


Comparison of carotid atherosclerotic plaques between subjects in Northern and Southern China: a Chinese atherosclerosis risk evaluation study

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ABSTRACT

Background and purpose To investigate differences in the characteristics of carotid atherosclerotic plaques of symptomatic subjects in northern and southern China using MRI.

Methods Sixty-three subjects in northern China (mean age: 59.1±8.6 years, 45 men) and 56 subjects in southern China (mean age: 60.4±8.6 years, 38 men) were included. All subjects underwent carotid artery multicontrast vessel wall MRI. Plaque morphology, calcification, lipid-rich necrotic core, intraplaque haemorrhage, luminal surface disruption and high-risk plaque were measured and identified. All plaque characteristics were compared between subjects in northern and southern China using Mann-Whitney U test or χ^2 test.

Results Compared with subjects in southern China, those in northern China had significantly greater areas for lumen (57.7±14.9 mm² vs 50.4±18.3 mm², p=0.009), wall (38.4±13.1 mm² vs 31.9±11.7 mm², p<0.001) and total vessel (96.1±20.2 mm² vs 82.4±22.7 mm², p=0.001) and mean wall thickness (1.25±0.43 mm vs 1.13±0.40 mm, p=0.019). χ^2 analysis showed that subjects in northern China tended to have a higher prevalence of intraplaque haemorrhage (14.3% vs 5.4%, p=0.106) and high-risk plaque (20.6% vs 10.7%, p=0.140) than those in southern China, although these differences were not statistically significant (all p>0.05).

Conclusion Subjects in northern China have significantly larger vessel size and may have a higher prevalence of vulnerable plaques than those in southern China. Our findings provide additional perspective to optimise the management of cerebrovascular disease in individuals in different regions in China.

Trial registration number NCT02017756

INTRODUCTION

Globally, stroke is the second leading cause of death and the third most common cause of disability.^{1,2} In China, stroke has become the leading cause of death and disability.³ Geographical variations in stroke incidence, mortality and prevalence have been reported in China.^{3,4} Wang *et al*⁴ demonstrated that the incidence of stroke in northern China is significantly higher than that in southern China (275.3/10⁵ vs 154.6/10⁵, p<0.002). It is

well evidenced that carotid vulnerable atherosclerotic plaques, defined as lesions with intraplaque haemorrhage (IPH), large lipid-rich necrotic core (LRNC) or luminal surface disruption, including ulcer and fibrous cap rupture,⁵ are associated with ischaemic stroke. Pu *et al*⁶ reported that subjects in northern China were more likely to have carotid atherosclerotic stenosis than those in southern China. However, the differences in lumen area, wall area and thickness, and plaque components in the carotid artery have not been fully investigated between northern and southern symptomatic Chinese patients.

Multicontrast vessel wall MRI has been established to be capable of accurately assessing the morphology and compositional features of carotid atherosclerotic plaque. Luo *et al*⁷ reported that multicontrast vessel wall MRI was well validated by histology in measuring the carotid atherosclerotic plaque burden and luminal stenosis. In addition, previous studies have indicated that carotid plaque components such as LRNC, calcification, IPH and luminal surface disruption can be accurately estimated by multicontrast vessel wall MRI.⁸

Above all, this study aimed to investigate the differences in the morphological and compositional features of carotid atherosclerotic plaques in symptomatic subjects in northern and southern China using multicontrast vessel wall MRI.

METHODS

Study population

All subjects were enrolled from CARE-II (Chinese Atherosclerosis Risk Evaluation), a cross-sectional, multicentre study. The aim of the CARE-II study was to assess the prevalence and characteristics of carotid high-risk atherosclerotic plaques in Chinese subjects with recent ischaemic stroke or transient ischaemia

