RESEARCH ARTICLE

Association of Plasma Biomarkers With Longitudinal Atrophy and Microvascular Burden on MRI Across Neurodegenerative and Cerebrovascular Diseases

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Abstract

Background and Objectives

Plasma biomarkers of Alzheimer disease (AD), neuroinflammation, and neurodegeneration are increasingly being used in clinical trials for diagnosis and monitoring of dementia. However, their association with longitudinal structural brain MRI changes, an important outcome measure across neurodegenerative and cerebrovascular diseases, is less known. We investigated how baseline plasma biomarkers reflect MRI markers of progression over time in patients with neurodegenerative and cerebrovascular diseases.

Methods

This longitudinal cohort study included patients from the Ontario Neurodegenerative Disease Research Initiative diagnosed with AD or mild cognitive impairment (AD/MCI), Parkinson disease (PD), frontotemporal dementia spectrum disorders (FTD), or cerebrovascular disease (CVD), followed annually for 2 years. Recruitment took place at specialized university-based

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Glossary

AD = Alzheimer disease; ***APOE*** = apolipoprotein E; **CAA** = cerebral amyloid angiopathy; **CIHR** = Canadian Institutes of Health Research; **CVD** = cerebrovascular disease; **FLAIR** = fluid attenuated inversion recovery; **FTD** = frontotemporal dementia spectrum disorder; **GFAP** = glial fibrillary acidic protein; **HC** = healthy control; ***MAPT*** = microtubule-associated protein tau; **MCI** = mild cognitive impairment; **NfL** = neurofilament light chain; **ONDRI** = Ontario Neurodegenerative Disease Research Initiative; **PD** = Parkinson disease; **p-tau181** = phosphorylated tau181; **p-tau217** = phosphorylated tau217; **PVS** = perivascular space; **SABRE-LE** = SABRE-Lesion Explorer; **WMH** = white matter hyperintensity.

dementia, movement disorders, and/or stroke clinics in the province of ON, Canada. MRI outcomes included markers of cerebral atrophy (ventricular CSF and regional gray matter volumes) and of small vessel disease pathology (white matter hyperintensity [WMH], perivascular spaces, and lacunar volumes). Hemorrhagic markers at baseline were also included. Plasma levels of glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), phosphorylated tau181 and tau217 (p-tau181, p-tau217), and β-amyloid ($A\beta_{42/40}$) were quantified from blood samples collected at baseline using Simoa and used as predictors in linear mixed models adjusted for time (months), age, sex, apolipoprotein E (*APOE*)-ε4 carrier status, kidney function, vascular risk factors, microtubule-associated protein tau (*MAPT*) diplotypes, waist-hip circumference ratio, and disease duration.

Results

We analyzed 1,240 MRIs from 473 patients (age: 69.2 ± 7.4 [range: 49–87]; 32.8% women). Elevated baseline levels of GFAP, NfL, p-tau181, and p-tau217, and to a lesser extent decreased levels of $A\beta_{42/40}$, were significantly associated with more cerebral atrophy and WMH burden at baseline ($|B|$ = 0.02 to 1.69, p = 0.044 to <0.001) and with progression over time ($|B|$ = 0.001 to 0.028, p = 0.049 to <0.001) in the pooled disease-agnostic group. Within disease-specific cohorts, GFAP and NfL were associated with cerebral atrophy and/or small vessel disease copathology in AD/MCI, PD, FTD, or CVD. P-tau181 and p-tau217 were associated with cerebral atrophy and/or small vessel disease copathology in AD/MCI, CVD, PD-MCI, or PD-dementia.

Discussion

Selected plasma biomarkers seem useful as prognosis and monitoring tools of longitudinal imaging changes within real-world populations of neurodegenerative and/or cerebrovascular diseases, and provide insight into overlap across diseases in shared pathologic burden.

Introduction

With the advent of ultra-sensitive blood-based immunoassays capable of quantifying novel plasma biomarkers, we have a scalable way to measure potent markers of neurodegeneration, neuroinflammation, and Alzheimer disease (AD) pathology.[1] Commonly studied plasma biomarkers include glial fibrillary acidic protein (GFAP; a marker of astrogliosis),[2] neurofilament light chain (NfL; a marker of neuroaxonal injury),[3] and phosphorylated tau181 and tau217 (p-tau181 and p-tau217; markers of tau pathology and amyloid burden), which reflect diverse pathologic processes present in AD and in other common neurodegenerative diseases.[4] Plasma β-amyloid (commonly $A\beta_{42/40}$ ratio) is another marker of amyloid burden, although it has several limitations and proves more useful in presymptomatic at-risk individuals.[5-7]

Some of these plasma biomarkers have high potential to eventually be widely adopted in clinical settings and are already being used in clinical trials. In fact, many have shown that they have promise in distinguishing AD from other neurodegenerative diseases and in identifying clinical disease stages to some extent.[8-14] We have recently shown how these plasma biomarkers relate to cognitive function, cognitive decline, and functional independence across neurodegenerative and cerebrovascular diseases.[15] These advances become increasingly relevant with an aging global population and emerging therapies. Plasma biomarkers are being recognized as important markers of neurodegenerative risk, diagnosis, and prognosis, as well as potentially for monitoring responses to drugs and also of theragnostic value.[16]

However, our knowledge is still lacking about how plasma biomarker levels relate to the state and progression of neurodegeneration and small vessel disease burden as measured by MRI. To gain insights into underlying pathology and to support the implementation of plasma biomarkers as tools for prognosis and monitoring, it is critical to better understand how they reflect cerebral atrophy—both global and regional, which are integral to most neurodegenerative diseases, and which are usually assessed by ventricular expansion and volume of gray matter. We also have to better understand how plasma biomarkers reflect small vessel disease pathology, which is often observed in the pathologic aging brain,[17-19] and which can be assessed by white matter hyperintensities (WMHs), enlarged perivascular spaces (PVSs), and lacunes.[20]

As these processes contributing to dementia and movement disorders are not unique to a specific disease, it is important to expand the focus from only a single disease, often AD, to include other common diseases associated with dementia, such as Parkinson disease (PD), frontotemporal dementia spectrum disorders (FTD), and cerebrovascular disease (CVD). Furthermore, these diseases do not generally occur alone because copathologies are extremely frequent in late-onset sporadic dementia,[17,18,21,22] making mixed disease more common than not, and raising the importance of finding meaningful signals that reflect these underlying pathologies across diseases and within.

Concurrently studying multiple diseases is possible in the context of the Ontario Neurodegenerative Disease Research Initiative (ONDRI), through its longitudinal data produced by harmonized assessments across multiple disease cohorts, namely, AD, PD, FTD, and CVD. We aim here for a comprehensive investigation on the association of plasma biomarkers across and within these disease cohorts, with baseline and longitudinal MRI markers of cerebral atrophy, such as ventricular expansion and regional gray matter atrophy, in addition to MRI markers of small vessel disease pathology, such as WMH, PVS, and lacunes. We hypothesized that higher levels of GFAP and NfL would be associated with worsening neurodegeneration in general. We also hypothesized that higher levels of p-tau217 and p-tau181 would be more specific to the AD cohort, but since AD copathology is common across the spectrum of neurodegenerative diseases, especially in Parkinson-Lewy body disorders and CVD, that these biomarkers would also potentially be associated with neurodegeneration across diseases.

