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RESEARCH ARTICLE

Plasma and neuroimaging biomarkers of small vessel disease and Alzheimer's disease in a diverse cohort: MESA

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Abstract

INTRODUCTION: Little is known about how Alzheimer's disease (AD) plasma biomarkers relate to cerebral small vessel disease (cSVD) neuroimaging biomarkers.

METHODS: The study involved 251 Wake Forest Multi-Ethnic Study of Atherosclerosis (MESA) Exam 6 participants with plasma AD biomarkers, magnetic resonance imaging, amyloid positron emission tomography (PET), and adjudicated cognitive sta-

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tus. Multivariable models examined cross-sectional relationships between plasma and neuroimaging biomarkers, considering comorbidities.

RESULTS: Lower amyloid beta (Aβ) 42/Aβ40 and higher glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and phosphorylated tau at threonine 217 (p-tau217) were associated with greater neurodegeneration. Lower plasma Aβ42/Aβ40 and higher p-tau217 and p-tau231 were associated with greater Aβ PET deposition. NfL was positively associated with white matter hyperintensities (WMH) and white matter (WM) free water. P-tau measures were positively associated with WM free water. Lower Aβ42/Aβ40 was associated with the presence of microbleeds. GFAP was positively associated with WMH.

DISCUSSION: We observed expected associations of plasma biomarkers with cognitive status and imaging biomarkers. GFAP, NfL, p-tau181, p-tau217, and p-tau231 are associated with cSVD in addition to AD-related pathology.

KEYWORDS
aging, Alzheimer's disease, imaging biomarkers, plasma biomarkers, small vessel disease

Highlights

- Plasma GFAP, NfL, p-tau181, p-tau217, and, to a lesser extent, p-tau231 are associated with cognitive status, AD pathology, comorbidities, and imaging biomarkers of SVD.
- We demonstrate novel associations of plasma AD biomarkers of p-tau and NfL with cSVD measures of WM structural health.

1 | BACKGROUND

Plasma biomarkers have great potential to inform disease etiology in Alzheimer's disease (AD) and related dementias (ADRD). Selected plasma biomarkers of amyloid, phosphorylated tau (p-tau), and neurodegeneration detect AD pathophysiology, monitor disease course, and predict future risk for ADRD – some more accurately than others.[1–6] Consequently, these biomarkers are being included in research and clinical programs,[7,8] often alongside existing magnetic resonance imaging (MRI) and positron emission tomography (PET) measures of AD/ADRD pathological changes.[9–11] As plasma biomarkers get incorporated into the etiologic classification scheme for AD/ADRD,[12] it is important to understand their specificity for aspects of neurodegeneration, amyloid pathology, and cerebral vascular disease commonly observed in ADRD. Several studies report associations of plasma AD biomarkers with vascular, metabolic, and renal comorbidities.[13,14] In addition, plasma p-tau levels increase with acute neuronal injury, such as cardiac arrest[15] and traumatic brain injury,[16] which may be related to release across the blood–brain barrier in the cerebral microvessels. However, few studies assessing plasma AD biomarkers evaluated measures of cerebral small vessel disease (cSVD) (e.g., brain microbleeds and white matter [WM] injury) common in older adults.[17–21] Biomarkers of cSVD are key for understanding the vascular contributions to cognitive impairment and dementia in the context of AD/ADRD.[22]

Importantly, blood and imaging biomarkers of AD/ADRD have been mostly studied in non-Hispanic White (NHW) individuals, with limited data on diversity in race, ethnicity, and socioeconomic factors.[8] Some recent reports suggest racial and ethnic differences in the ability of blood AD biomarkers to predict abnormal brain amyloid load,[23] consistent with observed racial and ethnic differences in cerebrospinal fluid biomarkers.[24–32] Yet most of these studies did not investigate the consistency of relationships between plasma AD biomarker levels and other biomarkers of AD and cSVD among various racial and ethnic groups. This is critically important because underrepresented groups tend to have a higher prevalence of cardiometabolic comorbidities contributing to cSVD (e.g., diabetes, hypertension, heart and kidney disease) than NHW participants.

