

# Risk Factors for Asymptomatic and Symptomatic Intracranial Atherosclerosis Determined by Magnetic Resonance Vessel Wall Imaging in Chinese Population: A Case–Control Study

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**Background and Purpose:** The association between risk factors and intracranial atherosclerosis disease (ICAD) determined by magnetic resonance (MR) vessel wall imaging in Chinese population has not been investigated. The aim of this study was to investigate the associations of conventional vascular risk factors with asymptomatic and symptomatic ICAD using MR vessel wall imaging in Chinese population.

**Methods:** The study population was recruited from two cohort studies of ICASMAP and CAMERA comprised 104 symptomatic ICAD subjects ( $57.1 \pm 11.1$  years; 35.6% females), 51 asymptomatic ICAD subjects ( $70.1 \pm 8.4$  years; 50.0% females) and 418 controls ( $58.0 \pm 13.3$  years; 61.0% females) defined as asymptomatic subjects without ICAD on MR vessel wall imaging. We compared the vascular risk factors between the three groups using a multivariate logistic regression analysis.

**Results:** Compared with controls, there was a significant positive association between age (OR: 1.07, 95% CI: 1.03–1.10,  $p < 0.001$ ) and hypertension (OR: 3.03, 95% CI: 1.45–6.36,  $p = 0.003$ ) and asymptomatic ICAD. There was a positive association of smoking (OR: 3.41, 95% CI: 1.57–7.42,  $p = 0.001$ ), hypertension (OR: 7.43, 95% CI: 3.81–14.49,  $p < 0.001$ ) and diabetes (OR: 3.54, 95% CI: 1.93–6.49,  $p < 0.001$ ) and an inverse association of high-density lipoprotein (HDL) ( $p < 0.017$ ) with symptomatic ICAD. Compared to asymptomatic ICAD, there was a significant inverse association of age (OR: 0.86, 95% CI: 0.81–0.92,  $p < 0.001$ ) and HDL ( $p < 0.001$ ) with symptomatic ICAD.

**Conclusion:** Old age and hypertension are associated with asymptomatic ICAD and smoking, hypertension, diabetes and lower HDL are associated with an increased risk of symptomatic ICAD in Chinese population.

**Clinical Trial Registration:** URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT03417063.

**Keywords:** intracranial artery, atherosclerosis, risk factors, magnetic resonance, vessel wall imaging

## Introduction

Stroke is one of the leading causes of death worldwide.<sup>1–3</sup> As one of the most common causes of ischemic stroke, intracranial atherosclerosis disease (ICAD) accounts for up to 50% of ischemic stroke or transient ischemic attacks (TIA) in Asia.<sup>4–6</sup> A number of studies have shown that age, gender, hypertension, hyperlipidemia, diabetes, obesity, and smoking are important risk factors for ICAD.<sup>7</sup>

Unfortunately, the ICAD in previous studies was mainly assessed by transcranial Doppler ultrasound or magnetic resonance (MR) angiography, which could not directly provide the information of the atherosclerotic plaques in the vessel wall. These imaging modalities lead to underestimation and even misdiagnosis, especially for the ICAD with positive remodeling. MR vessel wall imaging can accurately evaluate the morphology and compositions of atherosclerotic plaques in intracranial arteries with high spatial resolution and excellent reproducibility.<sup>8–10</sup> However, the relationship between risk factors and ICAD determined by MR vessel wall imaging in Chinese population has not been investigated. Better understanding the determinants of the risk of developing ICAD and cerebrovascular events is of importance for refining the management strategy of ICAD patients and prevention of future events.

We hypothesized that patients with symptomatic ICAD have different clinical profiles compared to those with asymptomatic ICAD or the normal subjects. The aim of this study was to determine the associations of conventional vascular risk factors with asymptomatic and symptomatic ICAD in Chinese population using MR vessel wall imaging.

## Materials and Methods

### Study Sample

This is a retrospective study. The study population was recruited from two cohort studies of ICASMAP (Intracranial Artery Stenosis MR imaging: Aetiology and Progression, NCT03417063) and CAMERA (Cardio- and Cerebro-vascular Accident Monitoring, Epidemiology and Care Quality System). The ICASMAP study was an observational and prospective study which aimed to investigate the etiology of intracranial artery stenosis (ICAS) and the progression rate of ICAD in symptomatic population using MR imaging. The design and rationale of the ICASMAP study have been published.<sup>11</sup> The inclusion criteria were as follows: 1) 18 to 80 years old; 2) patients within 2 weeks after onset of ischemic stroke or TIA; 3) patients with ICAS with a range from 30% to 100% stenosis in at least one vascular bed determined by computed tomography angiography or MR angiography. The ICAS lesions can be located in intracranial internal carotid artery, basilar artery, M1 segment of middle cerebral artery, A1 segment of anterior cerebral artery, or P1 segment of posterior cerebral artery. The exclusion criteria included: 1) severe carotid artery atherosclerotic disease (stenosis  $\geq 70\%$ ); 2)

