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ORIGINAL ARTICLE

BMI modifies the association between serum HDL cholesterol and stroke in a hypertensive population without atrial fibrillation

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Abstract

Purpose Both high-density lipoprotein cholesterol (HDL-C) and body mass index (BMI) have an impact on the prevalence of stroke. However, it is unclear whether BMI can modify the relationship between HDL-C and stroke. Therefore, we aimed to assess the effect of the BMI on the association between HDL-C and stroke in a hypertensive population without atrial fibrillation (AF).

Methods We analyzed data of 10,925 hypertensive patients without AF from the Chinese Hypertension Registry Study. BMI was categorized as <24 and ≥ 24 kg/m^2. Multivariate logistic regression and smooth curve fitting (penalized spline method) were used to analyze the association between HDL-C and stroke in different BMI groups. Subgroup analysis and interaction tests were used to explore the effect of other variables on this relationship.

Results The results showed a negative association between HDL-C and stroke in the BMI <24 kg/m^2 group, but HDL-C was not associated with stroke in the BMI ≥ 24 kg/m^2 group. In the BMI <24 kg/m^2 group, each 1 mmol/L increase in HDL-C was associated with a 50% decreased risk of stroke [odds ratio (OR) 0.50, 95% confidence interval (CI) 0.38–0.66]. No significant relationship between HDL-C and stroke was observed in the BMI ≥ 24 kg/m^2 group (OR 0.73, 95% CI 0.49–1.10). There was a significant interaction between BMI and HDL-C in regard to the prevalence of stroke in the hypertensive population without AF ($P_{\text{Interaction}} = 0.027$).

Conclusions We found an inverse association between HDL-C and stroke only in the BMI <24 kg/m^2 group. The finding suggested that BMI could modify the association between HDL-C and stroke in hypertensive populations without AF.

Keywords High-density lipoprotein cholesterol · Stroke · Body mass index · Hypertension · Atrial fibrillation

Introduction

Stroke has become the leading cause of disability and death, with over 2 million patients experiencing stroke annually in China [1]. It is worth noting that the most common and controllable risk factors for stroke include hypertension, atrial fibrillation (AF), dyslipidemia, diabetes, smoking and obesity [2]. Serum high-density lipoprotein cholesterol (HDL-C) is synthesized by the liver and can be combined with cholesterol deposited in peripheral blood vessels and then discharged from the body [3]. Many studies have shown that higher levels of HDL-C can significantly reduce the risk of cardiovascular disease (CVD) [4–6]. However, studies exploring the relationship between HDL-C and stroke are limited and inconsistent. Some previous studies have shown that higher levels of HDL-C were significantly associated with lower stroke risk [7–9], while other studies showed that the levels of

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HDL-C had no significant association with stroke [10, 11]. In contrast, a recent meta-analysis reported that the high levels of HDL-C might be associated with a higher risk of stroke [12]. Hence, this report raised concerns among researchers about the claim that treatments to increase HDL are beneficial for stroke.

Body mass index (BMI) is calculated as measured body weight (kg) divided by measured height squared (m^2), which can reflect the degree of obesity [13]. Previous studies showed that elevated BMI could lead to a reduction in HDL-C levels [14, 15]. When BMI status combined with HDL-C levels changes, it is unknown whether the risk of stroke changes with it. In addition, a previous study found that more than 75% of strokes were not caused by AF [1]. To our knowledge, few studies have reported the exact dose–response relationship between HDL-C and stroke in hypertensive populations without AF with different BMI status.

Therefore, we aimed to evaluate whether BMI modified the association between HDL-C and stroke in a hypertensive population without AF.

