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ORIGINAL RESEARCH

Plasma Markers of Alzheimer's Disease Pathology, Neuronal Injury, and Astrocytic Activation and MRI Load of Vascular Pathology and Neurodegeneration: The SMART-MR Study

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BACKGROUND: Two of the main causes for dementia are Alzheimer's disease (AD) and vascular pathology, with most patients showing mixed pathology. Plasma biomarkers for Alzheimer's disease-related pathology have recently emerged, including Aβ (amyloid-beta), p-tau (phosphorylated tau), NfL (neurofilament light), and GFAP (glial fibrillary acidic protein). There is a current gap in the literature regarding whether there is an association between these plasma biomarkers with vascular pathology and neurodegeneration.

METHODS AND RESULTS: Cross-sectional data from 594 individuals (mean [SD] age: 64 [8] years; 17% female) were included from the SMART-MR (Second Manifestations of Arterial Disease-Magnetic Resonance) study, a prospective cohort study of individuals with a history of arterial disease. Plasma markers were assessed using single molecular array assays (Quanterix). Magnetic resonance imaging markers included white matter hyperintensity volume, presence of infarcts (yes/no), total brain volume, and hippocampal volume assessed on 1.5T magnetic resonance imaging. Linear regressions were performed for each standardized plasma marker with white matter hyperintensity volume, total brain volume, and hippocampal volume as separate outcomes, correcting for age, sex, education, and intracranial volume. Logistic regressions were performed for the presence of lacunar and cortical infarcts. Higher p-tau181 was associated with larger white matter hyperintensity volume (*b* per SD increase=0.16 [95% CI, 0.06–0.26], *P*=0.015). Higher NfL (*b*=−5.63, [95% CI, −8.95 to −2.31], *P*=0.015) was associated with lower total brain volume and the presence of infarcts (odds ratio [OR], 1.42 [95% CI, 1.13–1.78], *P*=0.039). Higher GFAP levels were associated with cortical infarcts (OR, 1.45 [95% CI, 1.09–1.92], *P*=0.010).

CONCLUSIONS: Plasma biomarkers that have been associated with tau pathology, axonal injury, and astrocytic activation are related to magnetic resonance imagingmarkers of vascular pathology and neurodegeneration in patients with manifest arterial disease.

Key Words: dementia ■ neurodegeneration ■ neuroimaging ■ vascular

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RESEARCH PERSPECTIVE

What Is New?

- In this cross-sectional study in individuals all with manifest arterial disease, plasma biomarkers for tau pathology, axonal injury, and astrocytic activation were related to vascular pathology and neurodegeneration on magnetic resonance imaging.
- This study confirms the role of mixed pathology in individuals with manifest vascular disease.

What Question Should Be Addressed Next?

- Longitudinal studies should be performed to assess if individuals with both pathologies in plasma and magnetic resonance imaging have a higher risk of dementia.

Nonstandard Abbreviations and Acronyms

Aβ	amyloid-beta
GFAP	glial fibrillary acidic protein
NfL	neurofilament light
p-tau	phosphorylated tau
SMART-MR	Second Manifestations of Arterial Disease-Magnetic Resonance
TBV	total brain volume
WMH	white matter hyperintensity

Two of the main causes of dementia are Alzheimer's disease (AD) and vascular pathology.[1] The presence of AD-specific pathology, that is, the accumulation of Aβ (amyloid-beta) plaques and neurofibrillary tangles, can be established using cerebrospinal fluid or positron emission tomography (PET). Vascular pathology is typically assessed via MRI measures, such as white matter hyperintensities (WMHs) and lacunes.[2] Most patients with cognitive decline and dementia have mixed pathology,[3] as well as hippocampal and global brain atrophy.[4] The relationship between AD pathology with vascular pathology and neurodegeneration is not yet well known and has been hampered by the invasiveness and costs associated with cerebrospinal fluid and PET measurements.[5–8]

Recent advancements in the development of high-sensitivity plasma assays have allowed for the assessment of biomarkers representing Aβ and p-tau (phosphorylated tau) accumulation, as well as axonal injury (NfL [neurofilament light]) and astrocytic activation (GFAP [glial fibrillary acidic protein]) in large-scale studies.[9] Previous studies have highlighted a possible relation between these plasma biomarkers, specifically p-tau181, NfL, and GFAP with vascular pathology on MRI.[10–15] However, other studies found no association.[16–18] Regarding neurodegeneration on MRI, most studies have found that higher levels of p-tau181 and NfL are associated with greater atrophy, either globally[19,20] or specifically in the hippocampus.[10,16,18,19,21–23]

