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RESEARCH ARTICLE

Relationship between baseline plasma p-tau181 and longitudinal changes in cognition and structural brain measures in a cohort of cognitively unimpaired older adults

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Abstract

INTRODUCTION: Preclinical Alzheimer's disease (AD) affects a significant proportion of cognitively unimpaired (CU) older adults. Currently, blood-based biomarkers detect very early changes in the AD continuum with great accuracy.

METHODS: We measured baseline plasma phosphorylated tau (p-tau)181 using electrochemiluminescence (ECL)-based assay (MesoScale Discovery) in 533 CU older adults. Follow-up lasted up to 18 months. Cognitive performance assessment included memory and cognitive control. Structural brain measures included cortical thickness, which includes the AD magnetic resonance imaging (AD MRI) signature, and hippocampal volume.

RESULTS: In this cohort of CU older adults, baseline plasma p-tau181 levels were not associated with short-term changes in cognition and structural brain measures. Also, baseline plasma p-tau levels did not influence the effects of behavioral interventions (exercise or mindfulness) on cognitive and structural brain changes.

DISCUSSION: The short follow-up and healthy status of this CU cohort might have limited the sensitivity of plasma p-tau181 in detecting changes associated with AD pathology.

KEYWORDS
Alzheimer's disease, Alzheimer's disease magnetic resonance imaging signature, cortical thickness, hippocampal volume, plasma phosphorylated tau 181

1 | BACKGROUND

The diagnosis of Alzheimer's disease (AD) in its preclinical stages using biomarkers has become central in recent years.[1–3] A large proportion of cognitively unimpaired (CU) older adults shows evidence of significant amyloid beta (Aβ) deposition in the brain, especially at older ages. Although it has been argued that the majority of individuals with Aβ deposition will not develop AD dementia during their lifetimes,[4] the presence of an elevated brain amyloid burden is associated with a higher risk of development of clinical AD, especially over a long follow-up.[3–5] Currently, blood-based biomarkers can detect, with great accuracy, these very early changes related to AD pathology.[1]

RESEARCH IN CONTEXT

1. **Systematic review**: After conducting a review of the literature, we found that plasma phosphorylated tau 181 (p-tau181) has gained attention as a promising blood-based marker for early detecting Alzheimer's disease (AD) pathology. Recent studies have shown that p-tau181 can detect AD pathology in cognitively unimpaired (CU) individuals as early as 10 years before changes in cerebrospinal fluid or positron emission tomography scans for amyloid beta pathology are observed. However, it is unclear whether plasma p-tau181 can predict the short-term trajectory of cognitive decline and brain structural changes.
2. **Interpretation**: In the cohort studied, baseline plasma p-tau181 levels were not associated with short-term (18 months) changes in cognition and structural brain measures.
3. **Future directions**: Further research is necessary to determine the potential of plasma p-tau181 as a short-term predictor of AD-related clinical outcomes in CU older adults. Longer follow-up periods may be necessary to detect clinically significant changes in CU older adults and include a more heterogeneous participant population to assess the effectiveness of plasma p-tau181 as a diagnostic tool or outcome measure.

Plasma phosphorylated tau 181 (p-tau181) has emerged as a novel and one of the most studied blood-based biomarkers of AD.[6–10] A recent study has suggested that plasma p-tau181 can be an early diagnostic and prognostic biomarker of AD pathology and future diagnosis of dementia, detectable as early as 10 years before changes in cerebrospinal fluid (CSF) or positron emission tomography (PET) positivity for Aβ pathology can be identified in CU older adults.[11] However, recent reports have shown that other plasma p-tau species, like p-tau217, may have higher accuracy in identifying the earliest stages of AD pathology and show a strong association with the progression of clinical AD in CU individuals.[11–13] Nonetheless, the evaluation of plasma p-tau181 still has important uses in research and clinical settings, including as a biomarker for participant selection in clinical trials.[11] Higher plasma p-tau181 levels were found in individuals with dementia due to AD compared to CU older adults.[14–16] Also, it is considered an accurate biomarker of AD pathology,[7,17] with a significant correlation with brain Aβ and tau pathology burden in PET imaging and in *post mortem* neuropathology analyses.[7,14–18]

There is a paucity of studies investigating the performance of plasma p-tau181 as a predictor of cognitive decline or other AD-related clinical manifestations without a concomitant assessment with PET or CSF biomarkers as standards for AD diagnosis.[19–21] Also, most studies have focused on long-term follow-ups to determine the predictive capacity of plasma AD biomarkers to identify subjects at risk for AD pathology.[22–24] Shorter follow-up (e.g., < 2 years) study design may not be ideal to track the AD pathological process but can offer a window to understand the impact of AD pathology on cognitive performance and structural brain changes, especially in the context of cognitive-enhancing interventions. Finally, it remains unclear if plasma AD biomarkers can be used to predict response to both pharmacological and non-pharmacological cognitive-enhancing interventions in CU individuals.