cardiogenic thrombosis; 3) heart failure or respiratory failure; 4) renal dysfunction (serum creatinine  $>133\mu\text{mol/L}$ ); 5) serious disturbance of consciousness; 6) cerebral neoplasms; 7) intracranial hemorrhage; 8) claustrophobia; 9) contraindications to MR; and 10) pregnant or plan to get pregnant within recent 2 years. The CAMERA study is a community-based prospective study which aimed to evaluate the cerebrovascular risk of asymptomatic population at Tsinghua community. The inclusion criteria included: 1) age  $\geq 30$  years old; and 2) no cerebrovascular symptoms within recent 6 months. Subjects with contraindications to MR examination were excluded.

### Clinical Information Collection

For symptomatic patients, clinical information including age, gender, body mass index (BMI), overweight, smoking, alcohol use, hypertension, serum lipid levels (low-density lipoprotein [LDL], high-density lipoprotein [HDL], total cholesterol [TC], and triglycerides [TG]), statin use, diabetes mellitus and history of coronary heart disease (CHD), history of stroke and history of TIA were collected from the medical record. For subjects from CAMERA study, the above clinical data were obtained from the questionnaires. Overweight was defined as BMI  $\geq 25\text{ kg/m}^2$ . Current smoking was defined as at least one cigarette per day during the past one year.<sup>12</sup> Current alcohol use was defined as at least one drink per day during the past one year.<sup>13</sup> Hypertension was defined as history of elevated blood pressure (systolic blood pressure  $\geq 140\text{ mmHg}$  or diastolic blood pressure  $\geq 90\text{ mmHg}$ ) diagnosed by physician or treatment with antihypertensive drugs. Diabetes mellitus was defined as fasting blood glucose  $\geq 7.0\text{ mmol/L}$  ( $126\text{ mg/dL}$ ), a known past history of diabetes mellitus or use of hypoglycemic drugs therapy. Institutional review board approvals were obtained for the entire study and for each participating institution. All subjects provided written consent form before participation.

### MR Imaging

All the enrolled subjects from two cohorts underwent MR vessel wall imaging for intracranial arteries which included the intracranial internal carotid artery, basilar artery, M1 segment of middle cerebral artery, A1 segment of anterior cerebral artery, and P1 segment of posterior cerebral artery. The detailed imaging protocol and parameters for ICASMAP study have been published.<sup>11</sup> Briefly, the intracranial arterial MR vessel wall imaging at each participating center was performed on 3.0T Philips or Siemens MR scanners with 8-channel phase-array head coil or 16-channel neurovascular

coil. A standardized imaging protocol includes T1 volumetric isotropic turbo spin echo acquisition (T1-VISTA) at Philips MR platform or T1 sampling perfection with application-optimized contrast using different flip angle evolutions (T1-SPACE) sequence at Siemens MR platform. The T1-VISTA/SPACE imaging sequence was acquired using the following parameters: fast spin echo sequence, repetition time (TR) 800/900 ms, echo time (TE) 19/24 ms, field of view (FOV)  $200 \times 181 \times 45/158 \times 158 \times 158 \text{ mm}^3$ , matrix  $332 \times 300 \times 150/256 \times 256 \times 246$ , and scan time 7 min 1 sec/8 min 6 sec. The intracranial arterial MR vessel wall imaging of CAMERA study was performed on a 3T Philips MR scanner equipped with a 36-channel head coil. The imaging protocol was used to acquire the T1-VISTA sequence using the following parameters: turbo spin echo, transverse plane, TR/TE 800/21 ms, FOV  $200 \times 180 \times 40 \text{ mm}^3$ , matrix  $332 \times 332 \times 133$ , scan time 6 min 18 sec. An identical spatial resolution of  $0.6 \times 0.6 \times 0.6 \text{ mm}^3$  was used in both ICASMAP and CAMERA studies.