However, few studies focused on patients all with vascular, or arterial, disease. Neurodegeneration[24] and WMH are common in patients with arterial disease, and many patients show mixed AD and vascular pathology.[25,26] By focusing on a population with arterial disease, it is possible to shed light on the role of AD pathology in the neurodegeneration and WMH observed in patients with arterial disease. We took as a starting point the SMART-MR (Second Manifestations of Arterial Disease-Magnetic Resonance) study cohort, a population all with manifest arterial disease. We aimed to examine if blood-based biomarkers (ie, Aβ42/40, p-tau181, NfL, and GFAP) were associated with MRI measures of vascular pathology and neurodegeneration in individuals with manifest arterial disease and without dementia diagnosis. We hypothesized that NfL, as a general marker of axonal injury, would be related to global and hippocampal atrophy, whereas p-tau181, Aβ42/40, and GFAP, as more specifically related to amyloid positivity on PET, would be related to vascular pathology based on previous studies in non-vascular populations.

METHODS

Design of Study and Sample

Data were obtained from the SMART-MR study. The SMART-MR study is a prospective cohort study that aimed to investigate brain MRI changes in patients independently living with symptomatic atherosclerotic disease.[27,28] All patients that were recently referred to the University Medical Center Utrecht in the Netherlands with manifest arterial disease (ie, cerebrovascular disease, coronary artery disease, peripheral arterial disease, or an abdominal aortic aneurysm [prevalence shown in Table S1]) and without any MRI contraindications were invited to participate between May 2001 and December 2005. For this study, we used cross-sectional data from the second wave of the SMART-MR study (n=754).[27,29] A further selection was done for biomarker assessment, particularly being 50 years or older, having a brain MRI scan, and available cognitive measurements (n=594). There were no significant differences between the selected group and the rest of the cohort regarding demographics (ie, sex, education, cardiovascular risk factors), other than the

selected group having a higher age. MRI brain scans, physical examinations, blood sampling, and questionnaires were all performed during a 1-day visit at the hospital. Written informed consent was obtained from all participants. A local ethics committee approved the SMART-MR study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

This study was reported in accordance to the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

Plasma Assessment

Briefly, participants underwent venipuncture under overnight-fasting conditions between 2006 and 2009. Plasma was then centrifuged for 10 minutes at 1800*g* within 2 hours. Then, in polypropylene tubes, plasma was aliquoted in 0.5-mL aliquots and stored at -80 °C until use. Plasma markers were analyzed in 2021. Aβ40, Aβ42, NfL, and GFAP were all assessed using the Neurology 4-plex E kit (Quanterix).[30] P-tau181 was assessed using the V2 Advantage kit (Quanterix). Measurements were performed according to manufacturer's instructions, using automated sample dilution on board of the Simoa HD-X analyzer. The Neurology 4-plex E kit was run in singlicates, and the p-tau181 V2 kit was run in duplicates. We calculated Aβ42/40, to adjust for between-person differences in production rates and to correct for preanalytical sample handling effects.[31] All plasma markers were *Z* score standardized for analysis.

MRI Protocol

Brain MRI was performed using a 1.5 Tesla whole-body system (Gyroscan ACS-NT, Philips Medical System, Best, The Netherlands).[29] A transversal T1-weighted gradient-echo (repetition time [TR]/echo time [TE]: 235/2 milliseconds), T2-weighted (TR/TE: 2200/11 milliseconds), fluid-attenuated inversion recovery (TR/TE/inversion time: 6000/100/2000 milliseconds), and T1-weighted inversion recovery (TR/TE/inversion time: 2900/22/410 milliseconds) sequences were acquired with a voxel size of 1.0×1.0×4.0 mm^3 as part of the protocol.[29] For measurement of hippocampal volume, a sagittal T1-weighted 3D fast field-echo sequence was obtained (TR/TE: 7/3.2 milliseconds).[32]

Brain Segmentation

WMH and brain volumes were segmented using an automated segmentation program on the T1-weighted gradient-echo, the inversion recovery sequence, and the fluid-attenuated inversion recovery sequences. More details regarding the probabilistic segmentation technique can be found here.[33,34] The hippocampus was manually outlined by 2 trained investigators, blinded to all clinical information.[32] The hippocampus proper, subiculum, fimbria, alveus, and dentate gyrus were all included on an average of 40 slices.[35] TBV was defined as the sum of both gray and white matter, WMH, and infarct volumes. Total intracranial volume was the sum of both TBV as well as the volumes of sulcal and ventricular cerebrospinal fluid. Hippocampal volume was the sum of both right and left hippocampi, which were defined by multiplying the total number of voxels by the volume of a voxel (ie, 1.0×0.94×0.94 mm).