attack using multicontrast MRI. The study protocol of CARE-II study has been reported previously.⁹ In brief, the CARE-II study enrolled subjects aged 18–80 years old who suffered from a recent stroke or transient ischaemia attack and had atherosclerotic plaques in at least one carotid artery determined by B-mode ultrasound imaging. All subjects underwent carotid artery multicontrast vessel wall MRI. Geographically, China is divided into northern and southern regions according to the boundary of Yangtze River. Of the locations of 14 hospitals in the CARE-II study, two provinces, Heilongjiang and Guangdong, were selected to be representative of northern and southern China, respectively. In the present study, we finally included subjects recruited at Harbin Medical University Fourth Hospital and Qiqihar First Hospital in the province of Heilongjiang and subjects recruited at Zhujiang Hospital and Sun Yat-sen Memorial Hospital in the province of Guangdong. The clinical characteristics of all subjects, such as age, sex, height, weight, body mass index (BMI), history of smoking, hypertension, hyperlipidaemia, diabetes, coronary heart disease, statin use, anti-hypertension medication use, blood pressure and lipid levels, were collected from their medical records.

Carotid artery MRI

Multicontrast vessel wall MRI of the carotid arteries was performed for all included subjects on 3.0T MRI scanners (Achieva TX, Philips Healthcare, The Netherlands) with dedicated eight-channel carotid coils. In the multicontrast MRI protocol, time-of-flight (TOF), T1-weighted (T1W), T2-weighted (T2W) and magnetisation-prepared rapid acquisition gradient echo (MPRAGE) sequences were acquired using the following parameters: TOF: repeat time (TR)/echo time (TE) 20 ms/4.9 ms, field of view (FOV) 14×14 cm², flip angle 20°, matrix 256×256, and slice thickness 1 mm; T1W quadruple inversion recovery: TR/TE 800 ms/10 ms, FOV 14×14 cm², matrix 256×256, and slice thickness 2 mm; T2W multislice double inversion recovery: TR/TE 4800 ms/50 ms, FOV 14×14 cm², matrix 256×256, and slice thickness 2 mm; and MPRAGE: TR/TE 8.8 ms/5.3 ms, FOV 14×14 cm², flip angle 15°, matrix 256×256, and slice thickness 1 mm. All imaging was centred to the symptomatic side of carotid artery bifurcation with longitudinal coverage of 32 mm.

MRI analysis

Two trained reviewers with more than 3 years' experience in plaque imaging interpreted the carotid MRI using custom-designed software (CASCADE; University of Washington, Seattle, USA)¹⁰ and were blinded to clinical information with consensus. The lumen and wall boundaries were manually traced. The lumen area, wall area, total vessel area and mean wall thickness on each axial image of all subjects were measured. Normalised wall index, defined as the wall area divided by the total vessel area, was calculated. The presence or absence of calcification, LRNC, IPH and luminal surface disruption, including ulcer or fibrous cap rupture, at each axial

location was identified according to published criteria.¹¹ For each plaque component, its area at each axial image was measured and its volume was calculated. Large LRNC was defined as LRNC which occupied >40% of the wall area on any axial image. High-risk plaque (HRP) was defined as a lesion with large LRNC, IPH or luminal surface disruption.⁵ The luminal stenosis of carotid arteries was measured on three-dimensional (3D) TOF magnetic resonance angiography images reconstructed by maximum intensity projection algorithm using the North American Symptomatic Carotid Endarterectomy criteria,¹² and the presence or absence of ≥50% stenosis was determined.

Statistical analysis

The nine imaging slices covering 18 mm centred at the bifurcation of the symptomatic carotid artery were included in the analysis. Continuous variables are presented as mean±SD or median, and categorical variables are expressed as number with percentage. Mann-Whitney U test or χ^2 test was used to compare plaque features between subjects in northern and southern China and between the CARE-II subjects included and excluded from this study. Multivariate linear and logistic regression models were performed to determine the differences in plaque measurements between subjects in northern and southern China. Age, sex and clinical risk factors that were significantly different ($p<0.05$) between the two groups in the univariate comparison were included as adjustments in the multivariate models. A value of $p<0.05$ was considered statistically significant without adjustment for multiple comparisons. All statistical analyses were performed using SPSS V.16.0.

