BRIEF COMMUNICATION

Plasma phosphorylated tau181 and neurodegeneration in Alzheimer's disease

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Abstract

We examined if plasma phosphorylated tau is associated with neurodegeneration in Alzheimer's disease. We investigated 372 cognitively unimpaired participants, 554 mild cognitive impairment patients, and 141 Alzheimer's disease dementia patients. Tau phosphorylated at threonine 181, regional cortical thickness (using magnetic resonance imaging) and hypometabolism (using fluorodeoxyglucose positron emission tomography) were measured longitudinally. High plasma tau was associated with hypometabolism and cortical atrophy at baseline and over time, and longitudinally increased tau was associated with accelerated atrophy, but these associations were only observed in $A\beta$-positive

participants. Plasma phosphorylated tau may identify and track processes linked to neurodegeneration in Alzheimer's disease.

Introduction

Plasma P-tau181 is increased in Alzheimer's disease (AD), and correlates with brain deposition of aggregated β-amyloid (Aβ) and tau, the core AD hallmarks.[1–3] Plasma P-tau181 may potentially be used as a noninvasive proxy for tau pathology linked to neurodegeneration,[2,4] but longitudinal plasma P-tau181 data have not been examined. To better understand the performance of plasma P-tau181 to monitor tau pathology and subsequent neurodegeneration in AD, we need truly longitudinal analyses that incorporate change of both neuroimaging measures and P-tau181. We tested associations between longitudinal plasma P-tau181 and imaging measures for hypometabolism, using fluorodeoxyglucose positron emission tomography (FDG-PET) and for cortical atrophy, using magnetic resonance imaging (MRI), in a large cohort of cognitively unimpaired (CU) individuals, patients with mild cognitive impairment (MCI) and AD dementia patients. We tested the hypothesis that increased plasma P-tau181 was associated with signs of neurodegeneration, both at baseline and over time. Since plasma P-tau181 is strongly linked to AD,[1–3] we further hypothesized that these associations would only be seen in individuals who were on the AD trajectory (as indicated by a positive Aβ PET scan).

Methods

Study participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. For up-to-date information, see www.adni-info.org. We used data accessed at the ADNI database on 2020/06/25. We included all CU controls, MCI and AD dementia patients with plasma P-tau181 and at least one available MRI or FDG-PET scan. Inclusion and exclusion criteria have been described before.[5] In sum, CU participants had Mini Mental State Examination (MMSE) score ≥ 24, and Clinical Dementia Rating (CDR) score 0. MCI participants had MMSE score ≥ 24, objective memory loss tested by delayed recall of the Wechsler Memory Scale Logical Memory II, CDR 0.5, preserved activities of daily living, and absence of dementia. AD dementia patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD,[6] had MMSE 20–26 and CDR 0.5-1.0. The study data and samples were collected from 2005/10/24 to 2019/07/17. Ethical approval was given by the local ethical committees of all involved sites. All participants gave written informed consent.

Biomarker and imaging measurements

Plasma samples were taken annually. P-tau181 was analyzed on a Single molecule array (Simoa) HD-X Analyzer (Quanterix, Billerica, MA), using an in-house assay developed in the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden.[2] In the P-tau181 data file (UGOTPTAU181_06_18_20.csv at the ADNI database), we noted 33 outlying data points (P-tau181-concentrations more than three standard deviations above the mean, 63.3 ng/L) out of $N = 3758$ observations. We excluded those outliers from all analyses.

Structural brain images were acquired using 3 Tesla MRI scanners with T1-weighted MRI scans using a sagittal volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence. MRI scans were done at baseline, 3 months and 6 months, and thereafter annually. Free-Surfer (v5.1) was used for quantification of regional thickness and volumes according to the 2010 Desikan-Killany atlas.[7] We used cortical thickness for a meta-region of interest ("temporal composite") involving entorhinal, inferior temporal, middle temporal, and fusiform cortex.[8] FDG-PET scans were acquired annually. An FDG composite score was calculated as the average uptake in left and right angular, temporal, and posterior cingulate regions.[9] 18F-Florbetapir PET brain scans for Aβ deposition were acquired at baseline according to a previously described protocol,[9] using a cortical summary-ROI consisting of frontal, anterior/posterior cingulate, lateral parietal, lateral temporal brain regions and with whole cerebellum as reference. Aβ positivity was defined as 18F-florbetapir PET > 1.11 SUVR.[9]