Infarcts and WMH

Infarcts were rated visually by both an investigator and a neuroradiologist. Both were blinded to any clinical characteristics, and scans were reevaluated in a consensus meeting.[36] WMHs were defined as periventricular and deep lesions and were summed to represent the total volume of WMHs using a fully automated technique and visually checked.[29,36]

Infarcts were described as focal hyperintensities on T2-weighted images more than 3 mm in diameter and presumed of vascular origin.[37] If the T2 hyperintensities were within white matter, they also had to be hypointense on T1-weighted and fluid-attenuated inversion recovery images to be differentiated from WMHs. They were then characterized as lacunar or cortical infarcts. According to the Standards for Reporting Vascular Changes on Neuroimaging criteria,[2] lacunar infarcts were defined as focal lesions between 3 and 15 mm. Cortical infarcts were defined as being an area of tissue necrosis 4 mm or larger in cortical or cortico-subcortical areas.[38] Presence of any infarct was categorized as a dichotomous outcome (ie, yes/no). Lacunar and cortical infarcts were also categorized as any or none.

Covariates

Age, sex, education, smoking status, and alcohol use were given based on self-report. Education was categorized into less than high school education, at least some high school education, or college/university education based on the Dutch education system. Smoking status was categorized as never, former, or current smoker. Alcohol use was categorized as <1 drinks per week, 1 to 10 drinks per week, 11 to 20 drinks per week, and >20 drinks per week. Diabetes was defined as a (self-)reported history of diabetes, registered use of glucose-lowering medication (ie, insulin or oral antidiabetic drugs), or a glucose level of 7 mmol/L or higher. Hypertension was defined as self-reported use of antihypertensive medication, a mean systolic blood pressure of >140 mm Hg, or a mean diastolic blood pressure of >90 mm Hg.

Statistical Analysis

To address missing values (max: 10% missing on hippocampal volume), multiple imputation was performed using the *mice* package in R. Both outcomes and predictors were imputed if needed, using covariate information as predictors in the imputation.[39] We chose 10 imputed data sets, as a complete case analysis would be on 90% of the original sample size.[40] Pooled results are shown. Kruskal–Wallis tests were done to assess possible differences between sexes in plasma marker levels, and Pearson correlations were performed to assess the relationship between the plasma marker levels, brain volumes, and age. Linear regressions were performed to estimate the association between each standardized plasma marker and log-transformed WMH volume, TBV, and hippocampal volume, with age, sex, education, and intracranial volume as covariates. Logistic regressions were performed for the presence of infarcts (yes versus no), corrected for age, sex, and education. An additional model was performed correcting for further cardiovascular risk factors (ie, diabetes, hypertension, smoking status, and alcohol use). A sensitivity analysis was performed assessing the difference between lacunar and cortical infarcts by performing logistic regressions separately on cortical and lacunar infarcts. Another sensitivity analysis was done on the models of Aβ42/40 by adding 1/Aβ40 and Aβ42 as main effects, as suggested by previous work on the complexities of using a ratio in regression analyses.[41] We also report individual associations of Aβ40 and Aβ42 on all outcomes. Assumptions for both linear and logistic regressions were checked and met; therefore, no plasma markers were log-transformed. As there was moderate correlation between our outcomes, we used the Hommel method[42] for multiple comparison adjustment.[43]

