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Original Article

Vascular stiffness predicts plasma markers of neurodegeneration among older African Americans

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ABSTRACT

Background: Vascular health is a critical and potentially modifiable determinant of Alzheimer's disease (AD) risk, yet its contribution to early neurodegenerative processes remains incompletely understood, particularly among African Americans, who experience a disproportionate AD burden. Estimated pulse wave velocity (ePWV), derived from age and blood pressure, provides a scalable index of vascular stiffness.
Objectives: To examine associations between vascular stiffness and plasma biomarkers of AD-related neurodegeneration in older African Americans.
Design: Cross-sectional observational study.
Setting: Community-based aging cohort study conducted at an academic research center.
Participants: A total of 145 cognitively unimpaired older African Americans (mean age=71.18±6.83 years; 110 women).
Measurements: ePWV was calculated using validated equations based on age and blood pressure. Plasma biomarkers included phosphorylated tau217 (p-tau217; N=145), phosphorylated tau231 (p-tau231; N=126), glial fibrillary acidic protein (GFAP; N=126), neurofilament light chain (NfL; N=126), and amyloid-β42/40 ratio (Aβ42/40; N=126). Multivariable regression models adjusted for sex, education, pulse pressure, waist-to-hip ratio, global cognition, and hypertension status.
Results: Higher ePWV was significantly associated with higher plasma concentrations of p-tau217 (β=0.34, p=.006), GFAP (β=0.55, p<.001), and NfL (β=0.52, p<.001), but not with p-tau231 and Aβ42/40 (p>.05).
Conclusions: Greater vascular stiffness, indexed by elevated ePWV, was associated with circulating markers of tau-related neurodegeneration, astrocytic activation, and axonal injury in cognitively unimpaired older African Americans. The absence of association with p-tau231 and Aβ42/40 suggests preferential effects on neurovascular damage and later tau-related processes, but no primary effect on biomarkers related to Aβ pathology, still highlighting vascular health as a modifiable target for AD prevention.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of misfolded proteins, neuroinflammation, and synaptic and axonal degeneration [1]. Vascular health is a major and early determinant of AD risk, preceding and potentially accelerating amyloid and tau accumulation [2]. Vascular stiffness, characterized by the loss of elasticity in the arterial walls, is a hallmark of vascular health [3–5]. Age-associated increases in vascular stiffness heighten transmission of pulsatile blood pressure and blood flow to fragile cerebral microvessels, impairing microvascular function [6]. These hemodynamic alterations impair neurovascular coupling, intensify glial reactivity, and weaken blood–brain barrier integrity, thereby creating a biological environment that facilitates neurodegenerative processes relevant to AD [2,6].

Carotid–femoral pulse wave velocity (cfPWV) is the gold-standard noninvasive measure of vascular stiffness and quantifies the speed at which the pressure wave generated by each heartbeat travels between the carotid artery in the neck and the femoral artery in the groin [7]. Because pressure waves propagate more rapidly through stiff vessels than through elastic ones, higher cfPWV values reflect reduced elasticity of the central arteries, particularly the aorta, and diminished buffering of pulsatile blood flow. However, despite its strong physiological relevance, the clinical and research utility of cfPWV is limited by the need for specialized equipment, technical expertise, and standardized acquisition protocols [8,9]. To address these barriers, regression-based equations were developed to estimate pulse wave velocity from commonly collected clinical variables, primarily chronological age and blood pressure [10]. Estimated PWV (ePWV), derived from age and blood pressure, provides a practical and scalable index of vascular stiffness, demonstrating strong construct validity as a marker of vascular health [11]. It also correlates with cognitive impairment, small vessel disease, and dementia risk across multiple cohorts [12–15]. As it is inexpensive, noninvasive, and easily obtained from routine clinical assessment, ePWV offers a scalable tool for investigating how vascular stiffness contributes to brain vulnerability and AD-related neurodegeneration [16,17]. Understanding the neurobiological consequences of vascular stiffness is especially critical in older African American adults, who experience a disproportionate burden of both AD and vascular risk factors, particularly hypertension, yet remain markedly underrepresented in aging, neuroimaging, and biomarker research [18,19]. Identifying accessible vascular markers that capture early neurodegenerative susceptibility in this population is, therefore, a critical scientific and public health priority.

