ORIGINAL RESEARCH

High-Density Lipoprotein Cholesterol and the Risk of First Ischemic Stroke in a Chinese Hypertensive Population

Yue Zhang,[1] Jingyi Li,[2]
Chengzhang Liu,[3] Hongxiang Yu,[1]
Chen Chen,[1] Chonglei Bi,[4]
Chongqian Fang,[4] Hai Ma,[5]
Aimin Li,[6] Qing Dong,[7]
Lishun Liu,[8] Binyan Wang,[3]
Xiao Huang, [iD][9] Xiaoshu Cheng,[9]
Pierre Zalloua, [iD][10] Xiping Xu,[11]
Yong Huo, [iD][12] Gang Li [iD][1]

[1]Department of Neurology, East Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China; [2]State Key Laboratory of Natural Medicines, Research Center of Biostatistics and Computational Pharmacy, China Pharmaceutical University, Nanjing, People's Republic of China; [3]Shenzhen Evergreen Medical Institute, Guangzhou, People's Republic of China; [4]People's Hospital of Rongcheng, Rongcheng, Shandong, People's Republic of China; [5]Health and Family Planning Commission, Rongcheng, Shandong, People's Republic of China; [6]Department of Neurosurgery, Lianyungang Clinical College of Nanjing Medical University, Lianyungang, People's Republic of China; [7]Lianyungang Health Committee, Lianyungang, Jiangsu, People's Republic of China; [8]Beijing Advanced Innovation Center for Food Nutrition and Human Health, College of Food Science and Nutritional Engineering, China Agricultural University, Beijing, People's Republic of China; [9]Department of Cardiovascular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, People's Republic of China; [10]School of Medicine, Lebanese American University, Beirut, Lebanon; [11]Division of Nephrology, Nanfang Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease; State Key Laboratory of Organ Failure Research; Guangdong Provincial Institute of Nephrology, Guangzhou, People's Republic of China; [12]Department of Cardiology, Peking University First Hospital, Beijing, People's Republic of China

Correspondence: Gang Li
1800 Yuntai Road, Shanghai, 200123, People's Republic of China
Tel +86-21-38804518-22107
Fax +86-21-58798999
Email ligang@tongji.edu.cn

Background and Purpose: Elevated high-density lipoprotein cholesterol (HDL-C) levels have displayed protection against cardiovascular disease. However, the association between specific lipoprotein classes and first ischemic stroke (IS) has not been well defined, particularly in higher-risk hypertensive populations. Our study evaluated the associations of HDL-C with first IS in a Chinese hypertensive population.

Methods: The study population was obtained from a community-based cohort study of hypertension in Lianyungang and Rongcheng, China. A nested case-control design was used that included 2463 identified first IS cases and 2463 controls matched by age ± 1 year, sex, and region.

Results: After adjusting for potential confounders, HDL-C was inversely associated with first IS (adjusted odds ratio [aOR]: 0.91; 95% confidence interval [CI]: 0.85–0.98). HDL-C levels of at least 65.4 mg/dL displayed a significant protective effect for first IS (aOR: 0.82; 95% CI: 0.69–0.98). Conversely, adverse effects of first IS were observed for low-density lipoprotein cholesterol (LDL-C) levels ≥138.1 mg/dL (aOR: 1.20; 95% CI: 1.02–1.42) and triglyceride (TG) levels ≥140.8 mg/dL (aOR: 1.27; 95% CI: 1.09–1.49). The risk associations of LDL-C and TG with first IS were attenuated in the presence of high HDL-C (≥53.0 mg/dL); an increased risk of first IS was only found in the presence of low HDL-C (<53.0 mg/dL) when LDL-C (aOR: 1.66; 95% CI: 1.19–2.31) and TG (aOR: 1.47; 95% CI: 1.17–1.84) were combined with HDL-C for analysis.

Conclusion: In this community-based Chinese hypertensive population, higher HDL-C was a significant protective factor of first IS. These data add to the evidence describing the relationship between lipids and IS and suggest that HDL-C maybe is a marker of IS risk in Chinses hypertensive population.

