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Association of subclinical atherosclerosis and cognitive decline: a community-based cross-sectional study

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ABSTRACT

Background and aims Growing burden of dementia was considered as a global public health priority as its epidemic scale rises with the world's population increases in age. In the absence of effective treatment, early identification of decline in cognitive function and risk factors that lead to the onset of dementia is a critical issue. Subclinical atherosclerosis may be a potential risk factor for cognitive impairment and progression to dementia. Research is needed to identify which subclinical atherosclerosis risk factors can better predict cognitive decline.

Methods A total of 1554 participants (mean age 59.81±6.93 years) were enrolled from Beijing Research on Ageing and Vessel and underwent baseline evaluation. Carotid intima-media thickness, carotid plaque and brachial ankle pulse wave velocity (ba-PWV) were selected as subclinical atherosclerosis markers. Cognitive function assessment was conducted by standardised tasks to assess the associations with subclinical atherosclerosis markers.

Results Significant associations (p<0.001) were shown in the unadjusted models between all three subclinical atherosclerosis markers and cognitive function assessments. After adjusting for covariates, in the assessment of the association between carotid atherosclerosis and cognitive function, plaque numbers showed significant associations in Montreal Cognitive Assessment (MoCA) (β=−0.15, p=0.006) and verbal memory scores (β=−0.13, p=0.013). While in the assessment of the association between arterial stiffness and cognitive function, ba-PWV showed significant associations in MoCA (β=−0.09, p=0.009) and semantic fluency scores (β=−0.13, p=0.036).

Conclusions Positive associations shown between subclinical atherosclerosis and cognitive function. Subclinical atherosclerosis markers of plaque numbers were significantly associated with global cognitive functioning in MoCA, memory and semantic fluency, while ba-PWV was significantly associated with global cognitive functioning in MoCA and semantic fluency.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Beijing Research on Ageing and Vessel is a large community-based prospective, longitudinal study that analysed 1554 participants at the baseline survey in 2019.

⇒ The unique contribution of our study is the multiple assessed markers (intima-media thickness, carotid plaque and brachial ankle pulse wave velocity) of subclinical atherosclerosis and different cognitive assessment tests of both global cognitive function and specific cognitive domains.

⇒ This is a cross-sectional study, which can only present an observational result rather than a temporal inference cause–effect conclusion.

⇒ The composition of population was only as a single race of Chinese with ratio of men was much less in number that included in our study, thus, our findings may not be fully applied to the common population.

Individuals who suffer from this major neurocognitive disorder will eventually lose their independence in daily life functioning. As the world's population increasing in age, dementia affected a population of estimated 50 million people worldwide in 2018 and the epidemic scale will be likely to rise to about 152 million people in 2050,[2] causing a significant burden on affected individuals, family members, the healthcare system and society. The growing burden of dementia was considered a global public health priority by The WHO and Alzheimer's Disease International, and the greatest global health and social care challenge in the 21st century.[3]

The cognitive decline process leading to impairment often begins many years before dementia onset. Neurocognitive disorder stage occurred between healthy ageing and dementia with appeared objective cognitive decline symptoms but preserved daily activities.[4] In the absence and unsuccessful finding of curative or disease-modifying treatment for dementia, early life diagnosis of cognitive impairment and initial potentially preventive

INTRODUCTION

Dementia is a neurological condition characterised by cognitive and functional impairment, including deterioration in memory and at least one other cognitive domains.[1]

interventions that target modifiable risk factors will like to delay or halt the onset of dementia.[5]

Subclinical atherosclerosis may cause a decline in cognitive function through cerebral hypoperfusion and cerebrovascular disease.[6] Increasing arterial stiffness is an important cause of vascular damage and a predictor of the development of cardiovascular disease (CVD).[7] Brachial-ankle pulse wave velocity (baPWV) was known as an indicator of arterial stiffness, which was identified as an independent marker of predicting the risk of developing CVD risk in people with a low to intermediate CVD risk.[8] Measuring carotid intima-media thickness (IMT) and the presence of carotid plaque are widely used non-invasive approaches by carotid ultrasonography to assess carotid atherosclerosis. Increased IMT has been associated with a higher risk of cognitive decline and incident dementia,[9] however, other studies evaluating the association have yielded conflicting results.[10] While compared with early IMT, formed carotid plaques represent more advanced atherosclerosis leads to artery stenosis and thrombosis, indicating an increased risk of dementia and mortality.[11]

Despite these findings, the association between subclinical atherosclerosis and dementia is still controversial.[12–14] More research is needed to identify which subclinical atherosclerosis risk factors can better predict cognitive decline. In this study, we investigated the association between subclinical atherosclerosis and cognitive function using carotid IMT, carotid plaque and brachial ankle pulse wave velocity (ba-PWV) as markers.

