SVN Stroke & Vascular Neurology

Remnant cholesterol is associated with unstable carotid plaque in a neurologically healthy population

Wenbo Li,[1] Yang Liu,[2] Jie Liu,[1] Qirui Guo,[3] Jing Li,[4] Anxin Wang ,[1,4] Huaguang Zheng [2,4]

To cite: Li W, Liu Y, Liu J, *et al*. Remnant cholesterol is associated with unstable carotid plaque in a neurologically healthy population. *Stroke & Vascular Neurology* 2025;**10**: e002888. doi:10.1136/svn-2023-002888

Received 3 October 2023
Accepted 3 April 2024
Published Online First 16 May 2024

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]Health Management Center, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[3]Department of Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[4]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Correspondence to
Dr Huaguang Zheng; zhgdoc@163.com

ABSTRACT

Background Remnant cholesterol (RC) is considered to be one of the most significant and important risk factors for atherosclerotic cardiovascular disease (ASCVD). Nonetheless, the association between RC and unstable carotid plaque remains unclear. Our primary objective is to ascertain whether RC exhibits an independent and significant association with unstable carotid plaque in a neurologically healthy population.

Methods In the cross-sectional study, we enrolled neurologically healthy participants who visited our centre for health checkups between 2021 and 2022. All eligible participants underwent a standardised questionnaire, physical examinations and laboratory testing. The carotid plaque was evaluated with a standard carotid ultrasound and an advanced ultrasound imaging technique called superb microvascular imaging. The correlation between lipids and unstable carotid plaque was primarily assessed utilising univariate and multivariate logistic regression.

Results The study totally enrolled 1100 participants who had an average age of 57.00 years (IQR: 49.00–63.00), with 67.55% being men. Among the participants, 321 (29.18%) had unstable carotid plaque. In the multivariate logistic regression analysis, higher RC had an independent association with an elevated incidence of unstable carotid plaque compared with the lowest concentrations of RC (OR=1.673, 95% CI 1.113 to 2.515, p=0.0134), but not other lipids. In addition, apolipoprotein A1 was negatively related to unstable carotid plaque (OR=0.549, 95% CI 0.364 to 0.830, p=0.0045).

Conclusions Elevated concentrations of RC are independently and excellently correlated with unstable carotid plaque within a neurologically healthy population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Remnant cholesterol (RC) is seen as an important atherogenic factor and its progression factor. Atherosclerotic cardiovascular disease was found to be correlated with RC.

WHAT THIS STUDY ADDS

⇒ Higher RC concentrations are an independent and excellent risk factor for unstable carotid plaque within a neurologically healthy population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ RC is independently associated with unstable carotid plaque, even in those with normal or low-density lipoprotein cholesterol levels. Thus, we proposed to give more attention to those with a higher RC level for stroke prevention in a neurologically healthy population.

INTRODUCTION

Ischaemic stroke emerges as a primary disease leading to disability and mortality in China.[1] A growing number of studies showed that unstable plaque constituted a significant factor in atherosclerotic vascular disease. Occlusion and embolism due to unstable plaque are the main causes of vascular disease episodes, including myocardial infarction, ischaemic stroke and limb ischaemia.[2] Approximately 20% of ischaemic strokes are attributed to the rupture of vulnerable carotid plaques situated at the carotid bifurcation.[3] Intraplaque neovascularisation (IPN) is a characteristic of unstable carotid plaques and has gained widespread interest.[4 5] IPN is the crucial component in the transformation of stable plaque into unstable plaque and plaque rupture and is related to intraplaque haemorrhage (IPH) and secondary plaque rupture.[6 7] Superb microvascular imaging (SMI) is an advanced and non-invasive ultrasound imaging technique for assessment of carotid plaque stability that can display IPN without the use of intravenous contrast.[8]

Dyslipidaemia is the main risk factor for atherosclerotic cardiovascular disease (ASCVD) and cerebrovascular disease, featured as increased low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) or decreased high-density lipoprotein cholesterol (HDL-C).[9] The incidence of ASCVD has declined with excellent outcomes due to the advent of statins. However, there was residual ASVCD risk in the population that accepted statin therapy and had lower levels of LDL-C.[10] In recent studies, lower concentrations of TG-rich lipoproteins (TRLs) or TRL remnants were associated with a reduced incidence of ASCVD or ASCVD residual risk.

RC, the cholesterol within TRLs, is seen as an important atherogenic factor and its progression factor, resulting in arterial wall plaques in patients with ASCVD.[11] However, the correlation between unstable carotid plaque and RC has been scarcely assessed, particularly in healthy populations.

In our cross-sectional observational study, we will investigate whether RC correlates with the unstable carotid plaque in a neurologically healthy population.

METHODS

Participants and design

This was an observational study based on a healthy medical examination population. We used a healthy check-up registry at the Beijing Tiantan Hospital Health Management Center, Capital Medical University, from October 2021 to September 2022 to select the eligible participants. For this study, inclusion criteria were (1) the participants were aged at least 18 years old; (2) they completed a standardised questionnaire for this study; (3) they finished carotid ultrasonography and SMI examination and completed blood tests for routine laboratory biomarkers (including lipid parameters); (n=1212). Exclusion criteria were (1) history of central nervous system diseases (eg, cerebrovascular disease including cerebral infarction, transient ischaemic attack, cerebral haemorrhage, etc) or severe neurologic deficit (n=30); (2) lipid parameters were incomplete (n=33); (3) demographic characteristics, personal history or medical history were incomplete (n=49).

Ultimately, the study included 1100 eligible participants (figure 1). This study followed the guidelines of the Helsinki Declaration and obtained approval from the central ethics committee of Beijing Tiantan Hospital. Informed and written consent was obtained from all participants.

Laboratory measurements

Fasting blood samples were acquired from the antecubital vein at least after an 8-hour to 12-hour overnight fast. All biomarkers were performed within 2 hours after sampling, including estimated glomerular filtration rate (eGFR), fasting blood glucose (FBG) and lipid parameters: TG, total cholesterol (TC), HDL-C, LDL-C, apolipoprotein B (ApoB) and apolipoprotein A1 (ApoA1). The samples were collected, preserved and processed in accordance with the policies and procedures of the clinical laboratory at Beijing Tiantan Hospital.

