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Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau-PET and amyloid-PET

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Abstract

INTRODUCTION—We examined and compared plasma phospho-tau181 (pTau181) and total tau: 1) across the Alzheimer's disease (AD) clinical spectrum; 2) in relation to brain amyloid (Aβ) PET, tau PET, and cortical thickness; and 3) as a screening tool for elevated brain Aβ.

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METHODS—Participants included 172 cognitively unimpaired (CU), 57 mild cognitive impairment, and 40 AD dementia patients with concurrent Aβ PET(PiB), tau PET (AV1451), MRI, plasma total tau and pTau181.

RESULTS—Plasma total tau and pTau181 levels were higher in AD dementia patients compared to CU. Plasma pTau181 was more strongly associated with both Aβ and Tau PET. Plasma pTau181 was a more sensitive and specific predictor of elevated brain Aβ than total tau and was as good as, or better than, the combination of age and *APOE*.

DISCUSSION—Plasma pTau181 may have utility as a biomarker of AD pathophysiology and as a non-invasive screener for elevated brain Aβ.

Keywords

Plasma tau; Plasma phosphorylated tau; Amyloid PET; Tau PET; Alzheimer's disease; Predicting brain amyloid

1. Introduction

Blood-based biomarkers of Alzheimer's disease (AD) pathology (e.g., amyloid-beta [Aβ] or tau) will be essential for screening the general population, and in low/middle income countries, as the first step in a multistep process to determine which non-demented individuals are at greatest risk of AD dementia [1–3]. Because elevated brain Aβ is necessary for a diagnosis of AD dementia, and a requirement for some ongoing secondary prevention trials, a blood-based marker for predicting elevated brain Aβ would have great benefit. Several studies have examined either plasma or serum Aβ1–40 and Aβ1–42 peptides, but these measures have not consistently differed between AD dementia patients and cognitively unimpaired (CU) controls or were associated with cortical Aβ PET deposition [4,5].

Studies examining the clinical utility of plasma total tau have consistently reported that higher levels are associated with cognitive decline and risk of mild cognitive impairment (MCI) [6,7], but this relationship is independent of brain Aβ [7]. Phosphorylated-tau is thought to be more specific to AD pathogenesis than total tau [8]. Although blood measures of pTau have been difficult to measure to date due their low levels, recent studies have demonstrated it may be possible [9]. The goals of the present study using a novel assay for pTau were to: 1) examine and compare levels of plasma phospho-tau181 (pTau181) and plasma total tau by clinical diagnosis across the AD spectrum; 2) examine the associations between plasma pTau181 and total tau with Aβ PET, tau PET, and cortical thickness; and 3) determine the clinical utility of plasma pTau181 or total tau as a screening tool for elevated brain Aβ. Given the specificity of CSF pTau to AD pathophysiology [8], we hypothesized that plasma pTau181 would be a more precise marker than total tau for AD-specific patterns of Aβ PET, tau PET, and cortical thickness.

2. Methods

2.1. Participants

Mayo Clinic data was pooled from two sources: the Mayo Clinic Study of Aging (MCSA) and the Alzheimer's Disease Research Center (ADRC). The MCSA is a population-based epidemiological cognitive aging study of Olmsted County, MN residents [10,11] who were initially sampled using the Rochester Epidemiology Project medical records linkage system. Beginning in 2004, the MCSA enrolled residents aged 70–89 years; in 2012 enrollment was extended to include residents aged 50 years and older. The ADRC recruits and follows selected patients initially seen in the referral behavioral neurology practice at Mayo Clinic. All CU in this study were enrolled in the MCSA. Those with MCI or AD dementia were enrolled in either the MCSA or the ADRC. For both studies, same day imaging of both Aβ and Tau PET began in 2016. The present analyses included the first individuals enrolled in the MCSA or ADRC with a diagnosis of CU, MCI, or AD and with Aβ PET, tau PET, MRI and blood (for total tau and pTau181 assays) at the same study visit. The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

2.2. MCI and dementia diagnostic determination

For each participant, the clinical diagnosis was determined by a consensus committee including the neurologist, neuropsychologist, and the nurse who evaluated each participant. For MCSA participants, performance in a cognitive domain was compared with the age-adjusted scores of CU individuals previously obtained using Mayo's Older American Normative Studies [12]. This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Subjects with scores around 1.0 SD below the age-specific mean in the general population were considered for possible cognitive impairment. The operational definition of MCI was based on clinical judgment including a history from the patient and informant. Published criteria were used for the diagnosis: cognitive complaint, cognitive function not normal for age, essentially normal functional activities, no dementia [13]. A final decision about impairment in a cognitive domain was made after considering education, occupation, visual or hearing deficits, and reviewing all other participant information. The diagnosis of dementia [14] and AD dementia [15] were based on published criteria. Participants who performed in the normal range and did not meet criteria for MCI or dementia were deemed CU. Imaging was not considered in determining the clinical diagnosis.