MATERIALS AND METHODS
Participants
The Beijing Research on Ageing and Vessel (BRAVE) is a community-based, prospective, longitudinal study to investigate the contributions of vascular conditions to cognitive impairment causing dementia. At the baseline survey in 2019, all 1789 residents aged 40–80 years were invited from the Xishan community, Shijingshan District. A total of 1554 participants were initially enrolled and underwent baseline evaluation. Among them, 35 participants were excluded from this study due to missing data of atherosclerosis or cognitive assessment.

The study was approved by the Institutional Review Board of Peking University Health Science Center (IRB0001052-19060), all participants gave their informed written consent according to the Declaration of Helsinki.

Atherosclerosis assessment
Carotid artery ultrasound scans were obtained with an ultrasound machine (M6T, Mindray Bio-Medical Electronics, China) and quantitative analysis through Vascular Research Tools V.6 software (Medical Imaging Applications LLC, Iowa).

Measurement of IMT was made only at a plaque-free site on the left and right sides of the far wall of the common carotid artery (CCA), 10 mm segment proximal to the bifurcation and the internal carotid artery (ICA). The presence of plaques was scanned longitudinally and transversally at six sites (CCA, ICA and the bifurcation, both sides). Plaque was assessed as present if the wall thickness of localised protrusion into the vessel lumen was at least 50% thicker than adjacent IMT or the IMT at the location was greater than or equal to 1.5 mm.[15] The mean IMT and total plaque number of the measurements from the six sites were used in the analyses. All carotid images were analysed by one trained observer. We randomly selected 20 participants from the BRAVE and let the observer remeasured their IMT. The intraclass correlation coefficient for intraobserver reproducibility of IMT was 0.94 (95% CI 0.85 to 0.98, p<0.001).

Ba-PWV was measured with a non-invasive arteriosclerosis measuring device (Vascular Inspecting Apparatus MB3000, M&B Electronic Instruments, China). Measurements were conducted in the supine position after at least 5 min of rest. Occlusion cuffs were applied to both the left and right brachial and ankles, electrodes were placed on both wrists and a heart sound sensor was placed on the left margin of the sternum of subjects. The device simultaneously recorded the data of ECG, phonocardiogram, pulse volume waveform, heart rate and arterial blood pressure and automatically analysed the results.[16] The mean value of the left and right ba-PWV was used in the analyses.

Cognitive assessment
Cognitive function assessment was conducted by standardised tasks, including measures of global cognitive functioning, memory and semantic fluency.

Global cognitive functioning was assessed by the Montreal Cognitive Assessment (MoCA). Among the available cognitive screening tests for evaluation of cognitive impairment, MoCA is widely used for early evaluating of cognitive function in clinical settings. The MoCA is available in multiple languages and includes measures on various cognitive domains.[17] The Chinese version of MoCA Basic (MoCA-BC) was used to assess global cognitive function in the study. MoCA-BC was administered in 15 min that comprise individual tests to evaluate cognitive performance in executive function, memory, orientation, calculation, conceptual thinking, visual perception, language, concentration and attention domains. MoCA score was divided into quartiles to better display baseline characteristics of study population at different levels of cognitive function. The maximum score of MoCA-BC is 30 points with higher scores representing better cognition function. All examiners had completed the official MoCA training and certification programme before administering and scoring MoCA.