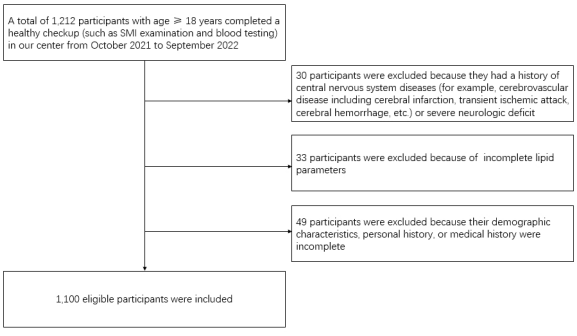

Figure 1 The flowchart of this study. SMI, superb microvascular imaging.

Using an autoanalyzer (Hitachi 008/008AS; Hitachi, Tokyo, Japan), TG was assessed using the glycerol phosphate oxidase-HMMPS-glycerol blanking method. TC was quantified by the cholesterol oxidase-HMMPS method.[12] LDL-C was measured using a direct test-select protection method. The measurement of HDL-C was assessed by a direct test-antibody blocking method. The concentrations of ApoA1 and ApoB were measured using immunoturbidimetric assays. Non-HDL-C was computed using the following formula: TC-HDL-C.[13] RC was determined using the following formula: RC=non-HDL-C–LDL-C.[14]

The FBG was measured with the hexokinase/glucose-6-phosphate dehydrogenase method. In this study, the Chronic Kidney Disease Epidemiology Collaboration creatinine equation with an adjusted coefficient of 1.1 was used to calculate eGFR. The measurement of serum creatinine levels at admission was conducted using the Jaffe method.[15]

Ultrasonography and SMI examination

The high-resolution ultrasound machine (Aplio A500, Canon Medical Systems Corporation, Japan) with an 11L4 linear array probe (frequency range, 4–11 MHz) was used to perform carotid artery ultrasonography and SMI examination. SMI is an advanced ultrasound imaging technique that is designed to surpass the constraints of traditional Doppler ultrasound while avoiding the requirement for intravenous contrast to display IPN.[8] Experienced radiologists who have many years of experience in carotid ultrasonography performed the carotid arteries on both sides of all participants and were blinded to the participant histories and lipid levels.

In longitudinal and transverse sections, the maximal thickness and length of each plaque were determined by dynamically scanning them in grayscale mode. The distance from the lumen-intima to the media-adventitia ultrasound interfaces comprises the intimamedia thickness (IMT). Carotid plaques are characterised as focal structures that encroach into a thickness of ≥1.5 mm IMT.[14]

After completing the standard ultrasound examination, we will adjust the ultrasound scanner settings to display the target plaque in both grayscale and SMI modes. An SMI-specific region of interest box was placed on the whole plaque. Several technical parameters will be modified as follows: dynamic range, mechanical index, frame rate and SMI velocity range. Plaques were initially examined in both transverse and longitudinal sections over a 2 min interval. Subsequently, the dynamic video images were saved on the device's hard disk.[16] After finishing the scan, we checked the video and observed whether there was neovascularisation with the plaque. IPN was detected using a strip-like or short-line hyperintense echo.[17]

Following the repeated SMI scans in various orientations, the segment exhibiting the greatest quantity of neovessels was selected for intraplaque neo-vessel classification. Blood flow signals are graded according to SMI as follows: IPN 0 (indicating a stable carotid plaque without blood flow signals in the plaque) and IPN 1 (indicating an unstable carotid plaque with intraplaque blood flow signals) are the grading criteria.

Assessment of covariates

We interviewed all participants using a standardised questionnaire designed specifically for this study, including demographic characteristics (sex, age, waist circumference, hip circumference, height and weight), smoking history and medical history (diabetes mellitus, hypertension, cardiovascular disease and dyslipidaemia). Beijing Tiantan Hospital assessed the whole set of biochemical indicators: LDL-C, TC, HDL-C, TG, ApoB, ApoA1, FBG and eGFR.

There are two types of smoking status: being a former or current smoker, or never smoking. The body mass index (BMI) was computed using the formula: BMI=weight (kg)/height (m^2). The waist-to-hip ratio (WHR) was determined by the formula: waist circumference (cm)/hip circumference (cm). Using an electronic sphygmomanometer to measure blood pressure when participants were in a seated position, the results were treated as diastolic blood pressure (DBP) and systolic blood pressure (SBP).

Hypertension was defined as any self-reported history of hypertension, or SBP ≥140 mm Hg or DBP ≥90 mm Hg.[18] Diabetes mellitus was characterised by the inclusion of individuals with a self-reported history of diabetes, utilising hypoglycaemic medication or having typical symptoms plus a random plasma glucose ≥11.1 mmol/L or FBG ≥7.0 mmol/L, haemoglobin A1c ≥6.5%,[19] glycated albumin ≥17.1%. Dyslipidaemia was defined as the inclusion of individuals with either the use of lipid-lowering drugs or any self-reported history. The definition of cardiovascular disease followed the guidelines of the European Society of Cardiology.[20] All clinical and laboratory factors were fully assessed for all participants.

Statistical analyses

Continuous variables for baseline characteristics were presented as median (IQR) and assessed using Wilcoxon or Kruskal-Wallis tests. For categorical variables, they were described as frequency (percentage) and were compared with the χ^2 test. According to the quartiles of RC, TG, TC, HDL-C, LDL-C, ApoA1, ApoB and non-HDL-C, all participants were separately divided into four categories. We evaluated the correlation between baseline characteristics and RC and further assessed the correlation of RC and other lipids with unstable carotid plaque. The study used univariate and multivariate logistic regression models to assess the correlation between IPN and lipids. Model 1 was adjusted for age and sex. Model 2 was further adjusted for BMI, SBP, DBP, WHR, FBG, eGFR, smoking history, hypertension, cardiovascular disease, dyslipidaemia and diabetes mellitus. Moreover, restricted cubic spline (RCS) was used to explore the non-linear correlation between lipids and unstable carotid plaque based on model 2.

All statistical analyses were conducted using R software V.4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS V.9.4 (SAS Institute, Cary, North Carolina). In all tests, a two-sided p<0.05 was deemed statistically significant.

RESULTS

Participants' baseline characteristics

The study ultimately enrolled 1100 eligible neurologically healthy participants with an average age of 57.00 years (IQR, 49.00–63.00) and 67.55% were men. The median (IQR) concentration of RC was 0.42 (0.32–0.55) mmol/L. Table 1 presented the baseline characteristics of healthy participants categorised according to the quartiles of RC. According to quartiles of RC, the participants with a higher concentration of RC were more likely to be older, men and smokers. Additionally, they had higher levels of BMI, WHR, SBP, DBP, TG, TC, LDL-C, ApoB, non-HDL-C, eGFR, FBG as well as a higher prevalence of diabetes mellitus (all p<0.05). Conversely, they had lower concentrations of HDL-C and ApoA1. The various quartiles of RC not exhibited any statistically significant differences concerning the history of hypertension, dyslipidaemia or cardiovascular disease.