Statistical analyses

We determined associations between continuous plasma P-tau181 and neuroimaging measures, using all available paired longitudinal data, in linear mixed-effects (LME) models with P-tau181 as predictor and neuroimaging

measures as response. We next tested if baseline plasma P-tau181 predicted change in neuroimaging measures. To use all available data for the imaging measures, we extracted slopes of change for temporal cortical thickness and FDG-PET in separate linear regression models (without requiring paired P-tau181 data). We then used neuroimaging slopes as response variables in linear regression models with continuous P-tau181 as the predictor. We also tested if longitudinal change in P-tau181 correlated with longitudinal change in neuroimaging measures. For this, we extracted slopes for P-tau181 in separate linear regression models (without requiring paired imaging data). We used those slopes as predictors in linear regression models with a change in neuroimaging measures as outcomes. All these models were adjusted for age, sex, diagnostic group, *APOE ε*4 status (positive = at least one ε4 allele, or negative = no ε4 alleles), Aβ status, and the interaction between Aβ status and P-tau181, and (for slope data) lag between first imaging scan and first P-tau181 sampling. For the final analyses, we used binary P-tau181 status. We defined a P-tau181 cut-point using two-component mixture modeling of the P-tau181 data in Aβ-negative CU, at the mean concentration plus two standard deviations of the lower component. We divided the data in four groups by combinations of positivity and negativity on P-tau181 and Aβ PET. We used this factor as the predictor of baseline and longitudinal neuroimaging measures in linear regression models, adjusted for age, sex, diagnostic group, and (for tests of slopes) lag between the first imaging scan and first P-tau181 measure. We also performed sensitivity analyses within diagnostic subgroups and in a restricted dataset with paired MRI and FDG-PET imaging data. All statistical analyses were done in R (v 4.0.0). Significance was determined at $P < 0.05$.

Results

Demographics are shown in Table 1.

Continuous plasma P-tau181 and temporal cortical thickness

Higher plasma P-tau181 was associated with thinner cortices in Aβ+, but not in Aβ- individuals (Fig. 1A; in subgroup analyses, this was found in MCI and AD, but not in CU, Figs. S1–S3). Higher baseline plasma P-tau181 was also associated with more rapid decline of cortical thickness in Aβ+, but not in Aβ- individuals (Fig. 1B; in subgroup analyses, this was found in MCI, but not in CU or AD, Figs. S1–S3). Greater slopes of plasma P-tau181 were associated with more rapid decline of cortical thickness in Aβ+ individuals, but not in Aβ- individuals (Fig. 1C; in subgroup analyses, this was found in CU and AD, but not in MCI, Figs. S1–S3).

Table 1. Demographics.

	CU	MCI	AD dementia
N	372	554	141
Sex (M/F)	196/176	241/313	59/82
Age (y)	73.6 (5.8)	71.9 (7.4)	74.4 (8.2)
Education (y)	16.6 (2.6)	16.1 (2.7)	15.7 (2.7)
*APOE ε*4 (−−/− +/++)	267/98/7	290/209/55	46/66/29
Baeline Aβ-status (−/+)	245/127	243/311	16/125
Baseline P-tau181 (ng/L)	15.2 (8.6)	18.4 (10.5)	22.8 (8.5)
Baseline temporal cortical thickness (mm)	2.82 (0.15)	2.76 (0.19)	2.53 (0.22)
Baseline FDG-PET (SUVR)	1.31 (0.11)	1.25 (0.14)	1.07 (0.15)
Nr of P-tau181 measures (median [IQR])	3 (2–4)	4 (3–5)	2 (1–2)
Duration from first to last P-tau181 measure (y) (median [IQR])	2.05 (1.98–3.97)	3.01 (2.00–3.99)	0.99 (0.00−1.05)
Nr of MRI scans (median [IQR])	5 (4–6)	5 (4–6)	4 (4–4)
Duration from first to last MRI scan (y) (median [IQR])	2.07 (1.98–4.00)	2.12 (1.98–4.00)	1.02 (0.98−1.95)
Nr of FDG-PET scans (median [IQR])	2 (1–2)	2 (1–2)	1 (1–1)
Duration from first to last FDG-PET (y) (median [IQR])	1.95 (0.00–2.03)	1.99 (0.00–3.97)	0.00 (0.00−0.00)

Continuous data are mean (standard deviation).