To address these questions, we investigated the associations between plasma p-tau181 levels and the trajectories of cognitive performance and structural brain changes over 18 months in CU older adults. We used data from a recently completed study, the Mindfulness, Education, and Exercise for Age-Related Cognitive Decline (MEDEX) clinical trial.[25] We hypothesize that higher plasma p-tau181 levels will be associated with changes in episodic memory, executive function, and cortical thickness over 18 months. We also evaluated if plasma p-tau181 levels moderated the effects of exercise and mindfulness on episodic memory, executive function, and cortical thickness over 18 months.

2 | METHODS

2.1 | Overview and design

This study is a secondary data analysis of the MEDEX study, identifier NCT02665481. The MEDEX study was conducted at Washington University in St. Louis, Missouri, and the University of California, San Diego, California. It started in November 2015 (first enrollment) and lasted until March 2020 (last follow-up assessment). A detailed description of the study methods has been published.[26] The MEDEX study was a 2 × 2 factorial design randomized controlled trial (RCT) to investigate the effects of mindfulness-based stress reduction (MBSR) and multimodal exercise to improve cognitive performance in CU older adults. The main findings were a non-significant effect of MBSR, exercise, and their combination on cognitive performance.[25]

2.2 | Participants

Participants were community-dwelling older adults between 65 and 84 years old. The study allowed for participants with self-reported age-related changes in cognitive function, which was defined by a positive response to whether they or others had noticed trouble with their memory or concentration. Nevertheless, the participants had to be CU, defined by scores less than 10 on the Short Blessed Test.[25] Participants with medical conditions that suggested shortened lifespan (e.g., metastatic cancer, unstable cardiovascular disease) or that would interfere with study assessments (e.g., diabetes medication, systemic glucocorticoids, magnetic resonance imaging [MRI] contraindications, severe hearing/visual impairment) were excluded. Additional details about the study goals and recruitment can be found elsewhere.[25]

2.3 | Comorbidities assessment

The Cumulative Illness Rating Scale-Geriatric (CIRS-G) was used to measure the number and severity of physical health problems. It consists of 14 items assessing 13 organ systems. A score range of 0 to 4 is given for each system, with an overall range of 0 to 56. Higher scores are indicative of more comorbidities and severe medical conditions.

2.4 | Apolipoprotein E genotyping

Genomic DNA was isolated from blood samples using QIAmp DNA blood mini kits from Qiagen. The E280A PS1 mutation was detected before genotyping of the apolipoprotein E (*APOE*) ε polymorphism was performed using polymerase chain reaction amplification of a 244 bp fragment followed by digestion with HhaI. Finally, genotyping of the *APOE* promoter polymorphisms (−219G/T, −491A/T, and −427 T/C) was performed.

2.5 | Plasma p-tau181

Plasma p-tau181 levels were measured in the plasma collected at the baseline assessment. We used the Meso Scale Discovery (MSD) platform by electrochemiluminescence using proprietary assays[27] with catalog numbers K151AGMS-2 with a lower limit of detection (LLOD) of 77 fg/mL and a dynamic range of 77 to 990,000 fg/mL.[28] The assay was performed on a small streptavidin spot plate using the MSD platform MESO QuickPlex SQ 120 MM. Plasma p-tau181 used biotinylated Human Tau (pT181) Antibody (mIgG, MSD cat. C2AGM-3) as the capture. In this study, the assay used TURBO-BOOST Human Tau Antibody (mIgG, MSD cat. D2AGP-3) as the detector. Each assay was calibrated using a calibrator provided by MSD, with p-tau 181 using Human Tau (pT181) Calibrator (MSD cat. C0AGM-2). All samples were run in singlicate.

2.6 | Cognitive assessments

Memory and cognitive control (executive function domain) were assessed at baseline and 3-, 6-, and 18-month follow-up evaluations. The memory test battery included list and paragraph immediate and delayed recall scores and the National Institutes of Health (NIH) Toolbox Picture Sequence Memory Test. The cognitive control test battery included the NIH Toolbox Flanker Inhibitory Control, List-Sorting Working Memory, and Dimensional Change Card Sort Tests (DCCS), as well as the Consonant Vowel Odd Even (CVOE) task, computerized Color Word Interference task, and Sustained Attention Response Task (SART). We created an episodic memory and cognitive control composite score by averaging the *z* scores of all available memory or cognitive control tests, standardized to the baseline composite score. Additional details on cognitive assessments can be found elsewhere.[26]

2.7 | Behavioral assessments

Depressive and anxiety symptoms were evaluated by the Patient Reported Outcomes Measurement Information System (PROMIS) self-report measures of anxiety and depression. PROMIS measures generate *t* scores, which are standard scores. The average *t* score and standard deviation (SD) are 50 and 10, respectively, in the US general population.

