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ORIGINAL RESEARCH

Associations Between Atherosclerosis and Subsequent Cognitive Decline: A Prospective Cohort Study

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BACKGROUND: This study aimed to examine whether baseline atherosclerosis was associated with subsequent short-term domain-specific cognitive decline.

METHODS AND RESULTS: This research was based on the BRAVE (Beijing Research on Aging and Vessel) study, a population-based prospective cohort study of adults aged 40 to 80 years, free of dementia. At baseline (wave 1, 2019), cognitive assessments and atherosclerosis measures, including carotid intima-media thickness, carotid plaques, coronary artery calcification, and brachial–ankle pulse wave velocity were conducted. Cognitive function was reassessed in wave 2 (2022–2023) using linear mixed models for analysis. A total of 932 participants (63.7% women; mean age, 60.0±6.9 years) were included. Compared with the lowest tertile of carotid intima-media thickness, carotid plaques, and brachial–ankle pulse wave velocity, or a coronary artery calcification score=0, the highest tertile of carotid intima-media thickness (β=−0.065 SD/y [95% CI, −0.112 to −0.017]; *P*=0.008), carotid plaques (β=−0.070 SD/y [95% CI, −0.130 to −0.011]; *P*=0.021), and brachial–ankle pulse wave velocity (β=−0.057 SD/y [95% CI, −0.105 to −0.010]; *P*=0.018), and a coronary artery calcification score≥400 (β=−0.081 SD/y [95% CI, −0.153 to −0.008]; *P*=0.029) were significantly associated with a faster decline in semantic fluency after multivariable adjustment. Moreover, greater carotid intima-media thickness, coronary artery calcification, and brachial–ankle pulse wave velocity were significantly associated with a faster decline in global cognition.

CONCLUSIONS: More significant atherosclerosis was associated with faster semantic fluency and global cognition declines.

Key Words: brachial–ankle pulse wave velocity ■ carotid intima-media thickness ■ carotid plaques ■ cognitive decline ■ coronary artery calcification

Dementia is a major public health concern, particularly as the global population ages. According to the World Health Organization, a new case of dementia occurs every 3 seconds, with ≈55.2 million people living with dementia in 2019, a number expected to rise to 152 million by 2050.[1,2] Dementia is a leading cause of dependency and disability among older adults, resulting in substantial health expenditure.[2,3] Given the limited efficacy of current treatments and the high cost and strict eligibility of novel amyloid-reduction drugs,[4–6] early prevention of cognitive deterioration through detecting modifiable risk factors and implementing targeted intervention is crucial.

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CLINICAL PERSPECTIVE

What Is New?

- In this population-based prospective cohort study of middle-aged and older adults, more significant atherosclerosis, including carotid intima-media thickness, carotid plaques, coronary artery calcification, and brachial–ankle pulse wave velocity, was associated with a faster decline in semantic fluency and global cognition over a relatively short follow-up period.

What Are the Clinical Implications?

- Participants with more significant atherosclerosis may represent a vulnerable population for cognitive decline and constitute an important target group for dementia prevention; thus, their neurocognitive status should be carefully monitored and timely interventions should be provided.
- Moreover, health professionals should pay additional attention to the early stages of atherosclerosis, as this may offer a critical time window for intervention.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
BRAVE	Beijing Research on Aging and Vessel
ba-PWV	brachial-ankle pulse wave velocity
CACS	coronary artery calcification score
cIMT	carotid intima-media thickness
DHS-Mind	Diabetes Heart Study–Mind Substudy
EHLS	Epidemiology of Hearing Loss Study
ELSA-Brazil	Brazilian Longitudinal Study of Adult Health
Health ABC	Health, Aging, and Body Composition
NOMAS	Northern Manhattan Study
PARTAGE	Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population
PWV	pulse wave velocity
TMT	Trail Making Test

Cardiovascular disease is a well-established risk factor for cognitive impairment and dementia.[7–12] Because dementia has a long preclinical period during which cardiovascular risk factors have adverse effects on cognitive function,[13–16] atherosclerosis, the most common pathological process of cardiovascular diseases, is increasingly recognized for its role in the development of cognitive impairment and dementia.[17–23] Atherosclerosis reflects cumulative exposure to cardiovascular risk factors over a lifetime[23,24] and could be measured directly and noninvasively. Although mixed results have been reported, several longitudinal cohort studies have shown that atherosclerosis is associated with a steeper cognitive decline.[17,18,25] However, cognitive function is frequently evaluated using general screening tools (such as the Mini-Mental State Examination),[26] which may not be sensitive enough to detect subtle cognitive changes over time. It remains unclear whether atherosclerosis preferentially affects specific cognitive domains. Moreover, some studies have focused on the association between baseline atherosclerosis and a single subsequent assessment of cognitive function rather than changes over time.[24,27–29] These studies predominantly evaluated atherosclerosis at the carotid artery, using measures such as carotid intima-media thickness (cIMT) and carotid plaques. Atherosclerosis is a systemic pathological process that could be evaluated at various vascular sites, with atherosclerotic burdens differing considerably across locations.[30–32] Different measures reflect the distinct aspects, stages, and severities of the atherosclerotic process.[33–35] It is possible that the relationship between atherosclerosis and cognitive decline varies across different vessels and that a more significant global atherosclerotic burden could be related to more pronounced cognitive decline.