Materials and methods

Study design and participants

The study population was obtained from the China Hypertension Registry Study. Briefly, the study was a real-world, observational registry of hypertension, and the primary objectives were to establish a national registry of patients with hypertension, investigate the prevalence and treatment of hypertension in China and assess the related factors affecting its prognosis. The inclusion criteria were as follows: (1) 18 years of age or older; (2) hypertension defined based on the usual 140/90 mmHg threshold, self-report history of hypertension, or the use of antihypertensive drug(s) at baseline [16]; and (3) signed informed consent. The exclusion criteria included the following: (1) psychological or nervous system impairment resulting in an inability to demonstrate informed consent; (2) unable to be followed-up according to the study protocol, or plans to relocate in the near future; or (3) those patients who were not suitable for inclusion or for long-term follow-up as assessed by study physicians. From March 2018 to August 2018, we recruited a total of 14,268 study participants in Wuyuan, Jiangxi Province, China as our study population and analyzed data from 10,925 of them.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Anhui Medical University Biomedical Institute. Informed written consent was obtained from all patients before their enrollment in this study.

Measurement of BMI and diagnosis of AF

The heights and weights of study participants were measured by trained staff members using standardized equipment and following standard procedures in strict accordance with the guidelines. BMI was calculated by dividing the weight (kg) by the squared height (m^2). According to the weight management guidelines of China, BMI was divided into two groups for analysis: underweight and normal weight (<24 kg/m^2) or overweight and obese (≥ 24 kg/m^2) [15]. The median BMI of our study population was 24 kg/m^2. Hence, BMI status was classified using 24 kg/m^2 as the cut-off point in our study. All subjects were examined by electrocardiogram (ECG). Each ECG report was analyzed by 2 doctors who were certified as medical practitioners and received strict training. AF was defined as the AF detected in the ECG record [17].

Laboratory assays

All the study subjects were told one day in advance that fasting venous blood samples would be collected the next morning. After an overnight fast, venous blood samples were obtained from all study participants. Next, the blood samples of all the subjects were collected, frozen and transported to the Biaojia Biotechnology Laboratory for analysis in Shenzhen, China. Serum concentrations of HDL-C (mmol/L), total cholesterol (TC, mmol/L), triglycerides (TGs, mmol/L), low-density lipoprotein-cholesterol (LDL-C, mmol/L), estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2), aspartate aminotransferases (AST, U/L) and alanine transaminase (ALT, U/L) were measured using automatic clinical analyzers (Beckman Coulter, USA) and the laboratory staff were blind to the research protocol.

Stroke

The self-reported history of stroke was obtained through a questionnaire. Each study subject was asked: "Has a doctor ever told you that you have a stroke?". If the subject answered "yes", then the subject was asked to show the medical documents related to the stroke; if the discharge diagnosis on the medical documents was stroke, the subject was determined to be a stroke patient. If the subject did not carry the relevant medical certificate, then the subject was asked about when the stroke occurred, the symptoms, the imaging examination, the place of treatment, and the medications currently used to treat the stroke. Strokes included hemorrhagic and ischemic strokes, excluding transient ischemic attacks and secondary strokes due to tumors and trauma [18].

Covariates

Continuous variables included age (years), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and pulse (bpm), measured by electronic sphygmomanometers after the subjects had rested for 10 min. Except for sex (male, female), data for other categorical variables were obtained by standard questionnaire, including smoking (yes or no), alcohol consumption (yes or no), diabetes mellitus (yes or no), lipid-lowering drugs (yes or no), antiplatelet drugs (yes or no), antidiabetes drugs (yes or no), and antihypertensive drugs (yes or no).

Statistical analysis

Continuous variables are presented as the mean ± SD and categorical variables are presented as percentage (%). Considering that lipid-lowering drugs have a large effect on blood lipids, we also excluded subjects treated with lipid-lowering drugs. The population characteristics were described by BMI classification and HDL-C tertiles to explore the distribution of each interval. With HDL-C as an independent variable and stroke as the dependent variable, multivariate logistic regression analyses were used to assess the odds ratio (OR) and 95% confidence interval (CI) of the association between HDL-C and stroke in different BMI status. When HDL-C was used as a continuous or categorical variable according to clinical cut-off point [19] and quartiles, the association between HDL-C and stroke was analyzed by multivariate logistic regression analysis. Meanwhile, the *P* values for trends of tertiles in HDL-C were also calculated by multivariate logistic regression analysis. Next, the *P* for the interaction test was used to compare whether there was a significant difference in the association between HDL-C and stroke between the BMI groups. Smooth curve fitting (penalized spline method) was used to visually show the relationship between HDL-C and stroke in two different BMI groups. The interactions of the association between HDL-C and stroke with sex, age, diabetes mellitus, eGFR, and smoking in different classifications of BMI were evaluated by interaction tests.