## MR Image Analysis

The vessel wall images of intracranial arteries were interpreted by two experienced radiologists with consensus blinded to all clinical information. Both radiologists had >3 years' experience in cardiovascular plaque imaging. The image quality was rated per artery on a 4-point scale (1, poor; 2, marginal; 3, good; and 4, excellent) according to the clearness and signal-to-noise-ratio of vessel wall boundaries and images with a quality rating <2 were excluded from this analysis.<sup>14</sup> The MR images with image quality  $\geq 2$  were interpreted. The ICAD was defined as presence of atherosclerotic plaque characterized by eccentric arterial wall thickening in any intracranial vascular bed for each subject.<sup>15</sup> The identification of ICAD was determined by experienced neuroradiologists (>5 years' experience) according to the characteristics of imaging in ICASMAP study.<sup>16</sup> Intracranial atherosclerotic plaque was characterized by eccentric wall thickening on MR vessel wall images. Presence or absence of atherosclerotic plaque at each vascular bed of intracranial arteries was determined. For each subject, if there was an atherosclerotic plaque in any vascular bed, this subject was identified to have atherosclerotic plaque.

## Statistical Analysis

The study population was divided into three groups: symptomatic ICAD group: the subjects of this group were from ICASMAP study who had intracranial atherosclerotic

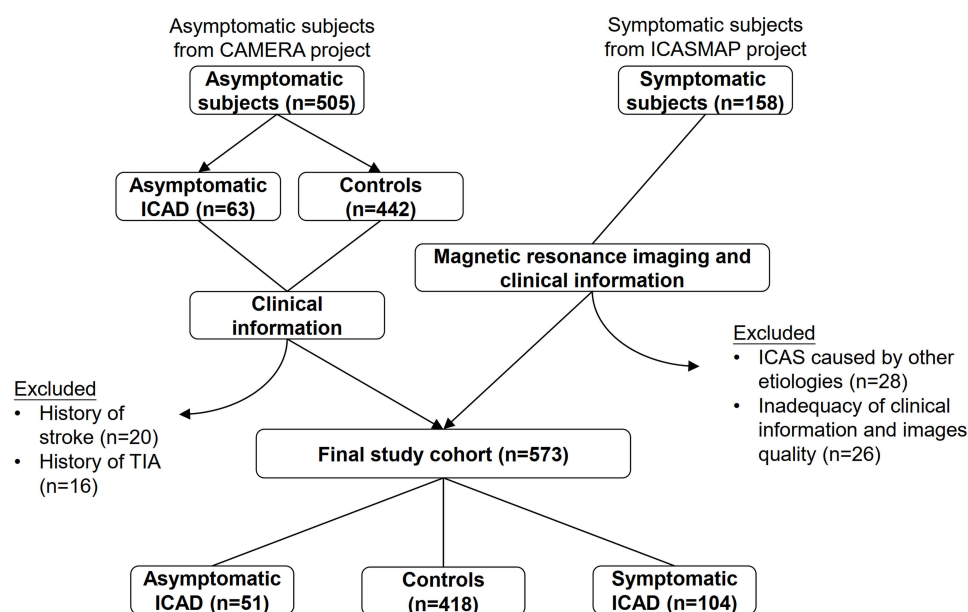
plaques and symptoms of ischemic stroke or TIA; asymptomatic ICAD group: the subjects of this group were from CAMERA study who had intracranial atherosclerotic plaques but were asymptomatic; and controls group: the subjects of this group were from CEMERA study who were asymptomatic and did not have intracranial atherosclerotic plaques. Continuous variables were summarized as mean  $\pm$  standard deviation and categorical variables were presented as percentage. Clinical characteristics were compared with One-way ANOVA and Tukey's studentized range testing for continuous variables and Chi-square analysis or Fisher's exact test for categorical variables among three groups, as appropriate. We compared the association between outcome variable (3 groups) and each risk factor including age, gender, overweight, smoking, alcohol use, hypertension, HDL, LDL, TC, TG, diabetes mellitus and history of CHD by using univariate logistic regression analysis. In the multivariate logistic regression models, we included all the covariates and used stepwise method to select the covariate. This statistical analysis may partially minimize the selective bias of study population from different cohort studies. Two-tailed p-values <0.05 were considered statistically significant. During above logistic regression, the level of significance was adjusted to  $p < 0.017$  after correcting multiple comparisons ( $0.05/3 = 0.017$ ). Statistical analysis was performed using the software of SPSS 16.0 (IBM, Chicago, IL) and SAS 9.4 (SAS Institute Inc, Cary, NC).

## Results

The derivation of the study groups is shown in Figure 1. Of 663 included subjects, 90 were excluded due to the following reasons: 1) other etiologies of ICAS ( $n = 28$ ) including 4 moyamoya disease, 2 artery dissection and 22 others; 2) insufficient clinical information ( $n = 16$ ) and poor image quality ( $n = 10$ ); and 3) asymptomatic subjects with history of stroke ( $n = 20$ ) and history of TIA in CAMERA study ( $n = 16$ ). The remaining 573 subjects were included in final statistical analysis.