Details of cognitive function assessment of memory and semantic fluency had been published previously.[18 19] Verbal memory test was used to assess memory through immediate and delayed free recall of a 10-word list. Participants had 2 min to recall and repeat the words as many as possible after trained examiners pronounced all of them with a 2 s interval. After a few minutes, the participant was asked to recall the word list again. The maximum score

of the memory test is 20, which was obtained through each correctly recalled word from the two repeats. Immediate and delayed recall tests had demonstrated good construct validity and consistency.[20] Animal fluency test was conducted for the evaluation of semantic fluency through category fluency for animal test. The participant was asked to give as many words of animals as possible in 1 min. The total score of semantic fluency was calculated by the sum number of unrepeated names of animals in category fluency for animals test and fruits in MoCA. Animal fluency test had well-established reliability and validity.[21]

Covariates

Demographic characteristics, vascular risk factors, previous medical and medications history were obtained at baseline.

Level of education was defined as higher education if the years of education were 9 years or more. A current drinker was defined as a person whose consumption of alcohol was at least one drink per week and lasted for 1 year and above. Smoking status was defined as a current smoker if the individual smoked at least one cigarette a day. Resting brachial systolic and diastolic blood pressure (SBP, DBP) was measured with an automatic device by specially trained personnel. The values were defined as the mean value of three measurements in sitting participants after a 5 min resting period. Blood samples were obtained from participants after overnight fasting and centralised standard measurements of glycated haemoglobin A1C and plasma glucose were performed. Genomic DNA was extracted from blood cells and PCR amplification was conducted to determine the apolipoprotein E (APOE) genotype. Participants were classified as APOE carriers by at least one copy of the APOE ε4 allele.

Information on medical health history was obtained by self-report via questionnaires. Hypertension was defined as a self-reported condition, or current use of antihypertensive medications or measured SBP ≥140 mm Hg, or DBP ≥90 mm Hg.[22] Diabetes was defined as self-reported condition, or current use of antidiabetics medications, or regular use of insulin or fasting glucose concentration ≥7.00 mmol/L or glycated haemoglobin A1C ≥6.5%.[23] Depressive symptoms were defined as a self-reported condition, or current use of anti-depressive medications, or the score of the Chinese version of Center for Epidemiological Studies ≥12.[24]

Statistical analysis

Descriptive statistics of baseline characteristics were analysed according to the MOCA quartiles. Data were presented as either means and SD for continuous variables or frequencies and percentages for categorical variables. P values for trend were analysed by linear regression test for continuous variables or by χ^2 test for categorical variables.

Standardised regression coefficients were used as effect size to compare the associations between atherosclerosis measurements and cognitive assessment test results. The results were assessed in three models: model 1 was univariate linear-regression model, model 2 adjusted for sex, age and education and model 3 further adjusted for marital status, smoking, alcohol, physical activity status, hypertension, diabetes, stroke, angina pectoris, myocardial infarction, depression, antihypertensive medications, antidiabetics medications, use of statins and APOE ε4. Subgroup analyses were performed to further evaluate the p for interaction value between subclinical atherosclerosis and MoCA, according to age (<60, ≥60 years), sex, the status of smoking and hypertension. The adjusted covariates were age, sex, education, marital status, smoking, alcohol, physical activity status, hypertension, diabetes, stroke, angina pectoris, myocardial infarction, depression, antihypertensive medications, antidiabetics medications, use of statins and APOE ε4, except where an adjusting variable was itself being tested. All the tests were two sided and a p value less than 0.05 was considered significant. Statistical analyses were conducted with SAS V.9.4 (SAS Institute, Cary, North Carolina).

Patient and public involvement

Participants and the public were not involved in the design, conduct, reporting and dissemination plans of this study.

RESULTS

Baseline characteristics of subjects

The mean and SD of the MoCA score of the study population is 24.60±3.37. The characteristics of the study population were distributed by quartiles of MoCA in table 1. The quartiles of MoCA score distribution were 23, 25 and 27 for the 25th, 50th and 75th percentiles, respectively.

The mean age of the 1519 participants enrolled in this study was 59.81±6.93 years, ranging from 40 years to 83 years and comprised 37.06% of men. For the entire sample, the mean ba-PWV, carotid IMT and plaque numbers were 15.15±2.66 m/s, 0.71±0.11 mm and 1.73±1.66, respectively.