All data analysis and form production used the statistical package R (https://www.R-project.org, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). Statistical significance was defined as two-tailed $P < 0.05$.

Results

Baseline characteristics of study participants

A total of 10,925 hypertensive participants without AF who were untreated with lipid-lowering drugs were selected for final data analysis (mean age: 63.99 ± 9.82 years; 48.33% males). In our study, the average incidence of stroke was 6.47% (707/10,925) and the average value of HDL-C was 1.51 ± 0.40 mmol/L. The distributions of study participant baseline characteristics according to BMI classification (< 24 and ≥ 24 kg/m^2) and HDL-C tertiles are presented in Table 1. In the BMI < 24 kg/m^2 group, the population with higher HDL-C levels had higher values for age, SBP, alcohol consumption, TC, LDL-C, AST, and ALT, and lower values for TGs, stroke, diabetes, and antidiabetes and antihypertensive drug use. In the BMI ≥ 24 kg/m^2 group, higher HDL-C levels were associated with higher values for age, SBP, TC, LDL-C and AST and lower values for male sex, DBP, smoking, TGs and antidiabetes drug use (all $P < 0.05$). In addition, the study participant baseline characteristics were also described by BMI classification (< 24 and ≥ 24 kg/m^2) as shown in Table S1. Except for SBP and antiplatelet drugs, other variables had significant differences between BMI classifications ($P < 0.05$).

Association between HDL-C and stroke in different classifications of BMI

Table 2 shows the effect of BMI on the association between HDL-C and stroke. In model 3, when HDL-C was used as a continuous variable, for every 1 mmol/L increase in HDL-C, the risk of stroke decreased by 50% in the BMI < 24 kg/m^2 group (OR 0.50, 95% CI 0.38–0.66; $P < 0.001$). In contrast, the relationship between HDL-C and stroke was not significant in the BMI ≥ 24 kg/m^2 group (OR 0.73, 95% CI 0.49–1.10; $P = 0.131$). BMI status had a significant effect on modifying the relationship between HDL-C and stroke ($P_{\text{Interaction}} = 0.027$). Furthermore, HDL-C was converted from a continuous variable to a categorical variable. In the BMI < 24 kg/m^2 group, higher HDL-C (≥ 1.0 mmol/L) was associated with a 42% reduction in stroke (OR 0.58, 95% CI 0.40–0.85, $P < 0.05$). Next, the HDL-C was divided into three groups according to tertiles. When compared with T1 (< 1.26 mmol/L), T2 (1.26–1.91 mmol/L), and T3 (≥ 1.91 mmol/L) were significantly reduced (T2: OR 0.67, 95% CI 0.53–0.85; T3: OR 0.49, 95% CI 0.38–0.64; all $P < 0.05$). In addition, the P for trend was significant, showing that the relationship between HDL-C and stroke was linear in the BMI < 24 kg/m^2 group ($P < 0.001$). Different from BMI < 24 kg/m^2, the association between HDL-C and stroke was still not significantly different between groups in the BMI ≥ 24 kg/m^2 group (all $P > 0.05$). Figure 1 shows an inverse association between HDL-C and stroke in the BMI < 24 kg/m^2 group, but HDL-C was not related to stroke in the BMI ≥ 24 kg/m^2 group. Table S2 reveals a negative association between BMI and stroke in our study.

