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High estimated pulse-wave velocity is associated with lower brain white matter microstructural integrity twelve years later

Kevin S. Heffernan [a,*], Derek C. Monroe [b], Andrew S. London [c,d], Jose Gutierrez [e], Adam M. Brickman [e,f], Ajay Kumar Nair [g,h], Nagesh Adluru [i,j], Stacey M. Schaefer [h]

[a] Department of Biobehavioral Sciences, Teachers College, Columbia University, New York, NY, USA
[b] Department of Exercise and Sport Science, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[c] Department of Sociology, Syracuse University, Syracuse, NY, USA
[d] The Aging Studies Institute, Syracuse University, Syracuse, NY, USA
[e] Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA
[f] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA
[g] Centre for Brain and Mind, National Institute of Mental Health & Neurosciences, Bangalore, India
[h] Institute on Aging, University of Wisconsin-Madison, Madison, WI, USA
[i] Waisman Center, University of Wisconsin-Madison, Madison, WI, USA
[j] Department of Radiology, University of Wisconsin-Madison, Madison, WI, USA

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ABSTRACT

High pulse wave velocity (PWV), a measure of increased arterial stiffness, is a risk factor for cerebrovascular disease. PWV can be estimated (ePWV) from age and blood pressure (BP). Elevated ePWV is associated with cerebral small-vessel disease, cognitive decline, and dementia risk in middle-aged and older adults. We examined data from the Midlife in the United States (MIDUS) Neuroscience Project to examine the association of ePWV with brain white matter microstructure. BP was measured in 132 middle-aged adults (mean age 53+/- 10 years, n = 77 women, n = 38 Black/African American) between 2004 and 2009 and used to calculate ePWV. Diffusion-weighted imaging (DWI) data were acquired between 2017 and 2022 and used to estimate: global white matter fractional anisotropy; axial, radial, and mean diffusivity and kurtosis; neurite density index; and orientation dispersion index. High ePWV was associated with: lower fractional anisotropy; axial, radial, and mean kurtosis; and neurite density index. High ePWV was also associated with higher axial, radial, and mean diffusivity, and orientation dispersion index. Except for axial diffusivity/kurtosis and orientation dispersion, all associations between high ePWV and white matter microstructure remained after adjusting for exogenous controls (sex and race), education, the constituent components of ePWV (age and blood pressure), and the time lag between BP and DWI measures. In conclusion, high ePWV in middle-aged adults is prospectively associated with compromised brain white matter microstructure more than a decade later. ePWV may be a useful metric of vascular aging that can be applied to the study of brain aging.

The brain is highly susceptible to the effects of vascular aging (Iadecola et al., 2023). With increasing age, large extracranial arteries, such as the aorta and carotid arteries, lose elasticity. Arterial stiffness exposes the brain to increased blood pressure pulsatility and other pulsatile hemodynamic forces (Mitchell et al., 2011). Chronic exposure to increased blood pressure pulsatility causes cerebrovascular damage and hypoperfusion, which negatively affects brain structure and function (Stone et al., 2015). Carotid-femoral pulse wave velocity (cfPWV) is the referent (i.e., gold standard) measure of arterial stiffness (Townsend et al., 2015). cfPWV is associated with several magnetic resonance imaging (MRI) markers of structural brain damage and cerebral small-vessel disease (cSVD), including greater white matter hyperintensity volume, enlarged perivascular space burden, lacunes, and microbleeds (Álvarez-Bueno et al., 2024; Badji et al., 2019; Bown et al., 2023; Lever-Megina et al., 2025). High cfPWV is also associated with cognitive decline (Alvarez-Bueno et al., 2020) and predicts the transition from mild cognitive impairment to dementia (Rouch et al., 2018). As such, cfPWV is a useful biomarker of vascular aging and Alzheimer's

* Correspondence to: Teachers College, Columbia University, New York, NY 10027, USA.
E-mail address: ksh2001@tc.columbia.edu (K.S. Heffernan).

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Disease and related dementia (ADRD) risk (Hughes et al., 2018).

Measuring cfPWV requires specialized equipment and technical ability that is not available in most clinical and research settings. Lack of accessibility, particularly in resource-constrained environments, has limited widespread adoption of cfPWV into clinical practice and research. Several different methods are being explored to estimate PWV as part of efforts to advance research on vascular aging. Among these methods, a regression-derived equation that uses two commonly measured clinical variables – age and blood pressure (BP) – is the most easily used. Estimated PWV (ePWV), derived from age and BP according to a formula, demonstrates construct validity as a measure of vascular aging (Heffernan et al., 2023) and is an independent predictor of cerebrovascular events and all-cause mortality (Gu et al., 2025; Heffernan et al., 2020, 2022b; Jae et al., 2021). Recent studies also highlight associations between elevated ePWV and increased risk for cSVD (Ariko et al., 2024), impaired cognitive function (Aimagambetova et al., 2024; Hao et al., 2024; Heffernan et al., 2022a), and increased risk for dementia (Heffernan et al., 2024), which supports the validity of using ePWV as a marker of vascular aging and ADRD risk. It is plausible that, in the absence of the capacity to measure cfPWV, ePWV can be used to study the impact of vascular aging on brain aging.