Table 1. Baseline Characteristics of the Study Population

	Study sample (n=594)
	Mean (SD) or n (%)
Demographics	
Age, y	64 (8)
Sex, women	101 (17%)
Education, college/university	57 (10%)
Current smoker	127 (21%)
Alcoholic drinks per week	1.14 (0.97)
Diabetes	131 (22%)
Hypertension	401 (68%)
Currently taking antihypertensive medication	461 (78%)
Petersen criteria	48 (8%)
Body mass index, kg/m^2*	27 (5)
High-density lipoprotein, mmol/L*	1.22 (0.47)
Low-density lipoprotein, mmol/L*	2.40 (0.90)
Plasma levels, pg/mL	
Aβ40	113.19 (30.64)*
Aβ42	6.79 (1.94)*
Aβ42/40	0.06 (0.01)*
Phosphorylated-tau181	1.37 (0.79)*
Neurofilament light	13.82 (9.56)*
Glial fibrillary acidic protein	86.33 (53.98)*
Magnetic resonance imaging markers	
White matter lesion volume, mL	1.24 (2.50)*
Hippocampal volume, mL	5.98 (0.75)
Total brain volume, mL	1137.43 (105.14)
Infarct presence	206 (35%)
Lacunar infarct presence	137 (23%)
Cortical infarct presence	83 (14%)

1% missing on education, 1% missing on smoking, 1% missing on alcohol use, 1% missing on diabetes, 1% missing on hypertension, 3% missing on Petersen criteria, and 10% missing on hippocampal volume. Aβ indicates amyloid-beta.

*Shown as median (interquartile range).

RESULTS

The characteristics of the study population are shown in Table 1. The mean age of the study population was 64±8 years. Approximately 17% of the individuals were women, and 10% had an education level of a college/university degree. Eight percent met Petersen criteria[44] for mild cognitive impairment. A Pearson correlation matrix on age, the plasma markers, and the MRI markers can be found in Figure S1. Kruskal–Wallis tests showed no sex differences in Aβ42/40 and p-tau181. Higher levels of NfL and GFAP were seen in women compared with men.

All plasma markers were nonnormally distributed. The respective median (10%–90% range) for Aβ42/40, p-tau181, GFAP, and NfL were 0.06 (0.05–0.07), 1.37 (0.85–2.54), 86.33 (47.28–151.97), and 13.82 (7.86–28.59) (shown in pg/mL). For the MRI markers, only WMH volume was nonnormally distributed. The mean (SD) for hippocampal volume and TBV were 5.98 mL (0.75) and 1137 mL (105), respectively. The median (10%–90% range) for WMH volume was 1.24 (0.29–8.12) mL. Thirty-five percent of our study population had at least 1 infarct, with 23% having at least 1 lacunar infarct and 14% having at least 1 cortical infarct.

Associations with MRI Markers of Vascular Pathology

Linear regression analysis showed that higher plasma p-tau181 was associated with higher WMH volume (*b* per SD increase: 0.16 [95% CI, 0.06–0.26], *P*=0.015), which remained after further correction (Table 2).

Table 2. Associations Between the Plasma AD Markers and MRI Markers of Vascular Pathology and Neurodegeneration

Plasma levels (per SD increase)	WMH volume, B (95% CI), adjusted *P* value	TBV, B (95% CI), adjusted *P* value	HV, B (95% CI), adjusted *P* value
Model 1			
Aβ42/40	−0.03 (−0.13 to 0.06), *P*=0.827	−1.39 (−4.00 to 1.23), *P*=0.827	0.01 (−0.04 to 0.07), *P*=0.827
p-tau181	0.16 (0.06 to 0.26), *P*=0.015*	−2.21 (−5.05 to 0.63), *P*=0.750	−0.02 (−0.07 to 0.05), *P*=0.827
NfL	0.17 (0.06 to 0.29), *P*=0.052	−5.63 (−8.95 to −2.31), *P*=0.015*	−0.05 (−0.12 to 0.02), *P*=0.781
GFAP	0.07 (−0.04 to 0.18), *P*=0.827	−1.14 (−4.31 to 2.04), *P*=0.827	−0.04 (−0.11 to 0.03), *P*=0.827
Model 2			
Aβ42/40	−0.04 (−0.13 to 0.05), *P*=0.785	−1.26 (−3.81 to 1.29), *P*=0.785	0.01 (−0.04 to 0.07), *P*=0.785
p-tau181	0.15 (0.06 to 0.25), *P*=0.028*	−1.76 (−4.54 to 1.01), *P*=0.785	−0.01 (−0.07 to 0.05), *P*=0.785
NfL	0.17 (0.05 to 0.29), *P*=0.052	−5.50 (−8.75 to −2.24), *P*=0.016*	−0.05 (−0.12 to 0.02), *P*=0.785
GFAP	0.09 (−0.03 to 0.20), *P*=0.738	−2.07 (−5.23 to 1.09), *P*=0.785	−0.05 (−0.12 to 0.02), *P*=0.738

