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***APOE* genotype modifies the association between central arterial stiffening and cognition in older adults**

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Abstract

Arterial stiffening is associated with cognitive impairment and prodromal Alzheimer's disease (AD). This study tested the interaction between arterial stiffening and an AD genetic risk factor (*APOE* genotype) on cognition among older adults. Vanderbilt Memory & Aging Project participants with normal cognition (NC, $n=162$, 72 ± 7 years, 29% *APOE*- $\epsilon 4$ carrier) and mild cognitive impairment (MCI, $n=121$, 73 ± 8 years, 42% *APOE*- $\epsilon 4$ carrier) completed neuropsychological assessment and cardiac MRI to assess aortic stiffening using pulse wave velocity (PWV, m/s). Linear regression models stratified by cognitive diagnosis related aortic PWV $\times$ *APOE*- $\epsilon 4$ status to neuropsychological performances, adjusting for demographic and vascular risk factors. PWV $\times$ *APOE*- $\epsilon 4$ related to poorer performance on measures of lexical retrieval ($\beta=-0.29$, $p=0.01$), executive function ($\beta=-0.44$, $p=0.02$), and episodic memory ($\beta=-3.07$, $p=0.02$). Among participants with higher aortic PWV, *APOE*- $\epsilon 4$ modified the association between central arterial stiffening and cognition, such that carriers had worse performances than non-carriers. Findings add to a growing body of evidence for *APOE*-vascular interactions on

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Disclosure Statement

The authors declare no conflicts of interest.

cognition in older adults and warrant further research into less heart-healthy cohorts where the association between PWV and cognition among older adults might be stronger.

Keywords

Alzheimer's disease; pulse wave velocity; cardiac MRI; vascular risk factors; microcirculation; aging

1. Introduction

Age-related changes in vascular structure and hemodynamics have been associated with cerebrovascular disease, a leading cause of cognitive impairment (Kivipelto et al., 2001). Increasing evidence suggests chronic risk factors for cerebrovascular disease, such as hypertension, may impair autoregulatory systems responsible for maintaining constant cerebral perfusion and protecting against mean arterial pressure changes (Immink et al., 2004). Systemic vascular changes, such as central arterial stiffening, may further compromise the brain's autoregulatory mechanisms and affect tissue integrity (Maillard et al., 2016).

Age-related arterial stiffening is postulated to drive end-organ damage through transmission of harmful pulsatile energy to the peripheral microcirculation, a phenomenon associated with microvascular abnormalities in high-flow organs, such as the kidney (Triantafyllou et al., 2014). The brain, another vulnerable high-flow organ, may be susceptible to pulsatile energy damage, including increased microvascular remodeling and impaired local blood flow regulation (see Mitchell, 2008 for review). Arterial stiffening is often characterized by increased pulse wave velocity (PWV), a noninvasive measure of arterial wall properties. Higher PWV has been linked to worse cognitive performance (Zhong et al., 2014), faster rates of cognitive decline (Waldstein et al., 2008; Watson et al., 2011), and mild cognitive impairment (MCI) (Meyer et al., 2017), though findings have been inconsistent (Poels et al., 2007).

One of the most well-established risk factors for cognitive decline is the *apolipoprotein E* $\epsilon 4$ allele (*APOE- $\epsilon 4$*), an Alzheimer's disease (AD) genetic susceptibility marker. *APOE- $\epsilon 4$* mediates blood-brain barrier breakdown (Halliday et al., 2016) and facilitates amyloid-beta ($A\beta$) accumulation (Castellano et al., 2011; Holtzman et al., 2000), which can induce endothelial damage and changes in vascular tone (Thomas et al., 1997; Thomas et al., 1996). Such *APOE- $\epsilon 4$* vascular effects purportedly occur prior to neuronal dysfunction and degeneration (Bell et al., 2012). Accordingly, *APOE- $\epsilon 4$* modifies the association between vascular disease and brain abnormalities (DeCarli et al., 1999) and relates to earlier, more progressive cognitive decline (Martins et al., 2005). *APOE- $\epsilon 4$* carriers may also be susceptible to cerebrovascular injury via subclinical central vascular changes, particularly elevated PWV.