2.3. Imaging methods

Aβ PET imaging was performed with Pittsburgh Compound B (PiB) [16] and tau PET with AV1451 [17] on the same day. Participants also completed computed tomography for attenuation correction. Late uptake Aβ PET images were acquired from 40–60 minutes and tau PET from 80–100 minutes after injection. All PET images were analyzed with our in-house fully automated image processing pipeline [18], where image voxel values are extracted from automatically labeled regions of interest (ROIs) propagated from an MRI template. An Aβ positron emission tomography (PET) standardized update value ratio

(SUVR) was formed from the voxel number weighted average of the median uptake in the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and precuneus ROIs normalized to the cerebellar crus gray median. Based on previous work, elevated Aβ PET was defined as SUVR>1.42 [19]. Our primary tau PET ROI was the median uptake in the entorhinal cortex normalized to the cerebellar crus gray median. We focused on this ROI due to its sensitivity to Aβ PET among CU individuals [20]. A tau PET cut-point for the entorhinal cortex has not yet been validated so tau PET was only analyzed as a continuous variable. PET data were "sharpened" but not partial volume corrected. That is, voxels whose probability of being CSF was greater than the probability of being gray or white matter were excluded from PET ROI measures. MRI was performed on one of two 3T GE systems. The MRI measure was a FreeSurfer (v5.3)-derived AD-signature meta-ROI composed of the surface-area weighted average of the mean cortical thickness in the following individual ROIs: entorhinal, inferior temporal, middle temporal, and fusiform.

2.4. Plasma total tau

Blood was collected in-clinic after an overnight fast. The blood was centrifuged, aliquoted, and stored at −80°C. Plasma total tau was measured on the Quanterix Simoa-HD1 Platform, as described previously [21]. Briefly, samples were thawed on wet ice, centrifuged at 500xg for 5 minutes at 4C, diluted 1:8 in kit sample buffer, and analyzed according to the kit protocol on the Simoa-HD1 [21].

2.5. Plasma pTau181

The pTau181 assay was designed to measure pTau181 in plasma and was optimized to measure disease-related differences through the selection of monoclonal antibodies (mAb) used in the assay. Selection of the mAb pair provided a unique combination of sensitivity and selectivity for the tau forms in plasma that are different between CU and AD subjects. Briefly, the assay was performed on a streptavidin small spot plate using the Meso Scale Discovery (MSD) platform. Biotinylated-AT270 was used as a capture antibody (anti-pT181 Tau antibody, Thermo Fisher, catalog number: MN1050) and SULFO-TAG-LRL (anti-tau mAb developed by Lilly Research Laboratory) for the detector. Antibodies were conjugated with Sulfo-NHS-Biotin (Thermo Scientific, catalog number: 21327) or MSD GOLD SULFO-TAG NHS-Ester (Meso Scale Discovery, catalog number: R91AO) according to the manufacturer's protocol. The assay was calibrated using recombinant tau (4R2N, NCBI tau v2) protein that was phosphorylated in vitro using a reaction with glycogen synthase kinase-3β (GSK3β) and characterized by mass spectrometry [22,23]. The same sample used for the plasma total tau assay was thawed again for use in pTau181 assay. The sample was thawed on wet ice, centrifuged at 500xg for 5 minutes and diluted 1:2.5 in Diluent 35 (Meso Scale Discovery, catalog #: R50AE) with the addition of HBR1 to a concentration of 200 μg/mL (Scantibodies Inc, catalog #: 3KC533).

2.6. Assessment of covariates

Participant demographics (e.g., sex, age, years of education) were ascertained during the in-person interview at the in-clinic exam. *APOE* genotyping was performed from a blood draw taken at the in-clinic exam.