Association between clinical characteristics and unstable carotid plaque

Table 2 illustrated that 779 of these participants (70.82%) with IPN=0 had stable carotid plaque, and 321 participants (29.18%) with IPN=1 had unstable carotid plaque. Meanwhile, it revealed the associations of baseline characteristics, RC and other lipids with unstable carotid plaque. Compared with participants with IPN=0, those with IPN=1 had a higher possibility of being male (77.57% vs 63.41%, p<0.0001) and smokers (34.89% vs 23.23%, p<0.0001). Furthermore, they had higher WHR (0.91 (IQR, 0.86–0.94) vs 0.89 (0.84–0.94), p=0.0073) and RC concentrations (0.45 (IQR, 0.35–0.58) vs 0.41 (0.30–0.55), p=0.0010) and conversely lower concentrations of HDL-C (1.39 (IQR, 1.19–1.63) vs 1.44 (1.24–1.66), p=0.0473) and ApoA1 (1.43 (IQR, 1.29–1.60) vs 1.51 (1.36–1.68), $p < 0.0001$). Table 2 also demonstrated unstable carotid plaque not related to SBP, DBP, age, BMI, TG, LDL-C, TC, non-HDL-C, ApoB, FBG, eGFR, diabetes mellitus, hypertension, cardiovascular disease or dyslipidaemia.

Table 3 demonstrated the correlation between unstable carotid plaque and lipids. The crude model of univariate logistic regression analysis showed that RC (per 1 mmol/L increase) was correlated with a 43.7% increased risk of unstable carotid plaque (95% CI 1036 to 1.994, p=0.0299). Compared with

Table 1 Baseline characteristics classified based on quartiles of RC

Characteristics	Total	RC, mmol/L				P value
		Quartiles 1 (< 0.32)	Quartiles 2 (0.32-<0.42)	Quartiles 3 (0.42-<0.55)	Quartiles 4(≥ 0.55)	
N	1100	269	263	272	296	
Age, year	57.00 (49.00–63.00)	56.00 (50.00–62.00)	58.00 (51.00–65.00)	56.00 (49.50–63.00)	55.00 (48.00–62.00)	0.0105
Male, N (%)	743 (67.55)	167 (62.08)	175 (66.54)	183 (67.28)	218 (73.65)	0.0317
BMI, kg/m²	25.02 (22.92–27.12)	24.17 (22.03–26.62)	24.19 (22.06–26.23)	25.39 (23.64–27.44)	26.27 (24.17–28.24)	< 0.0001
WHR	0.89 (0.85–0.94)	0.88 (0.82–0.92)	0.88 (0.83–0.92)	0.90 (0.86–0.94)	0.92 (0.88–0.96)	< 0.0001
SBP, mm Hg	128.00 (117.00–139.00)	124.00 (115.00–135.00)	128.00 (117.00–140.00)	127.00 (115.00–141.00)	131.00 (120.00–143.00)	< 0.0001
DBP, mm Hg	78.00 (71.00–86.00)	76.00 (68.00–84.00)	76.00 (69.00–85.00)	78.00 (71.00–85.00)	81.00 (74.00–88.00)	< 0.0001
TC, mmol/L	4.95 (4.27–5.55)	4.80 (4.05–5.39)	4.77 (4.09–5.38)	4.96 (4.27–5.55)	5.18 (4.52–5.85)	< 0.0001
TG, mmol/L	1.31 (0.93–1.96)	0.86 (0.65–1.04)	1.06 (0.84–1.33)	1.49 (1.22–1.77)	2.41 (2.01–3.25)	< 0.0001
HDL-C, mmol/L	1.42 (1.23–1.65)	1.60 (1.41–1.86)	1.53 (1.32–1.72)	1.37 (1.24–1.55)	1.23 (1.11–1.42)	< 0.0001
LDL-C, mmol/L	3.00 (2.34–3.55)	2.92 (2.18–3.50)	2.87 (2.18–3.40)	3.06 (2.40–3.62)	3.15 (2.50–3.68)	0.0009
Non-HDL-C, mmol/L	3.46 (2.79–4.07)	3.19 (2.44–3.74)	3.23 (2.55–3.77)	3.53 (2.88–4.11)	3.91 (3.25–4.52)	< 0.0001
RC, mmol/L	0.42 (0.32–0.55)	0.25 (0.21–0.29)	0.37 (0.34–0.39)	0.47 (0.44–0.51)	0.68 (0.60–0.86)	< 0.0001
ApoA1, g/L	1.49 (1.34–1.66)	1.56 (1.41–1.73)	1.52 (1.38–1.69)	1.47 (1.32–1.63)	1.42 (1.30–1.58)	< 0.0001
ApoB, g/L	0.90 (0.77–1.06)	0.82 (0.66–0.96)	0.84 (0.71–0.97)	0.93 (0.79–1.06)	1.01 (0.87–1.17)	< 0.0001
FBG, mmol/L	5.24 (4.89–5.92)	5.09 (4.81–5.50)	5.19 (4.89–5.80)	5.36 (4.96–6.04)	5.37 (4.99–6.39)	< 0.0001
eGFR, mL/min	109.42 (101.96–116.84)	108.82 (101.93–116.42)	107.95 (99.69–115.13)	110.50 (103.01–118.20)	110.27 (103.70–117.49)	0.0357
Smoking history, N (%)	293 (26.64)	55 (20.45)	75 (28.52)	69 (25.37)	94 (31.76)	0.0190
Hypertension, N (%)	399 (36.27)	84 (31.23)	90 (34.22)	103 (37.87)	122 (41.22)	0.0761
Diabetes mellitus, N (%)	230 (20.91)	36 (13.38)	56 (21.29)	67 (24.63)	71 (23.99)	0.0042
Dyslipidaemia, N (%)	181 (16.45)	35 (13.01)	46 (17.49)	42 (15.44)	58 (19.59)	0.1830
Cardiovascular disease, N (%)	68 (6.18)	16 (5.95)	17 (6.46)	9 (3.31)	26 (8.78)	0.0605

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio.