White matter hyperintensities are one of the hallmarks of cSVD (Pasi et al., 2016; Rost et al., 2010; Stewart et al., 2021). However, even normal-appearing white matter may have microstructural damage that can be detected via diffusion-weighted imaging (DWI) (de Groot et al., 2013; Vernooij et al., 2009). DWI infers tissue integrity and composition ('microstructure') based on the movement of water molecules within and across brain tissue (Croall et al., 2017). Advanced DWI sequences can be tuned to detect different water velocities, enhancing sensitivity to deviations in diffusion patterns (Steven et al., 2014; Zhang et al., 2012). This enables advanced biophysical modeling approaches that capture diffusion both within and between different tissue compartments (Beck et al., 2021; Motovylyak et al., 2022; Raghavan et al., 2021). As such, DWI is a sensitive neuroimaging tool that can be used to investigate subtle alterations in white matter microstructure that may precede white matter hyperintensities, gross volumetric structural changes, neurodegeneration, and cognitive impairment (Merluzzi et al., 2016; Nelson et al., 2024; van Leijsen et al., 2018; Weston et al., 2015). These patterns of white matter aging are likely to be particularly important in middle age, which is an optimal time to modify behaviors that might improve vascular health and promote white matter health. A cross-sectional analysis of a large cohort (n = 37,041) from the UK Biobank revealed relationships between surrogate measures of arterial stiffness (i.e., an arterial stiffness index derived from finger photoplethysmography) and white matter microstructure (Wartolowska and Webb, 2021). Similarly, studies using cfPWV to assess arterial stiffness have noted that elevated cfPWV is cross-sectionally associated with lower fractional anisotropy, and higher mean and radial diffusivity, indices of white matter microstructural damage (Maillard et al., 2016; Wei et al., 2020; Won et al., 2025). However, the prospective relationship between arterial stiffness in middle age and subsequent white matter microstructure is poorly understood.

The purpose of this study is to prospectively examine the association of arterial stiffness (i.e., ePWV) measured at baseline with global white matter microstructural integrity outcomes measured approximately 12 years later. White matter properties were determined from DWI with both diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI), accompanied by the application of advanced biophysical modeling with Neurite Orientation Dispersion and Density Imaging (NODDI). We hypothesized that high ePWV at baseline would be associated with lower white matter fractional anisotropy and neurite density index, and increased diffusivity and orientation dispersion index, averaged across the brain's white matter, all measured more than a decade later. Associations in the specified directions will be taken as evidence in support of ePWV as an early indicator of vascular aging and compromised white matter microstructural integrity.

1. Methods and study design

We conducted secondary analyses of data from the Midlife in the U.S. (MIDUS) Neuroscience Project. Survey data and BP were collected as part of MIDUS 2 between 2004 and 2009. Multi-shell diffusion-weighted imaging (DWI) data were acquired from a subset of participants as part of MIDUS 3, which collected data between 2017 and 2022. From the n = 231 participants in the MIDUS 3 Neuroscience study, n = 21 were excluded because they did not participate in the MIDUS 2 (baseline) survey and biomarker data collection, and n = 78 were excluded for not completing DWI. Final analyses were completed with data from n = 132 adults (n = 77 women, n = 38 Black/African American). The mean time lag between BP and MRI measures was 12 ± 2 years. All participants provided written informed consent to participate in MIDUS. The MIDUS Survey, Biomarker, and Neuroscience Projects were approved by the University of Wisconsin-Madison IRB (Radler, 2014).

1.1. Estimated pulse wave velocity (ePWV): primary independent variable

In MIDUS 2, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times, 30 s apart, with participants resting in the seated position. The average of the second and third measures was used for subsequent ePWV calculations. First, mean arterial pressure (MAP) was calculated as DBP+0.4*(SBP-DBP). Then, ePWV was computed as follows (Greve et al., 2016; Vlachopoulos et al., 2019):

$$9.587 - (0.402 * age)(4.560 * 0.001 * age^2) - (2.621 * 0.00001 * age^2 * MAP) + (3.176 * 0.001 * age * MAP) - (1.832 * 0.01 * MAP)$$