Recent advances in ultrasensitive plasma assays enable peripheral detection of molecular signatures central to AD pathology, including phosphorylated tau (p-tau), astrocytic activation, axonal injury, and amyloid dysregulation [20–22]. Plasma p-tau has emerged as a leading blood-based biomarker of AD risk, demonstrating diagnostic accuracy and strong disease specificity [23]. While plasma p-tau217 performs well across clinical stages of AD and shows robust associations with tau pathology [22–26], plasma p-tau231 may be particularly sensitive to very early pathological changes, potentially preceding overt amyloid accumulation [27–30]. Astrocytic activation is a hallmark of early AD, reflecting neuroinflammatory responses that emerge before overt neuronal loss [31]. Glial fibrillary acidic protein (GFAP) serves as a circulating marker of this process and has shown promise as an early indicator of AD-related neuroinflammation [32]. Axonal injury is another key feature of AD progression [33], and neurofilament light chain (NfL) provides a sensitive index of neuroaxonal damage, even among cognitively unimpaired individuals [34]. Disrupted amyloid processing, reflected by the plasma amyloid-β 42/40 ratio (Aβ42/40), initiates molecular cascades that drive downstream tau pathology and neurodegeneration [35]. Early alterations in these plasma biomarkers have been linked to elevated AD risk, years before the onset of clinical symptoms [22]. Despite growing evidence linking vascular health to AD risk, the relationship between vascular stiffness indexed by ePWV and circulating plasma biomarkers of AD pathology remains poorly characterized, particularly in African American populations at elevated vascular and AD risk. Specifically, elevated AD risk is defined at the population level and reflects older age and a high burden of vascular risk factors, notably hypertension, in African American adults, rather than individual-level amyloid positivity, family history, or genetic stratification [36]. Vascular stiffness may represent a mechanistic bridge linking compromised vascular health to early molecular signatures of neurodegeneration detectable in blood, positioning ePWV as a scalable marker of early neurodegenerative susceptibility.

In the present study, we examined associations between vascular stiffness indexed by ePWV and key plasma biomarkers of AD pathology, including p-tau217, p-tau231, GFAP, NfL, and Aβ42/40, in older African Americans. We hypothesized that greater vascular stiffness would be associated with higher levels of plasma biomarkers reflecting tau-related neurodegeneration, astrocytic activation, and axonal injury. By focusing on a population disproportionately affected by both diminished vascular health and elevated AD risk, this study aims to clarify vascular contributions to early neurodegenerative burden and identify accessible markers that may inform early detection and prevention strategies of AD among cognitively unimpaired older African Americans.

2. Methods

2.1. Participants

Participants were drawn from an ongoing longitudinal cohort at Rutgers University–Newark designed to characterize AD risk and aging trajectories in cognitively unimpaired older African American population. The cohort systematically integrates multidimensional data—including cognitive performance, cardiometabolic health, lifestyle factors, genetic risk, and multimodal neuroimaging—to elucidate determinants of brain aging. Recruitment was conducted through the *Aging & Brain Health Alliance*, a long-standing (established in 2006) university–community partnership that engages older adults across the greater Newark area through senior centers, public and subsidized housing networks, faith-based organizations, and local health and wellness agencies. This community-integrated framework enables sustained participation of a sample at elevated AD risk, traditionally underrepresented in aging and AD research.

Participants aged 60 years or older were eligible for inclusion in the current *Aging & Brain Health Alliance* study. Elevated AD risk in this cohort reflects epidemiologic and vascular risk factors associated with aging in African American populations and does not imply biomarker-confirmed Alzheimer's pathology, as amyloid status, family history, and genetic risk were not used as inclusion criteria. Exclusion criteria included any diagnosed neurodegenerative disorder; use of dementia-related pharmacologic agents (e.g., memantine, galantamine, donepezil); a history of learning disabilities; self-reported alcohol or substance abuse; exposure to general anesthesia within the preceding three months; and refusal or inability to provide saliva and/or blood samples. Cognitively unimpaired status was defined by the absence of a clinical diagnosis of mild cognitive impairment or dementia. All procedures were approved by the Rutgers University Institutional Review Board and conformed to the ethical guidelines of the Declaration of Helsinki.

2.2. Procedure

Potential participants first completed a telephone screening to determine preliminary eligibility. Individuals who met these criteria provided written informed consent and subsequently underwent in-person evaluations, including assessments of color vision and global cognitive status. Those who passed these screening procedures were invited for a comprehensive laboratory visit, during which cognitive testing was administered, and saliva and blood samples were collected.

Color blindness was an exclusion criterion at the time of cohort recruitment, as the broader neuropsychological battery administered in the Aging & Brain Health Alliance study includes several tasks that rely on color-based stimuli. Color vision screening was therefore conducted to ensure valid administration of these assessments and was not specific to the analyses presented in the current study.

Additional neuropsychological testing was conducted during laboratory visits as part of the larger longitudinal cohort study but was not used in the present analyses.

2.3. Measures

2.3.1. Demographics

Demographic variables included chronological age measured in years, sex, and years of education.