Table 2 Association of clinical characteristics and unstable carotid plaque

Characteristics	Total	IPN		P value
		IPN=0 (n=779)	IPN=1 (n=321)	
Risk factors				
Age, year	57.00 (49.00–63.00)	57.00 (50.00–63.00)	55.00 (49.00–63.00)	0.3721
Male, N (%)	743 (67.55)	494 (63.41)	249 (77.57)	< 0.0001
BMI, kg/m²	25.02 (22.92–27.12)	25.11 (22.86–27.14)	24.93 (23.17–27.06)	0.6327
WHR	0.89 (0.85–0.94)	0.89 (0.84–0.94)	0.91 (0.86–0.94)	0.0073
SBP, mm Hg	128.00 (117.00–139.00)	127.00 (117.00–138.00)	130.00 (117.00–142.00)	0.1029
DBP, mm Hg	78.00 (71.00–86.00)	78.00 (71.00–86.00)	78.00 (71.00–86.00)	0.9920
Smoking history, N (%)	293 (26.64)	181 (23.23)	112 (34.89)	< 0.0001
Hypertension, N (%)	399 (36.27)	271 (34.79)	128 (39.88)	0.1106
Diabetes mellitus, N (%)	230 (20.91)	152 (19.51)	78 (24.30)	0.0759
Dyslipidaemia, N (%)	181 (16.45)	136 (17.46)	45 (14.02)	0.1619
Cardiovascular disease, N (%)	68 (6.18)	46 (5.91)	22 (6.85)	0.5526
Baseline lipid parameters				
TC, mmol/L	4.95 (4.27–5.55)	4.90 (4.29–5.52)	5.02 (4.23–5.60)	0.5893
TG, mmol/L	1.31 (0.93–1.96)	1.31 (0.92–1.96)	1.32 (0.95–1.97)	0.7515
HDL-C, mmol/L	1.42 (1.23–1.65)	1.44 (1.24–1.66)	1.39 (1.19–1.63)	0.0473
LDL-C, mmol/L	3.00 (2.34–3.55)	2.98 (2.34–3.51)	3.05 (2.32–3.60)	0.7016
Non-HDL-C, mmol/L	3.46 (2.79–4.07)	3.42 (2.79–4.03)	3.51 (2.80–4.12)	0.2876
RC, mmol/L	0.42 (0.32–0.55)	0.41 (0.30–0.55)	0.45 (0.35–0.58)	0.0010
ApoA1, g/L	1.49 (1.34–1.66)	1.51 (1.36–1.68)	1.43 (1.29–1.60)	< 0.0001
ApoB, g/L	0.90 (0.77–1.06)	0.90 (0.77–1.05)	0.91 (0.77–1.08)	0.3249
Others				
FBG, mmol/L	5.24 (4.89–5.92)	5.24 (4.88–5.85)	5.27 (4.90–6.06)	0.2561
eGFR, mL/min	109.42 (101.96–116.84)	109.16 (102.10–116.70)	110.44 (101.23–117.11)	0.4753

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IPN, intraplaque neovascularisation; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio.

the Q1 (the lowest quartile) group of RC, the Q3 (the third quartile) and Q4 (the highest quartile) were significantly related to unstable carotid plaque (OR=1.976, 95% CI 1.343 to 2.909, p=0.0006 and OR=1.883, 95% CI 1.286 to 2.756, p=0.0011; p for trend=0.0016). After fully adjusting for all potential covariates, including sex, age, BMI, WHR, SBP, DBP, FBG, eGFR, smoking history, hypertension, diabetes mellitus, cardiovascular disease and dyslipidaemia, the positive correlation between higher RC concentration and an increased incidence of unstable carotid plaque remained significant (OR=1.930, 95% CI: 1.292 to 2.882, p=0.0013; OR=1.673, 95% CI: 1.113 to 2.515, p=0.0134). In model 2, the trend test indicated that the prevalence of unstable carotid plaque increased with higher quartiles of RC (p for trend=0.0164). Through continuous analysis, we observed that RC concentrations were significantly correlated with unstable carotid plaque.

Table 3 also shows that ApoA1 was significantly correlated with a reduced risk of unstable carotid plaque (OR=0.277, 95% CI 0.157 to 0.490, per 1 g/L increase, p<0.0001). Similar trends can be observed in the quartile-based categorisation of ApoA1 (Q2 (the second quartile) vs Q1: OR=0.651, 95% CI 0.454 to 0.934, p=0.0197; Q3 vs Q1: OR=0.548, 95% CI 0.382 to 0.787, p=0.0011; Q4 vs Q1: OR=0.461, 95% CI 0.319 to 0.668, p<0.0001; p for trend < 0.0001). Moreover, the same outcomes also occurred in multivariable-adjusted logistic regression analyses. Notably, we observed that RC concentrations still had a positive linear correlation with unstable carotid plaque after further adjusting LDL-C and ApoA1 based on model 2 (Q3 vs Q1: OR=1.786, 95% CI 1.190 to 2.680, p=0.0051; Q4 vs Q1: OR=1.526, 95% CI 1.007 to 2.312, p=0.0463) (table 4). In figure 2, we used multivariable-adjusted RCS analyses to flexibly visualise and model the non-linear relations between unstable carotid plaque and lipid parameters. The outcomes further suggested a linear

Table 3 Association between unstable carotid plaque and lipid parameters in the logistic regression analysis

