ARTICLE

Arterial stiffness and dementia pathology

Atherosclerosis Risk in Communities (ARIC)-PET Study

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Abstract

Objective

Arterial stiffness has been associated with evidence of cerebral small vessel disease (cSVD) and fibrillar β-amyloid (Aβ) deposition in the brain. These complex relationships have not been examined in racially and cognitively diverse cohorts.

Methods

The Atherosclerosis Risk in Communities (ARIC)–Neurocognitive Study collected detailed cognitive testing for adjudication of dementia and mild cognitive impairment (MCI), brain MRI, and arterial stiffness by pulse wave velocity (PWV, carotid-femoral [cfPWV] and heart-carotid [hcPWV]). The ARIC-PET ancillary study added Aβ imaging using florbetapir ([^{18}F]-AV-45) to obtain standardized uptake volume ratios and defined global Aβ-positivity as standardized uptake volume ratio >1.2. One-SD increase in PWV was related to brain volume, MRI-defined cSVD (e.g., cerebral microbleeds and white matter hyperintensity), and cortical Aβ deposition adjusted for age, body mass index, sex, race, and *APOE* ε4 status. We examined the cross-sectional relationships including interactions by race, *APOE* ε4 status, and cognition.

Results

Among the 320 ARIC-PET participants (76 [5] years, 45% black, 27% MCI), greater central stiffness (hcPWV) was associated with greater Aβ deposition (odds ratio [OR] = 1.31, 95% confidence interval [CI] 1.01–1.71). Greater central stiffness (cfPWV) was significantly associated with having lower brain volumes in Alzheimer disease–susceptible regions (in mm^3, β = −1.5 [0.7 SD], p = 0.03) and high white matter hyperintensity burden (OR = 1.6, 95% CI 1.2–2.1). Furthermore, cfPWV was associated with a higher odds of concomitant high white matter hyperintensity and Aβ-positive scans (OR = 1.4, 95% CI 1.1–2.1). These associations were strongest among individuals with MCI and did not differ by race or *APOE* ε4 status.

Conclusions

Arterial stiffness, measured by PWV, is an emerging risk factor for dementia through its repeated relationships with cognition, cSVD, and Aβ deposition.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ARIC** = Atherosclerosis Risk in Communities; **ARIC-NCS** = Atherosclerosis Risk in Communities–Neurocognitive Study; **baPWV** = brachial-ankle pulse wave velocity; **BP** = blood pressure; **cfPWV** = carotid-femoral pulse wave velocity; **CI** = confidence interval; **cSVD** = cerebral small vessel disease; **DBP** = diastolic blood pressure; **faPWV** = femoral-ankle pulse wave velocity; **hcPWV** = heart-carotid pulse wave velocity; **ICC** = intraclass correlation coefficient; **MCI** = mild cognitive impairment; **MPRAGE** = magnetization-prepared rapid-acquisition gradient echo; **OR** = odds ratio; **PWV** = pulse wave velocity; **ROI** = region of interest; **SBP** = systolic blood pressure; **SUVR** = standardized uptake value ratio; **WMH** = white matter hyperintensity.

Vascular disease is an important modifiable risk factor for clinically diagnosed Alzheimer disease (AD) dementia and related dementias.[1,2] A greater burden of midlife vascular risk factors is associated with a greater burden of β-amyloid (Aβ) deposition in the brain in late life.[3] It remains unclear what mechanisms relate vascular and AD risk factors and whether these processes are additive or interactive in influencing dementia pathology. A growing body of research shows that high blood pressure (BP) and the extent of underlying arterial stiffness are associated with cognitive dysfunction[4,5] and evidence of dementia-related pathology, including cerebral small vessel disease (cSVD)[6–8] and the extent of Aβ deposition in the brain.[9–13] Greater central arterial stiffness is associated with the extent of white matter disease and accumulation of Aβ in the brain over time in elderly adults without dementia, independent of BP.[11] Furthermore, individuals with greater arterial stiffness tend to have greater risk of concomitant white matter disease and Aβ deposition.[11]

Arterial stiffness may be one underlying mechanism linking hypertension to both evidence of cSVD and Aβ deposition in the brain. The overlap of cSVD and Aβ deposition in the brain is proposed to lower the threshold at which individual dementia pathology is expressed as cognitive symptoms and signs.[14] To date, only our previous work has examined the potential contribution of arterial stiffness to the overlap of cSVD and Aβ deposition in the brain in a modest sample of very elderly white adults.[11,13] It is unclear whether these observed associations differ between racial/ethnic groups. This is especially important for black older adults who are at a greater risk of AD and are twice as likely to have elevated levels of Aβ deposition in the brain compared to white adults.[15] Black older adults are also at a higher risk of hypertension, greater arterial stiffness,[16–19] stroke, and AD.[20] In this study, we examined the individual and joint associations for arterial stiffness with evidence of specific dementia pathologies in black and white older adults in the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesized that arterial stiffness is associated with evidence of both cSVD (e.g., white matter disease and cerebral microbleeds) and Aβ deposition, in both white and black older adults.

