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Hypertension may associate with cerebral small vessel disease and infarcts through the pathway of intracranial atherosclerosis

Marcelo Kenzo Naya Takahashi [a], Regina Silva Paradela [a], Lea Tenenholz Grinberg [b,c], Renata Elaine Paraizo Leite [b], Daniela Souza Farias-Itao [b], Vitor Ribeiro Paes [b], Maria Eduarda Braga [a], Michel Satya Naslavsky [d], Mayana Zatz [d], Wilson Jacob-Filho [a], Ricardo Nitrini [e], Carlos Augusto Pasqualucci [b], Claudia Kimie Suemoto [a,*]

[a] Division of Geriatrics, University of Sao Paulo Medical School, Sao Paulo 01246-903, Brazil
[b] Department of Pathology, University of São Paulo Medical School, Sao Paulo, SP 01246-903, Brazil
[c] Memory and Aging Center, Weill Institute for Neurosciences, Dept. of Neurology, University of California San Francisco, CA 94158, USA
[d] Human Genome and Stem Cell Center, Biosciences Institute, University of Sao Paulo, Sao Paulo 05508-090, Brazil
[e] Department of Neurology, University of Sao Paulo Medical School, SP 01246-903, Brazil

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ABSTRACT

Hypertension, a major modifiable risk factor for cardiovascular diseases, is linked to late-life neurocognitive disorders such as vascular dementia and Alzheimer's disease (AD). This study explores the associations between hypertension, intracranial atherosclerotic disease (ICAD), cerebral small vessel disease (cSVD), and Alzheimer's disease neuropathologic change (ADNC) in a large community-based autopsy study.

This cross-sectional study used data from the Biobank for Aging Studies of the University of São Paulo Medical School. Sociodemographic and clinical information was gathered from a reliable next-of-kin informant. Neurofibrillary tangles, neuritic plaques, lacunar infarcts, hyaline arteriolosclerosis, and cerebral amyloid angiopathy were evaluated. Causal mediation analyses with natural effect models were performed to examine indirect associations of hypertension with cerebrovascular pathologies and ADNC through morphometric measurements of intracranial artery lumen obstruction.

Hypertensive participants (n = 354) presented a higher rate of stenosed arteries (obstruction ≥ 50 %), critically stenosed arteries (obstruction ≥ 70 %), and more severe ICAD, shown by higher maximum and mean obstruction indexes compared to nonhypertensive participants (n = 166). These measurements of atherosclerosis were associated with neurofibrillary tangles and cSVD lesions. Hypertension was indirectly associated with hyaline arteriolosclerosis and lacunar infarcts through the pathway of ICAD. Presenting hypertension indirectly increased the odds of displaying hyaline arteriolosclerosis by 26 % (95 % CI: 1.08, 1.45, p = 0.002) and lacunar infarcts by 17 % (95 % CI: 1.01, 1.35, p = 0.029). Cognitive and APOE ε4 carrier status did not alter the investigated associations. In this community sample, hypertension was indirectly associated with cSVD through ICAD.

1. Introduction

Hypertension, occurring in nearly one-third of adults, is the primary modifiable risk factor for cardiovascular disease (Mills et al., 2020). Midlife hypertension also contributes to the development of late-life neurocognitive disorders, including vascular dementia and Alzheimer's disease (AD) (Nagai et al., 2010; Walker et al., 2019). Hypertension elicits hypertrophic remodeling of the tunica media and smooth muscle cells (Arnett et al., 2000), while also promoting atherogenesis by initiating endothelial damage and contributing to arterial stiffness later in life (Alexander, 1995). However, the exact mechanisms by which hypertension promotes cognitive impairment and the relationship of hypertension with neurodegenerative diseases remain elusive. Intracranial atherosclerotic disease (ICAD), besides cerebral small vessel disease (cSVD), may be involved in the link between vascular risk factors and the pathogenesis, progression, and clinical presentation of

* Correspondence to: Av. Doutor Arnaldo 455, room 1353, São Paulo, SP CEP 01246-903, Brazil.
E-mail address: cksuemoto@usp.br (C.K. Suemoto).

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neurodegenerative and vascular dementia (Faraco and Iadecola, 2013; Qiu et al., 2005).

Vascular lesions, mainly detected by magnetic resonance imaging (MRI) in T2 as white matter hyperintensities (WMH) or leukoaraiosis in computed tomography (CT) scans, are prevalent in older adults, and an increase of cSVD imaging is associated with cognitive decline (Rincon and Wright, 2014). It is recognized that vascular contributions to cognitive impairment and dementia go beyond cerebrovascular dysfunction, as metabolic disease, immune system interactions, and proteinopathy, including Alzheimer's pathology, may also result in cognitive decline (Zlokovic et al., 2020). Notably, the coexistence of cerebrovascular disease, both microinfarcts and stroke, and Alzheimer's disease neuropathologic change (ADNC) interact, lowering the threshold for cognitive impairment for a given ADNC burden (Arvanitakis et al., 2016, 2011; Smith et al., 2012; Snowdon et al., 1997).

The Circle of Willis (CW) is a set of arterial anastomoses providing collateral blood flow between the anterior and posterior circulations of the brain. Larger cerebral arteries from the CW branch out into pial arteries and penetrate as arterioles across the subarachnoid space. Although inconsistently, CW atherosclerosis has been associated with ADNC (Beach et al., 2007; Honig et al., 2005; Roher et al., 2003; Yarchoan et al., 2012), and it was previously reported to mediate associations between hypertension and AD pathology (Eglit et al., 2020).

Whether cardiovascular risk factors, including hypertension, promote cognitive impairment through vascular disease (including extracranial processes), in an independent but convergent process to neurodegenerative diseases, or whether cerebrovascular disease itself promotes mechanisms which in turn may initiate neurodegenerative diseases still demands investigation. The associations between hypertension, cerebrovascular large and small vessel disease, and ADNC were explored in this large community-based autopsy study. Whether *APOE* ε4 allele and cognitive performance modified associations was also investigated. Additional analyses examine the role of potential biases and comparability to reported findings from the literature.

2. Methods

2.1. Participants

Participants were recruited from January 2004 to January 2022 at the São Paulo Autopsy Service and enrolled in the Biobank for Aging Studies. Voluntarily signed consent was obtained from the deceased's next-of-kin informant (NOK), who also consented to brain donation. Individuals aged 50 years and older whose NOK had at least weekly contact with the deceased in the six months before death (n = 1237) were included. Participants without any data on intracranial artery samples (n = 665), with missing data for neuropathological lesions (n = 51), and for sociodemographic and clinical information (n = 1) were excluded. Data from 520 participants was analyzed. The present study was approved by the local ethics committee in accordance with the Declaration of Helsinki on human research ethics, and all participants signed an informed consent form.

2.2. Intracranial cerebral atherosclerosis measurements

Arteries are collected in less than 24 h after death. Direct morphometric intracranial atherosclerosis evaluation included the anterior communicating artery (ACoA), the basilar artery (BA), the right and left branches of the anterior cerebral arteries (ACA), the middle cerebral arteries (MCA), intracranial internal carotid arteries (ICA), posterior communicating arteries (PCoA), and posterior cerebral arteries (PCA) (totalling 12 per participant, Fig. 1). The arteries were filled with a gelatin solution to prevent arterial collapse and then fixed in 10 % formalin for up to 14 days. Each artery was cut in segments of 5 mm-thickness, and each transversal segment was evaluated for the presence of atherosclerotic plaque. The segment with the largest obstruction in each artery was photographed using a camera (Nikon® SMZ 1000) attached to a stereomicroscope (Leica® DMR). The contours of the lumen area and the outer area were determined using the ImageJ® software (Fig. 1). An obstruction index was calculated for each artery by dividing the difference between the outer area and the lumen area by the outer area and multiplying by 100 to obtain the percentage (Roher et al., 2003).

For each participant, the maximum and the mean obstruction index among the 12 cerebral arteries was calculated. The total number of stenosed arteries per participant represented the number of arteries with obstruction indexes equal to or greater than 50 %, and varied from 0 to 12. Following a similar classification for extracranial (cervical) atherosclerosis of the carotid artery (NASCET Steering Committee, 1991), critical stenoses were also counted, defined by an obstruction index equal to or greater than 70 %. An ordinal classification was also obtained from the data, classifying atherosclerosis into a 4-stage ordinal score (none, mild, moderate and severe) based on the number of arteries stenosed for each participant: zero, one or two, three to five, and six or more, respectively.

