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Morphometric measurements of extracranial and intracranial atherosclerotic disease: A population-based autopsy study

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Abstract

Background and aims—Intracranial (IAD) and extracranial atherosclerotic diseases (EAD) have been mostly investigated using imaging methods. Autopsy studies allow for a direct and complete evaluation of the atherosclerotic disease. We aimed to investigate the frequency of IAD and EAD, their association, and related risk profiles in a large cross-sectional autopsy study.

Methods—We measured the intima-media thickness and stenosis of the common (CCA) and internal carotid arteries (ICA), using morphometric measurements. The main outcome was stenosis (≥50%) in the artery with the largest obstruction among the 12 cerebral arteries. We used multivariable logistic regression models to investigate the association between EAD and IAD.

Results—In 661 participants (mean age = 71.3 ± 11.7 y, 51% male), stenosis was more common in IAD than in EAD (59% *vs.* 51%). EAD was associated with Caucasian race, hypertension, and smoking, while IAD was associated with older age, less years of education, hypertension, diabetes, and a previous history of stroke. Stenosis in CCA and ICA was associated with more than two

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Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Claudia K. Suemoto, study concept and design, acquisition of data, analysis, interpretation of data, and manuscript drafting.
Lea T. Grinberg, acquisition of data, critical revision of manuscript for intellectual content.
Renata E. P. Leite, acquisition of data, critical revision of manuscript for intellectual content.
Renata E. L. Ferretti-Rebustini, acquisition of data, critical revision of manuscript for intellectual content.
Wilson Jacob-Filho, critical revision of manuscript for intellectual content, study supervision.
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Carlos A. Pasqualucci, study concept and design, critical revision of manuscript for intellectual content, study supervision.

times the odds of having stenosis in the intracranial arteries (CCA: OR = 2.32, 95% CI = 1.64; 3.28; ICA: OR = 2.51, 95% CI = 1.76; 3.57).

Conclusions—In this population-based autopsy study, IAD was common, even more common than EAD, but correlated with EAD.

Keywords

Atherosclerosis; Carotid arteries; Cerebral arteries; Risk factors; Epidemiology

1. Introduction

Stroke is the second leading cause of mortality and the 7th leading cause of disability-adjusted life years (DALY) lost world-wide [1,2]. Nearly 90% of strokes are ischemic, and large artery atherosclerosis is one of the main causes of ischemic stroke [3]. Extracranial atherosclerotic disease (EAD) has been extensively associated with a higher risk of ischemic stroke in longitudinal studies, and it is more frequent in Caucasians [4,5]. On the other hand, less is known about intracranial atherosclerotic disease (IAD), probably because more accurate IAD detection was only recently possible with high-resolution magnetic resonance imaging and intravascular ultrasound [6]. IAD has also been associated with a higher risk of stroke recurrence [7], and it is more common among individuals from Asian, African, and Hispanic ancestries [8]. Moreover, IAD and EAD have been associated with different risk factors; age, race, education, metabolic syndrome, and stroke have been associated with IAD, while race, male sex, hypertension, heart disease, smoking, and alcohol use are associated with EAD [9].

The association between IAD and EAD has been evaluated in white and Asian patients with previous cardiac diseases or stroke [10–12] using imaging methods, which only allow for indirect measurements of atherosclerosis. Autopsy studies allow for the direct visualization of atherosclerotic plaques, and they could contribute to understand the true prevalence of IAD and determine the correlation with EAD and associated risk factors. This information may help target individuals at risk for ischemic stroke, which is important to develop new diagnostic techniques and/or new treatment paradigms. However, few autopsy studies have been conducted [13–15]. Mazighi et al. found an association between proximal EAD and intracranial internal carotid artery stenosis in subjects with fatal stroke; however, its association with atherosclerosis in other intracranial arteries was not investigated [13]. Therefore, we investigated the prevalence of IAD and EAD, their association, and their related risk factors using direct morphometric measurements of atherosclerotic disease in a large population-based autopsy study including diverse races.

