LDL-C/HDL-C and carotid plaques in patients with coronary heart disease: A Chinese cohort study

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Abstract

**Background:** Evidence of the association the low-/high-density lipoprotein cholesterol ratio (LDL-C/HDL-C) with the carotid plaques remains limited. The purpose of this study is to examine the association between LDL-C/HDL-C and carotid plaques of coronary heart disease (CHD), and to study what extent a healthy lifestyle reduces the risk of carotid plaques.

**Methods:** In this large-scale and multi-center retrospective study, a total of 9,426 participants to explore the association between LDL-C/HDL-C and carotid plaques. No smoking and no drinking were considered healthy lifestyle. Generalised estimating equation models and conditional logistic regressions were used in statistical analyses.

**Results:** In all the 9,426 participants, there were 6,989 (74.15%) patients having identified carotid plaques. High levels of LDL-C/HDL-C had a higher risk of carotid plaques than other lipid variables (OR:1.63; 95%CI:1.43-1.86). In stratified analyses by LDL-C/HDL-C triplet, participants in the LDL-C/HDL-C (≥3mmol/L) group had a higher risk of carotid plaques compared to other two groups. Compared with the unfavourable lifestyle, intermediate lifestyle or favourable lifestyle was associated with a significant 30% or 67% decrease in carotid plaques risk among patients with the LDL-C/HDL-C(≥3mmol/L) respectively. There were significantly additive and multiplicative interactions between lifestyle and LDL-C/HDL-C on carotid plaques.

**Conclusion:** Our findings provide evidence that a high level of LDL-C/HDL-C can increase the risk of carotid plaques in patients with CHD. And adhering to a healthy lifestyle has additive beneficial effects on reducing the risk of carotid plaques.

1. Introduction

Cardiovascular diseases (CVD) is a class of diseases Whose morbidity and mortality are highest in the world, and CVD mortality is expected to remain the world's highest until 2030, with coronary heart disease (CHD) second only to stroke in CVD[1]. Coronary atherosclerosis (AS), as the basis of CHD, usually occurs at the same time as carotid atherosclerosis[2].

Studies have shown that peripheral vascular atherosclerosis severely affects the most significantly prediction-related for deadliness and death of CVD. It has been reported that when the conventional lipid parameters triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) remain apparently normal, other lipids such as lipid ratios, including TC/HDL-C, LDL-C/HDL-C, TG/HDL-C, and non-HDL-C/HDL-C are the diagnosticate alternatives that have been shown to predict the risk of a cardiovascular event[3–5]. Studies have shown LDL-C that plays a key role in the pathogenesis of AS. However, clinical studies suggest that despite the treatment of reduced LDL-C, significant CVD events continue to occur, may be residual risks associated with lipid abnormalities, particularly dyslipidemia causing atherosclerosis, containing elevated TG and reduced
HDL-C\(^6,7\). Therefore, new goals need to be provided to complement the measures to prevent CVD. Recent studies have shown that LDL-C/HDL-C is a better indicator of AS than individual LDL-C/HDL-C\(^8,9\). Nevertheless, there is limited data on the association of LDL-C/HDL-C with carotid plaques in CHD.

The healthy lifestyle factors can prevent CVDs. Drinking and smoking, two very common and concurrent risk factors, are associated with a significant proportion of mortality of CVD\(^10\). Studies have shown that the need for a variety of health factors can effectively reduce the risk of complications of CVD\(^11\). To what extent to which a jointly healthy lifestyle can reduce the risk of CHD associated with carotid plaques is unknown.

Therefore, this study aims to explore the relationship between the clinical indicators of LDL-C/HDL-C and carotid plaques in CHD, and investigate to what extent a healthy lifestyle could mitigate the risk of CHD related to carotid plaques.

2. Participants And Methods

2.1 Participants

This large-scale and multi-center retrospective study included 107,301 patients with CHD who were hospitalized in the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin Nankai Hospital, Tianjin Chest Hospital, and Tianjin Medical University General Hospital from January 1, 2014, to September 30, 2020. Information was obtained from the medical records in the Hospital Information System (HIS). Participants were excluded as followed: (1) age less than 35 or greater than 75 years; (2) oncological, infectious, or serious liver or renal disease; (3) lack of lipid data or carotid ultrasound measurements. Finally, a total of 9,426 participants were enrolled in the study. A flow chart of patient selection is shown in Fig. 1.

