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Association of Retinal Arterial Narrowing With New-Onset Carotid Plaque: A Chinese Community-Based Nested Case-Control Cohort Study

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Keywords: arteriovenous ratio | nested case-control study | new-onset carotid plaque | retinal artery narrowing

ABSTRACT

To investigate whether retinal arterial narrowing is associated with incident carotid plaque in the general population. Individuals without carotid plaque in 2014 who developed new-onset carotid plaque in 2018 were selected as cases (n = 156) for the atherosclerosis group and matched for age and sex in a ratio of 1:1 for the control group. The effects of the baseline central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), and arteriovenous ratio (AVR) on the risk of new-onset carotid plaque were evaluated in multivariable conditional logistic regression models. Subgroup analyses were performed. The mean CRAE, CRVE, and AVR were 153.03 ± 12.77 μm, 232.41 ± 19.78 μm, and 0.66 ± 0.07, respectively. After adjusting for multiple variables, the risk of developing new-onset carotid plaque increased by 4% (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02–1.07, $p < 0.01$) with each 1-μm decrease in CRAE and 80% (OR 1.80, 95% CI 1.17–2.78, $p < 0.01$) with each 0.1-point decline in AVR. When CRAE and AVR were considered as categorical variables, compared with subjects in the highest CRAE and AVR groups, those in the lowest CRAE and AVR groups had a 159% (OR 2.59, 95% CI 1.34–5.01, $p < 0.01$) and 93% (OR 1.93, 95% CI 1.08–3.46, $p = 0.03$) increase in risk of developing new-onset carotid plaque, respectively. However, CRVE was not significantly related to new-onset carotid plaque. Subgroup and interaction analyses were performed, and no significant modification effect was found. In conclusion, retinal arterial narrowing was strongly related to the risk of incident carotid plaque.

1 | Introduction

Fundus photography provides a unique and non-invasive window for visualization of the retinal arteries and venules. It is readily accessible and widely used as a microvascular surrogate biomarker because retinal vessels have physiological properties and anatomical features similar to those of vascular systems in other organs [1]. Retinal arterial narrowing has been confirmed

Yimeng Jiang and Shenshen Yan contributed equally to this work.

to be associated with cardiovascular risk factors, changes in cardiac structure, heart failure, coronary artery disease, stroke, and cardiovascular mortality [2–8].

Carotid plaque, which can be assessed non-invasively by ultrasound, has provided a window for early detection of atherosclerosis. It is the primary pathological mechanism of most cardiovascular diseases, starting early in life and remaining latent and asymptomatic for a long time before progressing to an advanced stage [9] in apparently healthy persons. Previous research has shown that carotid plaque is associated with an increased risk of cardiovascular disease and can be used for prediction of risk [10, 11]. However, few studies have focused on the relationship between retinal vessel caliber and carotid plaque, and their findings are controversial. Moreover, no research has investigated whether retinal arterial narrowing, a surrogate marker of arteriosclerosis, can predict new-onset carotid plaque, which is an early stage of atherosclerotic cardiovascular disease.

In this prospective nested case-control study, we investigated this relationship using retinal vessel caliber as a marker of arteriosclerosis and carotid plaque as a marker of atherosclerosis.

2 | Methods

2.1 | Study Population

The subjects were from an ongoing prospective study of persons aged ≥40 years residing in the Gucheng and Pingguoyuan communities of the Shijingshan District in Beijing, China. The study design and protocol have been described in detail previously [12]. In brief, 9540 participants were enrolled in 2011 and 2012, and 3823 of 5962 participants with gene chip data at baseline volunteered for the first-round follow-up in 2014. A total of 4432 of the initial 9540 participants responded and underwent a second-round follow-up in 2018. The study was restricted to subjects both with retinography images and carotid ultrasound in 2014 and 2018, with data from 2014 deemed as the baseline and data from 2018 as the outcome. Participants without carotid plaque at baseline who developed new-onset carotid plaque in 2018 were selected as cases ($n = 156$). Next, one control was chosen for each case matched by age (within 2 years) and sex.

The study was reviewed and approved by the ethics committees of Peking University First Hospital and Peking University. Written informed consent was obtained before the examination.

2.2 | Data Collection

Questionnaires, anthropometry, and laboratory tests.

Trained staff performed structured interviews to collect information on sociodemographic and clinical characteristics, including age, sex, smoking and alcohol consumption, medical history of hypertension, diabetes mellitus, dyslipidaemia, stroke, and coronary artery disease, and anti-hypertensive, hypoglycaemic, and lipid-lowering medications.

Blood pressure (BP) was measured on three occasions, each separated by a 2-min interval, in the seated position using a HEM-7117 electronic sphygmomanometer (Omron, Kyoto, Japan) with standard calibrations after a 5-min rest. The three BP readings were averaged for analysis. Using standardized techniques and equipment, height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index was calculated by dividing weight (kg) by the square of height (m^2).

Fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and serum creatinine concentrations were measured using a C8000 Automatic Analyzer (Roche, Basel, Switzerland).