Methods

Participants

Participants were recruited to the ARIC-PET ancillary study from the ARIC–Neurocognitive Study (ARIC-NCS), a major ancillary to the ARIC study, as previously described.[21] The parent ARIC study began in 1987–1989 with 15,792 individuals from 4 US communities. At the fifth visit (2011–2013), 6,538 surviving ARIC-NCS participants received an extensive neuropsychological battery,[22] with informant interview in a subset, and expert classification of cognitive status, including dementia and mild cognitive impairment (MCI).[23] A subset of ARIC-NCS participants who received MRI also received Aβ-PET imaging at 3 ARIC sites (Jackson, MS; Washington County, MD; and Forsyth County, NC), as previously described.[21]

Standard protocol approvals, registrations, and patient consents

This study was approved by each institution's institutional review board. All participants provided written informed consent. The institutional review board at each ARIC site approved the conduct of this study.

Brain MRI and PET

MRI scans were performed on 3-tesla MRI scanners at each site; magnetization-prepared rapid-acquisition gradient echo (MPRAGE) was used for coregistration of PET images. Details about MRI analysis, completed at the ARIC MRI Reading Center (Mayo Clinic), were previously reported.[22] Briefly, white matter hyperintensity (WMH) volume (in cubic millimeters) was quantified from fluid-attenuated inversion recovery sequences, using an in-house algorithm,[24] and total intracranial volume (cubic millimeters) was measured on MPRAGE using FreeSurfer version 5.1. Using the FreeSurfer atlas, ARIC investigators prespecified regions of interest (ROIs) based on relevance to cognition, including an AD signature volume in cubic millimeters from ROIs from both right and left hemispheres: hippocampus, parahippocampal gyrus, entorhinal cortex, inferior parietal lobule, precuneus, and cuneus.[22] Cortical and subcortical brain infarcts, lacunar infarcts, and cerebral microbleeds were identified, counted, and measured by a trained imaging technician and confirmed by radiologists, as previously described.[25]

PET scans were performed at each site, within 1 year of the brain MRI. The florbetapir isotope was injected through a butterfly needle, with images acquired from 50 to 70 minutes for a 20-minute (4 × 5 minutes) uptake scan. Images were transferred to the PET image analysis center (Johns Hopkins) where they were reviewed qualitatively for incidental findings

and image quality, and quantified for standardized uptake value ratios (SUVRs). Images were coregistered to the MRI, spatially normalized, and 34 total ROIs were manually drawn and applied to the SUVR images. Global cortical measure of Aβ deposition was calculated as a weighted average of the gray matter uptake.

Arterial dynamics

Arterial stiffness was measured by pulse wave velocity (PWV) using a noninvasive and automated waveform analyzer (VP1000 plus; Omron Co., Komaki, Japan) at visit 5 (2011–2013). Participants were asked not to consume food or drinks and to refrain from tobacco and vigorous physical activity after midnight or for at least 8 hours before the visit. The instrument also calculates central aortic pressures: systolic BP (SBP) and pulse pressure. All measures were performed under standardized conditions as previously described.[26] PWV was measured across 3 vascular beds: central (carotid-femoral [cfPWV], heart-femoral PWV, heart-carotid [hcPWV]); peripheral (femoral-ankle [faPWV]); and mixed (brachial-ankle [baPWV]). PWV was calculated as the distance in centimeters between arterial sites of interest over time (in seconds) that the pressure waveforms traveled from the heart to the respective arterial sites. The average of 2 runs was calculated to determine average PWV. For baPWV, heart-femoral PWV, and faPWV, the right side measures were utilized in the analysis. Reproducibility of PWV measures obtained from this instrument in this cohort was accepted as high based on intraclass correlation coefficient (ICC): baPWV (ICC = 0.84), faPWV (ICC = 0.69), and cfPWV (ICC = 0.70).[26]

Demographic and covariate information

The primary demographic variables obtained from visit 5 (2011–2013) were included, as covariates in models: age at the time of PET scan (in years), body mass index (kg/m^2), sex, race, brachial SBP, and *APOE* ε4 status (by TaqMan assay; Applied Biosystems, Foster City, CA). Seated brachial SBP and diastolic BP (DBP) were measured twice with the participants in the seated position using an oscillometric automated sphygmomanometer, and the average of each measurement was used for analyses.