Keywords: high-density lipoprotein cholesterol, lipids, ischemic stroke, epidemiology

Introduction

China has one of the higher incidences of stroke in the world. The age-standardized prevalence, incidence, and mortality rates for stroke are 1114.8 per 100,000 people and 246.8 and 114.8 per 100,000 person-years, respectively.[1] Many studies have provided strong evidence for dyslipidemia as a risk factor for coronary heart disease (CHD).[2,3] These studies demonstrate a positive relationship between low-density lipoprotein cholesterol (LDL-C) and CHD[3] and an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and CHD.[2,4] However, these relationships have not been as clearly established for stroke, and some studies have even questioned whether cholesterol is a risk factor for stroke.[5]

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In Asian populations, dyslipidemia is dominated by low HDL-C; conversely, dyslipidemia is dominated by high LDL-C in Western populations.[6] In China, there is a higher prevalence of low HDL-C than of high LDL-C.[7] Therefore, the relationship between HDL-C and the risk of stroke requires further analysis in China. Data from statin trials show impressive reductions in stroke risk among persons with cerebrovascular disease (CVD).[8] However, some researchers have suggested that the improvement in cerebrovascular end points with statin agents cannot be completely explained by baseline values or treated LDL-C levels alone.[9] Few studies have evaluated the combined association of HDL-C with LDL-C on first IS.[10] Thus, it remains unclear whether people with high levels of both HDL-C and LDL-C have a lower risk of stroke than people with low levels of HDL-C and high levels of LDL-C.

Hypertension is the strongest risk factor for stroke. The incidence of hypertension among the Chinese population is very high. However, few studies have focus on the association between dyslipidemia and the risk of stroke in people with hypertension. The purpose of this study was to evaluate the individual and combined associations between specific lipid profiles and the incident risk of first IS in a Chinese hypertensive population without a history of prior stroke or CHD.

Methods
Study Population
The study population was obtained from the "H-type Hypertension Prevention and Control Public Service Project" (HHPCP), which is a community-based cohort study that was conducted in Lianyungang and Rongcheng, China, from 2016 to 2018. Eligible participants included individuals aged ≥35 years with hypertension, which was defined as a seated resting systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg at both the screening and recruitment visit, or as those who were taking antihypertensive medication. Physical examinations, questionnaire interviews, and biological samples were performed to collect the data. Baseline information on demographic, medical history, and lifestyle characteristics was collected via questionnaires and included data on age, sex, occupation, diet, sleep patterns, exercise, alcohol consumption, cigarette smoking, history of CHD, chronic kidney disease, diabetes mellitus, hypertension, hyperlipidemia and cancer, and

medication use. Measurements of height, weight, body mass index (BMI), waistline, SBP, and DBP at the baseline examination were obtained using standardized protocols. The incidence of first stroke, which was the only outcome in this analysis, was defined as a first nonfatal or fatal stroke and included ischemic and hemorrhagic stroke. However, this analysis only evaluated ischemic stroke because few cases of hemorrhagic stroke were available. Stroke endpoint data were obtained from local Centers for Disease Control and Prevention (CDC) surveillance data collected between 2016 and 2018.

The Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China, the Ethics Committee of Lianyungang Precision Health Institute, and the Ethics Committee of the Lianyungang Center for Advanced Research in Cardiovascular Diseases approved this study. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Nested Case-Control Study
This nested case-control study was established from the HHPCP based on the following criteria:[1] all registered patients were linked by their unique national ID with CDC surveillance data to identify the incidence of stroke between 2016 and 2018;[2] the first stroke incidence in the CDC database occurred subsequent to obtaining the baseline data in the community survey. The controls were comprised of individuals selected from the study population who did not have a history of stroke and had complete data. The controls were matched with cases by age (±1 year), sex, and region in a 1:1 ratio. The total eligible population included 3546 incident stroke cases and 3546 matched controls. None of the cases or controls had a history of self-reported or doctor-diagnosed stroke or transient ischemic attack. Finally, 2463 ischemic cases and 2463 controls were included for analysis after excluding 466 hemorrhagic cases and matched controls, participants with CHD (n = 558), those who were using lipid-lowering drugs (n = 35) and antiplatelet drugs (n = 76), and unmatched cases (n = 565) (Online Figure I).

Laboratory Assays
Fasting serum HDL-C, triglyceride (TG), total cholesterol (TC), glucose, and total homocysteine concentrations were measured with their respective automatic clinical analyzers (Beckman Coulter) in a commercial lab (Shenzhen Tailored

Medical laboratory, China). LDL-C concentrations were calculated according to the Friedewald formula.[11]

Statistical Analysis

The baseline characteristics are presented as means ± SDs for continuous variables and as proportions for categorical variables. Chi-square tests for categorical variables and t-tests for continuous variables were used to compare differences in baseline characteristics between the cases and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using a conditional logistic regression with and without adjustment for BMI, SBP, DBP, fasting glucose, total plasma homocysteine, smoking and consumption status, estimated glomerular filtration rate, antihypertensive drugs, and glucose-lowering drugs at baseline. When individual or combined lipids were analyzed, the other lipids were adjusted accordingly. Moreover, possible modifications of the associations between HDL-C or TG and first IS were assessed for variables including sex, age (<68 vs >68 years), BMI (<24 vs >24 kg/m^2), smoking status (never vs ever), alcohol consumption (never vs ever), SBP (<140 vs >140 mmHg), fasting glucose (<5.6 vs >5.6 mmol/L), total plasma homocysteine concentration (<15 vs >15 umol/L), TC (<200 vs >200 mg/dL), and LDL-C (<130 vs >130 mg/dL). Specifically, TG levels (<150 vs >150 mg/dL) were included when the association between HDL-C and first IS was explored, and HDL-C (males <40/females <50 vs males >40/females >50 mg/dL) was included when the TG-first IS association was explored.