RESULTS

The flow chart of recruitment of patients is presented in figure 1. In total, 279 subjects from the hospitals in northern and southern China were recruited into the study. Of the 279 subjects, 160 were excluded due to the following reasons: (1) side of symptomatic carotid artery was not available ($n=86$); (2) insufficient image quality ($n=41$); and (3) insufficient MRI coverage ($n=33$). Finally, 63 subjects in northern China (mean age: 59.1±8.6 years old, 45 men) and 56 subjects in southern China (mean age: 60.4±8.6 years old, 38 men) were included. Table 1 shows the clinical characteristics of this study population. Northern subjects had greater BMI (24.7±3.1 kg/m² vs 23.0±2.9 kg/m², $p=0.002$), height (169.3±5.7 cm vs 165.3±6.7 cm, $p=0.001$) and weight (71.0±10.4 kg vs 62.8±8.5 kg, $p<0.001$) and were more likely to have a history of smoking (55.6% vs 35.7%, $p=0.030$) than southern subjects. In contrast, northern subjects had a lower prevalence of diabetes compared with those in southern China (20.6% vs 39.3%, $p=0.026$).

Comparison of carotid plaque morphology

The comparison of plaque morphology is shown in table 2.

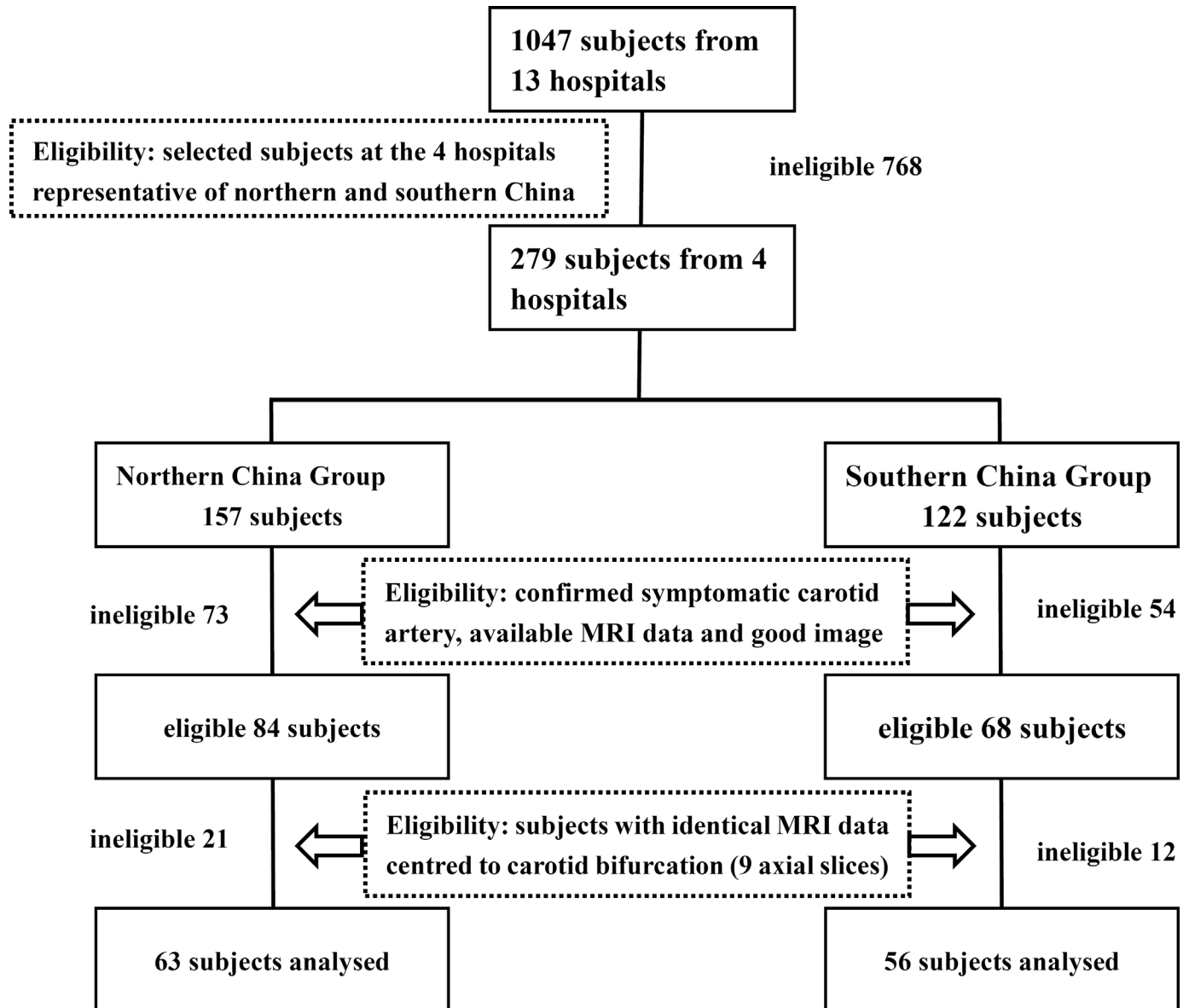


Figure 1 Flow chart of patient recruitment.

Before adjustment, northern subjects had significantly greater lumen area ($57.7 \pm 14.9 \text{ mm}^2$ vs $50.4 \pm 18.3 \text{ mm}^2$, $p=0.009$), wall area ($38.4 \pm 13.1 \text{ mm}^2$ vs $31.9 \pm 11.7 \text{ mm}^2$, $p<0.001$), total vessel area ($96.1 \pm 20.2 \text{ mm}^2$ vs $82.4 \pm 22.7 \text{ mm}^2$, $p=0.001$) and mean wall thickness ($1.25 \pm 0.43 \text{ mm}$ vs $1.13 \pm 