RESEARCH ARTICLE

Frequency of Microvascular Pathology and Hippocampal Atrophy on Magnetic Resonance Imaging in a Community Study of Alzheimer's Disease with Blood-Based Biomarkers

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Objective: Blood-based biomarkers for Alzheimer's disease (AD), representing antemortem indicators of AD pathophysiology, have greatly improved the accuracy of diagnosis. However, these biomarkers may not capture a frequent coincident pathology, such as cerebrovascular disease.

Methods: We measured plasma amyloid-β40, amyloid-β42, total tau, tau phosphorylated at threonine 181, tau phosphorylated at threonine 217, glial fibrillary acidic protein, and neurofilament light chain in 685 multiancestral individuals who had clinical assessments and brain magnetic resonance imaging. The cohort was represented by individuals of European, African American, and Caribbean Hispanic ancestry. Participants were then classified as biomarker-positive or -negative for AD based on previously established cutoffs: 2.65 pg/mL for, tau phosphorylated at threonine 181 and 0.39 pg/mL for tau phosphorylated at threonine 217. We used magnetic resonance images to compare white matter hyperintensity volume (WMH), silent brain infarcts, microhemorrhages, and hippocampus volume across groups by their clinical diagnosis and biomarker status.

Results: In the P-tau181 group ($n = 685$), 70 individuals (10.2%) had dementia or amnestic mild cognitive impairment. A total of 40 (57%) were biomarker-positive for AD, and 30 were classified as other dementia. Among 615 without dementia, 265 (40.3%) were preclinical AD, and 348 (50.8%) were biomarker-negative controls. In the tau phosphorylated at threonine 217 group ($n = 535$), 54 (10.1%) had dementia or amnestic mild cognitive impairment, including 33 biomarker-positive for AD and 21 with other dementia, whereas 183 (38.0%) were preclinical AD and 298 (61.9%) were biomarker-negative controls. Across both classifications, biomarker-positive for AD and other dementia individuals showed greater WMH volumes, more infarcts, and smaller hippocampus. However, P-tau217 positivity was more sensitive to WMH volume differences, whereas tau phosphorylated at threonine 181 better captured hippocampal atrophy and silent brain infarcts. Interestingly, ethnic differences may also influence detection of changes in WMH volumes, hippocampal volume, and infarcts in relation to specific biomarkers.

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Interpretation: The results indicate that cerebrovascular disease is consistently involved in dementia either directly or as a coincident pathology in AD. These results underscore the need to incorporate both blood-based biomarkers and structural imaging in the evaluation of patients with dementia.

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The diagnoses for Alzheimer's disease (AD) and mild cognitive impairment (MCI) have been based on clinical criteria[1–4] that require cognitive and functional decline. The addition of cerebrospinal fluid biomarkers provided the basis for a framework necessary to improve the diagnosis. The "A/T/N" criteria specified the presence of amyloidosis, tau pathology, and neurodegeneration, considered imperative to the diagnosis of AD,[5,6] but the authors acknowledged that cerebrovascular disease is a frequent copathology.[7]

Although the incorporation of biomarkers has contributed to diagnostic specificity, there can be variability in their application,[8–11] depending on the presence of comorbid disease and social factors.[12–14] The stratification of individuals into biomarker-positive or -negative dementia, and biomarker-positive or -negative controls raises several critical questions, 1 of which is whether this classification captures the known pathologic heterogeneity of AD with and without the presence of cerebrovascular disease.

In this cross-sectional study, we integrated magnetic resonance imaging (MRI) and blood-based biomarkers to investigate how white matter hyperintensity volume (WMH) volume, silent brain infarcts, microhemorrhages, hippocampal volume, and blood-based biomarkers characterize cognitive impairment and dementia among individuals in a community-based study in northern Manhattan, New York.

Methods

Source Population

The Washington Heights-Hamilton Heights-Inwood Columbia Aging Project (WHICAP) is a prospective cohort study of clinical and genetic risk factors for dementia. Individuals were recruited as representative of those living in the communities of northern Manhattan who were aged ≥65 years, and the study was completed in 3 waves in 1992, 1999, and 2009, all using similar study procedures. At the study entry, each person underwent a structured interview of general health and function, followed by a comprehensive assessment including medical, neurological, and psychiatric histories, and standardized physical, neurological, and neuropsychological examinations. Individuals were followed every 18–24 months with repeated examinations that were similar to the initial examination.

The institutional review board of Columbia University approved the study, and all participants provided written informed consent.

After data were collected, a review was conducted in a diagnostic consensus conference attended by 2 physicians and 2 neuropsychologists with expertise in dementia diagnosis. The panel used the results from the neuropsychological battery and evidence of impairment in social or occupational function. Initially, all-cause dementia was determined based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th and 5th Editions.[15,16] Furthermore, we used the criteria from the National Institute on Aging and Alzheimer's Association criteria to diagnose probable or possible AD.[2] For participants without dementia, MCI was assigned, as previously described specifically for this community,[17] if the participant had memory complaints or had cognitive impairment in ≥1 cognitive domains, but with preserved activities of daily living. Amnestic MCI (aMCI) was defined by the modified version of the Petersen criteria, as described previously.[18–20]

Blood-Based Biomarkers

Blood samples were collected by standard venipuncture in dipotassium ethylenediaminetetraacetic acid tubes. Plasma was prepared by centrifugation at 2,000*g* for 15 min at 4°C within 2 h after collection, aliquoted in polypropylene tubes, and frozen and stored at −80°C. Plasma biomarker assays were performed between using the single molecule array technology Quanterix Simoa®[21] HD-X platform (Quanterix, Billerica, MA, USA). All samples were assayed in duplicate using 3 Quanterix kits: Neurology 3-Plex A (catalog No. 101995) for amyloid-β40 and 42 (Aβ40, Aβ42), and total tau (t-tau); pTau-181 Advantage V2 (catalog No. 103714) for tau phosphorylated at threonine 181 (P-tau181); tau phosphorylated at threonine 217 (P-tau217) and Neurology 2-Plex B (catalog No. 103520) for neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP). Quantification functional lower limits for these analytes are 2.7 for Aβ40, 0.6 for Aβ42, 0.3 for T-tau, 0.3 for P-tau181, 0.06 for P-tau217,0.8 for NfL, and 16.6 for GFAP, all in pg/mL. Mean coefficients of variation are ≤5%. Ratios of Aβ42/Aβ40, P-tau181/Aβ42 and P-tau217/Aβ42 were calculated. Based on the literature, we a priori decided to focus on P-tau181,[22] P-tau217,[23,24] neurodegeneration

marker NfL,[25–27] neuroinflammatory reactive astrogliosis marker GFAP,[28] Aβ42/Aβ40,[29–31] P-tau181/Aβ42,[32] and P-tau217/Aβ42,[33] whereas analyses did not include the individual measures of Aβ42, Aβ40, and t-tau due to their lesser performance in classifying AD and neurodegeneration.[27,34] Blood for DNA extraction was also collected, and apolipoprotein E (*APOE*) genotyping was performed at LGC Genomics (Teddington, UK) and CD Genomics (New York, NY, USA).

MRI

Structural MRI scans for 246 (36.6%) participants were obtained using 1.5-T magnet samples, and 427 (63.4%) on a 3.0-T magnet.[35] We adjusted for field strength in each set of the analyses. MRI scans were selected for analyses using the scan date that was closest to the blood collection date.

We derived hippocampal volumes using FreeSurfer, as previously described.[35] FreeSurfer segmentations were visually inspected and manually corrected, if necessary, by a trained operator.