Using the best available non-invasive assessment of central arterial stiffening that directly approximates PWV across the proximal aorta, the current study evaluates how *APOE- $\epsilon 4$* interacts with PWV to modify the association between PWV and neuropsychological

performance among community-dwelling older adults free of clinical dementia and stroke. Our hypothesis is that the $PWV \times APOE-\epsilon 4$ interaction term will relate to neuropsychological performance, such that *APOE-ε4* carriers will have stronger associations between elevated PWV and poorer cognitive performance. We predict that $PWV \times APOE-\epsilon 4$ associations will be strongest in participants with prodromal dementia (MCI) because they are more susceptible to *APOE-ε4* effects. Based on prior findings, we further hypothesize that these effects will be especially prominent among information processing speed (Watson et al., 2011), executive function (Zhong et al., 2014), and episodic memory measures (Mitchell et al., 2011; Waldstein et al., 2008).

2. Methods

2.1. Study Cohort

The Vanderbilt Memory & Aging Project (MAP) is a longitudinal study investigating vascular health and brain aging, enriched for MCI (Jefferson et al., 2016). Inclusion criteria required participants be age 60 or older, speak English, have adequate auditory and visual acuity, and have a reliable study partner. At eligibility, participants underwent medical history and record review, clinical interview with the informant, and neuropsychological assessment. Participants were excluded for a cognitive diagnosis other than normal cognition (NC) or MCI (Albert et al., 2011), MRI contraindication, history of neurological disease (e.g., stroke), heart failure, major psychiatric illness, head injury with loss of consciousness >5 minutes, or a systemic or terminal illness affecting follow-up examination participation. At enrollment participants completed a comprehensive evaluation, including (but not limited to) fasting blood draw, physical examination, clinical interview, medication review, neuropsychological assessment, and cardiac magnetic resonance (CMR) imaging. Participants were excluded from the current study for missing PWV, *APOE* genotype, neuropsychological performance, or covariate data (see Figure 1). The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board, and written informed consent was obtained prior to data collection.

2.2. CMR Imaging – Aortic PWV

CMR imaging was acquired at Vanderbilt University Medical Center using a 1.5T Siemens Avanto system (Siemens Medical Solutions USA, Inc., Malvern, PA) with a phased-array torso receiver coil. Velocity-encoded flow data were acquired from the ascending and descending thoracic aorta (see Figure 2 for PWV measurement site details). Under the supervision of a board-certified radiologist (JJC), trained raters blinded to all clinical information (JGT, SN) used the 2-dimensional flow sequence to draw contours on the ascending and descending aorta using QFLOW 5.6 Enterprise Solution (Medis, Leiden, Netherlands). The thoracic aorta centerline length (cm) from the ascending aorta to descending aorta was measured using OsiriX (PIXMEO SARL, Bernex, Switzerland). Transit time was calculated using a custom MATLAB script to calculate the difference in time in milliseconds at half-max between the leading edge of the ascending and the leading edge of the descending aortic flow curves. PWV (m/s) was calculated as distance traveled across the aorta (meters) divided by time delay in onset of pulse waves (seconds). Inter-reader reliability for the measurement was determined by independent review of 34 scans by

two readers (JGT, SN) with coefficient of variation=6.6%. Higher PWV values suggest increased stiffness since pulsatile wave transmission increases with decreasing arterial wall elasticity. We directly measured PWV across the thoracic arch since this segment is the largest single contributor to systemic arterial compliance. CMR assessment of PWV provides a non-invasive direct measurement of blood flow in the thoracic aorta with substantially reduced measurement error compared to other available tools, and is thus an accurate measurement of the central path accounting for vessel tortuosity (Ohyama et al., 2017).