To date, few studies have assessed atherosclerosis at multiple vascular sites to enhance its potential impact on subsequent cognitive decline, which could indicate cognitive impairment and dementia.[36] Therefore, the present study aimed to investigate whether several indicators of atherosclerosis are associated with cognitive decline by using measurements from multiple vascular sites and comprehensive cognitive assessments, including global and domain-specific tests.

METHODS

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Study Population

The BRAVE (Beijing Research on Aging and Vessel) study is an ongoing, community-based cohort study

investigating the association of vascular structure and function with cognitive function in a Chinese population. Information regarding demographic characteristics, physical and psychosocial health, and cardiovascular risk factors were obtained at baseline (wave 1). The baseline survey was conducted from October to November 2019 and followed up every 3 years. All 1789 residents aged 40 to 80 years in the Xishan community of the Shijinshan District were invited to participate. A total of 1554 residents were recruited and underwent baseline assessments. The first follow-up survey (wave 2) was conducted from October to November 2022 and March to April 2023; the interruption in follow-up was due to the social distancing policy during the COVID-19 pandemic. The BRAVE study was conducted following the Declaration of Helsinki and received ethical approval from the Institutional Review Board of Peking University Health Science Center (IRB0001052-19060) and Fuwai Hospital (IRB2012-BG-006). Written informed consent was obtained from all participants.

As presented in Figure, among the 1554 participants recruited at baseline (wave 1), 229 participants were excluded due to missing data on cIMT, carotid plaques, coronary artery calcification (CAC), or brachial–ankle pulse wave velocity (ba-PWV) (n=223), cognitive function (n=1), education (n=2), or low-density lipoprotein cholesterol (n=3). An additional 393 participants were excluded due to missing cognitive function data in wave 2, primarily due to concerns about COVID-19 infection during the pandemic. A comparison of baseline characteristics between participants included and excluded in wave 2 revealed significant differences. Participants excluded in wave 2 had a higher proportion of lower education, depressive mood, and statin use; and lower levels of verbal memory, executive function, and global cognition at baseline (wave 1) (Table S1). Finally, 932 participants were included in the analysis.

Assessment of Atherosclerosis

An ultrasound machine (M6T, Mindray Bio-Medical Electronics, China) was used to measure cIMT and carotid plaques. cIMT was measured bilaterally at the plaque-free sites on the far wall of the common carotid arteries, at the 10-mm segment proximal to the bifurcation. Six sites (the common carotid artery, the bifurcation, and the internal carotid artery, bilaterally) were scanned longitudinally and transversally for carotid plaques. Carotid plaque was considered present if the cIMT at the location was ≥1.5 mm or if the wall thickness of localized protrusion into the vessel lumen was at least 50% thicker than adjacent cIMT.[37] The ultrasound images were analyzed by a trained observer through Vascular Research Tools V.6 software (Medical Imaging Applications LLC, Iowa). The reproducibility of the cIMT assessment was high, with an intraclass correlation coefficient of 0.94 for intraobserver reproducibility when the observer re-measured the cIMT of 20 randomly selected participants from the BRAVE study. The mean cIMT and total carotid plaques at the 6 sites were analyzed.

CAC was measured with a multislice computed tomography scanner (Brilliance iCT, Philips Healthcare,