Further, comorbidities can affect blood AD protein biomarker production and clearance mechanisms.[33,34] Recently, Mielke et al.[35] reported differences in plasma p-tau biomarkers by these comorbidities in a NHW cohort. It is important to understand how comorbidities affect plasma AD biomarkers in other populations with different rates

of age-related comorbidities.[14] Indeed, the higher prevalence of these comorbidities among racial and ethnic populations may contribute to group differences in AD biomarker levels and result in inaccurate diagnoses.[35,36]

The Multi-Ethnic Study of Atherosclerosis (MESA) is a unique, diverse study with over 20 years of extensive longitudinal vascular phenotyping as well as cognitive testing.[37,38] During MESA Exam 6, a diverse (White and Black/African American) cohort at the Wake Forest University (WFU) site underwent brain MRI, amyloid PET, and assessment of plasma AD biomarkers. Here, we leveraged data from the WFU site of MESA Exam 6 to examine cross-sectional relationships between plasma AD biomarkers (amyloid-beta [Aβ42/Aβ40 ratio], glial fibrillary acidic protein [GFAP], neurofilament light chain [NfL], p-tau181, p-tau217, and p-tau231), comorbidities, and neuroimaging biomarkers of vascular disease, neurodegeneration, and amyloid pathology underlying AD/ADRD among individuals self-reporting as NHW and Black/African American. We hypothesized that we would observe associations of plasma AD biomarkers with imaging measures of brain amyloid PET, cSVD, and neurodegeneration.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Relationships between AD plasma biomarkers and cSVD neuroimaging biomarkers in diverse cohorts are uncertain. Publications assessing links between plasma and imaging biomarkers, comorbidities, and cognitive function in diverse cohorts are appropriately cited.
2. **Interpretation**: By examining 251 participants from the Wake Forest site of MESA, the study provides insights into cross-sectional relationships between plasma AD biomarkers and neuroimaging markers, considering various comorbidities. Lower plasma amyloid and higher GFAP, NfL, and p-tau217 are linked to increased neurodegeneration. Lower plasma amyloid and higher p-tau217 and p-tau231 are associated with greater amyloid PET deposition.
3. **Future directions**: Data collection and analysis in MESA are ongoing and will comprehensively evaluate longitudinal trajectories of multi-omic datasets with biomarker and cognitive measures.

2 | METHODS

2.1 | Participants

MESA participants were recruited from six field centers and were free from clinical cardiovascular disease (including stroke) at baseline (2000 to 2002).[37,38] Only participants at the WFU field center at Exam 6 (2016 to 2018) were included in this analysis. Demographic, anthropometric, and standard clinical data were collected in MESA, as previously reported, including baseline years of education, self-reported gender, and self-reported race and ethnicity (viewed here as a social construct), as well as Exam 6 age, smoking status, and height and weight for body mass index (BMI). Estimated glomerular filtration rate (eGFR, in mL/min/1.73m^2; Exam 6) was calculated using the creatinine-based four-variable Modification of Diet in Renal Disease (MDRD) equation[39] with no race adjustment. DNA from baseline was analyzed for *APOE* genotypes as previously described[40]; *APOE* ε4 carriage was defined as the presence of one or more ε4 allele(s). The research protocol was approved by the local Institutional Review Board, with informed consent obtained for all participants, and was performed in accordance with the Declaration of Helsinki.

2.2 | Cognitive testing and adjudication

MESA Exam 6 participants at the WFU field center were administered the Uniform Data Set version 3 (UDSv3) neuropsychological battery,[41,42] including detailed cognitive testing; ratings of functional abilities by a person familiar with the participant; information about family history of AD, medications, and health history; clinician-assessed medical conditions and judgment of symptoms; and a neurological examination. All of these data were used in the adjudication process along with appropriate normative data.[38] The consensus panel consisted of neuropsychologists, geriatricians, neurologists, and other aging experts. Consensus-adjudicated cognitive status, according to published criteria,[43,44] included cognitively unimpaired (CU), mild cognitive impairment (MCI), and dementia.

2.3 | Plasma biomarker acquisition and processing

Plasma AD biomarker analysis was conducted from stored plasma samples from WFU field center participants at Exam 6. Plasma AD biomarker assay results of Aβ42, Aβ40, and their ratio, GFAP, NfL, p-tau181, p-tau217, and p-tau231. All biomarkers were measured on the Quanterix Single molecule array (Simoa) HD-X platform (Quanterix, Billerica, MA, USA) with a two-fold dilution factor in plasma. Plasma Aβ42, Aβ40, NfL, and GFAP concentrations were measured using commercially available Neurology 4-Plex E kits on the HD-X. Plasma p-tau181,[2] p-tau231,[4] and University of Gothenburg p-tau217[45] concentrations were measured on HD-X using methods published previously. Signal variations within and between analytical runs were assessed using three internal quality control samples at the beginning and the end of each run.