Cerebrovascular disease (white matter hyperintensities, microhemorrhages, and brain infarcts) was measured using software developed in-house.[36] Briefly, fluid-attenuated inversion recovery (FLAIR) images were reconstructed, reoriented, skull stripped, and bias field corrected. A Gaussian mixture model and expectation–maximization algorithm was applied within the white matter segment of each FLAIR image to extract 2 components representing hyperintense and non-hyperintense voxels. A Roberts edge detection function was applied to probability distribution maps representing the segmented WMH within the FLAIR images to label WMH voxels. The labeled voxels were added together and multiplied by their dimensions to yield total WMH volume in cm^3.

Microhemorrhages were visually rated on T_2*-weighted MRI following established criteria.[37–39] The primary measure is the presence or absence of microhemorrhages, and their locations were ascertained by trained raters. Brain infarcts were defined visually and rated as discrete hypointense lesions that were >5 mm on T_1 and confirmed on the FLAIR image as a hypointense lesion with a partial or complete hyperintense ring. For the statistical analysis of microhemorrhages and brain infarct, we used dichotomized values for each participant, categorizing them based on the presence or absence of microhemorrhages and brain infarcts, respectively.

Statistical Analysis

Data analyses were performed using R software version 4.2.0 (https://www.r-project.org/). Individuals were classified into 4 groups based on a previously established P-tau181 cut score of 2.648 pg/mL[40]: biomarker-negative controls (BM-CTL), biomarker-positive controls (BM + CTL), biomarker-negative with dementia (BM-Dem), and biomarker-positive with dementia (BM + AD). In addition to P-tau181, the individuals were classified based on a P-tau217 cut score of 0.39 pg/mL, which is determined using the same protocol as P-tau181. Proportions across groups were assessed using the χ^2 test for categorical variables, whereas the Kruskal–Wallis test was applied to continuous variables, with significance defined as $p < 0.05$. Outliers whose blood-based biomarker (Aβ40, Aβ42, Aβ ratio, total Tau, P-tau181, P-tau217, P-tau181/Aβ42 ratio, P-tau217/Aβ42 ratio, NfL, and GFAP) levels exceeded 1.5-fold the interquartile range beyond the first (Q1) or third (Q3) quartiles were removed.

The correlations among the raw structural MRI measures and plasma biomarkers were analyzed using Pearson's partial correlation method within BM-CTL, BM + CTL, and BM + AD groups, classified based on the P-tau181 cut score. The same analyses were repeated using the groups defined by the P-tau217 cutoff. Due to the small sample sizes, the BM + CTL and BM + AD groups were combined in the correlation analyses. We investigated correlations among structural MRI measures, including WMH volume and hippocampal volume, and other plasma biomarkers including Aβ40, Aβ42, Aβ ratio, total Tau, P-tau181, P-tau217, P-tau181/Aβ42 ratio, P-tau217/Aβ2 ratio, NfL, and GFAP. These analyses were adjusted for age, sex, ethnicity, intracranial volume, and magnetic field strength as covariates. The proportion of individuals scanned at 1.5 T versus 3.0 T differed between the BM-CTL and BM + CTL groups, but not the BM-Dem or BM + AD. Nevertheless, we adjusted for field strength in all analyses that included MRI outcomes. All the plasma biomarkers, including Aβ40, Aβ42, Aβ ratio, total Tau, P-tau181, P-tau217, P-tau181/Aβ42 ratio, P-tau217/Aβ42 ratio, NfL and GFAP, were adjusted for age, sex, and ethnic group in the correlation analysis. Outliers within the BM-CTL, BM + CTL, and BM + AD groups were excluded in the plasma biomarker data prior to analysis. The Pearson's partial correlation were plotted with the 'pheatmap'[41] and 'corrplot'[42] packages in R software. The scatter plots showing the correlation of MRI measures with plasma biomarkers were generated using the 'ggpubr'[43] package in R software.

Individuals were classified as biomarker-positive or -negative based on a P-tau181 cutoff of 2.648 pg/mL, and for subsequent analyses, classification as biomarker-positive or -negative was based on a P-tau217 cutoff of 0.39 pg/mL. Differences in WMH volume, hippocampal volume, NfL, and GFAP were analyzed among BM-CTL, BM + CTL, BM-Dem, and BM + AD groups using

analysis of covariance (ANCOVA). Extreme outliers for NfL (37 outliers removed) and GFAP (34 outliers removed) were removed if they exceeded 1.5-fold the interquartile range beyond the first (Q1) or third (Q3) quartiles. Similarly, differences in the frequency of silent brain infarcts and microhemorrhages were analyzed using logistic regression among different clinical groups. The WMH volume and hippocampal volume were adjusted for age, sex, ethnic group, field strength, and intracranial volume. Analyses involving, NfL, GFAP, silent brain infarcts, and microhemorrhages were adjusted for age, sex, and ethnic group. Subsequently, similar analyses stratified by ethnicity were performed with adjustments for the same covariates excluding ethnic group. We also evaluated the ethnicity differences within each clinical group of neuroimaging measures using ANCOVA by adjusting for age, sex, field strength and intracranial volume as covariates.

MRI measures and plasma biomarkers were compared between *APOE-ε4* carriers and non-carriers using ANCOVA. All the plasma biomarkers were adjusted for age, sex, and ethnic group as covariates, whereas the MRI phenotypes were adjusted for the same covariates as described above. The distribution of MRI measures and blood-based biomarkers (Figure S1A–D) was assessed, and the ANCOVA analysis was performed using the log transformed values (Figure S2A–C) if there was a skewness in the distribution along with analyses on raw values. The NfL and GFAP data were skewed, thus all raw values were log-transformed and 11 identified outliers (out of 685 individuals) were removed. Then, the ANCOVA was repeated using the log-transformed data across the clinical groups to determine whether the findings differed from those obtained with the raw data. Additionally, *APOE-ε4* carriers and non-carriers were stratified by biomarker-positive and -negative, and analyzed for differences in MRI measures and plasma biomarkers among these clinical groups using ANCOVA with similar covariate adjustments as those previously described.

Power Analysis

Power analyses for the ANCOVA models (WMH, hippocampal volume, NfL, and GFAP) were conducted using the 'pwr' package in R software.[44] Power analyses for logistic regression models involving microbleeds and silent brain infarcts were performed using the 'pwrss' package in R.[45] Assuming an effect size of 0.15 and 3 to 5 covariates, all ANCOVA comparisons within the P-tau181- and P-tau217-defined clinical groups achieved adequate power ranging from 0.85 to 0.99. In contrast, for the analyses involving microbleeds and silent brain infarcts, with an expected effect size of 2.0 and a desired power of 0.80, only the comparisons between the BM-CTL and BM + CTL groups were adequately powered.

Results

Demographics of Study Participants

A total of 685 individuals were included based on P-tau181-based clinical grouping. Among them, 70 (10.2%) individuals had dementia or aMCI. Of these, 40 (57%) were biomarker-positive and considered as having BM + AD, whereas 30 were biomarker-negative and considered as BM-Dem. There were 615 (81%) individuals without dementia or with minor cognitive deficits, 267 (40.3%) of whom were biomarker-positive and considered BM + CTL. The remaining 348 (50.8%) individuals were cognitively unimpaired and biomarker-negative, and considered BM-CTL. As seen in Tables 1 and 2, those with dementia (BM-Dem) were older and had fewer years of education than the BM-CTL or BM + CTL groups. There were also more women in the BM-Dem group compared with the other groups. Although the frequency of an *APOE-ε4* allele was highest in the BM + AD group, the difference was not statistically significant, possibly due to the small number of individuals in that group.

In the P-tau217-based classification group, 535 participants were assessed. Among them, 54 (10.13%) individuals had dementia or aMCI, and within this impaired subgroup, 33 (61.11%) were biomarker-positive and considered as having BM + AD, whereas 21 were biomarker-negative and considered as BM-Dem. The remaining 481 participants (89.9%) showed no dementia or only minor cognitive deficits. Of these, 183 (38.0%) were biomarker-positive (BM + CTL) and 298 (61.9%) were biomarker-negative (BM-CTL). Like the P-tau181 grouping, BM-Dem individuals were older and less educated (Tables 3 and 4). *APOE-ε4* frequency was again highest in BM + AD, but not significant, possibly due to the small number of individuals in that group.

