponding Lp(a) are 4.6, 10.3, and 23.2 mg/dL, respectively.

was assessed using conditional logistic regression models (*Table 3*). Compared with patients in the lowest quartile, the ORs and 95%CIs for log-transformed Lp(a) quartiles 2–4 were 1.88 (1.08, 3.12), 2.46 (1.43, 4.25) and 2.18 (1.28, 3.72), respectively, in the unadjusted model. Additional adjustment for hypertension, hyperlipidemia, and hsCRP yielded similar results [OR =1.93 (1.02, 3.67), 3.24 (1.65, 6.39), and 2.19 (1.12, 4.29) for quartiles 2–4, respectively, *vs.* the reference quartile 1, P=0.043, P<0.001 and P=0.022]. The correlation between Lp(a) level and the risk of hemorrhagic stroke also survived full adjustment for diabetes, hypertension, cardiovascular disease, hyperlipidemia, and hsCPR in Model 2. The stratified analysis that adjusted for hypertension, hyperlipidemia, and hsCPR was conducted according to sex and age. Similar to the ischemic stroke, elevated Lg-transformed Lp(a) concentration was associated with a higher risk of hemorrhagic stroke in men alone, after adjusting for potential confounding factors. Increased hemorrhagic stroke risk was associated with elevated Lg-transformed

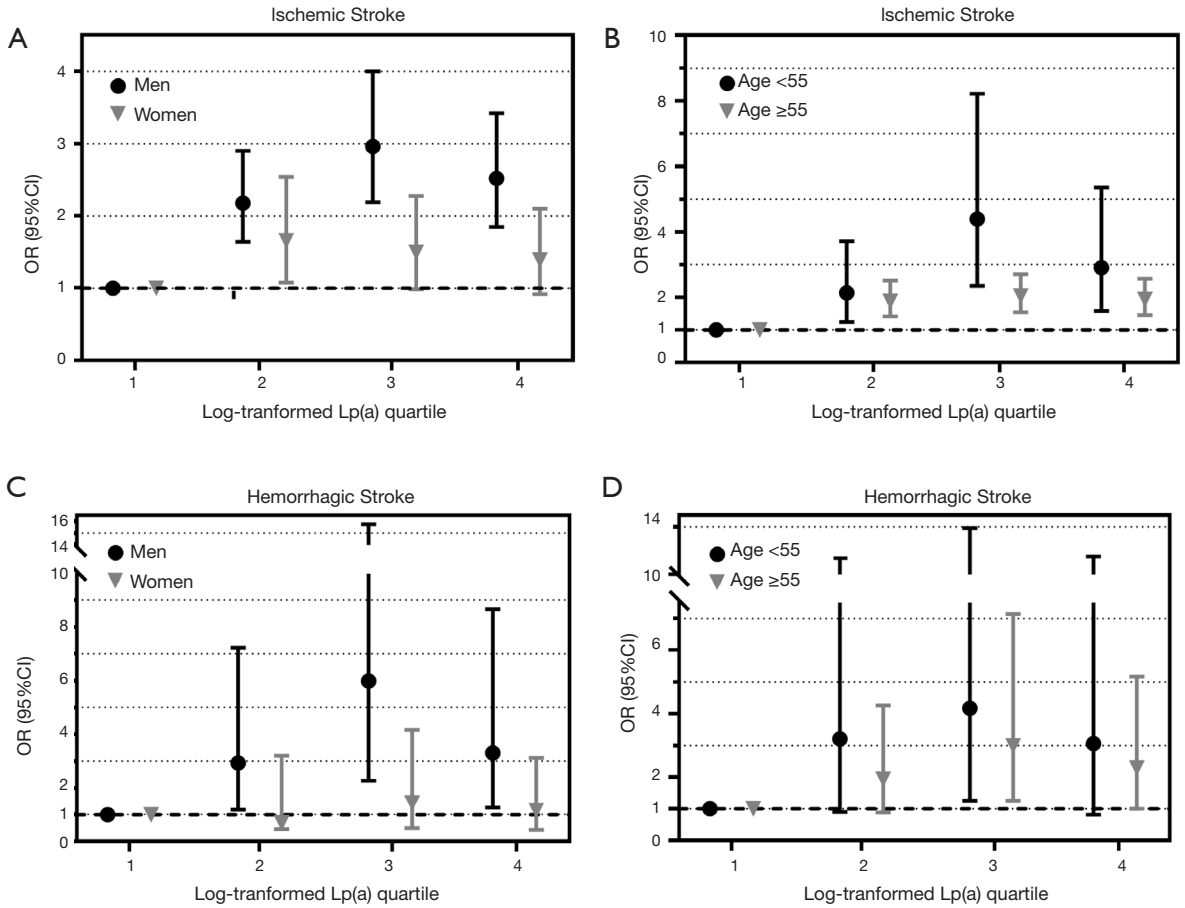

Figure 1 Odd ratios (95% confidence intervals) for ischemic stroke and hemorrhagic stroke of log-transformed Lipoprotein (a) quartiles stratified by sex (A, C) and age (B, D). The model was adjusted for hypertension, hyperlipidemia, hypersensitive C-reactive protein.

