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Elevated aortic pulse wave velocity relates to longitudinal gray and white matter changes

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Abstract

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Objective: To determine whether baseline aortic stiffness, measured by aortic pulse wave velocity (PWV), relates to longitudinal cerebral gray or white matter changes among older adults. Baseline cardiac magnetic resonance imaging will be used to assess aortic PWV while brain magnetic resonance imaging will be used to assess gray matter and white matter hyperintensity (WMH) volumes at baseline, 18 months, 3 years, 5 years, and 7 years.

Approach and Results: Aortic PWV (m/s) was quantified from cardiac magnetic resonance. Multimodal 3T brain magnetic resonance imaging included T_1 -weighted imaging for quantifying gray matter volumes and T_2 -weighted fluid-attenuated inversion recovery imaging for quantifying WMHs. Mixed-effects regression models related baseline aortic PWV to longitudinal gray matter volumes (total, frontal, parietal, temporal, occipital, hippocampal, and inferior lateral ventricle) and WMH volumes (total, frontal, parietal, temporal, and occipital) adjusting for age, sex, race/ethnicity, education, cognitive diagnosis, Framingham stroke risk profile, *APOE* (apolipoprotein E)- $\epsilon 4$ carrier status, and intracranial volume. Two hundred seventy-eight participants (73 ± 7 years, 58% male, 87% self-identified as non-Hispanic White, 159 with normal cognition and 119 with mild cognitive impairment) from the Vanderbilt Memory & Aging Project ($n=335$) were followed on average for 4.9 ± 1.6 years with PWV measurements occurring from September 2012 to November 2014 and longitudinal brain magnetic resonance imaging measurements occurring from September 2012 to June 2021. Higher baseline aortic PWV was related to greater decrease in hippocampal ($\beta = -3.6$ [mm^3/year]/[m/s], 95% CI = -7.2 to -0.02 , $p=0.049$) and occipital lobe ($\beta = -34.2$ [mm^3/year]/[m/s], 95% CI = -67.8 to -0.55 , $p=0.046$) gray matter volume over time. Higher baseline aortic PWV was related to greater increase in WMH volume over time in the temporal lobe ($\beta = 17.0$ [mm^3/year]/[m/s], 95% CI = 7.2 to 26.9 , $p < 0.001$). All associations may be driven by outliers.

Conclusions: In older adults, higher baseline aortic PWV related to greater decrease in gray matter volume and greater increase in WMHs over time. Because of unmet cerebral metabolic demands and microvascular remodeling, arterial stiffening may preferentially affect certain highly active brain regions like the temporal lobes. These same regions are affected early in the course of Alzheimer's disease.

Keywords

cerebrovascular disorders; leukoencephalopathies; magnetic resonance imaging; pulse wave analysis; vascular stiffness

Subject Terms

Hypertension; Magnetic Resonance Imaging (MRI); Vascular Disease

1. Introduction

Age-related vessel wall thickening and elastin loss result in aortic stiffening, which may impair autoregulatory mechanisms¹ and precede the development of hypertension.^{2,3} A healthy aorta is elastic and helps diffuse pressure waves leaving the heart,⁴ but this elasticity declines over one's life course. As the aorta stiffens, distal cerebral microvasculature receives damaging pressure waves, eventually resulting in vessel wall damage. Aortic

stiffening can even result in downstream cognitive consequences^{5,6} and has been shown to increase the risk of developing dementia.⁷

This study examined whether baseline aortic pulse wave velocity (PWV), a measure of velocity of pressure waves leaving the heart (and a proxy for arterial stiffness), related to longitudinal cerebral gray or white matter changes (separate models for each region of interest) among older adults. In the presence of high pulse pressures, cerebral microvasculature may lose its integrity⁸ and result in reduced brain perfusion and nutrient delivery. Reductions in perfusion drive atrophy-inducing excitotoxicity,⁹⁻¹¹ and reduced nutrient transport to the parenchyma^{12,13} results in ischemia and oligemia,¹⁴ which drive white matter hyperintensity (WMH) formation.^{15,16} Cross-sectionally in middle-aged and older adult cohorts, increased brachial-ankle PWV,¹⁷ carotid-femoral PWV,^{18,19} and aortic PWV²⁰ are associated with greater global WMHs¹⁷⁻²¹ while increased aortic PWV is correlated with lower global gray matter volume.²²

We aim to build upon previous literature by assessing whether increased PWV at study enrollment contributes to neurodegeneration and white matter damage over time. We hypothesize that increased aortic PWV contributes to greater decrease in gray matter volume²² and greater increase in WMH volume over time.¹⁷ We hypothesize that these associations will be more pronounced in *APOE* (apolipoprotein E) $\epsilon 4$ carriers (given it is a vascular risk modifier)^{23,24} and among participants with mild cognitive impairment (MCI),²⁰ due to greater brain homeostasis disruption, compared with participants with normal cognition (NC).

