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Serum lipoprotein (a) is associated with increased risk of stroke in Chinese adults: A prospective study

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HIGHLIGHTS

- The 5.1-year incidence of stroke was higher in participants with elevated serum Lp (a).
- Participants with higher serum Lp (a) levels had lower event-free survival rate in this Chinese population.
- Serum Lp (a) is associated with increased risk of incident stroke in this Chinese population.

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Keywords:
Prospective cohort study
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ABSTRACT

Background and aims: Epidemiological evidence on the association between elevated lipoprotein (a) (Lp (a)) with risk of stroke remains inconsistent. We aimed to investigate the association between serum Lp (a) level and the risk of stroke among middle-aged and elderly Chinese.

Methods: A community-based prospective cohort study of 8500 participants aged 40 years or older was conducted in Jiading district, Shanghai, China, in 2010. The incident strokes were documented at follow-up visit during 2014–2015.

Results: During a mean follow-up of 5.1 years, 444 incident cases of stroke occurred. The incidences of stroke were 4.44%, 5.14% and 6.14% from the lowest to the highest serum Lp (a) tertile, respectively. A significant association between serum Lp (a) tertile and the risk of incident stroke was observed (p for trend < 0.05). Compared with individuals in the lowest tertile of serum Lp (a), the multivariable adjusted hazards ratio (HR) and 95% confidence interval (CI) for incident stroke in Lp (a) tertile 3 were 1.34 (1.06–1.70).

Conclusions: Serum Lp (a) concentration was associated with increased risk of incident stroke in Chinese adults.

1. Introduction

Leading by coronary heart disease and cancer, stroke is the third most common cause of death in most Western countries [1,2], however, it has been the leading cause of death in China in recent years [3]. The age-standardized prevalence, incidence and mortality rates in China in 2012–2013 were 1115 per 100,000 people, 247 and 115 per 100,000 person-years, respectively. Applying to the whole population, there are approximately 11.1 million stroke survivors, 2.4 million new stroke and 1.1 million stroke-related death of stroke annually [4]. Pathologically, most of the strokes in the Chinese population are ischemic stroke (69.6%) [4]. As one third of stroke patients remain dependent in their daily routine, stroke places a tremendous financial burden on health resources in China [5]. Thus, prevention and control of risk factors are thought to be pivotal in reducing the incidence of stroke.

Although age and family history are considered to be major non-modifiable risk factors, there are related modifiable risk factors associated with risk of stroke, for example, hypertension [6], smoking, physical

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activity and diet [7]. In addition, some studies found that there is an association of traditional lipids, such as higher total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) [8–16], lower high-density lipoprotein cholesterol (HDL-C) [12,17,18], with increased risk of stroke.

Lipoprotein (a) (Lp (a)) is an LDL-like particle with glycoprotein apolipoprotein A (apo(a)) bound covalently to apolipoprotein B-100 (apoB-100) [19]. It mediates atherogenicity by its LDL moiety, which has a similar proportion of cholesterol content to traditional LDL particles. Furthermore, Lp (a) induces pro-inflammatory responses by accumulation of oxidized phospholipids [20] and potentially exerts prothrombotic effects by the plasminogen-like apo(a) moiety [21].

Previous studies have demonstrated that Lp (a) is associated with increased risk of stroke in Western countries [22–26]. The ARIC study found that a high Lp (a) concentration was associated with a higher incidence of ischemic stroke in Blacks and white women, but not in white men [22], and they also found the association of Lp (a) levels with increased ischemic stroke risk was primarily among individuals without atrial fibrillation, but not in those with atrial fibrillation. Otherwise, several meta-analysis revealed that elevated Lp(a) was a risk factor for incident stroke [23–25] and coronary heart disease [24].

However, less evidence was obtained in the Chinese population. One case-control study conducted among ethnic Chinese revealed that baseline Lp (a) concentration was significantly associated with risk of stroke [27], while another prospective cohort study indicated null relationship [28]. Therefore, in the current study, we further examined the association between serum Lp (a) level and the risk of stroke among middle-aged and elderly Chinese adults with an average follow-up of 5.1 years.

2. Patients and methods

2.1. Study population

A total of 10,375 residents aged 40 years or older were randomly recruited from Jia Ding District, Shanghai, China, between March and August 2010.10,359 participants were included after 16 individuals with missing data on serum Lp (a) and 288 individuals with pre-existing history of stroke were excluded. During August 2014 and May 2015, participants were asked to return for a follow-up visit. In prospective analysis, 35 participants had died and 1536 were lost to follow-up, which subsequently left 8500 participants in the final analysis.