2. Materials and methods

2.1. Participants

In the city of Sao Paulo (Brazil), subjects dying from natural death of an unknown cause undergo an autopsy exam to elucidate the cause of death. Autopsies are performed at the Sao Paulo Autopsy Service (SPAS) at the University of Sao Paulo within a short post mortem interval (mean of 10 h). Consistently, the main cause of death is cardiovascular related (60%

of cases), with stroke being responsible for 2% of deaths [16]. Details about our study design can be found elsewhere [17]. While the next of kin (NOK) waited for the autopsy, our team explained the study aims and asked for donations of the cerebral and carotid arteries. The NOK signed informed consent, allowing material collection and data provision. This study was approved by the local ethics committee. We collected samples from 2005 to 2008. We included subjects who were aged 50 years or older at the time of death. We excluded cases with post mortem interval >24 h (n = 120), and cases where NOK who did not see the deceased at least weekly or could not provide reliable clinical information (n = 88). We also excluded cases in which we could not collect the internal carotid artery due to anatomical difficulties in dissecting this artery (n = 247).

2.2. Atherosclerosis evaluation

Cerebral arteries were dissected from the brain, washed in water to remove blood clots, and stored in 70% alcohol for 24 h. We then injected gelatin inside the vessel lumen to prevent artery collapse and fixed it in 10% formalin. After fixation, we cut the artery into 3-mm thick cross-sections to evaluate the presence of atheromatous plaques in each of the 12 arteries from the Circle of Willis (CW) [right and left anterior cerebral arteries, anterior communicating artery, right and left middle cerebral arteries, right and left internal carotid arteries (close to the CW), right and left posterior communicating arteries, right and left posterior cerebral arteries, and the basilar artery]. In each artery, we selected the cross-section with the largest lumen obstruction and photographed it using a stereomicroscope (Nikon SMZ 1000; Nikon Inst., New York, USA). Using an image processor (ImageJ®), we measured the area delineated by the outer arterial wall and the lumen area (Fig. 1A). For each of the 12 cross-sections, we calculated a CW stenosis index by subtracting the lumen area from the outer area, dividing this difference by the outer area and multiplying it by 100.

Carotid arteries were dissected from the aortic arch and processed similarly as the CW arteries. After fixation in 10% formalin, carotid arteries were cut into 5-mm thick cross-sections. We selected the section of the common (CCA) and internal carotid arteries (ICA) with the largest atheroma plaques. Common carotid artery intima-media thickness (C-IMT) was measured 1 cm below the artery bifurcation, and internal carotid artery intima-media thickness (I-IMT) was measured 1 cm above the bifurcation (Fig. 1B a) following standard procedures. We prepared histological slides of the three selected sections with hematoxylin-eosin and Verhoeff's staining and photographed them with the stereomicroscope. Using ImageJ®, we measured the area delineated by the internal elastic lamina and the lumen area (Fig. 1B b). The carotid stenosis index was calculated similarly to the CW stenosis index. C-IMT and I-IMT were calculated by dividing the intima-media area (i.e. the area delineated by the external elastic lamina and the lumen) by the media perimeter (delineated by the external elastic lamina) (Fig. 1B c). We described additional details about the morphometric measurement of atherosclerosis elsewhere [18,19]. Atherosclerosis evaluation was performed by one rater (CKS) independently from clinical and statistical analysis.

2.3. Sociodemographic and clinical variables

Sociodemographic variables included age at death, sex, race (white, black, and Asian), and education. Clinical variables included a previous history of diabetes, hypertension,

dyslipidemia, stroke, heart disease, smoking (never, current, or past smokers), alcohol use (never, current, or past use), physical activity, and body mass index (BMI). Age information was retrieved from government-issued documents. Race and other clinical variables were reported by the NOK. The deceased was weighed in the supine position without clothes using an electronic scale, and height was measured using a stadiometer. BMI was calculated by dividing the weight in kg by the square of the height in meters.

2.4. Statistical analysis

We used the mean and standard deviation to present descriptive statistics of quantitative variables and relative frequencies for categorical variables. We compared the included and excluded subjects from this study using unpaired *t*-test for continuous variables, and Chi square test or Fisher's exact test for categorical variables. The association of stenosis (obstructions ≥50%) in EAD and in IAD with sociodemographic and clinical variables was investigated using multivariable logistic regression models including all variables. We used Venn diagrams to describe the relative frequency of stenosis in the EAD and IAD in our sample.

