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RESEARCH ARTICLE

Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer's disease

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Abstract

Introduction: Plasma-measured tau phosphorylated at threonine 217 (p-tau217) is a potential non-invasive biomarker of Alzheimer's disease (AD). We investigated whether plasma p-tau217 predicts subsequent cognition and positron emission tomography (PET) markers of pathology in autosomal dominant AD.

Methods: We analyzed baseline levels of plasma p-tau217 and its associations with amyloid PET, tau PET, and word list delayed recall measured 7.61 years later in non-demented age- and education-matched presenilin-1 E280A carriers (n = 24) and non-carrier (n = 20) family members.

David Aguillon and Stephanie Langella are co-first authors.

Results: Carriers had higher plasma p-tau217 levels than non-carriers. Baseline plasma p-tau217 was associated with subsequent amyloid and tau PET pathology levels and cognitive function.

Discussion: Our findings suggest that plasma p-tau217 predicts subsequent brain pathological burden and memory performance in presenilin-1 E280A carriers. These results provide support for plasma p-tau217 as a minimally invasive diagnostic and prognostic biomarker for AD, with potential utility in clinical practice and trials.

KEYWORDS
autosomal dominant Alzheimer's disease, blood biomarkers, dementia, presenilin-1, tau pathology

Highlights

- Non-demented presenilin-1 E280A carriers have higher plasma tau phosphorylated at threonine 217 (p-tau217) than do age-matched non-carriers.
- Higher baseline p-tau217 is associated with greater future amyloid positron emission tomography (PET) pathology burden.
- Higher baseline p-tau217 is associated with greater future tau PET pathology burden.
- Higher baseline p-tau217 is associated with worse future memory performance.

1 | BACKGROUND

In vivo imaging of tau neurofibrillary tangle accumulation via positron emission tomography (PET) has improved the study, diagnosis, and monitoring of early Alzheimer's disease (AD).[1] Measuring tau via cerebrospinal fluid (CSF) samples has similarly shown utility as an early and specific measure of AD pathology.[2] However, there is a critical need for sensitive, cost effective, and minimally invasive biomarkers of AD. Plasma-based measures of phosphorylated tau (p-tau), which are less costly and invasive compared to PET or CSF, increase early in the disease process and reliably discriminate between AD and other neurodegenerative diseases.[3] Further research is needed to determine the utility of plasma p-tau as a preclinical biomarker.

Plasma-measured tau phosphorylated at site threonine 217 (p-tau217) has emerged as a particularly promising and specific AD biomarker.[3–6] Growing evidence shows elevated plasma p-tau217 across preclinical to clinical disease stages,[5,7–9] particularly in adults with high brain amyloid beta (Aβ) load.[5,10–12] Further, p-tau217 may have better diagnostic ability than other plasma biomarkers in early stages (e.g., p-tau181, neurofilament light [NfL], Aβ40, Aβ42).[5,7,13,14] We previously showed in a kindred with autosomal dominant Alzheimer's disease (ADAD) due to a mutation on the presenilin-1 (*PSEN1*) gene that increased levels of plasma p-tau217 were able to distinguish carriers from age-matched non-carriers 20 years prior to their estimated age of symptom onset.[7]

The association between tau measured through plasma and PET is important to characterize, as tau PET remains the gold standard for in vivo quantification of tau pathology for research and clinical purposes. Plasma p-tau217 is correlated with concurrent tau PET in individuals with high Aβ, mild cognitive impairment (MCI), and AD.[5,15–17] Notably, a recent study found increased plasma p-tau217 in cognitively unimpaired individuals with positive Aβ PET imaging and negative tau PET, suggesting that plasma p-tau217 levels become abnormal before accumulation is detectable via tau PET.[15]

Less is known, however, about the association between plasma p-tau217 and subsequent tau PET accumulation. In sporadic AD (e.g., older adults with high Aβ), one study reported an association between plasma p-tau217 and increasing tau PET in the entorhinal cortex on average 1.6 years later.[15] A second study, similarly examining measurements 1 to 2 years from baseline, reported an association with increasing medial temporal lobe tau PET.[18] Further research into this association is critical to determine whether p-tau217 may serve as an early marker of AD pathology and aid in early detection. If plasma p-tau217 can predict future tau PET at a longer interval, clinical trials may be able to enroll individuals at an earlier stage.

In this study, we leveraged a cohort of carriers of the *PSEN1* E280A mutation for ADAD to examine whether baseline levels of plasma p-tau217 are associated with subsequent PET-based markers of AD pathology in the brain, measured on average 7.61 years after plasma collection. Secondarily, we examined the association between plasma

p-tau217 and subsequent cognition. These findings would inform the use of plasma p-tau217 as a biomarker for the selection, monitoring, and evaluation in clinical trials and other investigations.

2 | METHODS

2.1 | Study design and participants

This cohort study included 24 *PSEN1* E280A mutation carriers (23 Aβ-pathology positive) and 20 age- and education-matched non-carriers from the same kindred, enrolled in the Massachusetts General Hospital (MGH) COLBOS (Colombia–Boston) longitudinal biomarker study. Participants were recruited from the Alzheimer's Prevention Initiative (API) registry of familial AD, which currently includes more than 6,000 living members of the kindred and approximately 1,200 mutation carriers.[19] Characteristics of this kindred have been well characterized.[20–22] Notably, the onset of clinical impairment occurs in mid-life, with the median age of onset of MCI at 44 years old and dementia at 49 years old.[21]

Participants with a diagnosis of dementia at the time of blood sample collection or with a significant medical, psychiatric, or neurological disorder (e.g., stroke, seizures, substance abuse, and other disorders that affect motor, visuospatial or cognitive abilities) were excluded. Neither the participants nor raters were informed of the genetic status of the individuals. This study was approved by the institutional ethics review boards of the University of Antioquia in Medellin, Colombia, and the MGH in Boston, Massachusetts, USA. All participants provided written informed consent before inclusion in the study.