2.4 | MRI acquisition and processing

Brain MRI data were acquired for participants at WFU on a 3T Siemens Skyra scanner using a high-resolution 32-channel head coil. T1 MPRAGE (to quantify gray matter [GM] volume and cortical thickness) and T2 fluid-attenuated inversion recovery (FLAIR; to quantify white matter [WM] hyperintensities [WMH]) were acquired; sequence details were published previously.[46] Neurite orientation density and dispersion imaging (NODDI; 2.0 mm isotropic resolution, repetition time [TR] = 3500 ms, echo time [TE] = 106 ms, flip angle [FA] = 90, b = 714/1000/2855 s/mm^2, 131 directions) was acquired to examine isotropic volume fraction (i.e., so-called free water [FW]). Susceptibility-weighted imaging/quantitative susceptibility mapping (SWI/QSM) images were acquired (TR = 51 ms; multiple TE = 9.8, 16.6, 23.5, 30.4, 37.3, 44.2 ms; FA = 20; 0.6 × 0.6 × 2 mm) to enable visualization of microbleeds.

MRI data for this analysis were processed at the WFU field site. Regional volumes and cortical thicknesses were calculated on T1 using FreeSurfer version 5.3 (https://surfer.nmr.mgh.harvard.edu). We examined neurodegeneration using bilateral hippocampal volume (HCV) divided by FreeSurfer total intracranial volume (ICV; to correct for head size), as well as total GM volume (GMV) divided by ICV. We additionally calculated cortical thickness in a temporal lobe region of interest (ROI) shown to index neurodegeneration in regions characteristic of age-related dementias; this was calculated by averaging surface area-weighted cortical thickness of bilateral entorhinal, inferior/middle temporal, and fusiform regions.[47] WMH lesions were segmented as described previously[46] by the lesion growth algorithm (LGA) implemented in the LST toolbox version 2.0.15 (www.statistical-modelling.de/lst.html), running in MATLAB SPM12 (www.fil.ion.ucl.ac.uk/spm) using FLAIR with T1 as reference. Total WMH lesion volume was divided by FreeSurfer ICV and log-normalized to generate a global WMH volume measure (lnWMH). NODDI processing details were described previously[48]; briefly, the Johns Hopkins University (JHU) diffusion tensor imaging (DTI) atlas was overlaid on template-space FW images to extract mean signal across all supratentorial WM tracts to calculate mean global WM FW, and a set of all supratentorial Automated Anatomical Labeling (AAL) GM ROIs was overlaid on template-space FW images to calculate mean global GM FW. A single trained neuroradiologist (KDH) read cerebral microbleeds and lacunar infarctions according to STRIVE criteria[49,50] (on n = 236 participants with available imaging), which were binarized into presence/absence. For the purposes of these analyses, we classified MRI-based biomarkers into measures of neurodegeneration/neuroinflammation (HCV, GMV, cortical thickness, GM FW) and cSVD (lnWMH, WM FW, cerebral microbleeds, lacunar infarction).

2.5 | PET acquisition and processing

On a subset of n = 177 participants, [^{11}C] Pittsburgh Compound B (PiB)[51] was used for assessing fibrillar amyloid brain deposition on PET, using acquisition methods described previously.[46] Following a computed tomography (CT) scan for attenuation correction, participants were injected with ~370 MBq [^{11}C]PiB and scanned 40 to 70 min (6 × 5-min frames) after injection on a 64-slice GE Discovery MI DR PET/CT scanner.

Centiloid (CL)-based processing was conducted by the University of Michigan to generate global CL values (whole cerebellum reference region, 50- to 70-min data).[52] We examined continuous global CL values; additionally, a CL value of 12.2, which represents Consortium to Establish a Registry for Alzheimer's Disease moderate to frequent neuritic plaques,[53] was used as a primary threshold for Aβ PET positivity.

2.6 | Statistical analysis

This analysis was limited to 251 MESA Exam 6 participants at the WFU field center with MRI data, plasma AD biomarkers, and UDSv3-based adjudicated cognitive status. Chi-squared and ANOVA tests were used to examine differences in baseline demographics by cognitive classification. Prior to analysis in regression models, we standardized the distribution of each plasma AD biomarker by log2 transformation, where parameter estimates represent a doubling of each biomarker level.

We used multivariable general linear models (GLMs) to assess relationships between plasma AD biomarkers (Aβ42/Aβ40 ratio, GFAP, NfL, p-tau181, p-tau217, p-tau231) and MRI measures of brain SVD and neurodegeneration (GMV, HCV, cortical thickness, lnWMH, GM FW, WM FW), and PET measures of global amyloid deposition (Aβ positivity; 12.2 CL value). Prior to the construction of GLMs, we assessed collinearity among neuroimaging-based outcome variables (Figure S1). MRI brain volume estimates were corrected for total intracranial volume; global WMH volume was also log-transformed prior to analysis. For amyloid PET, we also examined the relationship with a 24.4-CL threshold, representing intermediate to high AD neuropathological changes,[53] and obtained results (not shown) for AD plasma biomarkers identical to those obtained for the 12.2-CL threshold.