2.3 | Measurement of Retinal Vessel Caliber

Photographs of both retinas were obtained using a digital retinal fundus camera (Canon, Tokyo, Japan) in a dark room; 45° fundus images centred on the optic disk (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) were captured by a well-trained operator. Retinal vessel caliber was measured using a computer-assisted semi-automated imaging program (IVAN, University of Wisconsin, Madison, WI, USA) by a well-trained grader followed by a standardized protocol. Optic disc-centred images of the right eye were used for measurement, and the images of the left eye were used if those on the right were unavailable. Retinal vessels were analyzed in the zone from a 0.5 to 1.0 disc diameter from the optic disc margin on each photograph.

After selecting six or more of the largest arterioles and venules, the IVAN software automatically combined vessel diameters into a pair of indices (Figure 1). The arterial and venular calibers were finally summarized as the central retinal artery equivalent (CRAE) and central retinal venule equivalent (CRVE) based on the revised Knudtson-Parr-Hubbard formula [13]. The arteriovenous ratio (AVR) was calculated as the ratio of the CRAE to the CRVE.

2.4 | Assessment of Carotid Plaque

The carotid intima–media thickness (IMT) and plaque were measured using an echo ultrasound system (Terason; Burlington, MA, USA) equipped with an 8-MHz linear probe by well-trained staff according to the standard recommendations. The carotid arteries measured consisted of the carotid bulb (1 cm proximal to the flow divider), the common carotid artery (between 1 and 2 cm proximal to the tip of the flow divider), and the internal carotid artery (1 cm distal to the flow divider). Patients were in a supine position during the examination, and the carotid IMT was measured in the far wall of the common carotid artery. Next, Vascular Research Tools 6 software (MIA Carotid Analyzer 6.0) was used to automatically measure the longitudinal static image of the common carotid artery. The presence of carotid plaque was defined as (1) a thickness ≥1.5 mm, (2) a focal structure that encroaches into the carotid artery lumen by ≥0.5 mm, or (3) a focal increase of 50% in the adjacent IMT [14].

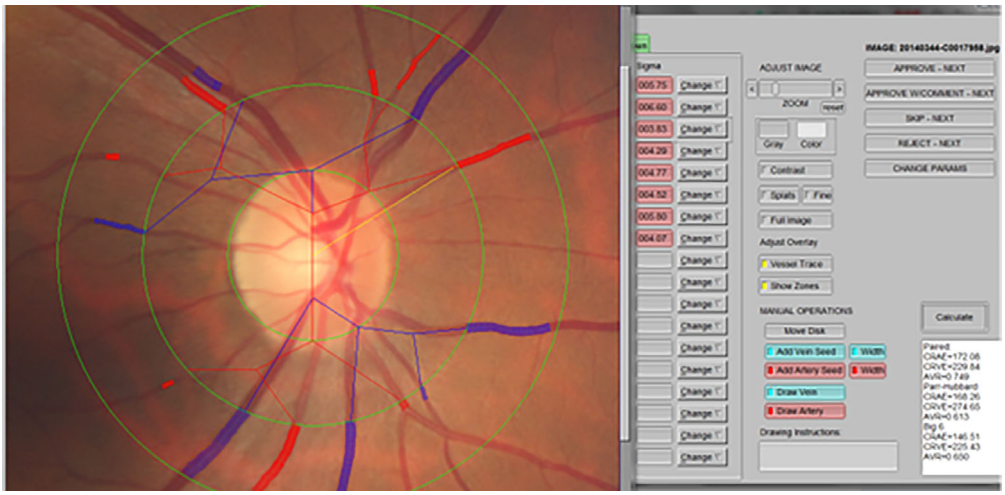

FIGURE 1 | Measurement of retinal vessles.

2.5 | Definition of Diseases

Diabetes mellitus was defined as any self-reported history of diabetes, fasting blood glucose ≥7.0 mmol/L, oral glucose tolerance test ≥11.1 mmol/L, or hypoglycaemic medication. Hypertension was defined as any self-reported history of high BP, systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or being on antihypertensive medication. Dyslipidemia was defined as any self-reported history of hyperlipidemia, triglycerides ≥1.70 mmol/L (150 mg/dL), total cholesterol ≥5.18 mmol/L (200 mg/dL), low-density lipoprotein cholesterol >3.37 mmol/L (130 mg/dL), high-density lipoprotein cholesterol <1.04 mmol/L (40 mg/dL), or being on lipid-lowering medication. Cardiovascular disease was defined as any self-reported history of coronary artery disease or stroke.

2.6 | Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation if distributed normally and as the median (interquartile) if distributed in a skewed manner. Categorical variables are reported as the number (percentage). Normally distributed variables were compared using a one-way analysis of variance and variables with a skewed distribution were compared using the Kruskal–Wallis test. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test.

