ORIGINAL RESEARCH

Central Arterial Stiffness Is Associated With Structural Brain Damage and Poorer Cognitive Performance: The ARIC Study

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***Background*—**Central arterial stiffening and increased pulsatility, with consequent cerebral hypoperfusion, may result in structural brain damage and cognitive impairment.

***Methods and Results*—**We analyzed a cross-sectional sample of ARIC-NCS (Atherosclerosis Risk in Communities–Neurocognitive Study) participants (aged 67–90 years, 60% women) with measures of cognition (n=3703) and brain magnetic resonance imaging (n=1255). Central arterial hemodynamics were assessed as carotid-femoral pulse wave velocity and pressure pulsatility (central pulse pressure). We derived factor scores for cognitive domains. Brain magnetic resonance imaging using 3-Tesla scanners quantified lacunar infarcts; cerebral microbleeds; and volumes of white matter hyperintensities, total brain, and the Alzheimer disease signature region. We used logistic regression, adjusted for demographics, apolipoprotein E ε4, heart rate, mean arterial pressure, and select cardiovascular risk factors, to estimate the odds of lacunar infarcts or cerebral microbleeds. Linear regression, additionally adjusted for intracranial volume, estimated the difference in log-transformed volumes of white matter hyperintensities, total brain, and the Alzheimer disease signature region. We estimated the mean difference in cognitive factor scores across quartiles of carotid-femoral pulse wave velocity or central pulse pressure using linear regression. Compared with participants in the lowest carotid-femoral pulse wave velocity quartile, participants in the highest quartile of carotid-femoral pulse wave velocity had a greater burden of white matter hyperintensities (P=0.007 for trend), smaller total brain volumes (−18.30 cm^3; 95% CI, −27.54 to −9.07 cm^3), and smaller Alzheimer disease signature region volumes (−1.48 cm^3; 95% CI, −2.27 to −0.68 cm^3). These participants also had lower scores in executive function/processing speed (β=−0.04 z score; 95% CI, −0.07 to −0.01 z score) and general cognition (β=−0.09 z score; 95% CI, −0.15 to −0.03 z score). Similar results were observed for central pulse pressure.

***Conclusions*—**Central arterial hemodynamics were associated with structural brain damage and poorer cognitive performance among older adults. **(*J Am Heart Assoc*. 2019;8:e011045. DOI: 10.1161/JAHA.118.011045)**

Key Words: arterial stiffness • cognition • magnetic resonance imaging • pulse wave velocity

Aortic stiffening and loss of arterial elasticity is common among older adults because of fragmentation of the vessel wall elastin and an increase in the synthesis and cross-linking of vascular collagens.[1] Several risk factors are associated with accelerated vascular aging, including elevated blood pressure,[2] elevated blood glucose levels,[3] and adiposity.[4] Central arterial stiffening results in increased pulsatile stress forward into the cerebrovascular microcirculation,[5] which can increase susceptibility to microvascular damage and remodeling in the brain, therefore resulting in impaired cognition.[6] Central arterial stiffening is therefore a plausible intermediate of previously observed associations of hypertension with cognitive decline and dementia in older adults.

A recent meta-analysis concluded that increased arterial stiffness is associated with markers of cerebral small-vessel disease, cognitive decline, and cognitive impairment.[5,6]

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Clinical Perspective

What Is New?

- Higher levels of aortic stiffness and pressure pulsatility are associated with a greater burden of structural brain damage and lower brain volumes in older adults.
- Among older adults, aortic stiffness and pressure pulsatility are associated with lower cognitive performance, particularly in the domain of executive functioning/processing speed.

What Are the Clinical Implications?

- Central aortic stiffness and pressure pulsatility warrant consideration as potential targets for reduction of adverse cognitive outcomes among older adults.
- Further research on arterial destiffening interventions (pharmacologic [eg, blood pressure–lowering agents] and nonpharmacologic [eg, physical activity]) is needed to assess their potential in reducing cognitive morbidity.

However, the body of work reviewed has several methodological limitations. For example, many studies used different equipment and/or methods to measure arterial stiffness, with unknown implications. Brachial-ankle pulse wave velocity was most often used.[7] Although correlated with central (aortic) stiffness, brachial-ankle pulse wave velocity is a peripheral measure of arterial stiffness less likely to have a measurable impact on cerebral microvasculature. The Mini-Mental State Examination, a screening test for dementia not sensitive to early cognitive deficits, was the most frequently cited measure of cognition. Last, lack of adjustment for clinically relevant covariates, such as apolipoprotein E ε4 genotype, limits several of the reports.

