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RESEARCH ARTICLE

Association of arterial structure and function with incident cardiovascular diseases and cognitive decline

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Abstract

Introduction: We examined the associations of carotid intima-media thickness (CIMT), arterial stiffness index (ASI), and pulse pressure (PP) with cerebrovascular disease, cognitive function and decline, and incident cardiovascular diseases (CVD) and dementia in the UK Biobank cohort.

Methods: The study consisted of 42,711 participants (mean age 64.2 years) with brain magnetic resonance imaging (MRI), vascular assessments, and cognitive testing. Cerebrovascular disease markers included white matter hyperintensities (WMH) and brain volumes. CIMT, ASI, and PP were measured using carotid ultrasound, photoplethysmography, and blood pressure, respectively. General cognitive ability (*g*-score) was derived from various cognitive tests using principal components analysis (PCA).

Results: Elevated CIMT, ASI, and PP were associated with increased WMH volume (WMHV). Increased PP was independently associated with poorer numeric memory ($\beta = -0.028, p = 0.002$), fluid intelligence (IQ) ($\beta = -0.060, p < 0.001$), and *g*-score ($\beta = -0.028, p < 0.001$) in cross-sectional analysis, but not longitudinally. CIMT showed the strongest association with incident CVD and dementia.

Discussion: CIMT had the most robust associations with WMHV, incident CVD, and dementia, suggesting its utility as an alternative endpoint.

KEYWORDS
aortic stiffness, cardiovascular disease, carotid artery stiffness, cerebrovascular disease, cognitive impairment

Highlights

- Effects of arterial stiffness on cognition, dementia, and CVD.
- Structural vascular parameters included CIMT.
- Functional properties included ASI and PP.
- CIMT, ASI, and PP were positively associated with WMHV.
- CIMT had the greatest associations with incident CVD and dementia.

1 | INTRODUCTION

Arterial stiffness increases with age, and is commonly linked with cardiovascular diseases (CVD). Previous studies have reported associations between arterial structure and function and cognitive impairment and dementia.[1,2] Although the mechanisms that underlie this association are not fully understood, potential mediators include cerebrovascular disease (CeVD), chronic ischemia, and endothelial dysfunction.[2–4] Utilizing prospective noninvasive vascular assessment methods can deepen our comprehension of these pathophysiological mechanisms, as well as shed light on the progression of CVD, cognitive impairment, and dementia.

Arterial wall thickening from plaque build-up can narrow the lumen, leading to chronic hypoperfusion and subsequent brain ischemia. Carotid intima-media thickness (CIMT), a marker for subclinical atherosclerosis and CVD, is negatively associated with cognitive function, likely mediated by factors such as small vessel disease, endothelial dysfunction, silent ischemia, and reduced cerebral blood flow.[5,6] However, the association between CIMT and cognitive impairment remains controversial as longitudinal studies show a null effect of CIMT on cognitive decline.[5] Similarly, functional vascular properties, such as brachial pulse pressure (PP) and pulse-wave arterial stiffness index (ASI), are negatively associated with cognitive function.[7,8] The reduced cushioning effect of stiffened larger arteries may result in increased pulsatile energy and flow load on the cerebral vasculature, consequently damaging the cerebral microcirculation,[9] and appearing as CeVD specifically white matter hyperintensities (WMH) on brain magnetic resonance imaging (MRI) scans which is a recognized biomarker for cognitive impairment.[10] Nevertheless, the negative correlation between arterial stiffness and cognition in cross-sectional studies is relatively weak,[11] and the influence of stiffness on cognitive decline reported in longitudinal studies remains inconsistent.[12] Furthermore, the utilization of various methodologies and variables to assess arterial stiffness may contribute to discrepancies in the predictive value of arterial stiffness for cognitive impairment and dementia.