A two-tailed P < 0.05 was considered statistically significant in all analyses. R software (version 3.3.1; http://www.R-project.org) was used for all statistical analyses.

Data Availability

The study protocol and statistical analysis plan of this article are available from the corresponding author upon reasonable request. All data requests should first be submitted to Gang Li for consideration. Access to available fully anonymized data may be granted 12 months after publication. Requesters will be asked to complete an application form detailing specific requirements, rationale, and proposed use. A data-sharing agreement must be signed. Requested data will be made available, along with supporting documentation (eg, data dictionary) on a secure server.

Results

Study Participants and Baseline Characteristics

We analyzed 2463 IS cases and 2463 matched controls (Table 1). The cases were more likely to have higher SBP (153.1 ± 21.9 vs 147.7 ± 20.8 mmHg, P < 0.001), DBP (90.0 ± 13.7 vs 86.7 ± 13.1 mmHg, P < 0.001), fasting glucose levels (6.5 ± 2.5 vs 6.0 ± 2.0 mmol/L, P < 0.001), BMI (26.0 ± 4.0 vs 25.5 ± 3.7 kg/m^2, P < 0.001), and total homocysteine levels (14.1 ± 7.8 vs 13.5 ± 8.8 umol/L, P = 0.009) than controls. Because of our matching criteria, cases and controls were similar in age and sex. In the analysis of baseline lipid profiles, compared to the controls, IS cases had significantly higher levels of TG (143.7 ± 96.0 vs 129.0 ± 86.2 mg/dL, P < 0.001) and LDL-C (128.7 ± 32.7 vs 126.1 ± 32.4, P = 0.004) but a significantly lower level of HDL-C (59.6 ± 15.1 vs 62.0 ± 15.6 mg/dL, P < 0.001); the mean TC level was similar in the two groups (213.2 ± 47.4 vs 212.8 ± 46.5 mg/dL, P = 0.751) (Table 1).

Associations of Specific Types of Blood Lipids with First IS

When HDL-C levels were examined as a continuous variable in an adjusted model that included potential confounders and TG and LDL-C levels, a protective effect was found with an adjusted odds ratio (aOR) of 0.91 (95% CI: 0.85–0.98) for one SD increase in the HDL-C level. This translated into a 9% reduction in the odds of experiencing stroke (Figure 1A). When HDL-C levels were categorized as tertiles, a significant protective effect was observed for IS in patients with levels of at least 65.4 mg/dL (aOR: 0.82; 95% CI: 0.69–0.98; P for trend = 0.029). However, this significant association was no longer present when HDL-C was categorized according to the current clinical criteria (<40 mg/dL in males and <50 mg/dL in females) (Table 2). Furthermore, none of the baseline variables showed effect modification of the associations between HDL-C and IS after the stratified analyses (Online Table I).

There was a significant positive association between TG levels and the risk of first IS after adjustment for potential confounders, as shown in Figure 1B. A one SD increase in TG concentration was associated with a 10% increased risk of first IS (aOR: 1.10; 95% CI: 1.02–1.17). When TG and LDL-C levels were categorized as tertiles, a significant adverse effect of first IS was observed for TG

Table 1 Baseline Characteristics of Study Participants with First Ischemic Stroke and Age- and Sex-Matched Controls

	Control Subjects (n= 2463)	First Ischemic Stroke (n= 2463)	P value
Age, yrs	67.6 ± 9.4	67.6 ± 9.4	0.998
Male, no. (%)	1110 (45.1)	1110 (45.1)	1.000
SBP, mmHg	147.7 ± 20.8	153.1 ± 21.9	<0.001
DBP, mmHg	86.7 ± 13.1	90.0 ± 13.7	<0.001
BMI, kg/m²	25.5 ± 3.7	26.0 ± 4.0	<0.001
Fasting glucose, mg/dL	6.0 ± 2.0	6.5 ± 2.5	<0.001
History of diabetes, yes, no. (%)	222 (9.0)	363 (14.7)	<0.001
TC, mg/dL	212.8 ± 46.5	213.2 ± 47.4	0.751
TG, mg/dL	129.0 ± 86.2	143.7 ± 96.0	<0.001
HDL-C, mg/dL	62.0 ± 15.6	59.6 ± 15.1	<0.001
LDL-C, mg/dL Total homocysteine, μmol/L	126.1 ± 32.4 13.5 ± 8.8	128.7 ± 32.7 14.1 ± 7.8	0.004 0.009
≥15μmol/L, no. (%)	558 (22.7)	675 (27.4)	<0.001