Model 1 included basic covariates of age, gender, race, and education. Model 2 included covariates from Model 1, plus *APOE* ε4 carrier status, smoking status, and comorbidities associated with plasma AD biomarker levels (BMI, eGFR; both treated as continuous variables when used as model covariates). Each analysis examined effect modification by comorbidities (BMI, eGFR), age (median split), race, gender, and *APOE* ε4 status. We also conducted a sensitivity analysis excluding n = 44 participants with severe chronic kidney disease (CKD, defined using eGFR≤60 mL/min/1.73m^2).

We examined the consistency of relationships of plasma AD biomarkers with MRI measures of brain SVD and neurodegeneration, and amyloid positivity on PET among self-reported White and Black older adults after considering differences in comorbidities. We further explored the impact of medical comorbidities, such as BMI and kidney function (assessed with eGFR), on plasma AD biomarker levels.[14]

Model significance is primarily reported at an exploratory $p < 0.05$ threshold; we note that models were additionally corrected for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR)[54] of 0.1, which leads to a critical value of 0.023, meaning all p values < 0.023 can be considered significant when FDR-corrected.

3 | RESULTS

3.1 | Participants

Demographics by cognitive status at Exam 6 for the 251 participants in the present study are presented in Table 1, with 69% adjudicated as CU, 27% with MCI, and 4% with probable dementia. Cognitive status groups differed by age, gender, and race. They also differed by eGFR and *APOE* ε4 carrier status, such that (continuous) eGFR was lower and the prevalence of *APOE* ε4 carrier status was higher in MCI and dementia groups. Those with MCI or dementia demonstrated a greater degree of neurodegeneration, with lower GMV, lower HCV, lower cortical thickness, and higher GM FW. In the subset of participants with amyloid PET data, amyloid positivity was higher in the MCI and dementia groups, compared to CU participants. There were no differences across cognitive groups in measures of vascular injury (WMH volume, WM FW, presence or number of microbleeds, and presence of lacunes). Table S1 describes associations between plasma AD biomarker levels and covariates included in models; notably, plasma biomarker levels were not significantly different between Black and White participants in this study. In addition, their associations with imaging biomarkers were similar between groups (Tables S2 and S3; Figure S2).

3.2 | Plasma AD biomarker differences across cognitive groups

We next investigated differences in cognitive status for each of the plasma AD biomarkers (Table 2). Participants with dementia exhibited a lower Aβ42/Aβ40 ratio and higher GFAP, p-tau217, and p-tau231 levels relative to CU participants and a lower Aβ42/Aβ40 ratio and higher GFAP levels compared to MCI. Additionally, MCI participants demonstrated higher p-tau217 levels compared to CU. We did not observe statistical differences in the levels of NfL or p-tau181 across groups.

3.3 | Plasma AD biomarker associations with imaging outcomes

Table 3 shows the associations between plasma AD biomarkers and imaging biomarkers of neurodegeneration and neuroinflammation in Model 2 (Model 1 presented in Table S4). In Model 2, lower Aβ42/Aβ40 was associated with lower GMV and hippocampal volume, higher GFAP was associated with lower hippocampal volume, and higher NfL was associated with lower GMV and hippocampal volume and with higher GM FW. Higher p-tau217 was associated with lower GMV in Model 2 and additionally associated with lower temporal cortical thickness in Model 1. Higher p-tau181 was associated with lower temporal cortical thickness only in Model 1. Plasma measures of p-tau231 were not associated with imaging biomarkers of neurodegeneration and neuroinflammation in this sample in either model. When excluding participants with CKD (Table S5), associations of Aβ42/Aβ40 and p-tau217 with GMV and of GFAP and NfL with hippocampal volume were no longer significant; however, associations of p-tau181 and p-tau217 with hippocampal volume became significant.

Table 4 shows the associations between plasma AD biomarkers and imaging biomarkers of cSVD in Model 2 (Model 1 presented in Table S6). Higher NfL was associated with higher WMH volume and WM FW in Model 2 and additionally associated with greater prevalence of lacunar infarcts in Model 1. All three plasma p-tau measurements (p-tau181, p-tau217, p-tau231) were positively associated with WM FW but not with other cSVD biomarkers in both models. A lower Aβ42/Aβ40 ratio was significantly associated with a greater prevalence of microbleeds in Model 2. Higher GFAP was associated with higher WMH volume in Model 2. When excluding participants with CKD (Table S7), associations of GFAP with WMH volume, NfL with WMH volume and WM FW, and p-tau231 with WM FW were no longer significant.