Lp(a) in both younger (<55 years) and older patients (≥55 years), but the effects were smaller in the older group (*Figure 1*).

Discussion

In this retrospective case-control study, we identified the associations between elevated Lp(a) and ischemic or hemorrhagic stroke risk compared with the age- and gender-matched healthy controls. Furthermore, we found an increased stroke risk associated with Lp(a) among younger patients. Interestingly, the effect of elevated Lp(a) on both stroke types was significant among men alone. Surprisingly, LDL-c, TC, and TG levels were lower in the stroke groups when compared with the controls, which may be due to the higher proportion of dyslipidemia in the stroke group with a lower proportion and target value for lipid-lowering treatment.

The effect of serum Lp(a) level on the risk of coronary heart disease is well-established; however, the effects on stroke risk remain controversial. Our results correspond with several previous studies on ischemic stroke. A meta-analysis of 126,634 individuals by the Emerging Risk Factors Collaboration demonstrated a significantly higher risk for ischemic stroke with a risk ratio (RR) of 1.10 (95% CI: 1.02–1.18) per 3.5-fold higher Lp(a) concentrations (9). However, >90% of the participants in this study were of European continental ancestry that attenuated the generalization to patients of all ethnicities. Nave *et al.* have summarized 20 articles comprising 90,904 cases and concluded that Lp(a) might be an independent risk factor for ischemic stroke with a pooled OR of 1.41 (95% CI: 1.26–1.57) for case-control studies and 1.29 (95% CI: 1.06–1.58) for prospective studies (10). In contrast, data from

Table 3 Odd ratios (95% confidence intervals) for hemorrhagic stroke and lg-transformed Lp(a) concentration

Group	Unadjusted model		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.88 (1.08, 3.12)	0.026	1.93 (1.02, 3.67)	0.043	2.06 (1.08, 3.93)	0.029
Quartile 3	2.46 (1.43, 4.25)	0.001	3.24 (1.65, 6.39)	<0.001	3.30 (1.66, 6.56)	<0.001
Quartile 4	2.18 (1.28, 3.72)	0.004	2.19 (1.12, 4.29)	0.022	2.22 (1.13, 4.38)	0.021

Model 1: adjusted for hypertension, hyperlipidemia, hypersensitive C-reactive protein. Model 2: adjusted for diabetes, hypertension, cardiovascular disease, hyperlipidemia, hypersensitive C-reactive protein. 25th, 50th, and 75th percentile cut-off points for corresponding Lp(a) are 4.5, 11.2, and 24.3 mg/dL, respectively.

the China Kadoorie Biobank (CKB) nested case-control study showed no significant association between Lp(a) and ischemic stroke in a sample of 32,869 incident ischemic stroke cases (14). It should be noted that the female rate in the ischemic group was higher in the CKB study, which might reduce the intergroup differences because of gender differences of the association between Lp(a) and ischemic stroke. Overall, the different conclusions of studies assessing Lp(a) and ischemic stroke risk might be due to differences in study design, definition of vascular end points, and participant sampling. Another factor related to the discrepancy between these results is the long-term storage of samples, since the Lp(a) measurement could be less reliable if samples are stored for longer than 6 weeks (4).

Mechanisms underlying the effect of Lp(a) on vascular diseases remain unclear and require further research. Nevertheless, the number of studies that have explored the correlation between ischemic subtypes and Lp(a) is limited. It has been reported that serum Lp(a) is significantly higher in large-artery atherosclerosis compared with other stroke subtypes (15,16). Additionally, the association between large-artery atherosclerosis subtypes of ischemic stroke and Lp(a) has been supported by genetic variant analysis of the Lp(a) related gene, *LPA* (4). However, we were unable to stratify our patient group by ischemic stroke subtypes due to limitations in our data collection.