1.2. Diffusion-weighted imaging (DWI): primary dependent variables

A multi-shell spin-echo, echo-planar imaging sequence was used to collect DWI data on a 3 Tesla GE MR750 scanner with a Nova 32 channel head coil. Three shells of different diffusion weighting were acquired at b-values of 500, 800, and 2000 s/mm^2 with 9, 18, and 36 uniformly distributed directions, respectively. There were six reference scans without any diffusion encoding (b = 0 s/mm^2). Other parameters included: repetition time/echo time (TR/TE) = 7000/91 ms; field of view (FOV) = 256 mm; 75 slices; voxel resolution = 2 x 2 x 2 mm^3. Processing of DWI data was performed using the DESIGNER pipeline (Ades-Aron et al., 2018), implemented in MRtrix3 (Tournier et al., 2019). The preprocessing steps include: denoising using Marčenko-Pastur Principal Component Analysis (MPPCA) (Veraart et al., 2016); followed by Gibbs ringing correction; then distortion correction for eddy currents (Andersson and Sotiropoulos, 2016) and EPI-induced field inhomogeneities (Jenkinson, et al., 2012); and B1 bias (Avants et al., 2011); and finally "Rician bias correction" (Chen et al., 2024) with the correction ($\sqrt{|M^2 - \sigma^2|}$, where M is the magnitude of the B1 bias corrected diffusion-weighted signal and σ is the noise variance estimated from the denoising step. Processed data were used to estimate traditional diffusion tensor imaging (DTI) metrics (Alexander et al., 2011) —fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD); diffusion kurtosis imaging (DKI) metrics (Jensen and Helpern, 2010; Jensen et al., 2005)—mean/axial/radial kurtosis (MK/AK/RK); and NODDI metrics—neurite density index (NDI) and orientation dispersion index (ODI)—on a voxelwise basis (Fick et al., 2019; Fieremans et al., 2013). For the DKI metrics, a mask was created using a threshold MK <0.3, and the mask was smoothed to effectively obtain a "weighting" map. Then, each of the DKI and white matter tract integrity metrics was smoothed and divided by the smoothed weighting mask, resulting in smoothed metrics that downweigh the influence of the low-MK/noisy DKI estimates (also known in the literature as "black holes") (Perrone et al., 2015; Tabesh

et al., 2011; Zhang et al., 2021). This approach was used as a refinement to the typical solution of isotropic smoothing of the DKI metrics inspired by the T-SPOON method, which aims to reduce the influence of misregistration errors in voxel-based analysis (Lee et al., 2009). Global parameters for each tissue (white matter, gray matter, and cerebrospinal fluid) were computed as the weighted median (Edgeworth 1887, 1888) derived from the FAST (FMRIB's Automated Segmentation Tool) (Zhang et al., 2001) white matter segmentation in FSL Jenkinson et al. (2012). The extracted global white matter parameters were used in the current analysis.

1.3. Covariate selection and analytic plan

We initially considered covariates for which there is evidence of influence on both vascular and brain aging outcomes. Specifically, we considered: sociodemographic characteristics (sex, race, education); history of chronic disease (heart disease, stroke/transient ischemic attack [TIA], hypertension, diabetes mellitus); the constituent components of ePWV (age, age-squared, systolic blood pressure, and diastolic blood pressure); cerebrovascular disease (CVD)-related biomarkers; and lifestyle risk factors (smoking, exercise habits). The CVD-related biomarkers included indicators of: cardiometabolic health (total cholesterol/HDL ratio, hemoglobin A1c, HOMA-insulin resistance, body mass index); inflammation (C-reactive protein, fibrinogen); and renal health (serum creatinine and urinary albumin-creatinine ratio).

In our analyses using SPSS v. 29, we treated ePWV as a dichotomous variable as has been done previously in the cfPWV literature. Choosing a cut-point can be subjective and introduce bias. There is currently no universally accepted clinical cut-point for ePWV, although some have been suggested (Badji et al., 2020). Therefore, we used k-means cluster analysis to statistically separate our sample into low (<8.9 m/s) and high (>8.9 m/s) ePWV. We analyzed continuous variables with independent samples *t*-tests and categorical variables with Chi-square tests. We then used multivariable linear regression to assess the association of ePWV at baseline with DWI outcomes measured approximately 12 years later. We estimated two models. Model 1 includes sex, race, education, the constituent components of ePWV (age, age-squared, systolic and diastolic blood pressure), and the time lag between baseline and the measurement of the dependent variables. Model 2 added several measures of chronic disease history (diabetes mellitus, stroke/TIA, hypertension) to Model 1. These additional covariates were selected because, in bivariate analyses, they were associated at $p < 0.10$ with at least one of the dependent variables. The CVD biomarkers and lifestyle risk factors did not differ between low versus high ePWV and were not associated at $p < 0.10$ with any of the DWI outcomes in this sample. We conducted supplemental sensitivity analyses using the median ePWV (8.7 m/s) and cut points of 8.5 m/s and 10.0 m/s, as suggested in the literature (Badji et al., 2020). Using a cut-point of >8.5 m/s or 8.7 m/s yielded similar results as using the cut-point of 8.9 m/s, while using a cut-point of 10 m/s yielded no significant associations. We also found that removing participants with a history of stroke/TIA (n = 3) did not substantively affect the results we report in this paper.