2. Material and Methods

2.1 Data Availability, Standard Protocol Approvals, Registrations, and Participant Consents

Due to participant consent restrictions in data sharing, a subset of data is available for purposes of reproducing results or replicating procedures. The data, analytic methods, and study materials can be obtained by contacting the corresponding author. The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Written informed consent was obtained before data collection.

2.2 Study Cohort

The Vanderbilt Memory and Aging Project is a longitudinal study investigating the intersection of brain aging and vascular health in older adults.²⁵ Participants were enrolled between September 2012 and November 2014 and seen for follow-up at 18-month, 3-year, 5-year, and 7-year timepoints. For enrollment, participants were required to be ≥ 60 years of age, have a reliable proxy, speak English, and have intact auditory and visual acuity to participate in the examinations. At eligibility, participants underwent an interview (including Clinical Dementia Rating²⁶ with a proxy and assessment of activities of daily living), medical history review, and neuropsychological assessment. Participants were excluded for the following: a cognitive diagnosis other than NC, early MCI,²⁷ or MCI;²⁸ history of neurological disease (eg, stroke, multiple sclerosis), clinical heart failure, head injury with

loss of consciousness >5 minutes, major psychiatric illness (eg, schizophrenia), or systemic or terminal illness affecting longitudinal participation; and magnetic resonance imaging (MRI) contraindication. At enrollment, participants completed a thorough evaluation, including (but not limited to) clinical interview, physical examination, echocardiogram, medication review, fasting blood draw, cardiac MR imaging, and brain MRI. Participants were excluded from the current study for missing baseline cardiac MR imaging data or for missing brain MRI data at all four epochs. For the present study, given diagnostic group comparisons, participants with early MCI²⁷ were excluded for their small sample size (n=27). An additional 30 participants were excluded for missing or unusable predictor, outcome, or covariate data. See Figure 1 for inclusion and exclusion details.

2.3 Aortic PWV

CMR imaging was acquired as previously described,²⁹ using a 1.5T Siemens Avanto system (Siemens Medical Solutions, Inc., Malvern, PA) with a phased-array torso receiver coil at Vanderbilt University Medical Center. Two blinded raters (J.G. Terry and S. Nair) overseen by a board-certified radiologist (J.J. Carr) quantified velocity-encoded flow data of the ascending and descending thoracic aorta. The ascending to descending aorta centerline length (centimeter) was measured and flow transit time was calculated as the difference in time (milliseconds) between the leading edge of the ascending and leading edge of the descending aortic flow curves at half maximum. Aortic PWV (m/s) was calculated as the ascending to descending aorta centerline length (meters) divided by the transit time (seconds). Aortic PWV is the best noninvasive measure of central arterial stiffening³⁰ because it provides a regional measurement and reduces distance measurement error³⁰ and reliably accounts for vessel tortuosity compared with other methods.³¹ Interreader reliability for the PWV measurement had a coefficient of variation of 6.6% as determined by independent review of 34 scans by 2 readers (J.G. Terry and S. Nair).

2.4 Brain MRI

Between 2012 and 2017, participants were scanned at the Vanderbilt University Institute of Imaging Science on a 3T Philips Achieva system (Best, the Netherlands) with an 8-channel SENSE receiver head coil. In 2017, the system was upgraded to a 32-channel dStream head coil with digital gradient coils and new software. T_1 -weighted (repetition time, 8.9 ms; echo time, 4.6 ms; spatial resolution, $1 \times 1 \times 1 \text{ mm}^3$) and T_2 -weighted fluid-attenuated inversion recovery (repetition time, 11 000 ms; echo time, 121 ms; spatial resolution, $0.45 \times 0.45 \times 4 \text{ mm}^3$) images were acquired as part of the larger multimodal neuroimaging protocol. As previously described,²⁵ T_1 -weighted images were post-processed using Multi-Atlas Segmentation³² and fluid-attenuated inversion recovery images were postprocessed using the Lesion Segmentation Tool toolbox for Statistical Parametric Mapping (SPM8).³³ Manual labeling edits were applied based off review of individual scans and confirmed by a board-certified neuroradiologist (L.T. Davis) blinded to clinical information. Intracranial volume was calculated based on a summation of individual gray matter, white matter, and CSF volumes using T_1 -weighted images with SPM8.

2.5 Analytical Plan

Covariates were derived as follows: systolic blood pressure was the mean of 2 measurements. Medication review determined antihypertensive medication use. Diabetes was defined as fasting blood glucose ≥ 126 mg/dL, hemoglobin A1c $\geq 6.5\%$, or oral hypoglycemic or insulin medication usage. Atrial fibrillation was self-reported and subsequently confirmed by echocardiogram, cardiac MRI, documented prior procedure/ablation for atrial fibrillation, or medication use for atrial fibrillation. Left ventricular hypertrophy was defined on echocardiogram as left ventricle mass index >95 g/m² in women or >115 g/m² in men. Current cigarette smoking was determined by self-report of yes or no within the year before baseline. Self-report prevalent cardiovascular disease (CVD) with supporting medical record evidence included angina, coronary heart disease, or myocardial infarction (heart failure was a parent study exclusion). The Framingham Stroke Risk Profile (FSRP) score was calculated by applying points by sex for age, systolic blood pressure, antihypertensive medication use, diabetes, atrial fibrillation, left ventricular hypertrophy, current cigarette smoking, and CVD.³⁴ *APOE* genotype was assessed as previously described,²⁵ by determining the 2 single-nucleotide polymorphisms that define the $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles. *APOE*- $\epsilon 4$ genotype was defined as positive ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$) or negative ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 3/\epsilon 3$).