CIMT provides insight into the extent of atherosclerotic burden resulting from prolonged exposure to vascular risk factors, while arterial stiffening is closely linked to elevated blood pressure and the resultant hemodynamic pulsatile damage. Despite this, there are limited studies directly comparing the predictive capabilities of structural and functional arterial characteristics for incident CVD and cognitive impairment.[3] In this study, we aim to investigate the distinct effects of structural (CIMT) and functional (PP, ASI) vascular parameters on neuroimaging markers of cognitive impairment, cognitive function and decline, and incident CVD and dementia within the UK Biobank cohort. While functional abnormalities such as endothelial dysfunction and impaired vasodilation may occur earlier and contribute to the onset and progression of disease, structural changes such as atherosclerotic plaque formation typically signify advanced stages of vascular damage and are associated with more severe manifestations of CVD.[13] Therefore, we hypothesize that CIMT will exert a greater influence on neuroimaging markers of cognitive impairment, cognitive function and decline, incident CVD and dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: Arterial stiffness is associated with cardiovascular disease (CVD), cognitive impairment, and dementia. However, the predictive value of arterial markers such as carotid intima-media thickness (CIMT), arterial stiffness index (ASI), and pulse pressure (PP), for dementia and cognitive decline have varied.
2. **Interpretation**: Our findings demonstrated the associations between increased CIMT, ASI, and PP with increased white matter hyperintensities volume (WMHV), with CIMT showing the strongest association with incident CVD and dementia in the UK Biobank Cohort.
3. **Future directions**: Further longitudinal studies are warranted to explore the causal role of CIMT and other vascular measures in dementia. Future research can also examine the underlying mechanisms linking vascular changes to cerebrovascular disease and neurodegeneration.

2 | METHODS

2.1 | Study population

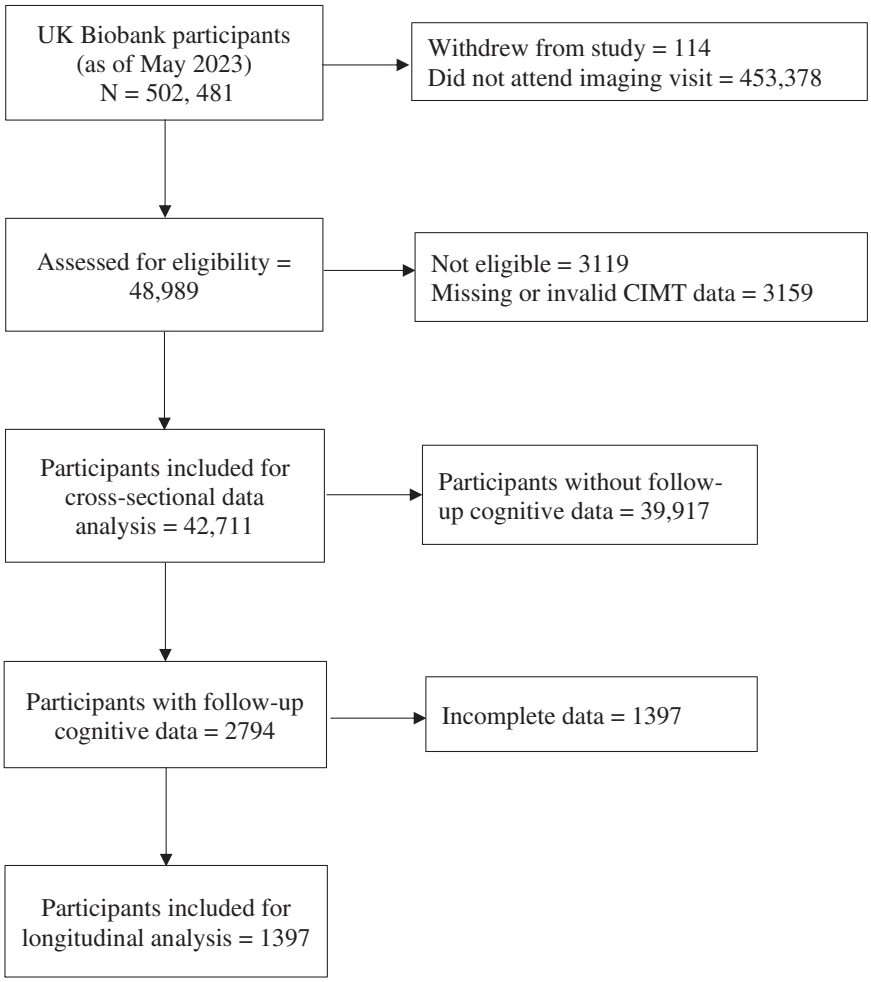
The UK Biobank, approved by the National Health Service National Research Ethics Service (June 17 2011, Ref: 11/NW/0382) comprises over 500,000 UK residents who provided informed consent. This study focused on participants who underwent vascular assessments during the imaging visit assessment in 2014. Data on social demographics, arterial stiffness, vascular risk factors, incident CVD, neuroimaging, and cognitive function were obtained. Figure 1 shows the study population flowchart. After exclusions based on missing or invalid CIMT scans, neuropsychiatric disorders, or substance abuse, our final sample for cross-sectional analysis included 42,711 participants. Detailed information on the exclusion criteria and list of variables included in this study are shown in Table S1 and Table S2 respectively. For longitudinal analysis, 2794 participants with follow-up cognitive data, and after excluding those with incomplete data, 1397 participants were included for analysis. The study was conducted in accordance with the Declaration of Helsinki, and the UK Biobank has obtained ethical approval from the Northwest Multi-Centre Research Ethics Committee.