Continuous plasma P-tau181 and hypometabolism

Higher plasma P-tau181 was associated with lower FDG-PET SUVR in Aβ+, but not in Aβ- individuals (Fig. 1D; in subgroup analyses, this was found in MCI, but not in CU or AD, Figs. S1–S3). Higher baseline plasma P-tau181 was also associated with more rapid decline of FDG-PET SUVR in Aβ+, but not in Aβ- individuals (Fig. 1E; in subgroup analyses, this was found in CU, but not in MCI or AD, Figs. S1–S3). Slopes of plasma P-tau181 were not associated with slopes of FDG-PET SUVR in either Aβ- or Aβ+ (Fig. 1F).

Dichotomous plasma P-tau181 and neurodegeneration

A cut-point for abnormal baseline plasma P-tau181 was defined in the Aβ-negative CU group (P-tau181 > 19.8 ng/L). The data were divided into four
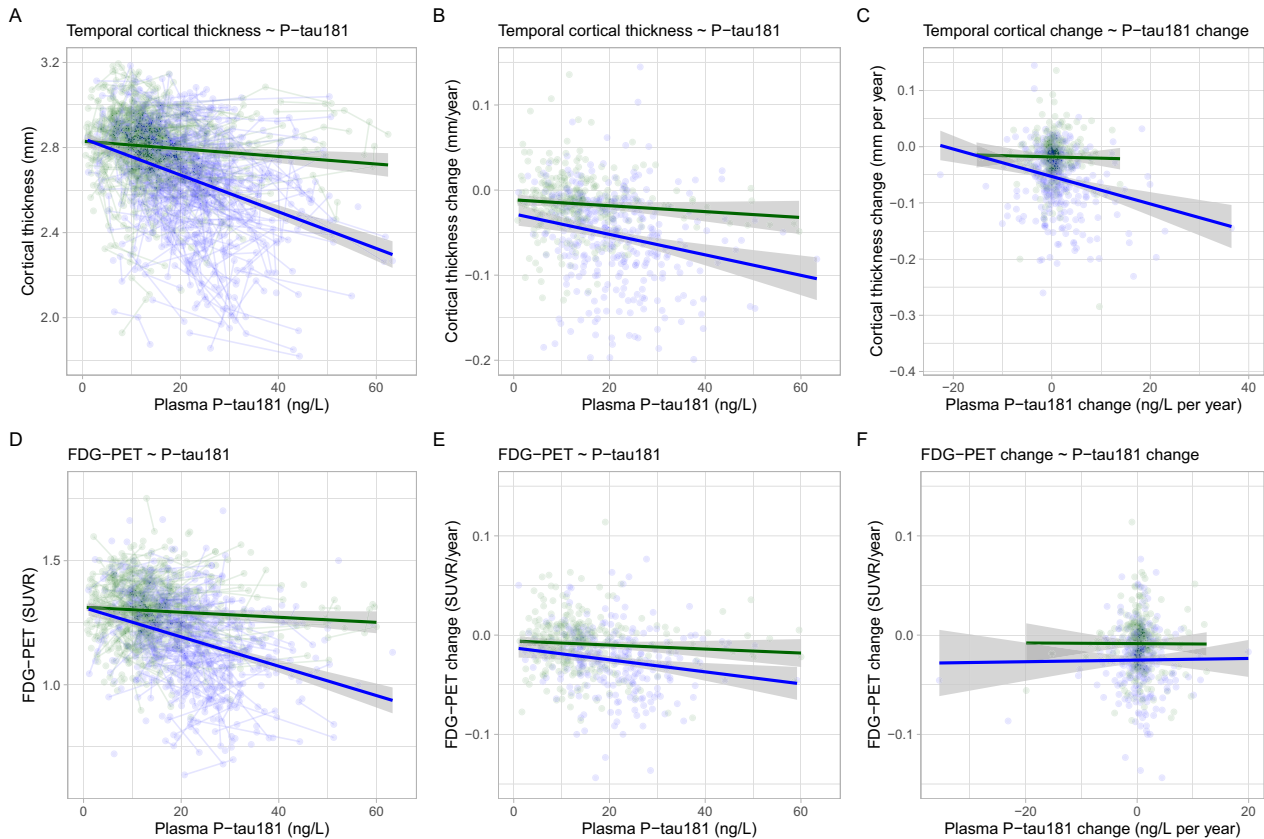
Figure 1. Plasma P-tau181 and imaging measures of neurodegeneration. Associations between temporal cortical thickness (panels A–C) and fluorodeoxyglucose PET (panels D–F) with plasma P-tau181 levels, testing associations with all available paired data (panels A and D), associations between slopes of imaging measures and baseline P-tau181 (panels B and E), and associations between slopes of imaging measures and slopes of P-tau181 (panels C and F). All models are adjusted for age, sex, diagnostic group, and Aβ status. Slope models are also adjusted for lag between the first imaging scan and first P-tau181 measure. The effects in Aβ-negative subjects are shown in green and effects in Aβ-positive subjects are shown in blue (for individual subjects and average effect). Panels A and D show results from linear mixed-effects models, with several data points per individual (individual subjects as a random factor). *P*-values are extracted from the models for associations in Aβ-negative and Aβ-positive subjects separately. *P*-values are also indicated for the difference in slopes between Aβ-positive and Aβ-negative subjects.