Participants in the fourth quartile of MoCA were younger, were more likely to be women and had a higher proportion of higher education level and lower proportion of vascular risk factors compared with the first quartile. Age, sex, education level, tobacco use, diabetes, hypertension, myocardial infarction, stroke, use of antihypertensive, antidiabetes were significantly decreased by increasing MoCA quartiles (p for trend <0.05). Moreover, in the assessment of subclinical atherosclerosis, lower MoCA scores were found in subjects with thicker IMT in the first quartile compared with the fourth. Similar association was identified when assessing plaque numbers and ba-PWV.

Association of carotid atherosclerosis and cognitive function

Multivariate regression analysis results of the associations between plaque numbers and cognitive assessment test

Table 1 Characteristics of the study population stratified by quartiles of MoCA test score (n=1519)

| Variables | MoCA test score | | | | |
	First quartile (n=493)	Second quartile (n=350)	Third quartile (n=379)	Fourth quartile (n=297)	P for trend*
Age	62.35±6.54	59.91±7.00	58.92±7.30	56.63±6.98	<0.001
Male	229 (46.45%)	138 (39.43%)	115 (30.34%)	81 (27.27%)	<0.001
Married	440 (89.25%)	308 (88.00%)	336 (88.65%)	265 (89.23%)	0.984
Higher education	219 (44.42%)	212 (60.57%)	254 (67.02%)	223 (75.08%)	<0.001
Smoker	128 (25.96%)	79 (22.57%)	70 (18.47%)	54 (18.18%)	0.003
Drinker	115 (23.33%)	84 (24.00%)	72 (19.00%)	59 (19.87%)	0.104
Active physical activity	76 (15.42%)	51 (14.57%)	45 (11.87%)	44 (14.81%)	0.461
Diabetes	168 (34.08%)	101 (28.86%)	93 (24.54%)	70 (23.57%)	<0.001
Hypertension	319 (64.71%)	225 (64.29%)	217 (57.26%)	167 (56.23%)	0.004
Myocardial infarction	33 (6.69%)	10 (2.86%)	12 (3.17%)	10 (3.37%)	0.015
Stroke	41 (8.32%)	27 (7.71%)	21 (5.54%)	15 (5.05%)	0.038
Angina pectoris	37 (7.51%)	21 (6.00%)	19 (5.01%)	15 (5.05%)	0.101
Depression	48 (9.74%)	20 (5.71%)	35 (9.23%)	16 (5.39%)	0.113
Atrial fibrillation	24 (4.87%)	10 (2.86%)	20 (5.28%)	19 (6.40%)	0.242
Heart failure	7 (1.42%)	3 (0.86%)	5 (1.32%)	2 (0.67%)	0.463
Anti-hypertensive	198 (40.16%)	127 (36.29%)	117 (30.87%)	89 (29.97%)	<0.001
Anti-diabetics	102 (20.69%)	48 (13.71%)	65 (17.15%)	39 (13.13%)	0.016
Statins	108 (21.91%)	73 (20.86%)	85 (22.43%)	58 (19.53%)	0.600
APOE ε4	85 (17.24%)	62 (17.71%)	68 (17.94%)	48 (16.16%)	0.804
Mean ba-PWV	15.74±2.70	15.24±2.63	14.82±2.74	14.49±2.54	<0.001
Max carotid IMT, mm	0.84±0.14	0.81±0.14	0.82±0.13	0.80±0.12	<0.001
Mean carotid IMT, mm	0.73±0.12	0.70±0.11	0.70±0.11	0.68±0.10	<0.001
Plaque numbers	2.12±1.87	1.71±1.49	1.54±1.64	1.35±1.50	<0.001

*Calculated by linear regression analysis or χ^2 test for trend.
APOE, apolipoprotein E; ba-PWV, carotid plaque and brachial ankle pulse wave velocity; IMT, intima-media thickness; MoCA, Montreal Cognitive Assessment.

scores are shown in table 2. There were significant associations of decreasing in all three cognitive assessment test scores for increasing plaque numbers, when variables were not adjusted in model 1. After adjusting for age, sex and education in model 2, the significant association remained. However, when further adjusting for other potential confounders in model 3, the significant associations were only shown in MoCA and verbal memory scores. Every 1 unit increase in carotid plaque number was associated with a 0.15-point decrease in MoCA scores (table 2).