Smoking status, no. (%)
  Never
  Former
  Current
	
	1786 (72.5)
	196 (8.0)
	481 (19.5)
		
		1754 (71.2)
		168 (6.8)
		541 (22.0)
			0.051

Alcohol consumption, no. (%)
  Never
  Former
  Current
	
	1785 (72.5)
	89 (3.6)
	589 (23.9)
		
		1849 (75.1)
		120 (4.9)
		492 (20.0)
			0.001

Antihypertensive drugs, yes, no. (%)	906 (36.8)	1193 (48.4)	<0.001
Glucose lowering drugs, yes, no. (%)	105 (4.3)	198 (8.0)	<0.001
eGFR, mL/min per 1.73 m²	95.0 ± 13.8	93.9 ± 14.6	0.007

levels of at least 140.8 mg/dL (aOR: 1.27; 95% CI: 1.09––1.49; P for trend = 0.003) and LDL-C levels of at least 138.1 mg/dL (aOR: 1.20; 95% CI: 1.02–1.42; P for trend = 0.027) (Table 2). When LDL-C levels were examined as a continuous variable, no significant positive association was found with an aOR of 1.04 (95% CI: 0.97–1.12) for one SD increase in the LDL-C level (Figure 1C) (Table 2). There was no significant relationship between TC levels and the risk of IS (Figure 1D) (Table 2).

Combined Associations of HDL-C and LDL-C or TG with First IS

We performed stratified analyses to assess the effect of LDL-C (per one SD increment) on first IS by HDL-C tertiles. Figure 2A, which displays the association between

LDL-C and the risk of first IS, indicates that there were different tendencies with different HDL-C levels. Only low HDL-C levels (<53.0 mg/dL) displayed a positive tendency with IS. The positive relationship between LDL-C and the risk of IS was attenuated in patients with higher HDL-C levels (≥53.0 mg/dL). Similarly, when LDL-C levels were categorized as tertiles, the highest risk for first IS was reported in participants with low HDL-C (<53.0 mg/dL) and high LDL-C (>138.1mg/dL) levels; these participants had a 66% higher risk of first IS than those with high HDL-C (>65.4 mg/dL) and low LDL-C (<111.4 mg/dL) levels (aOR: 1.66; 95% CI: 1.19–2.31; P = 0.003) (Table 3). The other combinations of HDL-C and LDL-C showed no significant associations with first IS.
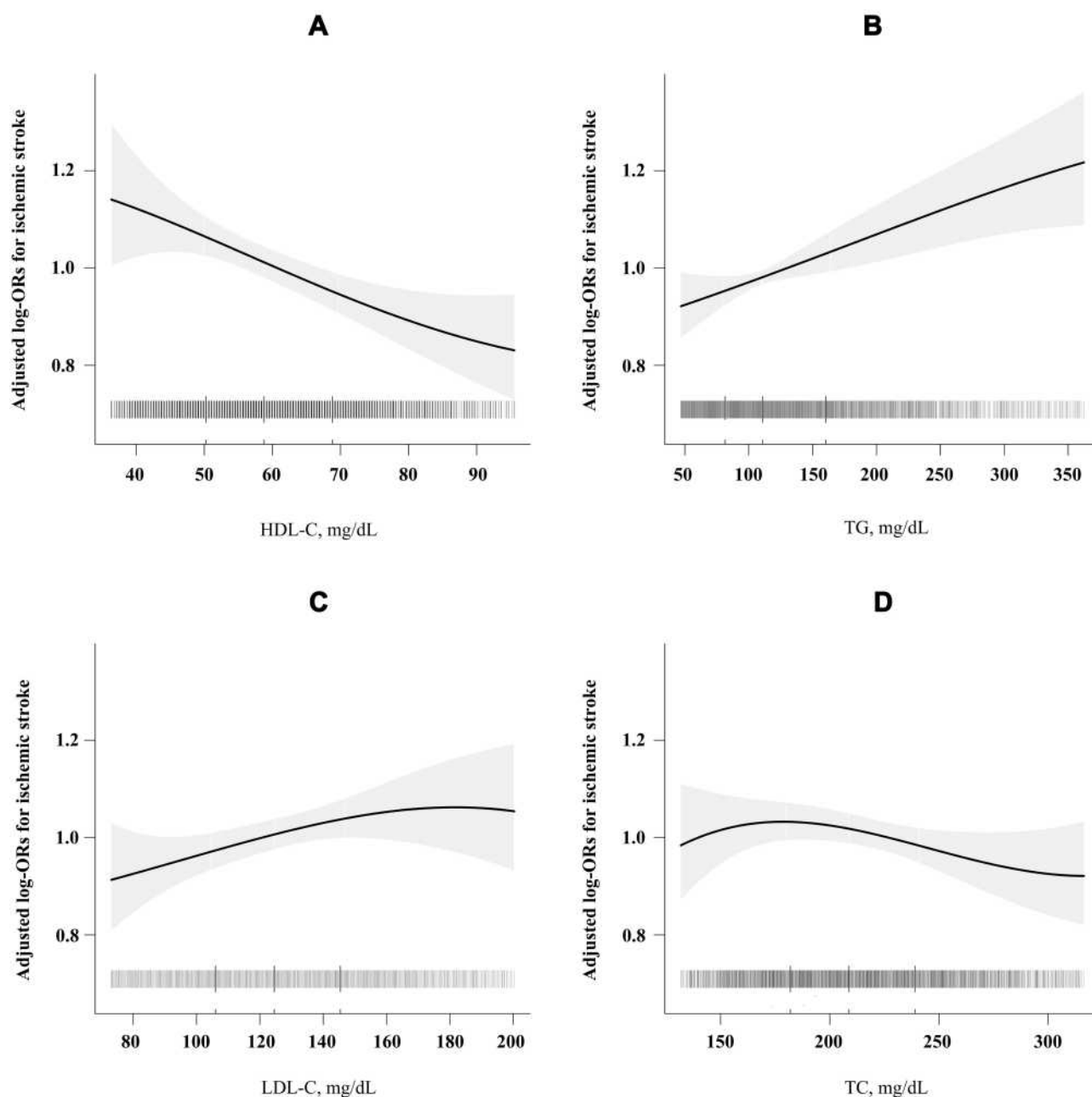
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Figure 1 Smoothing curves for the association of first IS with HDL-C, TG, LDL-C and TC. All the panels adjusted for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, smoking status, alcohol consumption, use of antihypertensive drugs, and glucose-lowering drugs, total homocysteine (tHcy), and estimated glomerular filtration rate (eGFR). HDL-C (**A**): adjusted for all the above variables plus TG and LDL-C.TG (**B**): adjusted for all the above variables plus TC. LDL-C (**C**): adjusted for all the above variables plus HDL-C and TG.TC (**D**): adjusted for all the above variables plus TG.