We used logistic regression models to examine the association between stenosis in the cerebral and carotid arteries. The dependent variable was the presence of stenosis (≥50%) in the cerebral artery with the largest obstruction among the 12 CW arteries [20]. The independent variables were C-IMT and I-IMT (in mm) and the presence of stenosis (obstruction ≥50%) in the CCA and in the ICA. The multivariable logistic regression models were adjusted for age at death, sex, race (white *versus* non-white), and education. We used Stata 12.0 (StataCorp LP, College Station, Texas, USA) for statistE analyses.

3. Results

Included participants (n = 661) were older, and had less diabetes and stroke than excluded subjects (n = 455) (Table 1). Among the included participants, the mean age was 71.3 ± 11.7 years, 51% were male, and 68% were white. Regarding cardiovascular risk factors, 65% had hypertension, 28% had diabetes, and 19% had heart disease. We evaluated 12 CW arteries from each of the 661 participants (total of 7932 arteries), and we selected the artery with the largest obstruction. Among the CW arteries with the largest obstruction, 387 (59%) had intracranial stenosis (obstruction ≥50%). We also selected the segment with the largest obstruction among the left and right CCA and ICA of each participant (2644 arteries). Among the carotid arteries, 337 (51%) had extracranial stenosis (obstruction ≥50%). Mean C-IMT was 1.01 ± 0.25 mm, mean I-IMT was 0.75 ± 0.27 mm, mean percentage of carotid artery obstruction was 52.9 ± 19.9%, and mean percentage of CW obstruction was 50.1 ± 32.8%.

Stenosis in the CW arteries was more common in the basilar, posterior, and middle cerebral arteries, and 37% of the sample had stenosis in 3 or more intracranial arteries (Fig. 2). Among 255 participants with stenosis in the CCA, we found that 69% had stenosis in at least one of the cerebral arteries. In addition, among 247 participants with stenosis in the ICA, 71% had stenosis in the CW (Fig. 3). In multivariate logistic regression analyses, IAD was associated with older age, fewer years of education, hypertension, diabetes, and previous

history of stroke. EAD was associated with Caucasian race, hypertension, and smoking (Table 2).

We observed that each one-mm increase of C-IMT and I-IMT was associated with more than 6 times the odds of having CW stenosis (≥50%) (for C-IMT: OR = 6.40, 95% CI = 3.18–12.87, $p < .0001$; for I-IMT: OR = 6.39, 95% CI = 3.15–12.97, $p < .0001$). Stenosis (≥50%) in the CCA and ICA was associated, with 2.3 and 2.5 times the odds of having an obstruction ≥50% in the CW, respectively (Table 3).

4. Discussion

In this study of 661 admixed subjects older than 50 years, who underwent autopsy, we had the following findings: EAD was strongly associated with IAD in our large autopsy study, and indeed, arterial stenosis and greater IMT in the CCA and ICA were associated with higher odds of stenosis in intracranial arteries. We also found that stenosis was more common in the intracranial arteries than in the extracranial arteries, and most of the participants with EAD had also IAD. We also observed different risk profiles associated with EAD and IAD.

We found that stenosis in CCA and ICA was correlated with IAD severity in a large population-based cohort that underwent autopsy. Approximately 20% of our subjects had a previous history of cardiac or cerebrovascular disease, while previous studies about the association between EAD and IAD have mostly investigated patients with coronary artery disease and stroke [10–13]. In 183 Turkish patients waiting for a coronary artery bypass graft and who had significant EAD (e.g., stenosis ≥50%), 28% of the subjects had IAD, but IAD and EAD severity was not related [10]. On the other hand, in 101 Japanese outpatients, baseline EAD was associated with IAD progression. In this study, IAD was evaluated only in the basilar and middle cerebral arteries [11]. In another clinicoradiological study of 142 Korean patients, 49% of patients with IAD had extracranial artery stenosis ≥50% [12]. In these studies, IAD was evaluated by angiography, and not all CW arteries could be evaluated by this method [10–12]. In an autopsy study of 339 French subjects who died from fatal stroke, the presence of extracranial carotid plaques and stenosis was associated with intracranial internal carotid artery stenosis. However, the associations between EAD and other intracranial arteries were not evaluated. In addition, both EAD and IAD were evaluated using a macroscopically ordinal score [13], while we used morphometric measurements and histological identification of EAD plaques and IMT.