The associations between IMT (max carotid IMT, mean carotid IMT) and cognitive assessment test scores are shown in table 3. IMT thickness was inversely associated with all three cognitive assessment test scores with significant associations in model 1. However, the associations

Table 2 Standardised regression coefficients of the associations between plaque numbers and cognitive test scores

| Plaque numbers | MoCA scores | | Verbal memory scores | | Semantic fluency scores | |
	β	p value	β	p value	β	p value
Model 1	−0.39	<0.001	−0.35	<0.001	−0.56	<0.001
Model 2	−0.15	0.006	−0.14	0.007	−0.21	0.029
Model 3	−0.15	0.006	−0.13	0.013	−0.17	0.083

Model 1: unadjusted.
Model 2: adjusted for age, sex and education.
Model 3: adjusted for as model 2 plus marital status, smoking, alcohol, physical activity status, hypertension, diabetes, stroke, angina pectoris, myocardial infarction, depression, anti-hypertensive medications, anti-diabetics medications, use of statins and APOE ε4.
APOE, apolipoprotein E; MoCA, Montreal Cognitive Assessment.

Table 3 Standardised regression coefficients of the associations between carotid IMT value and cognitive test scores

Carotid IMT	MoCA scores		Verbal memory scores		Semantic fluency scores	
	β	p value	β	p value	β	p value
Max carotid IMT						
Model 1	−2.57	<0.001	−2.66	<0.001	−5.01	<0.001
Model 2	0.97	0.149	0.41	0.526	−0.37	0.761
Model 3	1.06	0.126	0.44	0.506	0.07	0.957
Mean carotid IMT						
Model 1	−3.78	<0.001	−3.54	<0.001	−6.42	<0.001
Model 2	0.59	0.467	0.30	0.692	−0.56	0.704
Model 3	0.73	0.375	0.31	0.688	−0.15	0.919

Model 1: unadjusted.
Model 2: adjusted for age, sex and education.
Model 3: adjusted for as model 2 plus marital status, smoking, alcohol, physical activity status, hypertension, diabetes, stroke, angina pectoris, myocardial infarction, depression, anti-hypertensive medications, anti-diabetics medications, use of statins and APOE ε4.
APOE, apolipoprotein E; IMT, intima-media thickness.

were attenuated and lost significant, after adjusting for potential confounders in model 2 and model 3.

Association of arterial stiffness and cognitive function

As shown in table 4, ba-PWV predicted lower scores on all three cognitive assessment tests in model 1 with significant associations. After adjustment for age, sex and education in model 2, MoCA and semantic fluency scores remained significantly associated with ba-PWV. In model 3, adjustment of potential confounders, the associations of ba-PWV with cognitive assessment tests remained the same as in model 2. Every 1 unit increase in ba-PWV was associated with a 0.09-point decrease in MoCA scores (table 4).

Subgroup analyses of subclinical atherosclerosis and cognitive function

Subgroup analyses stratified by age, sex, the status of smoking and hypertension were conducted to evaluate the association between the three biomarkers of subclinical atherosclerosis and global cognitive function in MoCA. The results in figures 1 and 2 showed no significant interaction associations observed between subclinical atherosclerosis and global cognitive function in MoCA.

DISCUSSION

To the best of our knowledge, this was the first study in China to investigate the association between subclinical atherosclerosis and cognitive function among community-dwelling individuals. In the unadjusted model, significant associations were revealed between subclinical atherosclerosis markers (IMT, carotid plaque and ba-PWV) and cognitive function in MoCA scores, verbal memory scores and semantic fluency scores, respectively. The clinical implications provided by the significant associations between carotid plaques number, ba-PWV and MoCA score were noteworthy. The SD for the MoCA score was 3.37, while as indicated that a change of 0.5 SDs in a health-related indicator is clinically relevant.[25] Thus, according to the results from unadjusted models, participants with every 4–5 number increased in plaque