Blood sampling was performed at baseline. Neuroimaging and cognitive memory assessment were completed at follow-up (mean = 7.61 ± 4.05 years). All participants were cognitively unimpaired at baseline. At follow-up, all non-carriers and 18 carriers were cognitively unimpaired, and 6 carriers progressed to MCI. Participants were considered cognitively unimpaired if they had a Mini-Mental State Examination (MMSE)[23] score ≥26 and a Functional Assessment Staging Test (FAST)[24] score of 1 or 2. Impaired carriers were defined as having a FAST score of 3.

2.2 | Plasma p-tau217 assay

Plasma was collected in the morning (without fasting) at the University of Antioquia in aliquots of 1 mL. Samples were stored at −80°C. Concentrations of plasma p-tau217 were measured using immunoassays at Lilly Research Laboratories, using the MSD (Meso Scale Discovery) platform as previously described.[7] Biotinylated-IBA493 was used as a capture antibody and SULFO-TAG-4G10-E2 (anti-Tau) as the detector. Additional details of the plasma p-tau217 analysis are described in Palmqvist et al. Supplemental Material.[7]

RESEARCH IN CONTEXT

- **Systematic Review**: We used PubMed to review the literature on plasma tau phosphorylated at threonine 217 (p-tau217) in Alzheimer's disease (AD). Recent studies have reported converging results indicating plasma p-tau217 as a promising and specific biomarker for AD; however, the relationship between plasma p-tau217 and future positron emission tomography (PET) pathology has not been widely studied. Relevant citations are appropriately noted in the article.
- **Interpretation**: Our results demonstrate an association between baseline plasma p-tau217 and subsequent measures of in vivo brain pathology and cognition. These findings add to the growing literature supporting the utility of plasma p-tau217 as a minimally invasive diagnostic and prognostic marker of AD.
- **Future Directions**: Future studies should investigate the longitudinal relationships between plasma p-tau217 and tau PET pathology in both autosomal dominant and sporadic AD.

2.3 | Clinical and cognitive assessments

Clinical assessments were performed at the University of Antioquia. Participants underwent a clinical interview and were administered the MMSE, FAST, and a Spanish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list, which has been adapted for this Colombian population.[25] Other cognitive tests were performed in these participants as part of a Spanish neuropsychological test battery used by the Grupo de Neurociencias de Antioquia–Colombia[26] (data not shown in this article). Cognitive measures were administered in Spanish by a neuropsychologist, or a psychologist trained in neuropsychological assessment. Neurological examinations were performed by a neurologist or by a general practitioner trained in assessing neurodegenerative disorders.

2.4 | Image acquisition and processing

All participants in this study traveled from Colombia to Boston (USA) for PET at the MGH. PET data were acquired on a Siemens ECAT HR+ (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution; 2.4 mm slice interval).

11C-Pittsburgh compound B (11C-PiB) PET was acquired with an 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12 × 15 seconds, 57 × 60 seconds). 11C-PiB PET data were quantified as the distribution volume ratio

(DVR) with cerebellar gray as a reference region; regional time-activity curves were used to compute regional DVRs for each region of interest (ROI) using the Logan graphical method applied to data obtained between 40 and 60 minutes after injection.[27] 11C-PiB retention was assessed using a large cortical ROI aggregate that included frontal, lateral temporal, and retrosplenial cortices as described previously.[28]

[F18] Flortaucipir (FTP) was acquired between 80 and 100 minutes after a 9.0 to 11.0 mCi bolus injection in four separate 5-minute frames. [F18] FTP-specific binding was expressed in FreeSurfer ROIs as the standardized uptake value ratio (SUVR) to the cerebellum. The spatially transformed SUVR PET data were smoothed with an 8 mm Gaussian kernel to account for individual anatomic differences.[29] SUVR values were represented graphically on vertices at the pial surface. A priori ROIs were inferior temporal cortex, entorhinal cortex, and precuneus.[30,31]

Partial volume correction was applied using the extended Muller–Gartner method implemented in FreeSurfer for both PiB and FTP.[32]

2.5 | Genotyping

Genomic DNA was extracted from the blood by standard protocols, and *PSEN1* E280A characterization was done at the University of Antioquia using methods previously described.[33] Genomic DNA was amplified with the primers PSEN1-S 5′ AACAGCTCAGGAGAGGAATG 3′ and PSEN1-AS 5′ GATGAGACAAGTNCCNTGAA 3′. We used the restriction enzyme *Bsm*I for restriction fragment length polymorphism analysis. Each participant was classified as a *PSEN1* E280A carrier or non-carrier.

2.6 | Statistical analysis

Analyses and visualizations were performed in R (version 4.0.3) and used a significance threshold of two-tailed $P < .05$. Group differences in normally distributed continuous variables were compared using independent two-sample *t* tests (Levene's test was used for examining equality of variances). Group differences in non-normally distributed continuous variables were compared using Mann–Whitney U tests. Chi-square tests were used for categorical variables. Spearman correlation was used to test associations between continuous variables in the whole sample (reported in the main text), with and without covariates (age, sex, time between PET and blood measures). Correlations were additionally conducted within each group and are presented in the supporting information. One potential outlying value was identified (mutation carrier who converted to MCI at follow-up), and correlation analyses were repeated excluding this carrier, with consistent results (see Table S1 in supporting information).