The study protocol was approved by the Institutional Review Board of the Rui-jin Hospital affiliated to Shanghai Jiao-Tong University School of Medicine. Written informed consent was obtained from each participant before data collection.

2.2. Data collection and measurements

A standard questionnaire was used to obtain the information about demographic characteristics, education, lifestyle and history of chronic disease with face-to-face interviews by the trained investigators. The current smoker or drinker was defined as smoking cigarettes or consuming alcohol regularly in the past 6 months. Physical activity at leisure time was estimated using the short form of the International Physical Activity Questionnaire (IPAQ-SF) and ≥150 min of moderate or vigorous activity per week was defined as positive physical activity [29].

Body height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, while participants were wearing light clothes and no shoes. Body mass index (BMI) was calculated as body weight in kilograms divided by body height squared in meters (kg/m^2). Blood pressure was measured with an automated electronic device (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China) at a non-dominant arm, 3 times consecutively, with 1-min interval each, after at least 5 min of rest in a seated position. The three readings of systolic BP (SBP) and diastolic BP (DBP) were averaged for analysis.

All participants underwent a 75-g oral glucose tolerance test (OGTT) after an overnight fast of more than 10 h. Blood specimens for the glucose test were collected using vacutainers containing the anticoagulant sodium fluoride, and were centrifuged on site within 2 h of collection. Fasting plasma glucose (FPG), OGTT 2-h plasma glucose (2h-PG) were measured using the glucose oxidize method on an auto-analyzer (Modular P800; Roche, Basel, Switzerland). TC, LDL-c, HDL-c and triglycerides (TG) were determined using a chemiluminescence method with the auto-analyzer (Modular E170; Roche, Basel, Switzerland). Serum Lp (a) levels were measured by using murine monoclonal antibody (20–037, S0710-1; Jiemen BIO-TECH, Shanghai, China) by Latex enhanced immune transmission turbidimetry. For the laboratory test of serum Lp(a), the coefficient of variation (CV) within group was 8%, and the CV between groups was 10%. HbA1c was measured by high-performance liquid chromatography (Variant II Hemoglobin Testing System, Bio-Rad Laboratories, Hercules, California).

2.3. Diagnosis of diabetes, hypertension and stroke

According to the 1999 World Health Organization (WHO) criteria [30], diabetes was defined as FPG ≥ 7.0 mmol/L or 2h-PG ≥ 11.1 mmol/L or self-reported, with the use of anti-diabetic medications. Impaired glucose regulation (IGR) was diagnosed in participants who had no self-reported diabetes or hypoglycemic therapies but had a FPG ranging from 6.1 to 6.9 mmol/L or 2h-PG ranging from 7.8 to 11.0 mmol/L. Participants who were without diabetes or IGR were defined as having normal glucose regulation (NGR). Hypertension (HBP) was defined as SBP ≥140 mmHg or DBP ≥90 mmHg or the use of blood pressure lowering medications. Dyslipidemia was defined as TC ≥ 6.22 mmol/L or LDL-c ≥ 4.14 mmol/L or TG ≥ 2.26 mmol/L or HDL-c < 1.04 mmol/L. We collected the information about self-reported stroke by the questionnaire at follow-up visit. In this Shanghai Jiading Community, the trained staff collected the information about stroke using the same questionnaire with the REACTION study [31,32]. The question was open-ended: “Has a doctor or other health professional ever told you that you have stroke between baseline to follow-up visit. If “Yes”, please provide the date of diagnosis.” In fact, we previously performed validation of the self-reported incident cardiovascular disease (including coronary heart disease, stroke and myocardial infarction) in Shanghai Youyi Community, one of the 25 communities from REACTION study. The medical records from the relevant hospitalizations were reviewed by 2 physicians, who were blinded to the self-reported data, classified the cases as definite, questionable, or misdiagnosed, and the validation rate of stroke was 91.07% [31,32].