Table 5 shows associations between plasma AD biomarkers and imaging biomarkers of Aβ deposition (CL) and Aβ positivity in the subset with PET, in Model 2. As anticipated, a lower plasma Aβ42/Aβ40 ratio was associated with higher Aβ deposition and higher odds of Aβ positivity, and higher p-tau217 and p-tau231 were also associated with higher Aβ deposition and odds of Aβ positivity, such that a doubling in the level of p-tau217 and p-tau231 was associated with a two- to three-fold increase in the odds of Aβ PET positivity. Additionally, in Model 1 (presented in Table S8), higher GFAP was associated with higher Aβ deposition. These associations remained unchanged when excluding $n = 44$ participants with CKD (Table S9).

4 | DISCUSSION

While the prevailing consensus is that these plasma biomarkers represent measures of AD pathophysiology or related neurodegeneration, we confirmed these associations and showed that GFAP, NfL, p-tau181, p-tau217, and p-tau231 were *also* associated with vascular comorbidities and imaging biomarkers of cSVD. Interestingly, WM FW and, to a lesser extent, WMH were associated with multiple plasma biomarker levels. Specifically, higher plasma NfL levels indicative of neurodegeneration were most consistently associated with measures of cSVD, including higher burden of WMH and WM FW and greater odds of lacunar infarction. GFAP, representative of neuroinflammatory processes, was also significantly associated with WMH in this sample, but no other core features of cSVD.[49] Interestingly, we observed consistent positive associations of all p-tau isoforms (e.g., 181, 217, 231) with higher WM FW. Generally, lacunar infarcts were not associated with plasma biomarker levels, with one exception: the presence of lacunar infarcts was associated with higher NfL levels. In contrast, plasma amyloid

TABLE 1 Demographic and clinical characteristics by cognitive status.

	CU (*n* = 172)		MCI (*n* = 69)		Dementia (*n* = 10)		
	N / Mean	Percentage / SD	*N* / Mean	Percentage / SD	*N* / Mean	Percentage / SD	*p* value
Age (years)	71.6	6.9	74.4*	7.2	78.6*	4.9	<0.001
Education (years)	15.3	2.7	14.9	2.7	14.4	3.6	0.189
Gender							
Women	100	58%	34	49%	10*	100%	0.009
Men	72	42%	35	51%	0	0%	
Race							
White	92	53%	25*	36%	6	60%	0.022
Black	80	47%	44	64%	4	40%	
eGFR (mL/min/1.73 m^2)	79	19.5	71*	22.2	67.2	15.8	<0.001
APOE ε4 carrier							
Yes	46	27%	21	30%	7*	70%	0.021
No	122	71%	43	62%	3	30%	
Missing	4	2%	5	7%	0	0%	
Neuroimaging							
Gray matter volume/ICV	0.281	0.021	0.268**	0.020	0.263*	0.023	<0.001
Hippocampus/ICVx100	0.683	0.111	0.644*	0.116	0.571*	0.140	0.007
Cortical thickness (mm)	2.688	0.109	2.637*	0.136	2.573*	0.150	0.002
lnWMH/ICV	−13.166	1.297	−12.899	1.680	−12.488	1.116	0.366
Total WMH volume (Ml)	5.321	6.197	8.725*	9.833	8.409	8.431	0.017
GM free water fraction	0.199	0.032	0.211*	0.043	0.240**	0.048	0.001
WM free water Fraction	0.148	0.021	0.150	0.028	0.162	0.036	0.103
Microbleeds present							
No	106	66%	38	58%	5	56%	0.681
Yes	54	34%	27	42%	4	44%	
Microbleed count							
0	106	66%	40	60%	5	56%	0.325
1	32	20%	12	18%	4	44%	
2+	22	14%	15	22%	0	0%	
Lacune present							
No	112	70%	40	60%	6	67%	0.193
Yes	48	30%	27	40%	3	33%	
Aβ PET							
Neg	90	74%	21**	44%	1**	14%	<0.001
Pos	32	26%	27	56%	6	86%	

Abbreviations: APOE, apolipoprotein E; cortical thickness, cortical thickness in areas prone to age-related dementias; CU, cognitively unimpaired; eGFR, estimated glomerular filtration rate; GM, gray matter; ICV, intracranial volume; lnWMH, log-normalized WMH volume (scaled by ICV); MCI, mild cognitive impairment; PET, positron emission tomography; WM, white matter; WMH, white matter hyperintensities.
Pairwise comparison *p* values of significance relative to CU:
*$p < 0.05$.
**$p < 0.001$.