0.40 \text{ mm}$, $p=0.019$) than southern subjects (figure 2). However, mean normalised wall index and prevalence of $\geq 50\%$ stenosis were not significantly different between the two groups. After adjusting for age, sex, BMI and history of smoking and diabetes, wall area (β : 6.72, 95% CI 2.28 to 11.17, $p=0.003$) and total vessel area (β : 12.94, 95% CI 5.24 to 21.51, $p=0.001$) remained significantly greater and lumen area was marginally greater (β : 6.21, 95% CI -0.03 to 12.45, $p=0.051$) in northern subjects compared with southern subjects (table 3). The difference in mean wall thickness was marginally not significant after adjustment ($p=0.076$) and normalised wall index remained similar ($p=0.499$) between northern

and southern subjects in multivariate analyses. The absolute vessel measurements, including lumen, wall and total vessel areas, were highly correlated with height, and the differences in the absolute vessel measurements between northern and southern subjects decreased after adjusting for height. The differences in lumen ($p=0.15$) and wall area ($p=0.11$) were no longer significant after adjusting for height (data not shown).

Comparison of carotid plaque components

The prevalence of IPH (14.3% vs 5.4%, $p=0.106$) and HRP (20.6% vs 10.7%, $p=0.140$) tended to be higher in the northern subjects than that in the southern subjects, although these differences were not statistically significant (table 2). Figure 3 shows a patient in northern China who had carotid plaque with IPH identified on T1W, T2W, TOF and MPRAGE images. The comparison of the prevalence of plaque components showed