Statistical analysis

Associations among Aβ status (SUVR > 1.2), demographic factors, and cSVD were assessed by χ^2 tests and *t* tests and then adjusted for age using logistic regression. Associations between vascular measures and Aβ deposition were assessed first for Aβ status using logistic regression and then with log-transformed continuous measures of total cortical Aβ deposition using general linear models, both adjusted for covariates. Associations between vascular measures and MRI volumes for log-transformed WMH and AD signature volumes were assessed by general linear models adjusted for covariates and total intracranial volume.

Associations between vascular measures and cSVD burden were assessed first for each marker of cSVD individually and then as a composite of cSVD burden, which was created by adding together dichotomized (presence/absence = 0/1) definitions of cerebral microbleeds, lacunes, and high WMH burden to create an index from 0 to 3. For this composite, WMH was dichotomized (high/low) by median split (11,000 mm^3) adjusted for total intracranial volume. Because WMH is the most common form of cSVD and showed the strongest associations with both arterial stiffness and Aβ deposition in this and other cohorts, we simplified the overlap between cerebral Aβ deposition and cSVD into 4 groups by combining Aβ status (0/1) and WMH (0/1 by median split). Associations between overlapping high WMH and Aβ with vascular measures were assessed by multinomial logistic regression with low burden of WMH and low Aβ held as referent.

This study focuses on central measures of arterial stiffness (hcPWV and cfPWV, which is the gold standard for measuring central arterial stiffness)[27] and includes central pressures (central SBP and central pulse pressure) and how they relate to brain health. Results for peripheral vascular stiffness (baPWV and faPWV) are included in tables e-1 to e-6 (links.lww.com/WNL/A317). Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC) for all vascular measures shown per 1 SD. All multivariable models included the following covariates: age, body mass index, sex, race, and *APOE* ε4. Measures of arterial stiffness that remained significant after the above covariate adjustment were then fitted to a model that included covariates plus seated brachial SBP. Interaction terms were evaluated for potential effect modification by race, *APOE* ε4, and cognitive status for each model (significance level set at $p < 0.15$).

Results

Of the 346 participants with Aβ-PET imaging, 321 participants had detailed assessments of arterial stiffness and structural brain abnormalities (table 1). Table 2 describes the demographics of this sample by Aβ status (44% black race and 43% women). As previously reported,[15] the proportion of Aβ-positive participants was 53% (n = 169), which was more frequently seen among men, black participants, older age participants, and those with higher seated brachial SBP and DBP (table 2).

Arterial stiffness measures were correlated with SBP (with the exception of hcPWV; table e-1, links.lww.com/WNL/A317) and were similar between races (with the exception of measures of femoral segments; table e-2). Greater arterial stiffness measured from the heart to the common carotid artery (hcPWV) was significantly associated with approximately a 30% greater odds of being Aβ-positive per 1 SD increase in hcPWV (table 3; figure, A). This was only slightly attenuated after additional adjustment for brachial SBP (odds ratio [OR] = 1.28, 95% confidence interval [CI] 0.99–1.68). This relationship was further evidenced by strong linear

Table 1 Characteristics of dementia-related biomarkers in ARIC participants by age in this sample