parts based on P-tau181 and Aβ status (Fig. 2A). P-tau181+/Aβ+ (*N* = 302) had thinner baseline cortices (in subgroup analyses, this was found in MCI and AD, but not in CU, Figs. S4–S6), lower baseline FDG-PET SUVR (in subgroup analyses this was found in CU and MCI, but not in AD, Figs. S4–S6), and more rapid decline in cortical thickness (but not in subgroup analyses, Figs. S4–S6) and FDG-PET SUVR (in subgroup analyses, this was found in MCI, but not in CU or AD, Figs. S4–S6) than P-tau181−/Aβ+ (*N* = 261). There were no differences

between Ptau181-/Aβ- (*N* = 425) and P-tau181+/Aβ- (*N* = 79) for any comparison.

Sensitivity analyses with paired imaging data

In the main analyses, we included all available MRI and FDG-PET data, as measures of neurodegeneration. Although we did not aim to compare effects on MRI with effects on FDG-PET, we also did a sensitivity analysis

Figure 2. Fluorodeoxyglucose PET and temporal cortical thickness by groups av P-tau181 and Aβ-PET positivity. Panel A shows the overall P-tau181 and Aβ PET data, cut-points for P-tau181 (>19.8 ng/L) and Aβ PET (>1.11 SUVR) positivity, and the four groups created by combinations of P-tau181 and Aβ PET. Panels B–E show differences between groups for temporal cortical thickness and FDG-PET, at baseline and over time. The groups were compared in linear regression models, adjusted for age, sex, diagnostic group, and lag between the first imaging scan and first P-tau181 measure. *P*-values are extracted for comparisons between P-tau181−/Aβ- (reference) and all other groups, and between P-tau181-negative and -positive groups within the Aβ groups.