Table 1 Baseline characteristics of study participants

	BMI < 24 kg/m^2				BMI ≥ 24 kg/m^2			
	HDL-C (mmol/L) Tertiles				HDL-C (mmol/L) Tertiles			
Characteristics[a]	< 1.26	1.26–1.91	≥ 1.91	*P* value[b]	< 1.14	1.14–1.67	≥ 1.67	*P* value[c]
Number	2030	2112	2097		1540	1539	1607	
Male, *n* (%)	1051 (51.77)	1,055 (49.95)	1008 (48.07)	0.059	928 (60.26)	668 (43.40)	571 (35.53)	< 0.001
Age, years	65.69 ± 9.53	66.21 ± 9.46	67.05 ± 9.21	< 0.001	59.74 ± 9.67	61.02 ± 9.57	61.84 ± 9.10	< 0.001
SBP, mmHg	146.61 ± 18.34	147.42 ± 20.12	148.60 ± 18.28	0.003	145.74 ± 17.08	147.30 ± 18.05	147.89 ± 16.85	0.002
DBP, mmHg	86.89 ± 10.81	87.28 ± 14.39	87.42 ± 10.83	0.348	91.69 ± 10.64	91.02 ± 12.75	90.70 ± 10.58	0.045
Pulse, bpm	76.49 ± 14.91	75.83 ± 13.88	77.03 ± 16.05	0.192	77.44 ± 13.70	77.43 ± 12.99	77.99 ± 13.41	0.402
Smoking, *n* (%)	654 (32.22)	648 (30.68)	630 (30.04)	0.301	448 (29.09)	312 (20.27)	264 (16.43)	< 0.001
Drinking, *n* (%)	327 (16.11)	451 (21.35)	623 (29.71)	< 0.001	315 (20.45)	302 (19.62)	355 (22.09)	0.220
TC, mmol/L	4.51 ± 0.96	5.06 ± 0.98	5.59 ± 1.06	< 0.001	4.55 ± 0.92	5.21 ± 0.96	5.84 ± 1.11	< 0.001
TG, mmol/L	1.94 ± 1.39	1.48 ± 0.82	1.21 ± 0.61	< 0.001	2.70 ± 1.76	2.04 ± 1.23	1.75 ± 0.98	< 0.001
LDL-C, mmol/L	2.68 ± 0.68	2.87 ± 0.76	2.93 ± 0.83	< 0.001	2.78 ± 0.64	3.15 ± 0.72	3.39 ± 0.85	< 0.001
HDL-C, mmol/L	1.16 ± 0.16	1.54 ± 0.10	2.05 ± 0.30	< 0.001	1.06 ± 0.13	1.37 ± 0.08	1.78 ± 0.24	< 0.001
AST, U/L	24.54 ± 13.93	25.67 ± 9.06	29.13 ± 17.39	< 0.001	26.74 ± 30.27	27.13 ± 11.40	29.48 ± 14.76	< 0.001
ALT, U/L	17.79 ± 14.48	17.18 ± 9.78	18.41 ± 12.24	0.005	25.03 ± 29.92	24.01 ± 16.05	24.95 ± 18.47	0.365
eGFR, ml/min/1.73 m^2	84.23 ± 20.97	84.54 ± 19.63	84.38 ± 19.18	0.883	87.87 ± 20.76	88.08 ± 19.10	88.44 ± 18.01	0.705
Stroke, *n* (%)	193 (9.51)	138 (6.53)	100 (4.77)	< 0.001	92 (5.97)	100 (6.50)	83 (5.16)	0.276
Diabetes, *n* (%)	316 (15.57)	258 (12.22)	289 (13.78)	0.008	356 (23.12)	331 (21.51)	376 (23.40)	0.397
Antiplatelet drugs, *n* (%)	47 (2.32)	41 (1.94)	28 (1.34)	0.062	38 (2.47)	42 (2.73)	30 (1.87)	0.260
Antidiabetes drugs, *n* (%)	100 (4.93)	55 (2.60)	44 (2.10)	< 0.001	118 (7.66)	91 (5.91)	71 (4.42)	< 0.001
Antihypertensive drugs, *n* (%)	1273 (62.71)	1245 (58.95)	1174 (55.98)	< 0.001	991 (64.35)	972 (63.16)	1016 (63.22)	0.74