To address these limitations, we tested the hypothesis that higher central arterial stiffness, as measured by carotid-femoral pulse wave velocity (cfPWV), is associated with markers of structural brain damage detected by brain magnetic resonance imaging (MRI) and lower cognitive function. Secondary to cfPWV, we also explored the role of pressure pulsatility, measured as central pulse pressure (cPP), on these outcomes. The ARIC-NCS (Atherosclerosis Risk in Communities–Neurocognitive Study) provides an exceptional opportunity to examine these associations in a well-characterized, biracial cohort with assessments of multidimensional cognition, extensive brain MRI measures, and the gold standard measure of cfPWV.

Methods

Availability of data and detailed policies for accessing ARIC Study data can be found online.[8] The ARIC Study data are made available through the National Heart, Lung, and Blood Institute BioLINCC repository.[9]

Study Population and Design

The ARIC Study is a community-based prospective cohort study of 15 792 participants, aged 45 to 64 years at baseline (1987–1989), from 4 US communities (Washington County, Maryland; Forsyth County, North Carolina; Minneapolis, Minnesota; and Jackson, Mississippi).[10] The baseline visit of the ARIC Study was followed by 3 triennial visits: visit 2 (1990–1992, n=14 348), visit 3 (1993–1995, n=12 887), and visit 4 (1996–1998, n=11 656). A fifth examination was conducted 15 years later in 2011 to 2013 (n=6538). The current study is based on the fifth examination of the ARIC Study, which included ARIC-NCS. At this visit, participants completed a comprehensive neuropsychological battery and had arterial stiffness/pressure pulsatility measured. A subsample of the visit 5/ARIC-NCS participants (n=1978) underwent a brain MRI scan. As previously described,[11] participants were asked to undergo an MRI scan if they previously participated in the ARIC brain MRI ancillary study (2004–2006)[12] or had evidence of cognitive impairment at visit 5 (indicated as low cognitive test scores and longitudinal decline on administered tests). An additional random sample of the remaining participants was also asked to participate.

Among the 6538 participants who attended the fifth examination, we excluded participants with missing information on arterial stiffness/pressure pulsatility and cognitive function; those with body mass index ≥40 kg/m^2 or missing body mass index; those with major arrhythmias on ECG (Minnesota codes 8-1-3, 8-3-1, and 8-3-2: ≥10% atrial and ventricular premature beats, atrial fibrillation, or flutter); those with peripheral vascular disease, peripheral revascularization, aortic aneurysms, abdominal aorta ≥5 cm, history or presence of aortic graft or aortic stenosis, other major cardiovascular disease (history of coronary artery disease, heart failure, or stroke), and missing covariates. Because of small numbers, we additionally excluded nonblack/nonwhite participants and blacks from Minneapolis and Washington County. After these exclusions, our analytic sample for the cognitive function analyses included 3703 older adults. For the analyses of brain MRI markers, our analytic sample was 1255. Participants provided written informed consent at each examination, and institutional review boards at each study site approved the study.

Arterial Stiffness and Pressure Pulsatility

The measurement protocol for arterial stiffness/pressure pulsatility has been previously described.[13,14] Field center staff were trained and certified before the visit. Before measuring arterial stiffness/pressure pulsatility, brachial blood

pressure was measured in the sitting position after 5 minutes of rest, using the Omron HEM907XL (Healthcare, Kyoto, Japan) oscillometric sphygmomanometer. The average of 3 measurements was used for statistical evaluation. cfPWV and carotid artery pressure waveforms, for the subsequent calculation of cPP, were obtained using an automatic vascular screening device (VP-1000 Plus; Omron Healthcare, Kyoto, Japan). Carotid and femoral arterial pressure waveforms were acquired in the supine position after ≈5 minutes of rest by applanation tonometry sensors attached on the left common carotid artery (via neck collar) and left femoral artery (via elastic tape around the hip). Minimum data acquisition was 30 seconds. The set of measurements was repeated after a brief rest period (≈5 minutes). PWV was calculated as distance divided by transit time. Distance for cfPWV was measured with a segmometer (Rosscraft, Surray, Canada) and calculated as the distance between the suprasternal notch to carotid minus the carotid to the femoral distance. Study personnel were centrally trained, and an ongoing quality assurance program was in place by which a random sample of 40 records per month, stratified by center, was drawn for review by one of the investigators (H.T.). From this, feedback on data quality and completeness was provided to the technicians. The short-term (4–8 weeks) repeatability values (intraclass correlation coefficients and 95% CIs) were 0.70 (0.59–0.81) for cfPWV and 0.60 (0.48–0.72) for cPP.[15] In line with prior ARIC studies using cfPWV and cPP data, outlying values ≥3 SDs above/below the mean were removed. Higher values of cfPWV and cPP indicate higher arterial stiffness and pressure pulsatility, respectively.