Restricted cubic splines were applied to fit the smooth curves for the relationship between carotid plaque and CRAE, CRVE, AVR respectively using the logistic regression model in R package "rms." CRAE, CRVE, and AVR were analyzed as both continuous and categorical variables. Participants were divided into three groups according to their baseline CRAE, CRVE, and AVR. Multivariable conditional logistic regression models were used to evaluate the effects of baseline CRAE, CRVE, and AVR on the risk of new-onset carotid plaque. Adjustments were made for potential confounding variables, including body mass index, current smoking and alcohol consumption, estimated glomerular filtration rate (eGFR), fasting blood glucose, non-HDL-C, hypertension, diabetes mellitus, dyslipidemia, cardiovascular diseases, and anti-hypertensive, anti-diabetic, and lipid-lowering agents. Odds ratios (ORs) for new-onset carotid plaque were reported according to each 1-μm decrease in CRAE and CRVE and each 0.1 unit decrease in AVR for the three CRAE, CRVE, and AVR groups. Subgroup analyses were performed to determine whether the results were consistent across categories of possible confounders.

All statistics were performed using Empower(R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R software (www.R-project.org; The R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline Characteristics of Participants

A total of 156 cases with a new-onset carotid plaque were identified and matched to 156 controls. Table 1 summarizes the baseline characteristics of the cases and controls. There was no significant difference in age or sex between the two groups. Compared with the control group, participants with new-onset carotid plaque had smaller CRAE and AVR values, higher rates of diabetes mellitus and dyslipidemia, and were more likely to be taking hypoglycemic agents. There was no significant between-group difference in smoking and alcohol consumption rates, eGFR classification, CRVE, rates of hypertension and cardiovascular disease, or in use of anti-hypertensive and lipid-lowering agents.

3.2 | Association Between Retinal Vessel Caliber and New-Onset Carotid Plaque

The mean CRAE, CRVE, and AVR values were, respectively, 153.03 ± 12.77 μm, 232.41 ± 19.78 μm, and 0.66 ± 0.07 in cases and

TABLE 1 | Baseline characteristics in the cases and controls.

Variables	Cases ($n = 156$)	Controls ($n = 156$)	p value
Age, year	56.99 ± 6.53	56.09 ± 6.72	0.229
Male, *n* (%)	50(32.05%)	50(32.05%)	1.000
BMI, kg/m^2	25.82 ± 3.28	25.38 ± 3.48	0.244
Current smoking, *n* (%)	22 (14.10%)	25 (16.03%)	0.635
Current drinking, *n* (%)	16 (10.26%)	18 (11.54%)	0.716
eGFR classification, mL/min/1.73 m2, *n* (%)			0.825
≥90	12 (7.74%)	14 (8.97%)	
60–90	134 (86.45%)	131 (83.97%)	
<60	9 (5.81%)	11 (7.05%)	
Retinal vessel caliber			
CRAE, μm	153.05 ± 12.77	158.58 ± 10.74	<0.001
CRVE, μm	232.41 ± 19.78	232.54 ± 16.24	0.949
AVR	0.66 ± 0.07	0.68 ± 0.05	0.001
FBG, mmol/L	5.77 ± 1.31	5.55 ± 0.70	0.071
TG, mmol/L	1.77 ± 1.45	1.73 ± 1.56	0.787
TC, mmol/L	5.08 ± 0.94	5.11 ± 0.95	0.720
HDL-C, mmol/L	1.23 ± 0.31	1.30 ± 0.30	0.031
LDL-C, mmol/L	2.98 ± 0.79	2.97 ± 0.79	0.889
Hypertension, *n* (%)	55 (35.26%)	59 (37.82%)	0.640
Diabetes mellitus, *n* (%)	28 (17.95%)	12 (7.69%)	0.007
Dyslipidaemia, *n* (%)	127 (81.41%)	109 (69.87%)	0.018
Stroke, *n* (%)	3 (1.92%)	0 (0.00%)	0.082
Myocardial infarction, *n* (%)	3 (1.95%)	1 (0.64%)	0.308
Anti-hypertensive agent, *n* (%)	23 (14.74%)	27 (17.31%)	0.537
Hypoglycaemic agent, *n* (%)	15 (9.62%)	4 (2.56%)	0.009
Lipid-lowering agent, *n* (%)	11 (7.05%)	4 (2.56%)	0.064

Abbreviations: AVR, arteriovenous ratio; BMI, body mass index; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

158.58 ± 10.74 μm, 232.54 ± 16.24 μm, and 0.68 ± 0.05 in controls. Figures 2–4 show ed the trend of the association between baseline CRAE, CRVE, and AVR values and new-onset carotid plaque.

The odds of developing incident carotid plaque were evaluated according to CRAE, CRVE, and AVR categories in crude and multivariable adjusted models. Participants were divided into tertiles according to CRAE, CRVE, and AVR, respectively. Generally, a lower CRAE and AVR corresponded to a higher OR for new-onset carotid plaque (Table 2). When CRAE and AVR were treated as continuous variables, the risk of developing new-onset carotid plaque was negatively associated with the baseline CRAE (OR 1.04, 95% CI 1.02–1.06, $p < 0.01$) and AVR (OR 1.81, 95% CI 1.23–2.67, $p < 0.01$) in the univariate regression model. After adjustment, the risk of developing new-onset carotid plaque increased by 4% (OR 1.04, 95% CI 1.02–1.07, $p < 0.01$) with each 1-μm decrease in CRAE and 80% (OR 1.80, 95% CI 1.17–2.78, $p = 0.01$) with each 0.1-point decrease in the AVR. In the univariate regression model, when CRAE was considered to be a categorical variable, compared with subjects in the highest CRAE group, subjects in the lowest CRAE group had a 146% increase in risk of developing new-onset carotid plaque (OR 2.46, 95% CI 1.37–4.44, $p < 0.01$). In the multivariable-adjusted model, participants in the lowest CRAE group had a 159% increased risk (OR 2.59, 95% CI 1.34–5.01, $p < 0.01$) of having incident carotid plaque when compared with the highest CRAE group. Compared with subjects in the highest AVR group, those in the lowest AVR group had an 85% increase in development of new-onset carotid plaque (OR 1.85, 95% CI 1.10–3.11, $p = 0.02$) in the univariate regression model and a 93% increase (OR 1.93, 95% CI 1.08–3.46, $p = 0.03$) in the multivariate regression model.