Linear regression models related baseline aortic PWV to baseline gray matter (total, frontal, parietal, temporal, occipital, hippocampal, and inferior lateral ventricle volumes) and log-transformed WMH volumes (total, frontal, parietal, temporal, and occipital volumes). One region of interest variable was used per model. Mixed-effects regression models related aortic PWV at study entry to longitudinal gray matter (total, frontal, parietal, temporal, occipital, hippocampal, and inferior lateral ventricle volumes) and WMH volumes (total, frontal, parietal, temporal, and occipital volumes). One region of interest variable was used per model, resulting in 7 gray matter models and 5 WMH models. Hippocampus and inferior lateral ventricle regions were included due to their relevance in age-related atrophy³⁵ and Alzheimer's disease pathology.³⁵ Inferior lateral ventricle volume was included as a gray matter variable as the inferior lateral ventricle is adjacent to regions known to atrophy first in Alzheimer's disease, and increasing inferior lateral ventricle volume correlates with decreasing hippocampal volume.³⁶ Volumes were summed across hemispheres. Fixed effects included baseline age, sex, race/ethnicity, education, diagnosis, FSRP (minus age), *APOE*- $\epsilon 4$ carrier status, intracranial volume, and aortic PWV, as well as time (defined as years since first brain MRI) and an interaction term for *aortic PWV x time*, which is the term of interest. The term of interest, *aortic PWV x time*, captures change over time in the outcome attributed to aortic PWV reflecting either gray matter atrophy or WMH growth. Random effects included the intercept and time by each individual participant. Models were repeated testing an *aortic PWV x APOE- $\epsilon 4$ status x time* interaction term and an *aortic PWV x diagnosis x time* interaction term, followed by stratification by *APOE*- $\epsilon 4$ status (carrier or noncarrier) and by diagnosis (NC or MCI). Significance was set *a priori* at $p < 0.05$. False discovery rate correction for multiple comparisons was performed using the Benjamini-Hochberg procedure by MRI sequence adjusting for 7 gray matter volume analyses and separately adjusting for 5 WMH volume analyses. False discovery rate correction was used for all hypothesis-testing models but not for descriptive comparisons across groups. To

assess the role blood pressure plays in associations between arterial stiffness and structural brain changes, we performed 2 additional sets of post hoc analyses. First, we repeated all main effect models with systolic blood pressure as the predictor instead of aortic PWV. Second, we repeated main effect models with systolic blood pressure as an independent covariate instead of systolic blood pressure as a component of the FSRP. Statistical analyses were performed in R 3.5.2 (www.r-project.org).

3. Results

3.1 Participants Characteristics

Participants included 278 adults (73 ± 7 years, 58% male, 87% self-identified as non-Hispanic White), including 159 with NC and 119 with MCI, from the Vanderbilt Memory & Aging Project (n=335). Two hundred thirty-four participants were included at 18 months, 213 at 3 years, 181 at 5 years, and 54 at 7 years. During follow-up, 14 NC participants (8%) converted to MCI and 30 MCI participants (25%) converted to dementia based on the Clinical Dementia Rating global score. No participants were excluded based on a change in cognitive diagnosis across the follow-up period, but participants who dropped out of the study over the follow-up tended to have worse health at baseline. Aortic PWV ranged from 3.5 to 25.5 (8.2 ± 3.1) m/s and did not differ between NC and MCI participants ($p=0.93$). Participants with at-least 1 follow-up visit (n=240) were followed for an average of 4.9 ± 1.6 years up to 7 years with PWV measurements occurring from September 2012 to November 2014 and longitudinal brain MRI measurements occurring from September 2012 to June 2021. Mean annual volume changes were -5.10 cm³ for total gray matter and 1.95 cm³ for total WMHs. See Table 1 for more details. To assess possible regression to the mean effects on annual change in brain MRI measurements, we performed post hoc correlation analyses between each set of epochs for all longitudinal outcomes. Correlation coefficients ranged from 0.72 to 0.98 and were 0.88 for outcomes with significant main effect associations (ie, hippocampus volume, occipital lobe gray matter volume, and temporal lobe WMH volume), indicating any regression to the mean effect is small.