2.3.2. Global cognitive function

The Montreal Cognitive Assessment (MoCA) was administered as a descriptive measure of global cognition. This test evaluates multiple cognitive domains, including visuospatial and executive functioning, naming, memory, attention, language, abstraction, and orientation. Higher scores indicate better global cognitive performance [37–39].

MoCA score of ≥24 was used as a screening threshold to exclude moderate to severe cognitive impairment. Cognitively unimpaired status was further supported by the absence of a clinical diagnosis of mild cognitive impairment or dementia, as determined through clinical evaluation conducted by a licensed neuropsychologist as part of the larger cohort protocol.

2.3.3. Anthropometrics

Physical measurements included waist and hip circumference. These values were used to compute waist-to-hip ratio (WHR). Waist and hip circumferences were obtained according to WHO standardized procedures using a flexible, non-elastic measuring tape [40]. Measurements were taken with participants standing upright, feet shoulder-width apart, arms relaxed, and breathing normally.

Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, with the tape positioned horizontally and held snugly against the skin without compression. Measurements were taken at the end of a normal expiration.

Hip circumference was measured at the level of the maximum protuberance of the buttocks, with the tape held horizontally and parallel to the floor. All circumference measurements were recorded to the nearest 0.1 cm and were used to compute WHR.

WHR was selected as the primary anthropometric index because it more specifically reflects central adiposity and visceral fat distribution, which are closely linked to vascular stiffness, cardiometabolic dysfunction, and neurovascular risk in African Americans [41].

2.3.4. Blood pressure assessment

Blood pressure was measured using standardized clinical procedures [42]. Participants were seated with feet flat on the floor, back supported, and instructed to remain relaxed, still, and silent during measurement. An automated oscillometric monitor (Yuwell YE660E Electronic Blood Pressure Monitor, Yuwell, Jiangsu, China) was used to obtain systolic (SBP) and diastolic (DBP) blood pressure from the non-dominant arm. Proper cuff placement and alignment with the brachial artery were ensured for every assessment. If an elevated reading was detected, a confirmatory measurement was taken on the dominant arm.

Hypertension status was defined according to American Heart Association guidelines: SBP ≥130 mmHg was classified as hypertensive, whereas SBP < 130 mmHg was classified as normotensive [43].

2.3.5. Estimated pulse wave velocity (ePWV)

Vascular stiffness was indexed using ePWV, which was derived from each participant's age and mean arterial pressure (MAP) using previously validated regression equations [11,44]. Higher ePWV values indicate greater vascular stiffness and poorer vascular health. ePWV was calculated using the following formula, where chronological age is in years, and MAP is in mmHg. Pulse pressure (PP), MAP, and ePWV were calculated as:

$$\mathbf{PP} = \{SBP - DBP\}$$

$$\mathbf{MAP} = DBP + 0.40^{*}\{PP\}$$

$$\begin{aligned}\mathbf{ePWV} = {} & 9.587 - \{0.402 * age\} + \left\{4.560 * 0.001 * age^{2}\right\} \\ & - \left\{2.621 * 0.00001 * age^{2} * MAP\right\} \\ & + \{3.176 * 0.001 * age * MAP\} - \{1.832 * 0.01 * MAP\}\end{aligned}$$

ePWV values in older adults generally fall within the 8–17 m/s range, with higher values reflecting greater vascular stiffness and increased cardiometabolic and neurovascular risk.

2.3.6. Plasma biomarkers

Fasting plasma samples were analyzed to quantify circulating biomarkers of AD–related neuropathology, including phosphorylated tau isoforms, markers of astroglial activation, axonal injury, and amyloid processing. All blood samples were collected by a certified phlebotomist using 6–10 mL EDTA-coated tubes. Within one hour of collection, samples were centrifuged, and plasma was aliquoted into 0.5 mL polypropylene tubes and stored at –80°C until shipment for assay.

2.3.6.1. Plasma p-tau231, GFAP, NfL, and Aβ42/40 (Zetterberg laboratory). One 0.5 mL EDTA plasma aliquot per participant was shipped on dry ice to the Clinical Neurochemistry Laboratory at the University of Gothenburg for analysis. Plasma p-tau231, GFAP, NfL; Aβ42/40 were quantified using ultrasensitive Single Molecule Array (Simoa) assays on the Quanterix HD-X platform, following previously validated protocols [29]. Concentrations were expressed in pg/mL.

2.3.6.2. Plasma p-tau217 (Elahi laboratory). A separate 0.5 mL EDTA plasma aliquot from each participant was shipped on dry ice to the Icahn School of Medicine at Mount Sinai for quantification of plasma p-tau217. Plasma p-tau217 concentration (pg/mL) was measured using the ultra-sensitive Simoa™ assay on the LucentAD Diagnostics platform, following established analytical procedures [45].

