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

Priya Palta PhD; A. Richey Sharrett, MD; Jingkai Wei, MSPH; Michelle L. Meyer, PhD; Anna Kucharska-Newton, PhD; Melinda C. Power, ScD; Jennifer A. Deal, PhD; Clifford R. Jack, MD; David Knopman, MD; Jacqueline Wright, DrPH; Michael Griswold, PhD; Hirofumi Tanaka, PhD; Thomas H. Mosley, PhD; Gerardo Heiss, MD

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 cm³; 95% CI, −27.54 to −9.07 cm³), and smaller Alzheimer disease signature region volumes (−1.48 cm³; 95% CI, −2.27 to −0.68 cm³). 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

From the Department of Epidemiology, Gillings School of Global Public Health (P.P., J. Wei, A.K.-N., G.H.), and Department of Emergency Medicine (M.L.M.), University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Epidemiology, Johns Hopkins University, Baltimore, MD (A.R.S., J.A.D.); Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, George Washington University, Washington, DC (M.C.P.); Departments of Radiology (C.R.J.) and Neurology (D.K.), Mayo Clinic, Rochester, MN; National Heart, Lung, and Blood Institute, Bethesda, MD (J. Wright); Department of Medicine, University of Mississippi Medical Center, Jackson, MS (M.G., T.H.M.); and Department of Kinesiology and Health Education, University of Texas at Austin, TX (H.T.).

Correspondence to: Priya Palta, PhD, 123 W Franklin St, Suite 410, Chapel Hill, NC 27516-8050. E-mail: priya_palta@unc.edu

Received September 24, 2018; accepted December 5, 2018.

© 2019 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
Aortic Stiffness, Brain Structure, and Cognition  Palta et al

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.

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/m² 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.

For cfPWV was measured with a segmentometer (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 cm³. Freysurer (version 5.1)17 software was used to calculate regional cortical volumes, reported in cm³. 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 microhemorrhages.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-centric (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 χ² 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 weights20,21 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 cm³ (total brain) and 59.3 cm³ (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 cm³ [95% CI, −27.54 to −9.07 cm³]) and −1.48 cm³ (95% CI, −2.27 to −0.68 cm³), 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).
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 $/C0.08/z$ score [95% CI, $/C0.15$ to $/C0.01/z$ 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 ($/C0.17/z$ score over 20 years [95% CI, $/C0.22$ to $/C0.12/z$ 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 ($n=6,538$) 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
Aortic stiffness, brain structure, and cognition

Palta et al.

DOI: 10.1161/JAHA.118.011045

Journal of the American Heart Association

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 | Log2 WMH Volume β (95% CI) | Presence of Cerebral Microbleeds Odds Ratio (95% CI) | Presence of Lacunar Infarcts Odds Ratio (95% CI) | Total Brain Volume (cm³) β (95% CI) | Alzheimer Disease Signature Volume (cm³) 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 4, 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.
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), the Rotterdam Study, and the Health ABC (Health Aging and Body Composition) Study.

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. Most recently, in an analysis of the Framingham Offspring Cohort, 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 |
|----------|-------------------------------|--------|-------------------------------------|----------|
| 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 | General Cognitive Performance | Memory | Executive Function/Processing Speed | Language |
|----------|-------------------------------|--------|-------------------------------------|----------|
| 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 ɛ4, 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.
Aortic Stiffness, Brain Structure, and Cognition

Palta et al

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. 39,40 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\textsuperscript{41} and smoking cessation,\textsuperscript{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.

Acknowledgments

The authors thank the staff and participants of the ARIC (Atherosclerosis Risk in Communities) Study for their important contributions.

Sources of Funding

The ARIC (Atherosclerosis Risk in Communities Study) is carried out by the National Heart, Lung, and Blood Institute contracts (HHSN26820170000I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, and HHSN268201700004I). Neurocognitive data is collected by U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01 HL096917 from the NIH (NHLBI, NINDS, NIA and NIDCD), and with previous brain magnetic resonance imaging examinations funded by R01-HL07825 from the National Heart, Lung, and Blood Institute. Additional support was provided by the National Institute on Aging for the measures of arterial stiffness and pressure pulsatility (R01AG053938). Dr Palta is supported by grant K99AG052830 from the National Institute on Aging. Dr Deal is supported by grant K01AG054693 from the National Institute on Aging. The views expressed herein are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institute on Aging; the National Institutes of Health; or the US Department of Health and Human Services.

Disclosures

None.