Dementia-related biomarkers	Units, statistic	Total sample (n = 321)	Age category, y			
			65–70 (n = 41)	70–75 (n = 102)	75–80 (n = 87)	80–89 (n = 91)
Arterial stiffness						
hcPWV[a]	cm/s, mean (SD)	1,179 (432)	1,106 (394)	1,162 (407)	1,184 (465)	1,229 (444)
cfPWV	cm/s, mean (SD)	1,206 (335)	1,044 (289)	1,124 (295)	1,260 (328)	1,319 (354)
baPWV	cm/s, mean (SD)	1,698 (323)	1,506 (245)	1,660 (308)	1,746 (315)	1,777 (341)
WMH volume	mm^3, mean (SD)	1,552 (1,646)	732 (5,955)	12,945 (14,685)	16,927 (14,319)	20,757 (21,010)
AD signature volume	mm^3, mean (SD)	5,8961 (6,860)	61,187 (6,568)	60,305 (6,748)	58,058 (6,933)	57,286 (6,573)
Hippocampus	mm^3, mean (SD)	6,929 (977)	7,551 (864)	7,214 (777)	6,827 (847)	6,418 (1,078)
Parahippocampus	mm^3, mean (SD)	3,881 (570)	4,080 (549)	3,999 (513)	3,825 (575)	3,711 (587)
Entorhinal cortex	mm^3, mean (SD)	3,489 (594)	3,667 (595)	3,577 (629)	3,402 (581)	3,390 (536)
Inferior parietal	mm^3, mean (SD)	23,130 (3,430)	23,878 (3,705)	23,639 (3,250)	22,686 (3,616)	22,639 (3,227)
Precuneus	mm^3, mean (SD)	16,409 (2,215)	16,841 (2,080)	16,680 (2,411)	16,242 (2,069)	16,063 (2,146)
Cuneus	mm^3, mean (SD)	5,124 (856)	5,170 (604)	5,196 (917)	5,076 (959)	5,065 (779)
Total intracranial volume	mm^3, mean (SD)	1,370,429 (155,175)	1,358,298 (151,542)	1,356,177 (151,291)	1,372,112 (153,536)	1,390,281 (159,750)
Amyloid deposition	SUVR, mean (SD)	1.30 (0.26)	1.17 (0.12)	1.28 (0.24)	1.33 (0.45)	1.34 (0.31)
Amyloid-positive	SUVR > 1.2, n, %	169, 53	11, 27	52, 51	57, 66	49, 54
Burden of cSVD	0–3, mean (SD)	0.93 (0.26)	0.61 (0.74)	0.88 (0.85)	1.05 (0.91)	1.03 (0.82)
Cerebral microbleeds	Presence, n, %	80, 25	9, 22	29, 28	25, 28	17, 19
Lacunar infarcts	Presence, n, %	62, 19	7, 17	20, 20	16, 18	19, 21
High WMH	Presence, n, %	158, 49	9, 22	41, 40	50, 57	58, 64
Large infarcts	Presence, n, %	91, 28	8, 20	31, 30	24, 28	28, 31

Abbreviations: AD = Alzheimer disease; ARIC = Atherosclerosis Risk in Communities; baPWV = brachial-ankle pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; cSVD = cerebral small vessel disease; hcPWV = heart-carotid pulse wave velocity; SUVR = standardized uptake value ratio; WMH = white matter hyperintensity.
[a] n = 309, data missing for hcPWV for 11 individuals.

associations between hcPWV and the log-transformed extent of total cortical Aβ deposition (β = 0.04, SE = 0.01, $p < 0.01$) independent of covariates and brachial SBP (table 4). Associations between hcPWV and Aβ status appear to be modified by cognitive status (p interaction = 0.075) with a graded effect in cognitively normal participants (OR = 1.19, 95% CI 0.89–1.59) and most pronounced in MCI (OR = 3.59, 95% CI 1.15–9.20). Significant interactions were not observed for the central measures.

In support of the observed associations between central PWV measures and Aβ status, higher central aortic SBP was associated with nearly a 6-fold-higher odds of being Aβ-positive (OR = 6.08, 95% CI 1.40–26.21, adjusted for covariates; table 3). Central aortic SBP was highly correlated with brachial SBP, which precluded further adjustment for brachial SBP (table e-1, links.lww.com/WNL/A317). Central arterial stiffness was also associated with smaller brain volumes in areas affected by AD, where cfPWV was significantly associated with smaller AD signature regional volumes (in mm^3, β = −528, SE = 239, p value = 0.03), adjusted for covariates and intracranial volume (table 4), primarily driven by smaller volumes in the precuneus. Other measures of arterial stiffness and central pressures were not significantly associated with Aβ deposition (tables 3 and e-3).

Among this sample of ARIC participants, greater central arterial stiffness was also associated with a greater burden of cSVD as measured with a cumulative cSVD burden (2 or more forms of cSVD [n = 77], OR = 1.80, 95% CI 1.26–2.59; 1 form of cSVD [n = 154], OR = 1.27, 95% CI 0.93–1.74; compared with no evidence of cSVD [n = 115]), which was independent of covariates and SBP (figure, B). Associations between central arterial stiffness and evidence of cSVD were

Table 2 Participant characteristics and cortical Aβ deposition

Demographics	Total cortical Aβ deposition: Aβ-positive SUVR > 1.20 (n = 169) Mean (SD)	Total cortical Aβ deposition: Aβ-negative SUVR ≤ 1.20 (n = 152) Mean (SD)	Unadjusted *p* Value	Age-adjusted *p* Value
Age, y	77 (5)	75 (6)	0.006	—
Weight, kg	81 (17)	79 (17)	0.314	0.120
BMI, kg/m^2	30 (6)	28 (5)	0.064	0.258
Heart rate, beats/min	64 (12)	63 (10)	0.414	0.449
Systolic BP, mm Hg	132 (18)	126 (14)	<0.001	<0.001
Diastolic BP, mm Hg	67 (11)	64 (10)	0.002	<0.001