2.3 Genetic Testing

As previously published (Jefferson et al., 2016), a TaqMan® single-nucleotide polymorphism (SNP) genotyping assay from Applied Biosystems (Foster City, California, USA) was used to determine the two SNPs that define the $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles. Polymerase chain reaction (PCR) in 5 μ l reactions was performed on a Life Technologies 7900HT real-time PCR machine, and results were analyzed using Life Technologies SDS 2.4.1 software.

2.4. Neuropsychological Assessment

All participants completed a common, comprehensive neuropsychological protocol assessing language, information processing speed, executive functioning, visuospatial skills, and episodic memory (see Table 1 for list of assessment tools). Measures were carefully selected to preclude floor or ceiling effects. Note, these measures were not used as part of the screening or selection of participants into the study.

2.5. Analytical Plan

Body mass index (BMI) was calculated as $\text{weight(kg)}/[\text{height(m)}]^2$. Systolic blood pressure was the mean of two measurements. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL, hemoglobin A1C $\geq 6.5\%$, or oral hypoglycemic or insulin medication usage. Medication review determined anti-hypertensive medication use. Left ventricular hypertrophy was defined on echocardiogram as left ventricle mass index >115 g/m² in men or >95 g/m² in women. Self-report atrial fibrillation was corroborated by any one of the following sources: echocardiogram, documented prior procedure/ablation for atrial fibrillation, or medication usage for atrial fibrillation. Current cigarette smoking (yes/no within the year prior to baseline examination) was ascertained by self-report. Self-report prevalent cardiovascular disease (CVD) with supporting evidence from medical records included coronary heart disease, angina, or myocardial infarction (note, heart failure was an exclusion for the parent study). Framingham Stroke Risk Profile (FSRP) score was calculated by applying points by sex for age, systolic blood pressure, anti-hypertensive medication usage, diabetes mellitus, current cigarette smoking, left ventricular hypertrophy, prevalent CVD, and atrial fibrillation (D'Agostino et al., 1994). *APOE- $\epsilon 4$* allele carrier status 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 with ordinary least square estimates related PWV to neuropsychological test performance (one test per model), adjusting for age, race/ethnicity, education, BMI, and FSRP (excluding points assigned for age). To test our hypotheses related to *APOE- $\epsilon 4$* , models were repeated with a $\text{PWV} \times \text{APOE-}\epsilon 4$ interaction term, then

models were repeated stratifying by *APOE-ε4* positive versus *APOE-ε4* negative status and again stratifying by cognitive diagnosis (NC, MCI). Note, all lower order terms (including *APOE-ε4* and PWV) were retained in the interaction models. A follow-up sensitivity analysis was performed excluding participants with prevalent CVD or atrial fibrillation to test if these conditions accounted for significant results. In post-hoc analyses, significant models were re-analyzed to assess allele dosage effects where *APOE-ε4* status was defined as zero, one, or two *ε4* alleles. Significance was set *a priori* at $p < 0.05$. To account for the effect of multiple comparisons, the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was used to control the false discovery rate (FDR); thresholds were set at $Q = 0.05$ for main models and $Q = 0.10$ for *APOE-ε4* interaction models. All analyses were conducted using R version 3.2.3 (www.r-project.org).

Post-hoc power calculations for the $PWV \times APOE-ε4$ interaction were conducted using an F distribution based on increased R^2 for a model that included $PWV \times APOE-ε4$ plus covariates. Based on the available sample sizes ($n = 283$ and $n = 260$ after exclusion for CVD and atrial fibrillation) and Type I error of 0.05, the power to detect R^2 increases of 0.01 and 0.02 (1% and 2% variance explained by $PWV \times APOE$ interaction) given R^2 of 0.3 are 52% and 81%, respectively, for the entire cohort and 48% and 77%, respectively, after exclusion for CVD and atrial fibrillation. Power calculations suggest the study is sufficiently powered to detect as low as 2% variance explained by $PWV \times APOE-ε4$ using the entire cohort and after excluding participants with CVD and atrial fibrillation.