Lipid parameters	N (%)	OR (95% CI) P value		
		Crude model	Adjusted model 1	Adjusted model 2
RC, per 1 mmol/L increase	321 (29.18%)	1.437 (1036–1.994) 0.0299	1.364 (0.983–1.891) 0.0629	1.279 (0.905–1.807) 0.1633
Quartiles of RC				
Q1 (< 0.32)	56 (20.82%)	Ref.	Ref.	Ref.
Q2 (0.32-<0.42)	74 (28.14%)	1.489 (1.000–2.219) 0.0502	1.450 (0.969–2.169) 0.0706	1.377 (0.915–2.073) 0.1248
Q3(0.42-<0.55)	93 (34.19%)	1.976 (1.343–2.909) 0.0006	1.934 (1.310–2.857) 0.0009	1.930 (1.292–2.882) 0.0013
Q4(≥ 0.55)	98 (33.11%)	1.883 (1.286–2.756) 0.0011	1.774 (1.207–2.607) 0.0035	1.673 (1.113–2.515) 0.0134
p value for trend		0.0016	0.0048	0.0164
TC, per 1 mmol/L increase	321 (29.18%)	1.044 (0.920–1.185) 0.5005	1.111 (0.974–1.268) 0.1176	1.089 (0.945–1.256) 0.2377
Quartiles of TC				
Q1 (< 4.265)	83 (30.18%)	Ref.	Ref.	Ref.
Q2 (4.265-<4.95)	66 (24.26%)	0.741 (0.508–1.082) 0.1207	0.800 (0.544–1.177) 0.2572	0.823 (0.549–1.232) 0.3429
Q3(4.95-<5.55)	83 (30.63%)	1.021 (0.709–1.471) 0.9099	1.121 (0.770–1.631) 0.5523	1.148 (0.774–1.704) 0.4928
Q4(≥ 5.55)	89 (31.56%)	1.067 (0.744–1.528) 0.7248	1.246 (0.857–1.813) 0.2494	1.189 (0.796–1.775) 0.3978
p value for trend		0.4598	0.1261	0.2060
TG, per 1 mmol/L increase	321 (29.18%)	1.024 (0.92–1.129) 0.6340	1.003 (0.907–1.109) 0.9556	0.970 (0.869–1.084) 0.5956
Quartiles of TG				
Q1 (< 0.93)	73 (27.04%)	Ref.	Ref.	Ref.
Q2 (0.93-<1.31)	85 (30.69%)	1.195 (0.825–1.731) 0.3467	1.184 (0.814–1.722) 0.3770	1.112 (0.757–1.632) 0.5883
Q3(1.31-<1.96)	81 (29.35%)	1.121 (0.772–1.628) 0.5487	1.087 (0.745–1.585) 0.6647	1.008 (0.680–1.495) 0.9664
Q4(≥ 1.96)	82 (29.60%)	1.135 (0.782–1.647) 0.5057	1.062 (0.727–1.551) 0.7557	0.948 (0.625–1.438) 0.8031
p value for trend		0.6889	0.9836	0.6239
HDL-C, per 1 mmol/L increase	321 (29.18%)	0.708 (0.467–1.073) 0.1033	1.042 (0.662–1.640) 0.8598	1.065 (0.652–1.742) 0.8006
Quartiles of HDL-C				
Q1 (< 1.23)	90 (33.33%)	Ref.	Ref.	Ref.
Q2 (1.23-<1.42)	81 (30.80%)	0.890 (0.618–1.281) 0.5308	0.916 (0.635–1.321) 0.6376	0.948 (0.653–1.376) 0.7785
Q3(1.42-<1.65)	71 (25.18%)	0.673 (0.465–0.974) 0.0355	0.766 (0.526–1.116) 0.1649	0.778 (0.527–1.148) 0.2058
Q4(≥ 1.65)	79 (27.72%)	0.767 (0.534–1.102) 0.1513	1.037 (0.703–1.530) 0.8545	1.030 (0.682–1.557) 0.8874
p value for trend		0.0949	0.9934	0.9614
LDL-C, per 1 mmol/L increase	321 (29.18%)	1.024 (0.886–1.185) 0.7445	1.066 (0.917–1.239) 0.4086	1.050 (0.893–1.235) 0.5528
Quartiles of LDL-C		1.024 (0.886–1.185)0.7445	1.066 (0.917–1.239) 0.4086	1.050 (0.893–1.235) 0.5528
Q1 (<2.34)	82 (30.04%)	Ref.	Ref.	Ref.

Continued

Table 3 Continued

Lipid parameters	N (%)	OR (95% CI) P value		
		Crude model	Adjusted model 1	Adjusted model 2
Q2 (2.34≤3.00)	72 (26.09%)	0.822 (0.566–1.194) 0.3033	0.861 (0.589–1.259) 0.4407	0.872 (0.585–1.301) 0.5033
Q3(3.00≤3.55)	80 (28.99%)	0.951 (0.659–1.372) 0.7872	0.973 (0.668–1.418) 0.8878	0.948 (0.635–1.415) 0.7945
Q4(≥ 3.55)	87 (31.64%)	1.078 (0.750–1.549) 0.6852	1.170 (0.804–1.701) 0.4124	1.121 (0.750–1.674) 0.5785
p value for trend		0.5560	0.3350	0.4813
Non-HDL-C, per 1 mmol/L increase	321 (29.18%)	1.089 (0.953–1.245) 0.2104	1.119 (0.974–1.286) 0.1112	1.094 (0.941–1.270) 0.2423
Quartiles of Non-HDL-C				
Q1 (<2.79)	78 (28.78%)	Ref.	Ref.	Ref.
Q2 (2.79≤3.46)	73 (26.55%)	0.894 (0.614–1.301) 0.5591	0.911 (0.623–1.334) 0.6334	0.895 (0.601–1.332) 0.5834
Q3(3.46≤4.07)	79 (28.42%)	0.982 (0.678–1.422) 0.9246	1.015 (0.693–1.487) 0.9375	0.978 (0.656–1.458) 0.9136
Q4(≥4.07)	91 (32.97%)	1.217 (0.846–1.751) 0.2894	1.296 (0.891–1.886) 0.1755	1.229 (0.822–1.837) 0.3151
p value for trend		0.2519	0.1454	0.2593
ApoA1, per 1 g/L increase	321 (29.18%)	0.277 (0.157–0.490) <0.0001	0.397 (0.215–0.735) 0.0033	0.350 (0.185–0.664) 0.0013
Quartiles of ApoA1				
Q1 (< 1.34)	105 (39.03%)	Ref.	Ref.	Ref.
Q2 (1.34≤1.49)	78 (29.43%)	0.651 (0.454–0.934) 0.0197	0.683 (0.475–0.981) 0.0393	0.648 (0.448–0.938) 0.0213
Q3 (1.49≤1.66)	73 (25.98%)	0.548 (0.382–0.787) 0.0011	0.610 (0.422–0.882) 0.0085	0.576 (0.395–0.841) 0.0042
Q4 (≥1.66)	65 (22.81%)	0.461 (0.319–0.668) <0.0001	0.593 (0.398–0.882) 0.0100	0.549 (0.364–0.830) 0.0045
p value for trend		<0.0001	0.0087	0.0041
ApoB, per 1 g/L increase	32129.18%)	1.332 (0.748–2.371) 0.3302	1.414 (0.781–2.561) 0.2529	1.256 (0.658–2.396) 0.4898
Quartiles of ApoB				
Q1 (< 0.77)	80 (29.41%)	Ref.	Ref.	Ref.
Q2 (0.77≤0.90)	71 (26.49%)	0.865 (0.594–1.260) 0.4500	0.868 (0.593–1.272) 0.4691	0.871 (0.586–1.295) 0.4960
Q3 (0.90≤1.06)	80 (28.07%)	0.937 (0.649–1.352) 0.7265	0.948 (0.651–1.381) 0.7808	0.925 (0.623–1.373) 0.6982
Q4 (≥1.06)	90 (32.73%)	1.168 (0.812–1.678) 0.4023	1.194 (0.823–1.731) 0.3505	1.125 (0.754–1.677) 0.5642
p value for trend		0.3452	0.2897	0.4841

Crude model: unadjusted. Model 1: adjusted for sex and age. Model 2: adjusted for sex, age, BMI, WHR, SBP, DBP, FBG, eGFR, smoking history, hypertension, dyslipidaemia, diabetes mellitus, and cardiovascular disease.
ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio.

