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FEATURED ARTICLE

CSF biomarkers and plasma p-tau181 as predictors of longitudinal tau accumulation: Implications for clinical trial design

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Abstract

Introduction: Clinical trials targeting tau in Alzheimer's disease (AD) need to recruit individuals at risk of tau accumulation. Here, we studied cerebrospinal fluid (CSF) biomarkers and plasma phosphorylated tau (p-tau)181 as predictors of tau accumulation on positron emission tomography (PET) to evaluate implications for trial designs.

Methods: We included older individuals who had serial tau-PET scans, baseline amyloid beta (Aβ)-PET, and baseline CSF biomarkers (n = 163) or plasma p-tau181 (n = 74). We studied fluid biomarker associations with tau accumulation and estimated trial sample sizes and screening failure reductions by implementing these markers into participant selection for trials.

Results: P-tau181 in CSF and plasma predicted tau accumulation ($r > 0.36$, $P < .001$), even in AD-continuum individuals with normal baseline tau-PET (A+T–; $r > 0.37$, $P < .05$). Recruitment based on CSF biomarkers yielded comparable sample sizes to Aβ-PET. Prescreening with plasma p-tau181 reduced up to ≈50% of screening failures.

Discussion: Clinical trials testing tau-targeting therapies may benefit from using fluid biomarkers to recruit individuals at risk of tau aggregation.

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1 | INTRODUCTION

The presence of amyloid beta (Aβ) plaques and tau neurofibrillary tangles (NFT) in the brain is necessary for the neuropathological diagnosis of Alzheimer's disease (AD).[1] While it is believed that Aβ deposition is the event that triggers the cascade of pathological changes in AD, accumulating evidence now points specifically to NFT aggregation as the pathological process that most closely correlates with downstream neurodegeneration and overt clinical decline.[2–4] This tight association with clinical symptoms, together with repeated failures of anti-Aβ therapies,[5] has motivated a gradual increase in tau-targeting therapies in clinical trials for AD.[6,7] Under this new therapeutic paradigm, longitudinal positron emission tomography (PET) imaging with tau-sensitive radiotracers has emerged as a relevant outcome measure to evaluate both target engagement and efficacy of anti-tau drugs.[8] Hence, recruiting individuals who are at risk for greater longitudinal tau accumulation will likely result in more efficient and less costly trials. As such, the identification of accessible and cost-effective biomarkers that can predict longitudinal accumulation of aggregated tau as measured by tau-PET is key to facilitate the search for tau-targeting treatments.

To date, the only established AD biomarker that has consistently been found to predict longitudinal tau accumulation is Aβ-PET.[3,9–12] Nevertheless, despite the potential of Aβ-PET to robustly identify subjects at risk of higher tau accrual, the associated costs and the limited accessibility may hamper its use in clinical trials.

By contrast, the core cerebrospinal fluid (CSF) biomarkers for AD[13] are more affordable and accessible than Aβ-PET, and allow the simultaneous assessment of both Aβ and soluble tau pathology using a single procedure. In addition, phosphorylated tau at threonine 181 (p-tau181) in blood plasma has been recently proposed as an accessible, cost-effective diagnostic and prognostic marker of AD pathology.[14–22] However, no study has investigated how these markers associate with longitudinal tau accumulation on PET, nor evaluated the implications of using fluid biomarkers for participant selection in clinical trials using tau-PET endpoints.

Here, we investigated how CSF AD biomarkers and plasma p-tau181 associate with longitudinal tau accumulation, as measured with serial tau-PET, and compared their predictive performance head-to-head with that of Aβ-PET. Further, we studied potential implications of our results on the use of fluid biomarkers for clinical trial design using longitudinal tau-PET as outcome measure.