Pearson correlation was used in exploratory analyses of plasma p-tau217 and vertex-wise Aβ and tau PET within carriers. PET images were normalized to standard (Montreal Neurological Institute [MNI]) space and projected onto the average surface, and vertex-wise values were sampled at the midpoint of the gray matter. Partial volume correction was applied using the extended Muller–Gartner method implemented in FreeSurfer.[32] Results were displayed as −log10(p), significant at cluster-wise $P < .05$ (minimum cluster extent = 100 mm^2) after false discovery rate (FDR) correction for multiple comparisons. Clustering and multiple comparisons corrections were performed using FreeSurfer tools.

3 | RESULTS

3.1 | Baseline sample characteristics and plasma p-tau217 levels

A total of 24 *PSEN1* E280A carriers and 20 non-carriers were included in analyses (Table 1). Carriers and non-carriers did not differ in age at baseline ($t[42] = 1.71$, $P = .094$), years of education ($t[42] = 1.41$, $P = .167$), or sex ($\chi^2 = 0.78$, $P = .378$). Carriers had higher plasma p-tau217 levels than non-carriers ($W = 122$, $P = .005$). Neuroimaging occurred on average 7.61 years after plasma sample collection (median = 6.00 years), with a statistically significant longer interval for non-carriers than for carriers ($t[42] = 2.07$, $P = .044$).

3.2 | Group differences in biomarkers at follow-up assessment

Of the 24 carriers, 18 remained cognitively unimpaired and 6 converted to MCI at follow-up. Carriers exhibited elevated neuroimaging biomarkers at follow-up (Table 2), namely higher cortical Aβ DVR ($W = 11$, $P < .001$) and regional tau PET SUVR in the entorhinal cortex ($W = 51$, $P < .001$), inferior temporal cortex ($W = 141$, $P = .019$), and precuneus ($W = 86$, $P < .001$). CERAD word list delayed recall ($W = 357.5$, $P = .005$) and MMSE scores ($W = 366$, $P = .002$) were lower in carriers than non-carriers.

3.3 | Associations between plasma p-tau217 levels and age, cortical Aβ, regional tau, and cognition

To assess the utility of plasma p-tau217 as an early AD biomarker, we examined its associations with various concurrent and subsequent markers of AD in the whole sample. Older age at baseline was associated with higher levels of plasma p-tau217, $r = 0.41$, $P = .006$, 95% confidence interval (CI) [0.13, 0.63] (Figure 1A). Higher baseline plasma p-tau217 was associated with lower MMSE ($r = -0.57$, $P < .001$, CI [−0.74, −0.33]; Figure 1B) and delayed recall ($r = -0.52$, $P < .001$, CI [−0.71, −0.26]; Figure 1C) scores at follow-up. Higher baseline plasma p-tau217 was also associated with higher subsequent PET measures of cortical Aβ ($r = 0.55$, $P < .001$, CI [0.30, 0.73]; Figure 2A) and tau in all ROIs: entorhinal cortex ($r = 0.47$, $P = .001$, CI [0.20, 0.67]; Figure 2B), inferior temporal cortex ($r = 0.44$, $P = .003$, CI [0.16, 0.65]; Figure 2C), and precuneus ($r = 0.53$, $P < .001$, CI [0.28, 0.72]; Figure 2D). We additionally examined these relationships separately for carriers and

TABLE 1 Baseline demographic and plasma p-tau217 data

	Non-carriers ($n = 20$)	Carriers ($n = 24$)	Test statistic	*P*-value	95% CI
Age at baseline (years)	27.6 ± 6.98	31.1 ± 6.81	$t[42] = 1.71$	.094	[−7.78, 0.63]
Education (years)	11.3 ± 4.10	9.38 ± 4.63	$t[42] = 1.41$	.167	[−0.81, 4.56]
Sex (male/female)	11/9	10/14	$X^2(1) = 0.78$	.378	
p-tau217 (pg/mL)	2.53 ± 1.39	5.27 ± 4.69	$W = 122$	.005	[−3.07, −0.42]
Time between blood samples and PET scans (years)	8.95 ± 4.19	6.50 ± 3.65	$t[42] = 2.07$	.044	[−4.83, −0.07]

Note: Means and standard deviations given for age, education, p-tau217, and follow-up time. Group differences were assessed using *t* tests for normally distributed variables and Wilcoxon rank sum test for non-normally distributed variables.
Abbreviations: CI, confidence interval; PET, positron emission tomography; p-tau217, tau phosphorylated at threonine 217.

TABLE 2 Follow-up neuroimaging and cognitive data

	Non-carriers ($n = 20$)	Carriers ($n = 24$)	Test statistic	*P*-value	95% CI
11C PiB-PET (DVR)	1.11 ± 0.04	1.69 ± 0.39	$W = 11$	<.001	[−0.69, −0.37]
Entorhinal cortex FTP (SUVR)	1.02 ± 0.12	1.52 ± 0.45	$W = 51$	<.001	[−0.58, −0.26]
Inferior temporal FTP (SUVR)	1.21 ± 0.13	1.56 ± 0.68	$W = 141$	.019	[−0.29, −0.01]
Precuneus FTP (SUVR)	1.05 ± 0.13	1.72 ± 1.02	$W = 86$	< .001	[−0.59, −0.11]
Mini-Mental State Examination	29.0 ± 0.97	26.7 ± 3.50	$W = 366$	.002	[< 0.01, 2.00]
CERAD delayed recall	7.85 ± 1.18	5.17 ± 3.21	$W = 357.5$	.005	[1.00, 4.00]

Note: Means and standard deviations given. Group differences were assessed using *t* tests for normally distributed variables and Wilcoxon rank sum test for non-normally distributed variables.
Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's; CI, confidence interval; DVR, distribution volume ratio; FTP, flortaucipir; PiB, Pittsburgh Compound B; SUVR, standardized uptake value ratio.