Relationship Between Neuroimaging Measures and Blood-Based Biomarkers

Correlation analyses were conducted between MRI measures and blood-based biomarkers within the BM-CTL group, and a combined group of BM + CTL and BM + AD. These analyses were performed separately for clinical classifications based on both P-tau181 and P-tau217. Significant correlations ($p < 0.005$) were observed between MRI measures and biomarkers including Aβ40, Aβ42, Aβ42/40 ratio, total tau, P-tau181, P-tau217, P-tau181/Aβ42 ratio, P-tau217/Aβ42 ratio, NfL, and GFAP across both classification schemes (Figures 1A, B, and 2C, D).

TABLE 1. Demographic Characteristics of Study Participants Based on P-Tau181 Defined Groups

	Biomarker negative control (BM − CTL)	Biomarker positive control (BM + CTL)	Biomarker negative dementia (BM − Dem)	Biomarker positive Alzheimer's disease (BM + AD)	*p*-value
N	348 (50.8%)	267 (38.9%)	30 (4.4%)	40 (5.8%)	
Age, mean (SD)	75.05 (6.07)	77.41 (6.97)	80.93 (7.77)	80.23 (8.39)	<0.0001
Women (%)	67%	55.8%	83.33%	52.50%	0.03
Education, mean (SD)	12.44 (4.71)	11. 95 (5.00)	7.67 (4.83)	8.63 (4.83)	<0.0001
APOE ε4 (%)	85 (24.64%)	71 (26.14%)	9 (30%)	15 (37.50%)	0.349
Diabetes (*N*)	112 (32.2%)	81 (30.3%)	15 50%)	12 (30%)	0.18
Hypertension (*N*)	278 (79.9%)	232 (86.9%)	28 (93.3%)	36 (90%)	0.03
Microbleeds					
1.5 T (*N*)					
Positive (%)	0	0	0	0	N/A
3.0 T (*N*)	231	129	19	18	0.36
Positive (%)	12.9%	19.4%	10.5%	11.1%	
Silent brain infarcts					
1.5 T (*N*)	96	123	8	19	0.90
Positive (%)	48.9%	49.6%	62.5%	47.4%	
3.0 T (*N*)	247	137	19	18	0.01
Positive (%)	26.3%	35.0%	31.6%	61.1%	
White matter hyperintensity volume (cm^3)					
1.5 T	18.17	13.73	29.52	21.59	0.002
Mean (SD)	(18.39)	(16.04)	(27.46)	(14.34)	
3.0 T	6.77	9.33	11.51	26.59	<0.0001
Mean (SD)	(9.33)	(10.86)	(13.53)	(24.82)	
Hippocampus volume (mm^3)					
1.5 T	6746.12	6850.53	6368.63	6631.05	0.75
Mean (SD)	(865.59)	(850.25)	(1177.77)	(827.99)	
3.0 T	7257.01	6859.06	6751.11	6695.65	<0.0001
Mean (SD)	(822.26)	(912.17)	(789.62)	(795.99)	
Intracranial volume (mm^3)					
1.5 T Mean	1,316,801	1,304,781	1,342,526	1,306,466	0.88
3.0 T Mean	1,483,599	1,481,228	1,416,514	1,528,191	0.27
Field strength					
1.5 T	96	123	8	19	<0.0001
3.0 T	249	139	20	19	

cm^3 = cubic centimeter; mm^3 = cubic millimeter; *N* = total number; SD = standard deviation.

TABLE 2. Blood Based Biomarkers

	Biomarker negative control (BM − CTL)	Biomarker positive control (BM + CTL)	Biomarker negative dementia (BM − Dem)	Biomarker positive Alzheimer's disease (BM + AD)	*p*-value
N	348 (50.8%)	267 (38.9%)	30 (4.4%)	40 (5.8%)	
P-u181 (pg/mL)					
Mean (SD)	1.90 (0.50)	4.99 (5.49)	1.99 (0.43)	4.58 (2.20)	<0.0001
P-tau217 (pg/mL)					
Mean (SD)	0.31 (0.15)	0.57 (0.37)	0.36 (0.20)	0.86 (0.51)	<0.0001
Aβ40 (pg/mL)					
Mean (SD)	248.35 (81.97)	304.17 (119.23)	263.06 (113.04)	297.52 (3.83)	<0.0001
Aβ42 (pg/mL)					
Mean (SD)	10.34 (3.66)	11.89 (4.53)	10.40 (4.23)	11.21 (3.83)	0.001
Total tau (pg/mL)					
Mean (SD)	3.04 (1.30)	4.95 (2.03)	3.18 (1.54)	3.90 (1.80)	0.03
Aβ 42/40 ratio					
Mean (SD)	0.05 (0.04)	0.04 (0.014)	0.04 (0.01)	0.04 (0.01)	<0.0001
P-tau181/Aβ42 ratio					
Mean (SD)	0.29 (1.01)	0.49 (0.66)	0.35 (0.66)	0.48 (0.31)	<0.0001
P-tau217/Aβ42 ratio					
Mean (SD)	0.04 (0.04)	0.06 (0.05)	0.05 (0.05)	0.09 (0.09)	<0.0001
NfL (pg/mL)					
Mean (SD)	21.84 (15.84)	34.02 (23.64)	24.51 (10.18)	34.10 (15.53)	<0.0001
GFAP (pg/mL)					
Mean (SD)	168.52 (86.23)	253.05 (177.93)	196.18 (85.38)	283.66 (144.27)	<0.0001

N = total number; SD = standard deviation.

These associations remained significant after correcting multiple comparisons ($p = 0.05/144 = 3.47 \times 10^{-4}$).

Although WMH volume showed a nominally significant association with hippocampal volume ($p = 0.04$) in the P-tau181-based BM-CTL group, this did not remain significant after correction for multiple comparisons. Similarly, in the P-tau217-based combined group (BM + CTL and BM + AD), WMH was associated with Aβ42 ($p = 0.01$) and hippocampal volume was associated with GFAP ($p = 0.003$), but neither survived correction for multiple testing. No other significant associations were observed between WMH or hippocampal volume and the remaining blood-based biomarkers in any group. The scatter plots showing the correlations between MRI measures and blood-based biomarkers are provided in the Figures S3–S6.

Comparison of Neuroimaging Measures and Plasma Biomarkers Across Diagnostic Groups

We compared differences in WMH volume and hippocampal volume among the BM-CTL, BM + CTL, BM-Dem, and BM + AD groups defined by P-tau181 levels (Figure 2A, B). The BM-Dem ($F = 5.840$; $p = 0.02$) and BM + AD ($F = 33.18$; $p = 1.77 \times 10^{-08}$) groups had larger WMH volumes compared with the BM-CTL group (Figure 2A). Additionally, the BM + AD ($F = 24.65$; $p = 1.18 \times 10^{-06}$) groups had larger WMH volume compared with the BM + CTL group. Due to the skewed

TABLE 3. Demographic Characteristics of Study Participants Based on P-Tau217 Defined Groups.