2.2 Lipid and carotid ultrasound assessment

According to the HIS, the levels of TC, TG, HDL-C, and LDL-C were measured using standard procedures. The blood lipid-related variables were calculated as follows\(^{12,13}\): non-HDL-C = TC – HDL-C; non-HDL-C/HDL-C = (TC – HDL-C)/HDL-C.

The carotid ultrasound results were evaluated by trained and certified technicians. The carotid intima-media thickness (CIMT) was defined as the mean of the IMT of the right and left common carotid arteries. The number and echoproperties of carotid plaques were recorded by a professional physician based on the analysis of carotid color Doppler ultrasound results. The number of carotid plaques were classified as single (\(n = 1\)) and multiple (\(n \geq 2\)). Echoproperties of carotid plaques were varied from hypoechoic, isoechoic, hyperechoic, and mixed.

2.3 Covariates
HIS was used to collect information about the demographic characteristics, and medical history of participants. Assessment of lifestyle factors on smoking and drinking from the personal history. We defined smoking status and drinking as no and yes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured by trained physicians using an electronic device. In the study, we considered no smoking and no drinking healthy lifestyle factors. Participants were divided into three lifestyles based on smoking and drinking: Unfavourable was defined as participants who both smoking and drinking, intermediate was defined as those who smoking only or drinking only, and favourable was defined as those who no smoking and no drinking.

2.4 Statistical analyses

Using the Kolmogorov-Smirnov tested the normality of the continuous variable distribution. Descriptive data was represented in quartile (interquartile) for continuous variables and number (proportion) for classification variables. In conditional logistic regressions, the odds ratio (OR) and 95% confidence interval (CI) were estimated for the association between LDL-C/HDL-C and the risk of carotid plaques formation, the number of carotid plaques, and carotid plaques echogenicity. Age, sex, DBP, SBP, Hb1Ac and other lipid were considered as potential confounders in the logistics analysis. Missing values on smoking ($n = 19$), drinking ($n = 19$), SBP ($n = 30$), DBP ($n = 30$), Hb1Ac ($n = 765$) and carotid plaques echogenicity ($n = 104$) were imputed by multiple interpolation method.

The joint impact of LDL-C/HDL-C and lifestyle on the risk of carotid plaques was assessed by creating virtual variables based on the combined exposure of both factors. The existence of additional interactions was examined by estimating the associated excess risk (RERI), attributable ratio (AP), and synergistic index (SI). Furthermore, we studied the multiplicative interaction by merging two variables in the same model and their cross-product terms. All statistical analyses were used by SAS 9.4 (SAS Institute, Cary, NC, USA) and SPSS 24.0 (IBM Corp, New York, NY, USA).

3. Results

3.1 Baseline characteristics

All of the 9,426 participants, the average age of participants was 59.00 ± 5 years old, Males constituted 48.96% overall, and patients with carotid plaque accounted for 74.15%. The baseline characteristics of the participants were divided into three groups of LDL-C/HDL-C < 2mmol/L (T1), 2.15mmol/L ≤ LDL-C/HDL-C ≤ 3mmol/L (T2) and LDL-C/HDL-C > 3mmol/L (T3) according to the tridigits of LDL-C/HDL-C. LDL-C/HDL-C (T3) was more likely to be male and had higher SBP, DBP, HbA1c, TG, TC, LDL-C, TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, and a higher percentage of patients with smoking, drinking, and carotid plaques compared with participants in LDL-C/HDL-C (T1). The odds of carotid plaques, the number of carotid plaques, and carotid plaques echogenicity also differed among the different LDL-C/HDL-C groups. ($P$-values < 0.001). (Table 1)
Table 1
General characteristic of study participants.