Missing values for the stenosis index were present for 66 participants. We considered the missing values as not missing completely at random and used the multiple imputation by chained equations ('mice' package in R) as the imputation technique. The set of predictors for a given variable consisted of all other variables in the data. After building the imputation models by random forest, aggregating the prediction of

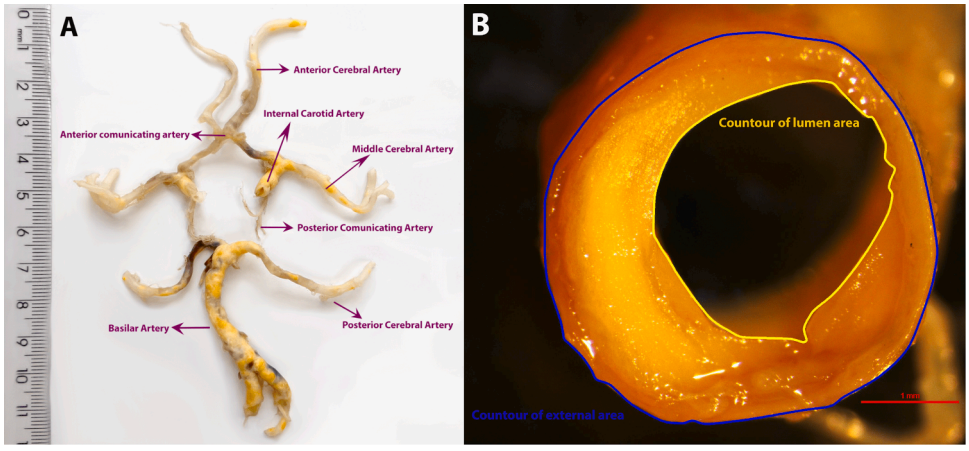

Fig. 1. Artery sections. (A) The Circle of Willis with its 12 arteries. (B) Section of the largest arterial obstruction at a right internal carotid artery. Blue: contour of the total sectioned area. Yellow: contour of the lumen area.

multiple decision trees to generate robust imputation estimates, regression analyses on each of the imputed datasets was conducted. These regressions were then pooled to provide final estimates and confidence intervals that reflect the uncertainty introduced by the imputation process.

2.3. Neuropathological assessment

Brains were obtained within 24 h after death and separated into two hemispheres. Selected areas were collected from the right hemisphere and frozen at −80 °C. The left hemisphere was fixed in 4 % buffered paraformaldehyde for at least 15 days. Then, the fixed hemisphere was sectioned into the following areas: middle frontal gyrus, middle and superior temporal gyri, angular gyrus, superior frontal and anterior cingulate gyrus, visual cortex, hippocampal formation at the level of the lateral geniculate body, amygdala, basal ganglia at the level of the anterior commissure, thalamus, midbrain, pons, medulla oblongata, and cerebellum. Brain regions were embedded in paraffin, sectioned into 5 μm-thick sections, and stained with hematoxylin and eosin. We performed immunohistochemistry with antibodies against β-amyloid (4G8, 1:10.000; BioLegend #800701) and phosphorylated tau (AT8, 1:400; Invitrogen MN1020) in selected brain regions (Grinberg et al., 2007; Suemoto et al., 2017).

AD pathology was scored using the Braak staging system for neurofibrillary tangles (NFT) of phosphorylated tau and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria for neuritic plaques (NP) of β-amyloid. The Braak staging is a system to measure the progression of NFT into six stages. The NFT changes start in the transentorhinal regions (stage I) and spread to the cornu ammonis 1 of the hippocampus (stage II). As the pathology progresses, the lesions extend to the subiculum, basal ganglia, and amygdala (stage III); and accumulate in the isocortex, mainly the temporal region (stage IV). Then, the lesions extend widely into the whole CA region, and the thalamus and hypothalamus are committed (stage V). Finally, the pathology reaches the occipital lobe and the fascia dentata of the hippocampus (stage VI) (Braak et al., 2006; Braak and Braak, 1991). The CERAD criterion is a semiquantitative approach that categorizes the frequency of neocortical NP into four stages: none (0), sparse (I), moderate (II), and frequent (III) (Mirra et al., 1991).

Cerebrovascular lesions were evaluated microscopically using hematoxylin and eosin-stained slides in sampled areas. Lacunar infarcts were registered by topography, stage, size, and number. The presence of lacunar infarcts was defined as one or more infarcts measuring 1.5 cm or less in any of the regions of the brain described above. Hyaline arteriosclerosis was classified according to the presence of moderate and/or severe microvascular changes in three or more cortical regions. The evaluation of cerebral amyloid angiopathy (CAA) was made according to the localization, as well as the severity and presence of capillary amyloid deposition. CAA was classified as present when it was widespread in the parenchyma in at least three different cortical areas (Suemoto et al., 2017).

2.4. Clinical assessment

A structured interview was conducted with the NOK by a trained team of gerontologists at the autopsy site. The interview collected information regarding demographics, previously diagnosed diseases (hypertension, diabetes, dyslipidemia, coronary artery disease, and stroke), lifestyle habits (alcohol use and smoking, classified as current, former, or never), medication intake, and cognitive status prior to death. Race was reported by the NOK and categorized as White, Black, and Asian. Educational attainment was measured by the number of years of formal education. Participants' weight and height were measured prior to the autopsy examination and used to compute the body mass index (BMI). Age at death and sex were inferred from government-issued documents. Hypertension was defined *postmortem* by the report of a previous diagnosis of hypertension any time during the life course or the use of antihypertensive medication.

Cognitive abilities were assessed *postmortem* by the Clinical Dementia Rating (CDR) informant section, considering the 3 months prior to the participant's death. The CDR evaluates six cognitive and functional domains, including memory, orientation, judgment, community affairs, home and hobbies performance, and personal care, using a semistructured interview with the NOK (Morris, 1993). Participants are classified as cognitively normal and independent functioning (CDR = 0), presenting mild difficulty in one domain (CDR = 0.5), and mild (CDR = 1), moderate (CDR = 2), and severe dementia (CDR = 3). Cognitive impairment was defined by a CDR equal to or greater than 0.5.

In a subset of 299 participants with available DNA samples from blood or brain tissue, apolipoprotein E (*APOE)* was genotyped by single-nucleotide polymorphisms rs429358 and rs7412 amplification in real-time polymerase chain reaction assays, performed in duplicate (Calero et al., 2009). Participants were classified into *APOE* ε4 carriers and noncarriers according to the presence of at least one ε4 allele.

2.5. Statistical analysis

Descriptive statistics are presented as means and standard deviations (SD) for continuous variables, and absolute and relative frequencies for categorical variables. Participants were compared regarding their hypertension diagnosis for sociodemographic, clinical, and neuropathological characteristics using the unpaired t-test or the Mann—Whitney U test for continuous variables, and the chi-squared or Fisher's exact test for categorical variables. Variance inflation factors were calculated and evidence of collinearity among the covariates included in the models was not found.

The association between hypertension and the atherosclerosis index measures was tested using linear regressions (for the mean and maximum value of the obstruction index) and quasi-Poisson regressions (for the number of stenosis and critical stenosis for each participant). The association between hypertension and neuropathological lesions was tested with logistic regression (for cerebrovascular lesions) and ordinal logistic regression (for the CERAD score and Braak staging). Models were adjusted for sociodemographic (age, sex, race, and years of education) and clinical factors (diabetes, dyslipidemia, coronary artery disease, BMI, alcohol consumption, and smoking), and *APOE* ε4 carrier status when available. Results are presented as estimates, incidence-rate or odds ratios, with 95 % confidence intervals.