2 | METHODS

2.1 | Study design

All data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. See Methods S1 in supporting information for a description of the ADNI study design. ADNI participants who were cognitively unimpaired (CU) or cognitively impaired (mild cognitive impairment [MCI] or AD dementia [CI]) were included if they had available Aβ- and tau-PET scans at baseline (acquired within 1.5 years) and at least one longitudinal tau-PET scan. Depending on the availability of CSF biomarkers or plasma p-tau181, participants were assigned to one of the following two (overlapping) study cohorts:

Cohort 1: Participants underwent lumbar puncture within 1.5 years from the baseline tau-PET scan (n = 163).

Cohort 2: Participants underwent blood sampling within 2 years from the baseline tau-PET scan (n = 74).

Additional details of eligible participants can be found in Methods S2 in supporting information and in Table 1. No *post mortem* neuropathological data from any study participant was readily available. The study was approved by the institutional review board of all participating ADNI centers, and all study participants, or their study partners, provided written informed consent.

2.2 | PET imaging

Tau-PET imaging in ADNI was performed with [^{18}F]flortaucipir (FTP). PET acquisition protocols and preprocessing steps in ADNI for scanner harmonization have been described previously[23] and are summarized in Methods S3 in supporting information. FTP quantification followed previously described methods[14,24,25] that are detailed in Methods S3. Mean FTP standardized uptake value ratio (SUVR) was measured in a previously defined temporal AD meta-ROI (region of interest).[26] In post hoc sensitivity analyses, we also analyzed FTP SUVR in the entorhinal and inferior temporal cortex ROIs.[27] Finally, we analyzed associations with FTP SUVR in a spatially exploratory manner using voxel-wise analyses (Methods S3). All the above-described steps were identically applied to both baseline and follow-up FTP scans.

Aβ-PET in ADNI was performed using either [^{18}F]florbetapir (FBP) or [^{18}F]florbetaben (FBB). Acquisition, preprocessing, and quantification steps for Aβ-PET in ADNI are described elsewhere[28,29] and summarized in Methods S3. To harmonize global cortical composite SUVR values between FBP and FBB ligands, we transformed these SUVR values to the Centiloid (CL) scale[30] using equations previously established by the ADNI PET core.[31]

2.3 | CSF biomarkers

CSF samples were extracted and processed at the ADNI Biomarker Core laboratory, University of Pennsylvania Medical Center according to the ADNI protocol.[32] Concentrations of A$\beta_{1\text{-}42}$ and p-tau181 in CSF were measured using the Elecsys β-Amyloid(1-42) and the Elecsys Phospho-Tau (181P) CSF immunoassays, respectively, on a cobas e 601 module.[33,34] Further details can be found in Methods S4 in supporting information.

2.4 | Blood plasma p-tau181 measurements

Blood samples were collected and processed following previously described procedures for ADNI.[32] Plasma p-tau181 concentrations were measured at the Clinical Neurochemistry Laboratory, University of Gothenburg (Mölndal, Sweden) using an assay developed in-house on a Simoa HD-X (Quanterix) instrument, as described previously.[19,20]

2.5 | Statistical analysis

Subject-specific longitudinal rates of change in FTP SUVR were estimated using previously described methods[14] and were used as outcome in following analyses, as described below.

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed the literature using standard search engines (e.g., PubMed and Google Scholar). Although new-generation clinical trials targeting tau in Alzheimer's disease (AD) will need to make use of cost-effective biomarkers to recruit individuals at increased risk for tau accumulation, no previous study has systematically investigated the potential of cerebrospinal fluid (CSF) AD biomarkers and plasma phosphorylated tau (p-tau)181 for predicting future positron emission tomography (PET)-measured tau aggregation or evaluated implications of implementing these markers into participant selection for tau-targeting clinical trials.
2. **Interpretation**: CSF biomarkers and plasma p-tau181 represent cost-effective predictors of future aggregated tau, even at very early stages of tau deposition in the AD continuum. The use of CSF biomarkers and plasma p-tau181 instead of amyloid beta-PET may result in significant reductions of the costs associated to biomarker screening.
3. **Future directions**: Future comparative studies are warranted to compare the value of plasma p-tau181 and CSF markers head-to-head as standalone biomarkers for sample enrichment in trials using tau PET outcomes.