2.4. Statistical analysis

Data on basic characteristics are presented as the mean ± SD or as the median with interquartile range for continuous variables and as proportions for categorical variables. One-way analysis of variance (ANOVA) and the χ^2 test were used for comparisons of continues and categorical variables between groups, respectively. The study participants were divided into three groups according to tertiles of serum Lp (a) concentrations. The event-free survival rates among groups were estimated by the Kaplan-Meier method and compared by the log-rank test. Relative risk regression was used to evaluate the association of serum Lp (a) concentrations and the risk of incident stroke. Potential confounders measured at baseline were adjusted for in the analysis. Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, smoking and drinking status, education, physical activity. Model 3 was further adjusted for SBP, HDL-c and TG based on Model 2. Significance tests were two-tailed and a $p < 0.05$ was stated as statistically significant. P-values for trends through tertiles of serum Lp (a) concentrations were calculated in regression analyses using Lp (a) as an ordinal variable. In addition, we performed stratified analysis on the association between serum Lp (a) concentrations and incident stroke according to sex, age, BMI, smoking status, drinking status, with or without HBP and dyslipidemia, and with different glucose metabolism status: NGR, IGR and diabetes.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and SPSS version 21.0 (IBM Corp., Armonk, New York).

Table 1
Baseline characteristics of the study participants according to serum lipoprotein (a) tertiles.

	Total population (n = 8500)	Serum Lp (a) tertiles			*p* for trend
		Tertile 1 (n = 2795)	Tertile 2 (n = 3016)	Tertile 3 (n = 2689)	
Lp (a), mg/dL	21.0 ± 15.5	6.60 ± 2.68	18.98 ± 4.66	38.22 ± 14.67	< 0.0001
Age, yr	58.4 ± 9.5	57.7 ± 9.5	58.6 ± 9.5	58.9 ± 9.6	< 0.0001
Male, n (%)	3216 (37.8)	1189 (42.5)	1107 (36.7)	920 (34.2)	< 0.0001
BMI, kg/m^2	25.1 ± 3.3	25.5 ± 3.3	25.1 ± 3.3	24.8 ± 3.2	< 0.0001
Current smoker, n (%)	348 (4.1)	109 (3.9)	127 (4.2)	112 (4.2)	0.62
Current drinker, n (%)	138 (1.6)	49 (1.8)	51 (1.7)	38 (1.4)	0.32
Physical activity (moderate to vigorous), n (%)	1216 (14.3)	407 (14.6)	422 (14.6)	387 (14.4)	0.85
Education status (high school or above), n (%)	1715 (20.2)	601 (21.5)	624 (20.7)	490 (18.2)	0.003
Family history of CVD, n (%)	606 (7.1)	211 (7.6)	211 (7.0)	184 (6.8)	0.31
SBP, mmHg	141.3 ± 20.1	142.4 ± 20.2	140.5 ± 19.9	141.1 ± 20.1	0.01
DBP, mmHg	82.9 ± 10.4	83.6 ± 10.4	82.5 ± 10.2	82.8 ± 10.4	0.003
FPG, mmol/L	5.56 ± 1.53	5.68 ± 1.70	5.50 ± 1.47	5.49 ± 1.37	< 0.0001
2h-PG, mmol/L	8.21 ± 4.32	8.63 ± 4.68	8.11 ± 4.20	7.89 ± 4.02	< 0.0001
HbA1c, %	5.83 ± 0.93	5.89 ± 1.04	5.81 ± 0.90	5.79 ± 0.86	< 0.0001
TG, mmol/L	1.36 (0.97–1.94)	1.50 (1.03–2.26)	1.34 (0.96–1.84)	1.29 (0.94–1.77)	< 0.0001
TC, mmol/L	5.34 ± 1.00	5.16 ± 1.00	5.32 ± 0.95	5.56 ± 1.01	< 0.0001
HDL-C, mmol/L	1.33 ± 0.32	1.28 ± 0.32	1.34 ± 0.31	1.38 ± 0.32	< 0.0001
LDL-C, mmol/L	3.19 ± 0.87	2.97 ± 0.83	3.21 ± 0.83	3.40 ± 0.89	< 0.0001

Data are expressed as mean ± SD, median [interquartile range] or as n (%).
Lp (a), lipoprotein (a); BMI, body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2h-PG, postprandial plasma glucose; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein.