We hypothesized hypertension was indirectly associated with dementia neuropathological lesions through the pathway of intracranial atherosclerosis. Causal mediation analysis via natural effect models using the 'medflex' R package was performed, utilizing the imputation-based approach with 1000-simulations to estimate unobservable potential outcomes of the counterfactual scenarios. Assumptions are illustrated in Fig. 2, representing a non-parametric structural equation model with independent error terms. Natural effect models allow us to express the estimates on more natural scales (i.e., a scale corresponding to the link-function of the corresponding model), and more intuitive outputs, with the natural direct and indirect effects each represented by a single regression coefficient (Steen et al., 2017). The total effect of hypertension on neuropathological lesions is decomposed in an indirect pathway through the atherosclerosis measurements and a direct pathway. The indirect pathway represents the odds of having the outcome (neuropathological lesions) for a participant with certain baseline covariate levels, when altering the hypertension status of hypertensive participants to levels that would have been observed for nonhypertensive participants while controlling the mediator variable (a measurement of intracranial atherosclerosis) at levels as naturally observed at any given level of the mediator variable. In the same framework, interactions between hypertension with the presence of *APOE* ε4 allele and cognitive impairment was interrogated (if the effect of hypertension on neuropathology mediated through intracranial

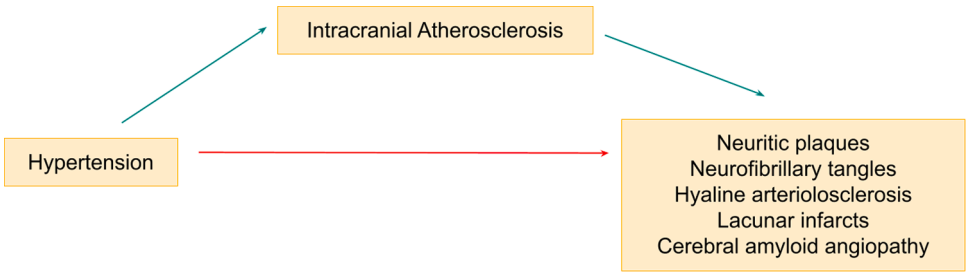

Fig. 2. Directed acyclic graph illustrating the conceptual causal mediation model of the associations between hypertension, intracranial atherosclerosis, and neuropathological lesions. The effect is decomposed into a direct (red line) and indirect pathway (green line). Confounding variables were age, sex, race, education, diabetes, dyslipidemia, coronary artery disease, body mass index, alcohol use, and smoking, and APOE ε4 when available.

atherosclerosis differed between *APOE* ε4 carriers and noncarriers, and those with cognitive impairment). Results are presented in estimated odds ratios and 95 % confidence intervals with bootstrapped 3000-simulations.

The intracranial atherosclerosis measures used as mediator variables were the maximum obstruction index, the mean obstruction index, the number of stenosed arteries, and the number of critically stenosed arteries for each participant. Additional analyses were performed, comparing participants stratified by cause and age at death (to explore potential causes of bias in this sample), cognitive performance, and using the ordinal classification of atherosclerosis (none, mild, moderate, severe) as a mediator. An alpha level of 5 % in two-tailed tests was considered. The statistical software R version 4.4.0 (R Core Team, 2024) was employed for all statistical analyses in the RStudio IDE (RStudio PBC, 2022).

3. Results

A total of 520 autopsy cases met the criteria for inclusion in analyses. Characteristics of the study groups are shown in Table 1. Participants' mean age was 75.8 ± 11.3 years old, the median education was 4 years (range 0–16.5 years), 51 % were women, and 66 % were white. Participants with hypertension ($n = 354$) were younger at the time of death, were more frequently women, had fewer years of formal education, and had a higher BMI. As expected, participants with hypertension also had a higher burden of comorbidities, as they presented higher frequencies of diabetes, dyslipidemia, coronary artery disease, and history of stroke. Hypertensive participants also presented better cognitive status than nonhypertensive participants, as shown by lower CDR scores. NOK were on average 47.3±13.5 years-old, 54 % were women, most frequently the deceased's daughter or son (64 %), or spouse (33 %). 82 % of NOK had daily contact with the deceased person. The subsample with genotyped *APOE* has their sociodemographic and clinical characteristics described and compared to the individuals without available genotype in Supplemental Table 1.

Participants with a history of hypertension had a similar burden of AD and cerebrovascular pathology compared to nonhypertensive participants (Table 2). However, there were significant differences in the severity of intracranial atherosclerosis across clinical groups. The highest severity and frequency of critically stenosed arteries were observed in the hypertensive group (Fig. 3). They showed a higher obstruction index for the internal carotid arteries, basilar artery, middle cerebral arteries, and posterior cerebral arteries. The total number of arteries with stenosis was similar for the two groups, but hypertensive participants presented more critical stenoses (Table 3). The five sets of arteries most affected by stenosis were the BA (45.6 %), the MCA (43.5 %), the PCA (43.1 %), and the ICA (30.1 %). The least affected were the ACA (24.1 %), the ACoA (15.4), and the PCoA (14.3 %). A similar trend regarding the communicating arteries was observed with critical stenoses, but with a decrease in the ICA (Supplemental Table 2). As for the anterior and posterior cerebral circulations, 132 participants (25.3 %) did not present any stenosis, while 296 (56.9 %) presented stenoses of both anterior and posterior cerebral circulations. 51 (9.8 %) participants only presented stenoses of the anterior but not anterior circulations, and 41 (7.9 %) only presented stenoses of the posterior but not anterior circulation.

Presenting a history of hypertension was associated with a higher maximum obstruction index (β = 10.1, 95 % Cl = 4.61; 15.6, $p = <$ 0.001), a higher mean obstruction index (β = 6.68; 95 % Cl = 2.7; 10.7, $p = 0.001$), a 37 % higher rate of stenosed arteries (IRR = 1.37; 95 % CI = 1.14; 1.66; $p = 0.001$), and a 61 % higher rate of critically stenosed arteries (IRR = 1.61; 95 % CI = 1.21. 2.16; $p = 0.001$) after adjustment for confounders (Table 4**)**. Intracranial atherosclerosis measurements were associated with neurofibrillary tangles, hyaline arteriolosclerosis, and lacunar infarcts. These associations remained significant after adjustment for covariates. However, hypertension was not directly associated with either AD pathology or cerebrovascular lesions (Table 5).

Potential selection bias by comparing causes-of-death, as classified by the 10th revision of the International Classification of Diseases (ICD-10) was investigated. Hypertensive participants presented more cardiovascular causes-of-death than nonhypertensive participants, though the overall distribution of causes-of-death was similar between the two groups (Supplemental Table 3). Stratified analyses for the association between hypertension and neuropathological lesions by age and cardiovascular cause-of-death were not significant (Supplemental Table 4).

3.1. *Intracranial atherosclerosis as a mediator between hypertension and neuropathology*

Hypertension was associated with hyaline arteriolosclerosis through the pathway of intracranial atherosclerosis with the maximum obstruction index, mean obstruction index, number of stenosed arteries, and number of critically stenosed arteries analyzed as mediators. Presenting hypertension, while controlling the maximum obstruction index and mean obstruction index as naturally observed, indirectly increased the odds of displaying hyaline arteriolosclerosis lesions by 26 % (95 % CI: 1.08; 1.45, p = 0.002) and 33 % (95 % CI: 1.07; 1.61, p = 0.006), respectively. While controlling the number of stenosed arteries and critically stenosed arteries, hypertension indirectly increased the odds of displaying arteriolosclerosis by 27 % (95 % CI: 1.06; 1.51, p = 0.007) and 16 % (95 % CI: 1.03; 1.30, p = 0.014), respectively. Hypertension associated with lacunar infarcts through the maximum obstruction index, while controlling the maximum obstruction index as naturally observed, it indirectly increased the odds of displaying lacunae by 17 % (95 % CI: 1.01; 1.35, p = 0.006). Hypertension was not associated with either ADNC or cerebral amyloid angiopathy through the pathway of atherosclerosis (Fig. 4 and Table 6). Hypertension was not associated with neuropathological lesions in the sensitivity analysis that used an ordinal classification of atherosclerosis as the mediator (Supplemental Table 5). In the subset of participants with available APOE genotyping (n = 299), models were also adjusted for APOE ε4 carrier status.

Table 1
Comparison of sociodemographic and clinical variables by hypertension status ($n = 520$).