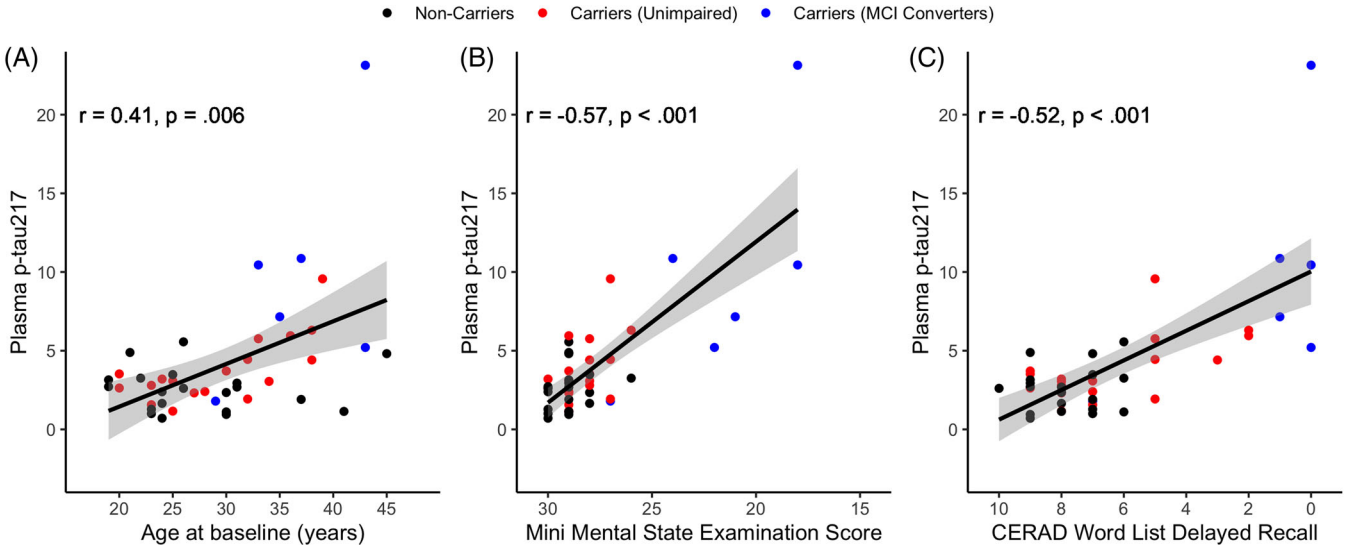

FIGURE 1 Plasma tau phosphorylated at threonine 217 (p-tau217) associations with age and cognition in the whole sample. Scatterplots with simple regression line and standard error showing the association between plasma p-tau217 (picograms per milliliter) and (A) age at baseline, (B) Mini Mental State Examination Score, and (**C**) Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list delayed recall. Black circles: non-carriers; red circles: carriers (unimpaired), blue circles: carriers (mild cognitive impairment [MCI] converters)

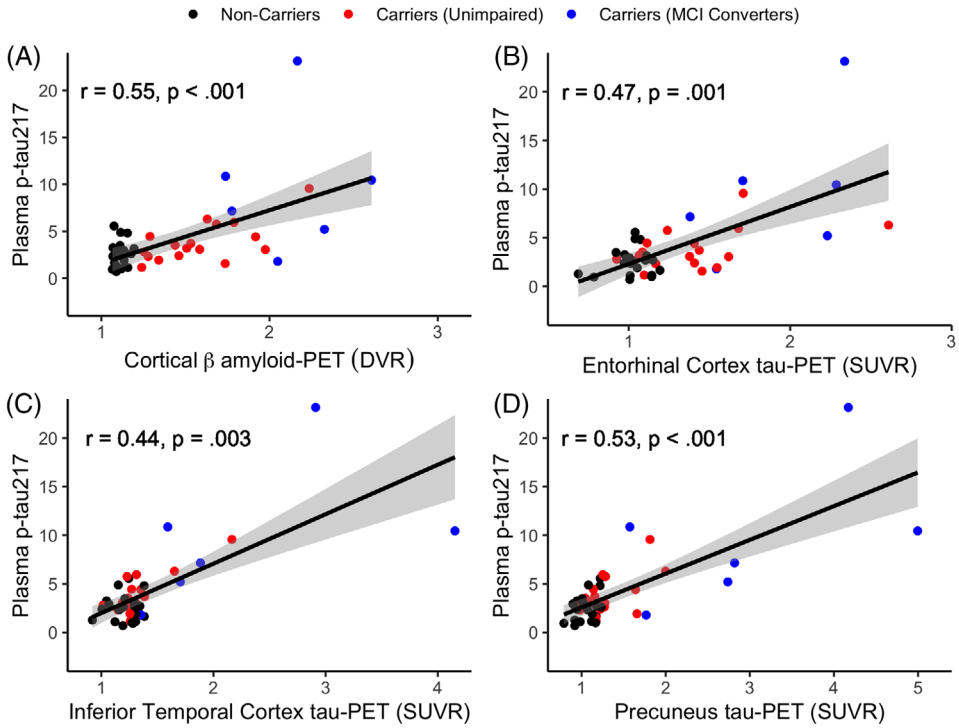

FIGURE 2 Plasma tau phosphorylated at threonine 217 (p-tau217) associations with positron emission tomography (PET)-based pathology in the whole sample. Scatterplots with simple regression line and standard error showing the association between plasma p-tau217 (picograms per milliliter) and (A) mean cortical amyloid beta (β amyloid) PET, (B) entorhinal cortex tau PET, (C) inferior temporal cortex tau PET, and (D) precuneus tau PET. Black circles: non-carriers; red circles: carriers (unimpaired), blue circles: carriers (mild cognitive impairment [MCI] converters). DVR, distribution volume ratio; SUVR, standardized uptake value ratio

non-carriers, finding that associations between p-tau217 and age, PET pathology, and cognition were only significant for carriers (Table S2 in supporting information).