2.2 | Vascular assessment

2.2.1 | CIMT

CIMT ultrasound measurements were acquired using a CardioHealth Station with a 5–13 MHz linear array transducer. CIMT measurements

FIGURE 1 Study flow of participants



were acquired at two predefined angles for each carotid artery: right 150°, right 120°, left 210°, and left 240°, and then averaged. Detailed information on the CIMT imaging protocol and quality assurance procedures is described elsewhere.[14]

2.2.2 | ASI

ASI was assessed using the PulseTrace PCA2, a finger photoplethysmographic device which records a 10–15 s pulse waveform on the participants' index finger. The pulse waveform consists of systolic peak and second diastolic peak. The transit time (peak-to-peak time; PPT) between these two peaks is related to the time it takes for the pulse wave to travel through the peripheral arterial tree. The participant's height is divided by the PPT to obtain the ASI, expressed in mm/s.

2.2.3 | PP

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automated blood pressure device (Omron 705 IT) twice, and the respective averages of the two readings were computed. The peripheral PP was calculated by subtracting the DBP from the SBP.

2.3 | Neuroimaging

Brain MRI scans were performed on 3T Siemens 32-channel RF receive head coil. Detailed information on the acquisition protocols and image processing pipeline was documented elsewhere.[15] The neuroimaging markers included in this study were deep WMH volume (DWHMV), periventricular WMH volume (PWMHV), normal appearing white matter (NAWM) volume, total brain volume, and total hippocampal volume. The NAWM volume was estimated by calculating the difference between total white matter volume adjusted for head size and WMH. All neuroimaging parameters were log-transformed.

2.4 | Cognition

Cognitive data from the imaging visit in 2014 and the first repeat imaging visit in 2019 onward were extracted for analysis, with average follow-up of 27 months. Cognitive function was evaluated using a general cognitive ability score (*g*-score), derived from a principal components analysis (PCA) of five cognitive tests: Pairs Memory (standardized and reversed), Reaction Time (standardized and reversed), Prospective Memory Fluid Intelligence (IQ), and Numeric Memory (Table S3). Psychometric properties, reliability, and validity of the UK

Biobank cognitive tests have been previously discussed.[16] Scree-plot eigen values, and test loadings indicated one component (Figure S1, Table S4). This component accounted for 33% of the total variance in the five cognitive tests. Scores on this unrotated principal component were saved and used as a measure of general cognitive ability (i.e., *g*-score). Higher cognitive scores indicated better cognitive ability.

2.5 | Incident CVD and dementia

Incident cases of myocardial infarction, ischemic heart disease, CeVD, cardiac arrest, heart failure, and all-cause dementia were treated as outcomes. As CIMT assessments were conducted during the imaging visit assessment in 2014, the subsequent occurrence of these diseases was identified as incident cases, which were ascertained from the primary care and inpatient hospital records, or self-reported medical condition (Table S2).

2.6 | Covariates

Participants' social demographics and lifestyle factors including age, sex, ethnicity (White vs. non-White), education (with or without a university/college education), smoking status, and frequent alcohol use (at least 3–4 times a week or daily) were extracted. Participants who had a medical history of hypertension, diabetes, atherosclerosis, and CVD were ascertained from International Classification of Diseases (ICD) codes, primary care and inpatient hospital records, self-reported medical conditions, or medication intake for cholesterol, hypertension, or diabetes. Detailed information on the list of covariates used in this study are reported in Table S2.

2.7 | Statistical analysis

Statistical analyses were performed using RStudio 4.0.3 (Boston, MA). The characteristics of the participants were summarized using means and standard deviations (SDs) for continuous variables, and numbers and percentages for categorical variables. Vascular parameters included CIMT, ASI, and PP, which were standardized into z-scores. The neuroimaging outcomes included DWMHV, PWMHV, NAWM volume, total brain volume, and total hippocampal volume. The cognitive outcomes were Pairs Memory, Reaction Time, Prospective Memory, Fluid IQ, and Numeric Memory. Incident cases of myocardial infarction, ischemic heart disease, CeVD, cardiac arrest, heart failure, and all-cause dementia were treated as outcomes.