Table 4 The relationship between unstable carotid plaque and RC concentrations

	Model 2+LDL-C	Model 2+LDL-C+ApoA1
RC, per 1 mmol/L increase	1.288 (0.912–1.819) 0.1511	1.249 (0.886–1.760) 0.2043
Quartiles of RC		
Q1 (< 0.32)	Ref.	Ref.
Q2 (0.32≤0.42)	1.378 (0.915–2.073) 0.1245	1.337 (0.887–2.016) 0.1654
Q3(0.42≤0.55)	1.922 (1.286–2.873) 0.0014	1.786 (1.190–2.680) 0.0051
Q4(≥0.55)	1.663 (1.104–2.505) 0.0150	1.526 (1.007–2.312) 0.0463
p for trend	0.0189	0.0624

Model 2: adjusted for age, sex, BMI, WHR, SBP, DBP, FBG, eGFR, smoking history, dyslipidaemia, hypertension, cardiovascular disease, and diabetes mellitus.
ApoA1, apolipoprotein A1; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

correlation between RC concentrations and unstable carotid plaque (p for non-linearity=0.055). In a neurologically healthy population, an elevated risk of unstable carotid plaque was observed at higher RC concentrations. Furthermore, ApoA1 concentrations were non-linearly correlated with unstable carotid plaque (p for non-linearity=0.041), not TG, TC, HDL-C, LDL-C, non-HDL-C and ApoB (p for non-linearity> 0.05). According to the piecewise linear models, there was inverse and linear evidence of association at ApoA1 concentrations below 1.49 g/L, whereas there was little evidence of such correlation at higher concentrations.

DISCUSSION

In this observational study, we found that RC concentrations were independently correlated with unstable carotid plaque, using SMI to assess intraplaque neovascularisation in a neurologically healthy population.

Our findings in the study, consistent with the previous studies, displayed that RC had an association with unstable carotid plaque. A retrospective study showed that non-HDL-C and RC were excellent risk factors for carotid plaque vulnerability in participants with acute ischaemic stroke. The study used the acoustic characteristics of

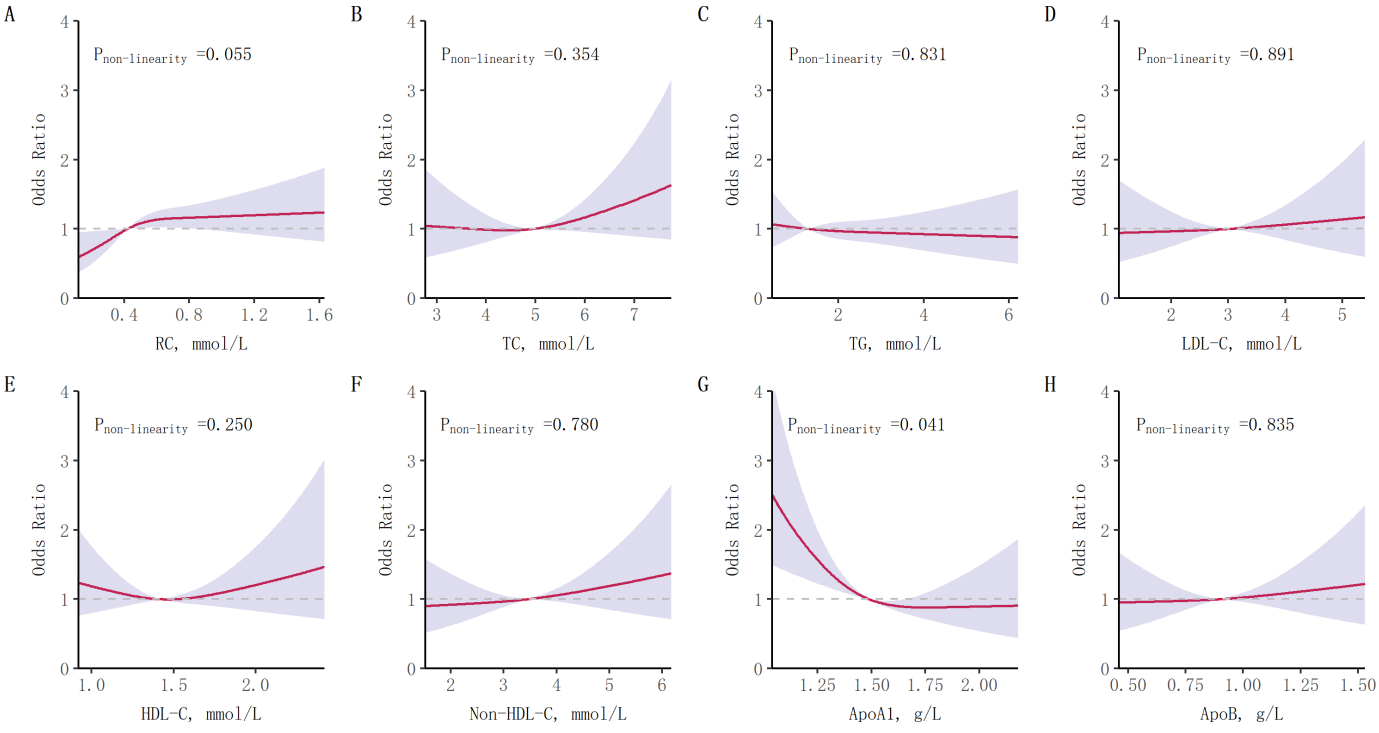

Figure 2 The nonlinear relationship between lipid parameters and unstable carotid plaque. RC, remnant cholesterol; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B. Adjusted for: sex, age, BMI, WHR, SBP, DBP, FBG, eGFR, smoking history, hypertension, diabetes mellitus, dyslipidaemia, and cardiovascular disease.

the plaques in ultrasound to define unstable plaques.[21] Zambon *et al* showed that very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) exhibited a significant correlation with macrophage content within the carotid plaque-a biomarker of unstable plaque-in participants with severe internal carotid artery stenosis.[22] Furthermore, in the population with stable angina, RC was verified to be related to coronary plaque vulnerability, not LDL-C or HDL-C levels.[23]