In the combined analysis investigating the associations of HDL-C and TG levels with first IS, the association of TG with first IS displayed a positive tendency only at lower HDL-C levels (<65.4 mg/dL); conversely, no significant association was found between the highest HDL-C tertile (>65.4 mg/dL) (Figure 2B). Similarly, patients with low HDL-C (<53.0 mg/dL) and high TG (>140.8 mg/dL) levels had a 47% higher risk of first IS (aOR: 1.147; 95%

CI: 1.17–1.84; P < 0.001) than those with high HDL-C (>65.4 mg/dL) and low TG (<89.5 mg/dL) levels (Table 4).

Discussion

To our knowledge, this is the first study to evaluate the prospective association between lipid profiles and the risk of IS in a community-based Chinese hypertensive

Table 2 Association of Fasting Serum Lipid Levels with Incident Risk of First Ischemic Stroke

	N	Cases (%)	Crude Model OR (95% CI)	P value	Adjusted Model* OR (95% CI)	P value
HDL-C[#], mg/dL						
Continuous, Per SD	4926	2463 (50.0)	0.84 (0.79,0.89)	<0.001	0.91 (0.85,0.98)	0.014
Tertiles						
T1 (<53.0)	1600	873 (54.6)	Ref		Ref	
T2 (53.0–65.4)	1685	846 (50.2)	0.83 (0.72,0.95)	0.007	0.92 (0.79,1.08)	0.328
T3 (≥65.4)	1641	744 (45.3)	0.67 (0.58,0.77)	<0.001	0.82 (0.69,0.98)	0.030
P for trend				<0.001		0.029
Clinical cut-off						
Males<40/Females<50	763	417 (54.7)	Ref		Ref	
Males≥40/Females≥50	4163	2046 (49.1)	0.79 (0.67,0.92)	0.004	0.93 (0.77,1.13)	0.454
TG[†], mg/dL						
Continuous, Per SD	4926	2463 (50.0)	1.20 (1.13,1.28)	<0.001	1.10 (1.02,1.17)	0.007
Tertiles						
T1 (<89.5)	1628	738 (45.3)	Ref		Ref	
T2 (89.5–140.8)	1647	810 (49.2)	1.18 (1.03,1.36)	0.017	1.06 (0.92,1.23)	0.405
T3 (≥140.8)	1651	915 (55.4)	1.55 (1.34,1.79)	<0.001	1.27 (1.09,1.49)	0.003
P for trend				<0.001		0.003
Clinical cut-off						
<150	3480	1666 (47.9)	Ref		Ref	
≥150	1446	797 (55.1)	1.36 (1.19,1.54)	<0.001	1.17 (1.02,1.34)	0.025
LDL-C[‖], mg/dL						
Continuous, Per SD	4926	2463 (50.0)	1.10 (1.04,1.17)	0.002	1.04 (0.97,1.12)	0.239
Tertiles						