Variables	Overall ($n = 520$)	No Hypertension ($n = 166$)	Hypertension ($n = 354$)	p
Age (years), mean (SD)†	75.8 (11.3)	77.5 (12.1)	75.0 (10.9)	0.017
Race, %‡				0.671
White	347 (66.2)	116 (69.9)	231 (65.2)	
Black	163 (31.9)	47 (28.2)	116 (32.8)	
Asian	10 (1.9)	3 (1.8)	7 (2.0)	
Women, *n* (%)#	265 (51)	70 (42.2)	195 (55.1)	0.008
Education (years), median (range)*	4 (0, 16.5)	4 (0, 16.5)	4 (0, 16)	0.030
Daily contact with the informant, *n* (%)#	427 (82.1)	136 (81.9)	291 (82.2)	1.000
Body mass index, mean (SD)†	23.3 (4.54)	21.9 (4.2)	23.9 (4.5)	< 0.001
Smoking, *n* (%)#				0.476
Never	272 (52.3)	84 (50.6)	188 (53.1)	
Current	97 (18.7)	36 (21.7)	61 (17.2)	
Former	151 (29.0)	46 (27.7)	105 (29.7)	
Alcohol use, *n* (%)#				0.716
Never	323 (62.1)	99 (59.6)	224 (63.3)	
Current	110 (21.2)	38 (22.9)	72 (20.3)	
Former	87 (16.7)	29 (17.5)	58 (16.4)	
Diabetes mellitus, *n* (%)#	166 (31.9)	29 (17.5)	137 (38.7)	< 0.001
Dyslipidemia, *n* (%)#	58 (11.2)	7 (4.2)	51 (14.4)	0.001
Coronary artery disease, *n* (%)#	111 (21.3)	26 (15.7)	85 (24.0)	0.040
Stroke, *n* (%)#	72 (13.8)	15 (9.0)	57 (16.1)	0.041
Presence of *APOE* ε4, *n* (%)‡ §				0.878
Heterozygous	72 (13.8)	23 (13.9)	49 (13.8)	
Homozygous	11 (2.1)	3 (1.8)	8 (2.3)	
Clinical Dementia Rating (CDR), *n* (%)#				0.001
0 – Cognitively normal	346 (66.5)	100 (60.2)	246 (69.5)	
0.5 – Questionable dementia	50 (9.6)	11 (6.6)	39 (11.0)	
1 – Mild dementia	34 (6.5)	10 (6.0)	24 (6.8)	
2 – Moderate dementia	31 (6.0)	13 (7.8)	18 (5.1)	
3 – Severe dementia	59 (11.3)	32 (19.3)	27 (7.6)	

APOE, apolipoprotein E gene; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; SD, standard deviation.
†Unpaired t test; ‡Fisher's exact test; #Chi-square test; *Mann—Whitney U test; §Data available for 299 participants.

Hypertension was indirectly associated with hyaline arteriolosclerosis through the maximum obstruction index (OR: 1.22, 95 % CI: 1.04; 1.44, $p = 0.014$) (Table 7).

3.2. Investigation of effect modification by APOE ε4 and cognitive performance

Whether there was an interaction between hypertension, *APOE* ε4 carrier status, and cognitive performance within this causal framework was interrogated. By investigating the indirect effect of hypertension on neuropathology lesions to be conditional on the interaction variables (i.e., APOE ε4 carrier status and CDR scores), there was no evidence of differential effects of hypertension among APOE ε4 allele carriers or participants with poorer cognitive performance (Supplemental Table 6). These results suggest the findings may be generalized to the whole sample. After stratification according to cognitive performance, there were significant associations of hypertension with hyaline arteriolosclerosis through the maximum obstruction index (OR: 1.33, 95 % CI: 1.05; 1.69, $p = 0.019$), the mean obstruction index (OR: 1.57, 95 % CI: 1.13; 2.19, p = 0.007), and the number of stenosed arteries (OR: 1.41, 95 % CI: 1.04; 1.89, $p = 0.026$) in participants with cognitive impairment. Interestingly, a direct association of hypertension with hyaline arteriolosclerosis was observed through the number of critically stenosed arteries (OR: 2.45, 95 % CI: 1.02; 5.92, $p = 0.046$), and a marginally non-significant indirect association with cerebral amyloid angiopathy through the maximum obstruction index (OR: 1.26, 95 % CI: 1.00; 1.61, $p = 0.051$) (Supplemental Table 7).

Table 2
Neuropathological lesions by hypertension status ($n = 520$).

Variables	No Hypertension ($n = 166$)	Hypertension ($n = 354$)	p
CERAD Score, *n* (%)†			0.131
None	91 (54.8)	230 (65.0)	
Sparse	28 (16.9)	43 (12.1)	
Moderate	28 (16.9)	43 (12.1)	
Frequent	19 (11.4)	38 (10.7)	
AD Braak-Braak Score, *n* (%)†			0.435
0	32 (19.3)	72 (20.3)	
I	23 (13.9)	71 (20.1)	
II	42 (25.3)	79 (22.3)	
III	30 (18.1)	62 (17.5)	
IV	15 (9)	32 (9)	
V	12 (7.2)	25 (7.1)	
VI	12 (7.2)	28 (7.9)	
Cerebral Amyloid Angiopathy, *n* (%)†	12 (7.2)	28 (7.9)	0.924
Hyaline Arteriolosclerosis, *n* (%)†	46 (27.7)	117 (33.1)	0.262
Lacunar Infarcts, *n* (%)†	21 (12.7)	34 (9.6)	0.368

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; AD, Alzheimer's disease; SD, standard deviation; †chi-square test.

4. Discussion

Intracranial atherosclerosis disease (ICAD) is a highly prevalent disorder that is associated with significant morbimortality, disproportionately impacting Hispanics, East Asians, and African-American populations (Qureshi and Caplan, 2014). Beyond ischaemic strokes and transient ischaemic attacks, a growing body of evidence links intracranial plaques and stenosis to neurocognitive disorders (Gorelick et al., 2011; Sabayan et al., 2023; Snyder et al., 2015; Zlokovic, 2011). In this community-based cross-sectional study, hypertension was associated with hyaline arteriolosclerosis and lacunar infarcts through ICAD. Causal mediation analyses may help elucidate mechanisms in the complex relationship between cardiovascular risk factors and dementia. It is important to note that the maximum obstruction index was the mediator which kept the association between hypertension and both arteriolosclerosis and lacunae, which might raise the hypothesis of a single critical stenosis being more impactful than a globally stenosed system. Chronic hypertension shifts cerebral autoregulation of blood flow in small vessels to a resting state of chronic hypoperfusion, contributing to neurovascular uncoupling which may, in turn, lead to the brain dysfunction underlying dementia (Girouard and Iadecola, 2006; Zlokovic, 2011). Yet, recent evidence from the Atherosclerosis Risk in Communities study (Zhao et al., 2024) highlighted an association of ICAD and an increased risk of incident dementia even when stenosis were low-grade (≤50 %), which is unlikely to reduce blood flow, suggesting alternative mechanisms for arteriosclerosis to promote cognitive impairment such as neuroinflammation, lipid homeostasis changes, or