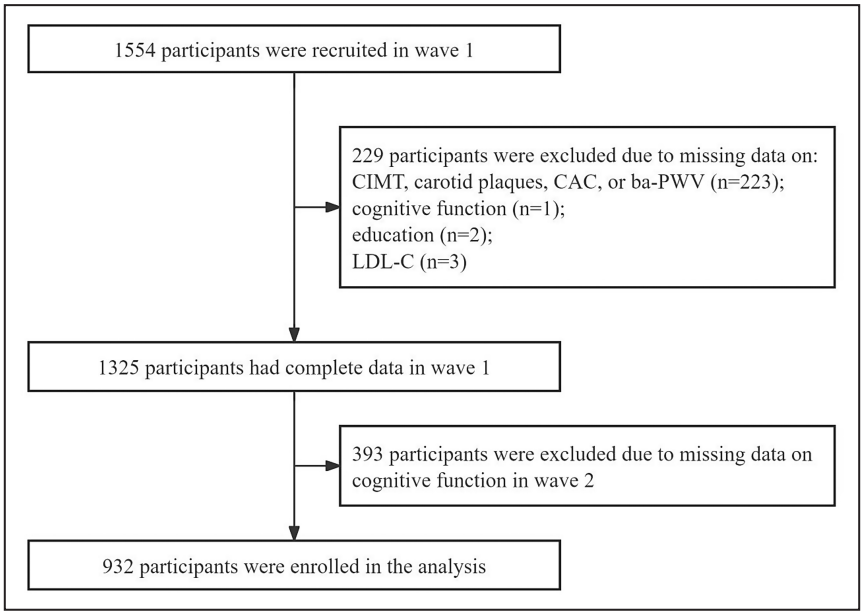

Figure. Flowchart of participant selection for this study.
ba-PWV indicates brachial–ankle pulse wave velocity; CAC, coronary artery calcification; cIMT, indicates carotid intima-media thickness; and LDL-C, low-density lipoprotein cholesterol.

Cleveland, OH). Computed tomography scans were performed by a skilled physician at a tube voltage of 120 V and a contiguous slice of 2.5 mm during a breath-holding period. Scanning began at the bifurcation of the trachea and proceeded to the cardiac apex. The physician independently assessed the computed tomography images using a workstation (Advantage Workstation Version 4.6; GE Healthcare, Chicago, IL). Coronary calcification, identified as the hyperattenuating region exceeding a computed tomography density of 130 Hounsfield units, was quantified using the Agatston method.[38] The Agatston score (coronary artery calcification score [CACS]) was the sum of the scores of all detected coronary calcification lesions. According to previous studies, CACS was categorized into 0, 1 to 399, and ≥400.[39,40]

ba-PWV was measured by a trained observer using an arteriosclerosis measuring device (Vascular Inspecting Apparatus MB3000; M&B Electronic Instruments, Beijing, China). Participants were requested to rest for at least 5 minutes before the measurement. Cuffs were applied to both arms and ankles, 2 electrodes were placed on the wrists, and a heart sound sensor was positioned in the second intercostal space over the sternum. The device automatically calculated ba-PWV. The mean values of the left and right ba-PWV were used for analysis.

Considering that cIMT and carotid plaques reflect early and advanced structural changes in the carotid arteries, respectively,[33] with carotid plaques indicating a heavier atherosclerotic burden, they were included in constructing a global atherosclerosis score. This score was created by summing points assigned to carotid plaques, CAC, and ba-PWV to represent the global burden of systemic atherosclerosis. Briefly, 0 to 2 points were assigned to ordinal variables of carotid plaques (0, 1–2, ≥3), CAC (CACS=0, CACS=1–399, CACS ≥400), and ba-PWV (tertile 1, ≤14.05 m/s; tertile 2, 14.06–16.04 m/s; tertile 3, ≥16.05 m/s). The global atherosclerosis score ranged from 0 to 6 points, with a higher score indicating a greater atherosclerotic burden.

Assessment of Cognitive Function

Global cognition was evaluated using the Chinese version of the Montreal Cognitive Assessment Basic, a widely used tool for cognitive assessment in clinical settings.[41] The Montreal Cognitive Assessment Basic evaluates 9 cognitive domains: executive function, verbal memory, semantic fluency, orientation, calculation, abstraction, visual perception, naming, and attention. The assessment takes ≈15 minutes and has a maximum score of 30 points. All examiners involved in the cognitive function evaluations completed the official Montreal Cognitive Assessment Training and Certification Program.

A robust battery of cognitive tests was administered to develop stable measures for 3 individual cognitive domains. Verbal memory was assessed using the immediate and delayed recall of 10 unrelated words (0–20 points). These tests have demonstrated good construct validity and consistency, with higher scores indicating better performance.[42] Semantic fluency was evaluated using the category fluency tests for animals and fruits included in the Montreal Cognitive Assessment Basic. The tests required participants to name as many animals or fruits as possible within 1 minute. The total score was the sum of unrepeated animals and fruits named in the 2 tests. The category fluency test for animals has good reliability and validity.[43] Executive function was assessed using the Trail Making Test (TMT), where participants were required to draw lines connecting consecutive numbers from 1 to 25 in ascending order (TMT-A) and to alternate between connecting numbers of different colors (pink and yellow) in TMT-B. The sum of the time (seconds) taken to complete both tasks, with a maximum of 3 minutes per test, was calculated and subsequently inverted to generate an executive function score, where a higher score indicates better performance.