References

1. Zhang Y, Agnoletti D, Xu Y, Wang JG, Blacher J, Safar ME. Carotid-femoral pulse wave velocity in the elderly. J Hypertens. 2014;32:1572 – 1576; discussion 1576.
2. Najar SS, Scuteri A, Shetty V, Wright JG, Muller DG, Fleg JL, Spurgeon HP, Ferrucci L, Lakatta EG. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol. 2008;51:1377 – 1383.
3. van Popele NM, Elizabeth Hak A, Mattace-Raso FU, Bots ML, van der Kuip LM, Mosley TH Jr; ARIC Neurocognitive Investigators. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. Stroke. 2015;46:433 – 440.
4. Scuteri A, Wang H. Pulse wave velocity as a marker of cognitive impairment in the elderly. J Alzheimers Dis. 2014;42(suppl 4):S401 – S410.
5. Laurent S, Cockcroft J, Van Bertel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588 – 2605.
6. Atherosclerosis Risk in Communities Study description. https://www2.cscce.nih.gov/arc/. Accessed October 25, 2018.
7. Laurent S, Cockcroft J, Van Bertel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588 – 2605.
8. Atherosclerosis Risk in Communities Study description. https://www2.cscce.nih.gov/arc/. Accessed October 25, 2018.
9. NHLBI Biologic Specimen and Data Repository Information Coordinating Center. https://biolinc.nhlibi.nih.gov/home/. Accessed October 25, 2018.
10. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. Am J Epidemiol. 1989;129:687 – 702.
11. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR Jr, Graff-Radford J, Schneider AL, Windham BG, Coker LH, Albert MS, Mosley TH Jr; ARIC Neurocognitive Investigators. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. Stroke. 2015;46:433 – 440.
12. Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, Sharrett AR, Mosley TH Jr. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. Neurology. 2011;76:1879 – 1885.
13. Meyer ML, Tanaka H, Palta P, Cheng S, Gouskova N, Aguilar D, Heiss G. Correlates of segmental pulse wave velocity in older adults: the Atherosclerosis Risk in Communities (ARIC) study. Am J Hypertens. 2016;29:114 – 122.
14. Tanaka H, Munakata M, Kawanoto Y, Oishi M, Shoji T, Sugawara J, Taniyama Y, Yamashina A, Yasuda H, Sawayaama T, Ozawa T. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. J Hypertens. 2009;27:2023 – 2027.
15. Meyer ML, Tanaka H, Palta P, Patel MD, Campain R, Couper D, Cheng S, Al Qunaibat A, Poon AK, Heiss G. Repeatability of central and peripheral pulse wave velocity measures: the Atherosclerosis Risk in Communities (ARIC) study. Am J Hypertens. 2016;29:470 – 475.
16. Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, Hyman BT, Blacker D, Detrkd-Morel L. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. Neurology. 2011;76:1395 – 1402.
17. Dearborn JL, Schneider AL, Sharrett AR, Mosley TH, Bezerra DC, Knopman DS, Selvin E, Jack CR, Coker LH, Alonso A, Wagenknecht LE, Windham BG, Gottdenker RF. Obesity, insulin resistance, and incident small vessel disease on magnetic resonance imaging: Atherosclerosis Risk in Communities Study. Stroke. 2015;46:3131 – 3136.
18. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O’Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabridt H, Decarli C, de Leeuw FE, Dubbel F, Duerinck M, Fox NC, Greenberg S, Hachinski V, Klimanl I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Wisanathan A, Werring D, Chen C, Smith C, van Buchem M, Norring B, Gorelick BP, Dichgans M; Standards for Reporting Vascular changes on nTomoaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurology. 2013;12:822 – 838.
19. Gross AL, Power MC, Albert MS, Deal JA, Gottesman RF, Griswold M, Wruck LM, Mosley TH Jr, Coresh J, Sharrett AR, Bandeen-Roche K. Application of latent variable methods to the study of cognitive decline when tests change over time. Epidemiology. 2015;26:876 – 887.
20. Gottesman RF, Rawlings AM, Sharrett AR, Albert M, Alonso A, Bandeen-Roche K, Coker LH, Coresh J, Couper DJ, Griswold ME, Heiss G, Knopman DS, Patel MD, Penman AD, Power MC, Selnes OA, Schneider AL, Wagenknecht LE, Windham BG, Wruck LM, Mosley TH Jr. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. Neurology. 2011;76:1879 – 1885.
21. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, Evans DA, Mendes de Leon CF. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. Epidemiology. 2012;23:119 – 128.
22. van Slotten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stenhower CD. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2015;53:121 – 130.
23. Stone J, Johnston DM, Mirtzofian J, O’Rourke M. The mechanical cause of age-related dementia (alzheimer’s disease): the brain is destroyed by the pulse. J Alzheimers Dis. 2015;44:395 – 373.
24. Thorin-Trescases N, de Montgolfier O, Pincon A, Raignaut A, Caland L, Labbe T, Thorin E. The impact of pulse pressure on cerebrovascular events leading to age-related cognitive decline. Am J Physiol Heart Circ Physiol. 2018;314:H1214 – H1224.
25. Thorin-Trescases N, Thorin E. Lifelong cyclic mechanical strain promotes large elastic artery stiffening: increased pulse pressure and old age-related organ failure. *Can J Cardiol*. 2016;32:624–633.