Methods

Participants

The ONDRI has been previously described, including recruitment criteria, assessment protocols, quality control procedures, and characteristics of the cohorts.[23-27] This study included AD/mild cognitive impairment (MCI), PD, FTD, and CVD participants from ONDRI, who had all met prevailing consensus diagnostic criteria for their disease at the time of recruitment.[28-35] Also included were β-amyloid PET–negative cognitively normal elderly healthy controls (HC) from the Brain-Eye Amyloid Memory study,[36] who were enrolled using the exact same harmonized assessments at baseline as participants from ONDRI, and who were included to serve as reference for plasma biomarker levels.

Recruitment of participants was accomplished through clinicians at tertiary clinics in 14 academic health centers across ON, Canada, between 2014 and 2017. Screening was performed applying diagnostic criteria by board-certified neurologists, geriatric psychiatrists, and geriatricians; MRI scans were also reviewed by a board-certified neuroradiologist to help identify supportive imaging features for diagnoses and to exclude incidental findings. Final baseline diagnoses for ONDRI participants were supported by clinical history, clinical examination, exclusionary blood work, and MRI, and were achieved by consensus review among relevant clinicians. Other key inclusion criteria included fluency in English, ≥8 years education, MoCA score of ≥18 (≥14 for FTD), having a reliable study partner, ability to walk, no other serious underlying disease, and no history of substance abuse.

The AD/MCI cohort included participants with typical AD, atypical AD, and single-domain or multidomain amnestic MCI presumed due to AD. Atypical AD was defined by (1) involvement of cognitive domains other than memory as the initial presentation or (2) shortly after an initial amnestic presentation, development of other symptoms to suggest a likely codiagnosis, that is, mixed disease, for example, visual hallucinations and parkinsonism suggest comorbid Lewy body pathology. The PD cohort included participants ranging from those who were cognitively intact to those with dementia (but none initially diagnosed with Lewy body dementia) and who all initially exhibited the typical motor syndrome responsive to levodopa. The FTD cohort included diagnoses of behavioral variant FTD, progressive supranuclear palsy, progressive nonfluent aphasia, semantic dementia, and corticobasal syndrome. The CVD cohort included participants with a mild or moderate ischemic stroke event at least 3 months before recruitment, confirmed by a neuroradiologist on CT or MRI; participants with history of cognitive impairment or dementia preceding the ischemic stroke event were not included.

All recruited participants underwent MRI, plasma biomarker, and genetic assessments at baseline visit, in addition to MRI assessments at 2 annual follow-up visits. The average interval between baseline and first annual MRI assessments was 12.0 ± 1.1 months (range: 7–16 months, 95% within 10–14 months), and the average interval between baseline and second annual MRI assessments was 24.2 ± 1.4 months (range: 18–31 months, 95% within 22–27 months).

Blood Collection, DNA, and Plasma Biomarkers

All participants had blood samples drawn at baseline visit by a LifeLabs Medical Laboratory Services location near their place of residence. Collection and storage of blood samples was performed according to standard operating procedures.[37] Samples were shipped on ice to the Ontario Brain Institute Biobank at Robarts Research Institute (Western University, Canada) and were not frozen before initial processing. DNA processing and genotyping have been previously described[38] and are detailed in eMethods. Blood samples for plasma biomarkers were processed within 24 hours for plasma isolation by centrifugation (2000 rpm, 15 minutes, and 4°C). Plasma samples were stored at −80°C until shipment to the Clinical Neurochemistry Laboratory (University of Gothenburg, Sweden) for quantification of plasma biomarkers (GFAP, NfL, p-tau181, p-tau217, $A\beta_{42}$, and $A\beta_{40}$) with ultra-sensitive single-molecule array (Simoa) immunoassays. Missing data for subthreshold concentrations were imputed using the functional lower limit of

quantification divided by 2; the $A\beta_{42/40}$ ratio was not calculated when either $A\beta_{42}$ or $A\beta_{40}$ samples were below the threshold. Detailed procedures are described in eMethods. All plasma biomarker levels were log-transformed because of skewness.

MRI Acquisition and Processing

Participants underwent 3T MRI assessments at baseline and at 2 annual follow-up visits. MRI scans were harmonized across sites using the Canadian Dementia Imaging Protocol[39] and the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards.[35] Phantom scans were acquired monthly at every site throughout the duration of the study to ensure scanner signal stability. The following sequences were performed on all participants: 3D T1-weighted (T1), T2-weighted fluid attenuated inversion recovery (FLAIR), interleaved T2-weighted and proton density (T2/PD), and T2*gradient recalled echo. The MRI protocol parameters, standardization procedures, and quality control procedures of the ONDRI neuroimaging platform have been described previously.[23,24] MRI quality was ensured by several automated conformance and quality assessment pipelines, in addition to manual evaluation by imaging scientists before image processing.

The SABRE-Lesion Explorer (SABRE-LE) semiautomated processing pipeline for volumetric quantification at the individual patient level used in this study has been thoroughly described previously.[23] This pipeline addresses many of the challenges resulting from the heterogeneity of neurodegenerative and cerebrovascular pathologies. Ventricular CSF volume, bilateral regional normal appearing gray matter volume (frontal, parietal, occipital, temporal, hippocampus, and basal ganglia/thalamus), WMH volume, PVS volume, and lacunar volume were all extracted using the SABRE-LE pipeline. Regional WMH volumes (deep, periventricular, and by lobe) were also extracted. Normal appearing gray matter volumes were corrected during processing for overestimation of gray matter due to cerebrovascular pathology or severe atrophy using coregistered PD/T2/FLAIR sequences. Ventricular CSF volume, normal appearing gray matter volumes, and WMH volume were head-size adjusted to account for individual variations in total intracranial volume, and are therefore expressed as percentages of total intracranial volume. WMH volume was further log-transformed because of skewness. PVS volume and lacunar volume were log-transformed (x + 1) because of skewness and the presence of zero-values among the data. Lesion counts of hemorrhagic MRI markers were obtained from the T2*gradient recalled echo sequences by a board-certified neurologist subspecialized in vascular cognitive impairment and confirmed by a research neuroradiologist (see eMethods).

Statistical Analyses

We assessed the association of imaging outcomes at baseline and over time with baseline levels of plasma biomarkers using linear mixed models. Imaging outcome variables of interest were markers of global cerebral atrophy (ventricular CSF volume), of regional gray matter atrophy (frontal, parietal, occipital, temporal, hippocampus, or basal ganglia/thalamus volumes), and of small vessel disease pathology (WMH volume, PVS volume, or lacunar volume). Predictors of interest were baseline levels of GFAP, NfL, p-tau181, or p-tau217. Covariates in all models included age, sex, apolipoprotein E (*APOE*) ε4 carrier status (presence of at least 1 ε4 allele; instead of dosage of ε4 alleles modeled continuously in eAppendix 1), time (defined as a continuous variable of months since initial visit, and included all available timepoints up to visit 3), and time X plasma biomarker interaction. Participant IDs were included as random effects. Several expanded sensitivity models each additionally adjusted for kidney function (estimated glomerular filtration rate, through the Chronic Kidney Disease Epidemiology Collaboration equation), vascular risk factors using a composite score (see eMethods), *MAPT* diplotypes (H1/H1, H1/H2, or H2/H2), waist-hip circumference ratio, or disease duration (from diagnosis; for patients with CVD, from most recent stroke event; or from CT/MRI confirmation when not precisely determinable).