We observed that IAD was more frequent than EAD, and most participants had concurrent EAD and IAD stenoses. In a large clinical study of 1196 Chinese patients with acute stroke, significant stenosis only in intracranial arteries was more common than isolated EAD (41% *vs.* 7%), while only 10% had significant stenosis in both intracranial and extracranial arteries [21]. The prevalence of intracranial plaques and stenosis in the French autopsy study (62% and 43%, respectively) was similar to ours [14]. Based on evidence from different countries, IAD seems to be more common in Asians, blacks, and Hispanics, while EAD is more common in Caucasians [8]. The high prevalence of IAD in our sample could be explained by that fact that the Brazilian population is ethnically admixed with more than 90% of their

ancestry derived from Africans and Europeans [22]. We could not find an association between race and IAD among our study participants, and EAD was more common in Caucasians, as expected. We used the race reported by the NOK, and future studies with ancestry genotyping will be important to define the relationships among the biological race differences between IAD and EAD.

Regarding risk factors, older age, lower educational attainment, hypertension, diabetes, and stroke were associated with IAD, while Caucasian race, hypertension, and smoking were associated with EAD. In a recent meta-analysis with data from 3787 subjects, female sex and metabolic syndrome were associated with IAD, while smoking and dyslipidemia were associated with EAD [9]. Clinicoradiological studies showed different risk profiles associated with IAD and EAD. In 933 white subjects without history of stroke, diabetes and metabolic syndrome were associated with IAD; and male sex, hypertension, smoking, and alcohol use were associated with EAD [23]. In two large studies with Korean patients with stroke, IAD was associated with older age and hypertension in one study [24] and only with metabolic syndrome in another study [25]. EAD was associated with older age, male sex, and dyslipidemia in both studies [24,25]. In another large Chinese study, both IAD and EAD were associated with age, male sex, and LDL-cholesterol, while diabetes was associated with IAD only [21].

However, our results should be examined with consideration of the study limitations. First, this is a cross-sectional study, which precluded any conclusions about causal inference. Second, we used different methods to calculate the stenosis index in the CW (i.e., directly on the arterial sections) and in the carotid arteries (i.e., using histological preparations to determine both carotid plaque and IMT). However, the stenosis index may not be substantially affected by these methodological differences since most of the stenosis is determined by the atherosclerotic plaque, and the intima layer minimally contributes to the stenosis index. Although autopsy studies allow for direct measurements of atherosclerosis, these studies also have limitations, which include tissue shrinkage and deformation by formalin fixation. To minimize the negative effects of formalin fixation, all samples were fixed during a similar amount of time, and we injected gelatin in the lumen to avoid artery collapse. In addition, atheroma composition was not presented this time, and future studies using immunohistochemistry will be important to determine the association of plaque composition in the CW and carotid arteries. Another limitation is related to the fact that participants died from unknown cause of death, and might represent a different cohort compared to the general population. However, most autopsy studies were based on convenience samples of patients who died from cerebrovascular diseases. Additionally, some characteristics of the included participants differ from the excluded subjects from this study. Moreover, we did not collect other arteries, as aorta and coronary arteries, and future studies will be important to investigate the association among different arterial sites. Finally, information about the risk factors was reported by the NOK. To assure accurate information, we restricted our sample to NOK who had at least weekly contact with the deceased. Moreover, our clinical interview had good accuracy, and risk factor prevalence was similar to the other Brazilian cohorts of older adults [26,27].