Structural Brain MRI and Cognitive Function Measures

Brain MRI scans using 3-T Siemens scanners were collected at each study site using a standardized protocol. MRI scans were processed centrally at the Mayo Clinic Alzheimer's and Dementia Imaging Research Lab. White matter hyperintensity (WMH) burden was measured using an algorithm developed at Mayo Clinic Rochester,[15,16] reported in cm^3. Fressurfer (version 5.1)[17] software was used to calculate regional cortical volumes, reported in cm^3. The Alzheimer disease (AD) signature region is a combined volume of the following: hippocampus, parahippocampal, entorhinal, inferior parietal lobules, and precuneus.[16] All volumetric analyses (WMH and total brain volume, AD signature region) included total intracranial volume as a covariate to account for differences in head size across participants. Brain infarcts were identified, counted, and measured by a trained imaging technician and confirmed by radiologists. Lacunar infarcts were defined as subcortical T2 fluid-attenuated inversion recovery lesions with central hypointensity >3 mm and hyperintensity ≤20 mm in maximum dimension located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, deep cerebral white matter, centrum semiovale, or corona radiata.[17,18] Cerebral microbleeds were identified as lesions on gradient-echo T2-weighted (T2*GRE) imaging sequences of ≤5 mm in maximum diameter and were divided into lobar and subcortical microhemmorrhages.[18]

Cognitive function was first measured at ARIC Study visit 2 (1990–1992) and again at visit 4 (1996–1998). Tests of memory (delayed word recall), executive function/processing speed (Digit Symbol Substitution Test), and language (phonemic fluency) were administered. Cognitive function was assessed with a comprehensive neuropsychological battery administered at ARIC-NCS/visit 5. The following domains and cognitive tests were examined at visit 5: memory (delayed word recall, logical memory, and incidental learning), executive functioning/processing speed (Trail Making Tests, parts A and B; Digit Span Backwards; and Digit Symbol Substitution Test), and language (semantic and phonemic fluency and Boston Naming Test). We used factor scores previously derived for general cognitive performance, executive functioning/processing speed, memory, and language, which leverage data from multiple cognitive tests to provide more robust measures of domain-specific function than those provided by individual tests.[19] The interpretation of our factor scores is similar to *z* scores because they were scaled to have a mean of 0 and a variance of 1.

Covariates

All covariates were assessed at ARIC-NCS/visit 5, except race-center (Minnesota whites, Maryland whites, North Carolina whites, North Carolina blacks, and Mississippi blacks), sex, and education (less than high school, high school or equivalent, and greater than high school), which were assessed at visit 1. Additional covariates included age (years); cigarette smoking status (never versus ever); diabetes mellitus (fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, self-reported history of diabetes mellitus diagnosis by a physician, or diabetes mellitus medication use); heart rate; total leisure-time physical activity in min/wk; and apolipoprotein E ε4 genotype (0 or ≥1 allele). Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of blood pressure–lowering medication.

Statistical Analyses

Descriptive analysis used χ^2 and ANOVA tests to examine differences in baseline demographic and disease characteristics across quartiles of cfPWV. Associations of cfPWV were examined on a continuous scale and in quartiles. Effectively, the same association was detected so we chose to present the latter. We used multivariable logistic regression to

quantify the odds of lacunar infarcts and cerebral microbleeds across quartiles of cfPWV and cPP, in reference to the lowest quartile (indicating the lowest levels of stiffness). We used multivariable linear regression models to estimate the mean difference in total brain volume, AD signature region, and log-transformed volumes of WMH. All models were adjusted for age, sex, education, race-center, smoking status, diabetes mellitus, leisure-time physical activity, mean arterial pressure, and apolipoprotein E ε4. Analyses of volumetric outcomes were additionally adjusted for intracranial volume. Analyses considering brain MRI outcomes were weighted to account for the stratified random sampling approach used to select people to MRI. We used multivariable linear regression to estimate the cross-sectional associations of arterial stiffness and pressure pulsatility with domain-specific cognitive factor scores. For all analyses, we further tested for effect modification by hypertension status.

As a secondary analysis, we further examined the association between arterial stiffness and pressure pulsatility with prior change in general cognitive performance from this analytic cohort's visit 2 (1990–1992) to visit 5 (2011–2013) test scores. Using time on study, we performed a longitudinal analysis using mixed-effects models with random intercepts and slopes. A linear spline was included at 6 years (visit 4, 1996–1998) to estimate the change in cognition from (1) 0 to 6 years and (2) 6 years to end of study. A random slope for spline 1 and a random slope for spline 2 were included in the models. We specified an independent covariance matrix for the random effects. An interaction term between quartiles of cfPWV or cPP and each time spline was incorporated to estimate the change separately for years 0 to 6 and 6 years to end of study, which were then combined to provide 20-year change estimates.