T1 (<111.4)	1647	769 (46.7)	Ref		Ref	
T2 (111.4–138.1)	1653	827 (50.0)	1.17 (1.02,1.35)	0.027	1.10 (0.95,1.28)	0.203
T3 (≥138.1)	1626	867 (53.3)	1.36 (1.17,1.57)	<0.001	1.20 (1.02,1.42)	0.027
P for trend				<0.001		0.027
Clinical cut-off						
<130	2825	1365 (48.3)	Ref		Ref	
≥130	2101	1098 (52.3)	1.20 (1.06,1.35)	0.004	1.11 (0.97,1.27)	0.116
TC[‡], mg/dL						
Continuous, Per SD	4926	2463 (50.0)	1.01 (0.95,1.08)	0.723	0.98 (0.91,1.05)	0.512
Tertiles						
T1 (<190.6)	1648	817 (49.6)	Ref		Ref	
T2 (190.6–229.3)	1637	824 (50.3)	1.03 (0.90,1.19)	0.648	1.06 (0.91,1.23)	0.441
T3 (≥229.3)	1641	822 (50.1)	1.03 (0.88,1.19)	0.742	0.96 (0.81,1.13)	0.606
P for trend				0.743		0.603
Clinical cut-off						
<200	2077	1034 (49.8)	Ref		Ref	
≥200	2849	1429 (50.2)	1.02 (0.90,1.15)	0.781	0.98 (0.86,1.12)	0.769

Notes: Adjusted model*: adjusted for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, smoking status, alcohol consumption, use of antihypertensive drugs, and glucose-lowering drugs, total homocysteine (tHcy), and estimated glomerular filtration rate (eGFR). [#]For HDL, adjusted for all the above variables plus TG and LDL-C. [†]For TG, adjusted for all the above variables plus TC. [‡]For TC, adjusted for all the above variables plus TG. [‖]For LDL, adjusted for all the above variables plus HDL-C and TG.
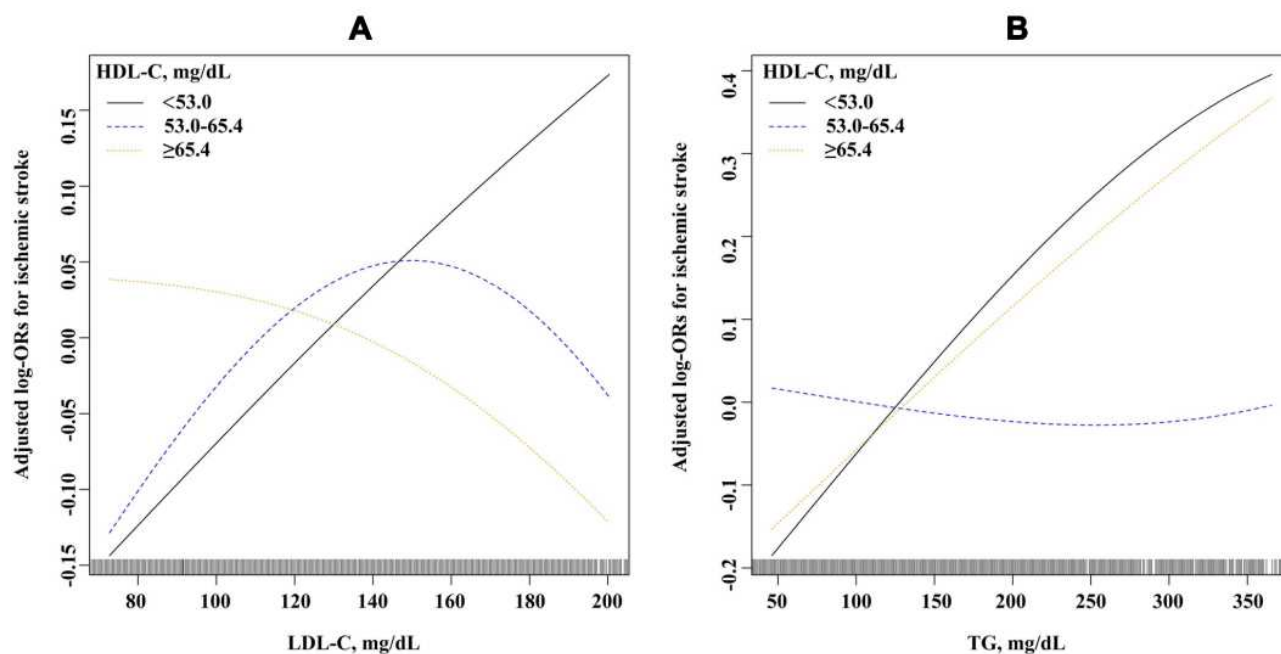
Figure 2 Association of LDL-C or TG with first IS stratified by HDL-C levels. (**A**) Adjusted for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, smoking status, alcohol consumption, use of antihypertensive drugs, and glucose-lowering drugs, total homocysteine (tHcy), and estimated glomerular filtration rate (eGFR) and TG (continuous). (**B**) Adjusted for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, smoking status, alcohol consumption, use of antihypertensive drugs, and glucose-lowering drugs, total homocysteine (tHcy), and estimated glomerular filtration rate (eGFR) and LDL-C (continuous).