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low density lipoprotein-cholesterol, *HDL-C* high density lipoprotein-cholesterol, *AST* aspartate aminotransferases, *LT* alanine transaminase, *eGFR* estimated glomerular filtration rate

[a]Data are presented as number (%) or mean ± standard deviation

[b]Comparisons among HDL-C tertiles in participants with BMI < 24 kg/m^2

[c]Comparisons among HDL-C tertiles in participants with BMI ≥ 24 kg/m^2

Subgroup analysis

Table 3 shows that HDL-C was negatively associated with stroke in subgroups with BMI < 24 kg/m^2, but HDL-C was still not related to stroke in subgroups with BMI ≥ 24 kg/m^2, except for the sex subgroup, with BMI < 24 kg/m^2 (*P* for interaction < 0.05). There were no significant differences in age, diabetes, eGFR, and smoking regardless of BMI status (all *P* for interaction > 0.05).

Discussion

Our study found that BMI could modify the association between HDL-C and stroke in hypertensive populations without AF. The results showed an inverse association between HDL-C and stroke in the BMI < 24 kg/m^2 group, but HDL-C was not related to stroke in the BMI ≥ 24 kg/m^2 group.

Previous studies have examined the relationship between HDL-C and stroke, but the conclusions of these studies have been controversial. In contrast to our study, several previous studies showed a positive association between HDL-C and stroke [12, 20]. However, possible mechanisms for the positive relationship were not mentioned in the literature. In addition, we believe the conclusions of these studies might be affected by some confounding factors, including AF, eGFR, lipid-lowering drugs and antiplatelet drugs. Notably, a number of studies reported that HDL-C was negatively associated with stroke, but the association was not statistically significant [21–24]. This might be due to insufficient statistical power resulting from insufficient sample size; moreover, the association between HDL-C and stroke was weak because of a lack of a synergistic effect with hypertension [25]. These conflicting results might be attributed to the study populations varying widely in different regions, and the adjusted factors were different in the above studies.

In our study, we found that an inverse relationship between HDL-C and stroke existed in a hypertensive population with BMI < 24 kg/m^2. Although the mechanism

Table 2 Effect modification of BMI on the association between HDL-C and stroke

HDL-C, mmol/L	Events, %	Model 1		Model 2		Model 3		Model 4	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
BMI < 24 kg/m^2									
Continuous	431 (6.91)	0.49 (0.38, 0.64)	< 0.001	0.50 (0.39, 0.65)	< 0.001	0.50 (0.38, 0.66)	< 0.001	0.51 (0.39, 0.68)	< 0.001
Categories									
< 1	37 (11.67)	Reference		Reference		Reference		Reference	
≥ 1	394 (6.65)	0.54 (0.38, 0.77)	0.001	0.55 (0.39, 0.79)	0.001	0.58 (0.40, 0.85)	0.005	0.60 (0.41, 0.89)	0.01
Tertiles									
T1 (< 1.26)	193 (9.51)	Reference		Reference		Reference		Reference	
T2 (1.26–1.91)	138 (6.53)	0.67 (0.53, 0.84)	< 0.001	0.67 (0.53, 0.84)	< 0.001	0.67 (0.53, 0.85)	0.001	0.68 (0.53, 0.86)	0.001
T3 (≥ 1.91)	100 (4.77)	0.48 (0.37, 0.61)	< 0.001	0.48 (0.38, 0.62)	< 0.001	0.49 (0.38, 0.64)	< 0.001	0.50 (0.38, 0.66)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001		< 0.001	
BMI ≥ 24 kg/m^2									
Continuous	275 (5.87)	0.77 (0.53, 1.11)	0.157	0.80 (0.55, 1.16)	0.236	0.73 (0.49, 1.10)	0.131	0.77 (0.51, 1.16)	0.209
Categories									
< 1	24 (5.85)	Reference		Reference		Reference		Reference	
≥ 1	251 (5.87)	1.00 (0.65, 1.54)	0.989	1.03 (0.67, 1.59)	0.893	0.95 (0.60, 1.51)	0.821	0.99 (0.62, 1.58)	0.978
Tertiles									
T1 (< 1.14)	92 (5.97)	Reference		Reference		Reference		Reference	
T2 (1.14–1.67)	100 (6.50)	1.09 (0.82, 1.47)	0.548	1.13 (0.84, 1.52)	0.417	1.05 (0.77, 1.44)	0.736	1.07 (0.78, 1.46)	0.668
T3 (≥ 1.67)	83 (5.16)	0.86 (0.63, 1.16)	0.323	0.90 (0.66, 1.22)	0.488	0.84 (0.60, 1.17)	0.294	0.88 (0.63, 1.23)	0.444
P for trend		0.327		0.492		0.285		0.435	
P value for interaction*		0.055		0.015		0.027		0.033	