## Comparison of Clinical Characteristics Among Three Groups

The clinical characteristics of the study subjects are shown in Table 1. Asymptomatic ICAD subjects were significantly older ( $70.1 \pm 8.4$  years vs  $57.1 \pm 11.1$  years and  $58.0 \pm 13.3$  years,  $p < 0.001$ ) and had higher prevalence of history of CHD (17.6% vs 6.7% and 5.0%,



**Figure 1** The derivation of the study groups.

**Abbreviations:** ICAD, intracranial atherosclerosis disease; ICAS, intracranial artery stenosis; TIA, transient ischemic attacks.

$p = 0.002$ ) than symptomatic ICAD and controls. Symptomatic and asymptomatic ICAD subjects showed more current alcohol use (15.4% and 21.6% vs 8.9%,  $p = 0.007$ ) and greater prevalence of hypertension (86.5% and 74.5% vs 40.2%,  $p < 0.001$ ) than controls. Symptomatic ICAD subjects are less likely to female (35.6% vs 50.0% and 61.0%,  $p < 0.001$ ) and had greater BMI ( $25.3 \pm 3.4 \text{ kg/m}^2$  vs  $24.6 \pm 3.2 \text{ kg/m}^2$  and  $24.3 \pm 3.3 \text{ kg/m}^2$ ,  $p = 0.018$ ), higher prevalence of overweight (69.2% vs 60.8% and 51.4%,  $p = 0.003$ ), current smoking (26.9% vs 7.8% and 5.0%,  $p < 0.001$ ), diabetes (44.2% vs 25.5% and 12.4%,  $p < 0.001$ ) and less statin use (9.6% vs 37.3% and 20.1%,  $p < 0.001$ ) than asymptomatic ICAD and controls. In contrast, the levels of HDL ( $1.11 \pm 0.24 \text{ mmol/L}$  vs  $1.53 \pm 0.44 \text{ mmol/L}$  and  $1.49 \pm 0.37 \text{ mmol/L}$ ,  $p < 0.001$ ) and TC ( $4.40 \pm 1.49 \text{ mmol/L}$  vs  $4.78 \pm 0.74 \text{ mmol/L}$  and  $4.85 \pm 0.92 \text{ mmol/L}$ ,  $p < 0.001$ ) of symptomatic ICAD subjects were significantly lower than asymptomatic ICAD and controls. There were no significant differences in LDL and TG among the 3 groups (all  $p > 0.05$ ).

## Asymptomatic ICAD Subjects versus Controls

Compared with controls, asymptomatic ICAD subjects were more likely to be older (OR: 1.08, 95% CI: 1.05–1.11,  $p < 0.001$ ) and have hypertension (OR: 4.63, 95%

CI: 2.27–9.44,  $p < 0.001$ ) and history of CHD (OR: 3.34, 95% CI: 1.33–8.38,  $p = 0.010$ ) (Table 2). After adjusted for all other risk factors (Model 1 with covariates of age and hypertension), the differences in age (OR: 1.07, 95% CI: 1.03–1.10,  $p < 0.001$ ) and hypertension (OR: 3.03, 95% CI: 1.45–6.36,  $p = 0.003$ ) between asymptomatic ICAD subjects and controls remained statistically significant (Table 3).

## Symptomatic ICAD Subjects versus Controls

Compared with controls, symptomatic ICAD subjects were less likely to be female (OR: 0.35, 95% CI: 0.22–0.55,  $p < 0.001$ ) and more likely to have overweight (OR: 2.11, 95% CI: 1.33–3.35,  $p = 0.001$ ), current smoking (OR: 6.50, 95% CI: 3.51–12.06,  $p < 0.001$ ), hypertension (OR: 9.93, 95% CI: 5.46–18.07,  $p < 0.001$ ), diabetes (OR: 5.55, 95% CI: 3.40–9.05,  $p < 0.001$ ), lower HDL (the second quantile (Q2)/the third quantile (Q3)/the fourth quantile (Q4) vs the first quantile (Q1), all  $p < 0.001$ ), lower LDL (Q3 vs Q1,  $p = 0.010$ ) and lower TC (Q2/Q3/Q4 vs Q1, all  $p < 0.001$ ) (Table 2). After adjusted for all other risk factors (Model 2 with covariates of smoking, hypertension, HDL, TC and diabetes), the differences in smoking (OR: 3.41, 95% CI: 1.57–7.42,  $p = 0.001$ ), hypertension (OR: 7.43, 95% CI: 3.81–14.49,  $p < 0.001$ ), HDL (Q2/Q3/Q4 vs Q1, all  $p < 0.017$ ), TC (Q2 vs Q1,  $p =$