2.8 | Neuroimaging assessment

Left and right hippocampal volume and left and right dorsolateral prefrontal cortex (DLPFC) surface area and cortical thickness were acquired from high-resolution T1-weighted MRI (magnetization-prepared rapid acquisition gradient echo; $1 \times 1 \times 1$ mm; repetition time = 2300 ms; inversion time = 900 ms; echo time = 2.95 ms; flip angle = 9°) at baseline, 6, and 18 months. Longitudinal FreeSurfer[29] processing generated the measurements. The AD MRI signature is another FreeSurfer-derived measure composed of the surface-area weighted average of the mean cortical thickness in the following individual regions of interest (ROI): entorhinal, inferior temporal, middle temporal, and fusiform.[30] We calculated the AD MRI signature composite for this sample by initially averaging the *z* scores across ROI before deriving a *z* score for the signature. A higher *z* score represents a higher cortical thickness in the ROI of the AD MRI signature.

2.9 | Statistical analyses

All statistical analyses were performed in R version 4.2.2. The baseline characteristics were summarized by mean and SD for continuous variables, frequencies, and percentages for categorical variables, overall and by quantiles. Low and high baseline plasma p-tau181 levels were separated based on a cut-off of 1.35 pg/mL, which refers to the 75th percentile of the raw baseline plasma p-tau181 level (Table 1). This dichotomous plasma p-tau181 variable is robust to the distribution of plasma p-tau181.

Selected potential confounders (covariates) for associations between baseline plasma p-tau181 and changes in cognition or structural brain measures included age at baseline, sex, education, medical comorbidity assessed by CIRS-G, *APOE* genotype, presence of baseline anxiety and depression, and the baseline level of an outcome of interest. The intervention group was not selected as a covariate based on previous results of the original RCT showing that mindfulness training, exercise, or both did not result in significant changes in episodic memory or executive function composite scores over time.[25]

In the analyses examining baseline plasma p-tau181 levels as a continuous variable, baseline plasma p-tau181 was log-transformed, followed by a *z* transformation to improve normality prior to analyses due to right skewness. Linear regression modeling was used to assess the associations of the plasma p-tau 181 levels with memory composite or cognitive control composite score, cortical thickness, and

TABLE 1 Demographics and clinical characteristics of the sample at baseline (whole sample and groups based on a plasma p-tau181 cut-off).

	Whole sample ($n = 585$)	Low plasma p-tau181 ($n = 398$)		High plasma p-tau181 ($n = 135$)	
		Q1 ($n = 133$)	Q2 ($n = 134$)	Q3 ($n = 131$)	Q4 ($n = 135$)
Sex (F) (%)	424 (72.5)	106 (27.7)	98 (25.6)	94 (24.5)	85 (22.2)
Age (years)	71.5 (4.8)	72.09 (5.1)	71.01 (4.5)	70.65 (4.5)	71.70 (5.0)
Education (years)	16.2 (2.2)	16.07 (2.1)	16.20 (2.3)	16.39 (2.1)	16.29 (2.1)
APOE ε4 (%)[2]					
noncarriers	409 (70.1)	96 (26.0)	98 (26.6)	85 (23.0)	90 (24.4)
Carriers	174 (29.9)	39 (23.8)	34 (20.7)	48 (29.3)	43 (26.2)
CIRS-G	6.8 (2.9)	6.58 (2.5)	6.47 (2.9)	7.17 (2.9)	6.83 (2.8)
Plasma p-tau181[52]	1.1 (1.0)	0.20 (0.1)	0.63 (0.1)	1.10 (0.1)	2.43 (1.2)
Anxiety questionnaire[4]	13.7 (4.8)	13.56 (4.6)	13.67 (4.8)	12.51 (4.3)	13.28 (4.4)
Depression questionnaire[3]	12.3 (4.9)	12.74 (5.4)	12.19 (5.0)	11.45 (3.7)	11.44 (4.1)
Cognitive control composite*	−0.0 (1.0)	0.10 (0.9)	0.21 (1.0)	0.09 (1.0)	−0.12 (0.9)
Memory composite*	0.0 (1.0)	0.06 (1.0)	0.16 (1.1)	0.18 (1.0)	−0.04 (1.0)
Cortical thickness[43]	2.8 (0.2)	2.74 (0.2)	2.78 (0.2)	2.85 (0.2)	2.87 (0.2)
AD MRI signature[43]	0.0 (3.2)	−1.07 (3.0)	−0.46 (2.9)	0.87 (3.2)	1.10 (3.1)
Hippocampal volume[43]	3591.7 (366.2)	3563.3 (371.8)	3552.9 (347.5)	3629.9 (399.5)	3654.6 (343.5)

[N]Number of subjects with missing data.

*Memory and cognitive control composites *z* scores, higher scores represent better performance; data presented as means unless otherwise noted; Q1–Q4, quantiles based on baseline plasma p-tau181 levels Q1 [< 0.41 pg/mL], Q2 [0.41–0.84 pg/mL], Q3 [0.84–1.35 pg/mL], and Q4 [>1.35 pg/mL].

Note: Plasma p-tau181, baseline plasma phosphorylated tau 181 in pg/mL; low and high plasma p-tau181, based on the baseline plasma p-tau181 cut-off of 1.35 pg/mL; cortical thickness in mm; hippocampal volume in mm^3.