2.4. Statistical analysis

Statistical analyses were conducted in Jamovi (version 2.7.31.0). Descriptive statistics, including means, standard deviations, and histograms, were examined to assess data distributions and identify potential outliers. Plasma biomarker distributions demonstrated right skewness and were therefore log-transformed (LN) prior to analysis to better meet assumptions of normality. All regression analyses involving plasma biomarkers were conducted in ln-transformed space.

Assumptions of normality were evaluated using visual inspection and skewness/kurtosis indices following transformation. Missing data were minimal (<5 % across variables) and were treated as missing during statistical analyses. No imputation procedures were applied, and all analyses were conducted using available data.

Analyses were performed using multiple linear regression models, with covariates included in every model to adjust for demographic, vascular, and clinical factors when estimating associations between ePWV and each plasma biomarker. Covariates included sex, years of education, pulse pressure, waist-to-hip ratio, MoCA scores, and hypertension status. For each model, we report overall model fit (R^2), standardized coefficients (β), and significance values. Bonferroni correction was applied for post-hoc analysis. Statistical significance was defined as

$p < .05$ (two-tailed).

3. Results

3.1. Participant characteristics

Demographic and clinical characteristics are summarized in Table 1. The final sample included 145 cognitively unimpaired older African American adults (mean age = 71.18 ± 6.83 years; 110 women). Participants had a mean of 14.04 ± 2.16 years of education and a mean MoCA score of 27.36 ± 1.90, consistent with intact global cognition. Systolic BP, diastolic BP, pulse pressure, hypertension status, ePWV, WHR, and LN-transformed values of plasma biomarkers [p-tau217 (N = 145), p-tau231 (N = 126), GFAP (N = 126), NfL (N = 126), and Aβ42/40 (N = 126)] are also reported in Table 1. Original (raw) plasma biomarker values are provided in Table 1.

A summary of all multivariable regression models examining associations between ePWV and plasma biomarkers is provided in Table 2.

Table 1
Distribution of demographic data.

			Mean ± SD	Min / Max
Demographics	Age (years)		71.18 ± 6.83	60 / 92
	Sex [N (%)]	Women	110 (75.9)	–
		Men	35 (24.1)	–
	Education (years)		14.04 ± 2.16	7 / 20
Cognition	MoCA		27.36 ± 1.90	20 / 30
Blood Pressure	Systolic BP (mmHg)		142.25 ± 20.33	99 / 203
	Diastolic BP (mmHg)		79.49 ± 10.08	55 / 106
	Pulse Pressure (mmHg)		62.75 ± 16.99	30 / 115
	HTN Status [N (%)]	Normotensive	73 (50.3)	–
		Hypertensive	72 (49.7)	–
Vascular Stiffness	ePWV (m/s)		8.90 ± 2.18	4.76 / 15.20
Anthropometrics	Waist Circumference (cm)		100.52 ± 18.60	39 /156
	Hip Circumference (cm)		111.44 ± 18.10	43 / 147
	WHR		0.90 ± 0.10	0.33 / 1.27
Plasma Biomarkers (LN-transformed concentrations) *	p-tau 217		-1.31 ± 0.59	-2.81 / 062
	p-tau 231		3.47 ± 1.00	2.06 / 5.24
	GFAP		4.91 ± 0.55	4.24 / 5.80
	NfL		2.87 ± 0.58	2.18 / 3.60
	Aβ42/40		-2.76 ± 0.13	-2.90 / -2.52
Plasma Biomarkers (Raw values)	p-tau 217		0.320 ± 0.6	0.06 / 1.87
	p-tau 231		51.4 ± 62.3	7.91 / 189.13
	GFAP		156 ± 92.2	69.6 / 332.0
	NfL		20.4 ± 11.5	9.90 / 36.8
	Aβ42/40		0.060 ± 0.004	0.05 / 0.08

Aβ = Amyloid beta; BP = Blood Pressure; ePWV = Estimated Pulse Wave Velocity; GFAP = Glial Fibrillary Acidic Protein; HTN = Hypertension; Max = Maximum; Min = Minimum; MoCA = Montreal Cognitive Assessment; N = Number; NfL = Neurofilament Light; p-tau = Phosphorylated tau; SD = Standard Deviation; WHR = Waist-to-hip ratio; % = Percentage

* Plasma biomarker values are natural log–transformed (LN) unless otherwise indicated.

3.2. Greater vascular stiffness (Higher ePWV) is associated with elevated plasma p-tau217, but not p-tau231, LN-Transformed concentrations

All participants (N = 145) had available measures of ePWV and plasma p-tau217 concentrations. Higher ePWV was significantly associated with higher plasma p-tau217 concentrations (β = 0.34, p = .006), accounting for 12 % of the variance (R^2 = 0.12; Fig. 1 a; Table 2).