All linear mixed models were first performed in a pooled disease-agnostic group regardless of primary diagnosis because of the value from this agnostic perspective despite the unbalanced number of diagnoses. Then, all linear mixed models were performed within each disease cohort separately. All tests were two-tailed, with a significance threshold of $p < 0.05$, and additional false discovery rate correction with the Benjamini-Hochberg procedure (q = 0.05) to control multiple comparisons for 10 models per plasma biomarker of interest. All statistical analyses were performed with Statistical Product and Service Solutions Statistics v29 (IBM, 2022).

Secondary Analyses

We performed exploratory analysis of disease interactions in the pooled disease-agnostic group by adding clinical diagnosis interaction terms (factor with 4 levels: AD/MCI, PD, FTD, and CVD) to the previous primary models.

Secondary analyses were also performed in selected subgroups. To explore the differences between cognitive subgroups within the PD cohort, the participants were classified according to the Movement Disorder Society Task Force Level II guidelines into those with cognitive impairment (PD-MCI or PD-dementia) and those cognitively unimpaired. To explore the contribution of WMH burden within the CVD cohort, the participants were classified by the rating scale on their clinical report form (none, mild to moderate, or extensive), adapted from the Fazekas rating scale,[40,41] and by median split according to quantitative WMH volume. For these secondary analyses, subgroups were first compared with *t* tests or χ^2, and interaction effects were then tested using linear mixed models including a classification X biomarker interaction term in addition to primary covariates. Interaction results are presented when interaction effects and at least one of the stratified effects are significant.

Finally, we also explored the association between imaging outcomes over time and plasma $A\beta_{42/40}$ or $A\beta_{42}$, similarly to the primary models. We further explored if plasma biomarkers were associated with specific regional distributions of WMH, by stratifying WMH volumes by deep and periventricular WMH, as well as by cerebral lobes, and repeating the primary linear mixed models.

Standard Protocol Approvals, Registrations, and Patient Consents

The ONDRI research protocol was approved by research ethics boards at all participating recruitment sites. Written and informed consent was provided by all participants before participation and in accordance with the Declaration of Helsinki.

Data Availability

All anonymized data sets from the ONDRI cohort are available by request from qualified researchers with Research Ethics Board approval through Brain-CODE.[42] Data sets relevant to this study are listed in eTable 1.

Results

Participant Characteristics

Forty-four HC and 473 participants with neurodegenerative and cerebrovascular diseases were included in this study, with comparable numbers in the AD/MCI, PD, and CVD cohorts, but a noticeably smaller FTD cohort. The extensive demographic and clinical characteristics of the ONDRI cohort have been described previously.[25] Key characteristics are given in Table 1. The age range across cohorts was 49–87 years old (AD/MCI: 53–87 years old; PD: 55–85 years old; FTD: 49–80 years old; CVD: 54–85 years old). Overall attrition stood at 11.4% at first follow-up, and 26.4% at second follow-up; there were no significant differences between those with (n = 419) or without (n = 54) at least 1 follow-up visit, for age, sex, plasma biomarker levels, or imaging outcomes ($|t|$ = 0.05 to 1.63; p = 0.103 to 0.962). Thirty-one patients (6.5%) were identified as having ≥2 hemorrhagic lesions (lobar intracerebral hemorrhage, lobar cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid hemorrhage): 11 AD/MCI (8.7%), 2 PD (1.4%), 3 FTD (5.7%), and 15 CVD (9.3%) patients. These patients were older (t = 3.34, p < 0.001) than the rest of the cohort, with no significant sex difference.

Plasma and Imaging Biomarkers

Descriptive statistics for plasma biomarkers are displayed in Figure 1. Relative to HC, GFAP levels were significantly elevated only in the AD/MCI cohort, while NfL levels were significantly elevated in all cohorts except for PD—although NfL levels were elevated in PD-MCI or PD-D patients (eAppendix 2). P-tau181 levels were significantly elevated in all cohorts, but the AD/MCI cohort still had noticeably higher average levels and range, while p-tau217 levels were significantly elevated only in the AD/MCI cohort. All plasma biomarkers were associated with age across the cohort: GFAP (r = 0.43, p < 0.001), NfL (r = 0.38, p < 0.001), p-tau181 (r = 0.17, p < 0.001), and p-tau217 (r = 0.32, p < 0.001). Women had higher levels of GFAP compared with men (t = 5.34, p < 0.001), and *APOE* ε4 carriers had higher levels of GFAP (t = 2.28, p = 0.023), p-tau181 (t = 4.99, p < 0.001), and p-tau217 (t = 7.25, p < 0.001) compared with noncarriers. Patients with ≥2 hemorrhagic lesions had higher levels of NfL (t = 2.64, p = 0.009), p-tau181 (t = 2.21, p = 0.028), and p-tau217 (t = 1.99, p = 0.047). Correlations were present between plasma biomarker levels (eTables 2–6).

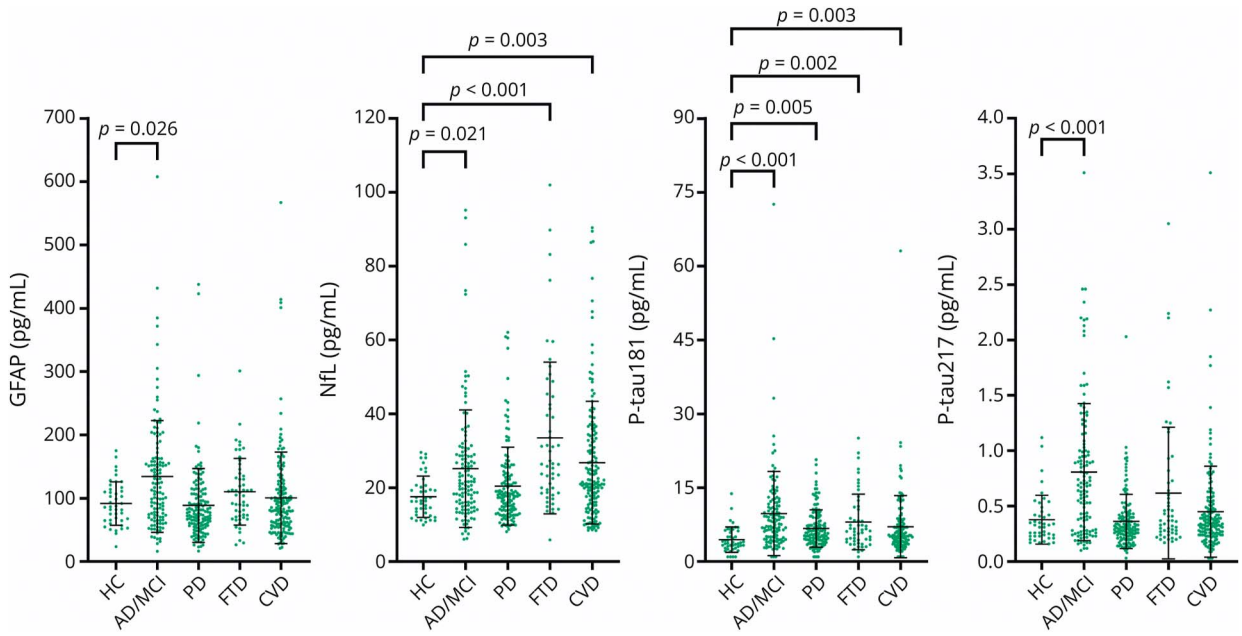
Baseline values and annualized rate of change for imaging outcomes in the pooled disease-agnostic group and within