Model 1: adjusted for none. Model 2: adjusted for age, sex. Model 3: adjusted for age, sex, SBP, DBP, pulse, TG, AST, ALT, eGFR, smoking, diabetes mellitus and antiplatelet drugs. Model 4: adjust for all covariables in model 3 plus adjusted for antidiabetes and antihypertensive drugs

OR odd ratio, *CI* confidence interval, *BMI* body mass index, *HDL-C* high-density lipoprotein cholesterol

**P* value for interaction test: 2-way interaction of BMI status and HDL-C (continuous) on stroke

by which the BMI classification modified the association between HDL-C and stroke is currently unclear, several possible mechanisms have been mentioned in previous studies. For a study population with normal BMI (< 24 kg/m^2), the relationship between HDL-C and stroke may not be affected by BMI. In this population, the decrease in HDL-C level may increase the risk of ischemic stroke by increasing the aggregation of platelets and erythrocytes, increasing blood viscosity and promoting the activity of coagulation-related tissue factors [26]. On the other hand, the lower HDL-C levels may weak the endothelial function of cerebral arteries, which may increase the incidence of hemorrhagic stroke [27].

We also found that HDL-C was not associated with stroke in a hypertensive population with BMI ≥ 24 kg/m^2. Consistent with our study, Bowman et al. [28] conducted a case–control study to investigate the risk factors of 296 patients with stroke (case group: mean age 61.0 ± 8.3 years; BMI 25.7 ± 3.48 kg/m^2; control group: mean age: 60.5 ± 8.1 years; BMI: 25.0 ± 2.90 kg/m^2), and found that HDL-C was not related to stroke. Wieberdink et al. [22] followed-up 12,526 patients for an average of 9.7 years (mean age 67.0 years; mean BMI 26.3 kg/m^2) and found that HDL-C was not associated with stroke regardless of the lipid-lowering medication status. Bots et al. [29] conducted a multiregional case–control study in Europe (mean age 62.1 ± 12.2 years; mean BMI: 26.9 ± 4.1 kg/m^2), and found that HDL-C was not associated with stroke regardless of sex. Our findings showed that the relationship between HDL-C and stroke was different between the BMI < 24 and BMI ≥ 24 kg/m^2 groups. This difference was partly because the two BMI groups had a different incidence of stroke. Table S1 shows that the BMI ≥ 24 kg/m^2 group had a lower stroke incidence than the BMI < 24 kg/m^2 group (< 24 kg/m^2: 431(6.91%); ≥ 24 kg/m^2: 275(5.87%); $P < 0.05$), so even if HDL-C and stroke was negatively correlated in the BMI ≥ 24 kg/m^2 group, the statistical power of this relationship was insufficient. On the other hand, perhaps the level and function of HDL-C are modified in people with higher BMI, consistent with our study (< 24 kg/m^2: 1.65 ± 0.45 mmol/L; ≥ 24 kg/m^2: 1.47 ± 0.37 mmol/L; $P < 0.001$). Several possible mechanisms could explain this phenomenon. In one study, higher BMI was associated with increased liver lipase activity, and liver lipase promoted the breakdown of HDL-C into apolipoprotein A1 and smaller HDL-C particles, which in turn led to a decrease in HDL-C