Among participants with available plasma p-tau231 data (N = 126), ePWV was not significantly associated with plasma p-tau231 concentrations (β = −0.05, p = .739) (Fig. 1 d; Table 2). The full multivariable model explained 23.6 % of the variance in plasma p-tau231 levels (R^2 = 0.24), with sex (p = .046) and education (p = .042) emerging as significant covariates.

3.3. Greater vascular stiffness (Higher ePWV) is associated with elevated GFAP and NfL LN-Transformed concentrations

Among the 145 participants, 126 had available plasma GFAP and NfL data. Higher ePWV was strongly associated with higher plasma GFAP concentrations (β = 0.55, p < .001), explaining 33 % of the variance (R^2 = 0.33; Fig. 1 b; Table 2).

Similarly, higher ePWV was significantly associated with higher plasma NfL levels (β = 0.52, p < .001), accounting for 25 % of the variance (R^2 = 0.25; Fig. 1 c; Table 2). This association remained significant after additional adjustment for plasma Aβ42/40 (β = 0.52, p < .001), with the adjusted model explaining 25 % of the variance in NfL (R^2 = 0.25), indicating that the relationship between ePWV and NfL was independent of amyloid-related pathology.

3.4. Greater vascular stiffness (Higher ePWV) is not associated with plasma Aβ42/40 LN-Transformed concentrations

Among participants with available amyloid data (N = 126), ePWV was not significantly associated with the plasma Aβ42/40 ratio (β = −0.13, p = .429) (Fig. 1 e; Table 2). The overall multivariable model explained 7.4 % of the variance in Aβ42/40 levels (R^2 = 0.07) and was not statistically significant (p = .551).

3.5. Comparison of ePWV with traditional blood pressure indices

To evaluate whether associations observed with ePWV were driven by traditional blood pressure measures, parallel multivariable regression models were conducted using SBP, DBP, and PP as primary predictors of plasma biomarkers.

Table 2
Multivariable regression models examining associations between ePWV and plasma biomarkers.

Plasma biomarker (LN-transformed)	N	Standardized β (ePWV)	R^2	p-value (ePWV)
p-tau217	145	0.34	0.12	0.006
p-tau231	126	−0.05	0.24	0.739
GFAP	126	0.55	0.33	< 0.001
NfL	126	0.52	0.25	< 0.001
Aβ42/40	126	−0.13	0.07	0.429

Aβ = Amyloid beta; BP = Blood Pressure; ePWV = Estimated Pulse Wave Velocity; GFAP = Glial Fibrillary Acidic Protein; LN = Log-transformed; N = Number; NfL = Neurofilament Light; p-tau = Phosphorylated tau.
Note: All models were adjusted for sex, years of education, pulse pressure, waist-to-hip ratio, MoCA score, and hypertension status. Plasma biomarkers were LN-transformed prior to analysis. For the NfL model, additional adjustment for plasma Aβ42/40 did not alter the association between ePWV and NfL.