On the other hand, our study has several advantages. We had one of the largest sample sizes among the few autopsy studies about EAD and IAD [13–15]. Indeed, all previous studies used a macroscopically ordinal classification of arterial stenosis while we used morphometric measurements to determine the exact percentage of arterial obstruction. In addition, the majority of the studies about this topic used imaging methods. As a result, EAD has been slightly more investigated than IAD, since the evaluation of carotid artery atherosclerosis is easier than the evaluation of intracranial cerebral atherosclerosis. Moreover, certain regions of intracranial atherosclerosis (i.e., posterior circulation and more distal arterial branches) and portions of the internal carotid artery are particularly difficult to evaluate using traditional imaging methods [28,29]. Finally, previous imaging and autopsy studies focused on subjects that had stroke or other cardiovascular diseases [10–14], while our sample represented community-dwelling older adults with better generalizability of the prevalence of EAD and IAD as well as their relationship with risk factors.

Using morphometric evaluation, EAD was associated with IAD in this large population-based sample of Brazilian subjects. Stenosis in the intracranial arteries was more common than in the extracranial arteries, and EAD and IAD had different risk profiles.

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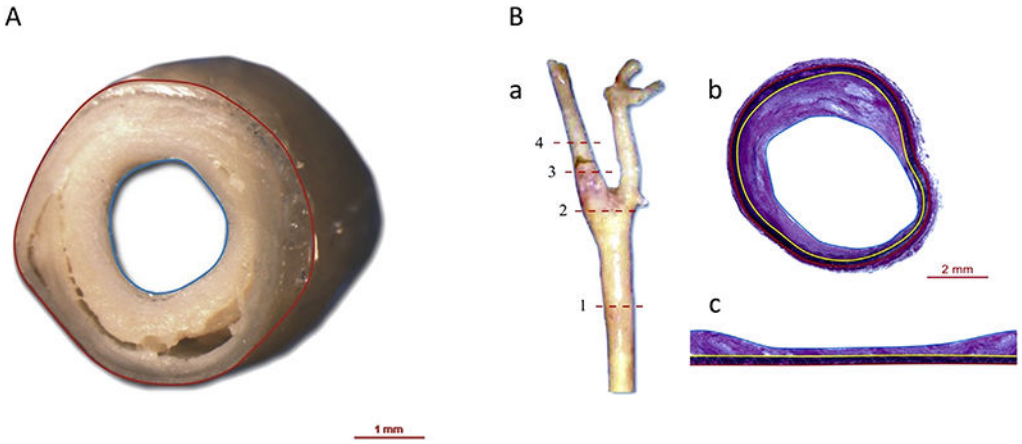

Fig. 1.

Artery sections.

(A) Section of the basilar artery. The red line represents the area delineated by the outer arterial wall and the blue line indicates the lumen area. (B) a. Sections in the right carotid artery were acquired at (1) the largest arterial obstruction in the common carotid artery, (2) 1 cm below the bifurcation, (3) 1 cm above the bifurcation, and (4) the largest arterial obstruction in the internal carotid artery. b. Section of the right common carotid artery. Red: external elastic lamina; yellow: internal elastic lamina; and blue: lumen. c. Representation of the common carotid artery for the carotid artery intima-media thickness measurement. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

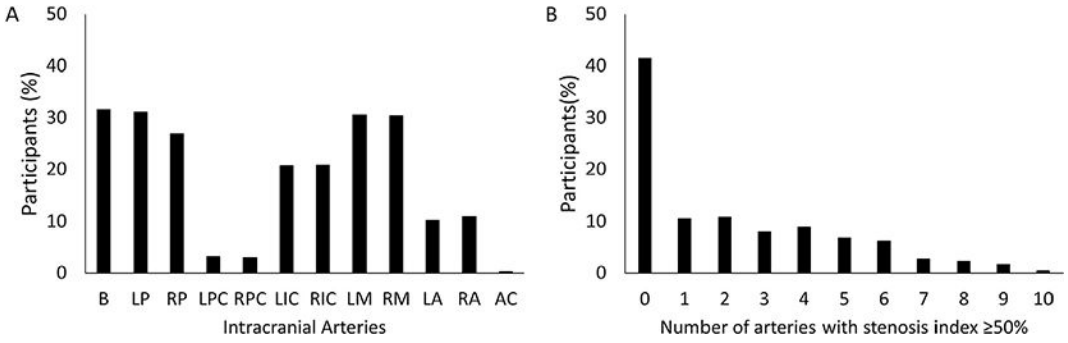

Fig. 2.