Table 1 Descriptive Characteristics of the Sample at Baseline

	Pooled diseases	AD/MCI	PD	FTD	CVD	HC	η^2 or w
N at baseline	473	126	140	52	155	44	—
N at first follow-up	419	109	122	41	147	—	—
N at second follow-up	348	90	98	26	134	—	—
Age, y	69.2 (7.4)	71.0 (8.2)	67.9 (6.3)	67.8 (7.1)	69.3 (7.4)	66.7 (6.0)	η^2 = 0.036
Sex, % of women	32.8	45.2	22.1	36.5	31.0	75.6	w = 0.305
***APOE* ε4 carriers, %**	32.3	49.2	23.6	36.5	25.2	22.7	w = 0.230
Education, y	15.0 (2.9)	15.2 (3.1)	15.5 (2.7)	13.9 (2.7)	14.7 (2.9)	16.3 (2.0)	η^2 = 0.045
MoCA, total score	24.3 (3.4)	22.7 (3.0)	25.8 (2.6)	21.5 (4.0)	25.3 (3.0)	28.1 (1.4)	η^2 = 0.288
MDS-UPDRS, total score	—	—	46.5 (19.8)	—	—	—	—
mRS, score	—	—	—	—	1.0 (0.8)	—	—

Abbreviations: MDS-UPDRS = Movement Disorder Society–Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; mRS = Modified Rankin Scale.
Data are presented as mean (SD) when applicable. Effect sizes are for comparison between AD/MCI, PD, FTD, CVD, and HC.

Figure 1 Plasma Biomarker Levels by Cohort at Baseline



Mean and SD are represented as bars on the graphs. One-way analysis of variance with Tukey post hoc used to compare disease cohorts with HC were performed with log-transformed plasma biomarker values, but raw data are displayed here. For display purposes, few outliers were removed: in the AD/MCI cohort, 1 participant for GFAP (1,248 pg/mL), 1 for NfL (309 pg/mL), 2 for p-tau181 (113 pg/mL, 284.4 pg/mL), and 1 for p-tau217 (7.31 pg/mL); in the CVD cohort, 1 for NfL (179 pg/mL). AD = Alzheimer disease; GFAP = glial fibrillary acidic protein; MCI = mild cognitive impairment.

disease-specific cohorts are given in Table 2 for descriptive purposes. The regional distribution of WMH is given in eTable 7. Overall, ventricular volume increased and gray matter volumes decreased over time across all regions. WMH volume and lacunar volume also increased over time, while PVS volume generally decreased over time. For these latter cerebrovascular imaging outcomes, large interindividual variations were observed, both in baseline values and rate of change.

Association Between Imaging Outcomes Over Time and Baseline Plasma Biomarkers

Significant results for the pooled disease-agnostic group are displayed in Figure 2 and in eFigures 1–3. Higher levels of GFAP, NfL, p-tau181, and p-tau217 were all associated with higher ventricular volume at baseline and ventricular expansion over time. Higher levels of GFAP, NfL, and p-tau217 were associated with lower gray matter volumes at baseline and decline over time, while levels of p-tau181 were only associated with decline over time. Only higher levels of NfL were associated with higher WMH volume at baseline, but levels of GFAP, NfL, p-tau181, and p-tau217 were all associated with increasing WMH volume over time. Higher levels of NfL were also associated with higher lacunar volume at baseline, while higher levels of p-tau217 were associated with lower lacunar volume at baseline. Effects remained largely consistent when adjusted for kidney function, vascular risk factors, *MAPT* diplotypes, waist-hip circumference ratio, or disease duration in addition to primary covariates (eAppendix 1). To facilitate comparison between associations relative to each other, standardized effect sizes are displayed in Figure 3. Exploratory interactions by clinical diagnosis were also performed (eTable 8). Additional associations between $A\beta_{42/40}$ or $A\beta_{42}$ and imaging outcomes over time were also explored (eAppendices 3 and 4).

Effects Within Disease-Specific Cohorts

Significant results are displayed in Figure 4, A and B, for AD/MCI and PD cohorts, and in Figure 5, A and B, for the FTD and CVD cohorts. Overall, levels of GFAP and NfL were associated with cerebral atrophy or small vessel disease copathology imaging markers in patients with AD/MCI, PD, FTD, or CVD. Levels of p-tau181 and p-tau217 were associated with cerebral atrophy or small vessel disease copathology imaging markers in patients with AD/MCI or CVD, but also within the PD cohort in patients with PD-MCI or PD-dementia.