3. Results

3.1. Participant Characteristics

The cohort was composed of 283 participants (73 ± 7 years, 59% male), including 162 NC and 121 MCI participants. PWV values ranged 3.5 to 25.5 m/s (8.2 ± 3.2) and did not differ between NC and MCI participant groups ($p = 0.87$). At least one *APOE-ε4* allele was present in 35% of the cohort, with higher *APOE-ε4* allele prevalence in the MCI (42%) compared to the NC group (29%, $p = 0.02$). As expected, the MCI group had worse neuropsychological performances compared to the NC group (all p -values < 0.001). See Table 1 for more details on participant characteristics.

3.2. PWV & Neuropsychological Performances

In the combined cohort, PWV was unrelated to all neuropsychological performances (all p -values > 0.23). In results stratified by cognitive diagnosis, PWV was also unrelated to all neuropsychological performances among NC (all p -values > 0.09) and MCI participants (all p -values > 0.35). See Supplementary Table 1 for PWV main effect results.

3.3. $PWV \times APOE-ε4$ & Neuropsychological Performances

APOE-ε4 status modified the relationship between PWV and neuropsychological performance on Boston Naming Test ($\beta = -0.29$, 95% CI -0.51 to -0.07 , $p = 0.01$), Delis-Kaplan Executive Function System (DKEFS) Tower Test ($\beta = -0.44$, 95% CI -0.82 to -0.07 , $p = 0.02$), and Biber Figure Learning Test (BFLT) Total Immediate Recall ($\beta = -3.07$, 95% CI -5.70 to -0.43 , $p = 0.02$). For each test, *APOE-ε4* carriers experienced worse

neuropsychological performances at higher PWV values (see Figure 3 for illustrations). Of these *APOE-ε4* interaction results, none survived FDR adjustment. In sensitivity analyses, results were no longer statistically significant after exclusion for CVD and atrial fibrillation though effect sizes were comparable to significant observations detected in the primary models. See Table 2 for complete $PWV \times APOE-ε4$ interaction results. When models were stratified by *APOE-ε4* status, PWV was related to neuropsychological performances in *APOE-ε4* positive participants on the DKEFS Tower Test ($\beta=-0.43$, 95% CI -0.79 to -0.07 , $p=0.02$).

When models were stratified by cognitive diagnosis, $PWV \times APOE-ε4$ was unrelated to neuropsychological performances in the NC cohort (all p -values >0.09). In the MCI cohort, *APOE-ε4* significantly modified the relationship between PWV and Biber Figure Learning Test (BFLT) Total Immediate Recall ($\beta=-4.11$, 95% CI -7.88 to -0.34 , $p=0.03$). When adjusting for FDR, this result did not remain significant, but it did persist after exclusion for CVD and atrial fibrillation ($p=0.049$).

In follow-up analyses examining *APOE-ε4* allele dosage effects, *APOE-ε4* allele count modified the relationship between PWV and neuropsychological performance in the combined cohort on Boston Naming Test ($p=0.02$). Participants with two copies of the *APOE-ε4* allele performed worse at higher PWV values than participants with one copy of the *APOE-ε4* allele (Supplementary Figure 1). This *APOE-ε4* allele count result did not survive FDR adjustment nor did it persist after exclusion for CVD and atrial fibrillation or when excluding participants with *APOE ε2/ε4* genotype. See Supplementary Table 2 for details. *APOE-ε4* allele dosage did not modify the relationship between PWV and neuropsychological performance in diagnostically stratified results.