Table 4 Standardised regression coefficients of the associations between ba-PWV value and cognitive test scores

ba-PWV	MoCA scores		Verbal memory scores		Semantic fluency scores	
	β	p value	β	p value	β	p value
Mean ba-PWV						
Model 1	−0.23	<0.001	−0.16	<0.001	−0.33	<0.001
Model 2	−0.08	0.019	−0.03	0.420	−0.13	0.029
Model 3	−0.09	0.009	−0.04	0.193	−0.13	0.036

Model 1: unadjusted.
Model 2: adjusted for age, sex and education.
Model 3: adjusted for as model 2 plus marital status, smoking, alcohol, physical activity status, hypertension, diabetes, stroke, angina pectoris, myocardial infarction, depression, anti-hypertensive medications, anti-diabetics medications, use of statins and APOE ε4.
APOE, apolipoprotein E; ba-PWV, carotid plaque and brachial ankle pulse wave velocity; MoCA, Montreal Cognitive Assessment.
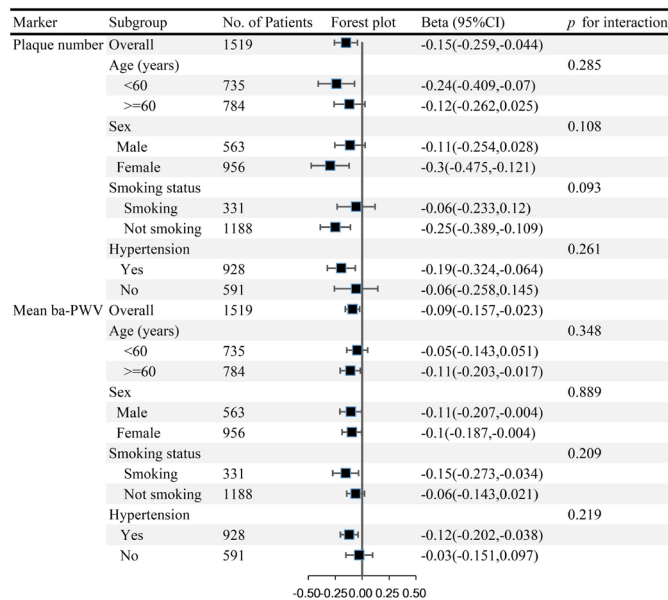
Marker	Subgroup	No. of Patients	Forest plot	Beta (95%CI)	p for interaction
Plaque number	Overall	1519		-0.15(-0.259,-0.044)	
	Age (years)				0.285
	<60	735		-0.24(-0.409,-0.07)	
	>=60	784		-0.12(-0.262,0.025)	
	Sex				0.108
	Male	563		-0.11(-0.254,0.028)	
	Female	956		-0.3(-0.475,-0.121)	
	Smoking status				0.093
	Smoking	331		-0.06(-0.233,0.12)	
	Not smoking	1188		-0.25(-0.389,-0.109)	
	Hypertension				0.261
	Yes	928		-0.19(-0.324,-0.064)	
	No	591		-0.06(-0.258,0.145)	
Mean ba-PWV	Overall	1519		-0.09(-0.157,-0.023)	
	Age (years)				0.348
	<60	735		-0.05(-0.143,0.051)	
	>=60	784		-0.11(-0.203,-0.017)	
	Sex				0.889
	Male	563		-0.11(-0.207,-0.004)	
	Female	956		-0.1(-0.187,-0.004)	
	Smoking status				0.209
	Smoking	331		-0.15(-0.273,-0.034)	
	Not smoking	1188		-0.06(-0.143,0.021)	
	Hypertension				0.219
	Yes	928		-0.12(-0.202,-0.038)	
	No	591		-0.03(-0.151,0.097)	

-0.50 -0.25 0.00 0.25 0.50

Figure 1 Associations between plaque number, mean ba-PWV and MoCA score, stratified by age, sex, the status of smoking and hypertension. ba-PWV, carotid plaque and brachial ankle pulse wave velocity; MoCA, Montreal Cognitive Assessment.