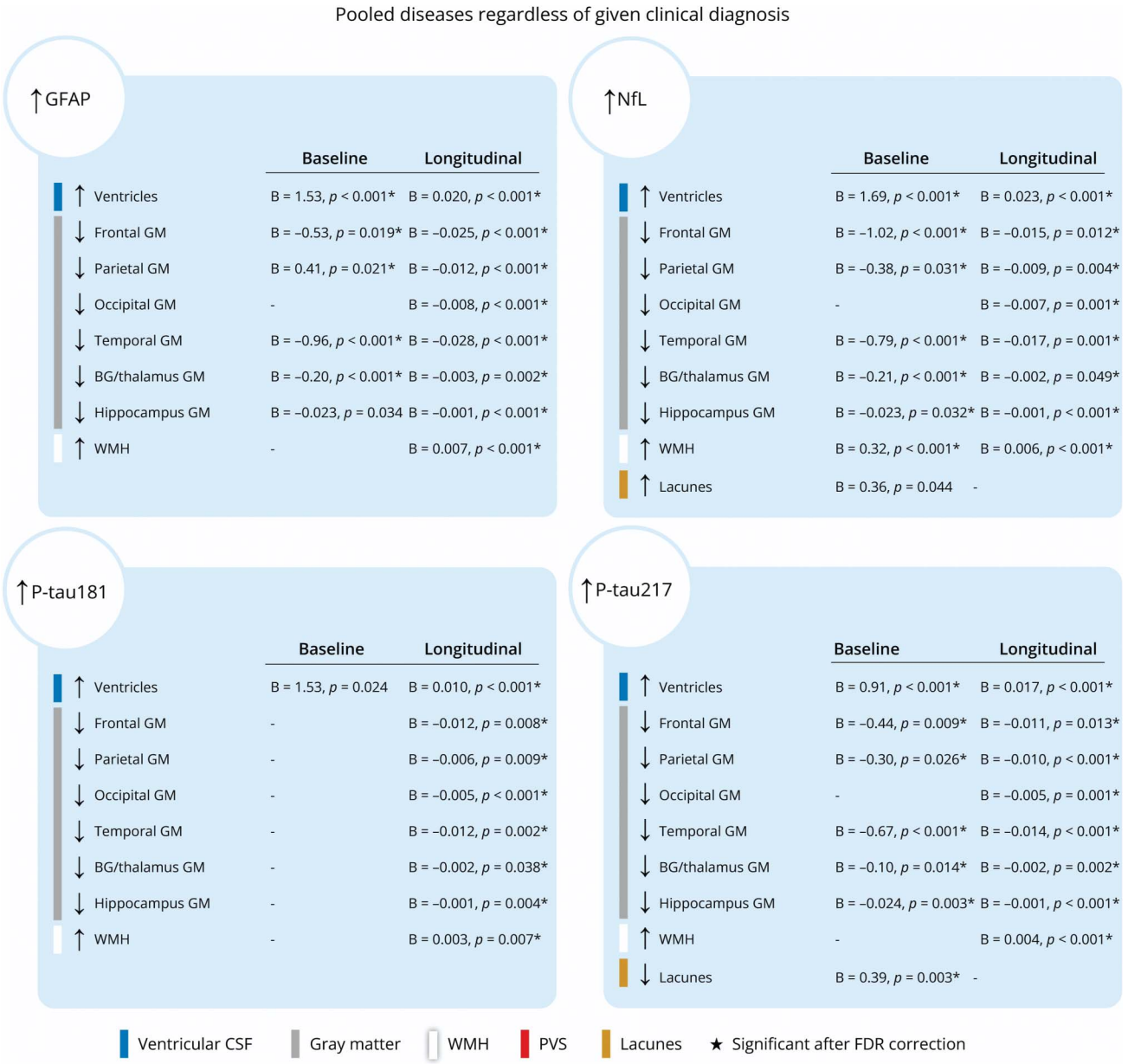
Differences and interactions found in the PD cohort with cognitive classification ranging from cognitively unimpaired to PD-MCI or PD-dementia (Movement Disorder Society Task Force Level II guidelines) are fully explored in eAppendix 2 using linear mixed models with a cognitive classification interaction term. Most notably, only in participants with PD-MCI or PD-D: higher levels of GFAP were associated with ventricular expansion over time (B = 0.015, p = 0.003), with decline in hippocampal gray matter volume over time (B = −0.001, p = 0.032), and with lower PVS volume at baseline (B = −0.52, p = 0.047); higher levels of p-tau217 were

Table 2 Imaging Outcomes at Baseline and Over Time

	Pooled diseases		AD/MCI		PD		FTD		CVD	
	Baseline	Annualized rate of change	Baseline	Annualized rate of change	Baseline	Annualized rate of change	Baseline	Annualized rate of change	Baseline	Annualized rate of change
Ventricles, % of TIV	3.28 (1.64)	0.18 (0.21)	3.60 (1.90)	0.24 (0.21)	2.88 (1.41)	0.11 (0.18)	3.50 (1.27)	0.39 (0.34)	3.32 (1.67)	0.12 (0.13)
Frontal gray matter, % of TIV	14.71 (1.25)	−0.09 (0.59)	14.71 (1.72)	−0.17 (1.10)	14.89 (0.90)	−0.01 (0.17)	14.14 (1.22)	−0.23 (0.29)	14.72 (1.03)	−0.04 (0.19)
Parietal gray matter, % of TIV	10.16 (0.97)	−0.08 (0.34)	10.19 (1.20)	−0.13 (0.61)	10.14 (0.81)	−0.03 (0.15)	9.95 (0.93)	−0.12 (0.20)	10.22 (0.91)	−0.06 (0.12)
Occipital gray matter, % of TIV	4.98 (0.56)	−0.02 (0.19)	5.00 (0.66)	−0.04 (0.33)	4.90 (0.44)	−0.00 (0.10)	5.14 (0.60)	−0.03 (0.11)	4.99 (0.55)	−0.01 (0.08)
Temporal gray matter, % of TIV	11.57 (1.16)	−0.12 (0.49)	11.48 (1.51)	−0.23 (0.91)	11.61 (0.88)	−0.04 (0.14)	10.98 (1.11)	−0.22 (0.21)	11.79 (1.00)	−0.07 (0.14)
BG/thalamus gray matter, % of TIV	1.76 (0.27)	−0.03 (0.08)	1.74 (0.29)	−0.05 (0.13)	1.83 (0.22)	−0.02 (0.06)	1.66 (0.25)	−0.06 (0.07)	1.76 (0.28)	−0.02 (0.05)
Hippocampus gray matter, % of TIV	0.39 (0.06)	−0.01 (0.02)	0.37 (0.07)	−0.01 (0.03)	0.40 (0.05)	−0.01 (0.01)	0.39 (0.05)	−0.01 (0.01)	0.41 (0.06)	−0.01 (0.01)
WMH, % of TIV	0.52 (0.72)	0.10 (0.17)	0.37 (0.40)	0.11 (0.17)	0.38 (0.44)	0.07 (0.12)	0.34 (0.37)	0.10 (0.11)	0.83 (1.05)	0.13 (0.21)
PVS, volume (mm^3)	64.21 (98.14)	−1.75 (33.45)	64.71 (87.01)	−0.21 (16.89)	52.71 (55.64)	−4.80 (32.59)	46.92 (42.67)	−3.15 (34.52)	79.99 (139.66)	0.09 (42.47)
Lacunes, volume (mm^3)	200.11 (515.93)	8.23 (102.94)	105.28 (237.20)	14.82 (75.42)	121.64 (348.79)	4.38 (60.93)	89.58 (252.28)	27.59 (70.98)	385.14 (766.65)	0.94 (148.14)

Abbreviations: BG = basal ganglia; PVS = perivascular space; TIV = total intracranial volume; WMH = white matter hyperintensity.
Data are presented as mean (SD). Gray matter values are bilateral normal appearing gray matter. Annualized rates of change are displayed only for descriptive purposes and are not used in the ulterior longitudinal linear mixed model analyses.

Figure 2 Significant Associations Between Plasma Biomarker Levels and Imaging Outcomes Across Diseases



Plasma biomarker levels were measured at baseline, and MRI were acquired annually over 3 visits. All imaging metrics represent volumetric data, with head-size adjustment when applicable. WMH volume, PVS volume, lacunar volume, and all plasma biomarkers were log transformed. Age, sex, *APOE* ε4 carrier status, and time (in months) since initial visit were accounted for in linear mixed models. -, nonsignificant. WMH = white matter hyperintensity.

associated with ventricular expansion over time (B = 0.012, p = 0.018) and with higher WMH volume at baseline (B = 0.43, p = 0.027); and lower levels of Aβ42/40 were associated with ventricular expansion over time (B = −0.031, p = 0.028).