Abbreviations: AD MRI signature, *z* score, Alzheimer's disease magnetic resonance imaging signature based on the cortical thickness of the entorhinal cortex, inferior temporal cortex, middle temporal cortex, and fusiform cortex; *APOE*, apolipoprotein E genotype; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; F, female; p-tau181, phosphorylated tau 181.

hippocampal volume, adjusting for age at baseline, sex, education, medical comorbidity assessed by CIRS-G, *APOE* genotype, presence of baseline anxiety and depression. We then used linear mixed-effects (LME) models to show the associations between baseline plasma p-tau181 (independent variable) and the temporal changes in memory and cognitive control, and cortical thickness (dependent variables). In that sense, β estimates associated with the transformed p-tau181 in the LME models are the mean changes per SD increase in log(p-tau181).

We fitted an LME model for each outcome including an interaction term for baseline plasma p-tau181 and time, random subject-specific intercepts, and slopes for time depending on the level of baseline plasma p-tau181, that is, outcome ~ baseline plasma p-tau181 + time + (baseline plasma p-tau181*time) + (time | subject) (Table S1 in supporting information). Additionally, we modeled the dichotomous p-tau181, adjusted for covariates modeled as fixed effects (Table 2). Finally, we evaluated the intervention effects in the adjusted models, comparing MBSR, exercise, or the combination of MBSR and exercise to health education (Table S2 in supporting information) overall and by the level of baseline plasma p-tau181 (low or high).

Parameters were estimated using the maximum likelihood approach, which offers a simple alternative to handle missing data under the missing-at-random assumption without requiring imputation.[31] Time was set as a continuous variable across all models and results were identical when using time as a categorical variable (0, 3, 6, and 18 months) and plasma p-tau181 as a continuous predictor. Two-sided *P*-values < 0.05 were considered statistically significant. Further details on methods are available in the Supplementary Methods in supporting information.

3 | RESULTS

3.1 | Overview and participants

A summary of the characteristics of the entire sample and by baseline p-tau 181 group is presented in Table 1. At baseline, 585 participants were included in the study. The mean age was 71.5 years, and the mean education was 16.2 years. Most participants were noncarriers of the *APOE* ε4 allele ($n = 409$, or 70.1%). From the 533 individuals with baseline plasma p-tau181 (mean concentration level 1.1 pg/mL), 135 subjects were in the high baseline plasma p-tau181 group (≧ 1.35 pg/mL).

3.2 | Baseline

In the unadjusted model, p-tau181 levels were significantly associated with cortical thickness ($\beta = 0.05$ [0.03, 0.07], $P < 0.001$). After controlling for covariates, the association between p-tau181 and cortical thickness remained statistically significantly ($\beta = 0.06$ [0.04, 0.07],

TABLE 2 Associations between baseline plasma p-tau181 and longitudinal changes in memory and cognitive control composites, and structural brain measures over time.

	Unadjusted				Adjusted			
	β	95% CI		*P*	*β*	95% CI		*P*
Memory composite								
Time	**0.030**	**0.026**	**0.033**	**<0.001**	**0.030**	**0.026**	**0.034**	**<0.001**
log(p-tau181)	−0.011	−0.096	0.074	0.799	0.014	−0.016	0.045	0.355
Plasma p-tau181 (high vs. low)	−0.033	−0.228	0.162	0.739	−0.002	−0.071	0.068	0.962
Cognitive control composite								
Time	**0.013**	**0.010**	**0.016**	**<0.001**	**0.013**	**0.009**	**0.017**	**<0.001**
log(p-tau181)	−0.061	−0.139	0.018	0.130	0.009	−0.019	0.037	0.523
Plasma p-tau181 (high vs. low)	−0.080	−0.261	0.100	0.383	0.014	−0.050	0.079	0.661
Cortical thickness								
Time	**−0.001**	**−0.002**	**−0.001**	**<0.001**	**−0.001**	**−0.002**	**−0.001**	**<0.001**
log(p-tau181)	**0.049**	**0.026**	**0.053**	**<0.001**	0.002	−0.001	0.004	0.251
Plasma p-tau181 (high vs. low)	**0.081**	**0.045**	**0.117**	**<0.001**	0.002	−0.005	0.009	0.589
AD MRI signature								
Time	0.001	−0.005	0.006	0.807	0.001	−0.006	0.007	0.825
log(p-tau181)	**0.932**	**0.626**	**1.239**	**<0.001**	0.019	−0.033	0.071	0.471
Plasma p-tau181 (high vs. low)	**1.375**	**0.658**	**2.092**	**<0.001**	0.064	−0.052	0.179	0.281
Hippocampal volume								
Time	**−3.080**	**−3.485**	**−2.674**	**<0.001**	**−3.080**	**−3.509**	**−2.650**	**<0.001**
log(p-tau181)	34.332	−3.510	72.175	0.076	0.207	−2.632	3.046	0.886
Plasma p-tau181 (high vs. low)	73.589	−12.883	160.059	0.096	−3.216	−9.685	3.252	0.331

Notes: Unadjusted and adjusted linear mixed-effects models. Adjusted models included age, sex, education, medical comorbidity (CIRS-G), *APOE ε4* genotype, baseline depression and anxiety, and the baseline level of an outcome of interest as covariates. Statistical significance set to $P < 0.05$, significant results marked bold. log(p-tau181), *z* scored log-transformed plasma p-tau181; low and high plasma p-tau181, based on the baseline plasma p-tau181 cut-off of 1.35 pg/mL.