	Biomarker negative control (BM − CTL)	Biomarker positive control (BM + CTL)	Biomarker negative dementia (BM − Dem)	Biomarker positive Alzheimer's disease (BM + AD)	*p*-value
N	295 (50.8%)	183 (38.9%)	21 (4.4%)	33 (5.8%)	
Age, mean (SD)	74.98 (6.15)	78.25 (6.82)	81.33 (8.42)	82.42 (7.14)	<0.0001
Women (%)	69%	60.01%	66.67%	69.70%	0.23
Education, mean (SD)	12.15 (4.82)	12.74 (4.92)	7.05 (4.22)	8.87 (5.30)	<0.0001
APOE ε4 (%)	68 (23.05%)	58 (31.69%)	5 (23.81%)	13 (39.39%)	0.06
Diabetes (*N*)	99 (33.5%)	60 (32.9%)	9 (42.9%)	10 (30.3%)	0.8
Hypertension (*N*)	244 (82.7%)	149 (81.4%)	19 (90.1%)	31 (93.9%)	0.24
Microbleeds					
1.5 T (*N*)	0	0	0	0	N/A
Positive (%)					
3.0 T (*N*)	224	118	15	21	0.57
Positive (%)	12.9%	18.6%	13.3%	9.5%	
Silent brain infarcts					
1.5T (*N*)	57	55	3	10	0.91
Positive (%)	45.6%	49.1%	33.3%	40.0%	
3.0 T (*N*)	237	127	16	20	0.04
Positive (%)	26.6%	33.1%	50.0%	45.0%	
White matter hyperintensity volume (cm^3)					
1.5 T Mean (SD)	14.80 (19.69)	12.80 (13.07)	22.59 (19.23)	27.86 (25.00)	0.002
3.0 T Mean (SD)	6.82 (8.15)	9.72 (12.72)	15.23 (17.97)	22.60 (23.25)	<0.0001
Hippocampus volume (mm^3)					
1.5 T	6794.93	6738.73	5605	6831.4	0.1
Mean (SD)	(723.77)	(872.15)	(526.97)	(581.11)	
3.0 T	7159.33	7066.54	6884.59	6642.36	0.04
Mean (SD)	(817.96)	(986.22)	(679.15)	(845.53)	
Intracranial volume (mm^3)					
1.5 T Mean	1296078.01	1320869.18	1272362.89	31686.55	0.84
3.0 T Mean	1481093.94	1485471.99	1473186.77	1465392.14	0.84
Field strength					
1.5 T	57	55	3	10	<0.0001
3.0 T	240	127	17	21	

cm^3 = cubic centimeter; mm^3 = cubic millimeter; *N* = total number; SD = standard deviation.

TABLE 4. Blood Based Biomarkers

	Biomarker negative control (BM−CTL)	Biomarker positive control (BM + CTL)	Biomarker negative dementia (BM − Dem)	Biomarker positive Alzheimer's disease (BM + AD)	*p*-value
N	295 (50.8%)	183 (38.9%)	21 (4.4%)	33 (5.8%)	
P-tau181 (pg/mL)					
Mean (SD)	2.42 (2.23)	3.96 (2.74)	2.29 (1.21)	4.09 (2.59)	<0.0001
P-tau217 (pg/mL)					
Mean (SD)	0.26 (0.07)	0.67 (0.33)	0.25 (0.08)	0.87 (0.45)	<0.0001
Aβ40 (pg/mL)					
Mean (SD)	261.32 (82.06)	284.36 (115.77)	276.72 (98.16)	285.68 (111.54)	0.07
Aβ42 (pg/mL)					
Mean (SD)	11.17 (3.67)	11.15 (4.34)	11.04 (3.54)	10.92 (4.33)	0.90
Total tau (pg/mL)					
Mean (SD)	3.07 (1.60)	3.26 (1.62)	3.71 (1.89)	3.34 (1.46)	0.21
Aβ 42/40 ratio					
Mean (SD)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	<0.0001
P-tau181/Aβ42 ratio					
Mean (SD)	0.25 (0.31)	0.40 (0.31)	0.22 (0.09)	0.47 (0.37)	<0.0001
P-tau217/Aβ42 ratio					
Mean (SD)	0.03 (0.04)	0.07 (0.05)	0.02 (0.02)	0.10 (0.09)	<0.0001
NfL (pg/mL)					
Mean (SD)	22.35 (15.57)	31.78 (21.20)	25.82 (10.32)	34.95 (16.62)	<0.0001
GFAP (pg/mL)					
Mean (SD)	173.86 (139.99)	234.99 (132.73)	193.74 (128.36)	279.25 (121.88)	<0.0001

N = total number; SD = standard deviation.

distribution of WMH, log-transformed WMH volumes were compared between the groups. Similar associations for larger volumes were observed with the log-transformed WMHs. Similarly, BM + CTL ($F = 13.76$; $p = 2.27 \times 10^{-4}$), BM-Dem ($F = 7.99$; $p = 4.97 \times 10^{-3}$), and BM + AD ($F = 9.87$; $p = 1.81 \times 10^{-3}$) had smaller hippocampal volume compared with BM-CTL (Figure 2B), indicating that greater hippocampal atrophy was observed in both forms of dementia, as well as in individuals in the pre-clinical stage of AD.

Similarly, we assessed WMH and hippocampal volumes across clinical groups defined by P-tau217 (Figure 3A, B). BM + AD ($F = 41.73$; $p = 3.95 \times 10^{-10}$), BM-Dem ($F = 8.33$; $p = 4.19 \times 10^{-3}$), and BM + CTL ($F = 4.21$; $P = 0.04$) groups showed larger WMH volumes compared with BM-CTL (Figure 3A). BM + AD ($F = 22.02$; $p = 4.99 \times 10^{-6}$) also had larger WMH volumes compared with BM + CTL. Log-transformed WMH values also showed similar patterns. This suggests that P-tau217 classification distinguishes WMH differences slightly better than P-tau181, despite a smaller sample size. For hippocampal volume, both BM + AD ($F = 6.87$; $p = 9.05 \times 10^{-3}$) and BM-Dem ($F = 4.68$; $p = 0.03$) had smaller volumes than BM-CTL (Figure 3B). However, these hippocampal changes were more pronounced under the P-tau181-based grouping than under P-tau217. Most results remained unchanged for the P-tau181-based clinical grouping after applying multiple testing correction for neuroimaging measures ($p = 0.05/24 = 2.00 \times 10^{-3}$), whereas in the P-tau217 based analysis, the BM + AD group remained significant.