In our multivariable analyses, we intentionally include ePWV and its constituent elements to determine whether ePWV adds to the variance explained by its undoubtedly influential constituent components (age, age-squared, systolic BP, and diastolic BP). In preliminary analyses (Online Table S1), we found that the constituent components of ePWV explained approximately 22–33 % of the variance in several DWI outcomes (fractional anisotropy, radial kurtosis and diffusivity, mean kurtosis and diffusivity, and neurite density index), and ePWV explained an additional and significant proportion of the variance for these same outcomes (R^2 change ranging from approximately 2–5 %).

Notably, including ePWV and its constituent components in the same model raises concerns about collinearity. We examined this and found that the variance inflation factor (tolerance) for ePWV across tests was 3.176 (0.315) for Model 1 and 3.252 (0.307) for Model 2. We considered these values to be reasonable.

Supplemental multiple regression analyses were also conducted, treating ePWV as a continuous variable. In these models, we included age as a dichotomous variable, with the cut-point at the median age, to reduce collinearity. Finally, Pearson correlation coefficients were used to examine the bivariate associations between ePWV and DWI outcomes.

2. Results

Table 1 presents a description of the analytic sample, as well as the subgroups characterized by low and high ePWV, respectively. Overall, the sample was predominantly White (68 %), with a higher proportion of female participants (58 %) than male participants. There were 58 participants with a 4-year college degree or higher (i.e., graduate school), 37 with some college education, and 37 with high school/GED or less education. There were no differences in educational attainment when comparing the high to the low ePWV group. The high ePWV group was older, had higher BP, and had a higher proportion of individuals with hypertension compared to the low ePWV group.

Table 2 displays DWI results from the overall sample, as well as dichotomized by low and high ePWV. The high ePWV group had lower FA, kurtosis measures, and NDI than the low ePWV group. The high ePWV group also had higher diffusivity measures and ODI than the low ePWV group. Figure S1 displays group maps for DWI indices. Fig. 1 displays scatter plots for bivariate associations between ePWV and DWI outcomes. Pearson correlation coefficients (*r*-values) are displayed on the bottom right side of each panel. Table 3 presents results from multivariable linear regression, treating ePWV as a dichotomous variable. As seen in Model 1, after adjusting for sex, race, education, age, age-squared, blood pressure (both systolic and diastolic), and the time-lag measure, high ePWV was associated with lower fractional anisotropy, radial kurtosis, mean kurtosis, and neurite density index. High ePWV was positively associated with radial diffusivity and mean diffusivity. Adjusting for the history of selected chronic diseases (diabetes mellitus, stroke/TIA, hypertension) in Model 2 did not substantively change our main findings.

Table S2 presents results from multivariable linear regression models that include ePWV as a continuous variable. We include age as a dichotomous variable and systolic and diastolic blood pressure in Model 1; we add history of selected chronic diseases (diabetes mellitus, stroke/TIA, hypertension) in Model 2. Results are similar to those we present above.

Table 1
Descriptive characteristics measured at MIDUS 2 (2004–2009).

Variable	All $n = 132$	Low ePWV $n = 70$	High ePWV $n = 62$	p-value
Age, years	53 ± 10	47 ± 6	59 ± 9	<0.001
Female sex, n	77	44	33	0.292
Race, n				0.354
White	90	44	46	
Black/African American	38	23	15	
Asian	2	1	1	
Asian Native American	2	2	0	
Systolic BP, mmHg	129 ± 16	121 ± 13	138 ± 15	<0.001
Diastolic BP, mmHg	78 ± 12	74 ± 10	82 ± 13	<0.001
H_x Heart Disease, n	7	2	5	0.250
H_x Hypertension, n	47	17	30	0.006
H_x Stroke/TIA, n	3	0	3	0.101
H_x Diabetes Mellitus, n	17	11	6	0.436
ePWV, m/s	8.8 ± 1.5	7.7 ± 0.7	10.1 ± 1.1	<0.001

BP, blood pressure; Hx, history; TIA, transient ischemic attack; ePWV, estimated pulse wave velocity

Table 2
DWI global white matter mean estimates for MIDUS 3 Neuroscience Project (2017–2022).

Variable	**All**	**Low ePWV**	**High ePWV**	**p-value**
Fractional Anisotropy	0.29 ± 0.02	0.30 ± 0.02	0.28 ± 0.02	<0.001
Mean Diffusivity, um^2/ms	0.86 ± 0.03	0.84 ± 0.03	0.88 ± 0.03	<0.001
Radial Diffusivity, um^2/ms	0.70 ± 0.04	0.68 ± 0.03	0.72 ± 0.03	<0.001
Axial Diffusivity, um^2/ms	1.17 ± 0.04	1.15 ± 0.03	1.19 ± 0.04	<0.001
Mean Kurtosis	0.80 ± 0.04	0.82 ± 0.03	0.78 ± 0.04	<0.001
Radial Kurtosis	0.87 ± 0.06	0.89 ± 0.05	0.84 ± 0.06	<0.001
Axial Kurtosis	0.73 ± 0.03	0.74 ± 0.03	0.72 ± 0.03	0.001
Neurite Density Index	0.50 ± 0.03	0.51 ± 0.02	0.48 ± 0.02	<0.001
Orientation Dispersion Index	0.34 ± 0.01	0.33 ± 0.01	0.34 ± 0.01	0.004