population with no history of stroke and CHD. Our study contributes the following new insights into the HDL-C-IS association, for which previous studies have yielded conflicting results. This community-based case-control study demonstrated a protective effect of higher HDL-C levels for IS in a Chinese hypertensive population. This protective relationship was also observed in the combined analysis of HDL-C levels with LDL-C or TG and the risk of IS. In this combined analysis, elevated LDL-C and TG

levels were no longer positively associated with first IS in the presence of higher HDL-C levels.

The relationship between abnormal serum lipid levels and stroke is less clear than this relationship for CHD. The protective effects of increased HDL-C levels on the risk of myocardial infarction have been established by numerous epidemiological studies;[6] however, this protective effect was not clear for stroke. Some cohort studies including the Framingham Heart Study have reported no association

Table 3 Combined Association of HDL-C and LDL-C Tertiles with First IS

HDL-C Tertiles mg/dL	LDL-C Tertiles mg/dL	N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	P-value
T1 (≥65.4)	<111.4	180 (40.8)	Ref	Ref	
	111.4 −138.1	236 (45.8)	1.22 (0.94,1.58)	1.10 (0.84,1.45)	0.483
	≥138.1	328 (47.9)	1.32 (1.03,1.69)	1.10 (0.85,1.43)	0.479
T2 (53.0–65.4)	<111.4	228 (46.5)	1.26 (0.97,1.64)	1.12 (0.85,1.47)	0.425
	111.4 −138.1	302 (49.7)	1.45 (1.13,1.86)	1.21 (0.92,1.57)	0.169
	≥138.1	316 (53.8)	1.69 (1.31,2.17)	1.27 (0.97,1.67)	0.088
T3 (<53.0)	<111.4	361 (50.4)	1.45 (1.14,1.85)	1.16 (0.89,1.51)	0.278
	111.4 −138.1	289 (54.5)	1.75 (1.35,2.27)	1.25 (0.94,1.67)	0.123
	≥138.1	223 (63.0)	2.47 (1.85,3.30)	1.66 (1.19,2.31)	0.003

Notes: *Adjusted for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, smoking status, alcohol consumption, use of antihypertensive drugs, and glucose-lowering drugs, total homocysteine (tHcy), and estimated glomerular filtration rate (eGFR), and TG (continuous).

Table 4 Combined Association of HDL-C and TG Tertiles with First IS

HDL-C Tertiles mg/dL	TG Tertiles mg/dL	N (%)	Crude OR (95% CI)	Adjusted OR# (95% CI)	P-value
T1 (≥65.4)	<89.5	346 (42.5)	Ref	Ref	
	89.5 −140.8	266 (46.1)	1.16 (0.93,1.44)	1.00 (0.79,1.26)	0.992
	≥140.8	132 (53.0)	1.53 (1.14,2.04)	1.23 (0.89,1.69)	0.205
T2 (53.0–65.4)	<89.5	255 (47.0)	1.22 (0.98,1.51)	1.10 (0.87,1.40)	0.410
	89.5 −140.8	314 (51.0)	1.43 (1.16,1.77)	1.23 (0.98,1.53)	0.074
	≥140.8	277 (52.6)	1.53 (1.23,1.92)	1.21 (0.95,1.54)	0.122
T3 (<53.0)	<89.5	137 (50.6)	1.38 (1.05,1.83)	1.18 (0.86,1.60)	0.302
	89.5 −140.8	230 (50.7)	1.39 (1.10,1.75)	1.13 (0.87,1.46)	0.356
	≥140.8	506 (57.8)	1.94 (1.59,2.37)	1.47 (1.17,1.84)	<0.001