We performed several sensitivity analyses. First, in our cross-sectional analyses, we accounted for attrition from visit 1 to 5 by incorporating inverse probability of attrition weights[20,21] to estimate the effect of attrition attributable to death or dropout on our results. An analysis excluding participants with a stroke diagnosis at the time of the visit 5 examination (n=90 for cognition analyses, and n=36 for MRI analyses) was done. We also performed an analysis excluding participants with a dementia diagnosis at the time of the visit 5 examination (n=94 for cognition analyses, and n=59 for MRI analyses). We obtained *P*-trend values using quartile numbers. STATA, version 14.0, was used for all analyses (StataCorp LLC, College Station, TX).

Results

Participant Characteristics

Demographic and clinical characteristics of the study population (n=3703) are provided in Table 1 by quartiles of cfPWV at ARIC-NCS/visit 5. Participants in the highest quartile of cfPWV (stiffer arteries) were older, black, or women; had lower education levels; and had a worse cardiometabolic risk factor profile, including a higher prevalence of diabetes mellitus and hypertension, a higher systolic blood pressure, and lower mean min/wk of physical activity. Unadjusted general cognitive performance factor scores were lower both at the visit 2 and visit 5 (ARIC-NCS) examinations in the groups with higher cfPWV. Weighted baseline characteristics of those with MRI (n=1255) compared with the entire analytic sample (n=3703) are provided in Table 2. The participants who were selected to undergo MRI were older and (by design) more often of black race. Other demographic and clinical characteristics were comparable between participants who did and did not undergo MRI. For all analyses, no significant interaction by hypertension was observed.

Arterial Stiffness and Structural Brain MRI Markers

Several structural brain MRI measures were examined in relation to arterial stiffness and pressure pulsatility (Tables 3 and 4, respectively). Participants with the highest (quartile 4) levels of cfPWV had greater burden of WMH compared with participants with the lowest (quartile 1) levels of cfPWV (P=0.03). No significant difference was observed in the odds of lacunar infarcts or cerebral microbleeds (P>0.05). Similar results were seen with analyses restricted to cerebral microbleeds in the subcortical region only. Compared with an average volume of 1016.5 cm^3 (total brain) and 59.3 cm^3 (AD signature region) in the whole study population, total brain and AD signature region volumes were smaller among participants in the highest cfPWV quartile compared with those in the lowest cfPWV quartile (−18.30 cm^3 [95% CI, −27.54 to −9.07 cm^3] and −1.48 cm^3 [95% CI, −2.27 to −0.68 cm^3], respectively). The highest quartile of pressure pulsatility was not associated with the structural brain MRI measures. Adjustment for height in the volumetric analyses did not influence the strength of the association. MRI results were robust to adjustment for lipids.

Arterial Stiffness and Cognitive Performance

Compared with those in the lowest quartile of cfPWV (quartile 1), participants in the highest quartile (quartile 4) had statistically significantly lower cognitive factor scores in the domains of executive function/processing speed (by −0.04 *z* score [95% CI, −0.07 to −0.01 *z* score]) and general cognitive performance (by −0.09 *z* score [95% CI, −0.15 to −0.03 *z* score], Table 5). Differences in memory and language factor scores across quartiles of cfPWV were not statistically supported (P>0.05).

Table 1. Weighted Baseline Participant Characteristics by Quartile of cfPWV, ARIC-NCS/Visit 5 (2011–2013, N=3703)