26. Saji N, Toba K, Sakurai T. Cerebral small vessel disease and arterial stiffness: tsunami effect in the brain? *Pulse (Basel)*. 2016;3:182–189.

27. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR; ACCT Investigators. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol*. 2005;46:1753–1760.

28. Cooper LJ, Woodward T, Sigurdsson S, van Buchem MA, Torjesen AA, Inker LA, Aspelund T, Eiriks dottir G, Harris TB, Gudnason V, Launer LJ, Mitchell GF. Cerebrovascular damage mediates relations between arterial stiffness and memory. *Hypertension*. 2016;67:176–182.

29. Poels MM, Zaccai K, Verwoert GC, Vernooij MW, Hofman A, van der Lugt A, Witteman JC, Breteler MM, Mattace-Raso FU, Ikram MA. Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan Study. *Stroke*. 2012;43:2637–2642.

30. Pase MP, Himali JI, Mitchell GF, Beiser A, Maillard P, Tsao C, Larson MG, DeCarli C, Vasan RS, Seshadri S. Association of aortic stiffness with cognition and brain aging in young and middle-aged adults: the Framingham Third Generation Cohort Study. *Hypertension*. 2016;67:513–519.

31. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, Wong D, Zhou Y, Knopman D, Mosley TH, Gottesman RF. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. *Neurology*. 2018;90:e1248–e1256.

32. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK. Arterial pulse wave velocity and cognition with advancing age. *Hypertension*. 2009;53:668–673.

33. Poels MM, van Oijen M, Mattace-Raso FU, Hofman A, Koudstaal PJ, Witteman JC, Breiter MM. Arterial stiffness is associated with cognitive decline and risk of dementia: the Rotterdam Study. *Stroke*. 2007;38:888–892.

34. Watson NL, Sutton-Tyrrell K, Rosano C, Boudreau RM, Hardy SE, Simonsick EM, Najjar SS, Launer LJ, Yaffe K, Atkinson HH, Satterfield S, Newman AB. Arterial stiffness and cognitive decline in well-functioning older adults. *J Gerontol A Biol Sci Med Sci*. 2011;66:1336–1342.

35. Benetos A, Wafsa G, Hanon O, Salvi P, Fanti F, Toulza O, Manckoundia P, Agnoletti D, Labat C, Gauthier S; PARTAGE Study Investigators. Pulse wave velocity is associated with 1-year cognitive decline in the elderly older than 80 years: the PARTAGE study. *J Am Med Dir Assoc*. 2012;13:239–243.

36. Scuteri A, Tesauro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. *J Hypertens*. 2007;25:1035–1040.

37. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension*. 2008;5:199–104.

38. Zeki Al Hazzouri A, Newman AB, Simonsick E, Sink KM, Sutton Tyrrell K, Watson N, Satterfield S, Harris T, Yaffe K; Health ABC Study. Pulse wave velocity and cognitive decline in elders: the Health, Aging, and Body Composition study. *Stroke*. 2013;44:388–393.

39. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2014;9:e110034.

40. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc*. 2011;86:876–884.

41. Petersen KS, Clifton PM, Lister N, Keogh JB. Effect of weight loss induced by energy restriction on measures of arterial compliance: a systematic review and meta-analysis. *Atherosclerosis*. 2016;247:7–20.

42. Yu-Jie W, Hui-Liang L, Bing L, Lu Z, Zhi-Geng J. Impact of smoking and smoking cessation on arterial stiffness in healthy participants. *Angiology*. 2013;64:273–280.

DOI: 10.1161/JAHA.118.011045