**Table I** The Clinical Characteristics of the Study Subjects

	Mean $\pm$ SD or n (%)			p
	Symptomatic ICAD (n=104)	Asymptomatic ICAD (n=51)	Controls (n=418)	
Age, years	57.1 $\pm$ 11.1	70.1 $\pm$ 8.4	58.0 $\pm$ 13.3	<0.001
Gender, female	37 (35.6)	22 (50.0)	239 (61.0)	<0.001
Body mass index, kg/m <sup>2</sup>	25.3 $\pm$ 3.4	24.6 $\pm$ 3.2	24.3 $\pm$ 3.3	0.018
Overweight	72 (69.2)	31 (60.8)	215 (51.4)	0.003
Smoking	28 (26.9)	4 (7.8)	21 (5.0)	<0.001
Drinking	16 (15.4)	11 (21.6)	37 (8.9)	0.007
Hypertension	90 (86.5)	38 (74.5)	168 (40.2)	<0.001
HDL, mmol/L	1.11 $\pm$ 0.24	1.53 $\pm$ 0.44	1.49 $\pm$ 0.37	<0.001
LDL, mmol/L	2.82 $\pm$ 1.16	2.89 $\pm$ 0.69	2.96 $\pm$ 0.87	0.353
TC, mmol/L	4.40 $\pm$ 1.49	4.78 $\pm$ 0.74	4.85 $\pm$ 0.92	<0.001
TG, mmol/L	1.89 $\pm$ 1.24	1.63 $\pm$ 0.7	1.69 $\pm$ 1.65	0.454
Statin use	10 (9.6)	19 (37.3)	84 (20.1)	<0.001
Diabetes	46 (44.2)	13 (25.5)	52 (12.4)	<0.001
History of CHD	7 (6.7)	9 (17.6)	21 (5.0)	0.002

**Abbreviations:** ICAD, intracranial atherosclerosis disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; CHD, coronary heart disease.

0.003) and diabetes (OR: 3.54, 95% CI: 1.93–6.49,  $p$  < 0.001) between asymptomatic ICAD subjects and controls remained statistically significant (Table 3).

## Asymptomatic ICAD Subjects versus Symptomatic ICAD Subjects

Compared with asymptomatic ICAD subjects, symptomatic ICAD subjects were more likely to be younger (OR: 0.87, 95% CI: 0.83–0.92,  $p$  < 0.001) and have current smoking (OR: 5.03, 95% CI: 1.44–17.57,  $p$  = 0.011), lower HDL (Q3/Q4 vs Q1,  $p$  < 0.001) and lower TC (Q2 vs Q1,  $p$  = 0.004; Q3 vs Q1,  $p$  = 0.015) (Table 2). After adjusted for all other risk factors (Model 3 with covariates of age and HDL), the differences in age (OR: 0.86, 95% CI: 0.81–0.92,  $p$  < 0.001) and HDL (Q3/Q4 vs Q1,  $p$  < 0.001) between asymptomatic and symptomatic ICAD subjects remained statistically significant (Table 3).

## Discussion

This study compared clinical characteristics that were known as conventional vascular risk factors among asymptomatic ICAD, symptomatic ICAD and controls. In our study, there were differences in the distribution of conventional vascular risk factors in three groups. Symptomatic ICAD subjects were significantly younger, more likely male, higher prevalence of overweight, current smoking, current alcohol use, hypertension, diabetes, less statin use, lower HDL, TC and history of CHD than

asymptomatic ICAD and/or controls. Compared with controls, asymptomatic ICAD subjects were more likely older and to have hypertension and symptomatic ICAD subjects were more likely to have current smoking, hypertension and diabetes. We also found that symptomatic ICAD subjects were younger and more likely to have lower HDL than those with asymptomatic ICAD. Our findings suggest that smoking cessation and modification of the level of blood pressure and blood glucose may be helpful for reducing the risk of developing intracranial atherosclerosis and cardiovascular events.

In our study, we found that old age and hypertension were associated with an increased risk of asymptomatic ICAD. The finding of higher prevalence of asymptomatic ICAD in older individuals is in line with previous reports.<sup>17–19</sup> The probable explanation may be the fact that vascular aging and cellular senescence are associated with increased expression of proinflammatory cytokines and adhesion molecules further promoting inflammation which accelerate the formation of atherosclerotic plaques.<sup>20</sup> Although hypertension is usually considered to be one of the major risk factors for ICAD,<sup>7</sup> its role in development of asymptomatic ICAD is controversial. Several transcranial Doppler studies documented that hypertension had a positive association with asymptomatic ICAD with odds ratios ranging from 1.43 to 2.23 (all  $p$  < 0.05).<sup>17,21,22</sup> An MR angiography study by Park et al reported an increased prevalence of