Abbreviations: *APOE*, apolipoprotein E genotype; *β*, estimates CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; p-tau181, phosphorylated tau 181.

$P < 0.001$). Plasma p-tau181 levels were not significantly associated with memory composite score ($\beta = 0.01$ [−0.09, 0.10], $P = 0.868$), cognitive control composite score ($\beta = -0.09$ [−0.18,−0.00], $P = 0.050$), or hippocampal volume ($\beta = 21.138$ [−13.87, 56.15], $P = 0.236$).

3.3 | Relationship between baseline plasma p-tau181 levels and longitudinal changes in the outcomes of interest

The scores from baseline to 3, 6, and 18 months in the cognitive outcomes and cortical thickness were plotted for participants based on quantiles of baseline plasma p-tau181 levels separately. All quantiles showed similar baseline levels and increasing trends in memory and cognitive control composite scores (Figures 1 and 2). Additionally, similar baseline levels and stable trends of cortical thickness were observed for quantile groups of baseline plasma p-tau 181(Figure 3).

None of the interaction terms for baseline plasma p-tau181 and time were statistically significant in the unadjusted models, which implied that the associations of p-tau181 with the outcomes did not significantly change with time (p-tau181 x time: $\beta = 0.001$ [−0.002, 0.004], $P = 0.531$ [memory composite]; $\beta = -0.000$ [−0.003, 0.003], $P = 0.885$ [cognitive control composite]; $\beta = 0.000$ [−0.000, 0.001], $P = 0.174$ [cortical thickness]), and were dropped from the models (Table S1). Table 2 presents the unadjusted and adjusted LME models' results modeling baseline plasma p-tau181 levels as a continuous variable (*z* score of log[p-tau181]) or a dichotomous variable (high vs. low) and each of the outcomes of interest. Continuous or dichotomous p-tau181 gave consistent results.

Memory and cognitive composites improved over time. However, there were no statistically significant associations between baseline plasma p-tau181 and these measures over time in both unadjusted and adjusted models (Table 2). Both unadjusted and adjusted models showed that, although statistically significant, cortical thickness and the AD MRI signature composite minimally changed with time. In contrast, hippocampal volume decreased over time, as shown by the negative *β* estimates for time.

Although baseline plasma p-tau181 was positively associated with longitudinal changes in cortical thickness in the unadjusted model, this association did not persist after adjusting for the baseline measure and