Most previous studies have focused on ischemic stroke or unclassified stroke. Our study also investigated the effect of Lp(a) on hemorrhagic stroke; however, the literature offers mixed results, ranging from negative to positive associations between Lp(a) and hemorrhagic stroke. Consistent with our results, a multicenter case-control study in Chinese patients with 499 events found increased Lp(a) levels led to a 1.64-fold increase (95% CI: 1.21–2.21) in the risk of hemorrhagic stroke (17). In contrast, results from a population-based prospective cohort study with 84 hemorrhagic stroke events suggest that decreased Lp(a) may be a predictive marker for future cerebral hemorrhage (18). A different study has reported no significant association between Lp(a) levels and hemorrhagic stroke (14). Furthermore, the Emerging Risk Factors Collaboration concluded that there was no significant association between Lp(a) and hemorrhagic stroke (adjusted RR: 1.06, 95% CI: 0.90–1.26) (9). The limited number of hemorrhagic events included in these studies might be a contributing factor for the inconsistent results. In addition, the causes of cerebral hemorrhage are varied and no study has detected a relationship with the stratification of hemorrhagic types, which might be another contributing factor.

In this study, we observed that the concentration of Lp(a) had a greater effect on ischemic and hemorrhagic stroke in men. The same trend was also observed in previous studies assessing ischemic stroke (10,19). This might be due to genetically predetermined differences in Lp(a) levels between sexes. Moreover, most studies did not adjust for differences in living habits, including smoking and dietary habits between the sexes. Studies that take into account sex differences in the association between Lp(a) and hemorrhagic stroke are lacking. Nonetheless, consistent with previous findings, we found a more pronounced association between Lp(a) and stroke risk in younger patients (10). A meta-analysis of four case-control studies also showed a positive association between elevated Lp(a) and stroke in children (OR: 4.24, 95% CI: 2.94–6.11) (20). This finding might be due to a lower absolute risk in younger patients was lower. Additionally, Lp(a) levels are closely linked to genetic factors (4), while environmental risk factors play an increasingly important role in stroke

with age. Thus, Lp(a) might be a potential risk factor for stroke in young adults.

Compared with observational studies, studies assessing whether the therapeutic lowering of Lp(a) reduces stroke risk could provide powerful evidence. However, this is not easy because effective, targeted Lp(a)-lowering therapies are limited. The currently available therapies for lowering Lp(a) include lipid apheresis, niacin, inhibitors of proprotein convertase subtilisin/kexin type 9, and cholesteryl ester transfer protein inhibitors (21). Antisense oligonucleotides targeting Apo(a), including IONIS-APO(a)Rx and IONIS-APO(a)LRx, have shown reductions in Lp(a) by ~65% and 92–99%, respectively (22). A further study selected patients with high Lp(a) levels, and reported that isolated lowering of Lp(a) could lower the incidence rate of cardiovascular events (23). Further prospective studies are required to evaluate this therapeutic effect on stroke risk.

There are several limitations in our study. Firstly, as a case-control study, the results can only show associations between Lp(a) levels and stroke; however, and they do not allow any assessment of causality. Secondly, although the concentration of Lp(a) is relatively stable throughout life (24), its concentration collected after a stroke may not accurately reflect pre-stroke exposure. Thirdly, the time intervals between Lp(a) measurement and stroke were differed between individuals. We were also limited by the selection of controls, who were recruited from the health examination center rather than a population-based sample. Fourthly, studies have reported that statins increase Lp(a) levels (25), which could be a bias of this study. Lastly, this study did not analyze the effect of Lp(a) concentration on the risk of different ischemic stroke types according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST), which might diminish the actual absolute risk and limit the detection of a pathogenic mechanism for Lp(a).

In conclusion, our study found that the concentration of serum Lp(a) was independently associated with both ischemic and hemorrhagic stroke risk, especially among younger individuals in a Chinese Han population. Further, this effect was only significant among men. A powerful and specific Lp(a) lowering method is required to demonstrate causality and guide methods of stroke prevention.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethics Committee of the PUMCH who waived the requirement for informed consent because this study used anonymized data in a retrospective analysis.