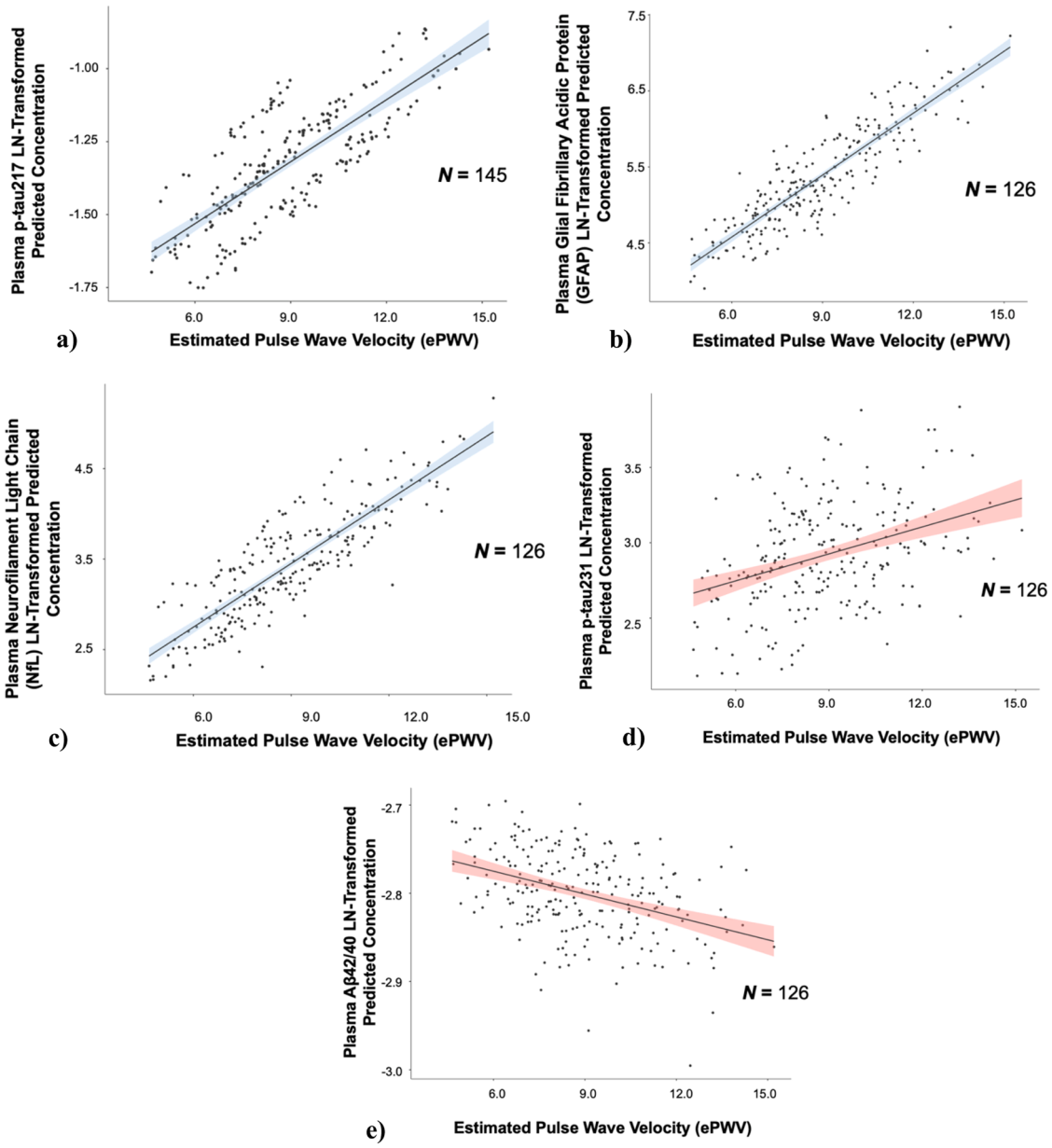

Fig. 1. Associations between estimated pulse wave velocity (ePWV) and plasma biomarkers of AD-related neurodegeneration. Panels depict the relationships between ePWV and LN-transformed plasma concentrations of (a) p-tau217 (N=145), (b) GFAP (N=126), (c) NfL (N=126), (d) p-tau231 (N=126), and (e) Aβ742/40 (N=126). Solid lines represent fitted lincar regression estimates, and shaded bands indicate standard errors of the predicted values.
Note: Each point represents an individual participant. Apparent clustering of data points reflects discretization of ePWV values derived from age and mean artirial pressure rather than biologically distinct subgroups. The apparent clustering of data points reflects discretization of ePWV values derived from age and mean arterial pressure rather than assay batch effects or artifacts of logarithmic transformation; this pattern is not observed when visualizing raw plasma p-tau217 values (see Supplementary Figure S1).

Across models, SBP and DBP were not significantly associated with plasma p-tau217, p-tau231, GFAP, NfL, or Aβ42/40 (all $p > .10$). Importantly, PP was significantly associated with plasma p-tau217 ($\beta = 0.28$, $p = .014$) and demonstrated a trend-level association with GFAP ($\beta = 0.24$, $p = .095$), but was not significantly associated with the other plasma biomarkers.

Overall, although PP demonstrated a relationship with p-tau217, associations observed with ePWV were stronger and more consistent across biomarkers than those observed with individual blood pressure components (Supplementary Table S1).

4. Discussion

In this cohort of cognitively unimpaired older African American adults, greater vascular stiffness, as indexed by higher ePWV levels, was strongly associated with elevated plasma p-tau217, GFAP, and NfL concentrations, markers of tau pathology, astrocytic activation, and axonal injury, respectively. These results provide evidence that ePWV may serve as a low-cost easily calculated marker of vascular and neurodegenerative burden. These findings also underscore the possibility that vascular stiffness interacts preferentially with tau and neurodegenerative pathways and highlight vascular health as an early, modifiable target for AD prevention in older African Americans.