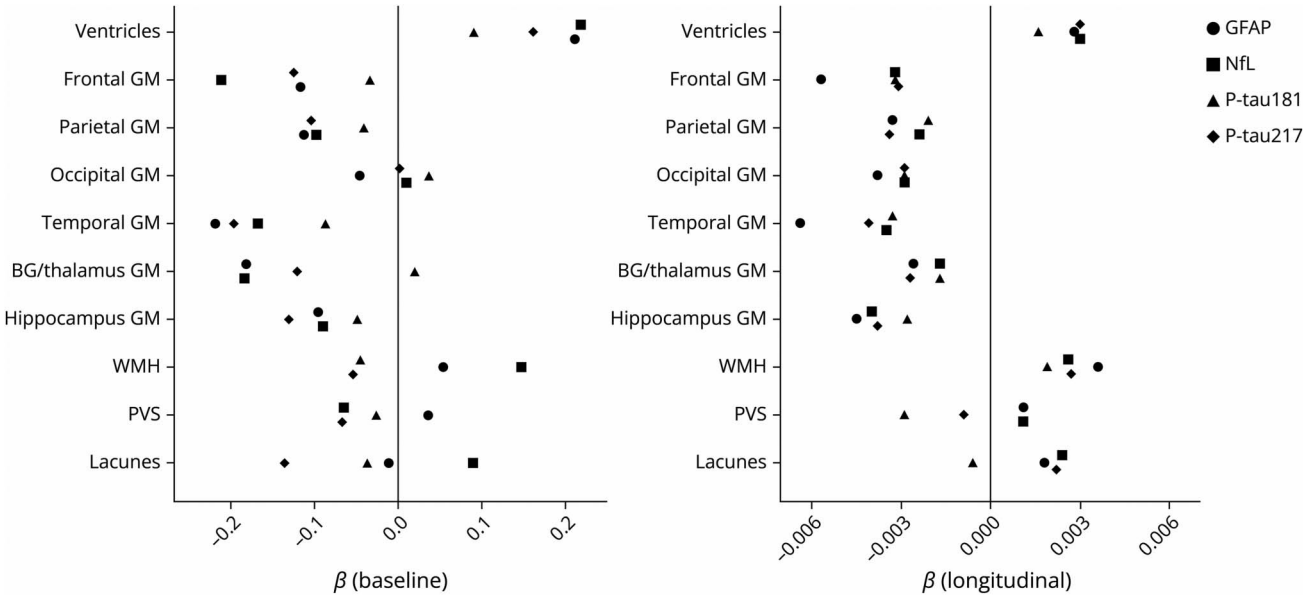
Differences and interactions found in the CVD cohort with WMH burden classification (using either quantitative volume [median split] or a visual rating scale) are fully explored as well in eAppendix 5.

When topologically stratifying WMH for all cohorts, several associations were found between levels of plasma biomarkers and periventricular WMH, but none with deep WMH; several associations were also found with specific regional distributions of WMH (eAppendices 6 and 7).

Discussion

Overall, we found many signals across diseases, that could contribute to the eventual implementation of plasma biomarkers beyond potential diagnostics and into prognosis and monitoring. This is especially in light of the current role of

Figure 3 Relative Standardized Effect Sizes Across Diseases

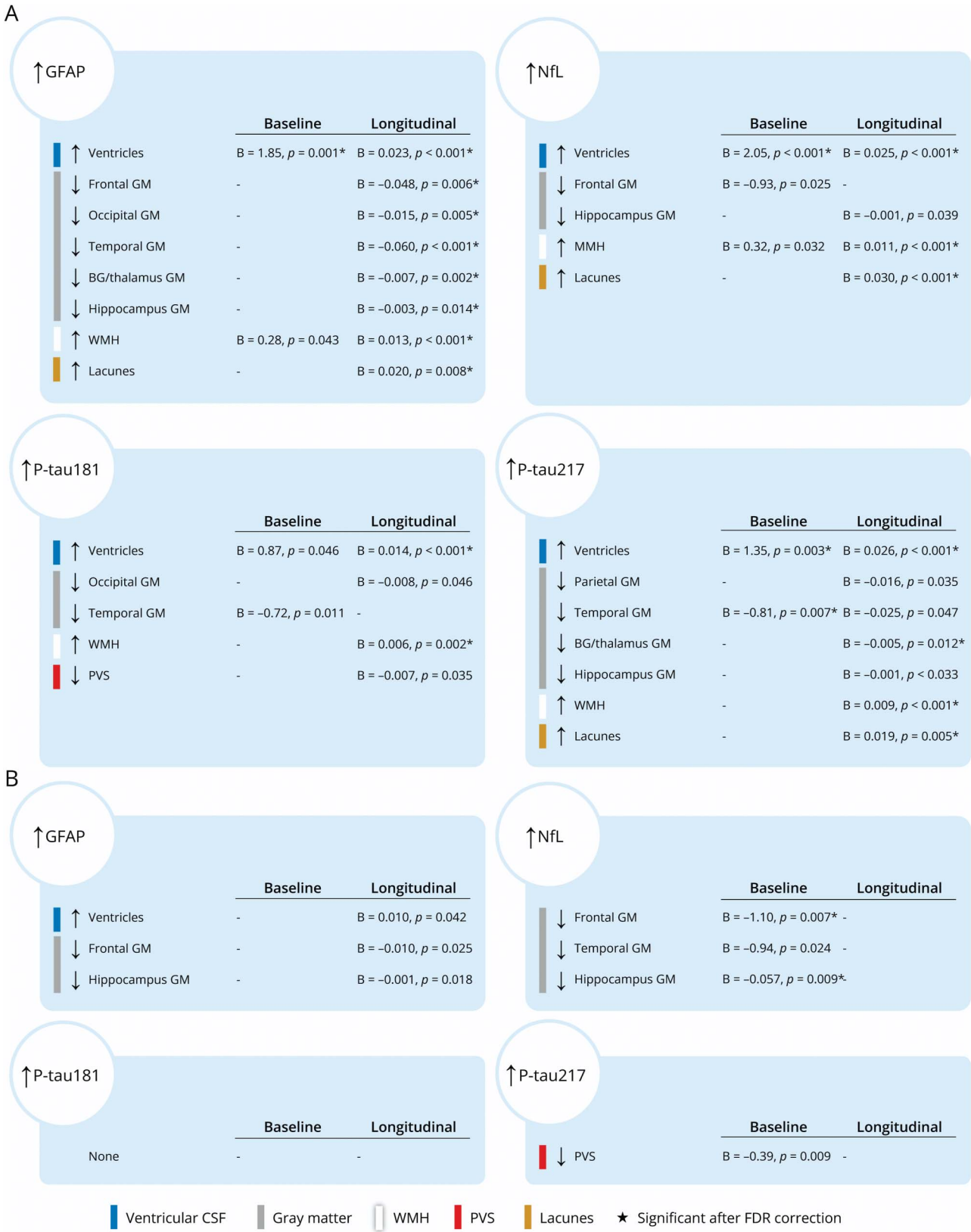


Plasma biomarker predictors and MRI outcomes were standardized before analysis for the purpose of this comparison. Plasma biomarker levels were measured at baseline, and MRI were acquired annually over 3 visits. All imaging metrics represent volumetric data, with head-size adjustment when applicable. WMH volume, PVS volume, lacunar volume, and all plasma biomarkers were log transformed. Age, sex, *APOE* ε4 carrier status, and time (in months) since initial visit were accounted for in linear mixed models. WMH = white matter hyperintensity.