TABLE 2 Adjusted models for each AD plasma biomarker.

	MCI versus CU (*n* = 66)			Dementia versus CU (*n* = 10)			Dementia versus MCI (*n* = 10)		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Aβ42/Aβ40	0.524	(0.199, 1.384)	0.192	0.027	(0.003, 0.263)	0.002	0.051	(0.005, 0.523)	0.012
GFAP	1.183	(0.762, 1.839)	0.454	3.842	(1.539, 9.591)	0.004	3.247	(1.262, 8.352)	0.015
NfL	1.510	(0.958, 2.379)	0.076	2.523	(0.892, 7.134)	0.081	1.671	(0.575, 4.856)	0.346
P-tau181	1.160	(0.896, 1.502)	0.261	1.294	(0.794, 2.110)	0.301	1.116	(0.681, 1.830)	0.664
P-tau231	1.157	(0.752, 1.780)	0.507	2.223	(1.103, 4.479)	0.025	1.594	(0.872, 2.913)	0.130
P-tau217	1.499	(1.036, 2.168)	0.032	2.389	(1.272, 4.487)	0.007	1.921	(0.944, 3.912)	0.072

Odds ratio and 95% confidence interval relative to CU (*n* = 167). For "MCI versus Dementia" models, results are shown relative to MCI (*n* = 66). *n* = 8 participants did not have all plasma biomarker data and are not included. We standardized distributions of each biomarker by log2 transformation. Models adjusted for age at Exam 6, years of education, race, gender, and eGFR.

Abbreviations: Aβ, amyloid beta; CI, confidence interval; CU, cognitively unimpaired; GFAP, glial fibrillary acidic protein; MCI, mild cognitive impairment; NfL, neurofilament light chain; p-tau, phosphorylated tau.

TABLE 3 AD plasma biomarkers and imaging biomarkers of neurodegeneration and neuroinflammation.

	GMV/ICV (*n* = 232)			Hippocampus/ICV (*n* = 232)			Cortical thickness (*n* = 232)			GM free water (*n* = 219)		
	B	SE	*p value*	B	SE	*p value*	B	SE	*p value*	B	SE	*p value*
Aβ42/Aβ40	0.009	0.004	0.039	0.072	0.020	<0.001	−0.009	0.024	0.720	−0.010	0.007	0.132
GFAP	−0.002	0.002	0.345	−0.019	0.009	0.045	0.011	0.011	0.290	0.003	0.003	0.303
NfL	−0.007	0.002	<0.001	−0.021	0.010	0.032	−0.005	0.011	0.642	0.009	0.003	0.006
P-tau181	−0.001	0.001	0.340	−0.009	0.006	0.094	−0.009	0.006	0.154	0.003	0.002	0.166
P-tau231	−0.002	0.002	0.181	−0.012	0.009	0.158	−0.003	0.010	0.744	0.005	0.003	0.074
P-tau217	−0.004	0.001	0.018	−0.014	0.007	0.063	−0.017	0.009	0.052	0.002	0.002	0.422

Model 2 adjusted for age at Exam 6, years of education, race, gender, smoking status, eGFR, *APOE*-ε4, and BMI. *n* = 8 participants did not have all plasma biomarker data and are not included. We standardized distributions of each biomarker by log2 transformation.

Abbreviations: Aβ, amyloid beta; GMV, gray matter volume; ICV, intracranial volume; NfL, neurofilament light chain; p-tau, phosphorylated tau; SE, standard error.

biomarker abnormalities, characterized by a lower Aβ42/Aβ40 ratio, follow a "classic AD pathology" through associations with *APOE* ε4 carriage, lower GM and hippocampal volumes, greater amyloid deposition, and dementia, as well as cerebral microbleeds (associated with cerebral amyloid angiopathy [CAA]) without evidence of other vascular biomarker involvement. The observed association between lower plasma Aβ42/40 ratio and cerebral microbleeds likely reflects underlying CAA, a vascular manifestation of amyloid pathology. Individuals with both elevated amyloid PET and microbleeds are more likely to exhibit CAA-related changes.