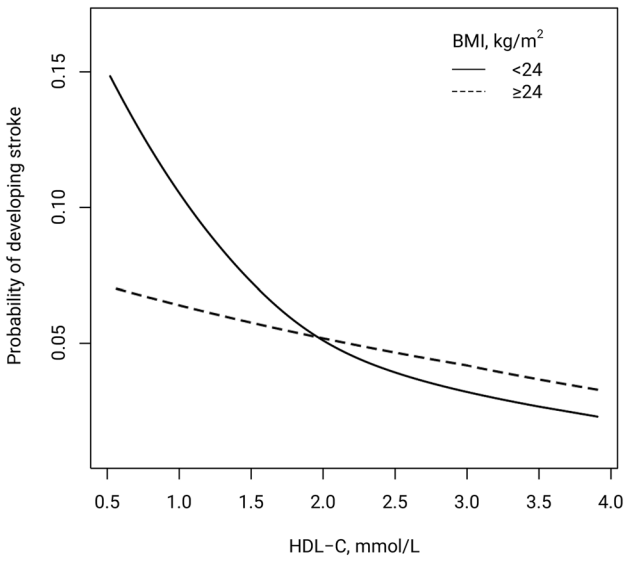

Fig. 1 Association between HDL-C and stroke stratified by BMI classification in a hypertensive population without AF. The smooth curve fitting presented an inverse association between HDL-C and stroke in BMI < 24 kg/m^2 group, but HDL-C was not related with stroke in BMI ≥ 24 kg/m^2 group. Adjusted for age, sex, SBP, DBP, pulse, TG, AST, ALT, eGFR, smoking, diabetes mellitus, and antiplatelet drugs

levels [30]. Another study reported that HDL-C degraded faster in people with higher BMI because of higher levels of leptin in the body [31]. Some researchers also thought that the accelerated degradation of HDL-C might be caused by the chronic inflammatory state in patients with high BMI [32]. On the other hand, the higher BMI levels also altered the function of HDL-C, including resulting in weakened anti-inflammatory effects, weakened antioxidant and protective effects on endothelial cells, and weakened reverse cholesterol transport [33–35]. The above mechanisms suggested that higher BMI levels lead to a decrease in HDL-C level and function, and further supported the hypothesis that BMI status might modify the relationship between HDL-C and stroke. However, further basic experiments are needed to fully elucidate the specific biological mechanism behind this connection.

It should be noted that antidiabetic and antihypertensive drugs might have an impact on the conclusion. We added these two variables to model 4 based on the adjustment variables of model 3 in multiple regression equations. The results of model 4 changed slightly when compared with model 3 in Table 2, but did not change our final conclusions. Moreover, most importantly, the relationship between HDL-C and stroke was controversial in previous research [7, 10]. With regards to SBP, TC, LDL-C and TGs, although these factors are closely related to stroke, a number of previous studies reported a positive relationship between these factors and stroke. To our knowledge, the positive association between these factors and stroke is not controversial [12, 21, 25]. On the other hand, no studies have reported the relationship between HDL-C and stroke in a hypertensive population without AF. Therefore, it is necessary for us to examine the relationship between HDL-C and stroke in a hypertensive population without AF. For AST, some studies have reported that AST was associated with stroke prognosis [36, 37]. Hence, AST and stroke may also be related, and we will attempt to explore this relationship in the future.