Demographics	Total cortical Aβ deposition: Aβ-positive SUVR > 1.20 (n = 169) n (%)	Total cortical Aβ deposition: Aβ-negative SUVR ≤ 1.20 (n = 152) n (%)	Unadjusted *p* Value	Age-adjusted *p* Value
***APOE* ε4**	66 (39)	30 (20)	<0.001	<0.001
Black race	91 (54)	51 (34)	<0.001	<0.001
Women	65 (38)	74 (49)	0.065	0.046
Mild cognitive impairment	60 (36)	25 (17)	<0.001	<0.001

Abbreviations: Aβ = β-amyloid; BMI = body mass index; BP = blood pressure; SUVR = standardized uptake value ratio.

primarily driven by evidence of high WMH (median split OR = 1.43, 95% CI 1.09–1.88) and total cerebral microbleeds (80/321 [25% prevalence], OR = 1.46, 95% CI 1.09–1.95; data not shown). No interactions among arterial stiffness, *APOE* ε4, or race were observed for other dementia-related outcomes (p interaction all >0.15; figure, A–C).

Arterial stiffness is associated with concomitant cSVD and Aβ deposition

Brain Aβ deposition was significantly associated with evidence of cSVD, specifically high WMH and deep microbleeds (table e-4, links.lww.com/WNL/A317). Greater arterial stiffness was associated with the overlapping burden of high WMH and Aβ deposition (92/321, 29%), where each SD increase in cfPWV was associated with a 44% higher odds of having both forms of dementia-related pathology (OR = 1.44, 95% CI 1.01–2.06) when compared to the individuals with little evidence of either pathology (tables 5 and e-5; figure, C).

Table 3 Associations among central arterial stiffness, hemodynamics, and brain Aβ deposition

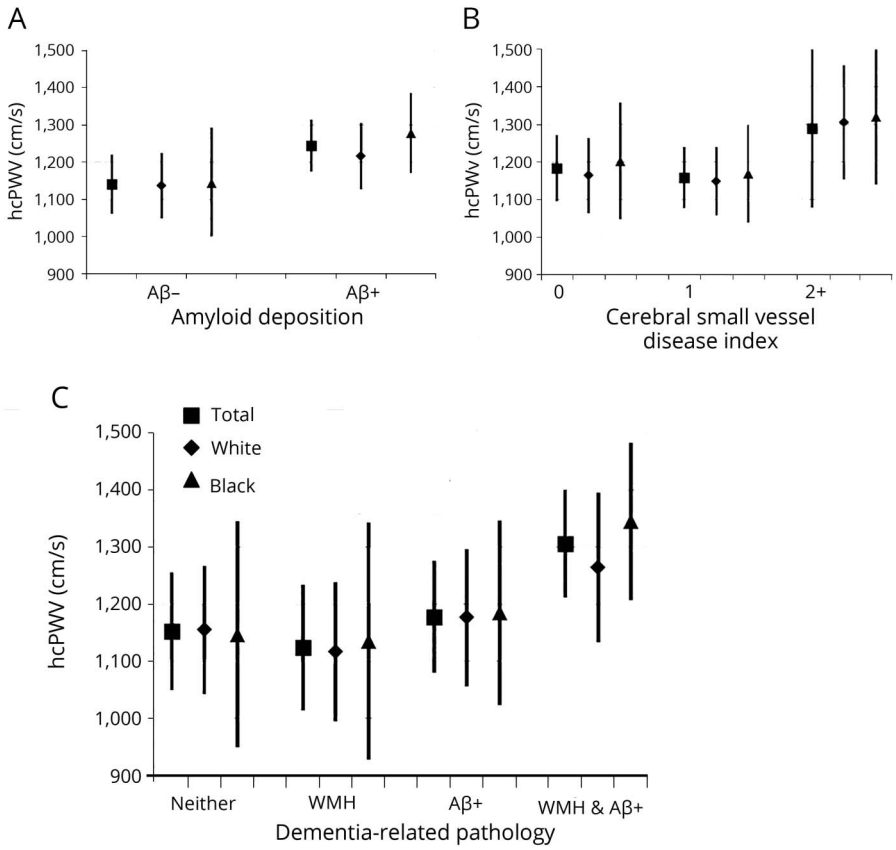
	No.	Total cortical Aβ deposition Aβ-positive, SUVR > 1.2, OR (95% CI)
cfPWV	321	1.04 (0.81–1.34)
hcPWV	309	1.31 (1.01–1.71)
cSBP, mm Hg	321	6.08 (1.40–26.21)
cPP	321	3.97 (0.70–22.50)