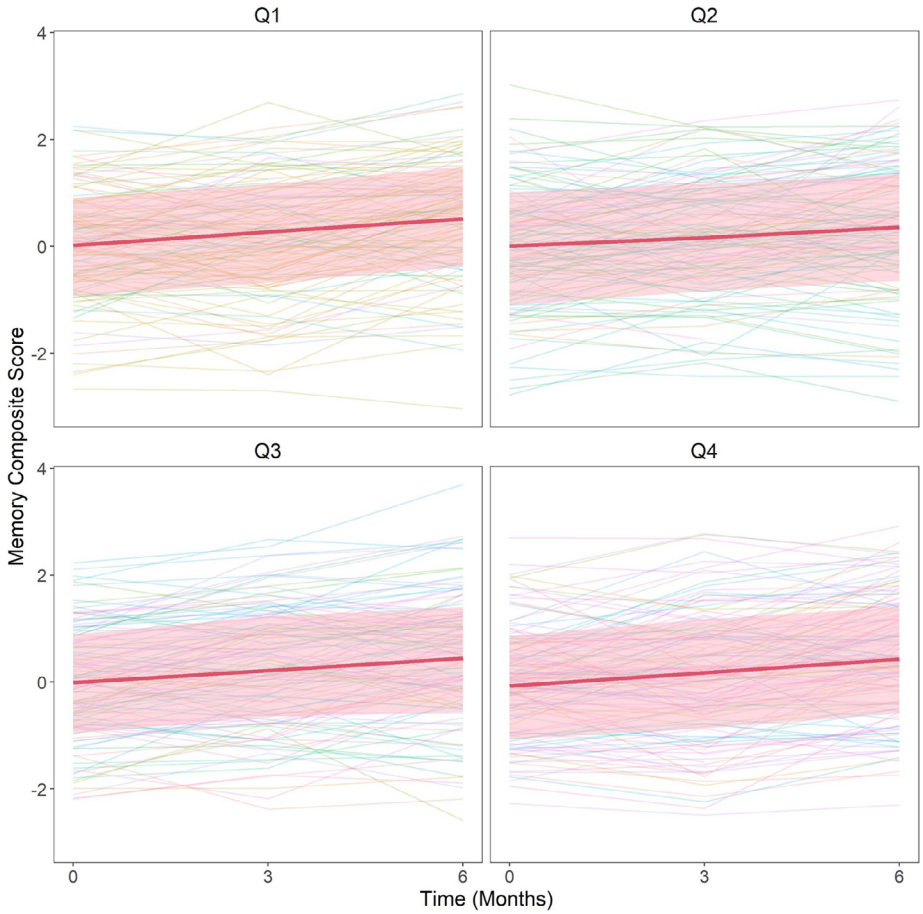

FIGURE 1 Individual memory composite scores over time, predicted means and 95% confidence intervals given time from the linear mixed effects models including random intercepts and the fixed effect of time (continuous) by quantiles (Q1–Q4) of baseline plasma phosphorylated tau 181 levels. Q1 [<0.41 pg/mL], Q2 [0.41–0.84 pg/mL], Q3 [0.84–1.35 pg/mL], and Q4 [>1.35 pg/mL]

other covariates. A similar result was found for the AD MRI signature composite score in the unadjusted model (Table 2). Finally, baseline plasma p-tau181 was not significantly associated with hippocampal volume changes over time (Table 2).

3.4 | Effect of interventions

One hundred fifty subjects (25.6%) were assigned to MBSR only, 138 (23.6%) to the exercise-only group, 144 (24.6%) to the MBSR plus exercise group, and 153 (26.2%) to health education classes. We ran LME models for the whole sample and by the level of baseline plasma p-tau181. There were no significant differences comparing any of the intervention groups (MBSR only, exercise only, and MBSR plus exercise) to the group of health education in changes in any of the outcomes regardless of modeling of p-tau181 levels (Table S2).

4 | DISCUSSION

In this study, we evaluated the association between baseline plasma p-tau181 levels and trajectory of cognitive performance (memory and executive function domains) and structural brain measures in CU older adults. In summary, we report in this study improvements in both memory composite and cognitive control composite scores over 18 months of follow-up. Also, both cortical thickness and hippocampal volume decreased over the same period, including the AD MRI signature. These findings, however, were not influenced by the levels of plasma p-tau181 at baseline. Also, baseline plasma p-tau levels did not influence the effects of exercise and mindfulness on trajectories of cognitive and structural brain changes. Our findings support previous findings that plasma p-tau181 does not predict short-term changes in cognitive performance. Additionally, plasma p-tau181 does not identify CU individuals that may or may not benefit from cognitive enhancing, non-pharmacological interventions.

Plasma p-tau181 has been previously associated with cognitive impairment in cross-sectional and longitudinal studies.[14,32,33] Moreover, it has been reported that plasma p-tau181 levels might indicate AD pathology even before Aβ biomarkers reach the positivity threshold.[34,35] However, most studies have relied on longer follow-up periods (over 2 years) when evaluating the relationship between plasma p-tau181 and cognitive or structural brain outcomes.[6,24,36] Our null findings suggest that plasma p-tau181 might correlate with these measures later in the disease process. In addition, sample