Percentage of participants.

(A) Percentage of participants with a stenosis index ≥50% in each intracranial artery. B, basilar; LP, left posterior; RP, right posterior; LPC, left posterior communicating; RPC, right posterior communicating; LIC, left internal carotid; RIC, right internal carotid; LM, left middle; RM, right middle; LA, left anterior; RA, right anterior; AC, anterior communicating arteries. (B) Percentage of participants with different numbers of arteries with a stenosis index ≥50%.

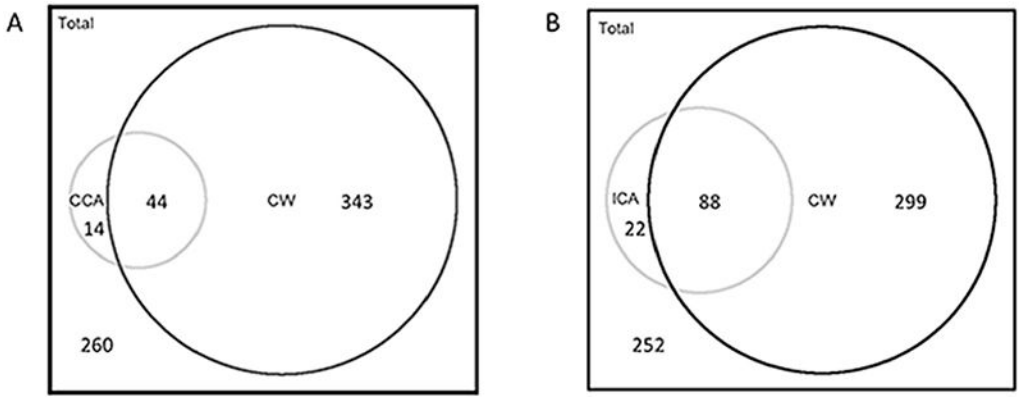

Fig. 3.

Venn diagram.

Venn diagram showing the relationship of a stenosis index ≥50% in any artery of the Circle of Willis (CW) with a stenosis index ≥50% in (A) the common carotid artery (CCA) and (B) the internal carotid artery (CCA). Numbers are absolute frequencies.

Table 1

Comparison of demographics and clinical variables between included and excluded participants (n = 1116).

Variable	Excluded n = 455	Included n = 661	*p*
Age (years), mean (SD)[a]	68.2 (11.7)	71.3 (11.7)	<0.0001
Male, %[b]	56.0	50.8	0.10
Race, %[c]			0.05
White	64.2	67.9	
Black	35.0	29.8	
Asian	0.8	2.3	
Education (years), mean (SD)[a]	4.8 (3.9)	4.3 (3.6)	0.05
Hypertension, %[b]	64.4	64.9	0.90
Diabetes, %[b]	34.0	28.1	0.04
Dyslipidemia, %[b]	10.5	10.0	0.67
Heart disease, %[b]	20.7	19.2	0.56
Stroke, %[b]	17.1	11.7	0.01
BMI (kg/m^2), mean (SD)[a]	23.7 (4.0)	23.2 (4.4)	0.10
Physical inactivity, %[b]	56.8	61.7	0.11
Smoking, %[b]			0.19
Never	44.8	48.1	
Current	29.2	24.1	
Past	26.0	27.8	
Alcohol use, %[b]			0.64
Never	56.3	59.1	
Current	25.3	24.1	
Past	18.4	16.8	

[a] Unpaired *t*-test.

[b] Chi-square test.

[c] Fisher's exact test.

Table 2

Association of demographics and clinical variables with stenosis in intracranial and extracranial arteries (n = 661).