All cognitive scores were converted to standardized *Z* scores by subtracting the mean scores at baseline (wave 1) and dividing by the SD at baseline to facilitate comparison across tests.

Covariates

Variables associated with both atherosclerosis and cognitive function were chosen as covariates in the study, including age, sex, education, body mass index, current smoking and drinking status (yes or no), physical activity, depressed mood, hypertension, diabetes, low-density lipoprotein cholesterol, statin use (yes or no), and apolipoprotein E4 status (carrier or noncarrier).[44,45] Education was categorized into ≤6 years, 7 to 12 years, and ≥13 years on the basis of years of schooling. Height and weight were measured in light clothing, and body mass index was calculated as weight in kilograms divided by height in square meters. Current smokers were defined as those smoking more than one cigarette per day. Current drinkers were identified when consuming alcohol more than once per week for >1 year. Physical activity was defined as engaging in moderate or vigorous physical activity for >10 minutes more than once per week. Depressed mood was identified with a Center for Epidemiologic Studies Depression Scale score of ≥12.[46] For each participant, brachial blood pressure was measured 3 times in a seated position after at least 5 minutes of rest, and the average of the second and third readings was used in the analysis. Plasma glucose and glycated hemoglobin were measured from venous blood after the participant had

fasted for at least 8 hours. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, a self-reported diagnosis of hypertension, or the use of antihypertensive medications. Diabetes was defined as plasma glucose ≥7 mmol/L, glycated hemoglobin ≥6.5%, a self-reported diagnosis of diabetes, or the use of antidiabetic drugs. Genomic DNA was extracted from blood cells to determine the genotype of apolipoprotein E4. Participants were classified as apolipoprotein E4 carriers if they had at least 1 copy of the apolipoprotein E ε4 allele.

Statistical Analysis

Baseline characteristics are presented as the mean±SD or median and interquartile range for continuous variables, and frequency (percentage) for categorical variables. Trends in baseline characteristics among participants with global atherosclerosis scores of 0 to 1, 2 to 3, and 4 to 6 were examined using the linear regression test or the Jonckheere–Terpstra trend test for continuous variables, the Cochran–Armitage test for dichotomous variables, and the Cochran–Mantel–Haenszel test for ordinal variables. We analyzed changes in standardized cognitive function scores (SD/y) by atherosclerosis levels from wave 1 to wave 2 using linear mixed models with a random intercept and a fixed slope. In each model, atherosclerosis variables were modeled as continuous and ordinal. Specifically, as continuous variables, CAC was handled as ln(CACS+1), and cIMT was handled as per 0.1 mm increment, in line with previous studies.[47] As ordinal variables, cIMT, carotid plaques, and ba-PWV were handled as tertiles, which were prespecified and have been widely used in previous studies to investigate their associations with cardiovascular disease.[48–50]

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). All analyses were 2-sided, and the significance for statistical testing was set at 0.05.

RESULTS

Baseline Characteristics

A total of 932 individuals (women, 594 [63.7%]; mean age, 60.0±6.9 years) were included in the final analysis (Figure). The mean±SD or median (interquartile range) values for cIMT, number of carotid plaques, CACS, and ba-PWV were 0.71±0.11 mm, 1 (1–2), 0 (0–60.5), and 15.27±2.45 m/s, respectively. Table 1 shows the baseline characteristics of participants grouped by the severity of global atherosclerosis. Generally, participants with more significant atherosclerosis tended to be older, men, less educated, and less physically active. They had higher body mass index, a more substantial proportion of current smokers and drinkers, more cases of hypertension and diabetes, higher statin use, and poorer performance in verbal memory, semantic fluency, executive function, and global cognition.