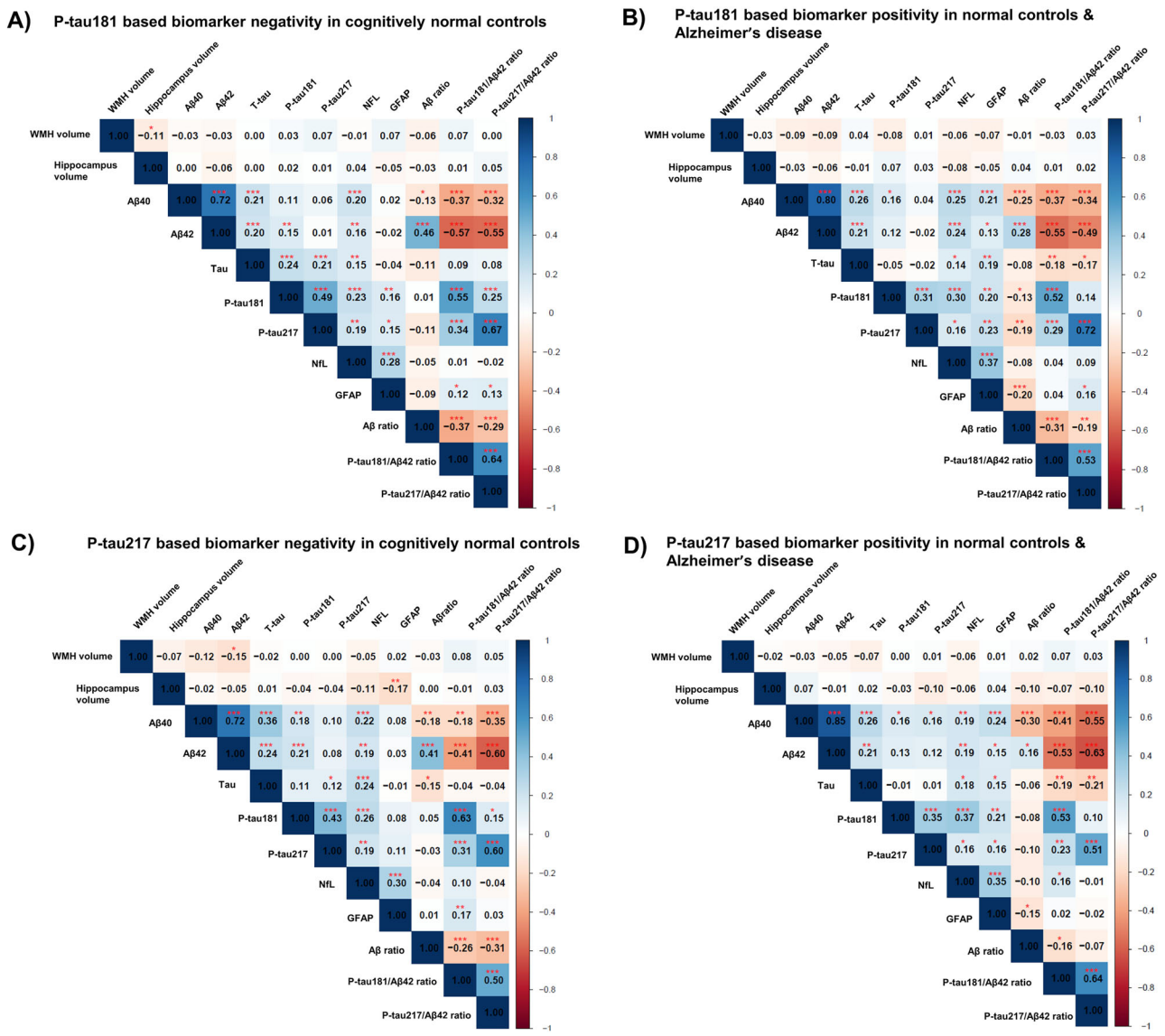

FIGURE 1: Correlation between plasma biomarkers and neuroimaging measures. Partial correlations are shown between plasma biomarkers and magnetic resonance imaging phenotypes, including white matter hyperintensity (WMH) volume and hippocampal volume. (A, B) Correlations for groups defined by tau phosphorylated at threonine 181 (P-tau181): (A) biomarker-negative cognitively normal controls (BM-CTL), and (B) biomarker-positive controls (BM + CTL) combined with Alzheimer's disease cases (BM + AD). (C, D) Corresponding correlations for groups defined by tau phosphorylated at threonine 217 (P-tau217): (C) BM-CTL and (D) BM + CTL + BM + AD. Plasma biomarkers include Aβ40, Aβ42, total tau (T-tau), P-tau181, P-tau217, neurofilament light (NfL), glial fibrillary acidic protein (GFAP), Aβ42/40 ratio, P-tau181/Aβ42 ratio, and P-tau217/Aβ42 ratio. WMH and hippocampal volumes were adjusted for age, sex, ethnicity, intracranial volume, and magnetic field strength. Plasma biomarkers were adjusted for age, sex, and ethnicity. The heatmap color scale indicates the correlation coefficient (r), ranging from −1 to +1. The red asterisks within each box denote significant correlations (*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$).

NfL and GFAP Levels Increase in Relation to BM + CTL and BM + AD

Not unexpectedly, NfL and GFAP levels differed across the P-tau181-based clinical groups (Figure 2C, D). BM + CTL ($F = 155.34$; $p = 1.01 \times 10^{-31}$), BM-Dem ($F = 10.50$; $p = 1.31 \times 10^{-3}$), and BM + AD ($F = 101.82$; $p = 3.09 \times 10^{-21}$) groups had increased NfL levels compared with BM-CTL (Figure 2C). Likewise, BM + CTL ($F = 6.68$; $p = 0.01$) and BM + AD ($F = 11.05$; $p = 1.48 \times 10^{-3}$) had higher NfL levels compared with individuals in the BM-Dem group (Figure 2C). In the P-tau217 based diagnostic groups, BM + AD ($F = 34.46$; $p = 1.10 \times 10^{-8}$), BM-Dem ($F = 5.74$; $p = 0.17$), and BM + CTL ($F = 71.57$; $p = 3.55 \times 10^{-16}$) showed higher levels of NfL compared with BM-CTL (Figure 3C). BM + AD ($F = 4.08$;

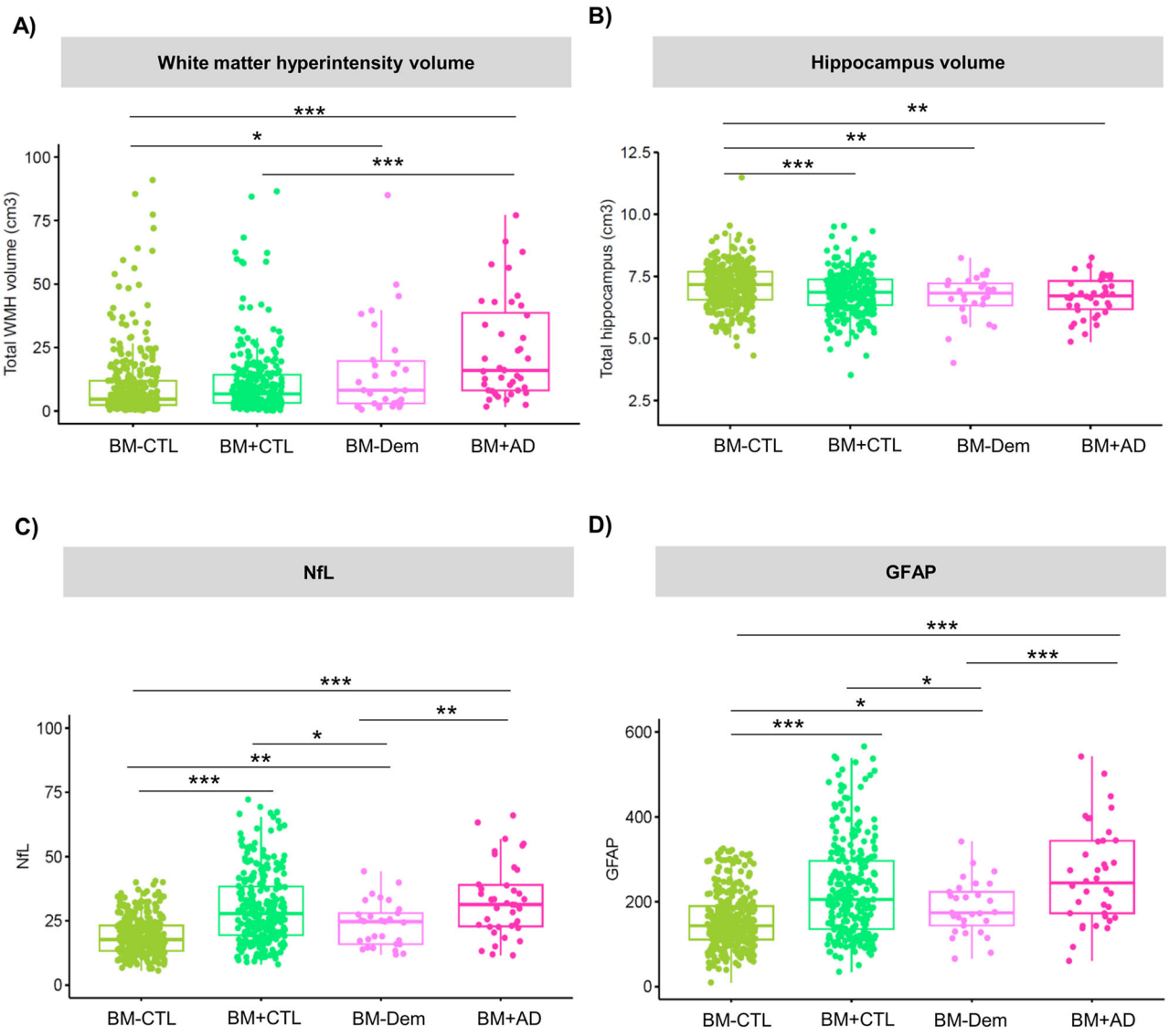

FIGURE 2: Comparison of neuroimaging measures and plasma biomarkers across clinical groups defined by P-tau181. Blood biomarkers and magnetic resonance imaging phenotypes including total white matter hyperintensities (WMH) and hippocampal volume were compared across different clinical groups stratified by tau phosphorylated at threonine 181 biomarker status. (A) Total WMH volume, (B) total hippocampal volume, (C) neurofilament light (NfL), and (D) glial fibrillary acidic protein (GFAP) association significance levels are shown above each comparison group (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). The boxplot shows the median, interquartile range (IQR), and the range of values from the smallest to the largest that do not exceed 1.5-fold the IQR.