Table 1 Clinical characteristics of the study population

	Mean±SD, or n (%)		P value*
	Northern subjects (n=63)	Southern subjects (n=56)	
Age, years	59.1±8.6	60.4±8.6	0.449
Male, sex	45 (71.4)	38 (67.9)	0.672
Body mass index, kg/m ²	24.7±3.1	23.0±2.9	0.002
Height, cm	169.3±5.7	165.3±6.7	0.001
Weight, kg	71.0±10.4	62.8±8.5	<0.001
History of smoking	35 (55.6)	20 (35.7)	0.030
History of hypertension	40 (63.5)	41 (73.2)	0.256
Systolic blood pressure, mm Hg	149.6±25.6	148.0±22.2	0.994
Diastolic blood pressure, mm Hg	89.4±14.0	87.4±12.1	0.453
History of hyperlipidaemia	30 (47.6)	28 (50.0)	0.795
LDL-C, mmol/L	3.18±0.90	3.17±1.09	>0.99
HDL-C, mmol/L	1.24±0.97	1.20±0.29	0.300
TC, mmol/L	4.69±1.19	4.84±1.28	0.598
TG, mmol/L	1.70±1.08	1.58±0.91	0.747
History of diabetes mellitus	13 (20.6)	22 (39.3)	0.026
History of coronary heart disease	9 (14.3)	3 (5.4)	0.106
Statin use	19 (30.2)	24 (42.9)	0.150
Antihypertension medication use	29 (46.0)	30 (53.6)	0.412

*P values were calculated by Mann-Whitney U test or χ^2 test. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

no statistical differences in calcification (38.1% vs 41.1%, $p=0.740$), LRNC (60.3% vs 55.4%, $p=0.584$) and luminal surface disruption (11.1% vs 7.1%, $p=0.456$) between northern and southern subjects before multivariate adjustment. For subjects with carotid calcified plaque, northern subjects had marginally significant larger volume of calcification (19.9 mm³ vs 8.0 mm³, $p=0.050$) than southern subjects. There was no significant difference in the volume of LRNC (29.4 mm³ vs 36.2 mm³, $p=0.629$) between the northern and southern subjects. Multivariate regression analyses were further performed to compare the prevalence of calcification and LRNC and no significant differences were found in the prevalence of calcification (OR: 1.15, 95% CI 0.48 to 2.79, $p=0.754$) and LRNC (OR: 1.54, 95% CI 0.64 to 3.70, $p=0.331$) between the northern and southern subjects after adjusting for age, sex, BMI, history of smoking and diabetes. When further adjusting for mean normalised wall index, the differences in the prevalence of calcification (OR: 1.02, 95% CI 0.35 to 2.92, $p=0.977$) and LRNC (OR: 1.10, 95% CI 0.37 to 3.30, $p=0.861$) were also not statistically significant. Multivariate analyses of

Table 2 Carotid plaque morphological and compositional characteristics

	Mean±SD, n (%) or median		P value*
	Northern subjects (n=63)	Southern subjects (n=56)	
Carotid morphology			
Mean lumen area, mm ²	57.7±14.9	50.4±18.3	0.009
Mean wall area, mm ²	38.4±13.1	31.9±11.7	<0.001
Mean total vessel area, mm ²	96.1±20.2	82.4±22.7	0.001
Mean wall thickness, mm	1.25±0.43	1.13±0.40	0.019
Mean normalised wall index, %	40.7±9.5	40.2±10.4	0.489
Luminal stenosis ≥50%	5 (7.9)	5 (8.9)	>0.99
Presence of plaque components			
Calcification	24 (38.1)	23 (41.1)	0.740
Lipid-rich necrotic core	38 (60.3)	31 (55.4)	0.584
Intraplaque haemorrhage	9 (14.3)	3 (5.4)	0.106
Luminal surface disruption	7 (11.1)	4 (7.1)	0.456
High-risk plaque	13 (20.6)	6 (10.7)	0.140
Volume of plaque components†			
Calcification, mm ³	19.9	8.0	0.050
Lipid-rich necrotic core, mm ³	29.4	36.2	0.629

*P values are Mann-Whitney U test or χ^2 test between northern and southern subjects.

†Only subjects with the corresponding component present were included in the comparison.

other plaque characteristics and component volumes could not be reliably performed due to small sample size.