HIGHLIGHTS

- Fluid biomarkers predicted future tau aggregation with similar performance as amyloid beta positron emission tomography (Aβ-PET).
- Elevated phosphorylated tau (p-tau)181 in cerebrospinal fluid (CSF) and plasma predicted future tau accrual in A+T− subjects.
- Trial recruitment based on CSF biomarkers yielded comparable sample sizes to Aβ-PET.
- Prescreening with plasma p-tau181 reduced the number of required biomarker tests.

We first investigated the strength of the correlations between baseline CSF biomarkers or plasma p-tau181 levels and FTP SUVR rates of change and compared these to those between baseline Aβ-PET and FTP SUVR rates of change. For this, we computed age- and sex-adjusted partial correlation coefficients (r). As statistical associations do not imply the ability to make predictions in a generalized manner,[35,36] we also calculated the leave-one-out cross-validated estimate[37] of the root mean square error (RMSE; Methods S5 in supporting information) to compare the biomarkers' predictive performance. Our covariate choice relies on findings from multivariable

TABLE 1 Characteristics of the study cohorts

	Cohort 1		Cohort 2	
Baseline characteristics	**CU**	**CI**	**CU**	**CI**
N	93	70	37	37
Age, years	73 (7)	72 (8)	74 (6)	77 (7)
Sex, M/F	41/52	38/32	17/20	24/13
Apolipoprotein E ε4 carriers, n (%+)	43 (47) Not assessed: 1	36 (55)Not assessed: 4	19 (51)	11 (30)
Education, years	16 (12 to 20)	16 (12 to 20)	16 (12 to 20)	18 (12 to 20)
MCI/AD	NA	52/18	NA	31/6
Aβ-positive (PET), n (%)	48 (52)	48 (69)	12 (32)	21 (57)
Aβ-positive, tau-negative (A+T–), n (%)	38 (41)	22 (31)	5 (14)	12 (32)
Aβ-PET Centiloid	25 (–15 to 140)	50 (–37 to 145)	10 (–7 to 126)	39 (–17 to 117)
CSF $A\beta_{1\text{-}42}$, pg/mL	988 (366 to 3308)	719(319 to 2043)	NA	NA
CSF p-tau181, pg/mL	22.5 (8.0 to 70.2)	25.8(8 to 96.9)	NA	NA
CSF p-tau181/$A\beta_{1\text{-}42}$	0.019 (0.006 to 0.131)	0.037(0.009 to 236)	NA	NA
Plasma p-tau181, pg/mL	NA	NA	14.1 (1.1 to 14.1)	15.2 (2.9 to 39.8)
AD meta-ROI FTP SUVR	1.22 (0.15)	1.44 (0.40)	1.22 (0.14)	1.28 (0.16)
Entorhinal cortex FTP SUVR	1.18 (0.15)	1.37 (0.25)	1.15 (0.10)	1.21 (0.15)
Inferior temporal FTP SUVR	1.24 (0.17)	1.49 (0.45)	1.25 (0.10)	1.27 (0.13)
Follow-up characteristics				
Tau-PET median follow-up time, years	1.9	1.5	2.0	1.5
Median number of follow-up tau-PET scans	2 (1 to 4)	1 (1 to 3)	1 (1 to 4)	1 (1 to 3)
AD meta-ROI FTP SUVR annual change	0.011 (0.012)	0.021 (0.021)	0.006 (0.014)	0.006 (0.014)
Entorhinal cortex FTP SUVR annual change	0.010 (0.014)	0.012 (0.015)	0.010 (0.014)	0.010 (0.018)
Inferior temporal FTP SUVR annual change	0.014 (0.016)	0.029 (0.030)	0.007 (0.016)	0.007 (0.017)