3. Discussion

We found that ePWV in midlife is associated with brain white matter microstructure measured approximately 12 years later. High ePWV (>8.9 m/s) was associated with higher mean diffusivity and radial diffusivity, and with lower fractional anisotropy, mean kurtosis, radial kurtosis, and neurite density index. Because we statistically adjusted for the constituent components of ePWV—age, age-squared, systolic BP, and diastolic BP—as well as potentially confounding comorbidities, we are reasonably confident that ePWV measures vascular aging effects beyond those associated directly with chronological age and BP. Our findings support an emerging literature linking the gold-standard measure of arterial stiffness—cfPWV—with measures of brain health. Our findings add to this literature by demonstrating that an easily obtained estimate of PWV is associated with novel and sensitive measures of white matter microstructure 12 years later. ePWV may be a useful and easily calculated metric of vascular aging that can be applied to the study of brain aging.

Arterial stiffness is an established harbinger of structural brain damage (Badji et al., 2019). Meta-analyses demonstrate that the presence/long-term development of cSVD, white matter hyperintensities, and cerebrovascular dysfunction in older adults is more likely among those with elevated PWV (Álvarez-Bueno et al., 2024; Badji et al., 2019; Lever-Megina et al., 2025; Scheuermann et al., 2023). Arterial stiffness may also predict the progression of white matter hyperintensities (Del Brutto et al., 2022) and white matter hyperintensity volume later in life (de Havenon et al., 2019). The working conceptual model is that increases in large artery stiffness begets transmission of pulsatile hemodynamic energy into the brain, damaging delicate microvasculature, and instigating detrimental remodeling (i.e., cerebral artery elongation and increased diameter, enlarged perivascular spaces), microbleeds/micro-hemorrhages, impaired cerebrovascular regulation, reduced neurovascular coupling, hypoperfusion, ischemia, subcortical lacunar infarcts, altered viscoelastic mechanical properties, axonal injury, demyelination, neuron loss, cortical atrophy, and impaired brain function (Bown et al., 2021; Palta et al., 2019; Saji et al., 2016; Wakita et al., 2002).

While numerous studies have examined associations between arterial stiffness and cSVD, fewer studies have used DWI to assess white matter microstructure (Han et al., 2021). Previous studies have shown that microstructural abnormalities and axonal fiber damage precede the formation of white matter hyperintensity lesions (de Groot et al., 2013; Vernooij et al., 2009). White matter microstructure is also associated with cognition and ADRD risk, independent of white matter hyperintensity burden (Ng et al., 2023). Previous studies have consistently found associations between elevated arterial stiffness, lower fractional