| Characteristic | Total | LDL-C/HDL-C tertile | \( P \)-value |
|----------------|-------|---------------------|---------------|
|                | \((N=9426)\) | T1 \((n=3130)\) | T2 \((n=3168)\) | T3 \((n=3128)\) |
| sex            |       |                    |               |               |
| Male           | 4615(48.96) | 1438(45.94) | 1466(46.28) | 1711(54.70) |
| Female         | 4811(51.04) | 1692(54.06) | 1702(53.72) | 1417(45.30) |
| Age, y         | 59.00(5.00) | 65.00(10.00) | 64.00(10.00) | 64.00(11.00) |
| SBP, mmHg      | 128.00(16.00) | 140.00(29.00) | 140.00(28.00) | 141.00(30.00) |
| DBP, mmHg      | 77.00(8.00) | 80.00(15.00) | 83.00(13.00) | 85.00(11.00) |
| HbA1c          | 5.60(0.90) | 5.90(1.10) | 6.00(1.40) | 6.20(1.70) |
| Smoking        |       |                    |               |               |
| No             | 5265(55.86) | 1879(60.03) | 1851(58.43) | 1535(49.07) |
| Yes            | 4161(44.14) | 1251(39.97) | 1317(41.57) | 1593(50.93) |
| Drinking       |       |                    |               |               |
| NO             | 4110(43.60) | 1539(49.17) | 1503(47.44) | 1068(34.14) |
| Yes            | 5316(56.40) | 1591(50.83) | 1665(52.56) | 2060(65.86) |
| TG, mmol/L     | 1.00(0.57) | 1.07(0.73) | 1.46(1.01) | 1.84(1.03) |
| TC, mmol/L     | 3.87(0.72) | 3.95(1.36) | 4.59(1.15) | 5.22(1.40) |
| HDL-C, mmol/L  | 0.93(0.22) | 1.15(0.43) | 1.00(0.26) | 0.96(0.22) |
| LDL-C, mmol/L  | 2.00(0.84) | 2.82(0.84) | 2.82(1.40) | 3.52(1.00) |
| non-HDL-C, mmol/L | 2.62(0.76) | 2.62(1.01) | 3.48(1.52) | 4.29(1.24) |
| TC/HDL-C, mmol/L | 3.46(0.94) | 3.17(0.77) | 4.19(0.75) | 5.51(1.28) |
| LDL-C/HDL-C, mmol/L | 1.95(0.71) | 1.72(0.54) | 2.78(0.35) | 3.62(0.90) |
| TG/HDL-C, mmol/L | 0.91(0.76) | 0.93(0.81) | 1.34(1.12) | 1.89(1.32) |
| non-HDL-C/HDL-C, mmol/L | 2.46(0.94) | 2.17(0.77) | 3.19(0.75) | 4.51(1.28) |

T1: LDL-C/HDL-C < 2; T2: \(2.15 \leq \text{LDL-C/HDL-C} \leq 3\); T3: LDL-C/HDL-C > 3. Data are presented as quartile (interquartile) or number (proportion, %); \( P \)-value was calculated by Kruskal-Wallis test.

SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.
### Table 1

| Characteristic                          | Total (N= 9426) | LDL-C/HDL-C tertile | P-value |
|----------------------------------------|-----------------|---------------------|---------|
|                                        |                 | T1 (n = 3130) | T2(n = 3168) | T3(n = 3128) |
| CIMT, mm                               | 1.00(0.20)      | 1.00(0.20)  | 1.00(0.15)  | 1.00(0.25)  | <0.001 |
| Carotid plaque                         |                 |                     |          |              | <0.001 |
| No                                     | 2437(25.85)     | 902(28.82)   | 924(29.17)  | 611(19.53)  |       |
| Yes                                    | 6989(74.15)     | 2228(71.18)  | 2244(70.83) | 2517(80.47) |       |
| No. of carotid plaque                  |                 |                     |          |              | <0.001 |
| 1                                      | 365(5.22)       | 98(4.40)      | 110(4.90)   | 157(6.24)   |       |
| 2                                      | 6624(94.78)     | 2130(95.60)  | 2134(95.10) | 2360(93.76) |       |
| Carotid plaque echo property           |                 |                     |          |              | <0.001 |
| Hypoechoic plaque                      | 454(6.50)       | 136(6.10)     | 164(7.31)   | 154(6.12)   |       |
| Isoechoic plaque                       | 510(7.30)       | 140(6.28)     | 150(6.68)   | 220(8.74)   |       |
| Hyperechoic plaque                     | 3950(56.52)     | 1293(58.03)   | 1276(56.68) | 1381(54.87) |       |
| Mixture plaque                         | 2075(29.69)     | 659(29.58)    | 654(29.14)  | 762(30.27)  |       |

T1: LDL-C/HDL-C < 2; T2:2.15 ≤ LDL-C/HDL-C ≤ 3; T3: LDL-C/HDL-C > 3. Data are presented as quartile (interquartile) or number (proportion, %); P-value was calculated by Kruskal-Wallis test.

SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

### 3.2 Associations between univariate and the risk of carotid plaques

In comparison with patients without carotid plaque, male, age, SBP, HbA1c LDL-C, non-HDL-C-HDL-C, smoking, drinking, and elevation were observed associated with carotid plaques. All lipid variables were risk factors for carotid plaques formation. HDL-C might be a protective factor associated with the number and echo properties of carotid plaques. LDL-C/HDL-C remained the highest risk associated with the number and echo properties of carotid plaques. (Fig. 2)

### 3.3 Association between LDL-C/HDL-C and carotid plaques

Three logistic regression models were constructed to assess the impact of LDL-C/HDL-C on carotid plaque.(Fig. 3) In the unadjusted model, LDL-C/HDL-C was shown as a continuous variable, significantly associated with the presence of carotid plaque (OR: 1.27; 95% CI: 1.24–1.29). After further adjustment, the chance of developing carotid plaques increased by 23% (OR 1.23; 95% CI 1.20–1.26) and 63% (OR 1.63; 95%CI 1.43–1.86). In the unadjusted and further adjustment model, logistic regression suggested
that the carotid plaques risk of LDL-C/HDL-C (T3) was 1.67, 1.75 and 1.18 fold that of the LDL-C/HDL-C (T1). In the further analysis, convert continuous LDL-C/HDL-C to classification variables (tridigits), and the $P$ for trend of the LDL-C/HDL-C with carotid plaques in the unadjusted or adjusted model was consistent with the results when the LDL-C/HDL-C served as a continuous variable. ($P < 0.001$ or $P < 0.05$)

Furthermore, we only adjusted sex, age, SBP, DBP and HbA1c to avoid excessive adjusted, multivariate logistic regression analysis showed that TC, LDL-C, non-HDL-C, TC/HDL-C, LDL-C/HDL-C and non-HDL-C/HDL-C except TG and TG/HDL-C, HDL-C were the risk factors for individual carotid plaques. And all lipid variables except HDL-C were risk factors for multiple carotid plaques. (ESM Table 1) In further analysis, all other lipid variables except TC and TG/HDL-C were risk factors for plaques of hypoechoic, Isoechoic. All lipid variables were risk factors for plaques of hyperechoic and Mixture. HDL-C might be a protective factor associated the number and echo properties of carotid plaques. LDL-C/HDL-C remained the highest risk associated with the number and echo properties of carotid plaques. (ESM Table 2)

| Lifestyle factor | No. of cases | Carotid plaques | OR (95% CI)$^a$ | OR (95% CI)$^b$ |
|-----------------|-------------|-----------------|-----------------|-----------------|
| Smoking         |             |                 |                 |                 |
| Yes             | 4158        | Reference       | Reference       | Reference       |
| No              | 5268        | 0.43(0.41–0.45)$^{**}$ | 0.51(0.48–0.54)$^{**}$ |
| Drinking        |             |                 |                 |                 |
| Yes             | 5297        | Reference       | Reference       | Reference       |
| No              | 4129        | 0.46(0.44–0.48)$^{**}$ | 0.53(0.51–0.56)$^{**}$ |
| Lifestyle       |             |                 |                 |                 |
| Unfavourable    | 2869        | Reference       | Reference       | Reference       |
| Intermediate    | 3736        | 0.71(0.67–0.75)$^{**}$ | 0.70(0.66–0.75)$^{**}$ |
| Favourable      | 2821        | 0.28(0.27–0.29)$^{**}$ | 0.31(0.29–0.33)$^{**}$ |

$^a$Model 1: unadjusted;

$^b$Model 2: adjusted for age, sex, SBP, DBP, HbA1c;

Compared with no carotid plaque: $^* P < 0.05$, $^{**} P < 0.01$.

### 3.4 Association between lifestyle-related factors and carotid plaques
Association between lifestyle factors and carotid plaques after adjusted models, being a no smoking and no drinking were interrelated with a reduced risk of carotid plaques. An intermediate lifestyle and a favourable lifestyle were significantly relevant with reduced risk of carotid plaques. (Table 2) After adjusted sex, age, SBP, DBP and HbA1c, which compared with an unfavourable lifestyle, an intermediate lifestyle or a favourable lifestyle was associated with a significant 30% (OR 0.70; 95% CI 0.64–0.78) or 67% (OR 0.33; 95% CI 0.29–0.37) decrease in carotid plaques risk among patients with LDL-C/HDL-C (≥3mmol/L) in CHD. (Fig. 4 and ESMTable 3)