However, whether deemed to be a continuous or categorical variable, CRVE was not significantly related to the risk of

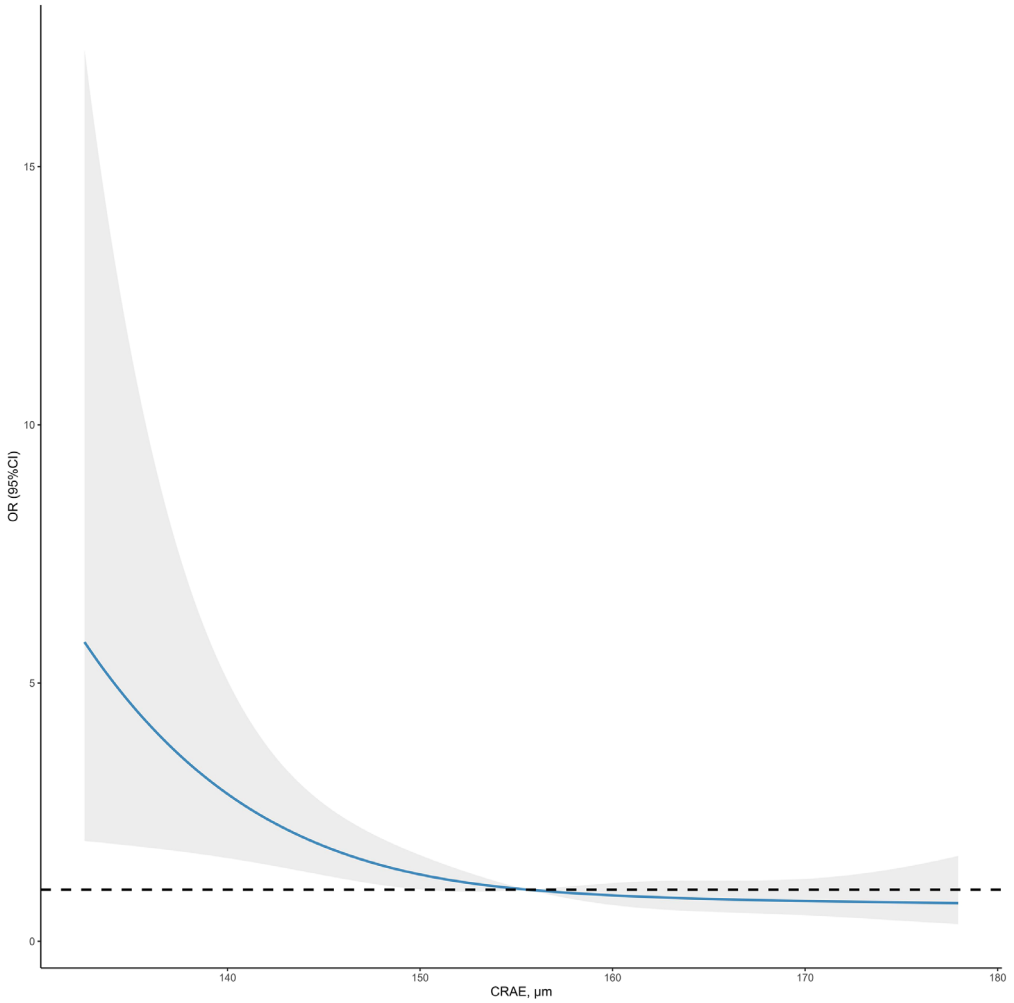

FIGURE 2 | Relationship between the central retinal arteriolar equivalent and the risk of incident carotid plaque.

developing new-onset carotid plaque (Table 2). Subgroup and interaction analyses were performed according to groups of confounding factors (Table 3). No significant interactions were found.

4 | DISCUSSION

In this prospective nested case-control study, AVR and CRAE, but not CRVE, as quantified by retinal photographs, were inversely associated with the risk of developing carotid plaque. Generally, the narrower the retinal arterial caliber, the greater the risk of developing new-onset carotid plaque. This association was independent of body mass index, current smoking and alcohol consumption, eGFR, hypertension, diabetes mellitus, dyslipidemia, cardiovascular diseases, and anti-hypertensive, hypoglycemia, and lipid-lowering agents. No significant modification effect was found by subgroup or interaction analysis.