$p = 0.04$) also had higher levels of NfL compared with BM-Dem (Figure 3C).

Compared with BM-CTL, BM + CTL individuals ($F = 93.67$; $p = 1.24 \times 10^{-20}$), BM-Dem ($F = 5.85$; $p = 0.02$), and BM + AD ($F = 80.57$; $p = 1.55 \times 10^{-17}$) had increased GFAP levels (Figure 2D). Compared with BM-Dem, GFAP levels were increased in BM + CTL ($F = 4.07$; $p = 0.04$) and BM + AD ($F = 13.05$; $p = 6.10 \times 10^{-4}$; Figure 2D). Likewise, within the P-tau217 based clinical groups, BM + AD ($F = 47.61$; $p = 2.87 \times 10^{-11}$) and BM + CTL ($F = 51.92$; $p = 2.36 \times 10^{-12}$) showed higher GFAP levels than BM-CTL (Figure 3D). Furthermore, BM + AD had significantly greater GFAP than BM-Dem ($F = 18.48$; $p = 8.37 \times 10^{-5}$), and BM + CTL ($F = 5.77$; $p = 0.02$) also exceeded BM-Dem (Figure 3D). Overall, both P-tau181- and P-tau217-based classifications capture alterations in NfL and GFAP levels. Almost all the analysis remained significant after multiple corrections for NfL and GFAP ($p = 0.05/24 = 2.00 \times 10^{-3}$).

Among the P-tau181-based clinical groups, the frequencies of silent brain infarcts in the BM + CTL (42.6%) and BM + AD (56.41%) groups were significantly higher than in the BM-CTL (32.36%) and BM-

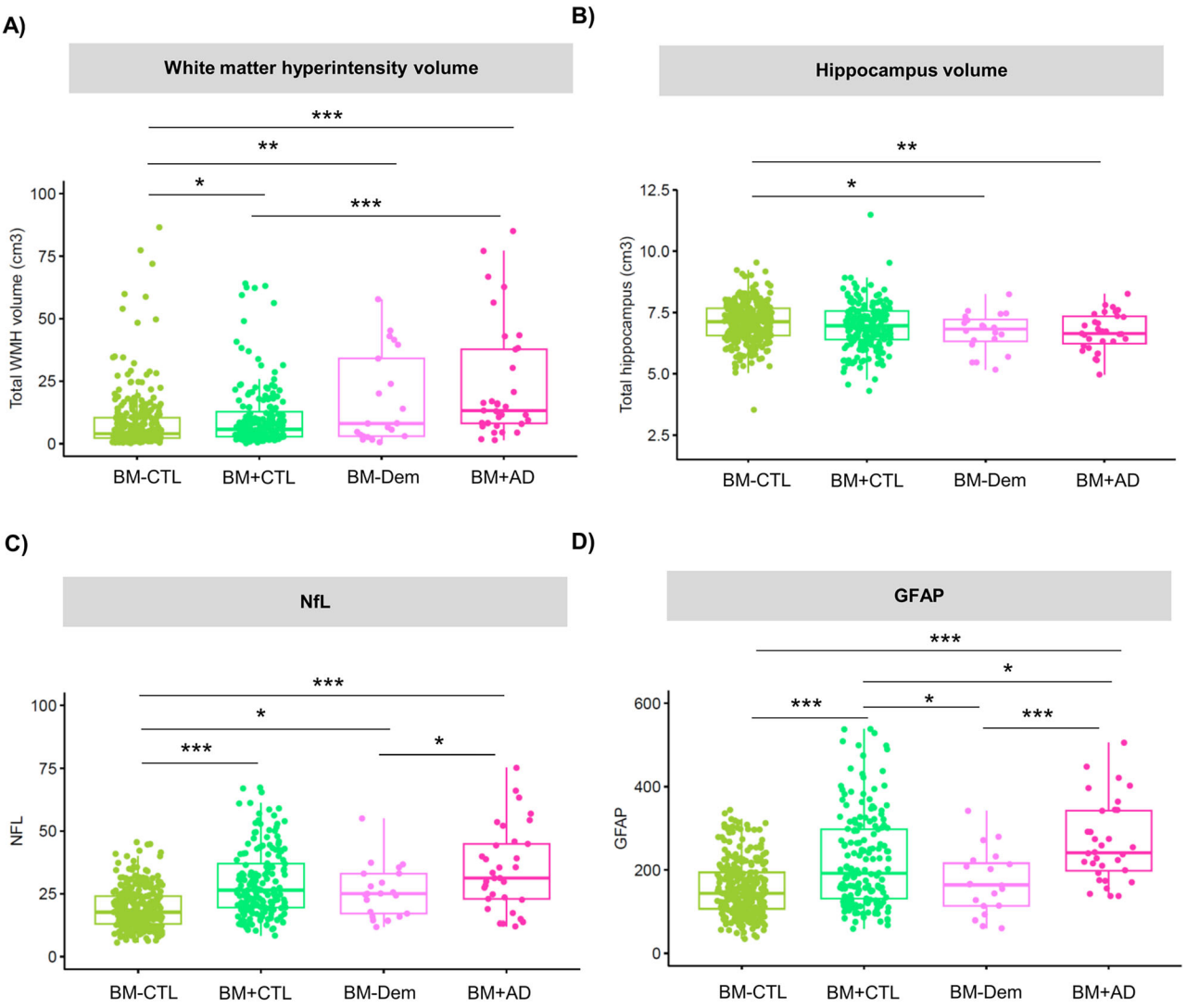

FIGURE 3: Comparison of neuroimaging measures and plasma biomarkers across clinical groups defined by tau phosphorylated at threonine 217 (P-tau217). Blood biomarkers and magnetic resonance imaging phenotypes including total white matter hyperintensities (WMH) and hippocampal volume were compared across different clinical groups stratified by P-tau217 biomarker status. (A) Total WMH volume, (B) total hippocampal volume, (C) neurofilament light (NfL), and (D) glial fibrillary acidic protein (GFAP) association significance levels are shown above each comparison group (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). The boxplot shows the median, interquartile range (IQR), and the range of values from the smallest to the largest that do not exceed 1.5-fold the IQR.

Dem (37.93%) groups (Figure S7A). Furthermore, the frequency of silent brain infarcts was highest among BM + AD ($\beta = 0.23$; $p = 9.51 \times 10^{-3}$) and BM + CTL ($\beta = 0.19$; $p = 0.03$) individuals (Figure S7A). The P-tau217-based clinical groups showed no significant differences in silent brain infarct frequencies, except for the BM-Dem group (50%; $\beta = 0.24$; $p = 0.03$), which was significantly higher than BM-CTL (38.25%; Figure S7C). These differences did not remain significant after multiple corrections ($p = 0.05/24 = 2.00 \times 10^{-3}$). There were also no significant differences in microhemorrhage frequencies across the 4 groups classified by either P-tau181 or P-tau217 (Figure S7B, D).