3. Results

3.1. Characteristics of the study participants

Baseline characteristics of the study population are shown in Table 1. The mean age of the study population was 58.4 ± 9.5 years, 37.8% participants were men. The mean serum Lp (a) level of the cohort study population was 21.0 ± 15.5 mg/dL, and the mean serum Lp (a) level was 6.60 ± 2.68 mg/dL, 18.98 ± 4.66 mg/dL, 38.22 ± 14.67 mg/dL from Lp (a) tertile 1 to tertile 3, respectively. With the increment of serum Lp (a) concentrations, participants tended to be older, with lower levels of BMI, SBP, DBP, FPG, 2h-PG, HbA1c, TG, with higher levels of TC, HDL-C, LDL-C (all p for trend < 0.05; Table 1). Moreover, the proportion of male participants and participants with high school or above decreased with serum Lp (a) tertiles (all p for trend < 0.05). There was no significant difference between serum Lp (a) levels and the proportion of current smoker, current drinker, and those who had moderate to vigorous physical activity and family history of CVD (all p for trend > 0.05).

3.2. Serum Lp (a) concentration and the risk of incident stroke

During a mean of 5.1 years follow-up, among 8500 participants without pre-existing stroke at baseline, 444 (5.22%) developed incident stroke. From the lowest to highest serum Lp (a) tertile, the incidence of stroke was 4.44%, 5.14% and 6.14%, respectively. Kaplan-Meier analysis (Fig. 1) showed that participants in the Lp (a) tertile 3 had the lowest event-free survival rate among the three groups [0 < Lp (a) < 11 mg/dL, 11 ≤ Lp (a) < 26 mg/dL and 26 ≤ Lp (a) < 162 mg/dL)] (log-rank p < 0.05), while there was no significant difference between that of Lp (a) tertile 2 and tertile 1 groups (log-rank p > 0.05). Cox regression analysis suggested that serum Lp (a) concentrations were significantly associated with increased risk of incident stroke. In the unadjusted model, the hazard ratios (HRs) and 95% confidence intervals (CIs) for serum Lp (a) tertile 2 and tertile 3 *vs*. tertile 1 as the reference were 1.16 (0.91–1.47) and 1.38 (1.09–1.74), respectively (p for trend < 0.05; p for tertile 3 *vs*. tertile 1 = 0.01; Table 2). After adjustment for age, sex, BMI, smoking and drinking status, education status, physical activity and family history of CVD, similar results were observed, HRs and 95% CIs for tertile 3 of serum Lp (a) concentrations *vs*. tertile 1 were 1.31 (1.04–1.66) (p = 0.02; Table 2). After further adjustment for SBP, HDL-C and TG, based on model 2, the results did not change significantly (Table 2). HRs and 95% CIs for serum Lp (a) tertile 3 *vs*. tertile 1 as reference was 1.34 (1.06–1.70) (P = 0.02; Table 2).

3.3. Stratified analysis for serum lp (a) concentrations and stroke risks according to baseline characteristics

In addition, we conducted the stratified analysis for serum Lp (a) concentrations and incident stroke according to sex, baseline age and BMI, current smoking/drinking or not, baseline status with hypertension or without, different glucose metabolism (NGR, IGR and DM), and dyslipidemia or without (Fig. 2). The model was fully adjusted for age, sex, BMI, smoking and drinking status, education status, physical activity, family history of CVD, SBP, HDL-C and TG. There were no significant differences between serum Lp (a) concentrations and incident stroke in women, those whose age was equal to or more than 60 years, those whose BMI was less than 25 kg/m^2, non-current smoker and current drinker, individuals without hypertension and dyslipidemia, those with diabetes or NGR at baseline (all p for lp (a) tertile 3 *vs*. tertile 1 ≥ 0.05). On the other hand, serum Lp (a) concentrations were significantly associated with an increased risk of incident stroke in a subgroup of men [HR (95%CI): 1.94 (1.30–2.91)], those aged ≤60 years [HR (95%CI): 1.48 (1.02–2.14)], those with BMI ≤ 25 kg/m^2 [HR (95%CI): 1.76 (1.26–2.45)], current smoker [HR (95%CI): 2.19 (1.24–3.87)] and non-current drinker [HR (95%CI): 1.31 (1.03–2.68)], those with hypertension [HR (95%CI): 1.32 (1.01–1.72)], those with dyslipidemia [HR (95%CI): 1.65 (1.13–2.40)], those with IGR [HR (95%CI): 2.29 (1.33–3.94)] at baseline (all p for lp (a) tertile 3 *vs*. tertile 1 < 0.05). No interactions have been detected in the stratified analysis.