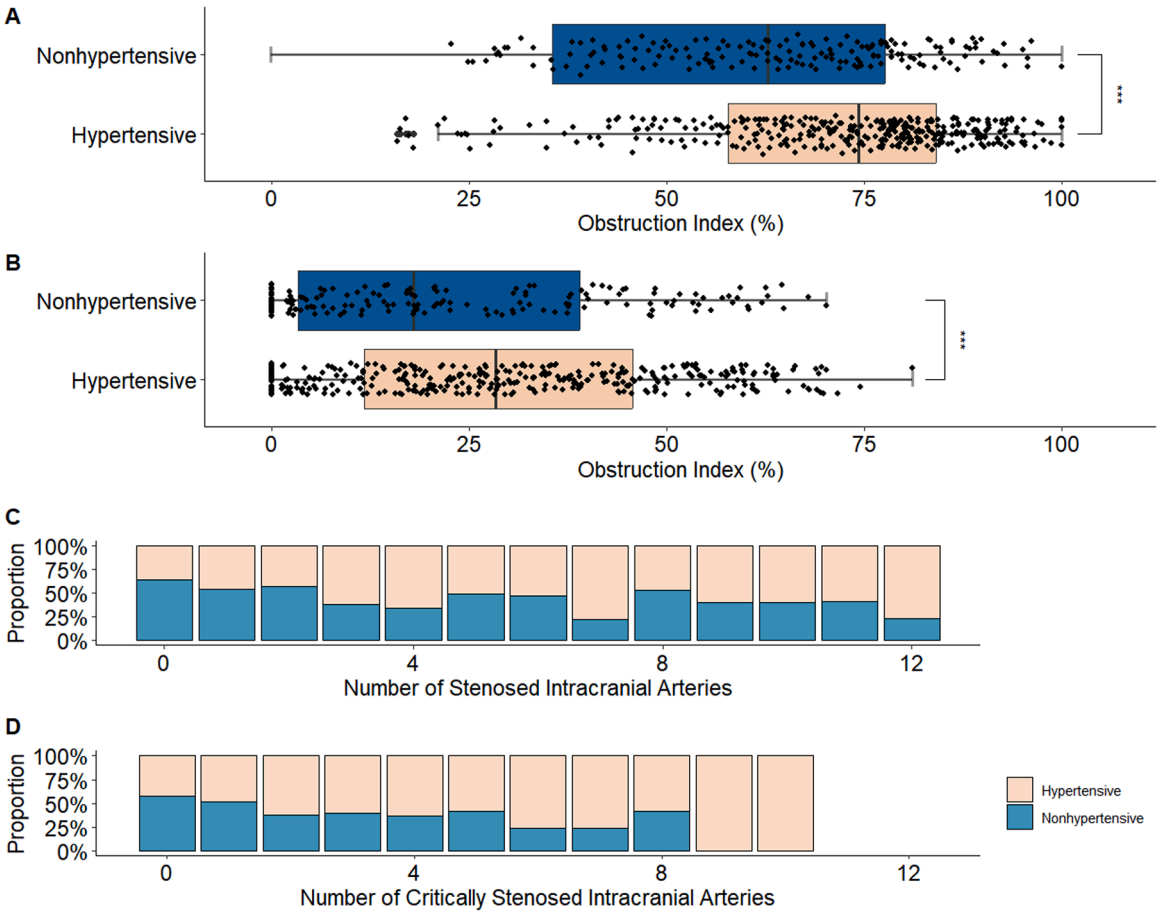

Fig. 3. Comparison of obstruction index measures and the number of stenosed intracranial arteries between hypertensive and nonhypertensive participants. (A) Highest intracranial obstruction indexes by hypertension status. (B) Mean obstruction indexes by hypertension status. Individual participants' obstruction indexes are represented as dots along the horizontal axis. (C) Stacked bar plot showing the number of stenosed arteries (≥ 50 % lumen occlusion) by hypertension status. (D) Bar plot showing the number of critically stenosed arteries (≥ 70 % lumen occlusion) by hypertension status. ***p-value > 0.001, unpaired t-test.

reduced phagocytic function (Duong et al., 2021).

ICAD is more difficult to study in large samples compared to cSVD and cardiovascular risk factors. Current methods to detect and quantify ICAD in-vivo, from least to most precise, are the transcranial Doppler ultrasound, the MRI angiogram, the CT angiogram, and the catheter-based angiogram. All present relatively high negative-predictive values, and the MRI and CT scans may also identify concurrent ischaemic lesions and hypoperfusion, but can also overestimate the degree of obstruction (Qureshi and Caplan, 2014), and even the catheter-based angiography may miss atherosclerotic lesions without stenosis. It is also well recognized that neurocognitive disorders are often a heterogeneous combination of mixed brain pathologies (Arvanitakis et al., 2016; Jellinger and Attems, 2010; Kawas et al., 2015; Schneider et al., 2007; Sonnen et al., 2007; Suemoto et al., 2017; Toledo et al., 2013). Clinical evaluation for major neurocognitive disorders are limited in distinguishing dementia subtypes, despite advancements in imaging and CSF biomarkers. These results prompt future research and development of more biomarkers of ICAD including non-stenotic disease.

Several studies investigated whether hypertension could be associated with an increased NP and NFT pathology burden, suggesting a relationship between hypertension and ADNC. Although there was great heterogeneity in the operationalization of hypertension, neuropathology assessment, and statistical analyses, studies with longer follow-up and larger samples tended more often to report an association between hypertension and ADNC (Abdulrahman et al., 2022). In this study, no significant association along the direct pathway between hypertension and neuropathology outcomes was found. Previous reports of the association between hypertension and atherosclerosis with ADNC were more frequent among dementia patients (Dolan et al., 2010; Eglit et al., 2020; Wijesinghe et al., 2016; Zheng et al., 2013). Evidence on the association between intracranial atherosclerosis and ADNC is also controversial. Some studies reported greater atherosclerosis ratings among AD patients compared to healthy controls, and cerebrovascular atherosclerosis was associated with increased NP (Honig et al., 2005) and NFT pathology (Beach et al., 2007; Eglit et al., 2020; Roher et al., 2003; Yarchoan et al., 2012). In contrast, three studies reported no association between CW atherosclerosis and either AD pathology: Kosunen et al. (1995) and Itoh et al. (1999) investigated specifically AD patients, while Dolan et al. (2010) also included cognitively normal participants at baseline.

This study did not find evidence for hypertension being associated with ADNC indirectly through intracranial atherosclerosis, which is contrasted with the single other study, to our knowledge, to perform mediation analysis on the association of hypertension, ICAD, and AD pathology. Eglit et al. (2020) analyzed the National Alzheimer's Coordinating Center database, which gathers data from Alzheimer's Disease Centers across the United States of America. Available objective blood pressure measurements, as well as a self-report of hypertension, were considered independent variables in the statistical analyses. AD pathology was evaluated similarly to this study, but Braak staging was classified into a four-category outcome, and vascular neuropathology, including CW atherosclerosis, was assessed as a global qualitative measurement, instead of the individual continuous measurements performed in this study. Hypertension was reported to have an inverse

Table 3
Intracranial atherosclerosis measurements by hypertension status ($n = 520$).

Variables	No Hypertension ($n = 166$)	Hypertension ($n = 354$)	p
Obstruction Indexes (OI), mean (SD)†			
Maximum OI per individual	54.6 (30.2)	65.1 (28)	< 0.001
Mean OI per individual	22.8 (20.5)	29.7 (20.8)	< 0.001
Basilar artery (BA)	35.7 (26.4)	44.8 (27.9)	< 0.001
Anterior communicating artery (ACoA)	10.7 (23.6)	13 (24.9)	0.311
Internal carotid arteries (ICA)	23.2 (23.8)	31.5 (25.7)	< 0.001
Highest OI#	30.9 (30.1)	39.5 (29.7)	0.002
Middle cerebral arteries (MCA)	30.1 (26.3)	41 (27.6)	< 0.001
Highest OI#	37.9 (30.1)	48.3 (30.5)	< 0.001
Anterior cerebral arteries (ACA)	18.6 (26)	23.4 (28.3)	0.069
Highest OI#	23.4 (31.6)	28.2 (33.2)	0.119
Posterior cerebral arteries (PCA)	29.1 (29.7)	38.4 (30.2)	0.001
Highest OI#	35.6 (34.4)	46.7 (34.2)	0.001
Posterior communicating arteries (PCoA)	12.2 (22.2)	14.8 (24)	0.242
Highest OI#	14.7 (27.6)	17.2 (29.3)	0.349
Number of arteries with stenosis, *n* (%)‡			0.607
None	130 (78.3)	267 (75.4)	
1–2	12 (7.2)	22 (6.2)	
3–5	11 (6.6)	24 (6.8)	
6 or more	41 (11.6)	13 (7.8)	
Average number of arteries with stenosis per participant, mean (IQR, SD)#	1.54 (1, 3)	1.27 (1, 2.7)	0.462
Number of arteries with critical stenosis, *n* (%)‡			0.003
None	128 (77.1)	214 (60.5)	
1–2	26 (15.7)	90 (25.4)	
3–5	10 (6.0)	38 (10.7)	
6 or more	2 (1.2)	12 (3.4)	
Average number of arteries with critical stenosis per participant, mean (IQR, SD)#	0.9 (2, 1.5)	1.5 (2, 1.9)	< 0.001

†Unpaired t-test; ‡Chi squared test; #Mann-Whitney U test; OI: Obstruction Index; SD: standard deviation; IQR: interquartile range.
#For the arteries with right and left segments, the 'highest OI' considers the highest value between the two contralateral segments.
Atherosclerosis was assessed in the 12 arteries of the Circle of Willis, and an index was calculated to represent plaque presence, with higher values indicating greater atherosclerosis burden. Obstruction indexes range from 0 to 100 (% of lumen).
Arteries with stenosis were defined by an obstruction index equal to or greater than 50 %, and critical stenosis represents an obstruction index equal to or greater than 70 %.

association with neuritic plaques along the direct pathway, and an indirect effect through CW atherosclerosis on NFT and NP in the overall sample. Objective measurements of blood pressure in their study were not associated with ADNC. Our study sample size might have also been underpowered to detect significant associations, as this sample was enriched with cognitively healthy participants, which may have reduced ascertainment bias (Chui et al., 2012). Yet, the reported odds ratios for the association between CW atherosclerosis and NFT pathology in our study (ranging 1.01–1.25) are aligned with previous results from the literature.