2.7. Statistical analyses

ANOVA and Chi-square tests were used to examine group (e.g., CU, MCI, AD) differences. Spearman's rho was used to measure the correlation between variables. The distribution of both plasma pTau181 and total tau was right skewed so the variables were log transformed prior to regression analyses. Linear regression was used to examine the relationship between each of the tau measures and continuous neuroimaging measures. Logistic regression was used when examining dichotomous neuroimaging outcomes (i.e., Aβ PET>1.42; cortical thickness<2.67mm). All models were adjusted for age, sex, and *APOE*.

We examined and compared the predictive value of plasma pTau181 and total tau for elevated Aβ PET and abnormal cortical thickness using areas under the receiver operating characteristic curve (AUROC). As mentioned earlier, a tau PET cut-point in the entorhinal cortex has not yet been validated so these analyses could not be performed. To determine the utility of the tau measures in a variety of clinical populations, we separately determined AUROC for all participants, non-demented participants, MCI only, and CU only. Age and the *APOE* ε4 allele are the strongest predictors of elevated brain Aβ and AD dementia. Therefore, for comparison purposes, we provided the AUROC for age alone, presence of an *APOE* ε4 allele alone, age and *APOE* ε4 allele, each plasma tau measure alone, and each plasma tau measure and age and *APOE* ε4 allele. Finally, to assess whether the predictive value of the tau measures differed by *APOE*, we stratified by the presence of an ε4 allele. The Liu method was used to identify cut-off values that maximized sensitivity and specificity [24]. Areas under ROC curves were compared using an algorithm suggested by DeLong, DeLong, and Clarke-Pearson (1988) [25]. All analyses were completed using Stata Version 13.0 (StataCorp, College Station, TX).

3. Results

3.1. Demographic, imaging, and plasma tau characteristics by group

Participants included 172 CU, 57 MCI, and 40 AD dementia. The AD dementia patients had a slightly lower mean age compared to the CU and MCI participants but there were no differences between the groups with regards to sex or education. As expected, clinical severity was associated with higher Aβ SUVR, higher tau PET entorhinal cortex SUVR, and lower cortical thickness in an AD-signature ROI (Table 1). Among all participants, the mean (SD) plasma level of total tau was 7.72 (8.51) pg/ml (median 5.79 pg/ml), and for pTau181 was 6.08 (2.30) pg/ml (median 5.55 pg/ml). Plasma total tau and pTau181 were modestly correlated (Spearman rho = 0.286, $P < .001$). AD dementia patients had significantly higher mean levels of total tau compared to MCI ($P = .029$) or CU participants ($P < .001$), but there was no difference between the CU and MCI participants. AD dementia participants also had higher mean levels of pTau181 compared to CU ($P < .001$), but not MCI ($P = .251$) participants. MCI had higher levels of pTau181 compared to CU, but the results did not reach statistical significance ($P = .060$).

3.2. Associations of plasma tau measures with Aβ PET, tau PET, and cortical thickness

Across the total study population, higher plasma tau and pTau181 levels were associated with all neuroimaging measures of Aβ PET, tau PET, and cortical thickness in an AD-

signature region after adjustment for age, sex, and *APOE* (Table 2). However, only higher plasma pTau181 levels, and not total tau, were associated with higher Aβ PET SUVR within each clinical diagnostic group (CU, MCI, AD). Dichotomizing Aβ PET SUVR>1.42, each log unit increase in plasma pTau181 was associated with a 2.8-fold (95% confidence interval (CI) 1.15–7.05) and a 5.7-fold increased odds (95% CI 0.86–38.16) of elevated brain Aβ among CU and MCI, respectively. Higher pTau181 was not significantly associated with higher tau PET entorhinal cortex SUVR among CU participants, but was associated with higher tau entorhinal cortex PET SUVR among both MCI and AD dementia participants. Plasma pTau181 was not significantly associated with cortical thickness in an AD-signature region. In contrast to plasma pTau181, total tau was associated with cortical thickness among both the CU and MCI participants but not with Aβ or tau PET.

3.3. Plasma tau measures by clinical diagnosis and elevated brain Aβ PET

Given the associations between pTau181 and Aβ PET, we next examined mean differences in the plasma tau measures by both clinical diagnosis and abnormal Aβ PET (Table 3, Fig. 1). Two of the clinically diagnosed AD dementia subjects were not found to have elevated Aβ PET and, thus, were excluded from this analysis.