Notes: All the participants in Cohort 1 had CSF biomarkers available at baseline, while all the participants in Cohort 2 had baseline plasma p-tau181 measurements. Age, PET SUVR measures, and PET SUVR annual change are reported as mean (standard deviation). Years of education, CSF biomarkers, plasma p-tau181 levels, and the number of follow-up tau-PET scans are reported as median (range). Mean rates of change were computed as the average of the subject-specific rates of change.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CI, cognitively impaired; CSF, cerebrospinal fluid; CU, cognitively unimpaired; FTP, [^{18}F]flortaucipir; PET, positron emission tomography; ROI, region of interest; SUVR, standardized uptake value ratio.

analyses, which found that age and sex are independently associated with tau accumulation on PET.[10,11] In complementary analyses, we explored whether these results changed when additionally adjusting for other covariates (Methods S6 in supporting information). CSF $A\beta_{1\text{-}42}$ levels were log-transformed to linearize the relationship with FTP SUVR change. No other imaging or fluid biomarker data were log-transformed. These analyses were performed separately for CU and CI (MCI and AD dementia pooled) individuals.

Next, we investigated whether elevations of p-tau181 in CSF or blood preceded overt elevations in tau-PET signal. To this aim, we studied how these markers associate with longitudinal tau accumulation among individuals on the AD continuum with non-pathologic tau-PET status (A+T−, CU and CI pooled, see Methods S7 in supporting information for the derivation of biomarker cut-points). The strength of the association between fluid biomarkers and FTP SUVR change in A+T− subjects was assessed using partial correlations adjusted for age and sex. For additional post hoc sensitivity analyses, we included baseline tau-PET SUVR, baseline Centiloid or CSF $A\beta_{1\text{-}42}$, and clinical diagnosis (CU, MCI, or AD dementia) as covariates. In addition, we exploratorily investigated whether elevations in baseline CSF p-tau181 measures or plasma p-tau181 were associated with faster progression rates to tau positivity (T+) using Cox proportional hazards regression adjusted for age and sex.

Finally, we investigated potential implications of the use of fluid biomarkers in clinical trials using tau-PET endpoints.

We assumed CSF biomarkers as "stand-alone" tests for subject selection and compared required sample sizes to those using Aβ-PET for inclusion. To this end, we estimated sample sizes per arm needed to detect a 25% reduction[38,39] in FTP SUVR change in a two-arm placebo-controlled trial over 24 months (see Methods S8 in supporting information for further details). Three different target groups were investigated: (1) CU individuals selected on the basis of standard Aβ-PET positivity (24.4 CL[40]), (2) CU individuals with high Aβ burden (> 68 CL), who show faster tau accumulation rates,[38] and (3) CI individuals with standard Aβ positivity (24.4 CL). To fairly compare required sample sizes when using CSF biomarkers for participant selection in these three scenarios, we set CSF entrance cut-points in an independent cohort of ADNI2 participants with concurrent Aβ-PET and CSF (Cohort 4, n = 1022, Methods S2 in supporting information) to result in the same positivity rates (and thus same screening failure rates) as Aβ-PET in the three different target groups (Methods S9 in supporting information). These cut-points were independently validated in Cohort 1, yielding highly similar positivity rates compared to Aβ-PET (Table S1 in supporting information).

We assumed a role for plasma p-tau181 as an easily accessible pre-screening marker prior to the assessment of well-validated Aβ-PET or CSF biomarkers for participant selection. We computed potential reductions in the required number of these biomarker tests after pre-screening with plasma p-tau181 in an independent cohort of ADNI2 participants with available Aβ-PET, CSF, and plasma p-tau181 biomarkers from the same study visit (Cohort 5, n = 775, Methods S2). This cohort had comparable distributions for age, sex, and clinical diagnoses compared to those in Cohort 1 (Table S2). Pathologic plasma p-tau181 status was determined by maximizing the Youden index for the classification of the specific biomarker test positivity using a leave-one-out cross-validation approach (see Methods S10 in supporting information).