3.2 Aortic PWV and Baseline Gray Matter and WMH Volumes

Baseline aortic PWV was not cross-sectionally related to gray matter ($p>0.06$) or WMH volumes ($p>0.48$). The *aortic PWV x APOE-e4 status* interaction term was unrelated to both cross-sectional gray matter and WMH volumes ($p>0.28$). The *aortic PWV x cognitive diagnosis* interaction term was significantly associated with cross-sectional occipital lobe gray matter volume ($p=0.03$), but all remaining associations with cross-sectional gray matter and WMH volumes were null ($p>0.14$).

3.3 Aortic PWV and Longitudinal Gray Matter Volume Changes

Higher baseline aortic PWV was associated with greater decrease in gray matter volume over the follow-up period in the hippocampus ($\beta=-3.6$ [mm³/year]/[m/s], 95% CI=-7.2 to -0.02, $p=0.049$) and occipital lobe ($\beta=-34.2$ [mm³/year]/[m/s], 95% CI=-67.8 to -0.55, $p=0.046$). See Table 2 for details, including false discovery rate-corrected P values, and Figure 2 for illustration. All remaining P values throughout the article are uncorrected. In sensitivity analyses excluding participants with CVD and atrial fibrillation, the association

between aortic PWV and greater decrease in gray matter volume in the hippocampus ($\beta=-4.2$ [mm³/year]/[m/s], 95% CI=-8.3 to -0.11, $p=0.04$) persisted, but the association with occipital lobe volume was attenuated. When excluding outliers, associations between baseline aortic PWV and longitudinal hippocampal and occipital lobe gray matter volumes were attenuated. See (Table I in the Data Supplement). We performed post hoc analyses where we log-transformed our PWV values to account for any skewness. Results from these analyses were largely similar to our primary analyses with all previously significant models remaining statistically significant. When models were repeated using systolic blood pressure as a continuous variable covariate (rather than as a component of the FSRP), the association between aortic PWV and longitudinal occipital lobe gray matter volume was attenuated ($p=0.06$). See (Table II in the Data Supplement).

The *aortic PWV x APOE-ε4 status x time* interaction term was unrelated to any longitudinal gray matter volume changes ($P>0.11$; Table 3).

The *aortic PWV x diagnosis x time* interaction term was unrelated to any longitudinal gray matter changes ($P>0.32$; Table III in the Data Supplement).

3.4 Baseline Aortic PWV and Longitudinal WMH Volume Changes

Higher baseline aortic PWV was associated with greater increase in WMH volume in the temporal lobe ($\beta=17.0$ [mm³/year]/[m/s], 95% CI=7.2 to 26.9, $p<0.001$). When excluding participants with CVD and atrial fibrillation, results were similar. In sensitivity analyses excluding outliers, associations between baseline aortic PWV and longitudinal temporal lobe WMH volume was attenuated ($p=0.40$). We performed post hoc analyses where we log-transformed our PWV values to account for any existing skewness. The results from these analyses were largely similar with all previously significant models remaining statistically significant. When models were repeated using systolic blood pressure as a continuous variable covariate (rather than as a component of the FSRP), results were unchanged.

The *aortic PWV x APOE-ε4 x time* interaction term was related to temporal lobe WMH volume ($\beta=-27.2$ [mm³/year]/[m/s], 95% CI=-50.3 to -4.0, $p=0.02$). Results persisted when excluding participants with CVD and atrial fibrillation, but when excluding outliers, results were attenuated ($p=0.15$). In stratified models, results were null among *APOE-ε4* carriers ($P>0.42$). Among *APOE-ε4* non-carriers, higher baseline aortic PWV was associated with greater increase in WMH volume in the temporal lobe ($\beta=24.0$ [mm³/year]/[m/s], 95% CI=11.6 to 36.3, $P<0.001$; Table 3). Results persisted after excluding for CVD and atrial fibrillation but were attenuated when excluding outliers ($p=0.07$).

The *aortic PWV x diagnosis x time* interaction term was unrelated to longitudinal WMHs ($P>0.21$; Table III in the Data Supplement).

3.5 Systolic Blood Pressure and Longitudinal Brain Changes

Systolic blood pressure was unrelated to any longitudinal gray matter volume changes ($p>0.16$). Systolic blood pressure was significantly associated with greater increase in WMH volume in the temporal lobe ($\beta=1.78$ [mm³/y]/[m/s]; [95% CI, 0.12-3.43] $P=0.04$; Table IV in the Data Supplement).

4. Discussion

This study leveraged multimodal MRI techniques to quantify aortic PWV and structural brain changes among community-dwelling older adults to better understand detailed associations between central arterial stiffness and longitudinal brain structure. All cross-sectional results assessing associations between aortic PWV and gray matter volumes, as well as WMH volumes were null. Higher baseline aortic PWV was associated with greater decrease in gray matter volume over the mean 4.2-year follow-up period in the hippocampus and occipital lobe. Neither *APOE-ε4* nor cognitive diagnosis modified associations. Higher baseline aortic PWV—a measure of the degree of aortic stiffness—was associated with greater increase in WMH volumes in the temporal lobe over the follow-up period. While associations were not modified by diagnosis, the *baseline aortic PWV x APOE-ε4* interaction term was related to longitudinal WMH volume in the temporal lobe. Associations between higher baseline aortic PWV and greater increase in WMH volume appear to be driven by *APOE-ε4* noncarriers.