Association Between Atherosclerosis and Cognitive Decline

Table 2 shows an association between baseline atherosclerosis and annual decline in semantic fluency observed across all 4 atherosclerosis indicators after multivariable adjustment over a follow-up of 3 years (waves 1–2). Specifically, compared with participants in the lowest tertile of cIMT (≤0.65 mm), those in the highest tertile (≥0.75 mm) exhibited a significant faster decline in semantic fluency at a rate of −0.065 SD/y (95% CI, −0.112 to −0.017; *P*=0.008). Each 0.1 mm increment in cIMT was associated with an annual change of −0.026 SD (95% CI, −0.043 to −0.009; *P*=0.003) in semantic fluency. Participants with ≥3 plaques experienced a faster decline in semantic fluency (−0.070 SD/y [95% CI, −0.130 to −0.011]; *P*=0.021) compared with those without plaques. Furthermore, a linear dose–response relation was found, with each additional plaque increasing the decline rate by −0.016 SD/y (95% CI, −0.028 to −0.004; *P*=0.010). Participants with a CACS ≥400 suffered a sharper decline in semantic fluency (−0.081 SD/y [95% CI, −0.153 to −0.008]; *P*=0.029) than those without CAC. Compared with participants in the lowest tertile of ba-PWV (≤14.05 m/s), those in the highest tertile (≥16.05 m/s) showed a faster decline in semantic fluency at a rate of −0.057 SD/y (95% CI, −0.105 to −0.010; *P*=0.018). The global atherosclerosis score, derived from carotid plaques, CAC, and ba-PWV, was associated with a decline in semantic fluency. Participants in the highest tertile (4–6 points) exhibited a faster decline of −0.071 SD/y (95% CI, −0.123 to −0.019; *P*=0.008) compared with those in the lowest tertile (0–1 points). Each additional point accelerated the decline by −0.020 SD/y (95% CI, −0.033 to −0.007; *P*=0.003).

Moreover, some atherosclerosis indicators were associated with global cognitive decline. For cIMT, each 0.1 mm increment was linked to a faster decline of −0.019 SD/y (95% CI, −0.036 to −0.001; *P*=0.036). Participants with a CACS ≥400 experienced a quicker decline in global cognition (−0.075 SD/y [95% CI, −0.148 to −0.002]; *P*=0.044) than those without CAC. Participants in the highest tertile (≥16.05 m/s) exhibited a faster decline in global cognition at a rate of −0.051 SD/y (95% CI, −0.100 to −0.003; *P*=0.039) compared with those in the lowest tertile (≤14.05 m/s). Each additional point in the global atherosclerosis score accelerated the decline by −0.014 SD/y (95% CI, −0.027 to −0.001; *P*=0.039).

DISCUSSION

This prospective, community-based cohort study of Chinese middle-aged and older adults demonstrated

Table 1. Baseline Characteristics of the Study Participants by Level of Atherosclerosis at Baseline (n=932)

Characteristic	Global atherosclerosis score			*P* for trend
	0–1 (n=270)	2–3 (n=419)	4–6 (n=243)	
Age, y	56.0±5.8	60.3±6.6	64.0±6.0	<0.001*
Women	199 (73.7)	275 (65.6)	120 (49.4)	<0.001‡
Education, y				
≤6	4 (1.5)	18 (4.3)	22 (9.1)	<0.001δ
7–12	192 (71.1)	331 (79.0)	198 (81.5)	
≥13	74 (27.4)	70 (16.7)	23 (9.5)	
Body mass index, kg/m^2	25.0±3.0	26.0±3.3	26.8±3.2	<0.001*
Current smoking	49 (18.2)	75 (17.9)	63 (25.9)	0.032‡
Current drinking	46 (17.0)	85 (20.3)	63 (25.9)	0.014‡
Physical activity	79 (29.3)	91 (21.7)	33 (13.6)	<0.001‡
Depressed mood	11 (4.1)	17 (4.1)	15 (6.2)	0.269‡
Hypertension	99 (36.7)	257 (61.3)	182 (74.9)	<0.001‡
Diabetes	39 (14.4)	113 (27.0)	101 (41.6)	<0.001‡
SBP, mm Hg	124.0±14.0	133.7±15.3	141.4±16.7	<0.001*
DBP, mm Hg	81.1±10.2	84.6±9.9	85.9±10.2	<0.001*
Glycated hemoglobin, %	5.80 (5.60–6.00)	6.00 (5.70–6.30)	6.10 (5.80–6.80)	<0.001†
Total cholesterol, mmol/L	4.90±0.83	4.97±0.92	4.86±1.04	0.640*
HDL-C, mmol/L	1.43±0.35	1.40±0.34	1.33±0.32	0.001*
LDL-C, mmol/L	3.16±0.77	3.18±0.87	3.11±0.96	0.536*
Antihypertensive drug use	54 (87.1)	149 (86.6)	121 (91.7)	0.240‡
Antidiabetic drug use	24 (8.9)	59 (14.1)	66 (27.2)	<0.001‡
Statin use	40 (14.8)	90 (21.5)	71 (29.2)	<0.001‡
Apolipoprotein E4 carrier	47 (17.4)	80 (19.1)	45 (18.5)	0.734‡
cIMT, mm	0.66±0.09	0.71±0.11	0.77±0.12	<0.001†
Carotid plaque number	1 (0–1)	1 (1–2)	3 (2–4)	<0.001†
CACS	0 (0–0)	0 (0–39.0)	105.9 (23.0–445.0)	<0.001†
0	245 (90.7)	248 (59.2)	21 (8.6)	<0.001δ
1–399	25 (9.3)	166 (39.6)	152 (62.6)	
≥400	0	5 (1.2)	70 (28.8)	
ba-PWV, m/s	13.21±1.28	15.34±1.91	17.44±2.45	<0.001†
Verbal memory	9.4±3.3	8.6±3.0	7.6±3.0	<0.001*
Semantic fluency	28.6±5.8	27.5±5.8	26.8±6.0	<0.001*
Executive function, s	176.8±50.4	199.1±58.4	213.3±59.2	<0.001*
Global cognition	25.6±3.0	24.8±3.2	24.3±3.2	<0.001*