**Table 2** Comparison of Vascular Risk Factor Prevalence Between 3 Groups by Univariate Logistic Regression Analysis

	Asymptomatic ICAD vs Controls		Symptomatic ICAD vs Controls		Symptomatic vs Asymptomatic ICAD	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.08 (1.05–1.11)	<0.001	0.99 (0.98–1.01)	0.807	0.87 (0.83–0.92)	<0.001
Gender, female	0.64 (0.34–1.19)	0.162	0.35 (0.22–0.55)	<0.001	0.55 (0.27–1.12)	0.103
Overweight	1.49 (0.78–2.82)	0.217	2.11 (1.33–3.35)	0.001	1.41 (0.67–2.95)	0.353
Smoking	1.29 (0.36–4.52)	0.687	6.50 (3.51–12.06)	<0.001	5.03 (1.44–17.57)	0.011
Drinking	2.50 (1.07–5.83)	0.033	2.04 (1.07–3.89)	0.029	0.81 (0.32–2.08)	0.673
Hypertension	4.63 (2.27–9.44)	<0.001	9.93 (5.46–18.07)	<0.001	2.14 (0.88–5.19)	0.091
HDL, mmol/L						
Q1	1.00		1.00		1.00	
Q2	0.95 (0.33–2.67)	0.924	0.33 (0.19–0.58)	<0.001	0.35 (0.12–1.05)	0.062
Q3	1.16 (0.44–3.06)	0.754	0.13 (0.06–0.26)	<0.001	0.11 (0.03–0.34)	<0.001
Q4	1.35 (0.52–3.49)	0.525	0.02 (0.004–0.08)	<0.001	0.01 (0.002–0.08)	<0.001
LDL, mmol/L						
Q1	1.00		1.00		1.00	
Q2	0.82 (0.34–1.95)	0.660	0.67 (0.37–1.19)	0.178	0.81 (0.31–2.13)	0.681
Q3	1.08 (0.48–2.45)	0.836	0.43 (0.23–0.82)	0.010	0.40 (0.15–1.03)	0.057
Q4	0.41 (0.15–1.16)	0.094	0.53 (0.29–0.97)	0.039	1.27 (0.42–3.88)	0.665
TC, mmol/L						
Q1	1.00		1.00		1.00	
Q2	1.06 (0.44–2.55)	0.886	0.25 (0.13–0.47)	<0.001	0.23 (0.08–0.64)	0.004
Q3	0.99 (0.41–2.38)	0.993	0.29 (0.16–0.54)	<0.001	0.29 (0.11–0.79)	0.015
Q4	0.63 (0.24–1.68)	0.363	0.34 (0.18–0.61)	<0.001	0.53 (0.18–1.54)	0.248
TG, mmol/L						
Q1	1.00		1.00		1.00	
Q2	1.48 (0.62–3.55)	0.368	1.00 (0.52–1.91)	0.993	0.67 (0.24–1.85)	0.442
Q3	1.53 (0.64–3.66)	0.332	1.37 (0.74–2.54)	0.301	0.89 (0.33–2.41)	0.830
Q4	0.94 (0.35–2.49)	0.911	1.52 (0.83–2.78)	0.166	1.61 (0.55–4.71)	0.380
Diabetes	2.33 (1.10–4.91)	0.025	5.55 (3.40–9.05)	<0.001	2.37 (1.08–5.21)	0.030
History of CHD	3.34 (1.33–8.38)	0.010	1.27 (0.52–3.08)	0.590	0.38 (0.12–1.16)	0.090

**Notes:** The levels of lipoproteins were divided into four equal parts including the first quantile (Q1), the second quantile (Q2), the third quantile (Q3), and the fourth quantile (Q4).

**Abbreviations:** ICAD, intracranial atherosclerosis disease; OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; CHD, coronary heart disease.

hypertension (OR: 2.40, 95% CI: 1.01–5.69,  $p < 0.05$ ) in asymptomatic ICAS subjects compared with those without stenosis.<sup>23</sup> However, another MR angiography study showed no association between hypertension and asymptomatic ICAD subjects (OR: 0.98, 95% CI: 0.89–1.08,  $p = 0.76$ ).<sup>24</sup> Despite the literature reports on the relationship between hypertension and ICAD are inconsistent, most of investigators believed that elevated blood pressure is a risk factor for the development of

atherosclerosis due to damage in the endothelium and vascular wall by elevated blood pressure through both mechanical and humoral factors.<sup>25</sup> Another explanation of the association of hypertension with ICAD is that the elevated blood pressure induces oxidative stress on the arterial wall companion with other atherogenic stimuli such as hyperlipidemia.<sup>26</sup> The role of blood pressure in development of asymptomatic ICAD needs to be further investigated in future studies.