Variable	Stenosis in intracranial arteries[a]				Stenosis in extracranial arteries[a]			
	No n = 274	Yes n = 387	OR (95% CI)	*p*	No n = 324	Yes n = 337	OR (95% CI)	*p*
Age (years), mean (SD)	68.0 (11.9)	73.6 (11.0)	1.05 (1.03; 1.07)	<0.0001	71.3 (11.8)	71.3 (11.6)	1.01 (1.00; 1.03)	0.05
Male, %	53.7	48.8	1.15 (0.78; 1.71)	0.48	47.2	54.3	1.09 (0.75; 1.58)	0.66
Race, %				0.48				0.03
Black	27.8	31.3	1.00 (reference)		34.2	25.5	1.00 (reference)	
White	70.4	66.1	0.84 (0.57; 1.23)		63.9	71.8	1.60 (1.11; 2.31)	
Asian	1.8	2.6	1.42 (0.42; 4.82)		1.9	2.7	2.14 (0.69; 6.63)	
Education (years), mean (SD)	5.0 (3.8)	3.8 (3.4)	0.94 (0.89; 0.99)	0.02	4.2 (3.7)	4.3 (3.5)	0.99 (0.95; 1.04)	0.82
Hypertension, %	53.1	73.1	2.11 (1.45; 3.07)	<0.0001	60.4	69.1	1.64 (1.14; 2.36)	0.008
Diabetes, %	21.2	33.1	1.69 (1.12; 2.54)	0.01	26.5	29.7	1.22 (0.84; 1.79)	0.30
Dyslipidemia, %	7.7	11.1	1.30 (0.70; 2.40)	0.41	9.3	10.1	0.89 (0.50; 1.56)	0.67
Heart disease, %	19.8	18.9	0.79 (0.51; 1.23)	0.30	21.0	17.5	0.83 (0.55; 1.26)	0.38
Stroke, %	6.2	15.5	2.12 (1.15; 3.92)	0.02	12.3	11.0	0.76 (0.46; 1.27)	0.30
BMI (kg/m^2), mean (SD)	23.1 (4.8)	23.3 (4.1)	1.03 (0.99; 1.08)	0.16	23.2 (4.5)	23.3 (4.2)	1.01 (0.97; 1.06)	0.47
Physical inactivity, %	57.7	64.6	1.14 (0.80; 1.63)	0.45	63.6	59.9	0.75 (0.53; 1.05)	0.09
Smoking, %				0.14				<0.0001
Never	49.6	47.0	1.00 (reference)		58.0	38.6	1.00 (reference)	
Current	24.5	23.8	1.62 (1.00; 2.60)		15.7	32.0	3.37 (2.12; 5.36)	
Past	25.9	29.2	1.23 (0.79; 1.92)		26.2	29.4	1.65 (1.09; 2.50)	
Alcohol use, %				0.51				0.18
Never	58.0	60.0	1.00 (reference)		64.2	54.3	1.00 (reference)	
Current	26.7	22.2	1.10 (0.69; 1.76)		21.9	26.1	1.14 (0.72; 1.78)	
Past	15.3	17.8	1.37 (0.80; 2.34)		13.9	19.6	1.60 (0.97; 2.64)	

Multivariable logistic regression, including all variables described in the Table.

[a] ≥50% obstruction.

Table 3

Odds ratio of having at least one Circle of Willis (CW) artery with obstruction ≥50%, according to carotid artery atherosclerosis (n = 661).

	Simple logistic regression	Multivariate logistic regression[b]
	OR (95% CI)	**OR (95% CI)**
C-IMT (1 mm)[a]	5.93 (3.05; 11.53)	6.40 (3.18; 12.87)
I-IMT (1 mm)[a]	5.39 (2.80; 10.37)	6.39 (3.15; 12.97)
CCA obstruction ≥50%	2.05 (1.48; 2.86)	2.32 (1.64; 3.28)
ICA obstruction ≥50%	2.32 (1.66; 3.24)	2.51 (1.76; 3.57)

p <0.0001 for all analyses.

C-IMT, common carotid artery intima-media thickness; I-IMT, internal carotid artery intima-media thickness; CCA, common carotid artery; ICA, internal carotid artery.

[a] C-IMT and I-MT are continuous variables; therefore, OR of having CW obstruction ≥50% for 1 mm increase in C-IMT and I-IMT.

[b] Multiple logistic regression adjusted for age, sex, race, and education.