3.5 Joint effect of LDL-C/HDL-C and lifestyle-related factors on carotid plaques risk

There was a significant additive interaction between LDL-C/HDL-C and lifestyle-related factors on risk of carotid plaques in the joint effect analysis (RERI 2.777; 95% CI 1.681–3.872; AP 0.209; 95% CI 0.142–0.276; SI 1.291; 95% CI 1.178–1.416). The multi-adjusted OR for LDL-C/HDL-C multiplied by unfavourable lifestyle was 1.17 (95% CI 1.05–1.30; \( P = 0.004 \)) for carotid plaques. (Table 3)

| Joint exposure | No. of participants | Carotid plaques |
|----------------|---------------------|-----------------|
| Lifestyle      | LDL/HDL             |                 |
| Intermediate/Favourable | NO | 4522            | 3015            | reference | reference |
| Unfavourable   | NO                  | 1776            | 1457            | 2.29(2.17–2.42)** | 1.86(1.74–2.00)** |
| Intermediate/Favourable | Yes | 2035            | 1574            | 1.71(1.62–1.79)** | 1.63(1.54–1.72)** |
| Unfavourable   | Yes                 | 1093            | 943             | 3.15(2.92–3.39)** | 2.59(2.37–2.82)** |

- \( \text{Model 1: unadjusted;} \)
- \( \text{Model 2: adjusted for age, sex, SBP, DBP, HbA1c;} \)

Compared with no carotid plaque: * \( P < 0.05, ** P < 0.01. \)

Measures of additive interaction for carotid plaques:

- Relative excess risk due to interaction (RERI): 2.777; 95% CI 1.681–3.872;
- Attributable proportion due to interaction (AP): 0.209; 95% CI 0.142–0.276;
- Synergy index (SI): 1.291; 95% CI 1.178–1.416
4. Discussion

In this large-scale and multi-center retrospective database of CHD, our findings provide evidence that a high level and independent positive correlation between LDL-C/HDL-C and carotid plaques. After adjusting other covariates, the participants increased carotid plaques by 1.63 fold. The classification variables also showed that LDL-C/HDL-C (T3) had a higher risk of carotid plaques than that of LDL-C/HDL-C (T1). Moreover, Patients with LDL-C/HDL-C (T3) who reported maintained a healthy lifestyle including no smoking and no drinking, and had a significantly lower risk of carotid plaques than patients with both smoking and drinking.

Studies show that coronary atherosclerosis and carotid stenosis are closely related\textsuperscript{[14]}. Most acute cardiovascular events are attributed to vulnerable carotid atherosclerotic plaque rupture and secondary thrombosis\textsuperscript{[15–16]}. Dyslipidemia is the main risk factor for atherosclerosis\textsuperscript{[17–18]}. LDL-C is considered a major cardiovascular risk factor, with a denser reduction in LDL-C more associated with reduced total and cardiovascular mortality in patients at baseline\textsuperscript{[19]}. Studies suggested a reverse relationship between the concentration of HDL-C in plasma and CHD. Studies showed that HDL-C neither has any protective function nor reflects the functionality of HDL-C. Therefore HDL-C protection is still controversial\textsuperscript{[20]}. Studies proved that the LDL-C/HDL-C was closely related to the onset of CHD and the progression of atherosclerosis\textsuperscript{[21–23]}. A prospective study showed that the LDL-C/HDL-C predicted the progress of CIMT better than HDL-C or LDL-C alone\textsuperscript{[24]}. These results are consistent with our results, which further investigate the relationship between LDL-C/HDL-C and the risk of carotid plaques formation, the number of carotid plaques, and carotid plaques echogenicity. In our study, LDL-C/HDL-C > 3mmol/L is considered a risk factor for carotid plaques in CHD.

Atherosclerotic plaques are rich in lipids, and the lipid composition is thought to affect the stability of atherosclerotic plaques. Furthermore, the lipid content strongly determines plaque impenetrability and the rate of stenosis\textsuperscript{[25]}. Recent studies have found that neovascularization in plaques has become an important marker for evaluating plaque stability\textsuperscript{[26,27]}. A relationship between neovascularization in plaques and different types of plaque echogenicity shown by conventional ultrasound has been reported, and neovascularization in isoechoic plaques and hypoechoic fibrous lipid plaques is more obvious than that in calcified plaques\textsuperscript{[28]}. Homogeneous hypoechoic plaques are mostly unstable plaques, rich in lipids, and prone to inflammatory reactions, which can promote the production of neovascularization in plaques. Neovascularization in hyperechoic plaques is rare\textsuperscript{[29]}. In our study, an elevated LDL-C/HDL-C ratio was significantly correlation with the occurrence of hypoechoic and isoechoic plaques. A possible explanation may be that the characteristics of unstable plaques are associated with denser LDL subgroup typing. The greater the LDL density, the easier to reach the lower endothelium, where they are more likely to be oxidized. Furthermore, high density LDL particles have higher affinity for proteinosan, which extends its stay on the wall and inducthe development of atherosclerosis. In addition, the size of HDL-C particles generally decreases with the LDL-C/HDL-C, suggesting the blockade of HDL maturity, which may be responsible for the progression of atherosclerosis\textsuperscript{[30, 31]}. 