A — Plasma P−tau181 & Aβ groups

B — Baseline temporal cortical thickness

C — Change in temporal cortical thickness

D — Baseline Fluordeoxyglucose PET

E — Change in fluordeoxyglucose PET
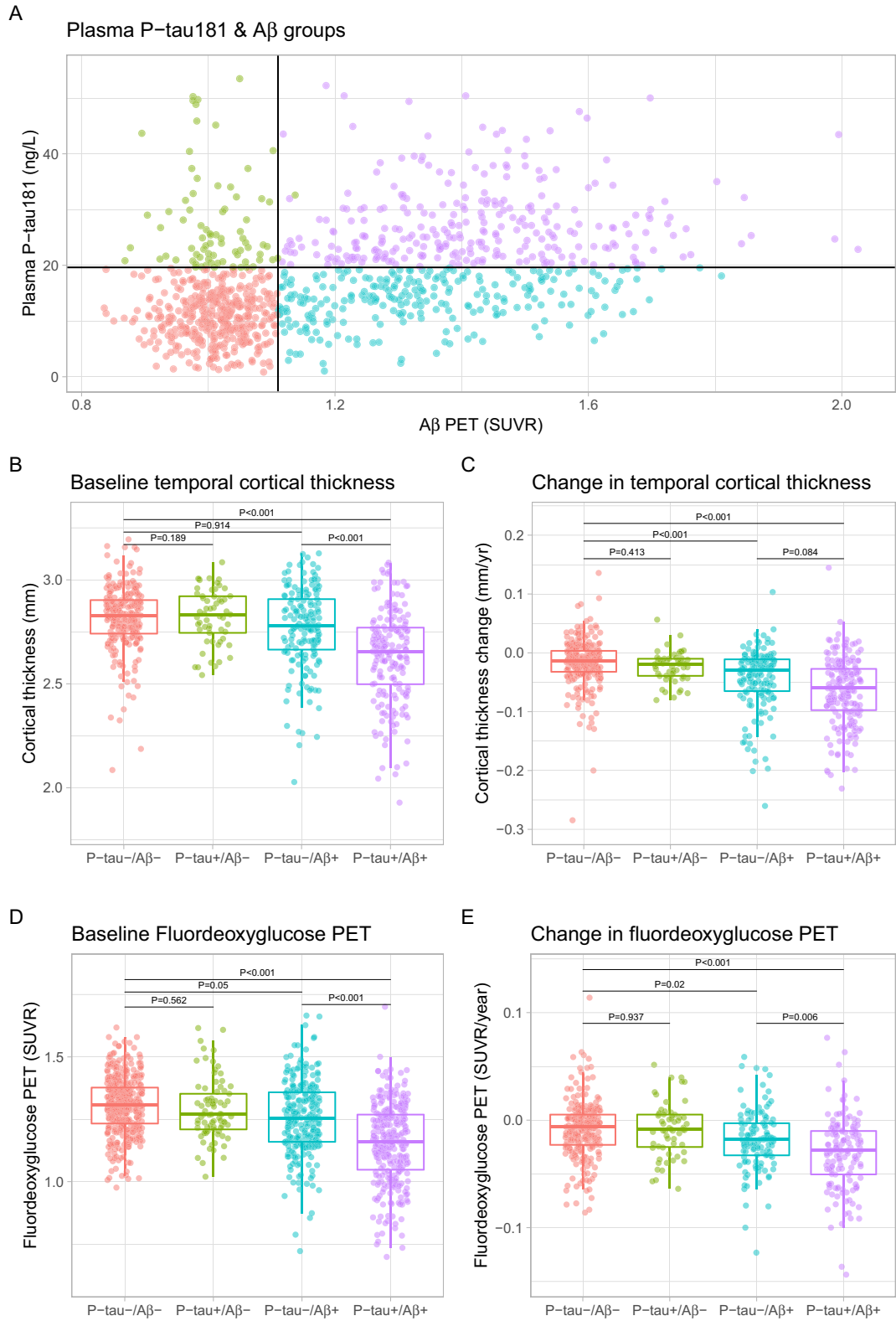
restricted to paired imaging data (from ADNI visits when both MRI and FDG-PET data were available). This resulted in a smaller dataset, with 206 CU, 376 MCI, and 88 AD dementia patients. Most findings remained significant or borderline significant in this restricted data set (Figs. S7 and S8). In sum, higher plasma P-tau181 remained associated with thinner cortices, more rapid decline of cortical thickness and lower FDG-PET SUVR in Aβ+ (but not in Aβ-) individuals. Greater slopes of plasma P-tau181 remained associated with more rapid decline of cortical thickness in Aβ+ individuals. P-tau181+/Aβ+ had thinner baseline cortices and lower baseline FDG-PET SUVR than P-tau181−/Aβ+, but the associations with decline in cortical thickness and FDG-PET SUVR were no longer significant in this subset.

Discussion

Higher plasma P-tau181 was associated with reduced brain glucose metabolism, reduced temporal lobe cortical thickness, and more rapid acceleration of hypometabolism and cortical atrophy, indicating worsening of neurodegeneration, but only in those with evidence of AD-type pathophysiology in the form of a positive Aβ PET scan. Longitudinal increases of plasma P-tau181 correlated with longitudinal cortical atrophy in Aβ PET-positive individuals. Taken together, this suggests that plasma P-tau181 reflects downstream longitudinal neurodegeneration due to AD, linked to either accumulation of paired-helical filament (PHF) positive neurites surrounding amyloid plaques or to intracellular tangles.