Notes: #Adjusted for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, smoking status, alcohol consumption, use of antihypertensive drugs, and glucose-lowering drugs, total homocysteine (tHcy), and estimated glomerular filtration rate (eGFR), and LDL-C (continuous).

between HDL-C and IS;[12] however, some epidemiological studies support an inverse association.[13–15] The absence of a consistent relationship between HDL-C and stroke may be partially explained by the heterogeneity of stroke, the focus on cardiovascular events rather than on stroke events, and the lack of classification of stroke subtypes. Furthermore, no significant reduction in CVD was observed including IS events in the AIM-HIGH and HPS2-THRIVE studies in association with HDL-C levels.[16,17] However, these studies evaluated patients with a history of CVD. In contrast to the many studies conducted in Western countries, few Asian studies have been performed in this field; moreover, HDL-C levels were reported to be inversely associated with the risk of first IS in these studies.[10,18,19] Our current study provides further evidence of a protective effect of HDL-C on first IS. Moreover, this protective association was not evident when using the current clinical binary threshold, which underscores the need to consider HDL-C as a continuous trait rather than the current binary cutoff. The mechanisms of how HDL-C protects against CVD including IS are often explained by the ability of HDL to remove cholesterol from the periphery for delivery to the liver and excretion in the bile, a process termed reverse cholesterol transport.[20] The reverse cholesterol transport capacity of HDL-C is a potent protection for LDL-C oxidation[21,22] and possesses anti-inflammatory properties.[23] Few previous studies have examined the combined associations of LDL-C and HDL-C with first IS. In a nested case-control study in the China Kadoorie Biobank (CKB) of Chinese populations, the associations of LDL-C and HDL-C with IS occurred independently of one another.[10] However, we found that the association between LDL-C and first IS differed by HDL-C levels. A positive

relationship was found between LDL-C and the risk of IS only when combined with a low HDL-C level (<53.0 mg/dL). In other words, high HDL-C might attenuate the association between LDL-C and IS. Notably, our participants and those from the CKB study display differing characteristics. First, the average age of IS cases in our study was 67.6 years whereas it was 54.3 years in the CKB study. Secondly, our study included participants with hypertension (mean SBP of 153.1 mmHg for IS cases), whereas only slightly more than half of the participants were hypertensive (56.8%) (mean SBP was 144.1 mmHg for IS cases) in the CKB study.

The role of TG levels in atherosclerosis has remained unclear, and clinical recommendations have fluctuated from a need to reduce levels to not providing any advice on treatment.[24] Some studies, but not all, support a positive association between TG and the risk of first IS.[25,26] Our study found that higher TG levels were a significant risk factor for the first IS incident in this Chinese hypertensive population. Furthermore, our study showed that the TG-IS association varied according to HDL-C levels. Only patients with low HDL (<53.0 mg/dL) and high TG (>140.8 mg/dL) levels had a significantly increased risk of first IS. The combined association of high TG and low HDL-C levels strongly predicted CHD in many studies.[27,28] Consistently, many studies have shown that adjusting for HDL-C attenuates the association of TG with the risk of CVD.[29] The attenuation of the TG effect on CVD risk by high HDL-C is most likely caused by metabolic interactions.[30]

Several limitations of our study design deserve discussion. The fact that this study was conducted in a community-based hypertensive population is both a strength and a limitation. The most important risk factor of atherosclerosis

at the population level is hypertension,[31] and a study found that the protective association between high HDL-C and stroke was more significant in the hypertension subgroup.[32] However, our findings must be interpreted cautiously in non-hypertensive populations. Our study population was drawn from two coastal areas of China and thus may not represent the entire Chinese population. We only examined fasting lipids status and statin use at baseline, and it is not entirely clear whether the participants made changes to their diet or medications during the follow-up period. Although we controlled for important covariables, we cannot exclude the possibility of residual confounding. Finally, as an observational study, we cannot make a causal conclusion between lipid levels and first IS.

Conclusions

In this Chinese hypertensive population, we have shown that HDL-C levels were a significant protective factor for IS risk. Elevated LDL-C and TG levels were no longer associated with first IS in the presence of high HDL-C. These findings, if further confirmed, suggest a new paradigm that possibly shifts from LDL-C as the center of focus to HDL-C as an important player in first IS in Chinese hypertensive populations.

Abbreviations

aOR, adjusted odds ratio; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HHPCP, H-type Hypertension Prevention and Control Public Service Project; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

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Disclosure

The authors report no conflicts of interest in this work.

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