The results are presented as the mean±SD, median (interquartile range), or frequency (percentage). ApoE4 indicates apolipoprotein E4; ba-PWV, brachial–ankle pulse wave velocity; CACS, coronary artery calcification score; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

*Calculated by using the linear regression test for continuous variables.

†Calculated by using the Jonckheere–Terpstra trend test for continuous variables.

‡Calculated by using the Cochran–Armitage test for dichotomous variables.

δCalculated by using the Cochran–Mantel–Haenszel test for ordinal variables.

significant associations between atherosclerosis and subsequent cognitive decline. More significant and extensive atherosclerosis was associated with a faster decline in semantic fluency and global cognition, not verbal memory or executive function.

The most important finding of our study is that middle-aged and older adults with more significant atherosclerosis, especially at multiple sites, might suffer a faster decline in semantic fluency and global cognition over a relatively short follow-up period. Compared with participants in the lowest tertile, those in the highest tertile of cIMT, carotid plaques, ba-PWV, and those with a CACS ≥400 experienced a faster decline in semantic fluency. This association was not observed in participants in the middle tertile. This finding underscores the importance of monitoring the atherosclerotic process,

Table 2. Association Between Atherosclerosis and Cognitive Change Rate (SD/Year)

	Verbal memory*	*P*	Semantic fluency*	*P* value	Executive function*	*P* value	Global cognition*	*P* value
cIMT, mm								
Tertile 1, ≤0.65	Reference	/	Reference	/	Reference	/	Reference	/
Tertile 2, 0.66–0.74	−0.025 (−0.082 to 0.033)	0.398	−0.045 (−0.092 to 0.003)	0.064	0.016 (−0.022 to 0.054)	0.416	−0.015 (−0.063 to 0.033)	0.547
Tertile 3, ≥0.75	−0.043 (−0.101 to 0.014)	0.142	−0.065 (−0.112 to −0.017)	0.008	−0.020 (−0.059 to 0.018)	0.305	−0.035 (−0.083 to 0.014)	0.163
Per 0.1 mm increment	−0.011 (−0.031 to 0.010)	0.322	−0.026 (−0.043 to −0.009)	0.003	−0.006 (−0.020 to 0.008)	0.396	−0.019 (−0.036 to −0.001)	0.036
Carotid plaques								
Plaque=0	Reference	/	Reference	/	Reference	/	Reference	/
Plaques=1–2	−0.003 (−0.062 to 0.057)	0.929	−0.013 (−0.062 to 0.036)	0.593	0.007 (−0.033 to 0.046)	0.746	0.006 (−0.045 to 0.056)	0.827
Plaques ≥3	0.031 (−0.041 to 0.103)	0.400	−0.070 (−0.130 to −0.011)	0.021	−0.024 (−0.072 to 0.025)	0.333	−0.032 (−0.093 to 0.029)	0.306
Number	0.004 (−0.011 to 0.019)	0.568	−0.016 (−0.028 to −0.004)	0.010	−0.008 (−0.018 to 0.002)	0.099	−0.007 (−0.020 to 0.006)	0.271
CAC								
CACS=0	Reference	/	Reference	/	Reference	/	Reference	/
CACS=1–399	−0.002 (−0.051 to 0.048)	0.953	−0.003 (−0.044 to 0.038)	0.886	−0.013 (−0.046 to 0.020)	0.440	0.011 (−0.030 to 0.052)	0.599
CACS ≥400	0.049 (−0.039 to 0.137)	0.272	−0.081 (−0.153 to −0.008)	0.029	−0.041 (−0.101 to 0.018)	0.170	−0.075 (−0.148 to −0.002)	0.044
ln(CACS+1)	0.004 (−0.005 to 0.014)	0.388	−0.004 (−0.012 to 0.004)	0.295	−0.004 (−0.010 to 0.003)	0.259	−0.002 (−0.010 to 0.007)	0.718
ba-PWV								
Tertile 1, ≤14.05 m/s	Reference	/	Reference	/	Reference	/	Reference	/
Tertile 2, 14.06–16.04 m/s	−0.004 (−0.062 to 0.053)	0.880	−0.043 (−0.091 to 0.004)	0.073	−0.030 (−0.068 to 0.009)	0.132	−0.033 (−0.082 to 0.015)	0.178
Tertile 3, ≥16.05 m/s	0.016 (−0.042 to 0.073)	0.597	−0.057 (−0.105 to −0.010)	0.018	−0.015 (−0.054 to 0.024)	0.447	−0.051 (−0.100 to −0.003)	0.039
Per 1 m/s increment	0.001 (−0.008 to 0.011)	0.774	−0.006 (−0.013 to 0.002)	0.165	−0.001 (−0.007 to 0.006)	0.935	−0.007 (−0.015 to 0.001)	0.083
Global atherosclerosis								
Tertile 1, score=0–1	Reference	/	Reference	/	Reference	/	Reference	/
Tertile 2, score=2–3	−0.021 (−0.076 to 0.035)	0.465	−0.038 (−0.084 to 0.008)	0.109	−0.013 (−0.050 to 0.025)	0.500	0.001 (−0.046 to 0.048)	0.964
Tertile 3, score=4–6	0.040 (−0.023 to 0.103)	0.215	−0.071 (−0.123 to −0.019)	0.008	−0.019 (−0.061 to 0.023)	0.377	−0.048 (−0.101 to 0.005)	0.077
Score	0.008 (−0.008 to 0.024)	0.327	−0.020 (−0.033 to −0.007)	0.003	−0.008 (−0.018 to 0.003)	0.150	−0.014 (−0.027 to −0.001)	0.039