numbers or 7.32 m/s increased in ba-PWV would then suffer clinically significant in cognitive alterations. After adjusting for potential confounders, the results revealed negative associations of cognitive function with carotid plaque numbers and ba-PWV. Increased carotid plaque numbers predicted poor global cognitive functioning in MoCA, memory and semantic fluency, while increased
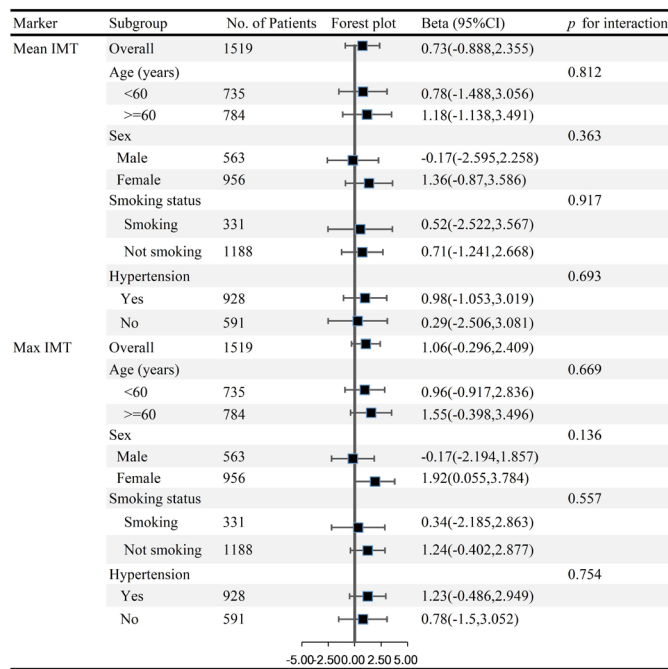

Marker	Subgroup	No. of Patients	Forest plot	Beta (95%CI)	p for interaction
Mean IMT	Overall	1519		0.73(-0.888,2.355)	
	Age (years)				0.812
	<60	735		0.78(-1.488,3.056)	
	>=60	784		1.18(-1.138,3.491)	
	Sex				0.363
	Male	563		-0.17(-2.595,2.258)	
	Female	956		1.36(-0.87,3.586)	
	Smoking status				0.917
	Smoking	331		0.52(-2.522,3.567)	
	Not smoking	1188		0.71(-1.241,2.668)	
	Hypertension				0.693
	Yes	928		0.98(-1.053,3.019)	
	No	591		0.29(-2.506,3.081)	
Max IMT	Overall	1519		1.06(-0.296,2.409)	
	Age (years)				0.669
	<60	735		0.96(-0.917,2.836)	
	>=60	784		1.55(-0.398,3.496)	
	Sex				0.136
	Male	563		-0.17(-2.194,1.857)	
	Female	956		1.92(0.055,3.784)	
	Smoking status				0.557
	Smoking	331		0.34(-2.185,2.863)	
	Not smoking	1188		1.24(-0.402,2.877)	
	Hypertension				0.754
	Yes	928		1.23(-0.486,2.949)	
	No	591		0.78(-1.5,3.052)	

-5.00 -2.50 0.00 2.50 5.00

Figure 2 Associations between mean IMT, max IMT and MoCA score, stratified by age, sex, the status of smoking and hypertension. IMT, intima-media thickness; MoCA, Montreal Cognitive Assessment.

ba-PWV predicted poor global cognitive functioning in MoCA and semantic fluency. The results were consistent in the subgroup analyses, no significant interaction associations were found between subclinical atherosclerosis and global cognitive function when subgroup analyses were performed to re-evaluate in different subgroups, according to age group (<60,≥60), sex, the status of smoking and hypertension.

Inconsistent associations of study results were found between subclinical atherosclerosis and cognitive function in previous studies. Our findings of the association between carotid plaques and cognitive function were in line with previously published results in the Rotterdam Study, which found a positive association of carotid plaques with dementia in cross-sectional analysis.[26] In the prospective studies, inconsistent associations were found between carotid plaques and cognitive decline, as some studies could not confirm the association,[11] while others found similar association after years of follow-up.[10] Progression of carotid plaques was also found to be correlated with increased cognitive impairment in a study of Alzheimer's disease subjects over 12 months.[27] Other studies had also indicated that total plaque burden was associated with cognitive impairment and maybe a sensitive tool in the prediction of atherosclerosis.[28 29] The association between the number of plaques with cognitive function was analysed in our study, which may to a certain extent reflect the total plaque burden in arteries, leading to cognitive impairment.