This work provides insights into the associations between plasma AD biomarkers and participant demographics and health characteristics. Importantly, plasma biomarker levels were not significantly different between Black and White participants in this study (Table S1), and their associations with imaging biomarkers were similar between groups (Tables S2 and S3; Figure S2). Plasma biomarkers showed broader involvement with vascular comorbidities and biomarkers than previously reported. Plasma biomarker associations in this study reflect overlapping contributions from AD and SVD, as framed by the A/T/N/I model. Inflammatory (I) markers, particularly GFAP, were associated with WMH and hippocampal volume, indicating vascular inflammation. Amyloid (A) biomarkers (e.g., lower Aβ42/40) were linked to amyloid PET positivity and cerebral microbleeds. Tau (T) biomarkers (p-tau217, p-tau231) were associated with amyloid burden, reduced GMV, and cortical thickness, and also with WM FW, suggesting vascular overlap. Neurodegeneration (N) markers, including NfL and GMV, were associated with hippocampal atrophy and GM FW, with NfL also linked to WMH and lacunar infarcts. These findings suggest that while some biomarkers (e.g., Aβ42/Aβ40, p-tau217) are more AD-specific, others (e.g., NfL, GFAP) reflect mixed neurodegenerative and vascular mechanisms, likely influenced by comorbidities, such as CKD, hypertension, and smoking. This aligns with recent neuropathologic evidence showing that distinct plasma biomarker profiles correspond to different burdens of AD and vascular pathology in older

TABLE 4 AD plasma biomarkers and imaging biomarkers of cSVD.

	lnWMH/ICV (*n* = 231)			WM free water (*n* = 224)			Cerebral microbleeds (*n* = 231)			Lacunar infarction (*n* = 233)		
	B	SE	*p*-value	B	SE	*p* value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Aβ42/Aβ40	−0.382	0.265	0.151	−0.009	0.005	0.064	0.386	(0.153, 0.976)	0.044	0.789	(0.308, 2.021)	0.621
GFAP	0.272	0.120	0.024	0.002	0.002	0.284	0.764	(0.504, 1.157)	0.204	1.067	(0.698, 1.632)	0.765
NfL	0.267	0.126	0.034	0.005	0.002	0.022	1.246	(0.815, 1.906)	0.309	1.284	(0.826, 1.998)	0.267
P-tau181	0.088	0.072	0.221	0.003	0.001	0.020	0.886	(0.684, 1.148)	0.359	0.927	(0.721, 1.19)	0.551
P-tau231	0.143	0.109	0.190	0.005	0.002	0.021	1.474	(0.996, 2.18)	0.052	1.085	(0.736, 1.6)	0.680
P-tau217	0.149	0.096	0.120	0.005	0.002	0.007	1.376	(0.979, 1.933)	0.066	1.124	(0.797, 1.585)	0.506

Model 2 adjusted for age at Exam 6, years of education, race, gender, smoking status, eGFR, *APOE* ε4, and BMI. *n* = 8 participants did not have all plasma biomarker data and are not included. We standardized distributions of each biomarker by log2 transformation. Odds ratio and 95% CI relative to CMB = 0 (*n* = 151), lacune = 0 (*n* = 161).

Abbreviations: Aβ, amyloid beta; apoE, apolipoprotein E; cSVD, cerebral small vessel disease; GFAP, glial fibrillary acidic protein; ICV, intracranial volume; lnWMH, log-normalized WMH volume (scaled by ICV); p-tau, phosphorylated tau; SE, standard error; WM white matter.

adults[55] and with findings that plasma NfL and GFAP are predictive of vascular cognitive impairment and associated brain changes in community and clinical cohorts.[56]

In addition, when excluding participants with eGFR ≤ 60, some associations with imaging biomarkers of neurodegeneration, neuroinflammation, and cSVD were tempered, suggesting that the relationships we observed may have been accentuated in participants with CKD. However, it is notable that associations with amyloid PET (CL or positivity) were unchanged when participants with CKD were excluded, strengthening our confidence in the associations of plasma biomarkers with amyloid PET.

While prior studies reported racial differences in plasma AD biomarkers, particularly in amyloid and tau levels,[23–25] we did not observe significant differences between Black and White participants in this sample (Table S1). This may reflect harmonized imaging and adjudication protocols at a single site, adjustment for comorbidities, or limited sample size. Further investigation in larger, multisite cohorts is warranted.