The AD dementia A+ group had higher mean pTau181 levels compared to both the CU A− (P =.002) and CU A+ (P =.025) groups. The MCI A+ group also had higher mean levels than the CU A− group (P =.033). There was no difference between the CU A+ and A− groups or the CU and MCI A+ groups. For total tau, the only significant group difference was higher mean levels for the AD dementia A+ group compared to the CU A− group (P =.016) and the MCI A− group (P =.015).

3.4. Correlation between plasma tau measures and tau PET by clinical diagnosis and elevated brain Aβ PET

Plasma pTau181 was more strongly correlated with higher tau PET SUVR in the entorhinal cortex among participants with elevated brain Aβ PET compared to those without (Table 4). The strength of the correlation between plasma pTau181 and tau PET increased with increasing disease severity, but was not found among the AD dementia A+. In comparison to plasma pTau181, the correlations between plasma total tau and tau PET were lower and only significant among the CU A−. Correlations of plasma pTau181 and total tau with all 47 tau PET regions are shown in Supplementary Table 1 and Supplementary Table 2.

3.5. Accuracy of the plasma tau measures for elevated Aβ PET

Within each group, plasma pTau181 was a better predictor of elevated Aβ PET compared to total tau (P < .01), age (P < .05), or *APOE* (P < .05) alone (Table 5). Plasma pTau181 was also as good as the combined predictive value of age and *APOE.* In *APOE* stratified analyses, the AUROC for pTau181, but not total tau, was higher than age (all P < .05) for both ε4 carriers and non-carriers.

4. Discussion

The present results demonstrate that plasma pTau181 and total tau are differentially associated with neuroimaging measures of AD pathology. Both plasma tau and pTau181 levels were elevated in AD dementia patients compared to CU. However across the diagnostic groups, pTau181 was consistently associated with both Aβ and Tau PET whereas total tau was associated with cortical thickness. Further, when examining the utility of plasma pTau181 and total tau for predicting elevated brain Aβ, pTau181 was the most accurate predictor and was as good as, or better than, the combination of age and *APOE*. In *APOE*-stratified analyses, pTau181 was a better predictor of elevated brain Aβ compared to age alone. Together, these results highlight the potential use of plasma pTau181 as a non-invasive blood-based screener of AD pathophysiology and for identifying individuals at greatest risk of AD dementia in the general population or for secondary AD prevention trials.

Although blood-based biomarkers of AD pathophysiology have the advantage over CSF or neuroimaging measures with regards to feasibility at the population-level, cost, and invasiveness, the field has been hampered by lack of reproducibility and clinical utilization. Indeed, across multiple cohorts and assays blood-based measures of Aβ1–40 or Aβ1–42 have not been consistently associated with the clinical diagnosis and prognosis of AD dementia, or with cortical Aβ PET deposition [4,5]. A recent publication using stable isotope labeling kinetics reported that plasma Aβ1–42 concentration correlated with the CSF Aβ42/Aβ40 ratio and had good accuracy for predicting the sensitivity and specificity of elevated brain Aβ [26] but additional studies are needed to validate and longitudinally examine this new blood-based measure.

In contrast to blood Aβ measures, studies examining the clinical utility of plasma total tau have been consistent. Across four cohorts and two independent laboratories, participants with MCI or AD dementia had higher plasma total tau levels compared to CU participants. However, there was considerable overlap between groups and no significant differences between CU and MCI [6,21,27]. Longitudinally, higher levels of plasma total tau have been associated with cognitive decline and risk of MCI [6,7], but this relationship was independent of brain Aβ [7]. Thus, plasma total tau could be a useful prognostic marker for cognitive decline but it is not specific to the AD pathophysiological process.

The total tau results of the present study, using a different population than previously published [7,21], are consistent. First, plasma total tau levels were higher among AD dementia patients compared to MCI or CU. Second, the difference between MCI and CU was not statistically significant and there was substantial overlap between all of the groups. Third, plasma total tau was more strongly associated with cortical thickness, albeit in an AD-signature region, than with Aβ or Tau PET. Taken together, these results further demonstrate that plasma total tau may be a useful marker of general cognitive decline or neurodegeneration, but is not specific to AD pathophysiology.