The association of *APOE-ε4* with MRI outcomes (WMH and hippocampal volume) and blood-based biomarkers (NfL, GFAP, Aβ40, Aβ42, T-tau, P-tau181, P-tau217, Aβ ratio, P-tau181/Aβ42 ratio, and P-tau217/Aβ42 ratio) was also evaluated (Figure S8A–L). Among these, *APOE-ε4* was associated with lower levels of plasma Aβ40 (Figure S8E; $F = 4.275$; $p = 0.04$), higher levels of P-tau217 (Figure S8I; $F = 6.89$; $p = 0.009$), and higher levels of P-tau217/Aβ42 ratio (Figure S8L; $F = 9.52$; $p = 0.002$) compared with non-*APOE-ε4* carriers.

Additionally, we examined the association across biomarker groups classified as P-tau181-positive and -negative among *APOE-ε4* carrier and non-carriers.

WMH volume was significantly higher in *APOE* non-ε4 (BM+) compared with *APOE* non-ε4 (BM−; $F = 4.83$; $p = 0.03$; Figure S9A). WMHs showed a trend toward larger volume in *APOE*-ε4 (BM+) compared with *APOE*-ε4 (BM−), but no significant association was found due to the small sample size. Similarly, hippocampal volume was significantly smaller in *APOE* non-ε4 (BM+) compared with *APOE* non-ε4 (BM−; $F = 9.65$; $p = 2.0 \times 10^{-3}$). Furthermore, hippocampal volume was also significantly reduced in *APOE* non-ε4 (BM+) compared with *APOE*-ε4 (BM−; $F = 6.804$; $p = 9.55 \times 10^{-3}$; Figure S9B). In the biomarker group classified by P-tau217-positive and -negative, and stratified by *APOE*-ε4 carrier and non-carriers, *APOE*-ε4 (BM+; $F = 4.79$; $p = 0.03$) and *APOE* non-ε4 (BM+; $F = 8.9$; $p = 3.19 \times 10^{-3}$) had larger WMH volume compared with *APOE*-ε4 (BM−; Figure S10A). As observed in Figures 2A and 3A, the WMH volume was better defined when based on P-tau217 rather than with P-tau181. However, the hippocampal volume showed no significant changes across the P-tau217 based grouping, which contrasted with P-tau181 based grouping (Figure S10B).

Similarly, in both P-tau181- and P-tau217-based grouping, higher NfL and GFAP levels were associated with *APOE*-ε4 (BM+; $p < 0.05$) carriers and *APOE* non-ε4 (BM+; $p < 0.05$) carriers compared with *APOE*-ε4 (BM−) and *APOE* non-ε4 (BM−) groups (Figures S9C, D, and S10C, D).

Differences by Ethnic Group With Respect to P-tau181 and P-tau217

Although non-Hispanic white, African American, and Caribbean Hispanic individuals showed differences in structural MRI brain measures across BM-CTL, BM + CTL, BM-Dem, and BM + AD groups classified by P-tau181, only the Caribbean Hispanic and African American groups showed statistically significant differences in the WMH (Figure S11A–C). Only the Caribbean Hispanic group showed differences in the hippocampal volume across the BM-CTL, BM + CTL, BM-Dem, and BM + AD groups, as well (Figure S11D–F).

In the groups classified by P-tau217, the African American group showed statistically significant differences in the WMH volume across BM + CTL, BM-Dem, and BM + AD groups. Additionally, the BM + AD group in the Caribbean Hispanic individuals and Non-Hispanic white individuals showed larger WMH volume compared with BM-CTL (Figure S14A–C). However, no significant differences were found for hippocampal volume across the clinical group in any of the ethnic groups (Figure S14D, F).

Among the P-tau181-based clinical groups, the levels of NfL and GFAP were elevated in BM + AD and BM + CTL ($p < 0.05$) across all 3 ethnic groups compared with BM-CTL. Interestingly, BM + AD showed a strong association with elevated levels of NfL in non-Hispanic white and Caribbean Hispanic individuals, but only a moderate association was found in African American ($p = 0.01$) individuals compared with BM-CTL (Figure S12A–C). Increased GFAP levels were associated with BM + AD across all 3 ethnic groups compared with BM-CTL. Similarly, elevated GFAP levels are associated with BM + CTL compared with BM-CTL (Figure S12D–F). In the P-tau217-based clinical groups, higher levels of NfL and GFAP were observed consistently across all ethnic groups; specifically, BM + AD and BM + CTL had significantly higher levels compared with BM-CTL ($p < 0.05$; Figure S15).

In the P-tau181-based clinical grouping, the frequency of brain infarcts was higher in BM + AD than in BM-CTL, with African American ($\beta = 0.35$; $p = 0.02$) and Caribbean Hispanic individuals ($\beta = 0.30$; $p = 0.02$) showing significant differences. Additionally, silent brain infarcts were more frequent in the BM-Dem group among African American individuals ($\beta = 0.37$; $p = 0.03$) compared with BM-CTL, but no differences were found in non-Hispanic white individuals (Figure S13A–C). We found no significant differences in the frequency of microhemorrhages in any of the 4 groups, but attributed this to the small sample size (Figure S13D–F). However, in the P-tau217-based clinical grouping, brain infarct and microhemorrhage frequencies did not differ significantly across any ethnicities among different clinical categories (Figure S16A–F).

We also evaluated ethnic differences within each P-tau181- and P-tau217-based clinical category for WMH burden and hippocampal volume. In the P-tau181-defined BM-CTL group, African American individuals had significantly larger WMH volumes than non-Hispanic white and Caribbean Hispanic individuals ($p < 0.05$). Similarly, within the P-tau217-defined BM-CTL group, both African American and Caribbean Hispanic individuals showed larger WMH volumes than non-Hispanic white individuals ($p < 0.05$). Among P-tau217-defined BM-AD participants, African American individuals showed larger WMH volumes than Caribbean Hispanic individuals ($p < 0.05$).

For hippocampal volume, in the P-tau181-defined BM + CTL group, African American and Caribbean Hispanic individuals had significantly smaller volumes than non-Hispanic white individuals ($p < 0.05$). Likewise, within the P-tau217-defined BM-CTL group, both African American and Caribbean Hispanic individuals showed smaller hippocampal volumes than non-Hispanic white individuals ($p < 0.05$). In the BM + AD group (regardless

of P-tau181 or P-tau217 stratification), no significant ethnic differences were observed for either WMHs or hippocampal volume.

Discussion

In this community-based study of older individuals living in northern Manhattan, New York, we investigated the MRI measures of cerebrovascular pathology and hippocampal volume in 4 groups defined by clinical measures and blood-based biomarkers for AD. Compared with BM-CTL, individuals characterized as BM + AD, BM + CTL, and BM-Dem had larger WMH volumes, more silent brain infarcts, and smaller hippocampal volumes. African American and Caribbean Hispanic individuals showed significant WMH differences across clinical groups, with only Caribbean Hispanic individuals showing substantial hippocampal volume changes. Across all ethnicities, the BM + AD and BM + CTL groups had elevated NfL and GFAP levels. Brain infarcts were more frequent in BM + AD among African American and Caribbean Hispanic individuals, with no significant differences noted for microhemorrhages. Ethnic-specific analyses suggested that associations between WMH or hippocampal volume and biomarker status may vary by ancestry. Interestingly, *APOE-ε4* was significantly associated with lower Aβ40 levels, higher P-tau217 levels, and increased P-tau217/Aβ 42 ratios, but no other biomarkers showed significant associations with the *APOE-ε4* genotype. *APOE* non-ε4 carriers who were P-tau181 biomarker-positive (BM+) had larger WMH volumes and smaller hippocampal volumes compared with those who were P-tau181 biomarker-negative (BM−). Although *APOE-ε4* BM+ individuals tended to have larger WMH volumes than BM− individuals, this difference did not reach statistical significance. Similarly, both *APOE* ε-4 carriers and non-carriers who were P-tau217 biomarker-positive (BM+) had larger WMH volumes than P-tau217 biomarker-negative (BM−) participants, suggesting that P-tau217 may be more sensitive to WMH volumes. However, in contrast to P-tau181, *APOE-ε4* carriers and non-carriers that were P-tau217 biomarker-positive (BM+) did not show significant differences in hippocampal volume with the BM-group. This suggests that P-tau181 may better reflect hippocampal atrophy than P-tau217, although the smaller sample size in the P-tau217 group should be taken into consideration. As differences are observed in both *APOE-ε4* carriers and non-carriers, these findings suggest that changes in WMH and hippocampal volumes are more closely linked to disease-stage biomarker elevation and not *APOE-ε4* status alone. In addition, higher levels of NfL and GFAP were observed in both P-tau181- and P-tau217-positive individuals, regardless of their *APOE-ε4* carrier status.