Visit 5 Characteristic	Quartiles of cfPWV			
	Quartile 1 (3.25–9.55 m/s) (n=926)	Quartile 2 (9.56–11.22 m/s) (n=927)	Quartile 3 (11.23–13.24 m/s) (n=925)	Quartile 4 (13.25–22.58 m/s) (n=925)
Age, y	73.7 (4.6)	74.4 (4.6)	75.6 (5.0)	77.1 (5.2)
Female sex, %	63.9	59.2	57.7	56.2
Black race, %	16.3	17.9	20.2	29.0
Less than high school education, %	8.6	10.6	11.6	17.7
Apolipoprotein E ε4 allele present, %	28.6	29.2	29.2	26.6
Ever smoker, %	55.1	57.2	56.9	53.9
Heart rate, beats/min	59.1 (8.9)	60.5 (8.8)	62.6 (9.8)	64.9 (10.6)
Body mass index, kg/m^2	27.7 (4.4)	28.1 (4.5)	27.8 (4.3)	27.5 (4.5)
Leisure-time physical activity, min/wk	227.7 (202.1)	214.7 (197.1)	200.0 (195.0)	169.8 (195.4)
Diabetes mellitus, %	16.8	20.0	25.3	35.7
Systolic blood pressure, mm Hg	122 (15)	127 (15)	132 (16)	138 (18)
Hypertension, %	60.0	67.7	76.2	80.8
Mean arterial pressure, mm Hg	84 (10)	87 (10)	89 (11)	91 (12)
General cognitive performance factor score				
Visit 2	0.46 (0.74)	0.39 (0.80)	0.29 (0.79)	0.12 (0.83)
Visit 4	0.34 (0.70)	0.25 (0.73)	0.18 (0.74)	0.02 (0.77)
Visit 5	−0.32 (0.82)	−0.41 (0.81)	−0.57 (0.83)	−0.84 (0.88)
MRI markers (n=1255)	n=314	n=314	n=314	n=313
White matter hyperintensities volume, cm^3	13.7 (15.0)	14.9 (13.8)	16.9 (16.6)	21.5 (19.7)
Cerebral microbleeds, %	21.5	22.0	19.6	32.4
Lacunar infarcts, %	13.1	14.3	18.8	23.1
Total brain volume, cm^3	1028.0 (100.3)	1028.4 (106.4)	1014.4 (107.0)	955.2 (110.1)
Alzheimer disease signature region volume, cm^3	60.3 (6.7)	60.3 (6.4)	59.4 (6.9)	57.4 (6.9)

Values are displayed as mean (SD) and percentage. ARIC-NCS indicates Atherosclerosis Risk in Communities–Neurocognitive Study; cfPWV, carotid-femoral pulse wave velocity; MRI, magnetic resonance imaging.

Similar patterns were observed for cPP (Table 6). However, significant differences in the domain of language were observed among participants in the highest quartile of cPP compared with those in the lowest quartile of cPP (by −0.08 *z* score [95% CI, −0.15 to −0.01 *z* score], Table 6). Further adjustment for lipids did not appreciably alter the results.

Arterial Stiffness and Prior 20-Year Change in General Cognitive Performance

Compared with participants with the lowest levels of cfPWV at ARIC-NCS/visit 5, those with the highest levels of cfPWV had faster prior 20-year rates of decline in general cognitive performance (−0.17 *z* score over 20 years [95% CI, −0.22 to −0.12 *z* score], Table 5). Similar patterns were observed for pressure pulsatility (Table 6).

Sensitivity Analyses

Results were robust to adjustment for attrition from visit 1 (n=15 792) to visit 5 (n=6538) using inverse probability of attrition weights in subsidiary analyses. Excluding participants with stroke before visit 5 also did not appreciably impact the results or inferences. Results were attenuated after exclusion of participants with a dementia diagnosis, but the overall inferences remained consistent.

Discussion

Consistent with our a priori hypothesis, higher levels of arterial stiffness and pressure pulsatility were associated with a greater burden of structural brain damage, lower brain volumes, lower cognitive performance, particularly for executive function/processing speed, and greater prior 20-year

Table 2. Weighted Baseline Participant Characteristics Among Participants With Versus Without a Brain MRI, the ARIC Study (2011–2013, N=3703)

Visit 5 Characteristics	Arterial Stiffness and Cognitive Function (N=3703)	Arterial Stiffness and MRI Outcomes (N=1255)*
Age, y	75.2 (5.0)	76.1 (5.2)
Female sex, %	59.3	58.9
Black race, %	20.8	27.4
Less than high school education, %	42.6	43.4
APOE ε4 allele present, %	28.4	29.1
Ever smoker, %	55.8	54.1
Heart rate, beats/min	61.8 (9.8)	61.5 (9.7)
Body mass index, kg/m^2	27.8 (4.4)	27.6 (4.5)
Leisure-time physical activity, min/wk	203.1 (198.5)	191.5 (190.2)
Diabetes mellitus, %	24.4	25.8
Systolic blood pressure, mm Hg	129.9 (17.2)	130.7 (17.1)
Hypertension, %	63.5	64.9

Values are displayed as mean (SD) and percentage. APOE indicates apolipoprotein E; ARIC, Atherosclerosis Risk in Communities; MRI, magnetic resonance imaging.
*Random subsample of ARIC Study participants who underwent MRI at ARIC–Neurocognitive Study (NCS)/visit 5. Weighted for selection into undergoing MRI at ARIC-NCS/visit 5.

decline in general cognitive performance. Prior reports show that age-associated central arterial stiffening and increased pulsatility may profoundly affect cerebral perfusion.[5,22] This may explain the associations found with the brain structural changes and consequent cognitive performance.