3 | RESULTS

3.1 | Associations of fluid biomarkers with longitudinal tau accumulation

In Cohort 1, voxel-wise analyses showed that baseline levels of all CSF biomarkers showed moderate to strong correlations with longitudinal FTP SUVR change among CU and CI individuals. CSF p-tau181/$A\beta_{1\text{-}42}$ ratio was the strongest predictor of FTP SUVR change in the AD meta-ROI, yielding similar RMSE values compared to Aβ-PET (Figure 1, see Figure S1 in supporting information for ROI scatter plots). These results were similar when further adjusting for additional covariates (Tables S3-S5 in supporting information) and when using alternative ROIs (Figure S2 in supporting information).

Among CU individuals in Cohort 2, baseline plasma p-tau181 levels were significantly associated with FTP SUVR change (Figure 2A and Figure S3A in supporting information). However, these effects were generally less pronounced and less spatially widespread compared to Aβ-PET. Yet, RMSE values were similar though slightly higher to those based on Aβ-PET (Figure 2A). By contrast, plasma p-tau181 was more closely correlated with FTP SUVR change in CI subjects, predicting tau accumulation with similar but slightly higher RMSE values than Aβ-PET (Figure 2B and Figure S3B). Similar to CSF biomarkers, results remained statistically significant when adjusting for additional covariates (Tables S5-S7 in supporting information), as well as when using alternative ROIs (Figure S4 in supporting information).

3.2 | P-tau181 levels associate with longitudinal tau accumulation in A+T− subjects

Next, we assessed how p-tau181 levels in CSF and blood associated with longitudinal changes in tau-PET signal among A+T− individuals. CSF p-tau181 and p-tau181/$A\beta_{1\text{-}42}$ levels were significantly associated with FTP SUVR change in A+T− subjects from Cohort 1 (Figure 3A, 3B). At the ROI level, CSF p-tau181 and p-tau181/$A\beta_{1\text{-}42}$ were associated with FTP SUVR change in the AD meta-ROI (Figure 3A, 3B) and the inferior temporal ROI (Figure S5B in supporting information) but not in the entorhinal cortex (Figure S5A). We obtained largely similar results using Aβ-PET instead of CSF $A\beta_{1\text{-}42}$ for establishing A status (Figures S6 and S7 in supporting information). Results remained statistically significant when further adjusting for baseline FTP SUVR in the AD meta-ROI ($r > 0.33$, $P < .01$), baseline CSF $A\beta_{1\text{-}42}$ ($r > 0.32$, $P < .05$), or clinical diagnosis ($r > 0.34$, $P < .05$). CSF p-tau181 also remained significantly associated after adjustment for baseline Centiloid (AD meta-ROI: $r = 0.28$, $P = .03$; inferior temporal: $r = 0.25$, $P = .06$) but CSF p-tau181/$A\beta_{1\text{-}42}$ did not (AD meta-ROI: $r = 0.20$, $P = .14$; inferior