Multivariable linear regression was performed to determine the associations of arterial stiffness with neuroimaging outcomes and cognition. The association between arterial stiffness and cognitive decline was analyzed using generalized estimating equations (GEE) with independent correlation structure to account for confounding and the correlation between repeated measurements taken during follow-up. Firth logistic regression analyses with 95% CIs were performed to examine the relationship between arterial stiffness and incident diseases. Participants with the prevalent disease were excluded from analyses. For all regression analyses, unadjusted models were reported as Model 1. Social demographics such as age, sex, ethnicity, and education were adjusted for in Model 2. Finally, hypertension, diabetes, hyperlipidemia, frequent alcohol use, and current smoking status were further adjusted for in Model 3. Complete case analysis was employed for all statistical analyses. The significance level of $p < 0.05$ was used for all analyses, with Bonferroni-corrected significance cutoffs at $p < 0.01$ for associations between arterial stiffness and cognition across five cognitive domains.

3 | RESULTS

The characteristics of the study participants in our analytical sample of 42,711 was presented in Table 1. The participants' age ranged from 44 to 82, with a median age of 65 (IQR = 12) years. The mean age was 64.2 (SD 7.73) years. 52% of the participants were female. Most of the participants were White individuals (97%) and had a university/college education (49%). A high proportion of participants do not have vascular risk factors such as hypertension, diabetes, atherosclerosis, as well as CVD, and CeVD. The majority of participants were nonsmokers (96%), and more than half reported that they were not frequent alcohol drinkers (54%). Vascular measures, risk factors and diseases, neuroimaging markers, and cognitive performance are further detailed in Table 1. Over an average follow-up of 27 months, the number of incident cases were as follows: 419 cases of myocardial infarction, 1135 cases of ischemic heart disease, 449 cases of CeVD, 76 cases of cardiac arrest, 458 cases of heart failure, and 31 cases of all-cause dementia

Table 2 presented the associations between vascular measurement and neuroimaging markers of cognitive impairment. Increased CIMT was associated with increased DWMHV ($ß = 0.059$, $p < 0.001$), PWMHV ($ß = 0.048$, $p < 0.001$), and hippocampal volume ($ß = 0.017$, $p = 0.002$), independent of age, sex, ethnicity, education, and vascular risk factors (Model 3). Similarly, ASI was independently and positively associated with increased DWMHV ($ß = 0.026$, $p = 0.005$), and PWMHV ($ß = 0.023$, $p < 0.001$) in Model 3. Increased PP was independently associated with increased DWMHV ($ß = 0.079$, $p < 0.001$), PWMHV ($ß = 0.051$, $p < 0.001$), brain volume ($ß = 0.018$, $p = 0.001$), and decreased hippocampal volume ($ß = -0.018$, $p = 0.003$) (Model 3).

The associations between vascular measures and cognition are shown in Table 3. In unadjusted Model 1, increased CIMT was associated with poorer performances on all cognitive tests and *g*-score (all $p < 0.001$). After adjusting for all covariates in Model 3, CIMT was positively associated with performance on the Pairs-B task ($ß = 0.044$, $p = 0.009$), independent of age, sex, ethnicity, education, and vascular risk factors. Although ASI was negatively associated with performance on Pairs-B task ($ß = -0.044$, $p = 0.004$) in univariate analyses (Model 1), ASI was not associated with performance on all cognitive tests after adjusting for covariates (Models 2 and 3). Additionally, PP was associated with performances on all cognitive tests in univariate Model 1, and after adjusting for all covariates, PP remained negatively