Consistent results were observed in the whole group after controlling for age, sex, and time between measurements: MMSE $r = -0.42$, $P = .006$, CI [−0.65, −0.13]; delayed recall $r = -0.30$, $P = .056$, CI [−0.56, 0.01]; cortical Aβ PET $r = 0.49$, $P = .001$, CI [0.22, 0.69]; entorhinal cortex tau PET $r = 0.39$, $P = .012$, CI [0.09, 0.62]; inferior temporal cortex tau PET $r = 0.31$, $P = .043$, CI [0.01, 0.57]; and precuneus tau PET $r = 0.48$, $P = .001$, CI [0.21, 0.69]. Within-group correlations were not significant after controlling for these covariates (Table S3 in supporting information). There was no significant relationship between p-tau217 and tau PET ROIs when including Aβ as a covariate, but the negative associations with cognition remained significant (Table S4 in supporting information). Further, cortical Aβ was a significant partial mediator of the relationship between plasma p-tau217 and tau PET (Table S5 in supporting information).

3.4 | Associations between plasma p-tau217 and whole-brain Aβ- and tau PET in *PSEN1* carriers

We assessed the relationship between plasma p-tau217 and vertex-wise PET pathology in mutation carriers. Plasma p-tau217 was positively correlated with Aβ burden in frontal, lateral temporal, parietal, and retrosplenial cortices. Correlations with tau PET were strongest in temporal and parietal regions, consistent with the known anatomy of early tau accumulation in mutation carriers, as well as involvement of frontal regions (Figure 3A). Limiting analyses to cognitively unimpaired carriers only (Figure 3B), Aβ and tau PET correlations with plasma p-tau217 were observed to a smaller extent, primarily in the left lateral temporal cortices.

Results were attenuated when adjusting for age, sex, and time between measurements in the carrier group, but the regional associations between p-tau217 and tau PET were similar to unadjusted results (Figure S1A in supporting information). Limiting analyses to unimpaired carriers only, the age-, sex-, and time-adjusted associations did not survive FDR correction. Similarly, including cortical Aβ as a covariate attenuated the associations in all carriers, and the associations did not remain significant when limiting to unimpaired carriers only (Figure S1B). As a supplementary analysis, we also examined the associations between p-tau217 and cortical thickness. Associations with cortical thickness were weaker than those with tau- and amyloid PET, and none of the thickness results survived multiple comparisons correction with FDR (Figure S2 in supporting information).

4 | DISCUSSION

The primary aim of this study was to examine whether plasma p-tau217 is associated with subsequent PET-based markers of AD pathology in the brain and cognitive performance. We examined this association