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Supplementary

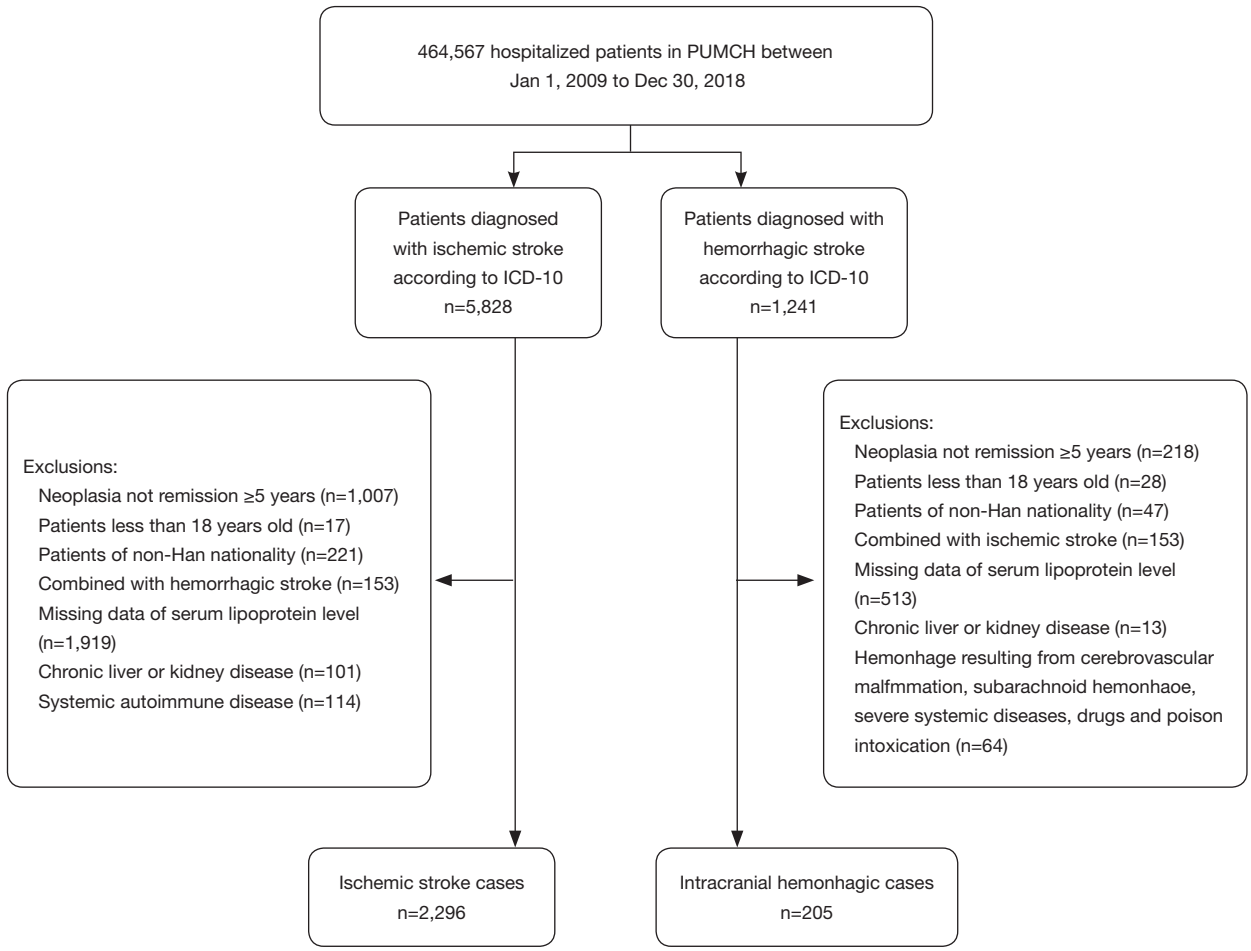

Figure S1 The data flow chart of the current study.

Table S1 Comparation of characteristics between ischaemic group and hemorrhagic stroke group

Characteristics	Ischemic stroke (n=1,953)	Hemorrhagic stroke (n=196)	P value
Age, years	62.38±11.82	57.90±13.78	<0.001
Male, %	64.98	55.61	<0.001
BMI, kg/m^2	25.21±3.67	24.46±3.64	0.066
Hypertension, %	69.53	60.2	0.007
DM, %	39.99	22.45	<0.001
CAD, %	23.70	12.8	0.005
Hyperlipidaemia, %	68.00	62.76	0.135
TC, mmol/L	4.09 (3.41, 4.92)	4.2 (3.77, 5.28)	<0.001
TG, mmol/L	1.29 (0.92, 1.82)	1.42 (0.96, 2.10)	0.123
HDL-c, mmol/L	0.99 (0.84, 1.19)	1.00 (0.80, 1.22)	0.815
LDL-c, mmol/L	2.41 (1.83, 3.07)	2.71 (2.16, 3.37)	<0.001
Lp(a), mg/dL	12.20 (5.80, 24.80)	14.40 (11.75, 18.45)	0.696
HCY, μmol/L	14.20 (11.40, 18.65)	13.05 (7.25, 25.33)	0.212
hsCRP, mg/dL	1.74 (0.68, 4.75)	3.26 (1.10, 14.71)	<0.001

Continuous variables presented as mean ± standard deviation or median (Q1, Q3).