Mechanisms involving altered cerebral autoregulation of blood flow, consequential hypoperfusion, and diminished perivascular clearance of Aβ might explain an atherosclerosis-dependent pathway for vascular risk factors to promote ADNC (Gupta and Iadecola, 2015). The endothelial cell response to cyclic mechanical stretch in hypertension potentially increases the deposition of Aβ by affecting the expression of endothelial nitric oxide synthase in small vessels and upregulating amyloid precursor protein (Avolio et al., 2018). Interestingly, such mechanisms were suggested to promote CAA pathology by disrupting small vessel integrity (Okamoto et al., 2012; Shah et al., 2012; Hawkes et al., 2014), but we did not observe such findings, which might be attributable to the strict criteria for CAA and independent variable (absent/-present) defined in this study (Suemoto et al., 2017). Studies from cerebrospinal fluid biomarkers of amyloid and tau suggest that hypertension (and cerebrovascular damage) are associated with tau but not with amyloid accumulation. Such studies found that cerebrovascular damage (manifested as WMH) in combination with tau mediates the relationship between cardiovascular risk and cognitive function (Bos et al., 2019; Laing et al., 2020; Yu et al., 2022). These findings provocatively suggest that cerebrovascular damage precedes detectable AD pathology by current available biomarkers.

This study presents several limitations. Causal mediation analysis to evaluate the direct and indirect effects of hypertension on neuropathological outcomes was performed, yet the cross-sectional nature of the study precludes causal inferences. Most evidence for the association between hypertension and cognitive impairment was reported during midlife (Iadecola et al., 2016), with some studies associating late-life hypertension to better cognition and lower AD pathology (Affleck et al., 2020; Corrada et al., 2017; Harrison et al., 2015; Sabayan et al., 2012). In this study, the timeline for cognitive assessment with the NOK considers the 3 months prior to the participant's death, to avoid perimortem events which could interfere with the cognitive function, such as the progression of underlying illnesses or delirium. The accuracy of the *postmortem* diagnosis regarding cognitive functioning with the CDR informant section has been investigated previously, and we found a 86.6 % sensitivity and 84.4 % specificity for dementia diagnosis, and a 65.3 % sensitivity and 93.7 % specificity for normal cognition compared to a specialized memory clinic (Ferretti et al., 2010). The independent variable in this study (a report of diagnosis or the use of antihypertensive medication during life) offered limited information on hypertension severity and diagnosis onset. This study also found hypertensive participants to be performing cognitively better than nonhypertensive participants. This finding might be attributable to selection bias, which is a common challenge in the research of noncommunicable diseases during the aging process. Hypertensive participants were younger and presented more cardiovascular comorbidities in our sample. Not including persons with premature mortality related to cardiovascular disease due to the cross-sectional design of this study could shift associations of cardiovascular risk factors with cognitive impairment or neuropathology. The older hypertensive participants may also represent a more resilient group to cerebral small vessel and Alzheimer's disease pathology, but not large vessel atherosclerosis. Adequate cerebral perfusion contributes to normal cognitive functioning and maintenance, so late-life hypertensive individuals could also be presenting a successful compensatory mechanism for age-associated vascular changes (Alosco et al., 2013; Corrada et al., 2017; Kitagawa et al., 2009; Leeuwis et al., 2017). In turn, we may hypothesize the indirect-only mediation results in this study might be due to an increased susceptibility to cSVD and ADNC lesions after the development of atherosclerosis. Adjustment for comorbidities such as diabetes, tobacco and alcohol use, and *APOE ε4* carrier status might have reduced confounding for the ICAD and ADNC associations, but residual confounding can not be ruled out: a confounder assumed to be related to exposure, mediator, and outcome, might have led to an overestimation (an exposure-outcome confounder) or underestimation (a mediator-outcome confounder) of results (VanderWeele et al., 2008). Even with the stratified analyses for age and cause-of-death suggesting no differential association between hypertension and neuropathological lesions, one can suppose that the effect would be in the wrong direction due to the presence of selection bias (i.

Table 4
Association of hypertension and intracranial atherosclerosis measurements ($n = 520$).

	Maximum OI†		Mean OI†		Number of stenosed arteries‡		Number of critically stenosed arteries‡	
	β[95 % CI]	*p*	β[95 % CI]	*p*	IRR [95 % CI]	*p*	IRR [95 % CI]	*p*
Univariate	10.4[5.14; 15.7]	< 0.001	6.92[3.09; 10.7]	< 0.001	1.41[1.18; 1.69]	< 0.001	1.66[1.27; 2.21]	< 0.001
Model 1	12.5[7.14; 17.8]	< 0.001	8.41[4.56; 12.3]	< 0.001	1.47[1.23; 1.77]	< 0.001	1.73[1.32; 2.32]	< 0.001
Model 2	10.1[4.61; 15.6]	< 0.001	6.68[2.7; 10.7]	0.001	1.37[1.14; 1.66]	0.001	1.61[1.21; 2.16]	0.001

†Linear regression model; ‡quasi-Poisson regression model; OI: obstruction index; OR: odds ratio; 95 %CI: 95 % confidence intervals; IRR: incidence rate ratio. Reference: Nonhypertensive participants.
Model 1: Regression model adjusted for age, sex, race, and education. Model 2: Regression model adjusted for age, sex, race, education, body mass index, dyslipidemia, diabetes mellitus, physical inactivity, smoking, alcohol use.
Atherosclerosis was assessed in the 12 arteries of the Circle of Willis, and an index was calculated to represent plaque presence, with higher values indicating greater atherosclerosis burden. Obstruction indexes range from 0 to 100 (% of lumen).
Maximum Obstruction Index: the highest obstruction index value for a participant. Mean Obstruction Index: the average obstruction index value for a participant. Arteries with stenosis were defined by an obstruction index equal to or greater than 50 %, and critical stenosis represents an obstruction index equal to or greater than 70 %.

Table 5
Associations of hypertension and intracranial atherosclerosis measurements with neuropathology lesions ($n = 520$).

	Hypertension		Highest OI		Mean OI		Number of stenosed arteries		Number of critically stenosed arteries	
Outcomes	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*
Neuritic plaques†	0.78[0.52; 1.19]	0.248	1.01[1.00; 1.01]	0.055	1.01[0.99;1.02]	0.122	1.04[0.98 1.11]	0.128	1.10[0.99; 1.22]	0.059
Neurofibrillary tangles†	0.83 [0.84; 1.72]	0.306	1.01 [1.01; 1.02]	0.001	1.01 [1.01; 1.02]	0.003	1.07[1.02; 1.12]	0.005	1.14 [1.04; 1.25]	0.003
Hyaline arteriolosclerosis‡	1.36[0.87; 2.15]	0.180	1.03 [1.02; 1.04]	< 0.001	1.05 [1.04; 1.06]	< 0.001	1.28 [1.20; 1.37]	< 0.001	1.30 [1.17; 1.45]	< 0.001
Lacunar infarcts‡	0.75 [0.40; 1.42]	0.363	1.02 [1.01; 1.03]	0.014	1.02 [1.01; 1.03]	0.019	1.12 [1.03; 1.22]	0.007	1.19 [1.03; 1.37]	0.018
Cerebral amyloid angiopathy‡	1.00 [0.47; 2.23]	0.994	1.00 [0.99;'1.01]	0.940	1.01 [0.99; 1.03]	0.308	1.03 [0.93; 1.14]	0.578	1.04 [0.86; 1.22]	0.673

†Ordinal logistic regression model; ‡Binary logistic regression model; OI: obstruction index.
Models adjusted for age, sex, race, education, body mass index, dyslipidemia, diabetes mellitus, physical inactivity, smoking, and alcohol use.
Atherosclerosis was assessed in the 12 arteries of the Circle of Willis, and an index was calculated to represent plaque presence, with higher values indicating greater atherosclerosis burden. Obstruction indexes range from 0 to 100 (% of lumen).
Maximum Obstruction Index: the highest obstruction index value for a participant. Mean Obstruction Index: the average obstruction index value for a participant. Arteries with stenosis were defined by an obstruction index equal to or greater than 50 %, and critical stenosis represents an obstruction index equal to or greater than 70 %.

e., hypertension being protective against neuropathology lesions).