TABLE 1 Characteristics of study population

Parameter	Overall (*N* = 42,711)
Age, mean (SD)	64.2 (7.73)
Sex, *n* (%)	
Female	22207 (52.0%)
Male	20504 (48.0%)
Ethnicity, *n* (%)	
Non-White	1293 (3.0%)
White	41307 (96.7%)
Education, *n* (%)	
With a university/college education	20796 (48.69%)
Vascular risk factors	
Hypertension, *n* (%)	14388 (33.7%)
Diabetes, *n* (%)	2157 (5.1%)
Atherosclerosis, *n* (%)	104 (0.2%)
Frequent alcohol drinker, *n* (%)	19336 (45.3%)
Current smoker, *n* (%)	1360 (3.2%)
CIMT, median (IQR)	6.50 (6.39, 6.63)
ASI, median (IQR)	2.35 (2.133, 2.52)
Blood pressure, mm Hg	
Systolic pressure	139 (18.8)
Diastolic pressure	78.70 (10.06)
PP	60.31 (14.73)
Neuroimaging markers, median (IQR), mm^3	
DWMHV	5.96 (5.17, 6.82)
PWMHV	7.78 (7.14, 8.47)
Total brain volume	1493080 (1441655, 1543410)
NAWM	695243 (667166, 723791)
Total hippocampal volume	7659 (7095, 8224)
Cognition, mean (SD)	
General cognitive ability	0.02 (−0.49, 0.50)
Reaction time	6.36 (6.26, 6.48)
Numeric memory	7 (6, 8)
Fluid IQ	7 (5, 8)
Prospective memory, correct on first attempt, *n* (%)	35823 (78%)
Pairs matching task	3 (2, 5)

Abbreviations: CIMT, carotid intima-media thickness; DWMHV, deep white matter hyperintensities volume; IQ, intelligence.; IQR, interquartile range; n, number; NAWM, normal appearing white matter; PP, pulse pressure; PWMHV, periventricular white matter hyperintensities volume; SD, standard deviation.

associated with performances on Numeric Memory ($\beta = -0.028$, $p = 0.002$), Fluid IQ ($\beta = -0.060$, $p < 0.001$), and *g*-score ($\beta = -0.018$, $p < 0.001$), independent of age, sex, ethnicity, education, and vascular risk factors (Model 3). However, in longitudinal analyses, CIMT, ASI, and PP were not associated with cognitive decline (Table S5). Table 4 presented the associations of vascular measures with incident CVD and dementia.

Increased CIMT was associated with increased risk of incident myocardial infarction (OR 1.126, 95% CI: 1.018,1.242), ischemic heart disease (OR 1.169, 95% CI: 1.099,1.241), CeVD (OR 1.167, 95% CI: 1.060,1.285), heart failure (OR 1.150, 95% CI: 1.050,1.260), and all-cause dementia (OR 1.590, 95% CI: 1.080,2.220), independent of age, sex, ethnicity, education, and vascular risk factors (Model 3). ASI was not independently associated with increased risk of incident CVD and dementia. On the other hand, increased PP was associated with increased risk of myocardial infarction (OR 1.365, 95% CI: 1.225,1.519) and ischemic heart disease (OR 1.110, 95% CI: 1.036,1.188).

4 | DISCUSSION

The present study examined the differential effects of structural (CIMT) and functional (ASI and PP) vessel wall properties on neuroimaging markers of cognitive impairment, cognitive function and decline, as well as incident CVD and dementia in the UK Biobank cohort. All vascular measures were found to be independently associated with increased WMHV. Although PP was independently associated with poorer cognitive function cross-sectionally, these associations did not persist for cognitive decline. Moreover, associations with incident CVD were more robust for CIMT compared to PP, with no significant associations observed for ASI. Interestingly, CIMT emerged as the sole vascular measure associated with incident dementia.

In this study, CIMT, ASI, and PP were independently associated with increased WMHV in the deep white matter and periventricular areas of the brain, consistent with similar findings in other population-based cohorts.[17,18] Arterial wall thickening may result in vessel lumen narrowing, reducing cerebral blood flow and leading to chronic ischemia.[5] Increased arterial stiffness may elevate systolic blood pressure, widening the PP as the left ventricle contracts against stiffer and less compliant arteries, thereby facilitating earlier wave reflection. In the brain, the heightened pulsatility resulting from arterial stiffening can damage the cerebral microcirculation, resulting in chronic ischemia manifested as WMH.[19]

The relationship between vascular pathology and neurodegenerative outcomes are well-established in both hospital- and community-based cohorts.[20–22] Our findings align with this evidence, demonstrating an independent negative association between PP and hippocampal volume. Elevated PP, as a marker of arterial stiffness, has been linked

TABLE 2 Association between vascular measures and neuroimaging markers (cross-sectional)