4. Discussion

In this prospective study, we found that serum Lp (a) concentrations were positively and independently associated with an increased risk of incident stroke in Chinese adults. To our knowledge, this is the first prospective cohort study demonstrating a positive association between serum Lp (a) concentrations and the risk of incident stroke in the Chinese population.

Lp (a) is one of the most complicated polymorphic lipoproteins firstly reported in 1963 [33–35]. Structurally, Lp (a) particle has an exclusive glycoprotein, apo(a), which is attached to the apoB-100 by a

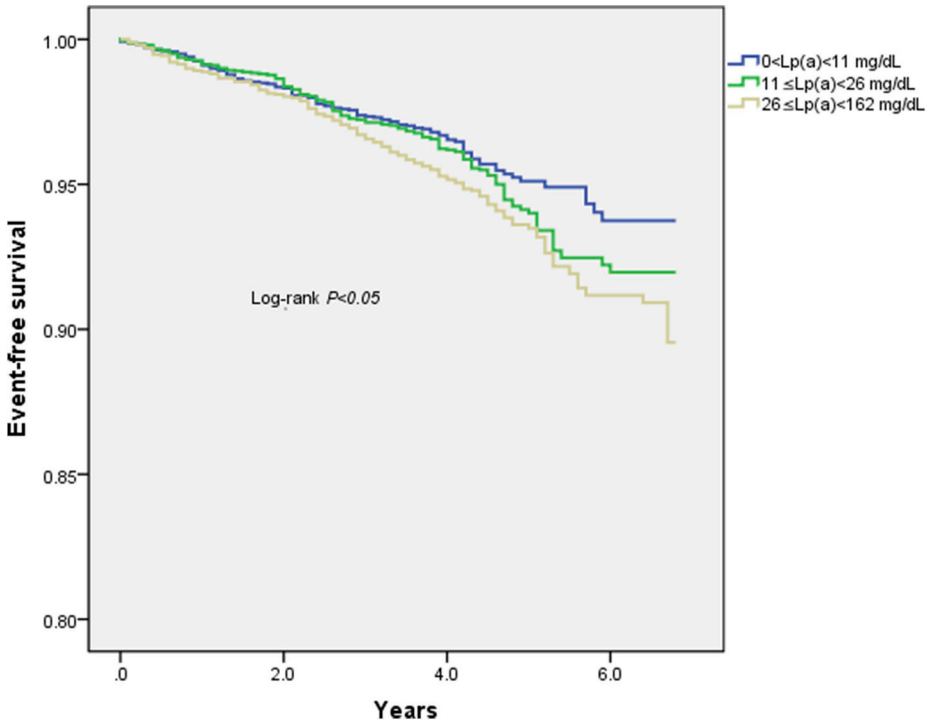

Fig. 1. Kaplan-Meier analysis according to baseline serum Lp (a) tertiles.
Lp (a), lipoprotein (a).

Table 2
Hazard ratios (95% confidence intervals) for incident stroke according to baseline serum Lp (a) tertiles.

	No. of cases/No. of participants	Incidence (%)	Person-years	Model 1	*p* value	Model 2	*p* value	Model 3	*p* value
Tertile 1	124/2795	4.44	12,828	1.00		1.00		1.00	
Tertile 2	155/3016	5.14	13,857	1.16 (0.91–1.47)	0.23	1.13 (0.89–1.44)	0.30	1.16 (0.92–1.48)	0.22
Tertile 3	165/2689	6.14	12,378	1.38 (1.09–1.74)	0.01	1.31 (1.04–1.66)	0.02	1.34 (1.06–1.70)	0.02
***p* for trend**				0.007		0.02		0.03	

Model 1. Unadjusted.
Model 2. Model 1 further adjusted for age, sex, BMI, smoking and drinking status, education status, physical activity, family history of CVD.
Model 3. Model 2 further adjusted for SBP, HDL-C and TG.