Our results suggest that central arterial stiffening predicts greater decrease in gray matter volume in the hippocampus. These observations are particularly interesting considering the regions affected by aortic stiffening overlap with regions that accumulate Alzheimer's disease pathology early in the disease process. Indeed, higher aortic stiffness has been related to increased cerebral amyloid deposition in older adults.^{37,38} Importantly though, baseline models relating PWV to gray matter and WMH volumes in this cohort were null, suggesting that aortic stiffening contributes little to interindividual differences at baseline. PWV does, however, predict the rate of neurodegeneration, suggesting aortic stiffening may create susceptibility to more rapid change once a pathological process is initiated. These observations provide subtle yet potentially important insights about drivers and rate of neurodegeneration that warrant further inquiry.

We previously reported higher aortic PWV was cross-sectionally associated with lower cerebral blood flow in several brain regions, including the temporal lobe, which contains the hippocampus, and occipital lobe in subsets of the cohort.²⁹ Reduced cerebral blood flow due to higher PWV is likely the result of microvascular remodeling and higher vascular resistance.²⁹ Chronic reductions in cerebral blood flow may lead to unmet cerebral metabolic demands, which disrupt cerebral homeostasis and result in cell dysfunction, death, and subsequent atrophy due to excitotoxicity.^{39,40} Interestingly, the hippocampus and temporal lobes are regions with particularly high energy consumption. The hippocampus is one of the most densely populated brain regions in terms of synapses,^{41,42} and the medial temporal lobes are involved in the highly active default mode network.⁴³ The metabolic demand of these regions may make them particularly vulnerable to excitotoxicity. However, it is plausible that other damaging cascades, such as oxidative stress or blood-brain barrier breakdown, play a role in the longitudinal atrophy observed here.

Our second major observation is that central arterial stiffening contributes to greater increase in WMH volume in the temporal lobe. One explanation aligned with the aforementioned discussion is that arterial stiffness is linked to reduced cerebral blood flow,²⁹ resulting in oligemia and possibly ischemia. Ischemia is a well-established driver of WMH formation in

limitations are worth mentioning when interpreting our results. Given the college-educated, predominantly White, older sample, generalizability of findings is limited. The possibility exists that in a less healthy cohort with increased aortic stiffness and more CVD, the present observations would be more robust (which is, in part, supported by our sensitivity analyses for which findings were attenuated when excluding outliers). Attrition occurred among the less healthy participants, which likely biases our results to the null hypothesis.

Focusing on how age-related systemic cardiovascular changes influence neurodegeneration is an essential aspect of understanding the multifactorial contributors to adverse cognitive aging and dementia risk. The present research serves to increase our knowledge by showing aortic stiffness is associated with longitudinal gray matter and white matter damage, particularly in the temporal lobes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non Standard Abbreviations

APOE-ε4	Apolipoprotein E ε4
CVD	Cardiovascular disease
FSRP	Framingham stroke risk profile
MCI	Mild cognitive impairment
NC	Normal Cognition
PWV	Pulse wave velocity
WMH	White matter hyperintensity
MRI	magnetic resonance imaging

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Highlights

- Higher baseline aortic pulse wave velocity was significantly associated with greater decrease in hippocampal and occipital lobe gray matter volumes.
- Higher baseline aortic pulse wave velocity was significantly associated with greater increase in temporal lobe white matter hyperintensity volumes.
- Arterial stiffening may preferentially affect certain highly active brain regions like the temporal lobes. These same regions are affected early in the course of Alzheimer's disease.