4. Discussion

Among community-dwelling older adults free of clinical stroke or dementia, PWV has a limited association with cognition but a modest interaction with *APOE-ε4* carrier status on multiple cognitive domains. Specifically, increased PWV is associated with worse lexical retrieval, visuospatial episodic memory, and executive function performance among *APOE-ε4* carriers. It is noteworthy that effects reported here are statistically independent of many shared vascular risk factors, only modestly attenuated by CVD and atrial fibrillation, and equivalent to over 3 years of accelerated cognitive aging when comparing the effect of one year of aging to the effect of $PWV \times APOE-ε4$ on cognition.

Notably, age-related central arterial stiffening results in increased PWV, transmission of damaging pulsatile energy, and microvascular dysfunction, including decreased blood flow to high-demand organs as purported by Mitchell (2008). The impact of cerebral hypoperfusion may have the greatest impact in distal vascular territories where tissue is farthest from blood supply, in regions susceptible to mechanical stress due to supply from the most direct perfusion branches, or in the most metabolically active regions, such as frontal cortex (Kochunov et al., 2009). The implication of memory and executive function here is interesting, as these domains are associated with the frontal cortex, parieto-occipital

cortex, and white matter, all of which are vulnerable to hypoperfusion (Maillard et al., 2016).

The presence of *APOE-ε4* may intensify the effects of age-related aortic stiffening to produce detectable neuropsychological changes in vulnerable older adults with prodromal AD symptoms, such as the MCI group. These individuals may experience a weakened vascular state in which normal protective mechanisms are compromised due to elevated systolic blood pressure and existing neuropathology, allowing associations between aortic stiffening and worse brain health to emerge at PWV levels that may not be as harmful or clinically manifest among NC individuals. As expected, the deleterious $PWV \times APOE-ε4$ associations on episodic memory were most prominent in MCI participants. Prior work has found reduced cerebral blood flow and higher cerebrovascular resistance in advanced age, MCI, and AD, suggesting impaired cerebrovascular regulation across the cognitive aging spectrum (Alsop et al., 2010; Clark et al., 2015; Nation et al., 2013). If cerebrovascular responses to central vascular changes are compromised, then end-organ damage in the brain may yield worse cognitive and behavioral outcomes. Recent cerebrovascular regulation studies in advanced aging and MCI suggest that if cerebrovascular responses to central vascular changes are compromised, then the brain may experience lower perfusion levels and compromised autoregulation, changes that are related to end-organ damage (Brickman et al., 2015; Jefferson et al., 2017). These changes may in turn yield worse cognitive and behavioral outcomes and faster declines for these groups.

A majority of findings were weakened in the sensitivity analyses excluding participants with prevalent CVD or atrial fibrillation. Such attenuation suggests PWV and *APOE-ε4* status may relate to cognition in more pathological cardiovascular states, such that CVD and atrial fibrillation are potential contributors (Jefferson, 2014). CVD conditions impair structural integrity and vessel health, while rhythm issues, such as atrial fibrillation, increase stroke risk by elevating clotting factors and relate to hippocampal atrophy (Knecht et al., 2008), cognitive impairment, and dementia (Forti et al., 2006). However, it is important to note that effect sizes from the primary models and the sensitivity models excluding CVD and atrial fibrillation were comparable suggesting the null sensitivity models might be explained by decreased power due to fewer available participants.

There are several strengths of the current project. First, direct CMR assessment of PWV across the aortic arch greatly reduces measurement error introduced by traditional measures (e.g., carotid-femoral PWV), which reflect mixed vascular properties along the arterial tree. CMR more accurately assesses the aortic path, which is uniquely implicated in peripheral health since it contributes an estimated 60–70% of total systemic compliance (Stergiopoulos et al., 1999). Second, our comprehensive neuropsychological protocol captures a diverse range of outcomes. Third, *APOE-ε4* genotyping and aortic PWV data were processed in batch in a core laboratory by technicians blinded to clinical information. Conversely, it is important to note that the cohort is not reflective of the general population since participants were older, predominantly White, well educated, and relatively healthy with a low prevalence of CVD (4%) compared to the general population over age 65 (24% to 37%) (Blackwell et al., 2014). Whether such variables limit the generalizability of our results is unknown, but we purport that in a less healthy cohort with greater vascular risk factors or