Comparison of carotid atherosclerosis between included and excluded subjects

In the present study, 119 subjects from the CARE-II study were included for final analysis. Of the 928 subjects who were excluded, 465 were selected for further comparison with the 119 subjects included. The other 463 subjects were not included in this comparison due to the following reasons: (1) side of symptomatic carotid artery was not available ($n=442$) and (2) insufficient MRI quality ($n=21$). We found that the 119 subjects included had significantly greater areas for lumen (54.3±16.9 mm² vs 44.4±15.6 mm², $p<0.001$), wall (35.4±12.8 mm² vs 32.3±11.6 mm², $p=0.011$) and total vessel (89.6±22.4 mm² vs 76.7±21.2 mm², $p<0.001$) and smaller mean normalised wall index (40.4%±9.9% vs 42.2±9.9%, $p=0.049$) than the

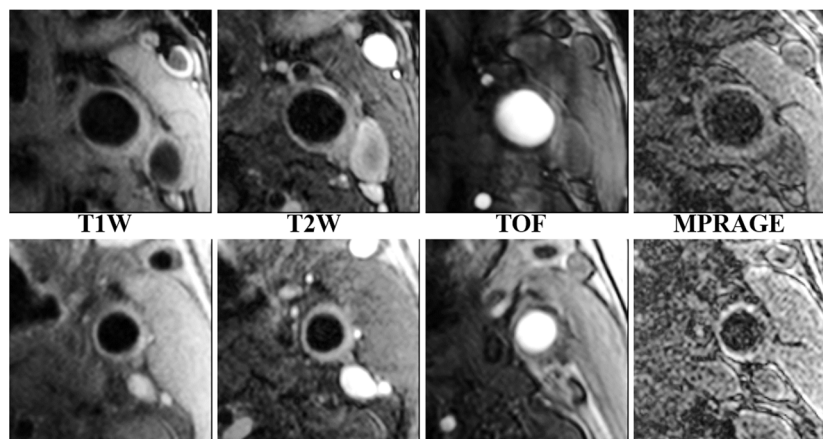


Figure 2 Comparison of carotid vessel morphology between subjects in northern and southern China. The top row represents a patient from the northern China group, and the bottom row represents a patient from the southern China group, with the same age and gender as the patient in the northern China group. All MRI images were taken from 8 mm below the carotid bifurcation. MPRAGE, magnetisation-prepared rapid acquisition gradient echo; T1W, T1-weighted; T2W, T2-weighted; TOF, time-of-flight.

465 subjects excluded. There were no significant differences in mean wall thickness and carotid compositional characteristics between the two groups (all $p > 0.05$). The results of the comparison are shown in the online supplementary table 1.

DISCUSSION

This study investigated the differences in the characteristics of carotid atherosclerotic plaques in symptomatic subjects in northern and southern China using multi-contrast vessel wall MRI. All data were enrolled from CARE-II, a multicentre, cross-sectional, observational study. We found that subjects in northern China had greater BMI, height and weight and were more likely to have a history of smoking than those in southern China, although the northern subjects were less likely to have diabetes than the southern subjects. For the carotid

plaque characteristics, subjects in northern China were found to have larger lumen area, wall area, total vessel area, mean wall thickness and calcification volume compared with those in southern China, although with similar NWI. The prevalence of IPH and HRP tended to be higher in the northern subjects than in the southern subjects, although these differences were not statistically significant.

In the present study, subjects in northern China were found to have greater BMI, height and weight than those in southern China. These results are in line with the findings of previous studies carried out among different populations.^{13 14} In addition, we found that among the subjects studied, there were more smokers in northern China than in southern China. Our results were consistent with the study by Astell-Burt *et al*¹⁵ in which current tobacco smoking prevalence was found

Table 3 Multivariate regression models for comparing carotid plaque features

	Multivariate model 1			Multivariate model 2		
	β or OR*	95% CI	P value	β or OR*	95% CI	P value
Carotid morphology						
Mean lumen area, mm ²	6.21	-0.03 to 12.45	0.051	-	-	-
Mean wall area, mm ²	6.72	2.28 to 11.17	0.003	-	-	-
Mean total vessel area, mm ²	12.94	5.24 to 21.51	0.001	-	-	-
Mean wall thickness, mm	0.14	-0.02 to 0.29	0.076	-	-	-
Mean normalised wall index, %	1.28	-2.46 to 5.01	0.499	-	-	-
Presence of plaque components						
Calcification	1.15	0.48 to 2.79	0.754	1.02	0.35 to 2.92	0.977
Lipid-rich necrotic core	1.54	0.64 to 3.70	0.331	1.10	0.37 to 3.30	0.861

Model 1 adjusting for age, sex, body mass index, history of smoking and diabetes. Model 2 further adjusting for the factors in model 1 and mean normalised wall index.