single disulfide bond [36]. In general, apo(a) isoform size is inversely related to Lp (a) concentration in most populations [37]. Thus, the presence of apo(a) gives unique synthetic and catabolic properties to Lp (a). Because of the structural similarity of apo(a) to plasminogen, Lp (a) inhibits fibrinolysis by competing with plasminogen binding to cells. Consequently, plasminogen activation, plasmin generation, and fibrinolysis are impaired [38,39]. Lp (a) can also bind to macrophages by a high-affinity receptor, which promotes foam cell formation and cholesterol deposition in atherosclerotic plaques [40]. Given to the combined pro-thrombotic and pro-atherogenic properties, and anti-fibrinolytic and lipid transport functions of Lp (a), Lp (a) may increase CVD risk and its development and progression. Lp (a) has been found within the intima of human arteries and vein grafts of re-operated coronary artery bypass patients [41–43]. The entry of Lp (a) particles into the intimal lining of arteries depends on Lp (a) concentration in the plasma, Lp (a) particle size, blood pressure, and arterial permeability [44]. Lp (a) can be oxidized and degraded or aggregated [41], and once it is oxidized, it is more readily taken up by macrophage scavenger receptors [45] and preferentially trapped in the arterial wall compared to LDL particles. Above all, increased Lp (a) levels may be leading to the higher risk of incident stroke.

Evidence from population studies on the association of Lp (a) levels and the risk of stroke remains controversial. A case-control study conducted by Sun et al. revealed that Lp (a) levels were significantly higher in cases than in controls, leading to a 97% increased risk for overall stroke [27]. Furthermore, a meta-analysis, including 9 prospective studies found, comparing high with low Lp(a) levels, the pooled estimated RR was 1.29 (95% CI, 1.06–1.58) for ischemic stroke [25]. However, results from the EPIC-Norfolk Prospective Population study demonstrated no association between Lp (a) and ischemic stroke [46]. Compared to the EPIC-Norfolk Prospective Population study, a lower proportion of male gender and current smoker, higher mean SBP level (141.3 mmHg *vs*. 134.6 mmHg) and different ethnicity in the current study might partially explain the potential causes for the different results between the two prospective population studies.

In the Chin-Shan Community Cardiovascular Cohort Study, a prospective study of 3484 ethnic Chinese (47% men; age from 35 to 97 years) exploring the association of Lp (a) and cardiovascular disease [28], with a median follow-up of 13.8 years, baseline Lp (a) concentration by quartile was not significantly associated with incident stroke. Compared to the Chin-Shan Community Cardiovascular Cohort Study, our study had a much larger sample size, a little higher of mean age, a lower proportion of male individuals, and we found a significant relation of serum Lp (a) concentrations to incident stroke.

In addition, a stratified analysis revealed a relation of Lp (a) levels and incident stroke in men but not in women in our study, which is consistent with a case-control study of young adults (18–55 years), consisting of 100 cases of ischemic stroke and 100 matched controls, suggesting that the relationship of Lp(a) concentration with stroke remains significant in men (OR, 3.55; 95% CI, 1.33–9.48, for the