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Although studies have shown that moderate drinking in the literature is associated with reducing the risk of CHD. A case-control study showed that changes in alcohol consumption during life could distort the relationship between real alcohol and CHD\[32\]. A case-cohort study showed that drinking was inversely associated with non-fatal CHD risk but positively associated with the risk of different stroke subtypes. A multivariable Mendelian randomization study found smoking was a risk factor for CVD even after adjusting for drinking\[33–34\]. Accordance with our results that lifestyle interventions, being no smoking and no drinking may greatly reduce the risk of carotid plaques in CHD.

5. Strengths And Limitations

This study has several advantages and limitations. Firstly, The ultrasound may not be as accurate as high-resolution magnetic resonance imaging (MRI) or computed tomography (CT) in assessing the presence of a plaque. However, the safety, noninvasive nature of ultrasound should be acknowledged. Furthermore, BMI is an important confounding factor in CHD and carotid plaques. Because much BMI data were missing in this study, BMI was not included in the model. Finally, because this study is a multi-center, large-scale study, no causal relationship between LDL-C/HDL-C and carotid plaques, which requires further prospective research.

6. Conclusion

LDL-C/HDL-C is an independent risk factor for the occurrence of carotid plaques in CHD patients, which is a higher risk factor than other lipid variables. In clinical treatment, the impact of a high level of LDL-C/HDL-C should be considered. In addition to the basic lowering of blood lipid treatment, attention should be paid to improve patients' lifestyle, strengthen self-management, promote a healthy lifestyle, and reduce the risk of carotid plaque in CHD.

Abbreviations

LDL-C/HDL-C: low-/high-density lipoprotein cholesterol ratio; CHD: coronary heart disease; CVD: cardiovascular diseases; AS: atherosclerosis; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; HIS: hospital information system; CIMT: carotid intima-media thickness; SBP: systolic blood pressure; DBP: diastolic blood pressure; OR: the odds ratio; CI: confidence interval.

Declarations

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Authors’ contributions
CY, SG and RY took responsibility for the study protocol and statistical analysis; ZL and QC analyzed the data together and drafting the article; YL, XC, SW, YH, MH, YL, XX conducted data collection; YX, LL and YZ revised the article critically. All authors revised the article for important intellectual content and approved the article. The final version of the manuscript has been approved by all authors.

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Availability of data and materials

The datasets used in the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of Tianjin University of Traditional Chinese Medicine (approval number: TJUTCM-EC20190008) and registered with the Chinese Clinical Trial Registry on July 14, 2019 (registration number ChiCTR-1900024535) and in ClinicalTrials.gov on July 18, 2019 (registration number: NCT04026724).

Consent for publication

Not applicable.

Declaration of conflict of interest

The authors declare no competing interests.

References

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 74: 1376-1414. https://doi.10.1161/CIR.0000000000000770.

2. Hirata T, Arai Y, Takayama M, et al. Carotid plaque score and risk of cardiovascular mortality in the oldest old: Results from the TOOTH study. J Atheroscler Thromb 2018; 25: 55-64. https://doi.10.5551/jat.37911.

3. Cappelletti A, Astore D, Godino C, et al. Relationship between Syntax Score and prognostic localization of coronary artery lesions with conventional risk factors, plasma profile markers, and carotid
atherosclerosis (CAPP Study 2). Int J Cardiol 2018; 257: 306-311. https://doi.10.1016/j.ijcard.2017.12.012.

4. Zhang XX, Wei M, Shang LX, et al. LDL-C/HDL-C is associated with ischaemic stroke in patients with non-valvular atrial fibrillation: a case-control study. Lipids Health Dis. 2020;19(1):217. https://doi.10.1186/s12944-020-01392-7.