Model 1 is adjusted for age, sex, education, and intracranial volume. Model 2 adds diabetes, hypertension, smoking status, and alcohol use. WMH volume is log-transformed. *P* values are adjusted using the Hommel method. Aβ indicates amyloid-beta; AD, Alzheimer's disease; GFAP, glial fibrillary acidic protein; HV, hippocampal volume; MRI, magnetic resonance imaging; NfL, neurofilament light; p-tau, phosphorylated tau; TBV, total brain volume; and WMH, white matter hyperintensity.

**P* values shown are corrected using the Hommel method, with *P*<0.05 denoting significance.

Higher NfL showed a trend toward higher WMH volume, but it did not survive correction for multiple comparisons. No other biomarkers were associated with WMH, also when adding 1/Aβ40 and Aβ42 as main effects or assessed individually (Table S2).

Regarding infarcts, higher plasma NfL was associated with higher odds of having an infarct (OR, 1.42 [95% CI. 1.13–1.78], *P*=0.039); however, this did not remain after further covariate adjustment (Table 3). When looking specifically at lacunar infarcts, higher plasma NfL was associated with higher odds of a lacunar infarct (OR, 1.36 [95% CI, 1.06–1.73], *P*=0.014). Regarding cortical infarcts, both higher plasma NfL and GFAP were associated with higher odds of having a cortical infarct (respectively OR, 1.58 [95% CI, 1.20–2.08], *P*=0.001 and OR, 1.45 [95% CI, 1.09–1.92], *P*=0.010) (Table 3). No other plasma markers were associated with the presence of infarcts (Table 3; Table S3).

Associations with MRI Markers of Neurodegeneration

Higher plasma NfL was associated with lower TBV (*b*: -5.63 [95% CI, −8.95 to −2.31], *P*=0.015), which remained after further covariate adjustment (Table 2). There were no associations between plasma markers and hippocampal volume, albeit an association was found for higher Aβ40 and lower hippocampal volume (Table S2).

DISCUSSION

In a sample of individuals with manifest arterial disease and WMH, we found that higher NfL was associated with infarcts and global brain atrophy, higher p-tau181 was associated with more WMH volume, and GFAP was related to the presence of 1 or more cortical

Table 3. Associations Between the Plasma AD Markers and Infarcts

Plasma levels (per SD increase)	Infarcts, OR (95% CI), adjusted *P* value	Lacunar infarcts, OR (95% CI), *P* value	Cortical infarcts, OR (95% CI), *P* value
Model 1			
Aβ42/40	1.18 (0.86–1.63), *P*=0.827	1.30 (0.84–2.02), *P*=0.240	1.04 (0.85–1.26), *P*=0.723
p-tau181	1.16 (0.96–1.40), *P*=0.729	1.22 (1.00–1.50), *P*=0.055	1.17 (0.92–1.50), *P*=0.202
NfL	1.42 (1.13–1.78), *P*=0.039*	1.36 (1.06–1.73), *P*=0.014*	1.58 (1.20–2.08), *P*=0.001*
GFAP	0.98 (0.79–1.21), *P*=0.827	0.86 (0.68–1.10), *P*=0.224	1.45 (1.09–1.92), *P*=0.010*
Model 2			
Aβ42/40	1.17 (0.83–1.64), *P*=0.785	1.27 (0.82–1.95), *P*=0.288	1.01 (0.84–1.23), *P*=0.883
p-tau181	1.13 (0.93–1.37), *P*=0.785	1.19 (0.97–1.47), *P*=0.101	1.13 (0.88–1.45), *P*=0.342
NfL	1.41 (1.12–1.79), *P*=0.052	1.36 (1.05–1.74), *P*=0.018*	1.54 (1.16–2.03), *P*=0.003*
GFAP	1.03 (0.82–1.30), *P*=0.785	0.87 (0.68–1.13), *P*=0.297	1.56 (1.16–2.10), *P*=0.003*

Model 1 is adjusted for age, sex, and education. Model 2 adds diabetes, hypertension, smoking status, and alcohol use. *P* values are adjusted using the Hommel method. Aβ indicates amyloid-beta; AD, Alzheimer's disease; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; OR, odds ratio; and p-tau, phosphorylated tau.