Consistent with our results, in the previous studies, RC had an association with the incidence of ASCVD but not LDL-C, even if the population received statin therapy and had lower LDL-C concentrations.[24–27] Castañer and colleagues analysed the data from the PREDIMED trial, and their results demonstrated that the concentrations of RC and TG were related to cardiovascular outcomes, not LDL-C, in a group of Mediterranean participants who had high cardiovascular risks.[28] Furthermore, one of the recent prospective studies suggested that in individuals without known ASCVD, elevated RC concentrations had an association with ASCVD but not non-HDL-C, ApoB or LDL-C. Compared with the participants with concordance, an elevated risk of ASCVD was found in the group with discordant high RC/low LDL-C, which did not occur in those with low RC/high LDL-C discordance.[29] Furthermore, studies have shown that higher RC concentrations have a correlation with an increased risk of ischaemic stroke and vascular stenosis. A cohort-based study showed higher concentrations of RC were correlated with increased risk of ischaemic stroke and myocardial infarction, especially peripheral artery disease-a fivefold increase in it.[30]

RC is the cholesterol content of TRLs, which consists of chylomicron remnants in the non-fasting state and VLDL and IDL in the fasting state.[31 32] The following mechanisms may explain the correlation between RC and unstable carotid plaque: first, RC mechanistically carries a bigger load of cholesterol than LDL-C. It preferentially is trapped via attachment to extracellular proteoglycans and enters into and deposits arterial intima. In addition, RC is absorbed by macrophages directly without oxidative modification, effectively resulting in the formation of macrophage foam cells. Finally, the activity of lipoprotein-lipase on the RC surface contributes to the release of monoacylglycerols, free fatty acids and other molecules that will contribute to local damage and inflammation.[9 19 29 33–35] Inflammatory hypoxic and destabilising microenvironments in the plaque lead to neovascularisation, and plaque destabilisation is likely to be caused by the neovascularisation and IPH inside the plaque.[36] These changes will increase the plaque's vulnerability and explain the correlation between RC and unstable carotid plaque.

In our study, we found a negative correlation between ApoA1 concentrations and unstable carotid plaque. A study showed that low concentrations of ApoA1 were related to carotid plaque in populations with metabolic syndrome.[37] The underlying mechanisms by which lower ApoA1 concentrations lead to an increased incidence of unstable carotid plaque may be attributed to the crucial role of ApoA1 in reverse cholesterol transport.[38] In addition, the ability of ApoA1 to restrain necroptosis in macrophages and inhibit the formation and development of necrotic cores in atherosclerosis may contribute to those mechanisms.[39]

Study limitations and strengths

There are some limitations in the study. First, our study was a single-centre and cross-sectional study in China, and our results may not generalise outcomes to other racial groups or other populations and should be confirmed in further large multicentre prospective studies. Second, we used the fasting samples to calculate the levels of RC, but some studies showed that non-fasting RC was more strongly correlated with ASCVD[29 33] than fasting and was a reliable biomarker of plasma atherogenic lipoprotein concentrations.[40] Finally, in our study, we used the formula to indirectly calculate the concentrations of RC. Compared with RC-direct, this method may perhaps underestimate the value of RC.[32]

Our study also has some strengths. First, RC is easily available from a standard lipid profile and does not require extra cost,[33] so it can be widely implemented in clinics. Second, we use SMI to evaluate and categorise IPN, and its accuracy is comparable to contrast-enhanced ultrasound (CEUS). SMI provides a non-invasive substitute for CEUS in assessing the vulnerability of carotid plaque.[8] Finally, the current study elaborates on the association between unstable carotid plaque and RC in a neurologically healthy Chinese population. Our findings can provide assistance for those who are neurologically healthy in the primary prevention of stroke.

CONCLUSIONS

Increased RC concentrations were positively related to unstable plaque, not LDL-C or ApoB. This implies that elevated RC causes unstable carotid plaque. RC is a superior biomarker to assess unstable carotid plaque and carotid artery atherosclerosis risk. We are supposed to give more attention to RC in the neurologically healthy population, especially when LDL-C concentrations achieve clinical standards. In the future, not only in primary and secondary prevention but also in related studies, we should put more focus on lowering RC concentration to avoid clinical events such as ischaemic stroke and myocardial infarction and their recurrence.

Acknowledgements The authors thank the study subjects for their participation and support of this study.

Contributors WL contributed to the study design, data acquisition, and data analysis and wrote the manuscript. YL, JL and HZ contributed to the study design. YL and JL contributed to the data acquisition. QG contributed data analysis and wrote the manuscript. JL and AW contributed to the data analysis. WL, HZ and AW reviewed and edited the intellectual content. All authors gave final approval for this version to be published. All authors read and approved the final manuscript. Guarantor:HZ.

Funding This study was supported by National Key Research and Development Program of China (2018YFC1311203).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by IRB of Beijing Tiantan Hospital, Capital Medical University KY 2020-085-02. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Anxin Wang http://orcid.org/0000-0003-4351-2877
Huaguang Zheng http://orcid.org/0000-0001-6400-5474