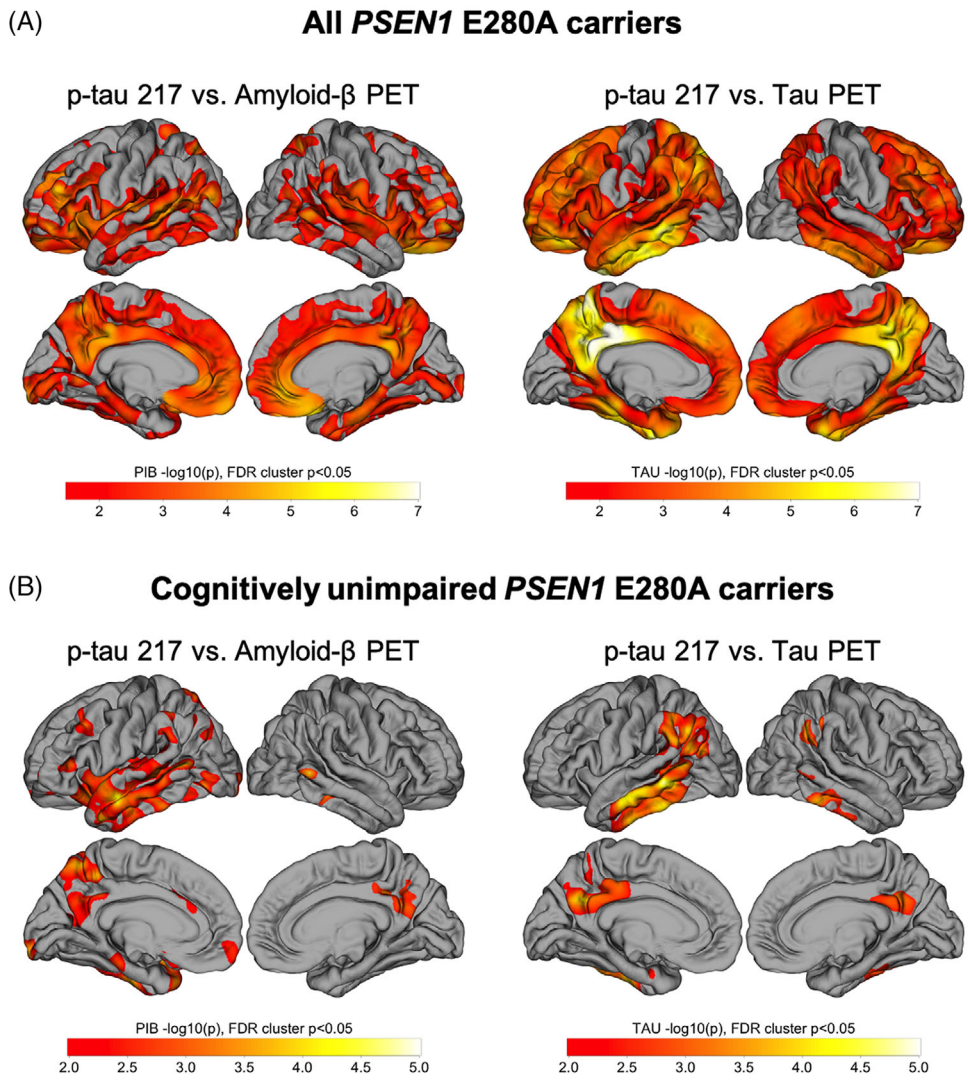

FIGURE 3 Whole-cortex analysis of amyloid beta (Aβ) and tau positron emission tomography (PET) versus plasma tau phosphorylated at threonine 217 (p-tau217). Pearson correlations were performed between p-tau217 concentrations and Aβ (left) and tau (right) PET. Results are displayed as −log10(p), significant at cluster $P < .05$ after false discovery rate (FDR) correction. Correlations performed in (A) all presenilin-1 (*PSEN1*) E280A carriers ($n = 24$) and (B) cognitively unimpaired *PSEN1* E280A carriers ($n = 18$)

in a cohort of *PSEN1* E280A carriers, who will develop dementia by mid-life, and non-carrier family members, using plasma p-tau217 and neuroimaging markers collected on average 7.61 years apart. Consistent with our hypotheses, plasma p-tau217 was elevated in cognitively unimpaired *PSEN1* carriers compared to non-carrier family members. Critically, baseline p-tau217 levels were associated with subsequent Aβ and tau PET deposits and lower memory performance. Together, our results suggest that plasma p-tau217 is a promising biomarker for early AD detection and progression.

In our sample, carriers had higher plasma levels of p-tau217 than non-carriers prior to the onset of cognitive impairment, and, within carriers, higher p-tau217 was associated with older age. The median age of onset of MCI in this kindred is 44 years,[21] more than a decade older than the average age of carriers in this sample at the time of plasma collection. Although these data are not longitudinal, due to the well-characterized clinical trajectory of the mutation carriers and near complete penetrance of the mutation, age serves as a proxy for time until clinical onset and provides a model for disease progression. As such, these associations provide evidence that plasma p-tau217 may be an early marker of preclinical AD and related to disease progression, potentially increasing as clinical onset approaches. Consistent results have been previously reported from this kindred[7] and from studies of sporadic AD, using comparisons of unimpaired older adults with high- versus low-Aβ.[15,34] However, longitudinal studies are required to describe the trajectory of plasma p-tau217 across disease stage.

Although converging findings indicate this early change in plasma p-tau217, little has been reported about its associations with subsequent PET-based pathology, the current gold standard in measuring in vivo AD pathology. Prior findings in older adults at risk for sporadic AD found an association between plasma p-tau217 and concurrent Aβ PET[17] and tau PET imaging;[5,16,17,35] however, only two studies, to our knowledge, have examined the relationship with future tau PET.

These prior studies, with measurements conducted approximately 1 to 2 years apart, found a relationship between plasma p-tau217 and subsequent medial temporal lobe tau PET.[15,18] Our study expands on these results by showing an association with widespread Aβ and tau pathology 7.61 years after plasma collection. Regional analyses revealed an association with mean cortical Aβ and regional tau PET in three key anatomical regions: interior temporal cortex, entorhinal cortex, and precuneus. Our findings in inferior temporal cortex and entorhinal cortex are consistent with prior findings in plasma PET investigations,[5,15,18,35] and we additionally show this association with precuneus, a region previously shown to be early impacted by AD pathology in this kindred.[31,36] Further, our study is the first to conduct whole-brain analyses, revealing the correlations between plasma and tau PET mirror the known progression of early tau pathology accumulation.[30,31] As expected early in the course of the disease, the correlations were limited to the temporal cortices in the cognitively unimpaired carriers. In contrast, when including the carriers with MCI, the spatial extent was much greater, including parietal and frontal cortices.

To note, the associations between p-tau217 and regional tau PET were no longer significant when controlling for cortical Aβ, which was shown to be a partial mediator of the plasma–tau PET relationship, and the voxel-wise associations were attenuated when controlling for cortical Aβ. Other findings have shown an association between p-tau217 and Aβ PET[15,37] and p-tau217 has been shown to do particularly well at discriminating between AD and other neurodegenerative diseases.[11,13] Together, these findings suggest that p-tau217 may be reflecting both Aβ- and tau-related processes, though more work is needed to determine the exact pathology that is indicated by p-tau217.