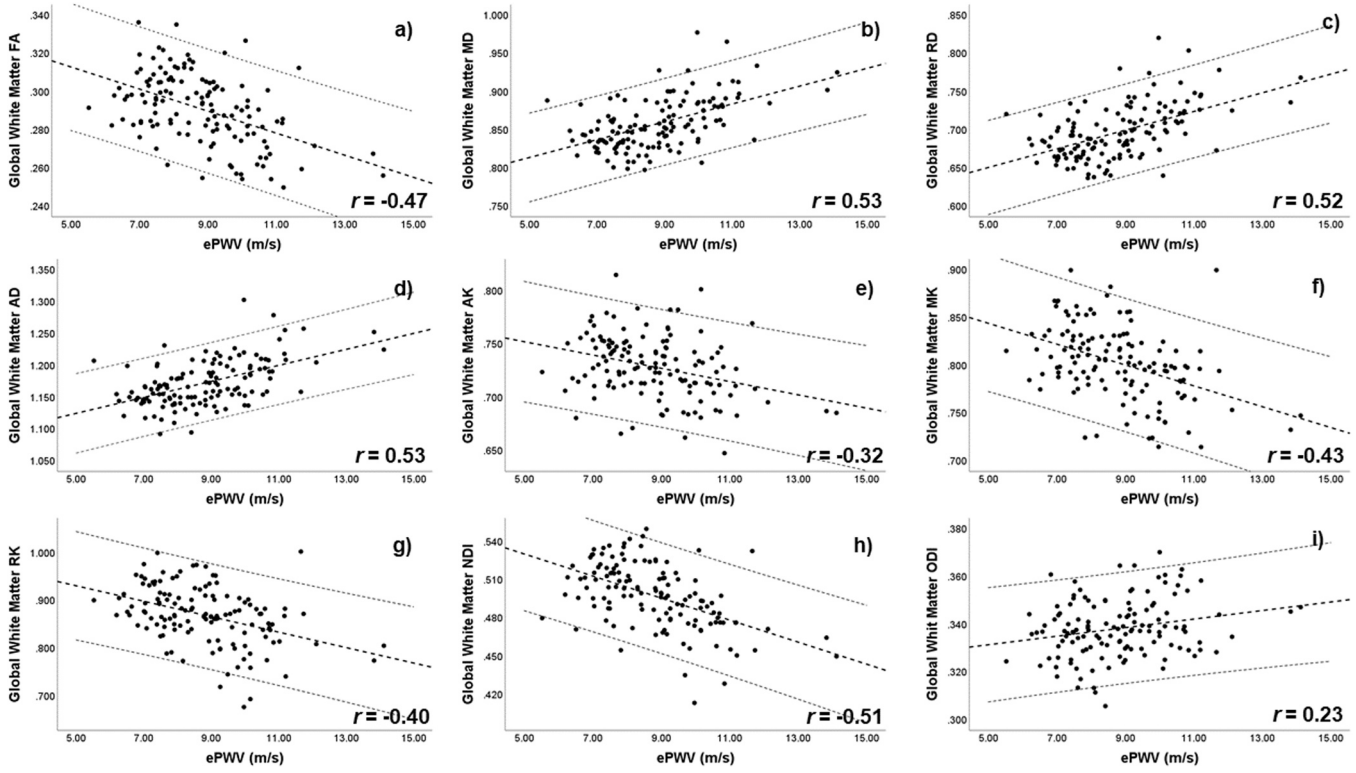

Fig. 1. Univariate associations between ePWV and DWI outcomes. a) FA, fractional anisotropy; b) MD, mean diffusivity; c) RD, radial diffusivity; d) AD, axial diffusivity; e) AK, axial kurtosis; f) MK, mean kurtosis; g) RK, radial kurtosis; h) NDI, neurite density index; i) ODI, orientation dispersion index.

Table 3
Multivariable linear regression evaluating the association between elevated ePWV at baseline and white matter DWI parameters ~12 years later.

	Model 1	Model 2
	β (SE)95 % CI	β (SE)95 % CI
Fractional Anisotropy	**-0.010 (0.005)** -0.019, -0.001	**-0.010 (0.005)** -0.020, -0.001
Mean Diffusivity, um^2/ms	**0.017 (0.009)** 0.001, 0.034	**0.019 (0.008)** 0.003, 0.035
Radial Diffusivity, um^2/ms	**0.021 (0.009)** 0.004, 0.039	0.023 (0.009) 0.006, 0.040
Axial Diffusivity, um^2/ms	0.013 (0.009) -0.006, 0.031	0.015 (0.009) -0.002, 0.033
Mean Kurtosis	**-0.026 (0.010)** -0.046, -0.006	**-0.025 (0.010)** -0.044, -0.006
Radial Kurtosis	**-0.041 (0.017)** -0.074, -0.007	**-0.040 (0.016)** -0.073, -0.008
Axial Kurtosis	-0.006 (0.008) -0.022, 0.010	-0.005 (0.008) -0.021, 0.011
Neurite Density Index	**-0.019 (0.007)** -0.032,-0.006	**-0.020 (0.006)** -0.032, -0.007
Orientation Dispersion Index	0.005 (0.004) -0.002, 0.012	0.005 (0.004) -0.002, 0.012

Coefficients represent unstandardized β coefficients (standard error, SE) with 95 % confidence intervals (CI). Bold font signifies significance ($p < 0.05$). Model 1: adjusted for sex, race, education, the constituent components of ePWV (age, age-squared, systolic blood pressure and diastolic blood pressure), and the time lag between baseline and the measurement of the dependent variables; Model 2 adds chronic disease measures (diabetes mellitus, stroke/TIA, and hypertension) to Model 1.

anisotropy, and higher mean and radial diffusivity (Maillard et al., 2016; Wei et al., 2020; Won et al., 2025). Results from the Framingham Heart Study suggest that arterial stiffness triggers a pathophysiological cascade that includes subtle white matter degeneration (i.e., demyelination and/or axon loss in neural fiber tracts) and the eventual development of white matter hyperintensities (Maillard et al., 2017). Mechanisms proposed to explain the association between arterial stiffness and white matter microstructure are similar to those proposed for cSVD and include hemodynamic pulsatility-mediated neurovascular damage.

Our findings support this literature by revealing associations between white matter microstructure and ePWV that are similar to those observed in studies using 'gold-standard' cfPWV. We extend this literature by utilizing a more advanced DWI sampling scheme and associated metrics, which provide more granular insight into the underlying white matter biology than non-specific DTI markers. For example, though fractional anisotropy derived from DTI is sensitive to axonal integrity, multiple factors can underlie bidirectional changes in fractional anisotropy (i.e., cell death, gliosis, demyelination, increase in extracellular or intracellular liquid content, inflammation, and axonal loss) (Alexander et al., 2007). This is one reason why diffusivity is usually investigated jointly with fractional anisotropy, to indicate whether changes in the latter can be attributed to the shrinkage or degeneration of axons and dendritic fibers. The term 'microstructure' is routinely used to reference the fine-scale anatomical and organizational features of white matter tissue. Our findings suggest ePWV in mid-life predicts a later-life white-matter signature dominated by compositional deterioration—chiefly demyelination and reduced neurite density—with accompanying, but not axon-specific, loss of microstructural integrity, rather than changes in geometric organization. These patterns raise the possibility that vascular aging may first compromise white matter 'quality', setting the stage for subsequent degradation of integrity. If this interpretation is accurate, it encourages the future use of precise white matter imaging techniques to guide preventative interventions in midlife.