more compromised cardiac function, the association between PWV and cognition among older adults would likely be stronger. Given the cross-sectional nature of the study, we cannot draw conclusions about causal relationships or cognitive trajectory. However, ongoing follow-up analyses will facilitate future examination of $PWV \times APOE-\epsilon 4$ interactions on the rate of cognitive decline and underlying pathophysiology of increased PWV and subclinical vascular changes to declining cognition, particularly microvascular integrity and cerebral perfusion deficits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Aβ	amyloid-beta
AD	Alzheimer's disease
APOE	<i>Apolipoprotein E</i>
BFLT	Biber Figure Learning Test
Boston Naming Test	Boston Naming Test-30 Item Odd Version
CDR	Clinical Dementia Rating
CMR	cardiac magnetic resonance imaging
CVD	cardiovascular disease
CVLT-II	California Verbal Learning Test- ^{2nd} Edition
DKEFS	Delis-Kaplan Executive Function System
FSRP	Framingham Stroke Risk Profile
MAP	Memory & Aging Project
MCI	Mild Cognitive Impairment

NC	Normal Cognition
PCR	polymerase chain reaction
PWV	pulse wave velocity
SNP	single-nucleotide polymorphism
WAIS-IV	Wechsler Adult Intelligence Scale-4 th Edition

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Highlights

- This study tests arterial stiffening and *APOE-ε4* status interactions on cognition.
- Increased PWV is associated with worse cognition among *APOE-ε4* carriers.
- PWV relates specifically with worse episodic memory in *APOE-ε4* carriers with MCI.
- Results support *APOE*-vascular interactions on cognition in AD-risk older adults.

Figure 1. Participant Inclusion/Exclusion Criteria

Figure 2. Representative PWV Measurement Sites in Aortic Arch

Note. PWV encoded flow data (A) was acquired from the ascending and descending thoracic aorta with slice angulation adjusted to maximize perpendicular flow (B)

Figure 3. PWV $\times$ APOE-ε4 Associations with Neuropsychological Performance

Note. Panel A, $p=0.01$. Panel B, $p=0.02$. Panel C, $p=0.02$. DKEFS=Delis-Kaplan Executive Function System; BFLT=Biber Figure Learning Test.

Table 1**Participant Characteristics**

	Total n=283	NC n=162	MCI n=121	p-value
Demographic & Health Characteristics				
Age, years	73±7	72±7	73±8	0.39 ^a
Sex, % male	59	59	58	0.81 ^b
Race, % Non-Hispanic White	87	87	86	0.79 ^b
Education, years	16±3	16±2	15±3	<0.001 ^a
Montreal Cognitive Assessment, total	25±3	27±2	23±3	<0.001 ^a
APOE-ε4, % carrier	35	29	42	0.02 ^b
Body mass index, kg/m ²	27.6±5	27.4±5	27.8±5	0.24 ^a
Framingham Stroke Risk Profile, total	12.2±4.2	11.8±4.2	12.8±4.2	0.06 ^b
Systolic blood pressure, mmHg	141±18	139±17	144±18	0.02 ^a
Anti-hypertensive medication usage, %	52	52	52	0.95 ^b
Diabetes, %	18	16	21	0.24 ^b
Cigarette smoking, % current	2	1	2	0.43 ^b
Prevalent CVD, %	4	4	3	0.86 ^b
Atrial fibrillation, %	5	5	5	0.99 ^b
Left ventricular hypertrophy, %	5	4	6	0.41 ^b
Aortic PWV, m/sec	8.2±3.2	8.2±3.0	8.3±3.4	0.87 ^a
Neuropsychological Performances				
Boston Naming Test	26.9±3.0	27.9±2.0	25.6±3.6	<0.001 ^a
Animal Naming	18.9±5.4	20.8±4.8	16.4±5.1	<0.001 ^a
WAIS-IV Coding	52.8±13.0	57.4±11.7	46.6±11.9	<0.001 ^a
DKEFS Number Sequencing, s [*]	41.8±19.4	36.0±12.8	49.6±23.6	<0.001 ^a
DKEFS Letter-Number Switching, s [*]	115±80	87±35	153±105	<0.001 ^a
DKEFS Tower Test	14.7±4.7	16.0±4.3	13.0±4.7	<0.001 ^a
DKEFS Color-Word Inhibition, s [*]	68.5±24.2	59.9±14.1	79.8±29.5	<0.001 ^a
Letter Fluency (FAS) Test	39.1±11.8	42.9±11.6	33.9±9.8	<0.001 ^a
Hooper Visual Organization Test	24.5±3.0	25.3±2.5	23.5±3.4	<0.001 ^a
CVLT-II Trials 1-5 Total Learning	40.5±12.2	46.9±9.7	32.0±9.8	<0.001 ^a
CVLT-II Delayed Recall	8.1±4.4	10.4±3.4	4.9±3.5	<0.001 ^a
CVLT-II Recognition	2.4±1.0	3.0±0.7	1.6±0.9	<0.001 ^a
BFLT Trials 1-5 Total Learning	114±42	137±30	83±36	<0.001 ^a
BFLT Delayed Recall	27±11.0	33±7.6	19±10.1	<0.001 ^a