**Table 3** Comparison of Vascular Risk Factor Prevalence Between 3 Groups by Multivariate Logistic Regression Analysis

	OR (95% CI)	p
Asymptomatic ICAD vs Controls*		
Age	1.07 (1.03–1.10)	<0.001
Hypertension	3.03 (1.45–6.36)	0.003
Symptomatic ICAD vs Controls <sup>#</sup>		
Smoking	3.41 (1.57–7.42)	0.001
Hypertension	7.43 (3.81–14.49)	<0.001
HDL, mmol/L		
Q1	1.00	
Q2	0.38 (0.19–0.73)	0.004
Q3	0.21 (0.10–0.47)	<0.001
Q4	0.03 (0.007–0.16)	<0.001
TC, mmol/L		
Q1	1.00	
Q2	0.30 (0.13–0.66)	0.003
Q3	0.51 (0.23–1.13)	0.099
Q4	0.75 (0.35–1.63)	0.481
Diabetes	3.54 (1.93–6.49)	<0.001
Symptomatic vs Asymptomatic ICAD <sup>†</sup>		
Age	0.86 (0.81–0.92)	<0.001
HDL, mmol/L		
Q1	1.00	
Q2	0.43 (0.12–1.45)	0.175
Q3	0.11 (0.03–0.40)	<0.001
Q4	0.01 (0.001–0.09)	<0.001

**Notes:** \*Model 1: covariate: age and hypertension; <sup>#</sup>Model 2: covariate: smoking, hypertension, HDL and diabetes; <sup>†</sup>Model 3: covariate: age and HDL; The levels of lipoproteins were divided into four equal parts including the first quantile (Q1), the second quantile (Q2), the third quantile (Q3), and the fourth quantile (Q4).

**Abbreviations:** OR, odds ratio; CI, confidence interval; ICAD, intracranial atherosclerosis disease; HDL, high-density lipoprotein; TC, total cholesterol.

In the present study, univariate logistic regression analysis showed that subjects with symptomatic ICAD were less female and more overweight than controls. Our results are in line with previous studies. Multiple studies have shown that high BMI among men who were overweight or obese was strongly associated with increased stroke mortality.<sup>27,28</sup> Bos et al found that more than 80% of elderly Caucasians have ICAD and the volume of atherosclerosis is larger in males than that in females.<sup>29</sup> The potential mechanisms for the subjects with symptomatic ICAD being less female and more overweight are complex. Estrogen, such as estradiol, which prevents fatty streak deposition and progression of atherosclerotic plaque, plays an important role in vascular protection and anti-atherosclerosis.<sup>30,31</sup> In addition, Obesity may activate and promote endothelial cell migration, smooth muscle cell proliferation and vascular calcification due to the

increase secretion of leptin, thus promotes the formation of atherosclerosis.<sup>32,33</sup> We also found that subjects with symptomatic ICAD were found to be more likely to have current smoking, hypertension, and diabetes. Our results are consistent with previous studies to some extent. A study of ICAD in Korean population showed that cigarette smoking is associated with multiple ICAS.<sup>34</sup> A Chinese acute ischemic stroke population study indicated that high diastolic blood pressure is a risk factor for ICAS (OR: 1.075, 95% CI: 1.016–1.138,  $p = 0.013$ ).<sup>35</sup> In addition, a Warfarin Aspirin Symptomatic Intracranial Disease study showed that systolic blood pressure  $\geq 140$  mm Hg (HR: 1.79,  $p = 0.0009$ , 95% CI: 1.27–2.52) was associated with an increased risk of stroke, myocardial infarction, or vascular death.<sup>36</sup> Furthermore, a transcranial Doppler study reported that hypertension was associated with a more than 2-fold higher likelihood of symptomatic ICAD (OR: 2.41, 95% CI: 1.02–5.67,  $P = 0.045$ ), while diabetes mellitus was the strongest predictive variable of symptomatic ICAD (OR: 4.25, 95% CI: 2.18–8.26,  $P < 0.001$ ).<sup>37</sup> Symptomatic ICAD is usually characterized by the following vulnerable plaque features: intraplaque hemorrhage, larger lipid-rich necrotic core, and fibrous cap rupture. Cigarette smoking promotes the development of vulnerable plaques and plaque rupture by enhancing inflammation and activating matrix metalloproteinases.<sup>38</sup> Recent studies proved that blood pressure, particularly pulse blood pressure or diastolic blood pressure,<sup>39–41</sup> is associated with occurrence of intraplaque hemorrhage in carotid artery, which is presumed to be caused by erythrocyte leakage from dysfunctional intraplaque micro-vessels.<sup>42</sup> Moreno et al found a larger content of high-risk plaque features such as a lipid core in coronary specimens of diabetics than in nondiabetics.<sup>43</sup> It has been hypothesized that the alterations in vascular homeostasis due to endothelial and smooth muscle cell dysfunction are the main features of diabetic vasculopathy favouring a pro-inflammatory/thrombotic state which ultimately leads to atherosclerosis.<sup>44</sup> The symptomatic ICAD may not be the outcome of only one risk factor, but the outcome of combination of multiple factors such as hypertension, high level of LDL and diabetes. In addition, TC was inversely associated with symptomatic ICAD which may be due to the higher proportion of statin use in control subjects than in symptomatic ICAD subjects.