*Values are the difference in plaque measurements between northern and southern subjects using the linear regression slope (β) for continuous measurements (plaque morphology) or the logistic regression OR for binary measurements (presence of plaque components).

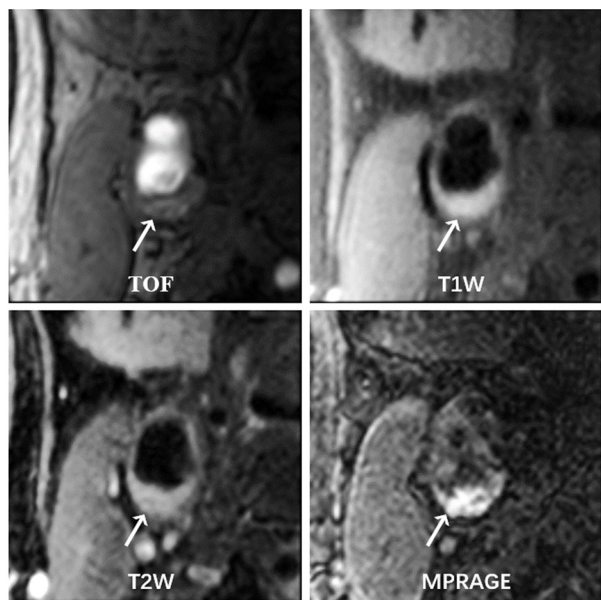


Figure 3 Example of a carotid atherosclerotic lesion with intraplaque haemorrhage (IPH) of a patient in the northern China group using multicontrast carotid vessel wall imaging. The IPH can be seen in the right carotid bifurcation, which is characterised by hyperintensities on TOF, T1W and MPRAGE images (arrow). MPRAGE, magnetisation-prepared rapid acquisition gradient echo; T1W, T1-weighted; T2W, T2-weighted; TOF, time-of-flight.

to be higher in the northern provinces than in the southern provinces. The present study also demonstrated that subjects in southern China had higher prevalence of diabetes compared with those in northern China (39.3% vs 20.6%, $p=0.026$). This difference is contradictory to previous studies which suggested that diabetes in the general population is more common in the northern region of China than in the southern region.¹⁶ However, our study is of a symptomatic population, which has a different distribution of risk factors relative to the general population.

In this study, we compared the characteristics of carotid artery morphology between subjects in northern and southern China and found that subjects in northern China had significantly larger vessel size than those in southern China, even after adjusting for age, gender, BMI, smoking and diabetes. This finding implies that there might be geographical variation in carotid artery size between patients in northern and southern China. The geographical variation in carotid artery size could be explained by the differences in the genetic diversity or environmental factors (such as temperature).^{17 18} In the present study, we also found that after adjusting for height, the differences in absolute vessel dimensions between subjects in northern and southern China decreased, suggesting that this phenomenon might be derived at least in part from the differences in body size rather than atherosclerotic disease in the arterial wall. Furthermore, total vessel area was correlated with height and weight in our study ($r=0.50$ and $r=0.39$, respectively,

$p<0.001$), similar to a previous report by Polak *et al*¹⁷ that found that the outer diameter of the common carotid artery was positively correlated with height and weight ($r=0.33$ and $r=0.30$, respectively; $p<0.0001$). On the other hand, arterial dilatation may be present when the temperature is lower,¹⁸ or in response to moderate or advanced atherosclerosis.¹⁹ Vessel diameters were subject to complex regulation involving wall thickness, hypertension, low-density lipoprotein cholesterol levels and alcohol consumption.²⁰ More studies need to be performed to investigate differences in this aspect.