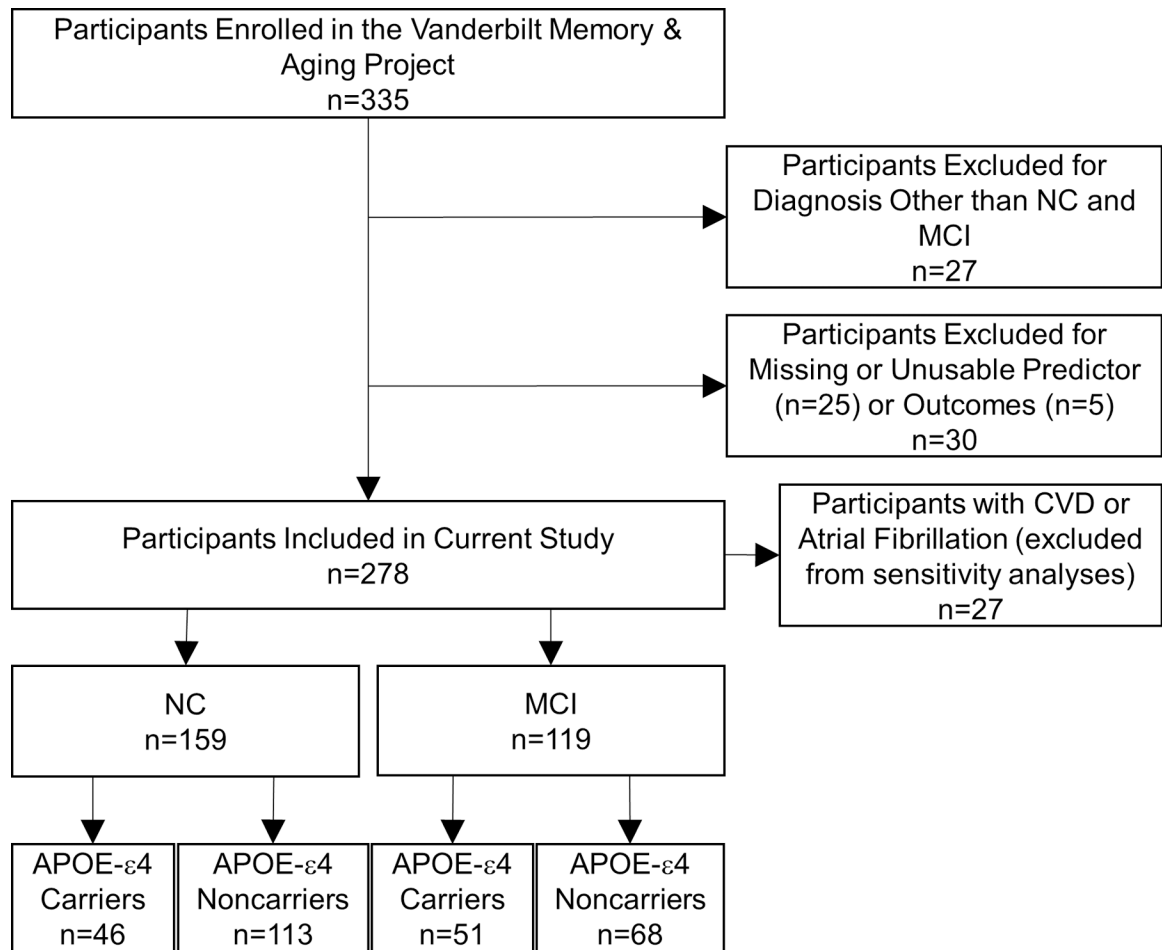


Figure 1. Participant Inclusion/Exclusion Details

Participant inclusion and exclusion details. Missing data categories are mutually exclusive. Sensitivity analyses excluded participants with CVD or atrial fibrillation. *APOE* indicates apolipoprotein E; CVD, cardiovascular disease; MCI, mild cognitive impairment; and NC, normal cognition.

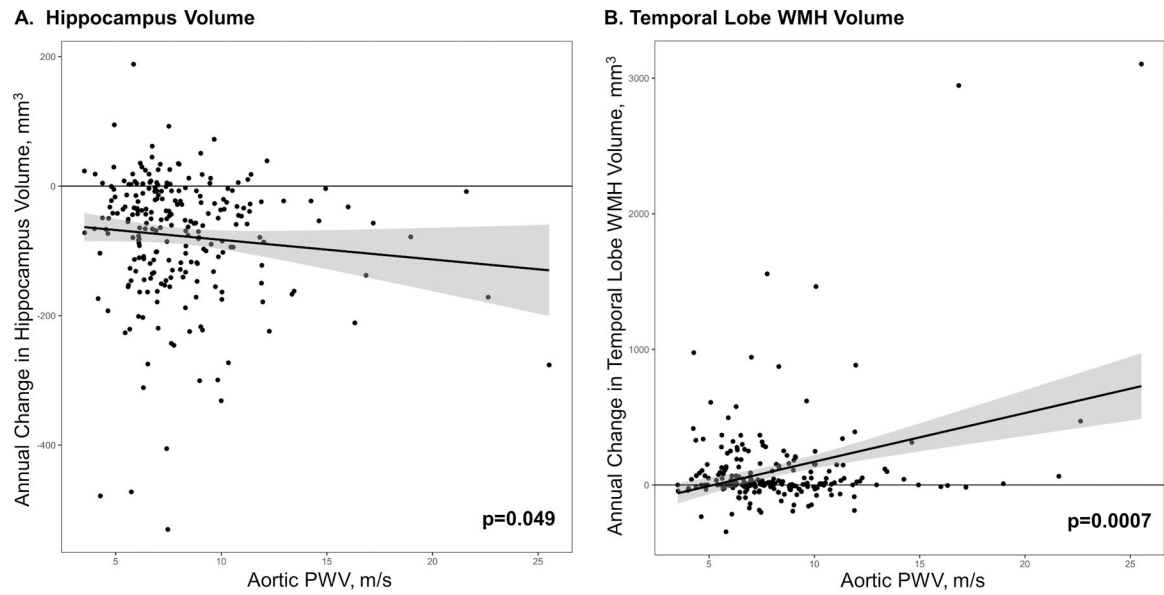


Figure 2. PWV and Longitudinal Cerebral Structural Changes

Baseline PWV associations with a) Hippocampus Volume and b) Temporal Lobe WMH Volume. PWV, pulse wave velocity. WMH, white matter hyperintensity. When outliers are excluded, associations with hippocampus volume and temporal WMH volume are attenuated ($p>0.14$).