Parameter	DWMHV	PWMHV	Total brain volume	NAWM	Total hippocampal volume
Estimate, *p*-value					
CIMT					
Model 1[a]	**0.265, $p < 0.001$***	**0.275, $p < 0.001$***	**−0.266, $p < 0.001$***	**−0.146, $p < 0.001$***	**−0.077, $p < 0.001$***
Model 2[b]	**0.074, $p < 0.001$***	**0.059, $p < 0.001$***	**−0.010, $p = 0.038$***	−0.005, $p = 0.341$	**0.014, $p = 0.010$***
Model 3[c]	**0.059, $p < 0.001$***	**0.048, $p < 0.001$***	−0.007, $p = 0.166$	−0.005, $p = 0.396$	**0.017, $p = 0.002$***
ASI					
Model 1	**0.074, $p < 0.001$***	**0.083, $p < 0.001$***	**−0.036, $p = 0.024$***	−0.009, $p = 0.202$	**0.013, $p = 0.017$***
Model 2	**0.035, $p < 0.001$***	**0.031, $p < 0.001$***	−0.002, $p = 0.951$	0.008, $p = 0.203$	0.005, $p = 0.317$
Model 3	**0.026, $p = 0.005$***	**0.023, $p < 0.001$***	0.002, $p = 0.669$	0.010, $p = 0.138$	0.007, $p = 0.162$
PP					
Model 1	**0.313, $p < 0.001$***	**0.296, $p < 0.001$***	**−0.252, $p < 0.001$***	**−0.163, $p < 0.001$***	**−0.141, $p < 0.001$***
Model 2	**0.111, $p < 0.001$***	**0.077, $p < 0.001$***	0.009, $p = 0.068$	−0.000, $p = 0.967$	**−0.023, $p < 0.001$***
Model 3	**0.079, $p < 0.001$***	**0.051, $p < 0.001$***	**0.018, $p = 0.001$***	−0.001, $p = 0.805$	**−0.018, $p = 0.003$***

Abbreviations: ASI, arterial stiffness index; CIMT, carotid intima-media thickness; DWMHV, deep white matter hyperintensities volume; NAWM, normal appearing white matter; PP, pulse pressure.; PWMHV, periventricular white matter hyperintensities volume.
[a]Model 1 showed unadjusted models.
[b]Model 2 adjusted for age, sex, ethnicity, and education.
[c]Model 3 adjusted for Model 2, hypertension, diabetes, hyperlipidemia, frequent alcohol use, current smoking.
*Levels of significance, $p < 0.05$.

TABLE 3 Associations between vascular measures and cognition (cross-sectional).

Parameter	Reaction time	Numeric memory	Fluid IQ	Prospective memory	Pairs matching task	*g*-Score
Estimate, *p*-value						
CIMT						
Model 1[a]	**−0.108, $p < 0.001$****	**−0.066, $p < 0.001$****	**−0.068, $p < 0.001$****	**−0.038, $p < 0.001$****	**−0.164, $p < 0.001$****	**−0.060, $p < 0.001$***
Model 2[b]	−0.002, $p = 0.669$	−0.006, $p = 0.493$	0.006, $p = 0.614$	−0.004, $p = 0.147$	**0.045, $p = 0.007$****	−0.001, $p = 0.943$
Model 3[c]	−0.005, $p = 0.382$	−0.001, $p = 0.893$	0.009, $p = 0.411$	−0.004, $p = 0.214$	**0.044, $p = 0.009$****	0.003, $p = 0.584$
ASI						
Model 1	0.005, $p = 0.302$	0.001, $p = 0.916$	0.004, $p = 0.699$	−0.004, $p = 0.118$	**−0.044, $p = 0.004$****	−0.004, $p = 0.373$
Model 2	−0.000, $p = 0.942$	0.003, $p = 0.772$	0.010, $p = 0.312$	−0.001, $p = 0.889$	−0.026, $p = 0.085$	0.002, $p = 0.612$
Model 3	−0.000, $p = 0.882$	0.007, $p = 0.470$	0.012, $p = 0.226$	−0.000, $p = 0.962$	−0.026, $p = 0.082$	0.004, $p = 0.360$
PP						
Model 1	**0.133, $p < 0.001$****	**−0.116, $p < 0.001$****	**−0.150, $p < 0.001$****	**−0.039, $p < 0.001$****	**−0.182, $p < 0.001$****	**−0.098, $p < 0.001$***
Model 2	0.006, $p = 0.263$	**−0.033, $p < 0.001$****	**−0.063, $p < 0.001$****	−0.001, $p = 0.715$	0.034, $p = 0.058$	**−0.021, $p < 0.001$***
Model 3	0.003, $p = 0.577$	**−0.028, $p = 0.002$****	**−0.060, $p < 0.001$****	−0.001, $p = 0.838$	0.036, $p = 0.046$	**−0.018, $p < 0.001$***