The present study also suggested that subjects in northern China may be more likely to have IPH (14.3% vs 5.4%, $p=0.106$) and HRP (20.6% vs 10.7%, $p=0.140$) compared with those in southern China, although these differences were not statistically significant. A larger cohort study needs to be performed to further investigate such differences. A study by van den Bouwhuijsen *et al*²¹ noted that hypertension and current smoking were both associated with the presence of IPH (OR: 1.4, 95% CI 1.1 to 1.8 and OR: 1.6, 95% CI 1.2 to 2.3, respectively). Our study revealed that northern China had significantly more smokers than southern China, suggesting that the higher prevalence of smoking among subjects in northern China may contribute to this region's higher prevalence of IPH. A previous study demonstrated that endothelial nicotine receptors play an important stimulating role in angiogenesis, which is assumed to be a major cause of IPH.²²

In addition, we found that subjects in northern China had marginally significantly larger volume of calcification compared with those in southern China. A study by van den Bouwhuijsen *et al*²³ revealed that the larger volume of calcification in carotid plaques was associated with a higher prevalence of IPH in asymptomatic patients. In the present study, we found that subjects in northern China tended to have a higher prevalence of IPH than those in southern China, suggesting that the larger volume of calcification in patients in northern China may be attributed to their higher prevalence of IPH. Nevertheless, the mechanism for the association between carotid plaque calcification volume and the prevalence of IPH remains unclear. This may be explained by the fact that IPH induces intraplaque inflammation by recruiting inflammatory contents,²⁴ while chronic inflammation links to calcium deposits.²⁵ Although the presence of calcification in carotid plaques has been traditionally considered a protective factor,²⁶ more studies have highlighted that the presence of calcification with certain size²³ and location²⁷ in carotid plaques may increase plaque vulnerability. The marginally significant differences in the volume of calcification ($p=0.050$) and the presence of IPH ($p=0.106$) between subjects in northern and southern China might be due to the insufficient sample size in this study.

Our study has several limitations. First, the sample size was small. Future studies with larger sample size to investigate geographical differences in the characteristics of



carotid plaques are warranted. Second, only two provinces, Heilongjiang and Guangdong, were selected to be representative of northern and southern China, respectively. However, there could be inhomogeneity in the subjects from different provinces not only in northern but also in southern China. In future studies, it is necessary to include subjects from more provinces in each geographical region. Third, we enrolled subjects with existing carotid plaques, but few subjects (8.4%) had advanced lesions with $\geq 50\%$ carotid stenosis. Future studies are suggested to include subjects with a wide range of plaque severity. Fourth, carotid vessel wall imaging was performed with a two-dimensional multi-contrast imaging technique, which yields limited longitudinal coverage (32 mm) and partial volume effect. Recently, 3D vessel wall MRI techniques with large coverage have been proposed for plaque assessment of carotid arteries.²⁸ These 3D imaging techniques allow comprehensive evaluation of atherosclerotic disease, particularly for lesions that occurred in more proximal common carotid artery and more distal internal carotid artery segments. Fifth, due to the small sample size and hypothesis-generating nature of the study, we did not adjust p values for multiple comparisons. Findings in this study need to be confirmed in larger studies. Finally, the genetic contributions to the variation of carotid plaques in different regions could not be investigated due to lack of blood sample in the study.

In conclusion, subjects in northern China have significantly larger vessel size and may have a higher prevalence of vulnerable plaques than those in southern China. Our findings provide additional perspective to optimise the management of cerebrovascular disease in individuals in different regions in China.

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Contributors XZ and CY conceived the overall study and handled funding and supervision. XZ, YJ and DW acquired and interpreted the data. DY, YJ and XZ drafted the manuscript. DY, YJ, XZ, HW and DH performed the statistical analysis. CY provided technology support and made critical revision to the manuscript. All authors read and approved the content of this manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the institutional review board, and written consent form was obtained from each subject.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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