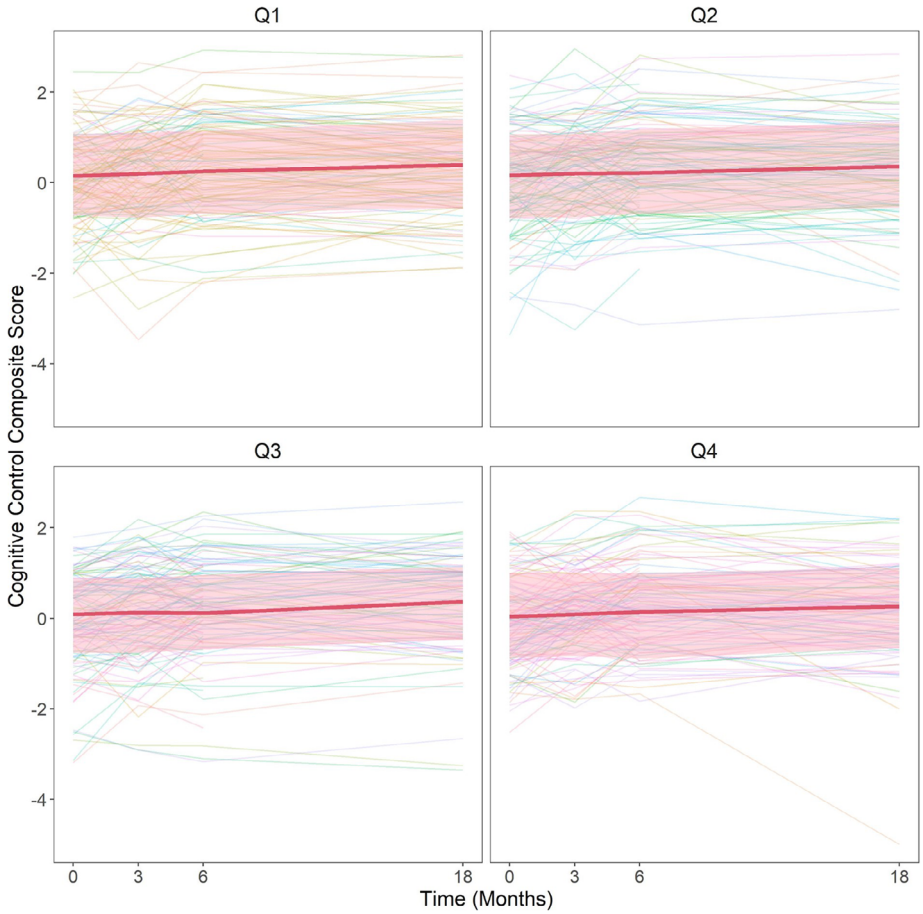

FIGURE 2 Individual cognitive control composite scores over time, predicted means and 95% confidence interval given time from the linear mixed effects models including random intercepts and the fixed effect of time (continuous) by quantiles (Q1–Q4) of baseline plasma phosphorylated tau 181 levels. Q1 [<0.41 pg/mL], Q2 [0.41–0.84 pg/mL], Q3 [0.84–1.35 pg/mL], and Q4 [>1.35 pg/mL]

characteristics might have played a role in these conflicting results. Some of the previous studies have investigated the relationship between plasma p-tau181 and cognitive performance in cohorts of CU older adults with a higher risk of developing AD, for example, cohorts originating from memory clinics and enriched with *APOE* ε4 carriers or with evidence of subjective cognitive decline (SCD) at baseline.[21,29,34] Although our sample had 29.9% of individuals with at least one *APOE* ε4 allele, higher than the general population, the recruitment process in some of these studies was designed to have at least 50% *APOE* ε4 carriers.[24,37] In addition, despite allowing for subjective cognitive complaints at enrollment, our study sampling might have included only cognitively robust subjects. Notably, the sampling of older adults to assess cognitive performance is frequently biased by the "healthy survivor" effect. Individuals with lower performances are less capable of participating in a study that selects mostly cognitively healthy subjects.[38] Also, a greater cognitive reserve might have influenced the lack of cognitive decline despite presenting elevated plasma p-tau181 levels. Finally, in the absence of AD-related effects on this sample during the follow-up period, the improvement observed in the cognitive measures was probably related to the well-described practice effects of serial testing in CU populations.[39] These aspects might have contributed to the differences in results between our study and prior reports in the literature.

In contrast to our primary hypothesis, higher baseline plasma p-tau181 was significantly associated with higher baseline cortical thickness. Similar findings have been reported in the literature for amyloid deposition from studies with preclinical AD.[40–44] Moreover, it has been reported that in the preclinical phase of the AD continuum, cortical thickening may occur before neuronal death and brain atrophy takes place.[45] A possible explanation for these findings is that the inflammatory response secondary to amyloid deposition may lead to neuronal hypertrophy and glial recruitment,[45] leading to transient cortical thickening in the early stages of preclinical AD. However, further studies are needed to investigate these patterns of change in other structural brain measures and their relationship to plasma p-tau181. Also, investigating the association of these measures with glial fibrillary acidic protein (GFAP), a product of astroglial activation and astrocytosis, might clarify these findings, as this biomarker has been associated with incipient axonal loss in CU individuals.[1,2,15,46] Another possible explanation is that older adults with reduced cortical thickness and hippocampal atrophy are more closely related to clinically significant cognitive impairment. Consequently, CU older adults with high plasma