Several studies have found correlations between CSF P-tau181 and neurodegeneration, although comparisons involving longitudinal CSF data are rare.[10–12] Previous studies have also suggested correlations between plasma P-tau181 and atrophy, using MRI.[2,4] Mielke et al. showed that higher plasma P-tau181 was associated cross sectionally with less cortical thickness in a group of 269 CU individuals, MCI and AD dementia patients, but there were no associations in the individual diagnostic groups.[4] Karikari et al. showed that plasma P-tau181 was associated with cross-sectional and 1-year longitudinal gray matter atrophy in 88 individuals, including CU, MCI, and AD dementia patients, but again there were no associations within individual diagnostic groups.[2] Our study is, to our knowledge, the first truly longitudinal study on the topic (using longitudinal data for both imaging measures and plasma P-tau181). We also found associations when adjusting for clinical diagnosis, which may otherwise confound the relationship between atrophy and biochemical measures.

The longitudinal link between plasma P-tau181 and signs of atrophy in people with (but not without)

biomarker signs of Aβ pathology, suggests that plasma P-tau181 may be useful as a noninvasive marker to track neurodegeneration in AD. Plasma P-tau181 also performs well as a diagnostic marker for AD.[1,2,4] Together, this suggests that measurement of plasma P-tau181 concentration may be useful in clinical trials (and perhaps in clinical practice) as a noninvasive, affordable way to monitor disease progression. As in previous studies,[1–3] we note high P-tau181 levels despite a normal Aβ PET scan in a minority of subjects. Since these subjects do not show signs of increased neurodegeneration, this may not indicate a malign condition.

One limitation was that only one cohort was used. ADNI is tailored to represent a clinical trial population, and further studies are needed on more general and diverse populations, where neurodegeneration is more likely to also be impacted by other (non-AD) processes. The study cohort did, however, include Aβ-negative MCI and (clinically diagnosed) AD dementia subjects, which are likely to have cognitive impairment due to non-AD conditions, including depression and cerebrovascular disease.[13,14] We only included subjects with Aβ data, so that we could stratify the analyses by Aβ-status, but we did not perform complete ATN classification,[15] since measures of neurodegeneration were key outcome data, and since we did not have an independent measure of T-status (tau PET data were lacking in most subjects, and CSF P-tau181 data were not suitable for this analysis, since it is very closely correlated with plasma P-tau181, the main predictor in this study[1,3]).

Author Contributions

NMC and OH conceived the study. NMC and NC performed the statistical analysis. HZ and KB were responsible for biochemical analyses. NMC and OH drafted the initial manuscript. All authors contributed to the revision and editing of the manuscript.

Conflict of Interest

NC, and NMC have nothing to disclose. OH has acquired research support (for the institution) from Roche, Pfizer, GE Healthcare, Biogen, Eli Lilly and AVID Radiopharmaceuticals. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Biogen and Roche. HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB has served as a consultant,

at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

Data Availability Statement

Anonymized study data for the primary analyses presented herein are available upon request from any qualified investigator for purposes of replicating reported results.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Plasma P-tau181 and imaging measures of neurodegeneration in CU subjects.

Figure S2. Plasma P-tau181 and imaging measures of neurodegeneration in MCI subjects.

Figure S3. Plasma P-tau181 and imaging measures of neurodegeneration in AD dementia subjects.

Figure S4. Fluorodeoxyglucose PET and temporal cortical thickness by groups av P-tau181 and Aβ-PET positivity in CU subjects.

Figure S5. Fluorodeoxyglucose PET and temporal cortical thickness by groups av P-tau181 and Aβ-PET positivity in MCI subjects.

Figure S6. Fluorodeoxyglucose PET and temporal cortical thickness by groups av P-tau181 and Aβ-PET positivity in AD dementia subjects.

Figure S7. Sensitivity analyses for plasma P-tau181 and imaging measures of neurodegeneration.

Figure S8. Sensitivity analyses for fluorodeoxyglucose PET and temporal cortical thickness by groups av P-tau181 and Aβ-PET positivity.

Data S1. Member list for the Alzheimer's Disease Neuroimaging Initiative.