brain MRI in neurodegenerative diseases as an important diagnostic tool and outcome measure. This study is critical to better understand whether and how blood-based biomarkers reflect MRI markers of progression over time in real-world patient populations diagnosed with late-onset sporadic forms of neurodegenerative diseases and CVD. Here, we found that elevated plasma GFAP and NfL were associated with cerebral atrophy and WMH across diseases at baseline, and with progression of atrophy and WMH over time. Plasma GFAP and NfL, as glial neuroinflammatory and neuroaxonal injury biomarkers, respectively, are nonspecific in nature and represent pathogenic processes common across all neurodegenerative diseases and CVD; they are reported to be elevated in many forms of neurodegenerative diseases, including in this study, and may also increase along with worsening disease severity.[2,3,11,12,15,43,44] As expected from general markers of neuroinflammation and neurodegeneration, they were also, overall, associated with MRI outcomes to various degrees within all disease cohorts. On the other hand, plasma p-tau181 and p-tau217 are considered specific biomarkers of AD and have shown promise in discriminating AD from non-AD dementia,[8-10,13,14] as they reflect tau pathology and amyloid plaque deposition, the 2 hallmarks of AD pathology. We found that elevated plasma p-tau181 and p-tau217 were also associated with cerebral atrophy and WMH across diseases at baseline, and with progression of cerebral atrophy and WMH over time. As expected with specific markers of AD pathology, they were mainly associated with MRI markers within the AD/MCI cohort, but also had surprising associations within some non-AD cohorts (e.g., PD-MCI, PD-D, and CVD). Compared with plasma p-tau181, p-tau217 had overall stronger associations with MRI markers both at baseline and over time. In addition, although p-tau181 was elevated within all cohorts compared with healthy elderly controls, although not to the levels seen in AD, p-tau217 was more specific and was only elevated within the AD/MCI cohort. Finally, we found that plasma $A\beta_{42/40}$, a biomarker of amyloid plaque deposition, was associated with more cerebral atrophy and WMH over time across diseases, despite the many limitations of measuring it in blood.[5-7] The causes of WMH in dementia are heterogeneous: they can be the result of ischemia and small vessel compromise, venous collagenosis, cerebral amyloid angiopathy (CAA), or a combination of these, or they may represent gliosis from underlying neuroaxonal degeneration due to the primary proteinopathy.[45] This last association supports that at least some of the small vessel disease burden seen may in fact be related to $A\beta_{42/40}$-related CAA, not only within an AD cohort, but across different cohorts of neurodegenerative diseases. This is also supported by our finding that 6.5% of ONDRI patients had significant presence of CAA-related hemorrhagic markers, with higher proportion in the AD and CVD cohorts.

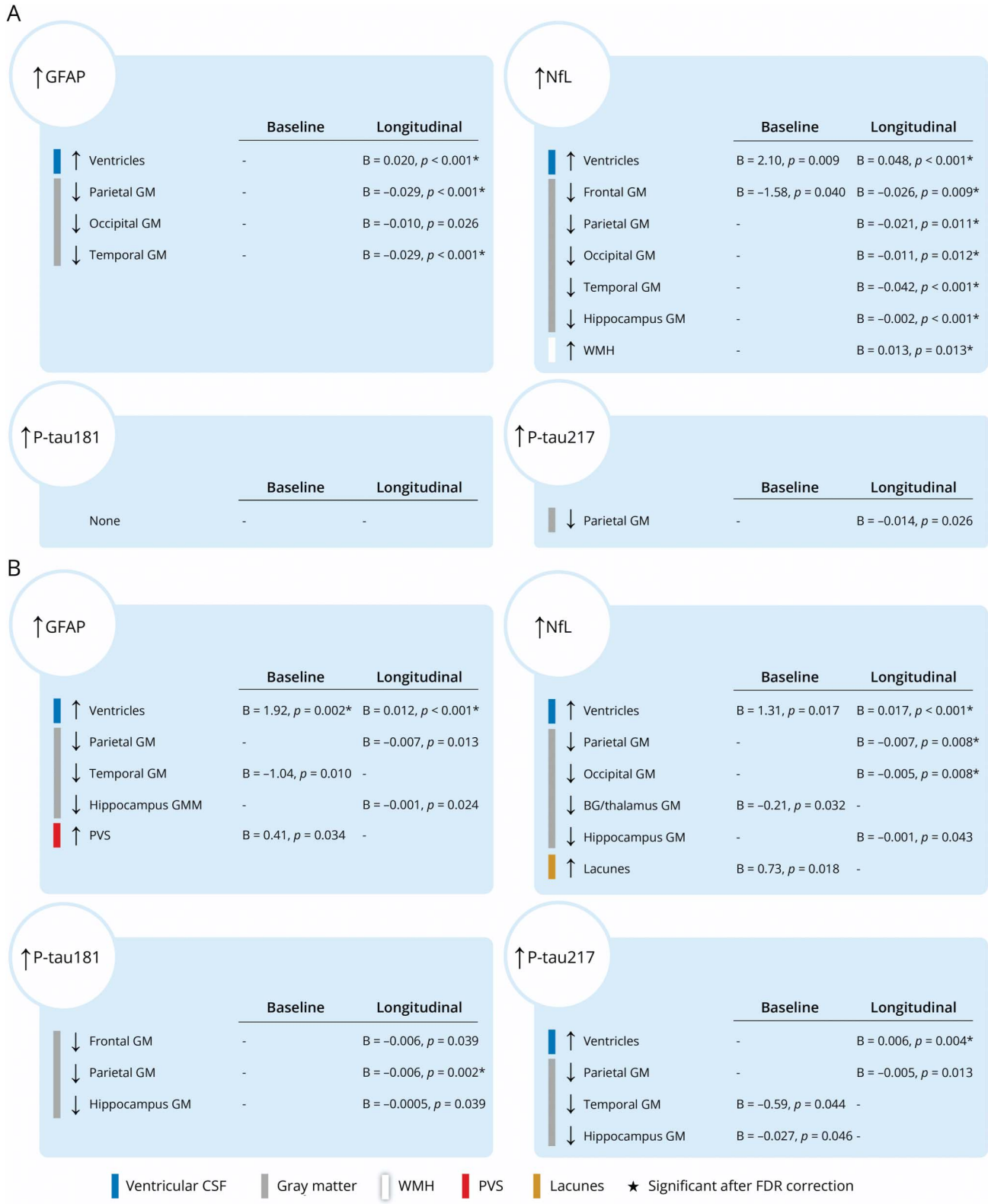
Overall, the associations we present in this study held true when accounting for common covariates such as age, sex, and *APOE* ε4 carrier status, but also for markers of kidney function, vascular risk scores, *MAPT* diplotypes, waist-hip circumference ratio, and disease duration, which can affect many factors within these analyses. Of interest, plasma biomarkers were only associated with periventricular but not deep WMH, which can have different etiologies.[46,47] Periventricular WMH, more than deep WMH, is shown to be associated with

Figure 4 Significant Associations Between Plasma Biomarker Levels and Imaging Outcomes Within (A) AD/MCI and (B) PD Cohorts



Plasma biomarker levels were measured at baseline, and MRI were acquired annually over 3 visits. All imaging metrics represent volumetric data, with head-size adjustment when applicable. WMH volume, PVS volume, lacunar volume, and all plasma biomarkers were log transformed. Age, sex, *APOE* ε4 carrier status, and time (in months) since initial visit were accounted for in linear mixed models. -, nonsignificant. AD = Alzheimer disease; MCI = mild cognitive impairment; PD = Parkinson disease.