Tables S1 and S2 showed that the BMI ≥ 24 kg/m^2 group had a lower incidence of stroke than the BMI < 24 kg/m^2 group. The previous literature has proposed the hypothesis of the obesity–stroke paradox, which was similar to our findings [38]. The possible reason for this paradox is that participants with a higher BMI have better medication adherence [39]. Similarly, Table S1 showed that the BMI ≥ 24 kg/m^2 group had a higher rate of antiplatelet and antihypertensive drug prescriptions than the BMI < 24 kg/m^2 group. Previous studies have confirmed that these drugs can effectively protect against stroke [40, 41]. As a result, the BMI ≥ 24 kg/m^2 group had a lower incidence of stroke than the BMI < 24 kg/m^2 group. In addition, patients with hypertension had a significantly higher risk of stroke than non-hypertensive population [42]. Our study also showed that the prevalence of stroke in patients with hypertension was significantly higher than that in the normal population (6.47% vs. 2.19%) [43]. Moreover, BMI is an easily regulated factor; therefore, controlling BMI levels in patients with hypertension may obtain greater clinical benefits.

Some limitations should be noted. First, as a cross-sectional study, our results failed to provide causality regarding the relationship between HDL-C and stroke in different BMI status groups. Second, we did not collect information as to specific stroke subtypes, so a sensitivity analysis could not be performed to assess whether the relationship between HDL-C and stroke was consistent across stroke subtypes. Third, although we found that the relationship between HDL-C and stroke was not statistically significant in the BMI ≥ 24 kg/m^2 group, we can still observe a decreasing trend in the prevalence of stroke with the increase in HDL-C. Therefore, a larger sample is needed to explore the relationship in this particular population in the future. Fourth, our study population was from China, and the criteria for BMI classification was based on Chinese guidelines; thus, the generalizability of the results to other populations remains to be verified.

In conclusion, we found an inverse association between HDL-C and stroke in the BMI < 24 kg/m^2 group, but HDL-C was not related to stroke in the BMI ≥ 24 kg/m^2 group. The findings suggested that BMI could modify the association between HDL-C and stroke in a hypertensive population without AF.

Table 3 Effect size of HDL-C on stroke in each subgroup stratified by BMI status

Subgroup	*N*	Events, %	Adjusted OR (95CI)	*P* for interaction
BMI < 24 kg/m²				
Sex				0.027
Male	3114	273 (8.77)	0.40 (0.28, 0.57)	
Female	3125	158 (5.06)	0.73 (0.48, 1.11)	
Age, years				0.656
< 65	2444	163 (6.67)	0.54 (0.35, 0.85)	
≥ 65	3795	268 (7.06)	0.48 (0.34, 0.67)	
Diabetes				0.628
No	5376	360 (6.70)	0.49 (0.36, 0.66)	
Yes	863	71 (8.23)	0.57 (0.32, 1.02)	
eGFR, ml/min/1.73 m^2				0.124
< 90	3199	257 (8.03)	0.58 (0.42, 0.82)	
≥ 90	3040	174 (5.72)	0.38 (0.25, 0.60)	
Smoking				0.681
No	4307	302 (7.01)	0.52 (0.38, 0.72)	
Yes	1932	129 (6.68)	0.46 (0.29, 0.75)	
BMI ≥ 24 kg/m²				
Sex				0.287
Male	2167	150 (6.92)	0.59 (0.33, 1.05)	
Female	519	125 (4.96)	0.90 (0.52, 1.57)	
Age, years				0.254
< 65	2915	152 (5.21)	0.60 (0.35, 1.03)	
≥ 65	1771	123 (6.95)	0.93 (0.53, 1.65)	
Diabetes				0.698
No	3623	194 (5.35)	0.70 (0.43, 1.12)	
Yes	1063	81 (7.62)	0.82 (0.40, 1.69)	
eGFR, ml/min/1.73m^2				0.729
< 90	2038	150 (7.36)	0.77 (0.45, 1.30)	
≥ 90	2648	125 (4.72)	0.67 (0.37, 1.21)	
Smoking				0.884
No	3662	218 (5.95)	0.74 (0.47, 1.16)	
Yes	1024	57 (5.57)	0.69 (0.28, 1.72)	

Adjusted for age, sex, SBP, DBP, pulse, eGFR, TG, AST, ALT, current smoking, diabetes mellitus and antiplatelet drugs, if not be stratified

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consents were obtained from all individual participants included in the study.

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