Unlike most of the studies previously published on the relationship of retinal vascular diameter with carotid IMT rather than carotid plaque, our data offer further information on the association between retinal vessel diameter and carotid plaque in the general population. Our results are consistent with those of some cross-sectional studies and not with others that showed no significant association between CRAE, AVR, and carotid plaque. In the cross-sectional population-based Rotterdam study, a lower AVR was associated with a higher carotid plaque score (per plaque increase, −0.002; 95% CI −0.003, −0.001) after additional adjustment for blood pressure [15]. The same study also explored the independent influence of arteriolar and venular diameters on AVR and found that the arterial diameter was not associated with the carotid plaque score (number of locations with scores). In contrast, a larger venular diameter was associated with a higher carotid plaque score. However, the pathophysiological mechanism of this association is still unclear. After adjusting for possible confounders, another cross-sectional study that included 229 healthy participants from the EVIDENT trial found in a logistic regression model that the OR of the first tertile of mean AVR for target organ damage (IMT >0.9 mm, plaque, pulse wave velocity >10 m/s, or ankle-brachial index <0.9) was 7.09 (p = 0.011) [16].

However, some studies have yielded different results. In one study that included 386 individuals with essential hypertension, there was no significant difference in the percentage of carotid plaques across the AVR quartiles. When individuals were categorized

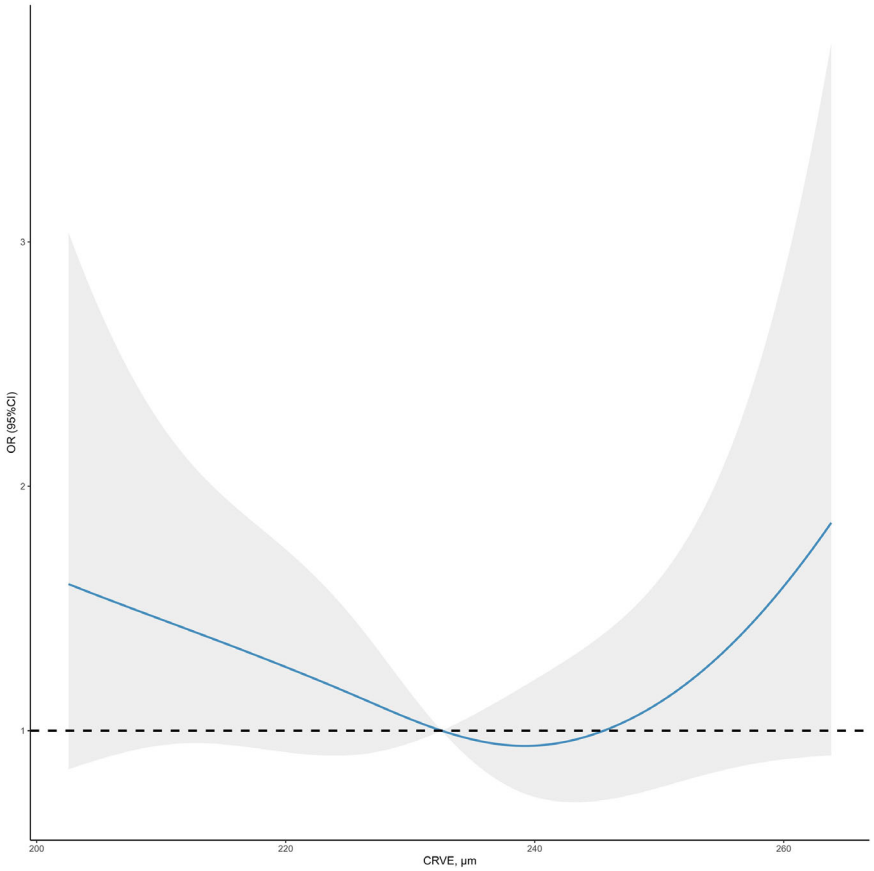

FIGURE 3 | Relationship between the central retinal venular equivalent and the risk of incident carotid plaque.