Table 1.

Participant Characteristics

	Total n=278	NC n=159	MCI n=119	p-value
Baseline Characteristics				
Age, y	73±7	72±7	73±7	0.39
Sex, % male	58	58	58	0.93
Race, % non-Hispanic white	87	87	87	0.95
Education, y	16±3	16±3	15±3	<0.001*
<i>APOE</i> -e4, % carrier	35	29	43	0.02*
Framingham Stroke Risk Profile, total [†]	12.3±4.3	11.9±4.3	12.8±4.2	0.06
Systolic blood pressure, mmHg	142±18	140±17	144±18	0.02*
Antihypertensive medication usage, %	53	53	52	0.90
Diabetes, %	18	16	20	0.41
Cigarette smoking, % current	2	1	3	0.23
Prevalent CVD, %	5	6	3	0.37
Atrial fibrillation, %	6	6	7	0.71
Left ventricular hypertrophy, %	4	3	6	0.27
Intracranial volume, cm ³	1507±154	1503±154	1512±155	0.78
Pulse wave velocity, m/s	8.2±3.1	8.1±3.0	8.3±3.3	0.93
Gray Matter Neuroimaging Markers, mm³/year				
Total gray matter annual change	-5101±8621	-4741±8590	-5620±8684	0.29
Frontal gray matter annual change	-2159±4261	-2143±4424	-2181±4036	>0.99
Temporal gray matter annual change	-691±1494	-458±1376	-1027±1596	0.005*
Parietal gray matter annual change	-1336±2097	-1319±2140	-1362±2044	0.42
Occipital gray matter annual change	-447±1054	-455±956	-435±1186	0.79
Hippocampal annual change	-77±96	-62±76	-98±116	0.01*
Inferior lateral ventricle annual change	157±204	100±108	239±272	<0.001*
WMH Neuroimaging Markers, mm³/year				
Total WMH annual change	1954±2953	1365±1806	2793±3923	0.001*
Frontal WMH annual change	1110±1525	825±986	1516±2000	0.009*
Temporal WMH annual change	103±347	66±310	154±390	0.002*
Parietal WMH annual change	541±864	381±563	769±1131	0.02*
Occipital WMH annual change	201±663	93±395	354±900	0.01*

Note. *APOE*-e4 indicates apolipoprotein E e4 allele; CVD, cardiovascular disease; MCI, mild cognitive impairment; NC, normal cognition.

* Meets the a priori significance threshold of 0.05

[†] A modified Framingham Stroke Risk Profile Score was included in statistical models, which excluded points assigned to age (total=6.5±3.1, NC=6.2±3.0, MCI=6.8±3.2). Annual change values represent the average change in tissue volume per year for each region of interest.

Table 2.

Aortic PWV Associations with Longitudinal Gray Matter Volume and WMH Volume

Gray Matter Neuroimaging Markers ((mm³/year)/(m/s))				
	β	95% CI	p-value	FDR p-value
Total gray matter	-184.8	-510.9, 141.4	0.27	0.49
Frontal gray matter	-21.94	-189.6, 145.7	0.80	0.92
Temporal gray matter	-42.52	-96.75, 11.71	0.12	0.40
Parietal gray matter	-51.40	-129.7, 26.89	0.20	0.43
Occipital gray matter	-34.19	-67.83, -0.55	0.046*	0.21
Hippocampus	-3.61	-7.19, -0.02	0.049*	0.21
Inferior lateral ventricle	5.76	-2.26, 13.77	0.16	0.41
WMH Neuroimaging Markers ((mm³/year)/(m/s))				
Total WMH	30.82	-62.37, 124.0	0.52	0.83
Frontal WMH	-2.74	-53.15, 47.68	0.92	0.92
Temporal WMH	17.04	7.17, 26.92	<0.001*	0.009
Parietal WMH	8.69	-21.68, 39.05	0.57	0.83
Occipital WMH	0.81	-15.95, 17.57	0.92	0.92

Note. Analyses performed on n=278 participants. Models were adjusted for age, sex, race/ethnicity, education, *APOE-ε4* status, cognitive diagnosis, and Framingham stroke risk profile (excluding points assigned for age). The parameter estimates (**β**) are for the *PWV*×*time* interaction term and is interpreted as the annual changes of outcomes associated with 1 unit change in PWV (per 1 m/s). FDR indicates false discovery rate; PWV, pulse wave velocity; and WMH, white matter hyperintensity.