Elevated ePWV is emerging as an important biomarker of cerebrovascular disease risk (Gu et al., 2025). ePWV is independently associated with an increased risk of stroke (Jae et al., 2021). Zhou et al. (2023) found a 31 % additional risk of silent lacunar infarct for each 1 m/s increase in ePWV, while Ji et al. (2020) demonstrated a 22 % increased risk of a combined metric of myocardial infarction, cerebral infarction, and cerebral hemorrhage for each 1 m/s increase in ePWV. ePWV is associated with cognitive impairment cross-sectionally and cognitive decline prospectively (Aimagambetova et al., 2024; Hao et al., 2024; Heffernan et al., 2022a; Jones et al., 2024). Using data from the Health and Retirement Study, Heffernan et al. (2024) showed an association between high ePWV and the risk of dementia. Ariko et al. (2024) found an association between ePWV and white matter hyperintensity volume and perivascular space volume. Additionally, each 1 m/s increase in ePWV was associated with 44 % increased odds of covert brain infarct and 44 % increased odds of cerebral microbleed in adjusted models (Ariko et al., 2024). The authors suggested that ePWV may serve as a better measure of biological age than chronological age because it includes age-related compounding vascular terms that could be prognostic of microvascular brain health (Ariko et al., 2024).

We wish to underscore that ePWV should not be used as a replacement for cfPWV—the gold standard measure of arterial stiffness—when cfPWV can be measured (Boutouyrie, 2022). However, our results suggest that in settings where BP can be measured but cfPWV cannot, ePWV may offer additional insight into vascular aging as it pertains to brain aging. Associations between ePWV and cfPWV vary from weak ($r = 0.2–0.3$) (Heffernan et al., 2022) to moderate ($r = 0.5–0.7$) (Hametner et al., 2021; Heffernan et al., 2023). Considering the nonlinear, interactive relationship between age and BP, ePWV may capture other aspects of vascular aging that extend beyond cfPWV (Ariko et al., 2024). In support of this hypothesis, Greve et al. (2016) found that ePWV predicts major CVD events even after statistically controlling for cfPWV. Heffernan et al. (2023) showed an association between ePWV and carotid augmentation index, carotid intima-media thickness, and carotid stiffness. In the Northern Manhattan Study (NOMAS), ePWV was inversely associated with diastolic carotid blood flow velocity (Ariko et al., 2024), an established predictor of cSVD (Chuang et al., 2021; Ellström et al., 2023). Carotid stiffness and hemodynamics may have greater associations with cSVD, brain amyloid deposition, and blood flow regulation than aortic stiffness measured with cfPWV (Pasha et al., 2020; Robert et al., 2024). Therefore, given its associations with measures of carotid stiffness and hemodynamics, ePWV may reflect key elements of vascular aging that underlie its associations with brain aging. In summary, it may be more appropriate to consider ePWV a vascular aging index rather than an estimate of cfPWV per se. In doing so, this would encourage further work on the mechanisms underlying the relationships between vascular aging, arterial stiffness, and brain health.

Middle age is a critical period in brain aging because changes in neurocognitive health during middle age are predictive of future neurocognitive health, while still being amenable to intervention (Dohm-Hansen et al., 2024). Neuroimaging studies show an acceleration of brain structural and functional changes occurring during middle age (Dohm-Hansen et al., 2024). Cortical white matter volume and thickness demonstrate a non-linear decline around the sixth decade of life, which coincides with declines in functional and structural connectivity of select neural networks (Dohm-Hansen et al., 2024). Evidence of cSVD becomes more apparent in the sixth decade of life as well. Middle age is also an important turning point for vascular aging. cfPWV demonstrates nonlinear and exponential increases after age 50; cfPWV increases approximately 0.5 m/s per decade before age 50 and approximately 2.0 m/s thereafter (McEniery et al., 2005; Mitchell, 2021). These temporal patterns support an association between vascular aging and brain aging. Future studies are needed to explore the clinical merit of targeting vascular aging in midlife as a strategy to preserve white matter microstructural integrity and prevent cSVD and related neurocognitive sequelae later in life.