Arterial stiffening and pressure pulsatility may be related to cerebral outcomes through various mechanisms. Age-related arterial wall remodeling results in arterial stiffening and increased pressure pulsatility.[23–25] In low-impedance, high-flow organs, such as the brain, the pulse propagation of the larger arteries impinges on the microcirculation.[23–25] Sustained high cPP and its pulsatility may thus manifest as a greater burden of cerebral small-vessel disease, as measured in this study by WMH volume, cerebral infarcts, and microbleeds.[26] The associations of structural brain damage were observed to be more robust for cfPWV than cPP in the present study. Age-related changes in pulse wave velocity and pressure pulsatility follow slightly different patterns: arterial stiffness increases fairly linearly with advancing age, whereas age-related changes in pressure pulsatility appear to be more marked in younger adults.[27] Also, brachial diastolic pressure was used in this study to estimate cPP and circulating volume as well as vasodilation are known to influence cPP.

Prior data similarly suggest that higher arterial stiffness is associated with microvascular damage.[28] Several recent studies have examined this in the brain. Our results both support and add to the findings from the Rotterdam Study, which was the first to use cfPWV in relation to brain outcomes,[29] showing greater arterial stiffness to be associated with white matter lesions, but not lacunar infarcts or cerebral microbleeds, in a sample of older adults. A more recent report from the Framingham Heart Study also showed a greater burden of WMHs in middle-aged participants with aortic stiffness.[30] In a subsample of ARIC-NCS participants who underwent an amyloid positron emission tomographic scan (n=320), we observed similar associations of cfPWV with AD signature region volumes and WMH burden.[31] A systematic review and meta-analysis (12 cross-sectional and 2 longitudinal studies) found a significant association between arterial stiffness and WMHs of similar magnitude to our results.[22] However, only 2 of the included studies had a measure of central arterial stiffness. The differential

Table 3. Multivariable Regression of the Association Between cfPWV With Structural Brain MRI Markers at ARIC-NCS/Visit 5 (2011–2013, N=1255)

Quartiles of cfPWV	Log_2 WMH Volume β (95% CI)	Presence of Cerebral Microbleeds Odds Ratio (95% CI)	Presence of Lacunar Infarcts Odds Ratio (95% CI)	Total Brain Volume (cm^3) β (95% CI)	Alzheimer Disease Signature Volume (cm^3) β (95% CI)
Quartile 1 (n=314)	Reference	Reference	Reference	Reference	Reference
Quartile 2 (n=314)	0.09 (−0.07 to 0.24)	1.24 (0.78 to 1.98)	0.88 (0.51 to 1.53)	−8.21 (−16.37 to −0.06)*	−0.59 (−1.35 to 0.17)
Quartile 3 (n=314)	0.09 (−0.07 to 0.24)	0.80 (0.49 to 1.31)	1.23 (0.71 to 2.12)	−13.92 (−22.46 to −5.39)	−0.44 (−1.18 to 0.29)
Quartile 4 (n=313)	0.24 (0.09 to 0.40)*	1.36 (0.85 to 2.17)	1.53 (0.87 to 2.70)	−18.30 (−27.54 to −9.07)*	−1.48 (−2.27 to −0.68)*
P value for trend	0.007	0.574	0.090	<0.001	0.002

Adjusted for age, sex, race-center, education, apolipoprotein E ε4, heart rate, body mass index, ever smoker, diabetes mellitus, minutes of leisure-time physical activity, mean arterial pressure, and intracranial volume (for WMH, total brain, and Alzheimer disease signature region volumes). Weighted for selection into undergoing MRI at ARIC-NCS/visit 5. ARIC-NCS indicates Atherosclerosis Risk in Communities–Neurocognitive Study; cfPWV, carotid-femoral pulse wave velocity; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.
*P<0.05 vs reference.

Table 4. Multivariable Regression of the Association Between Pressure Pulsatility Measures With Structural Brain MRI Markers at ARIC-NCS/Visit 5 (2011–2013, N=1255)

Quartile of Central Pulse Pressure	Log_2 WMH Volume β (95% CI)	Presence of Cerebral Microbleeds Odds Ratio (95% CI)	Presence of Lacunar Infarcts Odds Ratio (95% CI)	Total Brain Volume (cm^3) β (95% CI)	Alzheimer Disease Signature Volume (cm^3) β (95% CI)
Quartile 1 (n=314)	Reference	Reference	Reference	Reference	Reference
Quartile 2 (n=314)	0.08 (−0.06 to 0.22)	1.18 (0.76 to 1.86)	0.82 (0.48 to 1.39)	−1.66 (−10.27 to 6.94)	−0.39 (−1.18 to 0.39)
Quartile 3 (n=317)	0.18 (0.01 to 0.35)*	1.03 (0.63 to 1.67)	0.95 (0.55 to 1.62)	−6.46 (−15.13 to 2.22)	−0.88 (−1.64 to −0.12)*
Quartile 4 (n=310)	0.14 (−0.03 to 0.31)	1.23 (0.74 to 2.04)	0.88 (0.50 to 1.55)	−4.27 (−13.58 to 5.04)	−0.70 (−1.50 to 0.09)
P value for trend	0.056	0.587	0.815	0.230	0.040