Figure 5 Significant Associations Between Plasma Biomarker Levels and Imaging Outcomes Within (A) FTD and (B) CVD Cohorts



Plasma biomarker levels were measured at baseline, and MRI were acquired annually over 3 visits. All imaging metrics represent volumetric data, with head-size adjustment when applicable. WMH volume, PVS volume, lacunar volume, and all plasma biomarkers were log transformed. Age, sex, *APOE* ε4 carrier status, and time (in months) since initial visit were accounted for in linear mixed models. -, nonsignificant. FTD = frontotemporal dementia spectrum disorder; PVS = perivascular space; WMH = white matter hyperintensity.

cognitive and functional decline.[47,48] Furthermore, the relationships we found are largely consistent across assessment modalities, from the structural integrity of the brain in this study, to cognitive function and functional independence in activities of daily living in a previous study.[15] We also present findings within each disease cohort, which, in addition to helping understand the capabilities of these plasma biomarkers for prognosis and monitoring within real-world patient cohorts, can also provide insight into the nature and presence of copathologies.

First, in participants diagnosed with AD or MCI presumed due to AD, we found that elevated plasma GFAP, NfL, p-tau181, and p-tau217 were all associated with cerebral atrophy and small vessel disease pathology, including WMH and lacunes (see also eAppendix 8), to various degrees. Small vessel disease pathology is well-recognized as a contributing factor to outcomes in AD and other dementias.[19] We also found no associations with plasma $A\beta_{42/40}$; this was expected because amyloid starts accumulating very early in the AD trajectory,[49] with the largest changes in plasma expected to happen long before clinical onset.[7]

Second, in participants diagnosed with PD, we found that elevated plasma GFAP and NfL were associated with cerebral atrophy, regardless of the level of cognitive impairment. Of interest, associations with plasma biomarkers of AD pathology were also present in participants diagnosed with PD-MCI or PD-dementia, who also had more advanced cerebral atrophy and small vessel disease pathology compared with participants who were still cognitively unimpaired. For the former, elevated plasma p-tau217 and lower plasma $A\beta_{42/40}$ ratio were associated with cerebral atrophy and WMH, suggestive of probable concomitant AD/CAA copathology. AD and small vessel disease pathologies may each intertwine with PD pathology to accelerate cognitive decline in a subset of patients with PD.

Third, in participants diagnosed with FTD, we found that elevated plasma GFAP and NfL were associated with cerebral atrophy and WMH. This contrasts to a previous study in the same sample where we failed to detect effects relating to cognitive function and functional independence in activities of daily living,[15] possibly due to the limited sample size or due to diagnostic heterogeneity.[50] This difference in findings may also be explained by structural and vascular brain changes happening earlier along the neurodegenerative trajectory than cognitive and functional deficits, and by these brain MRI outcomes being less separated from the biological processes that plasma biomarkers are measuring than more downstream outcomes such as cognition and functioning.

Finally, in participants diagnosed with CVD, we found that elevated plasma GFAP and NfL were associated with cerebral atrophy, and expectedly due to the nature of the condition, with markers of small vessel disease pathology such as enlarged PVS and lacunes. More unexpected was that elevated plasma p-tau181 and p-tau217 were associated with cerebral atrophy within this non-AD cohort. This suggests that underlying AD copathology may be present within a subset of participants with CVD, a very common combination for the pathologic aging brain.[17,18] This also suggests that CAA, a condition characterized by amyloid deposition within cerebral blood vessels, may be a likely etiology of their observed small vessel disease. Indeed, plasma p-tau181 and p-tau217 were elevated in patients with ≥2 CAA-related hemorrhagic markers, and have been shown to be associated with the presence of CAA but not with other types of cerebrovascular pathologies,[51] as well as with lobar cerebral microbleeds.[52]

As participants within the ONDRI cohort were recruited at tertiary clinics across ON, Canada, they were overwhelmingly of European descent,[25] which may limit the generalizability of these results to other ethnicities. Although the most up to date diagnostic criteria were used at the time patients were being recruited, no CSF or PET biomarkers were available for confirmation of AD diagnoses due to logistical issues (e.g., cost, patient compliance with invasive procedures, and clinician time burden). Diagnoses were nonetheless rigorously achieved by consensus review among expert clinicians with supporting clinical history and examination, exclusionary blood work, and brain MRI. Although we are confident in these diagnoses, we acknowledge that misdiagnosis remains an issue even within specialized clinics, and it is likely that undetected AD copathology may be present for non-AD patients or that AD patients may have been misdiagnosed or comorbid with other neurodegenerative diseases. This is however reflective of how most clinical diagnoses are currently achieved in health care systems, and highlights the reality of mixed disease as being very common,[17,18,21,22] especially with increasing age, and therefore the importance of finding meaningful signals in "real-world" less "pure" cohorts and across the neurodegenerative disease spectrum as a whole. All non-AD ONDRI disease cohorts showed overlap with AD in plasma levels of p-tau species, in addition to associations with MRI markers of neurodegeneration within some subcohorts, which could suggest AD copathology. The findings of this study highlight potential diagnostic limitations of these included biomarkers. Although other proteinopathy biomarkers are needed for PD and FTD, the biomarkers presented in this study are likely to provide valuable complementary information, particularly in prognosis and in characterization of diseases and potential copathologies.

Author Contributions

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Disclosure

H. Zetterberg has served at 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 cofounder of Brain Biomarker Solutions in Gothenburg AB, which is a part of the GU Ventures Incubator Program (outside submitted work). M. Masellis holds additional grants unrelated to this work from the CIHR and Washington University, as well as from the Women's Brain Health Initiative and Brain Canada as part of the EU Joint Program for Neurodegenerative Disease Research; has clinical trials contracts with Roche and Alector; has received consulting fees from Alector, Biogen Canada, Wave Life Sciences, Eisai Canada, Eli Lilly Canada, and Novo Nordisk Canada; received royalties from the Henry Stewart Talks; has received payments from MINT Memory Clinics and ECHO Dementia Series; and holds unpaid scientific advisory board roles with Alzheimer's Society Canada and Parkinson Canada. All other authors report no disclosures directly relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org/N.

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