CACS indicates coronary artery calcification score.

*Adjusted for age, sex, education, current smoking, current drinking, physical activity, body mass index, depressed mood, hypertension, diabetes, low-density lipoprotein cholesterol, statin use, and apolipoprotein E4 status.

as there might be a critical time window in the early stages of atherosclerosis during which intervention could halt or at least delay cognitive decline, alongside preventing further progression of atherosclerosis. In addition, greater cIMT, representing the early stage of the atherosclerotic process, showed a linear dose–response association with a faster decline in semantic fluency and global cognition. This association suggests that cIMT may not need to reach a certain severity threshold to undermine cognitive function.

Previous studies investigating the associations between atherosclerosis indicators and cognitive decline yielded mixed findings. The ELSA-Brazil (Brazilian Longitudinal Study of Adult Health), with a median follow-up of 8 years, found that greater cIMT was associated with a faster decline in verbal

fluency, memory, executive function, and global cognition.[51] This finding partially aligns with our findings, although significant memory or executive function declines were not observed in the present study. Conversely, no significant association between cIMT or carotid plaques and cognitive decline was found in the EHLS (Epidemiology of Hearing Loss Study), the ARIC (Atherosclerosis Risk in Communities) study, or the NOMAS (Northern Manhattan Study).[18,52,53] Apart from differences in sample size, follow-up lengths, and racial and age distributions in study populations, this discordance might primarily relate to the distinct cognitive tests, each with unique properties. For instance, the EHLS study applied TMT-A and TMT-B to evaluate executive function, the Digit Symbol Substitution Test to assess psychomotor speed, the Rey Auditory Verbal Learning Test for memory evaluation, and the Verbal Fluency Test for phonemic fluency.[18] The ARIC study used the Delayed Word Recall Test for verbal learning and recent memory evaluation, the Digit Symbol Substitution Test for information processing speed, and the word fluency test for phonemic fluency.[52] In contrast, the NOMAS study assessed episodic memory, executive function, processing speed, and semantic memory, each evaluated by multiple tests.[53] Moreover, the differing statistical methods used may explain the negative findings in these studies. While some studies used ANCOVA, which uses the change from baseline to follow-up as the dependent variable and adjusts for baseline data, our study used linear mixed models. These models, designed to handle repeated measures data, include baseline and follow-up data as dependent variables, formally capturing both group (fixed effects) and individual (random effects) trajectory patterns.[54] These models correlate repeated-measures data correctly, lower the rates of false positives or negatives, and more accurately reflect cognitive changes.[55] The relationship between higher CACS and a faster decline in semantic fluency was observed in the DHS-Mind (Diabetes Heart Study–Mind Substudy), a cohort with a high prevalence of type 2 diabetes (>80%) and a mean follow-up of 6.7 years.[56] The present study adds to the existing literature by demonstrating the association between atherosclerosis and cognitive decline in a general community population. The Health ABC (Health, Aging, and Body Composition) study, which had a 9-year follow-up, found that greater carotid–femoral pulse wave velocity (PWV) was associated with a faster cognitive decline and a higher risk of cognitive impairment (defined as a decrease ≥5 in modified Mini-Mental State Examination).[57] This finding aligns with ours despite the differences in measurement sites for PWV. While carotid–femoral PWV reflects the stiffness of large elastic arteries, ba-PWV reflects the stiffness of both large and middle muscular arteries. The ba-PWV measurement is simple and reproducible, making it more suitable for practical applications such as primary care and epidemiological surveys. A Japanese study involving 932 adults over a 3.4-year follow-up period, similar to the present study, revealed that greater ba-PWV was associated with a higher risk of cognitive decline (defined as a decrease ≥2 in Mini-Mental State Examination).[58]