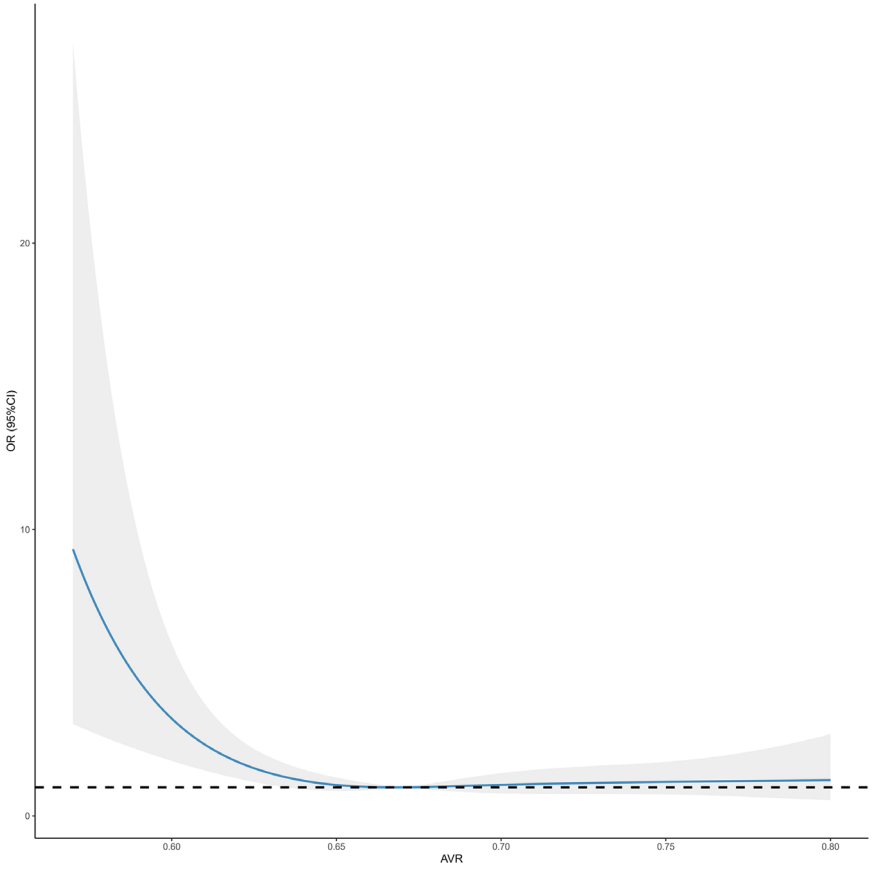

FIGURE 4 | Relationship between arteriovenous ratio and the risk of incident carotid plaque.

TABLE 2 | Association of retinal vessel caliber with incident carotid plaque in a conditional logistic regression model.

	Non-adjusted		Adjusted model	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
CRAE continuous, per 1 μm decrease				
	1.04 (1.02, 1.06)	<0.01	1.04 (1.02, 1.07)	<0.01
CRAE categories, μm				
≥161.62	1.0		1.0	
150.84–161.62	1.44 (0.83, 2.50)	0.20	1.51 (0.82, 2.80)	0.18
<150.84	2.46 (1.37, 4.44)	<0.01	2.59 (1.34, 5.01)	<0.01
CRVE continuous, per 1 μm decrease				
	1.00 (0.99, 1.01)	0.95	1.00 (0.99, 1.02)	0.80
CRVE categories, μm				
≥239.80	1.0		1.0	
225.89–239.80	0.73 (0.43, 1.25)	0.25	0.71 (0.38, 1.34)	0.29
<225.89	1.10 (0.64, 1.88)	0.73	1.03 (0.56, 1.91)	0.92
AVR continuous, per 0.1 decrease				
	1.81 (1.23, 2.67)	<0.01	1.80 (1.17, 2.78)	0.01
AVR categories				
≥0.69	1.0		1.0	
0.65–0.69	0.99 (0.58, 1.69)	0.98	1.03 (0.57, 1.84)	0.92
<0.65	1.85 (1.10, 3.11)	0.02	1.93 (1.08, 3.46)	0.03

Note: Model adjusted for BMI, current smoking and alcohol consumption, eGFR, fasting blood glucose, non-HDL cholesterol, hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, anti-hypertensive, anti-diabetic, and lipid-lowering agents.
Abbreviations: AVR, arteriovenous ratio; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; OR, odds ratio.

according to the presence or absence of carotid plaques, there was no significant intergroup difference in AVR [17]. Another study in 173 patients with hypertension did not show a significant association between carotid plaque and retinal arteriolar or venular caliber [2].

To the best of our knowledge, this prospective study is the first to demonstrate an inverse association of CRAE and AVR with the risk of incident carotid plaque. The relationship between AVR and carotid plaque is mainly driven by narrower arterial diameter. Retinal arterial narrowing may be related to new-onset carotid plaque through several mechanisms. First, the association may be a local effect of anatomic features, in view of the ARIC study, which found that participants with carotid plaque had a lower AVR, indicating retinal arterial narrowing [18]. Second, retinal arteriolar narrowing shares some common risk factors with atherosclerosis, including hypertension, smoking, inflammation, and endothelial dysfunction [19]. Furthermore, retinal arterial narrowing was found to be a surrogate marker of arteriosclerosis [20], and previous research indicates that atherosclerosis is a consequence rather than a cause of arteriosclerosis [21]. Aortic stiffening reduces the normal impedance gradient between the aorta and branching conduits and accentuates the penetration of pulsatile flow in downstream arteries (such as the carotid artery), thereby causing transmission of excessive pulsatility into the fragile microcirculation and leading to microvascular damage, remodeling and repair, and ultimately targeting the organ damage of carotid plaque [22]. A clear pathophysiological explanation for the irrelevant association between larger retinal venular diameter and carotid plaque is lacking. Wider CRVE was more relevant with diabetes, obesity, and inflammation, and previous cross-sectional research indicated that patients with ischemic stroke with widening CRVE were more likely to have severe ipsilateral carotid stenosis [23]. However, previous researches that indicated positive relationship between wider CRVE and carotid plaque score or carotid artery stenosis were cross-sectional and cannot prove the causal relationship.