While both CSF total tau and pTau are elevated in prodromal AD and AD dementia [4,28], total tau (but not pTau) is also elevated in traumatic brain injury, stroke, and Creutzfeldt-

Jakob disease [29–32]. Thus, CSF pTau is thought to be more specific for the pathophysiological state associated with the accumulation of AD-type tau pathology [8]. Based on this reasoning, the new A/T/N research criteria consider elevated CSF pTau indicative of accumulation of AD-like tau, “T”. In contrast, elevated CSF total tau is considered indicative of active neuronal injury, “N” [33]. Our findings, but now in plasma, similarly corroborate this distinction. Our measure of plasma pTau181 was associated with both Aβ and Tau PET, whereas plasma total tau was only associated with cortical thickness in an AD signature region.

Additional verification of the potential utility of plasma pTau181 was that its relationship with Aβ and tau PET followed the typical AD pathological progression. As demonstrated in Table 4, the correlation between plasma pTau181 and Tau PET entorhinal cortex SUVR was only present in A+ groups, and was stronger in MCI A+ compared to CU A+. The lack of correlation within the AD A+ group is likely due to the complexity in AV1451 binding. In our recent work, AV1451 preferentially bound to mature intracellular tangles and not extracellular “ghost” tangles seen later in the disease process [34]. This may have contributed to an insufficient range to see correlations in the AD A+ group. The correlation of plasma pTau181 with Aβ adds additional evidence to the amyloid cascade hypothesis and places the detection of abnormal tau on PET earlier in the trajectory of the disease, but still after onset of abnormal Aβ PET. This can be attributed to plasma pTau181 being more sensitive than Tau PET to detect the presence of NFT pathology and may allow for earlier intervention of tau targeting therapeutics. Additional studies will need to assess temporal changes in both Tau PET and plasma pTau181 and to determine which measure is more sensitive to treatment-induced changes.

Plasma pTau181 not only showed a stronger association with brain Aβ PET, but also had good sensitivity and specificity for predicting elevated brain Aβ across the clinical severity of the disease. To date, the strongest predictors of elevated brain Aβ are age and the *APOE* ε4 allele. To be a useful non-invasive screener, pTau181 should be as good as or better than the predictive value of the combination of age and *APOE*. Further, it should also enhance prediction among individuals who are *APOE* ε4- because there are currently no ways of identifying risk of elevated brain Aβ among these individuals other than age. In this study, plasma pTau181 was as good of a predictor of elevated brain Aβ, if not better, than the combination of age and *APOE*. Further, among both *APOE* ε4 carriers and non-carriers, plasma pTau181 was a significantly better predictor of brain Aβ than age across all diagnoses. Thus, pTau181 enhances the predictive value of elevated brain Aβ for both ε4 carriers and non-carriers. This is an important result given the urgent need to identify, in a cost-effective manner, which non-demented individuals have elevated brain Aβ.

There are multiple strengths to the study including the large sample size, well-characterized participants, and availability of same day Aβ and Tau PET imaging. However, the age of our AD group was relatively young compared to the average late-onset AD population. Given the lack of replication of most blood-based biomarkers, validation in another cohort is needed. Indeed, , It is encouraging that our plasma pTau181 and total tau results are aligned with CSF findings, that plasma pTau181 is more associated with the AD pathophysiological progress, and that our plasma total tau results are consistent with previous studies. To further

develop plasma pTau181 into a clinically useful biomarker, future research will need to assess intra-individual variability, identify sample collection procedures or participant characteristics that may affect pTau181 levels, determine the prognostic value of plasma pTau181 for clinical progression and the serial relationship between change in pTau181 to change in Tau PET, and identify the best context of use [1–3].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature using traditional (e.g., PubMed) resources. CSF phosphorylated tau has utility as a prognostic/diagnostic Alzheimer's disease (AD) biomarker. However, studies have not examined the utility of plasma phosphorylated tau 181 (pTau181) or compared it to plasma total tau.
2. Interpretation: Both plasma pTau181 and total tau increased with AD clinical severity. Plasma pTau181 was more strongly associated with amyloid- and tau-PET. In contrast, total tau was more strongly associated with cortical thickness. Plasma pTau181 was as good as or better than age and *APOE* in predicting elevated brain amyloid. These results suggest that plasma pTau181 may have utility as a marker of AD pathology and as a potential first-line screener in the population for AD pathology.
3. Future directions: Validation of these results in other populations is needed. Future research should also determine the factors affecting pTau181 levels and its best context of use.