We found that symptomatic ICAD subjects were more likely to be younger and have lower HDL compared with asymptomatic ICAD subjects. An association between

symptom and age was less evidenced previously. Similar findings about the effect of HDL on symptoms in patients with ICAD have been reported in previous studies. A study by Kim et al demonstrated that a high HDL level strongly predicted a favorable course for symptomatic ICAS ( $p = 0.005$ ).<sup>45</sup> It has been assumed that high level of HDL may prevent the development of the cerebrovascular symptoms. The explanation for the decreased frequency of symptoms in ICAD subjects is probably due to the reduction of plaque growth and inflammatory and favor positive vascular remodeling by high level of HDL.<sup>46–48</sup>

The major strengths of our study are as follows: (1) the use of MR vessel wall imaging guaranteed the accurate detection of atherosclerotic plaques in intracranial arteries which effectively avoided underestimation or misdiagnosis. (2) to investigate the conventional vascular risk factors of three groups may provide targets for ICAD therapy and clues for prevention the occurrence of ICAD symptoms. Several limitations in this study need to be acknowledged. Firstly, the inclusion criteria, the sample size and age distribution of each subject group of the present study are heterogeneous. For example, the sample size of the asymptomatic ICAD subjects ( $n = 55$ ) was small and the age of them ( $70.6 \pm 8.4$  years) were old. This study population may not represent the general population due to narrow range of the age. The power analysis showed that under the current sample size, the power to detect  $OR < 0.50$  was greater than 0.92. Secondly, MR scanners from multiple vendors were applied to this study which may introduce inter-platform bias due to the inconsistent imaging parameters. However, we believe this influence should be minor because we only determined presence or absence of atherosclerotic plaque and no quantitative measurements were performed. Finally, in our study, we only cross-sectionally evaluated the conventional vascular risk factors of symptomatic and asymptomatic intracranial atherosclerosis. Long-term follow-up studies are suggested to determine the effect of vascular risk factors on the time course of intracranial atherosclerosis in a single study population.

In conclusion, old age and hypertension are associated with asymptomatic ICAD and smoking, hypertension, diabetes and lower HDL are associated with an increased risk of symptomatic ICAD in Chinese population. Our findings suggest that management of the modifiable risk factors including smoking, hypertension, diabetes and HDL may reduce the risk of developing intracranial atherosclerotic plaques and cerebrovascular events.

## Abbreviations

BMI, body mass index; CHD, coronary heart disease; CAMERA, Cardio- and Cerebro-vascular Accident Monitoring, Epidemiology and Care Quality System; FOV, field of view; HDL, high-density lipoprotein; ICAD, intracranial atherosclerosis disease; ICAS, intracranial artery stenosis; ICASMAP, Intracranial Artery Stenosis MR imaging: Aetiology and Progression; LDL, low-density lipoprotein; MR, magnetic resonance; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attacks; TC, total cholesterol; TG, triglycerides; T1-VISTA, T1 volumetric isotropic turbo spin echo acquisition; T1-SPACE, T1 sampling perfection with application-optimized contrast using different flip angle evolutions; TR, repetition time; TE, echo time.

## Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author [X.Z. and G.L.]. The data are not publicly available due to them containing information that could compromise research participant privacy/consent.

## Ethics Approval and Consent to Participate

The study protocol was approved by institutional review board of Tsinghua University School of Medicine and each participating institution and the written consent forms were obtained from all the subjects prior to the initiation of this study.

## Author Contributions

Y.H. carried out the study, analyzed and interpreted data, and drafted the manuscript. R.Z. performed statistical analysis. D.Y., D.L. and H.H. participated in acquisition of data. H.Q. and S.C. carried out the study. Y.W. participated in acquisition of data and interpreted the data. M.Y. and Y. H. participated in acquisition of data. Z.W. made critical revision of the manuscript. X.Z. and G.L. carried out the conception, study design, revised the manuscript, and made critical revision of the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the



article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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