The main strength of this study is its prospective nested case-control design, which allowed analysis of the association between retinal vessel caliber and carotid plaque in a small sample. However, the study has some limitations, in particular its single-center design. Therefore, it is not fully representative and needs validation in other populations.

In conclusion, in the community-based general population of Beijing, retinal arterial narrowing was a predictor of new-onset carotid plaque. Retinal arterial narrowing may occur earlier than carotid plaque, indicating that retinal artery alterations precede atherosclerosis. Therefore, detecting changes in the retinal artery may be more sensitive than detecting atherosclerosis in large arteries. Retinal artery caliber may be an early sign of

TABLE 3 | Association of retinal vessel caliber with incident carotid plaque in subgroup analyses.

		CRAE		CRVE		AVR	
		Multivariable-adjusted model		Multivariate-adjusted model		Multivariate-adjusted model	
Variables	Subjects *n* (%)	OR (95% CI)	P interaction	OR (95% CI)	P interaction	OR (95% CI)	P interaction
Age, year							
<60 years	226	1.04 (1.02, 1.07)	0.248	1.00 (0.98, 1.01)	0.356	1.92 (1.18, 3.11)	0.760
≥60 years	85	1.07 (1.03, 1.12)		1.01 (0.98, 1.04)		2.22 (0.97, 5.11)	
Gender							
Male	99	1.06 (1.02, 1.10)	0.672	0.99 (0.96, 1.02)	0.329	3.01 (1.37, 6.61)	0.181
Female	212	1.05 (1.02, 1.07)		1.01 (0.99, 1.02)		1.62 (0.99, 2.65)	
BMI, kg/m^2							
<24		1.04 (1.00, 1.08)	0.575	1.01 (0.99, 1.04)	0.249	1.22 (0.62, 2.41)	0.105
≥24		1.05 (1.03, 1.08)		1.00 (0.98, 1.01)		2.49 (1.46, 4.23)	
eGFR, mL/min/1.73 m2							
<90	285	1.05 (1.03, 1.06)	0.641	1.00 (0.99, 1.01)	0.306	1.98 (1.28, 2.87)	0.893
≥90	26	1.07 (0.98, 1.17)		1.03 (0.97, 1.09)		1.74 (0.28, 10.7)	
Hypertension							
No	198	1.04 (1.01, 1.07)	0.240	1.01 (0.99, 1.02)	0.345	1.63 (0.98, 2.72)	0.242
Yes	113	1.07 (1.03, 1.12)		0.99 (0.97, 1.02)		2.78 (1.31, 5.93)	
Dyslipidemia							
No	76	1.10 (1.04, 1.17)	0.069	1.01 (0.98, 1.04)	0.548	2.31 (0.84, 6.37)	0.712
Yes	235	1.04 (1.02, 1.07)		1.00 (0.98, 1.01)		1.88 (1.18, 2.98)	
Diabetes mellitus							
No	271	1.05 (1.03, 1.08)	0.600	1.00 (0.99, 1.02)	0.178	1.83 (1.17, 2.84)	0.390
Yes	40	1.03 (0.97, 1.10)		0.98 (0.94, 1.02)		3.26 (0.91, 11.7)	
CVD							
No	289	1.05 (1.03, 1.08)	0.279	1.00 (0.99, 1.02)	0.204	1.95 (1.25, 3.03)	0.995
Yes	22	1.00 (0.93, 1.09)		0.98 (0.93, 1.02)		1.96 (0.51, 7.52)	

Multi-variate adjusted model adjusted for age, BMI, current smoking and alcohol consumption, eGFR, hypertension, diabetes mellitus, dyslipidemia, cardiovascular diseases, and anti-hypertensive, anti-diabetic, and lipid-lowering agents.

Abbreviations: AVR, arteriovenous ratio; BMI, body mass index; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

future atherosclerosis at a stage when other markers are not yet present.

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Ethics Statement

The study was reviewed and approved by the ethics committees of Peking University First Hospital and Peking University. Written informed consent was obtained before the examination.

Data Availability Statement

The summary data that support the findings of this study are available from the corresponding author on reasonable request.

References

1. C. Y. Cheung, M. K. Ikram, C. Sabanayagam, and T. Y. Wong, "Retinal Microvasculature as a Model to Study the Manifestations of Hypertension," *Hypertension* 60, no. 5 (2012): 1094–1103.

2. H. Huang, Y. Cao, J. Li, et al., "Association Between Retinal Arterial Narrowing and Left Ventricular Diastolic Dysfunction in Masked Hypertensives," *Journal of Clinical Hypertension (Greenwich, Conn.)* 22, no. 6 (2020): 1050–1058.

3. L. Huang, I. M. Aris, L. L. Y. Teo, et al., "Exploring Associations Between Cardiac Structure and Retinal Vascular Geometry," *Journal of the American Heart Association* 9, no. 7 (2020): e014654.

4. G. Lona, K. Endes, S. Kochli, D. Infanger, L. Zahner, and H. Hanssen, "Retinal Vessel Diameters and Blood Pressure Progression in Children," *Hypertension* 76, no. 2 (2020): 450–457.