REFERENCES

1 Wang Y-J, Li Z-X, Gu H-Q, *et al*. China stroke Statistics: an update on the 2019 report from the National center for Healthcare quality management in neurological diseases, China National clinical research center for neurological diseases, the Chinese stroke Association, national center for chronic and non-communicable disease control and prevention, Chinese center for disease control and prevention and Institute for global Neuroscience and stroke Collaborations. *Stroke Vasc Neurol* 2022;7:415–50.
2 Migdalski A, Jawien A. New insight into biology, molecular diagnostics and treatment options of unstable carotid Atherosclerotic plaque: a narrative review. *Ann Transl Med* 2021;9:1207.
3 Mura M, Della Schiava N, Long A, *et al*. Carotid Intraplaque haemorrhage: pathogenesis, histological classification, imaging methods and clinical value. *Ann Transl Med* 2020;8:1273.
4 Saba L, Saam T, Jäger HR, *et al*. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. *Lancet Neurol* 2019;18:559–72.
5 Saba L, Moody AR, Saam T, *et al*. Vessel wall-imaging biomarkers of carotid plaque vulnerability in stroke prevention trials: A viewpoint from the carotid imaging consensus group. *JACC Cardiovasc Imaging* 2020;13:2445–56.
6 Chistiakov DA, Orekhov AN, Bobryshev YV. Contribution of neovascularization and Intraplaque haemorrhage to Atherosclerotic plaque progression and instability. *Acta Physiol (Oxf)* 2015;213:539–53.
7 Michel J-B, Virmani R, Arbustini E, *et al*. Intraplaque Haemorrhages as the trigger of plaque vulnerability. *Eur Heart J* 2011;32:1977–85, .
8 Zamani M, Skagen K, Scott H, *et al*. Carotid plaque neovascularization detected with superb Microvascular imaging ultrasound without using contrast media. *Stroke* 2019;50:3121–7.
9 Tall AR, Thomas DG, Gonzalez-Cabodevilla AG, *et al*. Addressing Dyslipidemic risk beyond LDL-cholesterol. *J Clin Invest* 2022;132:e148559.
10 Hoogeveen RC, Ballantyne CM. Residual cardiovascular risk at low LDL: remnants Lipoprotein(A), and inflammation. *Clin Chem* 2021;67:143–53.
11 Burnett JR, Hooper AJ, Hegele RA. Remnant cholesterol and Atherosclerotic cardiovascular disease risk. *Journal of the American College of Cardiology* 2020;76:2736–9.
12 Wu J, Wang Y, Kang K, *et al*. Association between cumulative exposure to different lipid parameters and risk of newly developed carotid plaque. *Stroke Vasc Neurol* 2021;6:359–65.
13 Mach F, Baigent C, Catapano AL, *et al*. ESC/EAS guidelines for the management of Dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–88.
14 Liu B, Fan F, Zheng B, *et al*. Association of remnant cholesterol and lipid parameters with new-onset carotid plaque in Chinese population. *Front Cardiovasc Med* 2022;9:903390.
15 Pan Y, Jing J, Chen W, *et al*. Association between impaired renal function and stroke outcome in patients with versus without atrial fibrillation. *Eur J Neurol* 2018;25:1041–8.
16 Li Y, Zheng S, Zhang J, *et al*. Advance ultrasound techniques for the assessment of plaque vulnerability in symptomatic and asymptomatic carotid stenosis: a Multimodal ultrasound study. *Cardiovasc Diagn Ther* 2021;11:28–38.
17 Wang Y, Yao M, Zou M, *et al*. Assessment of carotid Intraplaque neovascularization using superb Microvascular imaging in high risk of stroke individuals: results from a community-based study. *Front Neurol* 2019;10:1146.
18 Williams B, Mancia G, Spiering W, *et al*. ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021–104.
19 Chait A, Ginsberg HN, Vaisar T, *et al*. Remnants of the Triglyceride-rich lipoproteins, diabetes, and cardiovascular disease. *Diabetes* 2020;69:508–16.
20 Knuuti J, Wijns W, Saraste A, *et al*. ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–77.
21 Zhao Z, Wang H, Hou Q, *et al*. Non-traditional lipid parameters as potential predictors of carotid plaque vulnerability and stenosis in patients with acute ischemic stroke. *Neurol Sci* 2023;44:835–43.
22 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;230:106–9.
23 Björkegren JLM, Hägg S, Talukdar HA, *et al*. Plasma cholesterol-induced lesion networks activated before regression of early, mature, and advanced Atherosclerosis. *PLoS Genet* 2014;10:e1004201.
24 Varbo A, Benn M, Tybjærg-Hansen A, *et al*. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation* 2013;128:1298–309.
25 Elshazly MB, Mani P, Nissen S, *et al*. Remnant cholesterol, coronary Atheroma progression and clinical events in Statin-treated patients with coronary artery disease. *Eur J Prev Cardiol* 2020;27:1091–100.
26 Lee SJ, Kim S-E, Go T-H, *et al*. Remnant cholesterol, low-density lipoprotein cholesterol, and incident cardiovascular disease among Koreans: a national population-based study. *Eur J Prev Cardiol* 2023;30:1142–50.
27 Delialis D, Georgiopoulos G, Aivalioti E, *et al*. Remnant cholesterol and Atherosclerotic disease in high cardiovascular risk patients beyond LDL cholesterol and Hypolipidemic treatment. *Hellenic J Cardiol* 2022;66:26–31.
28 Castañer O, Pintó X, Subirana I, *et al*. Remnant cholesterol, not LDL cholesterol, is associated with incident cardiovascular disease. *J Am Coll Cardiol* 2020;76:2712–24.
29 Quispe R, Martin SS, Michos ED, *et al*. Remnant cholesterol predicts cardiovascular disease beyond LDL and Apob: a primary prevention study. *Eur Heart J* 2021;42:4324–32.
30 Wadström BN, Wulff AB, Pedersen KM, *et al*. Elevated remnant cholesterol increases the risk of peripheral artery disease, myocardial infarction, and ischaemic stroke: a cohort-based study. *Eur Heart J* 2022;43:3258–69.
31 Nordestgaard BG. Triglyceride-rich lipoproteins and Atherosclerotic cardiovascular disease: new insights from epidemiology, Genetics, and biology. *Circ Res* 2016;118:547–63.
32 Stürzebecher PE, Katzmann JL, Laufs U. What is 'remnant cholesterol *Eur Heart J* 2023;44:1446–8.
33 Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014;384:626–35.
34 Rosenson RS, Shaik A, Song W. New therapies for lowering Triglyceride-rich lipoproteins: JACC focus seminar 3/4. *J Am Coll Cardiol* 2021;78:1817–30.
35 Levin MG. Remnant lipoproteins as a target for Atherosclerosis risk reduction. *Arterioscler Thromb Vasc Biol* 2021;41:2076–9.
36 Chistiakov DA, Melnichenko AA, Myasoedova VA, *et al*. Role of lipids and Intraplaque hypoxia in the formation of neovascularization in Atherosclerosis. *Ann Med* 2017;49:661–77.
37 Abi-ayad M, Abbou A, Abi-Ayad F zahra, *et al*. Apoa1 and VLDL-TG as biomarkers for the carotid plaque presence in patients with metabolic syndrome. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2018;12:175–9.
38 Teague HL, Li H, Berg AR, *et al*. The relationship between circulating APOA-1 and Atherosclerosis initiation and progression in psoriasis. *J Invest Dermatol* 2023;143:1947–54.
39 Kluck GEG, Qian AS, Sakarya EH, *et al*. Apolipoprotein A1 protects against necrotic core development in Atherosclerotic plaques: Pdzk1-dependent high-density lipoprotein suppression of Necroptosis in Macrophages. *Arterioscler Thromb Vasc Biol* 2023;43:45–63.
40 Sandesara PB, Virani SS, Fazio S, *et al*. The forgotten lipids: triglycerides, remnant cholesterol, and Atherosclerotic cardiovascular disease risk. *Endocr Rev* 2019;40:537–57.