Plasma p-tau217 has emerged as one of the most promising

biomarkers for clinical translation, demonstrating diagnostic accuracy comparable to positron emission tomography (PET) and cerebrospinal fluid measures of AD pathology [22,24,46,47]. Beyond its sensitivity to AD-related tau deposition, accumulating evidence suggests that p-tau217 may also capture tau abnormalities associated with vascular injury [48]. Greater vascular stiffness, measured with cfPWV, and increased pressure pulsatility have been associated with higher regional tau burden on PET imaging in cognitively unimpaired adults, independent of amyloid burden, implicating stiffened aortic hemodynamics in early tau accumulation [49]. Likewise, greater vascular stiffness, measured with MRI, has been linked to in vivo biomarkers of tau phosphorylation, neuroinflammation, and neurodegeneration in older adults [50]. In parallel with these findings, we observed that greater vascular stiffness (estimated from age and blood pressure as ePWV) significantly predicted elevated plasma p-tau217 concentrations among cognitively unimpaired older African Americans at risk for AD. The presence of this association prior to overt cognitive impairment suggests that chronic vascular strain may contribute to early tau dysregulation before clinical symptoms emerge. Collectively, these findings reinforce plasma p-tau217 as a clinically meaningful marker of early neurodegenerative processes shaped by vascular health and underscore its relevance for characterizing preclinical vulnerability in older African Americans. In contrast, plasma p-tau231 was not significantly associated with ePWV. Differences in variability across plasma biomarkers may also have contributed to the observed pattern of results; in particular, the greater dispersion of p-tau231 values relative to other biomarkers may have reduced statistical power to detect an association with ePWV in the current sample. Visual inspection of model-predicted raw p-tau217 values confirmed that the observed association with ePWV was not driven by transformation artifacts or assay-related batch effects, supporting the robustness of the p-tau217 findings (Supplementary Figure S1). As p-tau231 is thought to reflect earlier, amyloid-linked stages of tau pathology, this dissociation suggests that compromised vascular health may preferentially influence downstream tau-related changes rather than the initial amyloid-associated steps of the AD cascade [28,29]. This pattern aligns with evidence indicating that tau isoforms vary in their sensitivity to vascular, metabolic, and inflammatory stressors.

GFAP and NfL are well-established blood-based markers of early AD, as well as other neurodegenerative diseases, with elevated levels frequently observed in individuals showing preclinical neuroinflammation and neuroaxonal injury—key processes that mark the transition from healthy aging to preclinical AD [51,52]. Elevated GFAP reflects astrocytic activation triggered by microvascular injury, blood–brain barrier disruption, or chronic inflammatory signaling, all of which are closely linked to compromised vascular health and increased vascular stiffness [32,51]. In contrast, NfL serves as a sensitive but non–disease-specific indicator of axonal injury and neuroaxonal stress [34,53–55]. The observed association between NfL and ePWV suggests that poorer vascular health, reflected by greater vascular stiffness, may contribute to low-grade neuroaxonal injury even in the absence of overt cognitive decline, rather than reflecting AD–specific pathology. Supporting this interpretation, Guzman et al. reported that increased blood flow pulsatility was linked to higher concentrations of blood-based markers of neurodegeneration, including GFAP and NfL [56]. Similarly, Norling et al. demonstrated that greater cfPWV—the gold-standard measure of large-vascular stiffness—intensified the relationship between NfL-related axonal degeneration and cognitive decline [55]. Consistent with these findings, we observed that greater vascular stiffness (higher ePWV levels) significantly predicted elevated plasma GFAP and NfL concentrations, and the association between ePWV and NfL remained significant after adjustment for plasma Aβ42/40, indicating independence from amyloid-related processes. Together, these results support the view that vascular stiffness, as an index of compromised vascular health, may operate via glial activation and axonal injury during preclinical stages of neurodegeneration.

Aβ pathology is a central feature of AD and is widely considered an initiating event in the neurodegenerative cascade; however, its relationship with vascular health appears heterogeneous across studies [57]. Several studies have reported associations between vascular stiffness and amyloid pathology. For example, higher vascular stiffness, measured with cfPWV, has been linked to greater cerebral amyloid deposition measured by PET imaging and to longitudinal amyloid accumulation in cognitively unimpaired older adults [58]. Similarly, elevated PWV measured using phase-contrast magnetic resonance imaging has been associated with both cognitive impairment and increased cerebral amyloid burden in older adults [59], and vascular stiffness has been related to amyloid pathology alongside other dementia-related brain changes in community-based cohorts [60]. In contrast, weak or non-significant associations between vascular stiffness indices have been reported and amyloid-related measures after accounting for demographic and vascular covariates, highlighting variability across cohorts, vascular metrics, and amyloid assessment modalities [61]. Consistent with this latter body of work, we did not observe a significant association between ePWV and the plasma Aβ42/40 ratio. Taken together, these findings suggest that while compromised vascular health may relate to amyloid pathology under certain conditions, its influence appears to be more robust and consistently expressed in downstream tau-related and neurodegenerative pathways, particularly during preclinical stages of AD.