5. Y. Tanabe, R. Kawasaki, J. J. Wang, et al., "Retinal Arteriolar Narrowing Predicts 5-Year Risk of Hypertension in Japanese People: The Funagata Study," *Microcirculation* 17, no. 2 (2010): 94–102.

6. Y. He, S. M. Li, M. T. Kang, et al., "Association Between Blood Pressure and Retinal Arteriolar and Venular Diameters in Chinese Early Adolescent Children, and Whether the Association Has Gender Difference: A Cross-Sectional Study," *BMC Ophthalmology* 18, no. 1 (2018): 133.

7. T. Y. Wong, R. Klein, A. R. Sharrett, et al., "Retinal Arteriolar Narrowing and Risk of Coronary Heart Disease in Men and Women. The Atherosclerosis Risk in Communities Study," *Journal of the American Medical Association* 287, no. 9 (2002): 1153–1159.

8. J. J. Wang, G. Liew, R. Klein, et al., "Retinal Vessel Diameter and Cardiovascular Mortality: Pooled Data Analysis From Two Older Populations," *European Heart Journal* 28, no. 16 (2007): 1984–1992.

9. Y. M. Hong, "Atherosclerotic Cardiovascular Disease Beginning in Childhood," *Korean Circulation Journal* 40, no. 1 (2010): 1–9.

10. Y. Inaba, J. A. Chen, and S. R. Bergmann, "Carotid Plaque, Compared With Carotid Intima-Media Thickness, More Accurately Predicts Coronary Artery Disease Events: A Meta-Analysis," *Atherosclerosis* 220, no. 1 (2012): 128–133.

11. A. N. Nicolaides, A. G. Panayiotou, M. Griffin, et al., "Arterial Ultrasound Testing to Predict Atherosclerotic Cardiovascular Events," *Journal of the American College of Cardiology* 79, no. 20 (2022): 1969–1982.

12. F. Fan, L. Qi, J. Jia, et al., "Noninvasive Central Systolic Blood Pressure Is More Strongly Related to Kidney Function Decline Than Peripheral Systolic Blood Pressure in a Chinese Community-Based Population," *Hypertension* 67, no. 6 (2016): 1166–1172.

13. M. D. Knudtson, K. E. Lee, L. D. Hubbard, T. Y. Wong, R. Klein, and B. E. Klein, "Revised Formulas for Summarizing Retinal Vessel Diameters," *Current Eye Research* 27, no. 3 (2003): 143–149.

14. P. J. Touboul, M. G. Hennerici, S. Meairs, et al., "Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004-2006-2011). An Update On Behalf of the Advisory Board of the 3rd, 4th and 5th Watching the Risk Symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011," *Cerebrovascular Diseases* 34, no. 4 (2012): 290–296.

15. M. K. Ikram, F. J. de Jong, J. R. Vingerling, et al., "Are Retinal Arteriolar or Venular Diameters Associated With Markers for Cardiovascular Disorders? The Rotterdam Study," *Investigative Ophthalmology & Visual Science* 45, no. 7 (2004): 2129–2134.

16. L. Garcia-Ortiz, J. I. Recio-Rodriguez, C. Agudo-Conde, et al., "The Role of Retinal Vessels Caliber as a Marker of Vascular Aging in Large Arteries," *Journal of Hypertension* 33, no. 4 (2015): 818–826. Discussion 826.

17. M. Masaidi, C. Cuspidi, V. Giudici, et al., "Is Retinal Arteriolar-Venular Ratio Associated With Cardiac and Extracardiac Organ Damage in Essential Hypertension?," *Journal of Hypertension* 27, no. 6 (2009): 1277–1283.

18. R. Klein, A. R. Sharrett, B. E. Klein, et al., "Are Retinal Arteriolar Abnormalities Related to Atherosclerosis?: The Atherosclerosis Risk in Communities Study," *Arteriosclerosis, Thrombosis, and Vascular Biology* 20, no. 6 (2000): 1644–1650.

19. C. Palomboand M. Kozakova, "Arterial Stiffness, Atherosclerosis and Cardiovascular Risk: Pathophysiologic Mechanisms and Emerging Clinical Indications," *Vascular Pharmacology* 77 (2016): 1–7.

20. K. Kawashima-Kumagai, Y. Tabara, K. Yamashiro, et al., "Association of Retinal Vessel Calibers and Longitudinal Changes in Arterial Stiffness: The Nagahama Study," *Journal of Hypertension* 36, no. 3 (2018): 587–593.

21. I. B. Wilkinson, C. M. McEniery, and J. R. Cockcroft, "Arteriosclerosis and Atherosclerosis: Guilty by Association," *Hypertension* 54, no. 6 (2009): 1213–1215.

22. L. L. Cooper, T. Woodard, S. Sigurdsson, et al., "Cerebrovascular Damage Mediates Relations Between Aortic Stiffness and Memory," *Hypertension* 67, no. 1 (2016): 176–182.

23. D. A. De Silva, G. Liew, M. C. Wong, et al., "Retinal Vascular Caliber and Extracranial Carotid Disease in Patients With Acute Ischemic Stroke: The Multi-Centre Retinal Stroke (MCRS) Study," *Stroke; A Journal of Cerebral Circulation* 40, no. 12 (2009): 3695–3699.