	Total n=283	NC n=162	MCI n=121	p-value
BFLT Recognition	0.7±0.2	0.8±0.2	0.6±0.2	<0.001 ^a

Note: Values denoted as mean±standard deviation or frequency; Framingham Stroke Risk Profile (minus age) scores are 6.4±3.0 for the combined cohort (NC=6.1±2.9, MCI=6.8±3.1); All neuropsychological performance values are total correct excluding timed tasks measured in s=seconds;

* Higher values in speeded test results indicate worse performance; *p*-values are presented for comparisons between NC and MCI group; Tests used:

^aWilcoxon test,

^bPearson test; NC=normal cognition; MCI=mild cognitive impairment; *APOE*=*Apolipoprotein E*; PWV=pulse wave velocity; CVD=cardiovascular disease; Boston Naming Test=Boston Naming Test-30 Item Odd Version; WAIS-IV=Wechsler Adult Intelligence Scale, 4th Edition; DKEFS=Delis-Kaplan Executive Function System; CVLT-II=California Verbal Learning Test, 2nd Edition; BFLT=Biber Figure Learning Test.

Table 2PWV $\times$ *APOE*- ϵ 4 Associations with Neuropsychological Performance

	β	95% CI	<i>p</i> -value	Adjusted R ²
Combined Sample				
Boston Naming Test	-0.29	-0.51, 0.07	0.01	0.30
Animal Naming	-0.12	-0.52, 0.27	0.53	0.30
WAIS-IV Coding	0.33	-0.61, 1.26	0.49	0.31
DKEFS Number Sequencing, s *	-0.61	-2.06, 0.83	0.40	0.27
DKEFS Letter-Number Switching, s *	3.76	-2.23, 9.75	0.22	0.26
DKEFS Tower Test	-0.44	-0.82, -0.07	0.02	0.18
DKEFS Color-Word Inhibition, s *	0.29	-1.55, 2.13	0.76	0.24
Letter Fluency (FAS) Test	0.11	-0.80, 1.02	0.81	0.21
Hooper Visual Organization Test	-0.23	-0.46, 0.004	0.05	0.22
CVLT-II Trials 1–5 Total Learning	-0.14	-0.94, 0.66	0.73	0.43
CVLT-II Delayed Recall	-0.12	-0.40, 0.17	0.42	0.44
CVLT-II Recognition	-0.03	-0.10, 0.03	0.32	0.42
BFLT Trials 1–5 Total Learning	-3.07	-5.70, -0.43	0.02	0.48
BFLT Delayed Recall	-0.69	-1.40, 0.02	0.06	0.45
BLFT Recognition	-0.01	-0.03, 0.002	0.08	0.36
NC Participants				
Boston Naming Test	-0.15	-0.47, 0.18	0.37	0.20
Animal Naming	0.43	-0.39, 1.24	0.30	0.15
WAIS-IV Coding	0.47	-1.44, 2.38	0.63	0.21
DKEFS Number Sequencing, s *	0.58	-1.41, 2.57	0.57	0.28
DKEFS Letter-Number Switching, s *	-0.93	-6.29, 4.43	0.73	0.28
DKEFS Tower Test	-0.66	-1.41, 0.10	0.09	0.09
DKEFS Color-Word Inhibition, s *	-1.88	-4.22, 0.47	0.12	0.19