Abbreviations: ASI, arterial stiffness index; CIMT, carotid intima-media thickness; IQ, intelligence; PP, pulse pressure.
[a]Model 1 showed unadjusted models.
[b]Model 2 adjusted for age, sex, ethnicity, and education.
[c]Model 3 adjusted for Model 2, hypertension, diabetes, hyperlipidemia, frequent alcohol use, current smoking.
*Levels of significance, $p < 0.05$.
**Bonferroni-corrected *p*-value (0.05/5 = 0.01), $p < 0.01$.

to impaired endothelial function and increased blood-brain barrier permeability, leading to the extravasation of plasma proteins and accumulation of ß-amyloid peptides, which result in neuronal dysfunction and neurodegenerative outcomes.[23] These mechanisms likely explain the negative associations observed between PP and hippocampal volume. Conversely, it is unexpected to observe a positive association between CIMT and hippocampal volume. While the underlying mechanism for this finding remain unclear, we hypothesize that this may reflect an adaptive vascular remodeling process aimed to support cerebral perfusion and, in turn, potentially preserving hippocampal

TABLE 4 Associations between vascular measures and incident cardiovascular disease and dementia over a 2-year follow-up

Parameter	Myocardial infarction	Ischemic heart disease	Cerebrovascular disease	Cardiac arrest	Heart failure	All-cause dementia
OR (95% CI)						
CIMT						
Model 1[a]	**1.419 (1.303–1.541)***	**1.444 (1.369–1.522)***	**1.419 (1.303–1.541)***	**1.582 (1.305–1.894)***	**1.555 (1.435–1.682)***	**1.816 (1.361–2.355)***
Model 2[b]	**1.170 (1.059–1.289)***	**1.205 (1.134–1.279)***	**1.224 (1.110–1.346)***	1.200 (0.962–1.480)	**1.190 (1.080–1.300)***	**1.620 (1.100–2.270)***
Model 3[c]	**1.126 (1.018–1.242)***	**1.169 (1.099–1.241)***	**1.167 (1.060–1.285)***	1.170 (0.936–1.452)	**1.150 (1.050–1.260)***	**1.590 (1.080–2.220)***
ASI						
Model 1	**1.036 (1.012–1.069)***	**1.036 (1.012–1.069)***	**1.032 (0.996–1.057)***	1.043 (0.993–1.069)	**1.036 (1.007–1.063)***	**1.050 (1.001–1.076)***
Model 2	1.029 (0.969–1.053)	1.029 (1.002–1.058)	1.032 (0.986–1.057)	1.040 (0.882–1.070)	1.040 (1.000–1.060)	1.050 (1.000–1.080)
Model 3	1.029 (0.946–1.054)	1.024 (0.995–1.050)	1.029 (0.972–1.054)	1.040 (0.791–1.070)	1.030 (0.993–1.050)	1.060 (1.000–1.090)
PP						
Model 1	**1.590 (1.452–1.738)***	**1.394 (1.315–1.476)***	**1.361 (1.241–1.489)***	**1.359 (1.076–1.691)***	**1.361 (1.242–1.493)***	1.357 (0.942–1.889)
Model 2	**1.482 (1.334–1.643)***	**1.215 (1.136–1.299)***	**1.151 (1.040–1.276)***	1.050 (0.796–1.360)	1.030 (0.927–1.145)	1.070 (0.670–1.640)
Model 3	**1.365 (1.225–1.519)***	**1.110 (1.036–1.188)***	1.028 (0.923–1.143)	0.993 (0.753–1.295)	0.943 (0.847–1.050)	1.030 (0.639–1.590)

Abbreviations: ASI, arterial stiffness index; CIMT, carotid intima-media thickness; OR, odds ratio; CI, confidence interval; PP, pulse pressure.
[a]Model 1 showed unadjusted models.
[b]Model 2 adjusted for age, se@#@x, and ethnicity. Education was further adjusted for dementia outcomes.
[c]Model 3 adjusted for Model 2, hypertension, diabetes, hyperlipidemia, frequent alcohol use, current smoking.
*Levels of significance, $p < 0.05$.

volume.[24–26] However, this hypothesized compensatory effect may diminish over time as CIMT progresses and atherosclerosis advances, eventually leading to reduced cerebral perfusion and hippocampal atrophy.[27,28] Given the current study's relatively short follow-up duration of 2 years, we may not be able to observe the negative associations between CIMT and hippocampal volume beyond this compensatory phase. Further investigations are required to explore the validity of this potential compensatory effect.