Abbreviations: Aβ = β-amyloid; cfPWV = carotid-femoral pulse wave velocity; CI = confidence interval; cPP = central pulse pressure; cSBP = central aortic systolic blood pressure; hcPWV = heart-carotid pulse wave velocity; OR = odds ratio; SUVR = standardized uptake value ratio.
OR and 95% CI per 1 SD relative to Aβ-negative status (SUVR ≤ 1.2) adjusted for age, body mass index, sex, race, and *APOE* ε4 status.

Discussion

In this biracial cohort of older adults in the ARIC Study, we observed that arterial stiffness of the central and carotid segments was associated with the burden of multiple forms of dementia-related pathology, including cSVD, Aβ deposition, and smaller brain volumes in AD-prone regions of the brain. These relationships were similar for black and white older adults and the strongest among individuals with MCI. Greater arterial stiffness, measured by higher hcPWV, corresponds to the faster speed at which the pulse travels from the heart to the carotid artery and was most strongly associated with greater Aβ burden in this study. This marked increased pulsatile flow velocity and central pressure observed among Aβ-positive individuals was equivalent to a 103 cm/s faster PWV and a 25 mm Hg higher central aortic SBP relative to Aβ-negative individuals (figure, A–C). Greater arterial stiffness was strongly associated with the overlap of dementia-related pathology (WMH, cerebral microbleeds, and Aβ deposition) and lower brain volumes in regions susceptible to AD and Aβ deposition. The observed findings replicate our previous

Figure hcPWV as it relates to dementia-related pathology by race



hcPWV (measured in centimeters per second) relates to (A) Aβ deposition (Aβ status, positive or negative, based on SUVR > 1.2) measured by PET; (B) the burden of cerebral small vessel disease (0, 1, and 2 or more forms); and (C) the overlap of common dementia-related pathology, Aβ status, and high WMH volume (high vs low, based on median split) measured by MRI. Shown as means and 95% confidence interval adjusted for age, sex, race, and *APOE* ε4 status. Aβ = β-amyloid; hcPWV = heart-carotid pulse wave velocity; SUVR = standardized uptake value ratio; WMH = white matter hyperintensity.

results relating arterial stiffness to both white matter disease and the extent of Aβ deposition in white older adults[11,13] and extend them to a younger cohort of black and white older adults to show no differences by race and stronger associations with MCI.

This work contributes to a growing literature showing that arterial stiffness and elevated central pulsatility are important modifiable risk factors for dementia pathology in older adults. Arterial stiffness increases monotonically with age across multiple vascular beds and is accelerated by cardiometabolic

Table 4 Relationships for continuous measures of arterial stiffness with brain β-amyloid deposition and MRI regions

	cfPWV			hcPWV		
	β	**SE**	***p* Value**	**β**	**SE**	***p* Value**
Global amyloid burden,[a] SUVR	−0.02	0.0141	0.2124	0.04	0.01	0.0093
AD signature volume,[b] mm³	−528.16	239.91	0.0284	−102.11	244.83	0.6769
Hippocampus	−19.18	50.07	0.7020	−21.13	50.48	0.6758
Parahippocampus	15.84	31.92	0.6201	−51.23	32.07	0.1112
Entorhinal cortex	−22.39	32.10	0.4861	13.86	32.53	0.6702
Inferior parietal	−183.39	144.37	0.2049	4.70	146.40	0.9744
Precuneus	−276.44	83.48	0.0010	−48.59	84.77	0.5669
Cuneus	−42.60	40.43	0.2929	28.01	40.68	0.4916

Abbreviations: AD = Alzheimer disease; cfPWV = carotid-femoral pulse wave velocity; hcPWV = heart-carotid pulse wave velocity; SUVR = standardized uptake value ratio.
[a] Adjusted for age, body mass index, sex, race, and *APOE* ε4 status.
[b] Adjusted for age, body mass index, sex, race, *APOE* ε4 status, and intracranial volume.