Highlights

- Plasma total tau and phosphorylated tau 181 (pTau181) increased with AD severity
- Plasma pTau181, but not total tau, was higher among those with elevated brain Aβ
- Plasma pTau181 was associated with both Aβ and Tau PET; total tau was associated with cortical thickness
- Plasma pTau181 was a more sensitive and specific predictor of elevated brain Aβ than total tau
- Plasma pTau181 was as good as, or better than, age and *APOE* alone in predicting brain Aβ

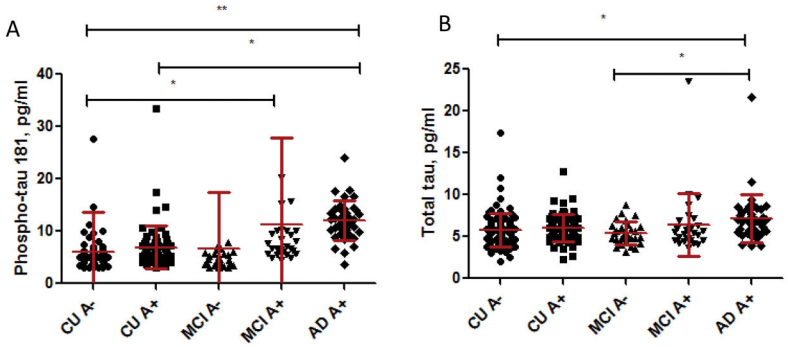

Fig. 1.

(A) Mean (SD) plasma phospho-tau 181, and (B) mean (SD) total tau by clinical diagnosis and elevated Aβ PET. Abbreviations: AD, Alzheimer's disease dementia; CU, cognitively unimpaired; MCI, mild cognitive impairment. For illustrative purposes only, the following outliers were not included: (A) 1 CU at 75.7 pg/ml and 2 MCI at 62.4 and 93.3 pg/ml; (B) none. *$P < .05$; **$P < .01$

Table 1

Participant characteristics, mean (IQR) or N (%), by clinical diagnosis

	CU (N = 172)	MCI (N = 57)	AD (N = 40)		
	Mean (SD)/N(%)	Mean (SD)/N(%)	Mean (SD)/N(%)	F value	P value*
Age	71.9 (9.5)	71.4 (10.7)	67.7 (9.2)	3.08	.048
Male	119 (69.2%)	45 (79.0%)	23 (57.5%)		.077
Education	15.2 (2.5)	15.0 (3.3)	15.1 (2.8)	0.16	.850
≥1 *APOE* ε4	50 (29.1%)	20 (35.1%)	28 (70.0%)		< .001
Aβ PET SUVR	1.5 (0.4)	1.8 (0.6)	2.4 (0.4)	76.24	< .001
Aβ PET>1.42 SUVR	72 (41.9%)	28 (49.1%)	38 (95.0%)		< .001
Tau PET entorhinal cortex	1.1 (0.1)	1.2 (0.2)	1.8 (0.3)	177.84	< .001
Cortical thickness	2.7 (0.1)	2.6 (0.2)	2.3 (0.2)	75.73	< .001
Cortical thickness<2.67mm	68 (39.5%)	35 (61.4%)	37/39 (94.9%)		< .001
Plasma phospho-tau 181	6.4 (6.4)	9.0 (13.9)	11.6 (4.1)	7.08	< .001
Plasma total tau	5.9 (1.9)	5.9 (2.8)	7.2 (2.8)	5.44	< .001

Abbreviations: AD, Alzheimer's disease dementia; Aβ, amyloid-beta; *APOE*, apolipoprotein E; CU, cognitively unimpaired; IQR, interquartile range; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standard uptake value ratio .

*Analyses of group differences included chi-square tests for dichotomous variables and ANOVA for continuous variables.

Table 2

Associations between plasma pTau181 or total tau and continuous and dichotomous neuroimaging measures of Aβ PET, tau PET, and cortical thickness in an AD-signature region