5. Sturlaugsdottir R, Aspelund T, Bjornsdottir G, et al. Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study. BMJ Open 2016; 6: e012457. https://doi.10.1136/bmjopen-2016-012457.

6. Qi Z, Chen H, Wen Z, et al. Relation of low-density lipoprotein cholesterol to ischemic stroke in patients with nonvalvular atrial fibrillation. Am J Cardiol. 2017;119:1224-1228. https://doi: 10.1016/j.amjcard.2016.12.031.

7. Tziomalos K, Giampatzis V, Bouziana SD, et al. Prognostic significance of major lipids in patients with acute ischemic stroke. Metab Brain Dis. 2017;32:395–400. https://doi: 10.1007/s11011-016-9924-9.

8. Nishikido T, Oyama J, Keida T, et al. High-dose statin therapy with rosvastatin reduces small dense LDL and MDA-LDL: the Standard versus high-dose therApy with Rosuvastatin for lipiD lowering (SARD) trial. J Cardiol 2016;67:340–6. https://doi: 10.1016/j.jjcc.2015.05.017.

9. Kunutsor SK, Zaccardi F, Karppi J, et al. Is High Serum LDL/HDL Cholesterol Ratio an Emerging Risk Factor for Sudden Cardiac Death? Findings from the KIHD Study. J Atheroscler Thromb. 2017 Jun 1;24(6):600-608. https://doi: 10.5551/jat.37184. Epub 2016 Oct 26.

10. Katcher HI, Hill AM, Lanford JL, et al. Lifestyle approaches and dietary strategies to lower LDL-cholesterol and triglycerides and raise HDL-cholesterol. Endocrinol Metab Clin North Am. 2009 Mar;38(1):45-78. https://doi.10.1016/j.ecl.2008.11.010.

11. Rosoff DB, Davey Smith G, Mehta N, et al. Evaluating the relationship between drinking, tobacco use, and cardiovascular disease: A multivariable Mendelian randomization study. PLoS Med. 2020;17(12):e1003410. https://doi.10.1371/journal.pmed.1003410.

12. Hou QT, Li SY, Gao Y, et al. Relations of lipid parameters, other variables with carotid intima-media thickness and plaque in the general Chinese adults: an observational study. Lipids Health Dis 2018; 17:107. https://doi.10.1186/s12944-018-0758-9.

13. Olamoyegun MA, Oluyombo R, Asaolu SO. Evaluation of dyslipidemia, lipid ratios, and atherogenic index as cardiovascular risk factors among semi-urban dwellers in Nigeria. Ann Afr Med 2016; 15: 194-199. https://doi.10.4103/1596-3519.194280.

14. Cademartiri F, Balestrieri A, Cau R, et al. Insight from imaging on plaque vulnerability: similarities and differences between coronary and carotid arteries-implications for systemic therapies. Cardiovasc Diagn...
15. Zhu GM, Hom Jason, Li Y, et al. Carotid plaque imaging and the risk of atherosclerotic cardiovascular disease. Cardiovasc Diagn Ther 2020; 10: 1048-1067. https://doi.10.21037/cdt.2020.03.10.

16. Li Y, Zhu GM, Ding V, et al. Assessing the relationship between atherosclerotic cardiovascular disease risk score and carotid artery imaging findings. J Neuroimaging 2019; 29: 119-125. https://doi.10.1111/jon.12573.

17. Hou QT, Li SY, Gao Y, et al. Relations of lipid parameters, other variables with carotid intima-media thickness and plaque in the general Chinese adults: an observational study. Lipids Health Dis 2018; 17: 107. https://doi.10.1186/s12944-018-0758-9.

18. Yang L, Li Z, Song Y, et al. Study on urine metabolic profiling and pathogenesis of hyperlipidemia. Clin Chim Acta. 2019 Aug;495:365-373. https://doi: 10.1016/j.cca.2019.05.001.

19. Navarese EP, Robinson JG, Kowalewski M, et al. Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. JAMA. 2018 Apr 17;319(15):1566-1579. https://doi: 10.1001/jama.2018.2525.

20. Barbalho SM, Tofano RJ, de Oliveira MB, Quesada KR, Barion MR, Akuri MC, Oshiiwa M, Bechara MD. HDL-C and non-HDL-C levels are associated with anthropometric and biochemical parameters. J Vasc Bras. 2019 Apr 1;18:e20180109. https://doi.10.1590/1677-5449.180109.