Adjusted for age, sex, race-center, education, apolipoprotein E ε4, heart rate, body mass index, ever smoker, diabetes mellitus, minutes of leisure-time physical activity, mean arterial pressure, and intracranial volume (for WMH, total brain, and Alzheimer disease signature region volumes). Weighted for selection into undergoing MRI at ARIC-NCS/visit 5. ARIC-NCS indicates Atherosclerosis Risk in Communities–Neurocognitive Study; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.
*$P<0.05$ vs reference.

associations of high cfPWV with the AD signature region volumes and memory function are consistent with prior data indicating that cerebral structural changes precede changes in cognitive function and cognitive symptoms. The cross-sectional nature of the data available to us at this time limits our ability to examine whether cfPWV relates to changes in cerebral MRI markers and changes in cognitive function.

In our analyses of cfPWV and cPP, we observed the strongest association with the domain of executive function/processing speed, as is often reported to be associated with cerebrovascular brain injury. Our results also validate those observed in several other community-based longitudinal studies, including the MSLS (Maine-Syracuse Longitudinal Study),[32] the Rotterdam Study,[33] and the Health ABC (Health Aging and Body Composition) Study.[34]

We observed faster 20-year decline in general cognitive performance among participants with high compared with low levels of cfPWV, also consistent with prior longitudinal studies of arterial stiffness and cognitive decline.[34–38] Most recently, in an analysis of the Framingham Offspring Cohort,[30] elevated arterial stiffness and pressure pulsatility were associated with greater decline in several domains, most notably executive functioning. Our results add to the state of the knowledge by overcoming several of the limitations of these reports, including small sample sizes, homogeneous study populations (primarily white and educated), and using the Mini-Mental

Table 5. Adjusted Mean Difference (95% CI) and 20-Year Rate of Change in Standardized Domain-Specific Cognition Factor Scores Across Quartiles of cfPWV, ARIC-NCS/Visit 5 (2011–2013, N=3703)

Quartile	General Cognitive Performance	Memory	Executive Function/Processing Speed	Language
Cross sectional: adjusted mean difference in factor score				
Quartile 1 (n=926)	Reference	Reference	Reference	Reference
Quartile 2 (n=927)	−0.02 (−0.07 to 0.04)	−0.02 (−0.10 to 0.07)	−0.005 (−0.03 to 0.02)	−0.03 (−0.09 to 0.04)
Quartile 3 (n=925)	−0.05 (−0.10 to 0.01)	−0.05 (−0.14 to 0.04)	−0.02 (−0.04 to 0.01)	−0.02 (−0.09 to 0.04)
Quartile 4 (n=925)	−0.09 (−0.15 to −0.03)*	−0.07 (−0.16 to 0.02)	−0.04 (−0.07 to −0.01)*	−0.06 (−0.13 to 0.01)
P value for trend	0.002	0.110	0.013	0.123
Longitudinal: adjusted difference in 20-y rate of change in factor score				
Quartile 1 (n=926)	Reference	…	…	…
Quartile 2 (n=927)	−0.02 (−0.07 to 0.03)	…	…	…
Quartile 3 (n=925)	−0.08 (−0.13 to −0.03)*	…	…	…
Quartile 4 (n=925)	−0.17 (−0.22 to −0.12)*	…	…	…
P value for trend	<0.001	…	…	…

Estimates are β values (95% CIs). Adjusted for age, sex, race-center, education, apolipoprotein E ε4, heart rate, body mass index, ever smoker, diabetes mellitus, minutes of leisure-time physical activity, and mean arterial pressure. ARIC-NCS indicates Atherosclerosis Risk in Communities–Neurocognitive Study; cfPWV, carotid-femoral pulse wave velocity.
*$P<0.05$ vs reference.