3.1. Considerations, limitations, and future directions

Various non-vascular hypotheses have been suggested to explain white matter damage. For example, in the context of ADRD, gray matter neuronal loss may lead to Wallerian degeneration in associated white matter tracts, accompanied by neuroinflammation and further white matter neurodegeneration (Garnier-Crussard et al., 2023). It is interesting to note that this hypothesis does not discount vasculogenic contributions (Brickman and Rizvi, 2023). Arterial stiffness and related hemodynamic pulsatility may also be entwined with cerebral amyloid angiopathy (Stone et al., 2015). Arterial stiffness is associated with cerebrospinal fluid and circulating biomarkers of neuroinflammation and neurodegeneration, such as tau, neurogranin, soluble triggering receptor expressed on myeloid cells 2, and β-amyloid (Cooper et al., 2022; Hughes et al., 2014, 2018; Moore et al., 2021), as well as MRI measures of axonal myelin degeneration such as aggregate *g*-ratio (Laporte et al., 2023). Moreover, arterial stiffening may act synergistically with APOE genotype and ADRD biomarkers to influence cognitive function (Bangen et al., 2021). More research will be needed to examine associations between ePWV and biomarkers of neuroinflammation and neurodegeneration, and whether there is additional effect modification by APOE genotype.

A novel aspect of our investigation is our use of a predictive correlational / cross-temporal study design. But our ability to infer temporality is hindered by the fact that we have MRI measures at a single time point. Although there was MRI imaging in MIDUS 2, it was limited to structural and functional MRI and did not include DWI measures. Those were not included until MIDUS 3. Thus, we cannot yet examine changes in white matter microstructural integrity as a function of stability and change in ePWV. However, data from wave 4 of the MIDUS sample are currently being collected, which will allow for novel examinations of change in DWI measures over time. It is possible that ePWV was already associated with brain white matter microstructure at baseline. Although we adjusted for confounders, residual confounding could still exist. Given the sample size, we did not perform analyses stratified by race or ethnicity. We acknowledge that race is a social, not a biological, construct that is informed by systemic institutional discriminatory factors. While it would be preferable to include race-specific factors that might confound the associations we are studying, those are not available. Including race as a covariate can perpetuate bias and obscure underlying social determinants of racial variation (Briggs, 2022), but in the absence of other measures, it is frequently done to indirectly take race-related social influences on outcomes into account. Our sample lacks diversity concerning ethnicity since the MIDUS study did not include many Hispanic Americans. The NOMAS study demonstrated that the association between ePWV and cSVD is stronger in Hispanic adults compared to non-Hispanic adults (Ariko et al., 2024), a finding supported by Rundek et al. (2017), who noted that the association between carotid stiffness and white matter hyperintensity burden is more pronounced in Hispanic adults. Therefore, studies are needed to further corroborate the utility of ePWV as a research tool to study the intersection of vascular aging and brain aging in racially and ethnically diverse cohorts that include measures of race- and ethnicity-related social determinants of vascular and brain aging. The classical NODDI framework is based on several assumptions (Alsameen et al., 2023), including fixed intrinsic diffusivities and compartmental signal fractions that may not fully capture the complexity of tissue microstructure. In consideration of this limitation, we employed the multi-tissue response functions in estimating the NODDI parameters that account for the different tissue types (white matter, gray matter, and cerebrospinal fluid) to mitigate biases in the derived measures (Fick et al., 2019).

Previous work from Cooper et al. (2016) noted that the association between cfPWV and cognitive function (appraised as memory) is mediated by cerebrovascular damage (appraised as white matter hyperintensities) (Cooper et al., 2016). Interestingly, work from Aimagambetova et al. (2024) has shown that while the presence of white matter damage is higher among individuals with higher ePWV, the association between ePWV and cognitive function (appraised as memory, executive function, and processing speed) cross-sectionally and over time is retained after statistically adjusting for white matter hyperintensity volume and presence of silent brain infarcts. More work is needed to examine interconnections between ePWV, white matter damage, and cognitive function. Future work from our group will explore white matter microstructure as a potential mediator of potential associations between ePWV and cognitive function in MIDUS.

3.2. Conclusions

High ePWV captured in midlife is associated with lower brain white matter microstructural integrity measured later in life. Our results support a broader geroscience theory that vascular health in middle age is associated with brain health in later life. For studies that do not use referent measures of arterial stiffness, such as cfPWV or carotid stiffness, ePWV estimated from age and BP may be a useful measure of vascular aging that can be applied to the study of brain aging.

CRediT authorship contribution statement

Adam M. Brickman: Writing – review & editing, Writing – original draft. **Andrew S. London:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Jose Gutierrez:** Writing – review & editing, Writing – original draft. **Kevin S. Heffernan:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization. **Derek C. Monroe:** Writing – review & editing, Writing – original draft, Conceptualization. **Stacey M. Schaefer:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ajay Kumar Nair:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nagesh Adluru:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Verification

- All authors have contributed equally to this work.
- We have no conflicts of interest to disclose.
- We clearly acknowledge funding sources and data availability in our document.
- We used Grammarly to proof spelling but did not use generative AI.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2025.07.015.

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