Table 5 Central arterial stiffness and pressure as they relate to the overlap between white matter disease and Aβ deposition

		Burden of white matter disease and Aβ deposition			
	No.	Low WMH and Aβ− (n = 86)	High WMH and Aβ− (n = 66)	Low WMH and Aβ+ (n = 77)	High WMH and Aβ+ (n = 92)
cfPWV	321	Reference	1.18 (0.80–1.72)	0.84 (0.57–1.24)	1.44 (1.01–2.06)
hcPWV	309	Reference	0.93 (0.62–1.40)	1.07 (0.72–1.58)	1.41 (0.98–2.02)
cSBP, mm Hg	321	Reference	0.39 (0.05–3.36)	4.59 (0.78–26.90)	3.52 (0.60–20.62)
cPP	321	Reference	0.43 (0.03–5.77)	3.36 (0.39–29.02)	2.21 (0.25–19.36)

Abbreviations: Aβ = β-amyloid; cfPWV = carotid-femoral pulse wave velocity; cPP = central pulse pressure; cSBP = central aortic systolic blood pressure; hcPWV = heart-carotid pulse wave velocity; WMH = white matter hyperintensity.
Data represent odds ratio (95% confidence interval) unless otherwise indicated. Models adjusted for age, body mass index, sex, race, and *APOE* ε4 status.

disorders.[28–32] Arterial stiffening is proposed to be a key hemodynamic process that results in the transmission of excessive pulsatile pressure from the aorta to the distal vascular beds, which damages the microvascular structure of the brain and kidneys, evidenced by white matter disease, other forms of cSVD, and renal disease.[32] This study provides consistent evidence that greater arterial stiffening may contribute to dementia through its associations with white matter disease, cerebral microbleeds, and Aβ deposition, pathology that is consistent with both cerebral amyloid angiopathy and AD.

We have already shown that greater arterial stiffness is also associated with a higher rate of Aβ accumulation over time in older adults,[13] but it remains unclear how arterial stiffening may contribute directly to Aβ deposition in the brain.[33] It is possible that these 2 common age-related processes occur in parallel and do not contribute directly to the progression of the other. There is considerable ongoing research and debate as to whether carotid or intracerebral stiffness, distensibility, and pulsatility are more important for brain health than central aortic stiffness.[34] Given the associations between arterial stiffness and greater intracerebral vascular pulsatility[35] and cSVD, it is likely that excess pulsatile pressure delivered by stiffer arteries damages the cerebral microvasculature of the basil ganglia while delivering lower cortical cerebral blood flow to the cortex and subcortical white matter. The key locus of this injury is the arterioles and perivascular spaces within the cerebral cortex: alterations in the penetrating arterioles can be hypothesized to disrupt intramural and lymphatic transport of Aβ from the brain.[35] The lack of consistent associations between cSVD measures and Aβ burden presented here and in other studies suggests that these forms of dementia pathology are largely unrelated.[14] Thus, arterial stiffness may link the progression of these independent forms of dementia pathology.

The associations among central arterial stiffness, WMH, and brain Aβ deposition have been documented in very elderly adults aged 80+ years[11] and here in a younger, biracial cohort of older adults aged 70+ years. These data suggest that life course factors that promote arterial stiffness would also be associated with Aβ deposition in the brain. This remains to be investigated in cohorts specifically with hypertension and metabolic disorders that contribute to the faster progression of central arterial stiffness with age.[31,36,37] Greater midlife and antemortem pulse pressure are associated with a greater burden of Aβ plaque and neurofibrillary tangles in the brain.[38,39] While elevated brachial SBP, DBP, and hypertension have been associated with greater Aβ deposition in the brain,[9,10,12] here we show that associations between arterial stiffness and Aβ largely remain independent of brachial pressure. Taken together, this study adds to a growing literature linking cardiometabolic disorders to accelerated arterial stiffness[37] and from arterial stiffness to multiple aspects of dementia pathology.[40] Arterial stiffness may serve as an important intermediary linking cardiometabolic disorders and dementia pathology in both white and black older adults.

There are some important limitations to this study. First, this study is cross-sectional in nature, but consistent with our previous longitudinal work.[13] Second, it is possible that these results may still be biased by unmeasured confounding, especially in the absence of microvascular measures and tau pathology that may fall within the causal pathway. Specifically, future work would benefit from more direct measures of intracranial pulsatility and blood flow as well as novel microinfarcts visible on MRI.[41] Additional cerebral hemodynamic measures may mediate the relationships between arterial stiffness and cerebral pathology and provide mechanistic insights into causal pathways. It is important to note that these modest associations are observed in older adults free from dementia, who are by selection less likely to show signs of later-stage disease processes, including severe amyloid deposition, neurodegeneration, and cognitive and functional disabilities. Participants in this study are on average 10 years younger than those in our previous work and show less arterial stiffness.[11,13] Selection bias may mitigate the relationships between arterial stiffness and brain structural abnormalities; however, we still detect associations between arterial stiffness and dementia-related pathology in the brain. Future

longitudinal studies assessing changes in arterial stiffness, brain structural abnormalities, cognitive decline, and conversion to dementia are ongoing.