Other plasmatic biomarkers, such as p-tau181, have been associated with markers of neurodegeneration in AD-related areas through magnetic resonance imaging, fluorodeoxyglucose PET, amyloid PET, and tau PET,[38,39] and have been able to differentiate AD from other neurodegenerative diseases.[40] P-tau181 has also been found to predict tau pathology 6 years later in temporoparietal regions that are associated with AD.[41] However, in several studies, p-tau217 has shown superiority and greater diagnostic accuracy than other biomarkers in plasma and CSF, such as p-tau181.[5,7,13,14]

In addition to pathological markers, elevated plasma p-tau217 was associated with lower subsequent delayed recall and global cognition. Tau PET burden has been consistently associated with worse cognition in this kindred,[31,36,42] though only one prior study has reported an association between plasma p-tau217 and cognition in this kindred.[7] In sporadic AD, longitudinal increases in plasma p-tau217 were associated with worse cognition.[12] However, another study found that tau PET had a stronger association with cognition than did plasma p-tau217.[35] More work is needed to clarify the association between plasma p-tau217 and cognition and the extent to which it can predict declines in various cognitive domains and global cognitive changes.

This study has several strengths and limitations. A primary strength of this study is the kindred with a single variant mutation for autosomal dominant AD, whose clinical trajectory is well characterized.[20,21] Due to the early median age of onset for MCI in this kindred, typical age-related confounds prevalent in studies of older adults are mitigated in this sample. This is particularly important for studies of tau pathology, which can accumulate with age in the absence of other AD pathology.[42] Another strength is the 7.61-year interval between plasma collection, at which time all participants were cognitively unimpaired, and neuroimaging measures, at which time only six participants converted to MCI, thereby highlighting the utility of early plasma p-tau217 for predicting pathology prior to conversion to dementia. Despite the advantages provided by studying this kindred, our sample size is relatively small for a biomarker study, and the extent to which these findings can be generalized to sporadic AD is unknown. Recent findings indicate similar in vivo pathology in sporadic and autosomal dominant AD, including CSF measures of p-tau.[43] However, future studies in additional autosomal dominant and sporadic AD populations are needed to investigate plasma biomarkers' generalizability. Additionally, analysis of blood samples was not available at follow-up in our sample. Future studies would benefit from longitudinal collection of both plasma p-tau217 and tau PET to assess the trajectory of each biomarker, as well as investigate potential differences in the plasma–PET association at varying follow-up intervals.

In sum, our results show that baseline levels of plasma p-tau217 predict subsequent levels of amyloid and tau burden and worse future memory performance in *PSEN1* E280A carriers. These findings add to the growing literature suggesting that plasma p-tau217 is an early marker for AD by demonstrating an association between plasma and PET measures of pathology. Our results provide support for plasma p-tau217 as a potential minimally invasive diagnostic and prognostic biomarker of AD pathology and cognition, with promising utility in clinical practice and trials.

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CONFLICTS OF INTEREST

Dr. Langella was supported by a grant from the Alzheimer's Association (AA Research Fellowship). Dr. Vila-Castelar was supported by a grant from the Alzheimer's Association (AA Research Fellowship). Dr. Quiroz was supported by grants from the National Institute on Aging (R01 AG054671, RF1AG077627), the Alzheimer's Association, and Massachusetts General Hospital ECOR. Dr. Quiroz reports receiving consulting fees from Biogen. Dr. Hansson is supported by the Swedish Research Council (2016-00906), the Knut and Alice Wallenberg foundation (2017-0383), the Marianne and Marcus Wallenberg

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REFERENCES

1. Chandra A, Valkimadi P, Pagano G, Cousins O, Dervenoulas G, Politis M. Applications of amyloid, tau, and neuroinflammation PET imaging to Alzheimer's disease and mild cognitive impairment. *Hum Brain Mapp*. 2019;40(18):5424-5442.
2. Bjerke M, Engelborghs S. Cerebrospinal fluid biomarkers for early and differential Alzheimer's disease diagnosis. *J Alzheimers Dis JAD*. 2018;62(3):1199-1209.
3. Leuzy A, Cullen NC, Mattsson-Carlgren N, Hansson O. Current advances in plasma and cerebrospinal fluid biomarkers in Alzheimer's disease. *Curr Opin Neurol*. 2021;34(2):266-274.
4. Telser J, Risch L, Saely CH, Grossmann K, Werner P. P-tau217 in Alzheimer's disease. *Clin Chim Acta Int J Clin Chem*. 2022;531:100-111.
5. Thijssen EH, La Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol*. 2021;20(9):739-752.
6. Wennström M, Janelidze S, Nilsson KPR, et al. Cellular localization of p-tau217 in brain and its association with p-tau217 plasma levels. *Acta Neuropathol Commun*. 2022;10(1):3.
7. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2020;324(8):772-781.
8. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. *Alzheimers Dement J Alzheimers Assoc*. 2021;17(8):1353-1364.
9. Bayoumy S, Verberk IMW, den Dulk B, et al. Clinical and analytical comparison of six Simoa assays for plasma P-tau isoforms P-tau181, P-tau217, and P-tau231. *Alzheimers Res Ther*. 2021;13(1):198.
10. Cullen NC, Leuzy A, Janelidze S, et al. Plasma biomarkers of Alzheimer's disease improve prediction of cognitive decline in cognitively unimpaired elderly populations. *Nat Commun*. 2021;12(1):3555.
11. Barthélemy NR, Horie K, Sato C, Bateman RJ. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. *J Exp Med*. 2020;217(11):e20200861.
12. Mattsson-Carlgren N, Janelidze S, Palmqvist S, et al. Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease. *Brain J Neurol*. 2020;143(11):3234-3241.
13. Barthélemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nat Med*. 2020;26(3):398-407.
14. Pichet Binette A, Palmqvist S, Bali D, et al. Combining plasma phospho-tau and accessible measures to evaluate progression to Alzheimer's dementia in mild cognitive impairment patients. *Alzheimers Res Ther*. 2022;14(1):46.
15. Janelidze S, Berron D, Smith R, et al. Associations of plasma phospho-tau217 levels with tau positron emission tomography in early Alzheimer disease. *JAMA Neurol*. 2021;78(2):149-156.