Beyond the histomorphometric measurements of atherosclerosis, other factors which do not narrow the lumen were not evaluated, as atheroma plaque composition (intima or internal elastic lamina calcifications, noncalcified plaques, and plaque instability) has recently been suggested to play differential roles in downstream vascular changes contributing to neurodegeneration and cognitive impairment (Melgarejo et al., 2023; van den Beukel et al., 2024). Additionally, despite the anatomic spatial context given by the ICAD measures, the spatial evaluation of the neuropathology lesions in this study were limited: the co-occurrence of neurodegenerative and vascular lesions was not evaluated. Novel immunohistochemical multiplexing tools, which can maintain the spatial context, may provide insights into the complex phenotypes portrayed by older persons (Blom et al., 2017).

Findings from the Atherosclerosis Risk In Communities Study (Zhao et al., 2024) recently raised the hypothesis of the anterior cerebral artery (ACA) being a key contributor to cognitive impairment as it supplies the cholinergic nucleus basalis of Meynert. Our study corroborated their findings of the ACA being less likely affected by plaque (together with the anterior and posterior communicating arteries in our study). Moreover, hypertensive and nonhypertensive participants did not differ on ACA atherosclerotic indexes. It may be a case of differential ICAD stages, as smaller arteries may be more resilient to atherosclerotic disease and the influence of risk factors such as hypertension. Alternatively, as the communicating arteries provide important anastomoses between contralateral regions, stenoses in these arteries may prompt more severe disease processes. Notably, the posterior circulation of the brain is less affected by arteriosclerosis compared to the anterior circulation, as virtually all adults develop calcifications in the ICA throughout their life (Kockelkoren et al., 2018), but the A1 (horizontal segment) of the ACA, the PCoA, and the ACoA are also prone to variations in diameter due to hypoplasia and ipsilateral compensation, which may be associated with the development of aneurysms in these vessels due to asymmetric hemodynamic stress (Perlmutter and Rhoton, 1976; Rhoton, 1980; Takahashi, 2010). The sample in this study presented a high burden of atherosclerosis, with both anterior and posterior cerebral circulation being affected by stenosis, and few individuals only presenting one stenosed system but not the other. Only the intracranial portion of the ICA was considered in this study, which might have influenced how the obstruction indexes were relatively lower for the ICA. Besides, premature death due to ruptured aneurysms and hemorrhagic stroke could also have contributed to the lower rate of atherosclerosis measurements found in the ACA, PCoA, and ACoA.

The main strengths of this study include the broad inclusion criteria, with the recruitment of community-dwelling participants, including people without dementia diagnoses during life, and the morphometric arterial measurements, which provide a continuous measure of ICAD, in contrast to previous autopsy-based studies (Roher et al., 2003; Honig et al., 2005; Beach et al., 2007; Eglit et al., 2020). Moreover, the Biobank for Aging Studies is the largest brain bank in Latin America, with an admixed sample of participants presenting a thorough collection of clinicopathological variables and different levels of dementia severity,

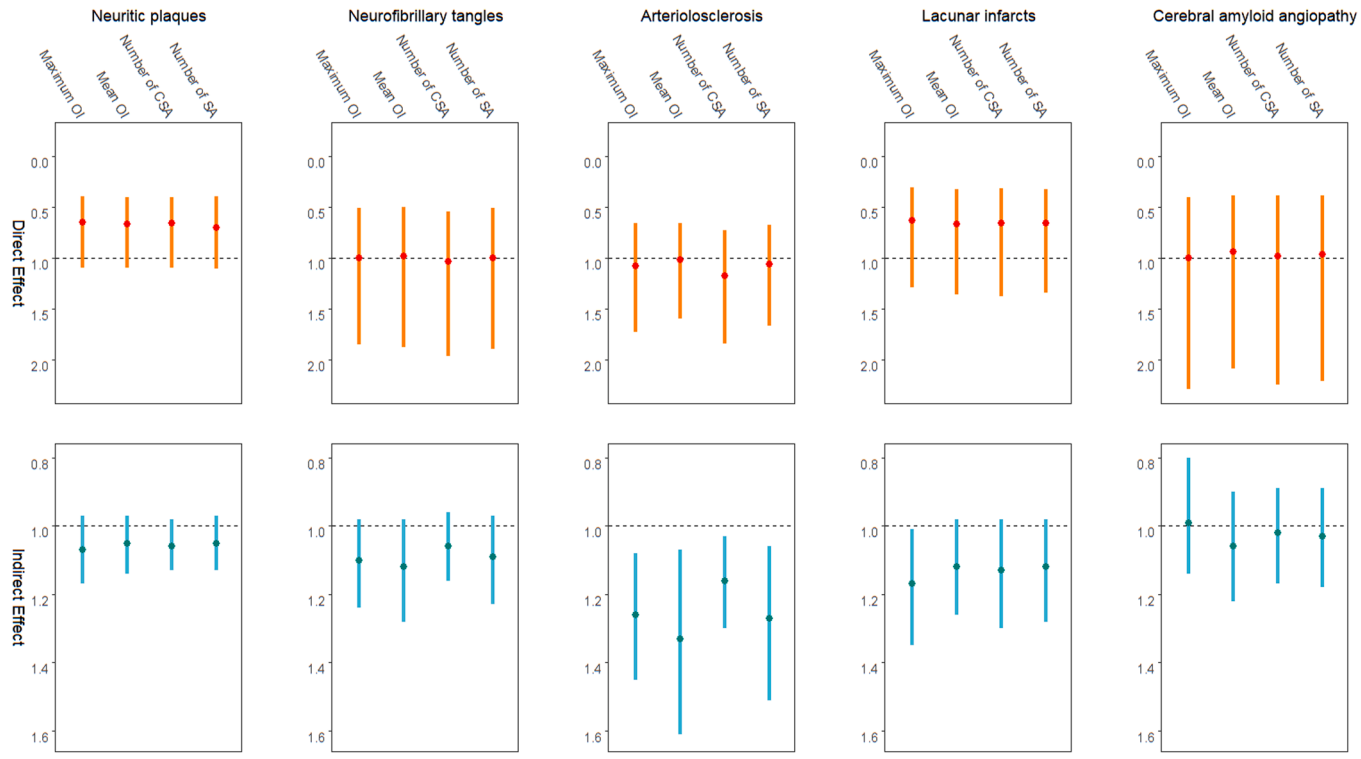

Fig. 4. Odds Ratios and 95 % confidence intervals for direct (red) and indirect effects (green) of hypertension on neuropathology lesions through intracranial atherosclerosis measurements. OI: obstruction index. SA: stenosed arteries (≥ 50 % lumen occlusion). CSA: critically stenosed arteries (≥ 70 % lumen occlusion).

Table 6
Direct and indirect effects of hypertension on neuropathology lesions considering an indirect effect through intracranial atherosclerosis measurements (n = 520).