**P* values shown are corrected using the Hommel method, with *P*<0.05 denoting significance.

infarcts. None of the biomarkers were associated with hippocampal volume.

Higher levels of plasma NfL were associated with infarcts, which is in line with previous literature.[12] As NfL has been linked to axonal damage,[45] the relationship between NfL and infarcts could be explained by persisting axonal damage due to vascular pathology.[46] Additionally, we found an association between higher NfL and lower TBV, which is in line with a previous longitudinal study.[20] However, we did not find an association of plasma NfL with hippocampal atrophy, whereas some studies found an association.[18,22,23,47] Further, in this cohort, memory has not been associated with hippocampal volume.[48] Hippocampal atrophy in vascular patients may have a different pathological mechanism than global atrophy and may not show a clear relation to memory decline. As this is the first study to our knowledge focusing on plasma AD biomarkers and brain volume in individuals with arterial disease, this needs to be validated in other studies of a similar population. We did not find an association after correction for multiple comparisons between NfL and WMH, which is in line with a former study on a population with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[17] In contrast, studies in populations with mild cognitive impairment and AD have reported such an association.[13,14,49,50] This apparent contradiction may be explained by being in a later stage of cognitive impairment or may be due to a loss of power in the current study, as our findings were approaching significance. As studies assessing NfL and MRI markers of vascular pathology are scarce, further studies need to be performed to replicate this result.

However, higher p-tau181 was associated with more WMH volume, which is in line with previous studies.[10,11] One study found that amyloid PET pathology was associated with WMH in the general population, with cerebral amyloid angiopathy possibly explaining this role.[51] As p-tau181 in plasma is associated with amyloid PET positivity,[52] cerebral amyloid angiopathy could explain the relation between AD-specific biomarkers and WMH. Surprisingly, we did not find an association with p-tau181 and hippocampal volume, even though many previous studies have found an association.[10,16,19,21,22] However, 2 studies also found a null association.[53,54] Hippocampal atrophy in this population with manifest arterial disease may be independent to AD-specific neuronal loss and solely of vascular origin.

Additionally, GFAP was associated with cortical infarcts. This is in line with a previous study on serum GFAP that found an association of GFAP with infarcts, but not with subcortical vascular pathology such as WMHs.[46] The specificity to cortical infarcts was also reflected in a previous study, highlighting that the site of injury may determine if GFAP is released into the blood.[55] However, as this is the first study to our knowledge assessing GFAP in plasma with brain infarcts, future research should validate these findings. Aβ and p-tau181 were not associated with infarcts, which is in line with a previous study.[5] Infarcts may not have a direct relationship to AD pathology, possibly due to the anatomical location of infarcts compared with WMH.[56]

The current study had important strengths. We assessed multiple plasma markers using an ultrasensitive Simoa assay. Further, we used multiple imputation to account for missing data, corrected for multiple covariates, and also used a strict correction for multiple comparisons to prevent any Type I errors. However, the study also had limitations. The study population was relatively young and healthy, as the included participants were a subsample of the SMART-MR study that participated in the first follow-up assessment. Further, participants were predominantly White and male; thus, the generalizability to other populations is low. Other studies have highlighted that plasma p-tau181 and NfL may not accurately represent brain amyloidosis in Black adults compared with White individuals.[57] Future studies need to be done on marginally underrepresented individuals to assess any differences regarding plasma AD biomarkers and vascular pathology in these populations. Further, plasma biomarker assessment was performed more than 12 years after blood was collected and stored. Although studies have shown the reliability of blood biomarker assessment after long-term storage, slight increases in variability can be expected after 14 years.[58] Additionally, we did not have information on microbleeds, so we unfortunately could not assess the relation between the plasma AD markers on cerebral microbleeds.

CONCLUSIONS

Plasma biomarkers that have been associated with tau accumulation, axonal injury, and astrocytic activation are related to MRI markers of vascular pathology and neurodegeneration in patients with manifest arterial disease. The current study suggests a relationship between AD-related and vascular pathology in individuals with manifest arterial disease, highlighting the role of mixed pathology in these individuals. Future longitudinal studies should explore if individuals with both of these pathologies are at an increased risk of dementia.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figure S1

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