16. Mielke MM, Frank RD, Dage JL, et al. Comparison of plasma phosphorylated tau species with amyloid and tau positron emission tomography, neurodegeneration, vascular pathology, and cognitive outcomes. *JAMA Neurol*. 2021;78(9):1108-1117.
17. Mattsson-Carlgren N, Janelidze S, Bateman RJ, et al. Soluble P-tau217 reflects amyloid and tau pathology and mediates the association of amyloid with tau. *EMBO Mol Med*. 2021;13(6):e14022.
18. Leuzy A, Smith R, Cullen NC, et al. Biomarker-based prediction of longitudinal tau positron emission tomography in Alzheimer disease. *JAMA Neurol*. 2022;79(2):149-158.
19. Reiman EM, Langbaum JBS, Fleisher AS, et al. Alzheimer's prevention initiative: a plan to accelerate the evaluation of presymptomatic treatments. *J Alzheimers Dis JAD*. 2011;26(Suppl 3):321-329.
20. Fuller JT, Cronin-Golomb A, Gatchel JR, et al. Biological and cognitive markers of presenilin1 E280A autosomal dominant Alzheimer's disease: a comprehensive review of the colombian kindred. *J Prev Alzheimers Dis*. 2019;6(2):112-120.
21. Acosta-Baena N, Sepulveda-Falla D, Lopera-Gómez CM, et al. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. *Lancet Neurol*. 2011;10(3):213-220.
22. Lopera F, Ardilla A, Martínez A, et al. Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. *JAMA*. 1997;277(10):793-799.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
24. Reisberg B. Functional assessment staging (FAST). *Psychopharmacol Bull*. 1988;24(4):653-659.
25. Aguirre-Acevedo DC, Gómez RD, Moreno S, et al. Validity and reliability of the CERAD-Col neuropsychological battery. *Rev Neurol*. 2007;45(11):655-660.
26. Torres VL, Vila-Castelar C, Bocanegra Y, et al. Normative data stratified by age and education for a Spanish neuropsychological test battery: results from the Colombian Alzheimer's prevention initiative registry. *Appl Neuropsychol Adult*. 2021;28(2):230-244.
27. Logan J, Fowler JS, Volkow ND, et al. Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab*. 1990;10(5):740-747.
28. Amariglio RE, Mormino EC, Pietras AC, et al. Subjective cognitive concerns, amyloid-β, and neurodegeneration in clinically normal elderly. *Neurology*. 2015;85(1):56-62.
29. Johnson KA, Schultz A, Betensky RA, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Ann Neurol*. 2016;79(1):110-119.
30. Quiroz YT, Sperling RA, Norton DJ, et al. Association between amyloid and tau accumulation in young adults with autosomal dominant Alzheimer disease. *JAMA Neurol*. 2018;75(5):548-556.
31. Sanchez JS, Hanseeuw BJ, Lopera F, et al. Longitudinal amyloid and tau accumulation in autosomal dominant Alzheimer's disease: findings from the Colombia-Boston (COLBOS) biomarker study. *Alzheimers Res Ther*. 2021;13(1):27.
32. Greve DN, Svarer C, Fisher PM, et al. Cortical surface-based analysis reduces bias and variance in kinetic modeling of brain PET data. *NeuroImage*. 2014;92:225-236.
33. Lendon CL, Martinez A, Behrens IM, et al. E280A PS-1 mutation causes Alzheimer's disease but age of onset is not modified by ApoE alleles. *Hum Mutat*. 1997;10(3):186-195.
34. Janelidze S, Palmqvist S, Leuzy A, et al. Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma Aβ42/Aβ40 and p-tau. *Alzheimers Dement J Alzheimers Assoc*. 2022;18(2):283-293.
35. Ossenkoppele R, Reimand J, Smith R, et al. Tau PET correlates with different Alzheimer's disease-related features compared to CSF and plasma p-tau biomarkers. *EMBO Mol Med*. 2021;13(8):e14398.
36. Guzmán-Vélez E, Diez I, Schoemaker D, et al. Amyloid-β and tau pathologies relate to distinctive brain dysconnectomics in preclinical autosomal-dominant Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2022;119(15):e2113641119.
37. Pontecorvo MJ, Lu M, Burnham SC, et al. Association of donanemab treatment with exploratory plasma biomarkers in early symptomatic Alzheimer disease: a secondary analysis of the TRAILBLAZER-ALZ randomized clinical trial. *JAMA Neurol*. 2022.
38. Moscoso A, Grothe MJ, Ashton NJ, et al. Longitudinal associations of blood phosphorylated Tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. *JAMA Neurol*. 2021;78(4):396-406.
39. Tissot C, L Benedet A, Therriault J, et al. Plasma pTau181 predicts cortical brain atrophy in aging and Alzheimer's disease. *Alzheimers Res Ther*. 2021;13(1):69.
40. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19(5):422-433.
41. Moscoso A, Grothe MJ, Ashton NJ, et al. Time course of phosphorylated-tau181 in blood across the Alzheimer's disease spectrum. *Brain J Neurol*. 2021;144(1):325-339.
42. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol (Berl)*. 2014;128(6):755-766.
43. Morris JC, Weiner M, Xiong C, et al. Autosomal dominant and sporadic late onset Alzheimer disease share a common in vivo pathophysiology. *Brain J Neurol*. 2022;145(10):3594-3607. awac181.

SUPPORTING INFORMATION

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

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