Nonetheless, the ability of PP to accurately track hippocampal volume could be attributed to its recognized status as a clinically-accessible surrogate of arterial stiffening, in contrast to CIMT and ASI, which often detect subclinical vasculopathy. While both PP and ASI serve as stiffness markers, they exhibit weak correlation and may indicate distinct properties of the vasculature.[29] In older individuals, evaluating ASI can be difficult as the systolic and diastolic peaks on the arterial waveform contour converge with the rapid propagation of the reflected wave.[30] A previous study has indicated that ASI might be less precise in measuring vascular stiffness when compared to a reference standard.[31]

Regarding cognition, PP exhibited stronger and broader associations with cognitive performance compared to CIMT and ASI. Increased PP was significantly linked to poorer performance in numeric memory, fluid IQ, and global cognitive function (*g*-score), irrespective of social demographics and vascular risk factors. These results support the hypothesis that heightened pressure pulsatility can negatively impact cognition, likely through mechanisms such as small vessel disease (e.g., WMH), endothelial dysfunction, or cerebral hypoperfusion.[2,32] Additionally, the site specificity of the CIMT measurement could lead to contrasting associations with cognition—the Framingham Offspring Study indicated that internal CIMT, but not common CIMT, was linked to poorer cognition.[33]

Despite the clear cross-sectional associations between PP and cognition, these associations were not evident in our longitudinal analysis for all measures of arterial stiffness and cognitive decline. The lack of findings with cognitive decline may be attributed to the relatively short average follow-up time (approximately 2 years), which may not have allowed sufficient time to detect significant changes in cognitive decline.

We observed that CIMT exhibited stronger and more widespread associations with CVD and dementia compared to ASI and PP. These associations remained significant even after accounting for conventional vascular risk factors. Although CIMT was linked to an increased risk of dementia, it did not show associations with cognitive function or decline. This disparity could be attributed to the use of different

cognitive tests for diagnosing dementia, such as the Mini-Mental State Examination (MMSE) or detailed neuropsychological batteries, unlike the brief, customized, and unsupervised digital assessments in the UK Biobank.

Studies have previously shown that CIMT is linked to a higher risk of CVD events.[34,35] Incorporating CIMT into risk assessment models such as the Framingham Risk Score modestly improves predicting the 10-year risk of myocardial infarction or stroke.[36] Additionally, interventions targeting CIMT progression are associated with a reduction in CVD risk,[37] thus supporting CIMT as a surrogate marker for medical intervention. Findings on the associations between CIMT and dementia are varied. The Three-City Study have shown that the presence of carotid plaques predicts incident vascular dementia over a defined period,[38] whereas the Rotterdam Study reported an initial association between higher CIMT quintiles and increased dementia incidence, which diminishes over time, potentially due to the strong link between atherosclerosis and mortality.[39] The ARIC Study demonstrated a modestly elevated risk of dementia in individuals with the highest CIMT quintile. Notably, the association between carotid plaque and incident dementia has shown inconsistency across studies.[40]

The strength of the current study was the use of a large community-dwelling cohort from the United Kingdom. The UK Biobank study uses a standardized protocol for data collection across all the study sites and has a rigorous procedure in following up with participants' health information by accessing patient records and national health statistics. However, as the study population was predominantly White individuals, findings may not be generalized to other population groups. The duration of follow-up to assess cognitive decline was relatively short, precluding the detection of significance changes in cognitive function. Technical limitations related to the use of fingertip photoplethysmography to assess arterial stiffness, as aforementioned, could have affected the results.

5 | CONCLUSION

This study examined the differential effects of structural and functional arterial properties on neuroimaging markers of cognitive impairment, cognitive function and decline, as well as incident CVD and dementia. We found that all measures of arterial stiffness were associated with WMH. PP was associated with cognitive function but not decline. Although CIMT was not associated with cognition, it was associated with an increased risk of dementia. This discrepancy in findings could be attributed to differences in the cognitive tests used in the UK Biobank compared with conventional tests for diagnosing dementia. CIMT had the most robust associations with incident CVD and dementia, independent of vascular risk factors, thus indicating that CIMT can be used as an alternative endpoint for cardiovascular events in observational and intervention studies. Future studies with a longer follow-up duration may address discrepancies in our findings for the associations between arterial stiffness and cognitive decline.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

The data of the present secondary data analysis study was obtained from the UK Biobank Study, which was approved by the National Health Research Ethics Service (June 17 2011, Ref: 11/NW/0382). All human subjects provided informed consent to take part in the UK Biobank Study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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