* Meets the a priori significance threshold of 0.05

Aortic PWV x *APOE*- ϵ 4 x Time Interactions and Stratifications by *APOE*- ϵ 4 Status with Longitudinal Magnetic Resonance Imaging Outcomes

Table 3.

	β	95 % CI	p-value	FDR p-value
<i>APOE</i>-ϵ4 Status Interaction Gray Matter Neuroimaging Markers ((mm³/year)/(m/s))				
Total gray matter	-164.8	-903.8, 574.2	0.66	0.86
Frontal gray matter	-14.69	-384.8, 355.4	0.94	0.94
Temporal gray matter	-99.42	-232.9, 34.02	0.14	0.47
Parietal gray matter	-19.15	-187.7, 149.4	0.82	0.94
Occipital gray matter	-29.49	-111., 51.97	0.48	0.69
Hippocampus	-4.45	-13.55, 4.66	0.34	0.55
Inferior lateral ventricle	13.32	-2.84, 29.47	0.11	0.46
<i>APOE</i>-ϵ4 Status Interaction WMH Neuroimaging Markers ((mm³/year)/(m/s))				
Total WMH	-138.9	-355.8, 78.08	0.21	0.54
Frontal WMH	-61.02	-180.7, 58.65	0.32	0.55
Temporal WMH	-27.16	-50.30, -4.02	0.02*	0.14
Parietal WMH	-40.71	-111.9, 30.53	0.26	0.55
Occipital WMH	2.50	-38.78, 43.78	0.91	0.94
<i>APOE</i>-ϵ4 Carriers Gray Matter Neuroimaging Markers ((mm³/year)/(m/s))				
Total gray matter	-485.4	-1190, 219.6	0.18	0.37
Frontal gray matter	-106.6	-448.2, 234.9	0.54	0.69
Temporal gray matter	-132.1	-268.4, 4.21	0.06	0.26
Parietal gray matter	-100.1	-252.8, 52.52	0.20	0.37
Occipital gray matter	-69.59	-152.9, 13.74	0.10	0.30
Hippocampus	-7.97	-17.96, 2.01	0.12	0.30
Inferior lateral ventricle	21.50	-0.92, 43.92	0.06	0.26
<i>APOE</i>-ϵ4 Carriers WMH Neuroimaging Markers ((mm³/year)/(m/s))				
Total WMH	-58.09	-320.3, 204.1	0.66	0.69
Frontal WMH	-35.55	-172.9, 101.8	0.61	0.69
Temporal WMH	-6.98	-23.84, 9.87	0.42	0.67
Parietal WMH	-19.05	-105.3, 67.19	0.66	0.69
Occipital WMH	8.11	-31.63, 47.85	0.69	0.69

	β	95 % CI	p-value	FDR p-value
<i>APOE-ε4</i> Non-carriers Gray Matter Neuroimaging Markers ((mm³/year)/(m/s))				
Total gray matter	-89.79	-465.9, 286.4	0.64	0.82
Frontal gray matter	15.46	-183.9, 214.8	0.88	0.88
Temporal gray matter	-28.64	-84.82, 27.54	0.32	0.51
Parietal gray matter	-30.13	-123.3, 63.09	0.53	0.76
Occipital gray matter	-25.96	-62.2, 10.29	0.16	0.35
Hippocampus	-3.48	-6.98, 0.02	0.05	0.33
Inferior lateral ventricle	4.88	-2.07, 11.83	0.17	0.35
<i>APOE-ε4</i> Non-carriers WMH Neuroimaging Markers ((mm³/year)/(m/s))				
Total WMH	70.26	-20.74, 161.3	0.13	0.35
Frontal WMH	10.10	-40.96, 61.17	0.70	0.82
Temporal WMH	23.95	11.59, 36.32	<0.001*	0.003
Parietal WMH	19.73	-9.78, 49.23	0.19	0.35
Occipital WMH	2.08	-16.20, 20.37	0.82	0.88

Note. Analyses performed on n=278 participants and subsequently stratified by *APOE-ε4* status for n=97 *APOE-ε4* positive participants and n=181 *APOE-ε4* negative participants. The interaction term was aortic PWV x time x *APOE-ε4* status. Models were adjusted for age, sex, race/ethnicity, education, *APOE-ε4* status, and Framingham Stroke Risk Profile (excluding points assigned for age), *APOE-ε4*, apolipoprotein E $\epsilon 4$ allele. CI, confidence interval; FDR p-value, false discovery rate corrected p-value. For the *APOE-ε4* Status interaction model, the parameter estimates (β) are for the *PWV x APOE-ε4 x time* interaction term and is interpreted as the difference in annual changes of outcomes between *APOE-ε4* positive participants and *APOE-ε4* negative participants associated with one unit change in PWV (per 1 m/s). For stratified models by *APOE-ε4* status, the parameter estimates (β) are for the *PWV x time* interaction term and is interpreted as the annual changes of outcomes associated with one unit change in PWV (per 1 m/s).

* Meets the a priori significance threshold of 0.05