The observed associations between plasma AD biomarkers and participant demographics and comorbidities are consistent with prior studies,[13] suggesting that age, kidney function, and smoking status impacted biomarker levels. Recently, similar associations were reported for plasma NfL with WMHs and temporal lobe atrophy, but not microbleeds or lacunar infarcts.[57] Several of the observed associations between plasma biomarkers and SVD imaging markers are consistent with prior reports[17,20,56–58]; differential associations may reflect distinct biological processes underlying SVD, including axonal injury, astroglial activation, and microstructural disruption. In contrast, Qu et al. reported associations between higher NfL and the presence of microbleeds[58] while also reporting associations with lacunar infarcts, WMHs, and total cSVD burden. These associations between cSVD and tau pathology are also supported by neuropathology studies. In 982 deceased individuals with *ex vivo* MRI, WMHs were associated with greater tau-tangle pathology but not amyloid, while evidence of arteriolosclerosis in the posterior watershed areas was associated with higher tau pathological changes.[59]

The tau isoform-specific associations we observed were anticipated based on prior studies,[3,4,21] which suggested that p-tau217 was more closely linked to AD-related neurodegeneration, while p-tau231 and p-tau181 may reflect complementary or earlier stages of tau pathology. The differential associations observed here may indicate varying sensitivity to regional vulnerability or coexisting vascular changes and support the utility of combining p-tau isoforms to improve diagnostic specificity.

4.1 | Limitations

This work from MESA represents data from a single site, with a sample size limited to those participants with neuroimaging, cognitive adjudication, and plasma AD biomarker data. The cohort assessed was composed of participants who self-reported as Black and White and thus may not be generalizable to Hispanic and Chinese American par-

TABLE 5 AD plasma biomarkers and amyloid PET.

	Centiloids (*n* = 177)			Aβ+ (≥12.2 CL) (*n* = 177)		
	B	SE	*p* value	Odds ratio	95% CI	*p* value
Aβ42/Aβ40	−34.221	6.986	<0.001	0.031	(0.007, 0.142)	<0.001
GFAP	5.831	3.409	0.089	1.173	(0.695, 1.978)	0.550
NfL	5.050	3.795	0.185	1.192	(0.66, 2.152)	0.560
P-tau181	1.136	1.988	0.569	1.12	(0.833, 1.507)	0.452
P-tau231	8.507	2.892	0.004	2.214	(1.25, 3.922)	0.006
P-tau217	11.869	2.419	<0.001	2.635	(1.542, 4.503)	<0.001

Model 2 adjusted for age at Exam 6, years of education, race, gender, smoking status, eGFR, *APOE* ε4, and BMI. *n* = 8 participants did not have all plasma biomarker data and are not included. We standardized distributions of each biomarker by log2 transformation. Odds Ratio and 95% CI relative to Aβ- (<12.2 CL; *n* = 113).

Abbreviations: Aβ, amyloid beta; APOE, apolipoprotein E; CI, confidence interval; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau, phosphorylated tau; SE, standard error.

ticipants recruited at other MESA sites. In addition, this work does not represent all forms of cSVD. While arteriosclerosis is a common form of cSVD observed on neuropathology, imaging biomarkers of arteriosclerosis are in development and not widely available or validated. The current study also lacked direct measures of tau aggregation with PET, which was not collected in this cohort. Although the sample sizes for MRI and PET analyses were relatively modest, the presence of imaging abnormalities was quite common in this cohort, with microbleeds observed in 32%, lacunes in 29%, and amyloid PET positivity in 36% of participants. Measures like PSMD (peak width of skeletonized mean diffusivity), a widely used DTI metric for SVD, were not available in the current dataset; PSMD and other DTI-based measures will be used as they become available in MESA to complement the NODDI-derived FW metrics used here. Finally, although regional amyloid deposition was not examined in this study, future work using larger samples and regional PET quantification may improve sensitivity and regional specificity, enabling more precise characterization of CAA-related pathology.

4.2 | Future directions

These results call for further studies on the pathophysiological mechanisms underlying differences in AD blood biomarkers. Repeated plasma and MRI biomarker measurements are being collected across all sites and racial and ethnic groups within MESA. In future work, expanding on the current study, we plan to replicate these results and extend to longitudinal associations in a larger and more diverse cohort of self-reported White, Black, Hispanic, and Chinese American participants of MESA.

5 | CONCLUSIONS

This work provides important observations about the potential relationships between cSVD and plasma biomarkers that are being developed for AD biomarker panels. It clearly shows that plasma biomarkers of NfL and p-tau are associated with imaging biomarkers of AD and cSVD. Plasma p-tau and Aβ42/40 are associated with AD pathological biomarkers across age groups, ethnicities, and comorbidity burden. These results are confirmatory for NfL and may be novel for p-tau isoforms. They suggest that these plasma biomarkers may associate not only with AD pathology but also with evidence of cSVD.

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CONFLICT OF INTEREST STATEMENT

HZ has served on scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant and on advisory boards for AbbVie, AC Immune, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd., Neurimmune, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served on data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials, and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai, and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. SNL is a full-time employee at Perceptive Inc. and has served on the DSMB for the WALL-e study (NCT04908358). Other authors report no disclosures. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

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