21. Zhong Z, Hou J, Zhang Q, et al. Assessment of the LDL-C/HDL-C ratio as a predictor of one year clinical outcomes in patients with acute coronary syndromes after percutaneous coronary intervention and drug-eluting stent implantation. Lipids Health Dis. 2019 Feb 2;18(1):40. https://doi:10.1186/s12944-019-0979-6.

22. Zhang XX, Wei M, Shang LX, et al. LDL-C/HDL-C is associated with ischaemic stroke in patients with non-valvular atrial fibrillation: a case-control study. Lipids Health Dis. 2020 Oct 7;19(1):217. https://doi:10.1186/s12944-020-01392-7.

23. Aizawa M, Inagaki S, Moriyama M, et al. Correction: Modeling the natural history of fatty liver using lifestyle-related risk factors: Effects of body mass index (BMI) on the life-course of fatty liver. PLoS One 2019; 14: e0226059. https://doi.10.1371/journal.pone.0226059.

24. Enomoto M, Adachi H, Hirai Y, et al. LDL-C/HDL-C ratio predicts carotid intima-media thickness progression better than HDL-C or LDL-C alone. J Lipids 2011; 2011: 549137. https://doi.10.1155/2011/549137.

25. Puig N, Jiménez-Xarrié E, Camps-Renom P, et al. Search for reliable circulating biomarkers to predict carotid plaque vulnerability. Int J Mol Sci 2020; 21: Doi:10.3390/ijms21218236. https://doi.10.3390/ijms21218236.
26. Mao Y, Liu XQ, Song Y, Zhai CG, Xu XL, Zhang L, Zhang Y. Fibroblast growth factor-2/platelet-derived growth factor enhances atherosclerotic plaque stability. J Cell Mol Med. 2020 Jan;24(1):1128-1140. https://doi: 10.1111/jcmm.14850.

27. Gupta A, Kesavabhotla K, Baradaran H, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke 2015; 46: 91-97. https://doi.10.1161/STROKEAHA.114.006091.

28. Kawasaki M, Iwasa M, Kanamori H, et al. Relationship between coronary plaque stability evaluated by intravascular ultrasound and laboratory parameters. Rinsho Byori 2016; 64: 319-326. Japanese. PMID: 27363224

29. Komatsu T, Iguchi Y, Arai A, et al. Large but nonstenotic carotid artery plaque in patients with a history of embolic stroke of undetermined source. Stroke 2018; 49: 3054-3056. https://doi.10.1161/STROKEAHA.118.022986.

30. Zambon A, Puato M, Faggin E, et al. Lipoprotein remnants and dense LDL are associated with features of unstable carotid plaque: a flag for non-HDL-C. Atherosclerosis 2013; 230: 106-109. https://doi.10.1016/j.atherosclerosis.2013.06.024.

31. Uematsu M, Nakamura T, Horikoshi T, et al. Echolucency of carotid plaque is useful for selecting high-risk patients with chronic coronary artery disease who benefit from intensive lipid-lowering therapy. J Cardiol 2021; Doi:10.1016/j.jjcc.2021.01.002. https://doi.10.1016/j.jjcc.2021.01.002.

32. Ricci C, Wood A, Muller D, et al. Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study. BMJ. 2018 May 29;361:k934. https://doi.10.1136/bmj.k934.

33. Fan AZ, Ruan WJ, Chou SP. Re-examining the relationship between drinking and coronary heart disease with a new lens. Prev Med. 2019 Jan;118:336-343. https://doi.10.1016/j.ypmed.2018.11.022.

34. Si J, Li J, Yu C, et al. Improved lipidomic profile mediates the effects of adherence to healthy lifestyles on coronary heart disease. Elife. 2021 Feb 9;10:e60999. https://doi.10.7554/eLife.6099.

**Figures**
Figure 1

Flow chart of patient recruitment.
Figure 2

Associations between univariate and the risk of carotid plaques.
Figure 3

Association of LDL-C/HDL-C and carotid plaques. Crude: unadjusted; Model 1: adjusted for age, sex, SBP, DBP, HbA1c; Model 2: adjusted for age, sex, SBP, DBP, HbA1c, smoking, drinking, TC, TG, HDL-C, LDL-C, TC/HDL-C, TG/HDL-C, non-HDL-C, non-HDL-C/HDL-C.
Multi-adjusted ORs (95% CI) of carotid plaques in relation to lifestyle among patients with the high levels LDL-C/HDL-C(≥3mmol/L) in CHD. Odds ratios were adjusted for sex, age, SBP, DBP, HbA1c.

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