WMH are known to increase dramatically with age, even among individuals without dementia.[46] Since the initial descriptions of "leukoaraiosis," WMH were presumed to represent small vessel ischemic injury. They are associated with pre-existing comorbidities, such as hypertension and diabetes, as well as cognitive impairment and stroke. However, WMH may also reflect demyelination and axonal degeneration,[47] and are also associated with cerebral amyloid angiopathy[48,49] and neurodegeneration within the parenchyma.[50] It has been suggested that WMH on brain MRI represent vascular- and non-vascular-related effects associated with aging and dementia,[51,52] but this point remains controversial.[53] Postmortem studies indicate that WMH are related to myelin loss, gliosis, and small infarcts.[54,55] Individuals with dementia who were biomarker-negative showed increased WMH volumes compared with cognitively normal individuals. Despite the lack of biomarker positivity, this elevated WMH volume in dementia is likely attributed to the presence of cerebrovascular disease. The increased frequency of silent brain infarcts in the combined BM + CTL and BM + AD groups might suggest a vascular etiology of the WMH.

Comorbid diseases are also associated with AD and lead to cerebrovascular disease,[56] including hypertension (55.1%), diabetes (25.7%), and cardiovascular disease (22.7%).[57] Several recent studies suggest that both type 2 diabetes and hypertension are the leading risk factors for WMH among the aging population, and for stroke and dementia.[45,58–60] Diabetes affects millions worldwide,[56] and is a risk factor for AD[61,62] and vascular dementia, and causes alterations in insulin resistance, which disrupt amyloid metabolism, insulin signaling, and cause inflammation.[63] Hypertension is also associated with AD,[64] especially in middle age, resulting in ischemic small vessel disease, arterial stiffness, stroke, and endothelial dysfunction.[65] African American and Hispanic individuals also have a higher frequency of diabetes,[57,66–68] obesity, and metabolic syndrome.[69–74] In our cohort, hypertension (90%) and diabetes (30%) were highly prevalent among individuals with AD. In this study, we found that hypertension was significantly associated with WMH ($F = 6.15$; $p = 0.01$), and the frequency of diabetes was higher among African American (33.18%) and Hispanic individuals (42.14%) compared to non-Hispanic white individuals (17.64%). Along with comorbidities, some factors, such as hypertension and antihypertensives, alcohol, body mass index, and renal disease can directly alter P-tau levels.[10,71,75–77]

Among blood-based biomarkers, P-tau181 and P-tau217 are both strongly associated with amyloidosis

and AD. Elevated levels of P-tau181 and P-tau217 are considered reliable and valid biomarkers for detecting AD pathology and monitoring disease progression.[40,78,79] P-tau181 and P-tau217 are both associated with progression to AD among individuals with MCI.[22,76] Although associated with progressive changes in memory and cognition, P-tau181 and P-tau217 are also correlated with reduced hippocampal volume and increased WMH volume in the Alzheimer's Disease Neuroimaging Initiative cohort[80,81] and in a previous investigation in WHICAP.[82] Consistent with these previous studies, we found that not only WMH volume, but also hippocampal volume and silent brain infarcts were associated with both P-tau181 and P-tau217 levels. Unique to other studies, WHICAP includes individuals of Caribbean Hispanic and African ancestry.

We observed strong associations between P-tau181 and P-tau217, GFAP, and NfL. These biomarkers have been investigated in both cerebrospinal fluid and plasma, and have been used for establishing diagnoses and monitoring disease progression.[83–86] Although GFAP and NfL are non-specific biomarkers reflecting damage to the brain and spinal cord, they are strongly related to neurodegeneration and, therefore, useful in assessing disease progression.

Our study did have limitations. The number of individuals in the BM + AD and BM-Dem diagnostic groups were small. P-tau181 is an excellent blood-based biomarker, but P-tau217 appears to have better sensitivity and specificity.[23,87–89] We found these 2 measures of P-tau were strongly correlated. Nevertheless, we consider the relationships between P-tau181 and P-tau217, the other blood-based biomarkers, and the imaging findings to be clinically important, and will be maintained with other P-tau biomarkers.

Taken together, these results suggest that combining MRI imaging with blood-based biomarkers offers clarity regarding the existence of cerebrovascular copathologies in AD. In addition, if we assume the BM + CTL reflects the preclinical stage of AD, then cerebrovascular pathology may appear very early in the development of AD. The presence of cerebrovascular disease among individuals with other forms of dementia is not unexpected. In a large study including postmortem data of individuals with dementia, the frequency of participants with a predominate vascular cause for dementia in the absence of AD or other neurodegenerative disorders was 20.9%.[90] The results presented here are consistent with these findings, indicating that cerebrovascular pathology can be the underlying pathology coincident to AD or independent of AD. In addition, the results here also indicate that small vessel disease is a frequent copathology in AD, and strongly associated with the key biomarkers for this disease, P-tau181 and P-tau217, GFAP, and NfL.

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Author Contributions

Tamil Iniyan Gunasekaran: Formal analysis; investigation; data curation; visualization. **Danurys Sanchez:** Investigation; methodology. **Dolly Reyes-Dumeyer:** Investigation; methodology. **Rabel Ventura:** Investigation; methodology. **Clarissa Morales:** Investigation; methodology. **Mohamad Alshikho:** Investigation; methodology. **Annie J. Lee:** Investigation; methodology. **Rafael A. Lantigua:** Investigation; methodology; writing – review and editing. **Yian Gu:** Investigation; methodology; formal analysis. **Lawrence S. Honig:** Methodology; writing – review and editing; formal analysis; investigation; data curation. **Badri N. Vardarajan:** Conceptualization; supervision; writing – original draft; writing – review and editing; investigation; methodology; formal analysis. **Adam M. Brickman:** Conceptualization; investigation; writing – original draft; validation; methodology; formal analysis; supervision. **Richard Mayeux:** Conceptualization; investigation; funding acquisition; writing – original draft; writing – review and editing; validation; project administration; data curation; supervision; resources.

Potential Conflicts of Interest

A.M.B. is an inventor of a patent for white matter hyperintensity quantification that was used in this study (US Patent US9867566B2). The other authors have nothing to report.

Data Availability

The WHICAP is a community-based longitudinal study, recruiting older adult participants from Northern Manhattan. Cohorts were established in 1992, 1999, and 2009. Participants are evaluated every 18–24 months. The cohort has clinical data, blood-based biomarkers, genome-wide array and genome sequencing, and brain MRI. This web survey includes fields for all of the items needed for a proposal to be reviewed by the Publications committee. Please complete and submit the form. Questions can be sent to Richard Mayeux (rpm2@columbia.edu) or Jennifer

Manly (jjm71@columbia.edu). IRB approval is required for proposed analyses, and a Data Use Agreement or Material Transfer agreement may need to be obtained.

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