In line with the conceptualization of ePWV as an integrated index of vascular aging, we found that traditional blood pressure measures did not show the same pattern of associations with plasma biomarkers. PP has been widely recognized as an index of arterial pulsatility and has been associated with structural brain changes, white matter injury, and cognitive decline across aging cohorts [16,62–64]. Prior work has linked elevated PP to cerebral small-vessel disease, tau-mediated neurodegeneration, and progression to dementia, underscoring the biological relevance of pulsatile hemodynamic stress to brain aging [65–67]. Consistent with this literature, PP was significantly associated with plasma p-tau217 and demonstrated a trend-level association with GFAP in the present study, supporting a role of pulsatile hemodynamic load in tau-related and astrocytic processes. However, ePWV demonstrated stronger and more consistent relationships across multiple neurodegenerative biomarkers. Unlike PP, which reflects a single linear blood pressure component, ePWV incorporates nonlinear and interactive effects between age and blood pressure, thereby capturing compounded vascular aging processes. As suggested in population-based studies, ePWV may therefore serve as a more comprehensive index of biological vascular aging and may better reflect cumulative microvascular stress relevant to early neurodegeneration.

4.1. *Several limitations should be acknowledged when interpreting these findings*

First, the cross-sectional design prevents causal inference; therefore, we cannot determine if vascular stiffness precedes increases in plasma p-tau217, GFAP, and NfL concentrations, or if early neurodegenerative processes influence vascular function. Future longitudinal studies incorporating repeated assessments of vascular stiffness and plasma biomarkers will be essential to establish temporal ordering and to evaluate vascular aging as a prospective predictor of biomarker progression and cognitive decline.

Second, although ePWV is a validated and practical surrogate for vascular stiffness, it remains an estimated rather than directly measured index and may not capture all dimensions of vascular health. Future studies should incorporate direct assessments of vascular stiffness, such as cfPWV, which quantifies the speed at which the arterial pressure wave travels between the carotid and femoral arteries and serves as the gold-standard measure of central arterial stiffness, as well as central pressure pulsatility, which reflects the magnitude of beat-to-beat blood pressure fluctuations within the central arteries and indexes the ability of the

proximal aorta to buffer pulsatile cardiac output [7,8]. Inclusion of these complementary measures will allow for a more comprehensive characterization of vascular health and improved validation of associations with plasma markers of neurodegeneration.

Third, genetic factors that are particularly relevant in individuals of African ancestry, including the ABCA7 (rs115550680) risk allele and APOE-ε4, were not included in the present analyses. These variants influence both vascular health and AD-related biomarker expression, and their omission limits the ability to evaluate gene–vascular interactions underlying early neurodegenerative processes. Future studies are needed to explicitly examine AD genetic risk markers to test how genetic susceptibility modifies the relationship between vascular stiffness and plasma biomarkers, thereby clarifying pathways of vulnerability and resilience in individuals of African ancestry.

Fourth, hypertension status was determined based on blood pressure measurements obtained at a single study visit, which may not fully reflect chronic blood pressure exposure or longitudinal variability.

Finally, because the present study included only African American participants, the findings should be interpreted within the context of this population and do not permit direct comparisons or inferences regarding ancestry-specific biological mechanisms relative to other racial or ethnic groups. Future studies incorporating racially and ethnically diverse cohorts with harmonized vascular and biomarker assessments will be essential to determine the extent to which these vascular–biomarker relationships are shared across populations or reflect population-specific risk profiles.

5. Conclusion

In conclusion, greater vascular stiffness, indexed by ePWV, was strongly associated with plasma markers of tau pathology, astrocytic activation, and axonal injury among cognitively unimpaired older African Americans. These findings suggest that compromised vascular health may play a central role in shaping early neurodegenerative processes before the onset of clinical symptoms. Because ePWV is derived from routine clinical measurements, it represents a scalable and cost-effective tool for detecting early biological vulnerability to AD prior to cognitive decline. Collectively, this work highlights vascular stiffness as a key upstream correlate of tau-related and neurodegenerative pathology and supports vascular health as a promising target for early risk stratification and prevention efforts in populations at elevated risk for AD.

Disclosure statement

The authors confirm that there are no known conflicts of interest associated with the publication of this manuscript. The authors confirm that there are no known conflicts of interest associated with the publication of this manuscript.

Declaration of the use of generative ai and AI-assisted technologies

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the writing of this manuscript or in the creation of figures, images, or artwork.

CRediT authorship contribution statement

Miray Budak: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Kevin S. Heffernan:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **Victoria Paruzel:** Investigation, Formal analysis. **Soodeh Moallemian:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Bernadette A. Fausto:** Writing – review & editing, Supervision, Conceptualization. **Nicholas Ashton:** Writing – review & editing, Supervision. **Henrik Zetterberg:** Writing – review & editing, Supervision. **Fanny M. Elahi:** Writing – review & editing, Supervision. **Mark A. Gluck:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100523.

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