Table 6. Adjusted Mean Difference (95% CI) and 20-Year Rate of Change in Standardized Domain-Specific Cognition Factor Scores Across Quartiles of cPP, ARIC-NCS/Visit 5 (2011–2013, N=3703)

Quartile	General Cognitive Performance	Memory	Executive Function/Processing Speed	Language
Cross sectional: adjusted mean difference in factor score				
Quartile 1 (n=931)	Reference	Reference	Reference	Reference
Quartile 2 (n=921)	−0.03 (−0.09 to 0.02)	−0.02 (−0.10 to 0.07)	−0.01 (−0.04 to 0.01)	−0.03 (−0.10 to 0.03)
Quartile 3 (n=929)	−0.11 (−0.17 to −0.05)*	−0.04 (−0.12 to 0.05)	−0.05 (−0.08 to −0.02)*	−0.08 (−0.15 to −0.01)*
Quartile 4 (n=922)	−0.10 (−0.16 to −0.04)*	−0.02 (−0.12 to 0.07)	−0.06 (−0.09 to −0.03)*	−0.08 (−0.15 to −0.01)*
P value for trend	<0.001	0.575	<0.001	0.015
Longitudinal: adjusted difference in 20-y rate of change in factor score				
Quartile 1 (n=931)	Reference	…	…	…
Quartile 2 (n=921)	−0.10 (−0.15 to −0.05)*	…	…	…
Quartile 3 (n=929)	−0.13 (−0.18 to −0.08)*	…	…	…
Quartile 4 (n=922)	−0.19 (−0.24 to −0.15)*	…	…	…
P value for trend	<0.001	…	…	…

Estimates are β values (95% CIs). Adjusted for age, sex, race-center, education, apolipoprotein E ε4, heart rate, body mass index, ever smoker, diabetes mellitus, minutes of leisure-time physical activity, and mean arterial pressure. ARIC-NCS indicates Atherosclerosis Risk in Communities–Neurocognitive Study; cPP, central pulse pressure.
*$P<0.05$ vs reference.

State Examination as the main measure of cognitive function. The association we observed of arterial stiffness with prior cognitive decline (rather than just cognitive performance at a single point in time) adds plausibility to the interpretation of the relationship between arterial stiffness/pressure pulsatility and cognition. This is because the estimates of declines in cognition over time are less likely to be confounded by a person's stable characteristics, which are known to have strong effects on cognitive performance (eg, education, other elements of cognitive reserve, or social disadvantage).

Some limitations of our study should be noted. Although it is implausible that cognitive performance or MRI-based measures of structural brain damage influence central artery stiffness, our cross-sectional analyses preclude certain assignment of antecedent versus consequent elements and are potentially open to reverse causality. Furthermore, our analytic set of participants at the visit 5 examination of the ARIC Study cohort is a subsample of the original cohort recruited at baseline (n=15 792), and this may permit bias attributable to attrition, with the healthiest ARIC Study participants remaining in the study. However, our results were robust to adjustment for attrition using inverse probability of attrition weights.[20,21] Longitudinal studies of changes in arterial stiffness, subsequent morphologic brain changes, and prospective measures of cognitive function are warranted to support these results. Last, although the ARIC Study included a biracial cohort of men and women, we chose not to conduct race-stratified analyses. Although the study size limits the informativeness of race-specific analyses, when our analyses were restricted to white participants only, the results were similar across the cognitive domains, with the exception of executive function/processing speed, for which the results were attenuated and not statistically significant.

Several strengths should also be mentioned. The well-characterized ARIC-NCS cohort provides >20 years of collected data, allowing us to examine the rate of cognitive change. Central arterial stiffening was measured using cfPWV, which is the reference standard measure of arterial stiffness. Several prior studies of brain outcomes included peripheral arterial stiffness, such as brachial-ankle pulse wave velocity, which is less likely to influence the brain microvasculature. An additional strength of our study is the use of calibrated general and domain-specific cognitive factor scores, validated as previously reported[14] by comparing the associations of diabetes mellitus with cognitive outcomes derived as factor scores versus averaged standardized tests.

Even if pharmacologic treatments to prevent AD and related dementias become available, efforts to decrease arterial stiffness and application of nonpharmacologic interventions will still be critical because they contribute to cognitive morbidity. Pharmacologic arterial "destiffening" has been studied: certain blood pressure–lowering agents (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) reduce arterial stiffness. Efforts to reduce arterial stiffness or pressure pulsatility through targeted nonpharmacologic interventions also are promising. Several intervention studies of physical activity have also shown promising results for both destiffening of arteries[39] and lowering the risk of cognitive impairment and related dementia.[40] Other behavioral lifestyle interventions,

including weight loss[41] and smoking cessation,[42] may be useful targets for improving arterial stiffness in adults. In conclusion, central arterial stiffening and pressure pulsatility are plausible microvascular contributors to cognitive aging, providing new information on a potentially modifiable pathway for improving cognitive outcomes among older adults.

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Disclosures

None.

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