	Log Plasma phospho-tau 181		Log Plasma total tau	
	b or OR (95% CI)	***P***	***b or OR (95% CI)***	***P***
All (N=269)				
Aβ PET	**0.23 (0.18, 0.28)**	**<0.001**	**0.12 (0.03, 0.22)**	**0.010**
Aβ PET >1.42 SUVR	**7.13 (3.27, 15.54)**	**<0.001**	**2.83 (1.12, 7.13)**	**0.027**
Tau PET entorhinal cortex	**0.19 (0.14, 0.23)**	**<0.001**	**0.16 (0.08, 0.23)**	**<0.001**
Cortical thickness	**−0.15 (−0.19, −0.11)**	**<0.001**	**−0.20 (−0.27, −0.13)**	**<0.001**
Cortical thickness <2.67mm	**3.39 (1.77, 6.48)**	**<0.001**	**6.31 (2.35, 16.89)**	**<0.001**
CU (N=172)				
Aβ PET	**0.10 (0.03, 0.17)**	**0.003**	0.004 (−0.09, 0.10)	0.926
Aβ PET >1.42 SUVR	**2.84 (1.15, 7.045)**	**0.024**	1.94 (0.61, 6.16)	0.262
Tau PET entorhinal cortex	0.02 (−0.02, 0.07)	0.251	0.04 (−0.03, 0.11)	0.287
Cortical thickness	−0.02 (−0.06, 0.02)	0.368	−0.05 (−0.11, 0.01)	0.090
Cortical thickness <2.67mm	1.01 (0.47, 2.20)	0.973	**3.43 (1.01, 11.61)**	**0.047**
MCI (N=57)				
Aβ PET	**0.17 (0.06, 0.27)**	**0.003**	0.001 (−0.22, 0.22)	0.993
Aβ PET >1.42 SUVR	5.72 (0.86, 38.16)	0.071	1.52 (0.19, 12.41)	0.696
Tau PET entorhinal cortex	**0.13 (0.06, 0.20)**	**<0.001**	0.16 (−0.03, 0.35)	0.100
Cortical thickness	−0.07 (−0.14, 0.01)	0.072	**−0.20 (−0.33, −0.07)**	**0.003**
Cortical thickness <2.67mm	4.47 (0.68, 29.54)	0.120	1.80 (0.27, 12.11)	0.546
AD (N=40)				
Aβ PET	**0.20 (0.06, 0.34)**	**0.005**	0.10 (−0.10, 0.30)	0.300
Aβ PET >1.42 SUVR*				
Tau PET entorhinal cortex	**0.18 (0.06, 0.30)**	**0.013**	0.07 (−0.22, 0.36)	0.609
Cortical thickness	−0.14 (−0.32, 0.05)	0.147	−0.21 (−0.45, 0.03)	0.086
Cortical thickness <2.67mm*				

Abbreviations: AD, Alzheimer's disease dementia; Aβ, amyloid-beta; CI, confidence interval; CU, cognitively unimpaired; MCI, mild cognitive impairment; OR, odds ratio; PET, positron emission tomography; SUVR, standardized uptake value ratio. All models adjusted for age, sex, and *APOE*.

* Dichotomous models could not be run because 38 of the 40 had elevated Aβ PET and 37 of 40 had reduced cortical thickness.

Table 3

Participant characteristics by clinical diagnosis and elevated brain Aβ PET

	CU A- (N = 100)	CU A+ (N = 72)	MCI A- (N = 29)	MCI A+ (N = 28)	AD A+ (N = 38)		
	Mean (SD)/N(%)	Mean (SD)/N(%)	Mean (SD)/N(%)	Mean (SD)/N(%)	Mean (SD)/N(%)	F value	*P* value
Plasma phospho-tau 181	6.0 (7.6)	6.9 (4.1)	6.7 (10.8)	11.3 (16.5)	12.0 (3.8)	5.11	< .001
Plasma total tau	5.8 (2.0)	6.0 (1.7)	5.4 (1.3)	6.4 (3.7)	7.2 (2.9)	3.45	.009
Age	70.4 (9.8)	74.0 (8.8)	66.7 (9.3)	76.3 (10.0)	67.2 (9.2)	7.14	< .001
Male	72 (72.0%)	47 (65.3%)	27 (93.1%)	18 (64.3%)	22 (57.9%)		.023
Education	15.4 (2.4)	15.0 (2.7)	15.0 (3.6)	14.9 (2.9)	15.1 (2.8)	0.34	.853
APOE ε4	16 (16.0%)	34 (47.2%)	5 (17.2%)	15 (53.6%)	28 (73.7%)		< .001
Aβ PET SUVR	1.3 (0.1)	1.8 (0.4)	1.3 (0.1)	2.2 (0.5)	2.5 (0.4)	146.82	< .001
Aβ PET>1.42 SUVR	0 (0%)	72 (100%)	0 (0%)	28 (100%)	38 (100%)		< .001
Tau PET entorhinal cortex	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.3 (0.3)	1.8 (0.3)	131.50	< .001
Cortical thickness	2.7 (0.1))	2.7 (0.2)	2.7 (0.2)	2.6 (0.2)	2.3 (0.2)	40.23	< .001
Cortical thickness<2.67mm	34 (34.0%)	34 (47.2%)	13 (44.9%)	22 (78.6%)	35 (94.6%)		< .001

Abbreviations: AD, Alzheimer's disease dementia; Aβ, amyloid-beta; *APOE*, apolipoprotein E; CU, cognitively unimpaired; IQR, interquartile range; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standardized uptake value ratio.