The precise pathways linking atherosclerosis to cognitive decline are not fully understood; however, several possible explanations exist. Atherosclerosis may lead to cerebral hypoperfusion and hypoxia, resulting in neuronal destabilization and contributing to neurodegenerative processes.[59] Atherosclerosis is associated with cerebral small-vessel disease and structural brain abnormalities. Greater cIMT was associated with a greater white matter hyperintensity, covert brain infarcts, lacunar infarcts, cerebral microbleeds, reduced cerebral volumes, and cortical gray matter.[53,60–62] Carotid plaques have been associated with a greater white matter hyperintensity, cortical infarcts, and reduced metabolism of cerebral areas affected by dementia.[63–65] Increased CAC has been related to worse microstructural integrity of white matter and reduced gray matter volumes.[66] Brain circulation is characterized by passive perfusion throughout systole and diastole by pulsatile flow.[67] Increased arterial stiffness, as reflected by greater PWV, could increase pulsatile pressure in small vessels, progressively damaging microcirculation.[67] Moreover, this increased pulsatile pressure might hinder the clearance of β-amyloid from the brain to blood and spinal fluid, resulting in increased deposition in the brain.[68,69]

The present study has several strengths. First, the prospective design and repeated assessments of cognitive function allowed us to explore the rate of cognitive decline related to atherosclerosis using linear mixed models. Second, atherosclerosis was measured at different sites, and a global atherosclerosis scoring system was created, enabling us to examine both individual and combined effects of varying atherosclerosis indicators. Third, a general cognitive assessment (Montreal Cognitive Assessment Basic) and 3 domain-specific cognitive tests were applied, which are more sensitive to cognitive decline.

Despite these strengths, some limitations should be considered when interpreting the results. First, a causal relationship cannot be established due to the study's observational nature. Second, 393 participants without cognitive function data in wave 2 were excluded, which might lead to selection bias. Third, although controlled for potential confounders, the possibility of residual confounding, such as diet, cannot be ruled out. Fourth, the relatively short follow-up period and the examination of cognitive function over only 2 time points were disadvantageous, which limited us

to investigate the long-term association between atherosclerosis and cognitive changes with the existing data; however, this association will be further explored in the subsequent follow-ups of the BRAVE study. Despite this brevity, a significant association between atherosclerosis and cognitive decline was observed, highlighting the potential of using atherosclerosis indicators to predict subsequent cognitive decline and emphasizing the detrimental impact of atherosclerosis on cognitive performance. Similarly, a 1-year prospective cohort, the PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study has found that greater PWV was related to more pronounced cognitive decline over 2 visits.[70] Fifth, there is a possibility that cognitive function assessed in wave 2 might have been influenced by learning effects resulting from the repeated use of the same cognitive tests. However, evaluating and controlling for learning effects with only 2 time points is challenging, and this factor should be considered when interpreting the results.

CONCLUSIONS

This study demonstrated that more significant atherosclerosis was associated with a faster cognitive decline in semantic fluency and global cognition over a relatively short follow-up. This finding suggests that atherosclerosis indicators, including cIMT, carotid plaques, CAC, and ba-PWV, could be noninvasive markers to predict subsequent cognitive deterioration. From the clinical perspective, participants with more significant atherosclerosis may represent important targets for planning dementia prevention strategies in the future, and health professionals should pay attention to the neurocognitive function of this vulnerable population during regular health surveillance and initiate timely and proper interventions. Furthermore, these findings highlight the importance of closely monitoring the progression of atherosclerosis, as there might exist a critical window during the early stages of this process for intervention to halt or delay further cognitive decline.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1

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