Letter Fluency (FAS) Test	1.10	-0.90, 3.10	0.28	0.11
Hooper Visual Organization Test	-0.10	-0.52, 0.32	0.63	0.16
CVLT-II Trials 1–5 Total Learning	0.82	-0.86, 2.49	0.34	0.11
CVLT-II Delayed Recall	0.17	-0.42, 0.76	0.56	0.08
CVLT-II Recognition	0.01	-0.12, 0.14	0.86	-0.01
BFLT Trials 1-5 Total Learning	-1.26	-6.37, 3.86	0.63	0.12
BFLT Delayed Recall	-0.17	-1.49, 1.15	0.80	0.11
BLFT Recognition	-0.005	-0.03, 0.02	0.74	0.07
MCI Participants				
Boston Naming Test	-0.33	-0.69, 0.03	0.07	0.18
Animal Naming	-0.30	-0.81, 0.21	0.25	0.17
WAIS-IV Coding	0.96	-0.25, 2.17	0.12	0.16

	β	95% CI	p-value	Adjusted R ²
DKEFS Number Sequencing, s *	-1.05	-3.54, 1.44	0.41	0.10
DKEFS Letter-Number Switching, s *	5.00	-6.06, 16.07	0.37	0.10
DKEFS Tower Test	-0.51	-1.01, 0.003	0.05	0.06
DKEFS Color-Word Inhibition, s *	0.90	-2.34, 4.13	0.58	0.03
Letter Fluency (FAS) Test	-0.002	-1.09, 1.08	>0.99	0.02
Hooper Visual Organization Test	-0.23	-0.58, 0.11	0.19	0.13
CVLT-II Trials 1–5 Total Learning	-0.62	-1.68, 0.44	0.25	0.05
CVLT-II Delayed Recall	-0.24	-0.62, 0.14	0.21	0.04
CVLT-II Recognition	-0.06	-0.15, 0.04	0.24	0.05
BFLT Trials 1–5 Total Learning	-4.11	-7.88, -0.34	0.03	0.11
BFLT Delayed Recall	-0.90	-1.95, 0.15	0.09	0.14
BLFT Recognition	-0.02	-0.04, 0.004	0.11	0.08

Note: Analyses performed on n=283 participants and subsequently stratified by diagnosis for n=162 NC participants and n=121 MCI participants. Models were adjusted for age, race/ethnicity, education, Framingham stroke risk profile (FSRP) minus age, and BMI; Models were additionally adjusted for diagnosis in main analysis (Combined) or stratified by diagnosis in subsequent analyses; Adjusted R² indicates the percentage of outcome variability accounted for by the model; All neuropsychological performance values are total correct excluding timed tasks measured in s=seconds;

* Higher values in speeded test results indicate worse performance; CI=confidence interval; NC=normal cognition; MCI=mild cognitive impairment; Boston Naming Test=Boston Naming Test-30 Item Odd Version; WAIS-IV=Wechsler Adult Intelligence Scale, 4th Edition; DKEFS=Delis-Kaplan Executive Function System; CVLT-II=California Verbal Learning Test, 2nd Edition; BFLT=Biber Figure Learning Test.