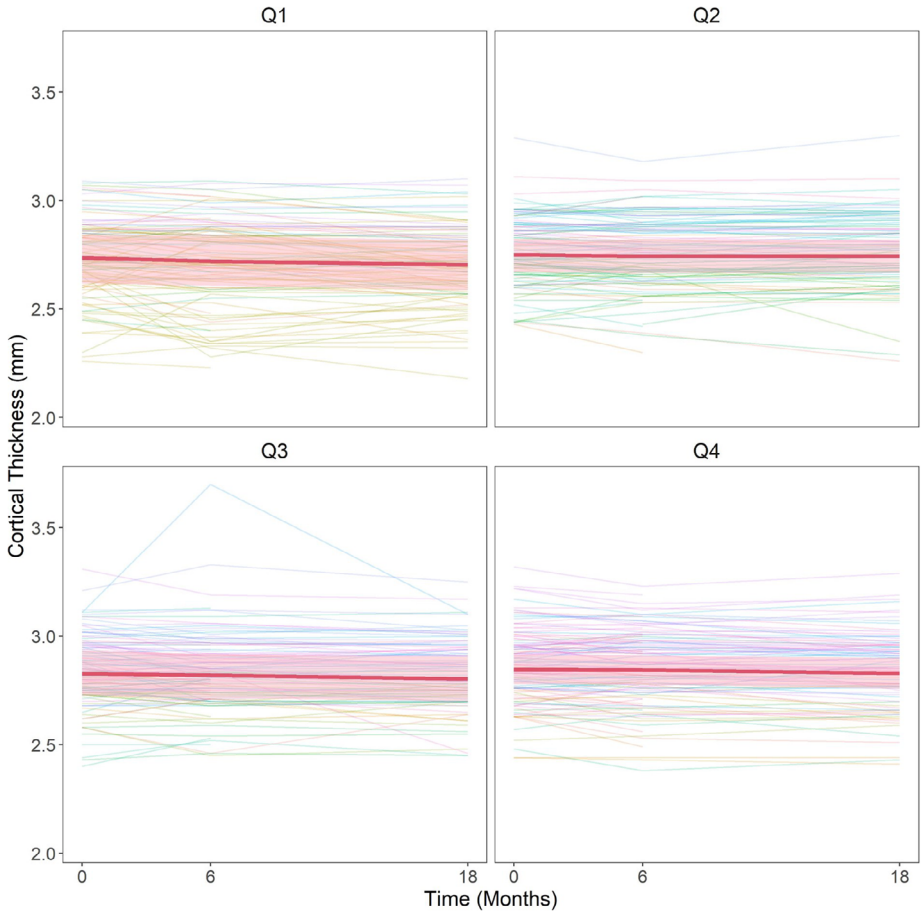

FIGURE 3 Individual cortical thickness over time, predicted means and 95% confidence intervals from the linear mixed effects models including random intercepts and the fixed effect of time (continuous) by quantiles (Q1–Q4) of baseline phosphorylated tau 181 levels. Q1 [<0.41 pg/mL], Q2 [0.41–0.84 pg/mL], Q3 [0.84–1.35 pg/mL], and Q4 [>1.35 pg/mL]

p-tau181 might still have preserved or increased structural brain measures. These findings may also reflect a group of older adults with a greater biological reserve that can counteract the deleterious effect of the earliest AD pathological changes, reflected by the elevation in plasma p-tau181. However, no studies have specifically investigated the association between plasma p-tau181 levels and incipient structural brain changes, and it is still unclear which pathological processes are specifically reflected by plasma p-tau181.[16] Finally, in the absence of direct assessment of brain AD-related pathology in this sample, the changes in structural brain measures during the follow-up period were likely due to age-related atrophy.

The results were unchanged after we split the sample into groups with high or low p-tau181 levels based on the 75th percentile of the raw levels of baseline plasma p-tau181. To date, there are no universally accepted cut-off values for plasma p-tau181 that have been externally validated in different cohorts. Differences in the values reported to date are related to numerous aspects such as the type of assays used (e.g., MSD, single molecule array [Simoa], or mass spectrometry [MS]-based assays), characteristics of the sample, and the presence of comorbidities.[47] Importantly, although it was not the objective of our study to derive a cut-off value for plasma p-tau181, the value we used for classifying the sample in high versus low baseline plasma p-tau181 levels is in line with values reported in the literature using the same assay (i.e., MSD) and method of calculation (75th percentile).[48]

Our study is not without limitations. First, we included a sample of CU older adults with low variability and relatively stable cognitive performance over time. Also, the short follow-up time may have influenced the lack of significant association between baseline p-tau181 and cognitive decline. Moreover, we included a physically healthy cohort with few medical comorbidities, which can influence the levels of plasma AD biomarkers and the trajectory of cognitive decline.[48,49] Finally, another limitation of our study is that other established plasma biomarkers, for example, plasma p-tau217 and p-tau231, were not available, limiting the scope of our work. Our findings, thus, suggest that plasma p-tau181 in a selected, CU, and physically fit population, with no further assessment with more established AD biomarkers, may be of little value to detect those at high risk of cognitive decline in a short-term follow-up, even in those individuals with high baseline plasma p-tau181 levels. Additionally, these findings add evidence to the current understanding of the role of different plasma p-tau species as biomarkers of AD pathology. Plasma p-tau217, in general, is better associated with

disease progression,[11,12] and plasma p-tau231 may be more suited to reflect very early AD-related changes.[11,13] However, when plasma p-tau181 is the only available tool, the high levels identified in an individual might indicate the need for further investigation. Importantly, plasma p-tau181 is already in use as a biomarker for the selection of individuals to enter clinical trials to test the disease-modifying or cognitive-enhancing effects of interventions in CU older adults. Thus, investigating the dynamic of this biomarker in different samples adds important information to the field.

In conclusion, baseline plasma p-tau181 levels were not associated with short-term (18 months) changes in cognition and structural brain measures in CU older adults. Also, baseline plasma p-tau181 levels did not influence the response to cognitive-enhancing non-pharmacological interventions. Therefore, our findings suggest that plasma p-tau181 is not an ideal biomarker to detect very early changes in cognition and structural brain measures in healthy, CU older adults. Longer follow-up times combined with longitudinal assessment of plasma biomarkers of AD in a more diverse population sample might be essential to determine their performance as diagnostic tools or outcome measures in clinical trials.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Ethics approval was provided by the universities' institutional review boards. All participants provided written informed consent.

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SUPPORTING INFORMATION

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

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