Increased risk of cognitive decline correlated with IMT thickening in the CCA and ICA has been found in previous population-based studies of elderly subjects.[30 31] Some studies found that carotid IMT was associated with dementia, especially with Alzheimer's disease. In the Rotterdam Study and Cardiovascular Health Study, similar results were found that the highest quartile of baseline carotid IMT in the CCA and ICA could predict Alzheimer's disease. Conversely, no association of IMT and cognitive function was found in our study as may due to measurements of IMT were conducted in sites free of carotid plaque, which the results were in line with The Three-City Study.[32] Positive associations of IMT and cognitive function were found in previous studies, when carotid plaques were included in the measurement of carotid IMT at carotid segments.[11 13] The severity condition of atherosclerosis may not be better assessed if measurement of carotid IMT was conducted in a plaque-free site. From the inconsistent findings of the association between carotid IMT and cognitive function, it is essential to focus on methods of conducting carotid IMT measurement.

Our cross-sectional study demonstrated that arterial stiffness as measured by ba-PWV was associated with the level of cognitive function in both global cognitive function and specific cognitive domain. The findings in our study of the association between arterial stiffness and cognitive impairment were consistent with prior cross-sectional studies.[33 34] Longitudinal studies had also found the associations between arterial stiffness and greater

cognitive decline after long-term follow-up.[35] Previous studies found significant association between higher PWV and greater cognitive decline in specific cognitive domains but did not provide evidence for an association for global cognitive function.[36 37] PWV is an integrative marker of arterial function and the gold standard for non-invasive estimation of arterial stiffness to the progressive decline in cognitive function.[38] Arterial stiffness has also been identified as an independent predictor of CVD and important predictor of cognitive decline.[39 40]

Several possible pathophysiogical mechanisms may contribute to the association between subclinical carotid atherosclerosis and cognitive function. Subclinical atherosclerosis may cause chronic cerebral hypoperfusion when narrowed of vessel lumen caused by increased arterial wall thickness, decreased of pressure in intracranial arterial perfusion and reduced of velocity in blood flow.[41] These effects may consequently to chronic ischaemic injuries and reduced energy supply, which may in turn cause brain dysfunction.[42] Cerebral emboli formed by unstable carotid plaques could manifests as silent strokes, leading to cognitive function impairment.[6 43] Brain infarcts and white matter hyperintensities that detected by MRI were found to be related with carotid plaques and associated with cognitive decline and incident dementia.[44 45]

Other possible pathophysiological explanations hypothesised that subclinical atheroscleroses were markers of pathogenic pathways. Vascular inflammation and endothelial dysfunction that included in these pathways may increase arterial stiffness possibly leading to formation and rupture of plaque and development of CVD.[46] The increased arterial stiffness process will further increase the risk of CVD development with mircovascular damage in large and small vessels as the cushioning effect of the large arteries and coronary blood flow was decreased and cardiac afterload was increased.[47] Pathogenic pathways were also associated with structural brain changes, such as atrophy in the brain leading to cognitive decline.[48 49] Thus, the relationship between subclinical carotid atherosclerosis and cognitive function by possible pathophysiological explanations should be considered.

The strengths of this investigation were the large sample size of community-based population, multiple assessed markers (IMT, carotid plaque and ba-PWV) of subclinical atherosclerosis and different cognitive assessment tests of both global cognitive function and specific cognitive domains. Limitations were the cross-sectional study design, which can only present an observational result rather than a temporal inference cause–effect conclusion from our study. Moreover, the ratio of men was much less in number in the recruited population. The composition of population was only as a single race of Chinese that included in our study, thus, our findings may not be fully applied to the common population. Data of atherosclerosis and cognitive function assessment in 35 participants were failed to obtain at baseline and there may be other unmeasured confounding factors, which could cause bias the association results

Our findings suggested that subclinical atherosclerosis markers of plaque numbers and ba-PWV were associated with cognitive function. Concerns should be made to focus on cognitive function in the population with severe atherosclerosis. Future prospective studies and longitudinal analyses are essential to verify the evidence from this cross-sectional study.

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