These findings show that greater arterial stiffness as measured by PWV is associated with greater evidence of multiple dementia-related pathologies in the brain, adding to a growing literature showing that arterial stiffness is a risk factor for age-related dementias. The mechanical transference of greater pulsatile pressure waveforms along stiff arteries is proposed to result in mechanical damage to the cerebral small vessels, which may contribute to cSVD and accelerated Aβ accumulation in older adults, through yet unknown means. These 2 forms of dementia pathology are common in older adults and appear to exacerbate brain atrophy and cognitive decline. Interventions aimed at reducing cerebral pulsatility by improving central vascular function may affect dementia risk by preventing dementia-related pathology.

Author contributions

Timothy M. Hughes: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Lynne E. Wagenknecht: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding. Suzanne Craft: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. Akiva Mintz: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, study supervision. Gerardo Heiss: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, obtaining funding. Priya Palta: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Dean F. Wong: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Yun Zhou: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. David S. Knopman: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Thomas H. Mosley: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Rebecca F. Gottesman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding.

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Disclosure

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FULL-LENGTH ARTICLE NPub.org/2vdu4t

Arterial stiffness and dementia pathology

Atherosclerosis Risk in Communities (ARIC)-PET Study

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Study question

Is arterial stiffness associated with evidence of cerebral small vessel disease (cSVD) and β-amyloid (Aβ) deposition in both white and black older adults?

Summary answer

Arterial stiffness is associated with greater burden of cSVD, Aβ deposition, and their co-occurrence in white and black older adults.

What is known and what this paper adds

Hypertension is linked to cSVD and Aβ deposition, but the overlying mechanism(s) remains unclear. This study provides evidence for the role of arterial stiffness in mediating this link irrespective of race.

Participants and setting

This study examined 321 participants (age, 65–89 years; 44% black; 26% with mild cognitive impairment) from the Atherosclerosis Risk in Communities study who underwent detailed assessments of arterial stiffness and structural brain abnormalities by MRI and PET. These assessments took place in 2011–2013 at sites in MS, MD, and NC.

Design, size, and duration

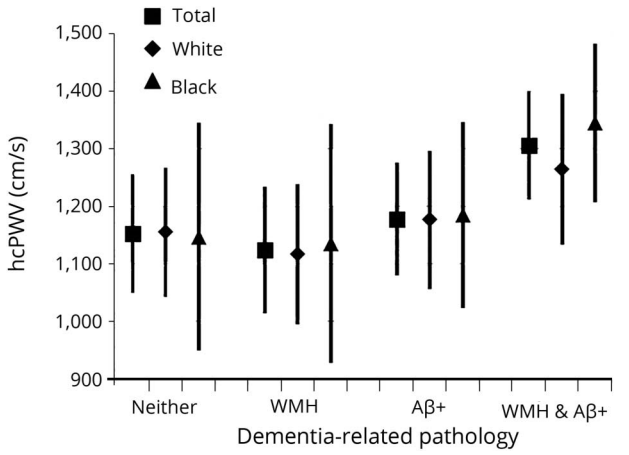
This study assessed central arterial stiffness by measuring pulse wave velocity (PWV), including carotid-femoral PWV (cfPWV), and heart-carotid PWV (hcPWV). Aβ deposition was measured with ^{18}F-AV-45 PET. Signs of cSVD such as white matter hyperintensities (WMHs) were detected with MRI.

Primary outcomes

The primary outcomes were associations of PWV measurements with cSVD-related signs and Aβ deposition.

Main results and the role of chance

Greater hcPWV-measured central arterial stiffness was associated with greater Aβ deposition (odds ratio, 1.31; 95% CI, 1.01–1.71). Greater cfPWV-measured central arterial stiffness



was associated with having lower brain volumes in regions susceptible to Alzheimer disease (β = −1.5 ± 0.7 mm^3; p = 0.03), higher WMH burden (odds ratio, 1.6; 95% CI, 1.2–2.1), and higher odds of co-occuring high WMH burden and Aβ-positive scans (odds ratio, 1.4; 95% CI, 1.1–2.1). The observed associations between arterial stiffness and dementia pathology were similar for White and Black participants.

Bias, confounding, and other reasons for caution

This study was cross-sectional rather than longitudinal. Findings were not validated with histopathologic measurements for microvascular and tau pathologies.

Generalizability to other populations

While findings are evident in both Black and White older adults, generalization to younger cohorts is limited.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.