		Maximum OI		Mean OI		Number of stenosed arteries		Number of critically stenosed arteries	
	Natural effects	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p	OR [95 % CI]	p
Neuritic plaques	Direct	0.65 [0.40; 1.10]	0.091	0.67[0.41; 1.10]	0.108	0.70 [0.40; 1.11]	0.121	0.66 [0.41; 1.10]	0.107
	Indirect	1.07[0.97; 1.17]	0.167	1.05 [0.97; 1.14]	0.208	1.05 [0.97; 1.13]	0.206	1.06 [0.98; 1.13]	0.120
Neurofibrillary tangles	Direct	1.00 [0.51; 1.85]	0.999	0.98 [0.50; 1.88]	0.949	1.00 [0.51; 1.89]	0.986	1.04 [0.55; 1.96]	0.908
	Indirect	1.10 [0.98; 1.24]	0.118	1.12 [0.98; 1.28]	0.076	1.09 [0.97; 1.23]	0.131	1.06 [0.96; 1.16]	0.230
Hyaline arteriolosclerosis	Direct	1.08 [0.66; 1.73]	0.203	1.02 [0.66; 1.60]	0.905	1.06 [0.68; 1.67]	0.772	1.18 [0.73; 1.84]	0.491
	Indirect	1.26 [1.08; 1.45]	0.002	1.33 [1.07; 1.61]	0.006	1.27 [1.06; 1.51]	0.007	1.16[1.03; 1.30]	0.014
Lacunar infarcts	Direct	0.63[0.31; 1.29]	0.205	0.67[0.33; 1.36]	0.257	0.66 [0.33; 1.34]	0.241	0.66 [0.32; 1.38]	0.255
	Indirect	1.17 [1.01–1.35]	0.029	1.12 [0.98; 1.26]	0.083	1.12 [0.98; 1.28]	0.079	1.13 [0.98; 1.30]	0.069
Cerebral amyloid angiopathy	Direct	1.00 [0.41; 2.29]	0.985	0.94 [0.39; 2.09]	0.902	0.97[0.39; 2.21]	0.951	0.98 [0.39; 2.24]	0.963
	Indirect	0.99 [0.85; 1.14]	0.949	1.06 [0.90; 1.22]	0.464	1.03 [0.89; 1.18]	0.674	1.02 [0.89; 1.17]	0.729

OR: odds ratio; 95 %CI: 95 % confidence intervals; OI: obstruction index. Mediation analysis via natural effect models fit with imputed counterfactuals (3000-simulation bootstrapped normal confidence intervals), adjusted for age, sex, race, education, body mass index, dyslipidemia, diabetes mellitus, physical inactivity, smoking, and alcohol use.
Atherosclerosis was assessed in the 12 arteries of the Circle of Willis, and an index was calculated to represent plaque presence, with higher values indicating greater atherosclerosis burden. Obstruction indexes range from 0 to 100 (% of lumen).
Maximum Obstruction Index: the highest obstruction index value for a participant. Mean Obstruction Index: the average obstruction index value for a participant. Arteries with stenosis were defined by an obstruction index equal to or greater than 50 %, and critical stenosis represents an obstruction index equal to or greater than 70 %.

enriched with people without cognitive impairment (Grinberg et al., 2007). The sample is representative of the population from a low-to-middle-income country with a lower educational attainment, a more ethnically diverse background, and a higher frequency of cardiovascular comorbidities compared to previous studies conducted in high-income countries.

In this study, hypertension was associated with a higher burden of hyaline arteriolosclerosis and lacunar infarcts indirectly through ICAD. We highlight the results with the maximum obstruction index, raising the hypothesis of a single critical stenosis being more impactful than a globally stenosed system. Still, a randomized clinical trial showed percutaneous transluminal angioplasty in ICAD to be equivalent to aggressive pharmacological therapy regarding cognitive outcomes (Turan et al., 2016). Another trial with cSVD patients evidenced benefits of remote ischemic conditioning (an intervention inducing a transient ischemia of the limbs), slowing cognitive decline and WMH over the course of a year (Wang et al., 2017). The benefits of remote ischemic conditioning in cSVD point to the potential of targeted vascular interventions to manage microvascular damage and its cognitive consequences, unlike in larger vessel diseases like ICAD, which also presents negative effects beyond blood flow restriction. These findings raise the question on how co-occurrence of ICAD and cSVD interact, if it lowers the threshold for cognitive decline on vascular injury, and future trials might investigate differential effects by better characterizing these

Table 7
Direct and indirect effects of hypertension on neuropathology lesions considering an indirect effect through intracranial atherosclerosis measurements adjusted for APOE ε4 carrier status ($n = 299$).

		Maximum OI		Mean OI		Number of stenosed arteries		Number of critically stenosed arteries	
	Natural Effects	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*	OR [95 % CI]	*p*
Neuritic plaques	Direct	0.86[0.45; 1.65]	0.650	0.89[0.46; 1.70]	0.723	1.10[0.47; 1.72]	0.763	0.89[0.46; 1.72]	0.737
p	Indirect	1.05[0.93; 1.21]	0.397	1.02[0.94; 1.11]	0.597	1.00[0.94; 1.07]	0.888	1.02[0.96; 1.08]	0.561
Neurofibrillary tangles	Direct	1.18[0.51; 2.75]	0.697	1.21[0.51; 2.87]	0.667	1.25[0.53; 2.94]	0.615	1.29[0.56; 3.00]	0.547
	Indirect	1.14[0.96; 1.35]	0.123	1.12[0.93; 1.34]	0.227	1.08[0.93; 1.26]	0.305	1.04[0.93; 1.16]	0.456
Hyaline arteriolosclerosis	Direct	0.83[0.46; 1.50]	0.531	0.85[0.47; 1.52]	0.581	0.88[0.49; 1.58]	0.664	0.95[0.52; 1.74]	0.882
	Indirect	1.22[1.04; 1.44]	0.014	1.19[0.99; 1.44]	0.064	1.15[0.98; 1.35]	0.085	1.06[0.96; 1.17]	0.251
Lacunar infarcts	Direct	0.72[0.33; 1.56]	0.406	0.77[0.36; 1.66]	0.503	0.76[0.35; 1.65]	0.467	0.77[0.35; 1.66]	0.500
	Indirect	1.14[0.99; 1.36]	0.074	1.08[0.94; 1.25]	0.271	1.09[0.94; 1.26]	0.252	1.08[0.94; 1.26]	0.262
Cerebral amyloid angiopathy	Direct	1.11[0.33; 3.80]	0.861	1.04[0.32; 3.34]	0.946	1.06[0.33; 3.37]	0.927	1.03[0.33; 3.21]	0.956
	Indirect	0.92[0.77; 1.11]	0.399	1.01[0.88; 1.12]	0.875	0.98[0.86; 1.10]	0.704	1.00[0.93; 1.07]	0.967

OR: odds ratio; 95 %CI: 95 % confidence intervals; OI: obstruction index.
Mediation analysis via natural effect models fit with imputed counterfactuals (3000-simulation bootstrapped normal confidence intervals), adjusted for age, sex, race, education, body mass index, dyslipidemia, diabetes mellitus, physical inactivity, smoking, alcohol use and APOE ε4 carrier status.
Atherosclerosis was assessed in the 12 arteries of the Circle of Willis, and an index was calculated to represent plaque presence, with higher values indicating greater atherosclerosis burden. Obstruction indexes range from 0 to 100 (% of lumen).
Maximum OI: the highest obstruction index value for a participant. Mean OI: the average obstruction index value for a participant. Arteries with stenosis were defined by an OI equal to or greater than 50 %, and critical stenosis represents an OI equal to or greater than 70 %.

vascular phenotypes. These results linking cSVD and ICAD further highlight the importance of accounting large and small vessel disease to cognitive impairment and the assessment of interventions, also prompting future research on arteriosclerosis characterization beyond arterial lumen obstruction and calcifications.

CRediT authorship contribution statement

Claudia Kimie Suemoto: Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Carlos Augusto Pasqualucci:** Writing – review & editing, Resources, Investigation, Data curation. **Daniela Souza Farias-Itao:** Writing – review & editing, Visualization, Investigation. **Renata Elaine Paraizo Leite:** Writing – review & editing, Resources, Investigation, Data curation. **Maria Eduarda de Avila Braga:** Writing – review & editing, Investigation. **Vitor Ribeiro Paes:** Writing – review & editing, Investigation. **Mayana Zatz:** Writing – review & editing, Resources, Investigation. **Michel Satya Naslavsky:** Writing – review & editing, Resources, Investigation. **Ricardo Nitrini:** Writing – review & editing, Resources, Funding acquisition. **Wilson Jacob-Filho:** Writing – review & editing, Resources, Funding acquisition. **Marcelo Kenzo Naya Takahashi:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Lea Tenenholz Grinberg:** Writing – review & editing, Resources, Investigation, Data curation. **Regina Silva Paradela:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation.

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Verification. Statement

All authors take full responsibility for the data analyses and interpretation, and the conduct of the research; they had full access to all the data and had the right to publish these data. All authors have reviewed and approved the contents of the manuscript. None of the authors report a potential, real, or perceived conflict of interest. All authors fulfilled the ICMJE criteria for authorship. The manuscript has not been submitted or published elsewhere.

Competing interests and disclosures

The authors declare no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.11.001.

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