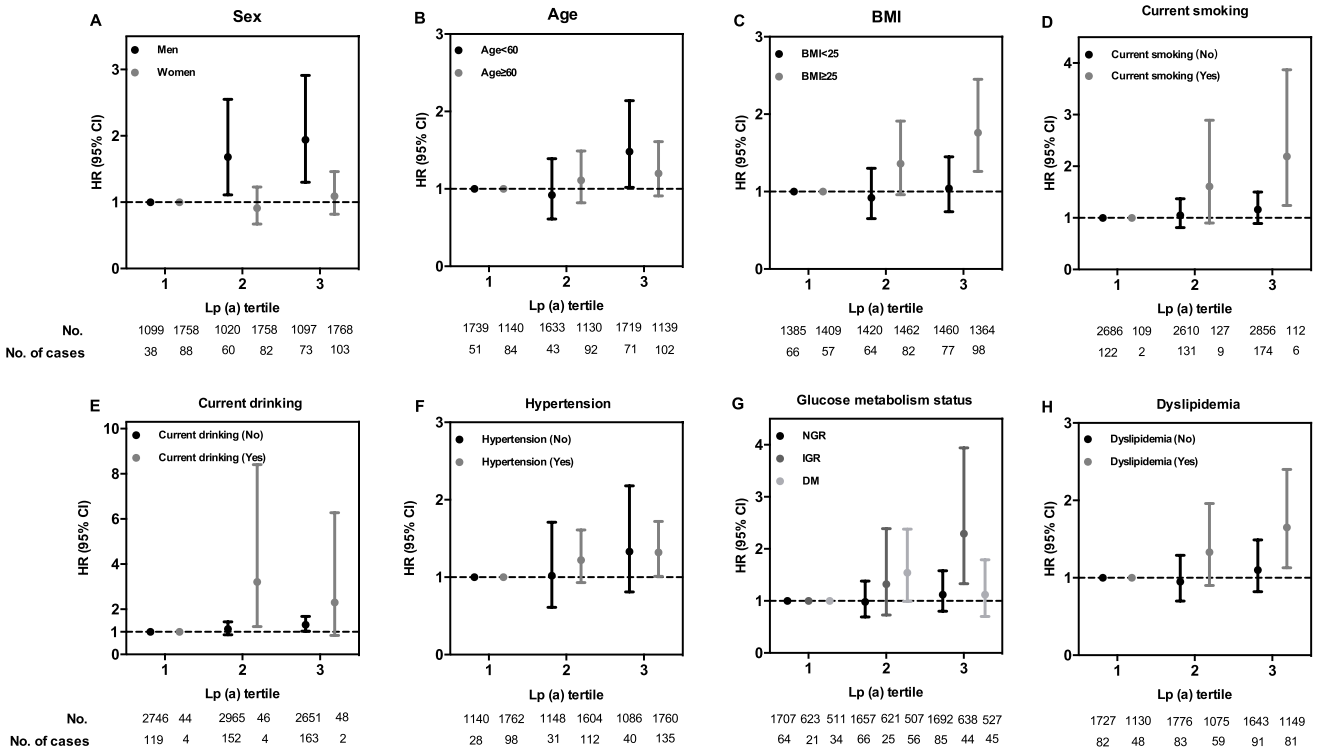

Fig. 2. Hazard ratios (95% confidence intervals) for incident stroke of Lp (a) tertiles stratified by sex (A), age (B), BMI (C), current smoking (D), current drinking (E), hypertension (F), glucose metabolism status (G) and dyslipidemia (H).
The model was adjusted for age, sex, BMI, smoking and drinking status, education, physical activity, family history of CVD, SBP, HDL-C and TG. Lp (a), lipoprotein (a); BMI, body mass index.

comparison of the highest and lowest tertile) but not in women (OR, 0.42; 95% CI, 0.14–1.26) [47]. On the one hand, it is well-documented that the incidence of stroke is higher in men than women in all age groups, and women are, on average, older than men when they suffer their first stroke [48]. On the other hand, current smokers are almost men in our study population, and previous studies showed that smoking, high cholesterol levels and hypertension were associated with vessel atherosclerosis [49,50], a certain independent risk factor for incident stroke, which is consistent with our stratified analysis that the association of Lp (a) with incident stroke was statistically positive among men, current smokers, and those who with hypertension or dyslipidemia.

Our study has several limitations. First, the 5.1 year follow-up may not be long enough to fully capture the risk of incident stroke. A prospective cohort study with a longer follow-up period is necessary to further investigate this hypothesis. Second, the study was conducted in a middle-aged and elderly Chinese population, which may not be representative of the general population in ethnic Chinese. Third, laboratory data were only collected at baseline, thus the predictive value of changes in serum Lp (a) concentrations during follow-up for incident stroke cannot be evaluated. Fourth, the stroke in this study was self-reported, which might lead to inevitable recall bias about the events of stroke and the precise date of the diagnosis, and we could not classify strokes as ischemic or hemorrhagic. Although a previous epidemiological study showed that about 69.6% stroke were ischemic in China [4], and, in a multicenter case-control study, the association of Lp (a) and risk of stroke was observed both in ischemic and hemorrhagic stroke in China [27], it will be interesting to assess the association between Lp(a) and risk of hemorrhagic or ischemic strokes in a prospective cohort study in the future work.

In conclusion, our study found that serum Lp (a) concentration is an independent risk factor for incident stroke, and this association was independent of conventional lipid profiles, such as TG and HDL-C, firstly verified in a Chinese population. Except traditional lipids, the middle-aged and elderly Chinese population should pay more attention to their Lp (a) level, for the purpose of stroke prevention. Furthermore, prospective studies in ethnic Chinese, with a longer follow-up period and wider age range, should be conducted to capture reliable evidence to guide the management and prevention of stroke.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

JZ, RD, KP and YC had access to all data and take responsibility for its integrity and analysis. KP conceived the hypotheses and analyses. JZ drafted the paper. RD provided statistical analysis. JZ, RD and KP collected the data. SW and WW revised the manuscript. YC, XW, CH, ML, YX, MX, JL and YB refined interpretation and the final manuscript. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Appendix A. Supplementary data

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