*Analyses of group differences included chi-square tests for dichotomous variables and ANOVA for continuous variables.

Table 4

Correlation between plasma pTau181 or total tau with tau PET entorhinal cortex SUVR by clinical diagnosis and elevated Aβ PET

Clinical diagnosis and Aβ PET status*	Phospho-tau 181		Total tau	
	Spearman's rho	*P* value	Spearman's rho	*P* value
CU A−	−0.057	0.573	**0.238**	**0.017**
CU A+	**0.287**	**0.015**	0.069	0.563
MCI A−	0.284	0.136	0.212	0.270
MCI A+	**0.437**	**0.020**	0.104	0.598
AD A+	0.125	0.456	0.159	0.341
All A−	0.018	0.835	**0.228**	**0.009**
All A+	**0.580**	**<0.001**	**0.194**	**0.022**

Abbreviations: AD, Alzheimer's disease dementia; Aβ, amyloid-beta; CU, cognitively unimpaired; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standardized uptake value ratio.

*A+ = Aβ PET SUVR>1.42.

Table 5

Predictive accuracy of plasma pTau181 and total tau for elevated Aβ PET

	All (CU+MCI+AD) (N=269)	All Non-demented (CU+MCI)(N=229)	CU only (N=172)	MCI only (N=57)
	AUCROC (95% CI)	*AUCROC (95% CI)*	*AUCROC (95% CI)*	*AUCROC (95% CI)*
All				
Age	0.582 (0.514, 0.650)	0.643 (0.572, 0.715)	0.597 (0.512, 0.682)	0.777 (0.653, 0.902)
*Age, APOE ε4−	0.610 (0.521, 0.699)	0.649 (0.558, 0.739)	0.586 (0.475, 0.696)	0.840 (0.712, 0.968)
*Age, APOE ε4+	0.614 (0.477, 0.752)	0.681 (0.543, 0.820)	0.670 (0.494, 0.846)	0.720 (0.486, 0.954)
≥1 APOE ε4 allele	0.699 (0.647, 0.751)	0.664 (0.605, 0.722)	0.656 (0.588, 0.724)	0.682 (0.564, 0.799)
Age + ≥1 APOE ε4 allele	0.750 (0.691, 0.808)	0.747 (0.683, 0.811)	0.709 (0.629, 0.790)	0.839 (0.737, 0.940)
Plasma Phospho-tau 181	0.803 (0.749, 0.856)	0.750 (0.685, 0.814)	0.704 (0.624, 0.785)	0.852 (0.752, 0.952)
Plasma Total tau	0.598 (0.531, 0.666)	0.564 (0.489, 0.639)	0.566 (0.479, 0.653)	0.565 (0.414, 0.717)
*_APOE ε4−_				
Plasma Phospho-tau 181	0.737 (0.656, 0.817)	0.691 (0.601, 0.781)	0.653 (0.541, 0.766)	0.772 (0.622, 0.923)
Plasma Total tau	0.571 (0.479, 0.663)	0.558 (0.460, 0.656)	0.563 (0.450, 0.675)	0.542 (0.329, 0.754)
*_APOE ε4+_				
Plasma Phospho-tau 181	0.860 (0.761, 0.958)	0.821 (0.705, 0.937)	0.765 (0.608, 0.922)	0.960 (0.871, 1.000)
Plasma Total tau	0.698 (0.575, 0.821)	0.636 (0.492, 0.779)	0.656 (0.490, 0.823)	0.547 (0.226, 0.868)

Abbreviations: Aβ, amyloid-beta; *APOE*, apolipoprotein E; AUROC, area under the receiver operator characteristic curve; CI, confidence interval; CU, cognitively unimpaired; MCI, mild cognitive impairment; PET, positron emission tomography.

*There were 171 participants without an APOE ε4 allele; 159 were non-demented, including 122 CU and 37 MCI. There were 98 participants with an APOE ε4 allele; 70 were non-demented, including 50 CU and 20 MCI.