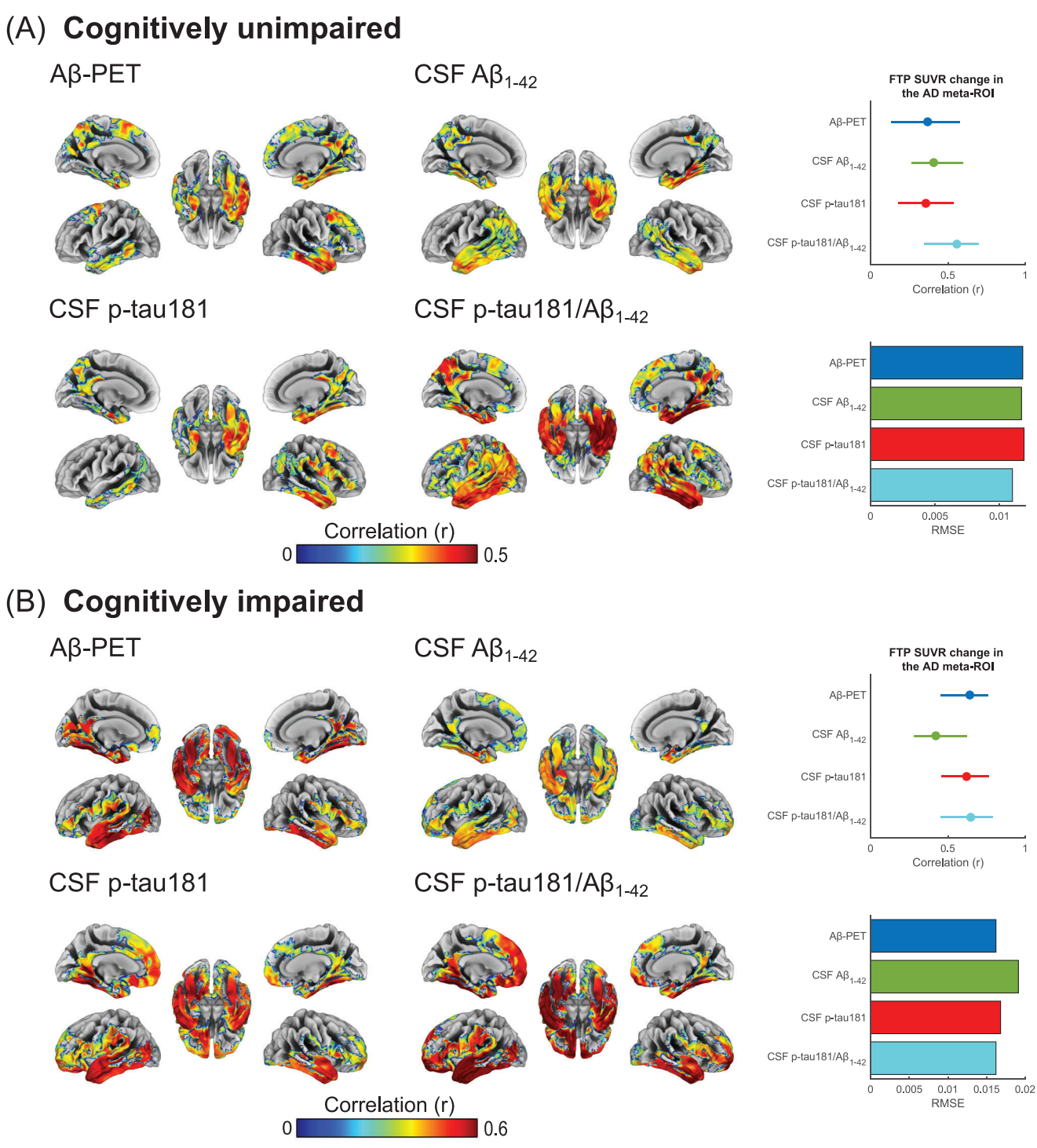

FIGURE 1 Associations of baseline amyloid beta positron emission tomography (Aβ-PET) and baseline cerebrospinal fluid (CSF) biomarkers with FTP standardized uptake value ratio (SUVR) annualized change for (A) cognitively unimpaired and (B) cognitively impaired individuals in Cohort 1. Brain surface renderings depict Pearson correlation coefficients adjusted for age and sex (r) representing the strength of the association between the different biomarkers and [^{18}F]flortaucipir (FTP) SUVR change in each brain region. The right upper panel represents age and sex-adjusted Pearson correlation coefficients (r), along with *P* values, for the association between the biomarkers and FTP SUVR change in the Alzheimer's disease (AD) meta-ROI (region of interest). Regression coefficients are reported in Table S11 in supporting information. RMSE is the root mean square error for the prediction of FTP SUVR change in the AD meta-ROI by a linear model with the biomarker as predictor and age and sex as covariates. RMSE was estimated using leave-one-out cross-validation. Voxel-wise statistical maps were thresholded using a cluster-forming threshold of $P < .01$ (uncorrected) at the voxel level and further thresholded at the cluster level using a family wise error (FEW)–corrected $PFWE < .05$

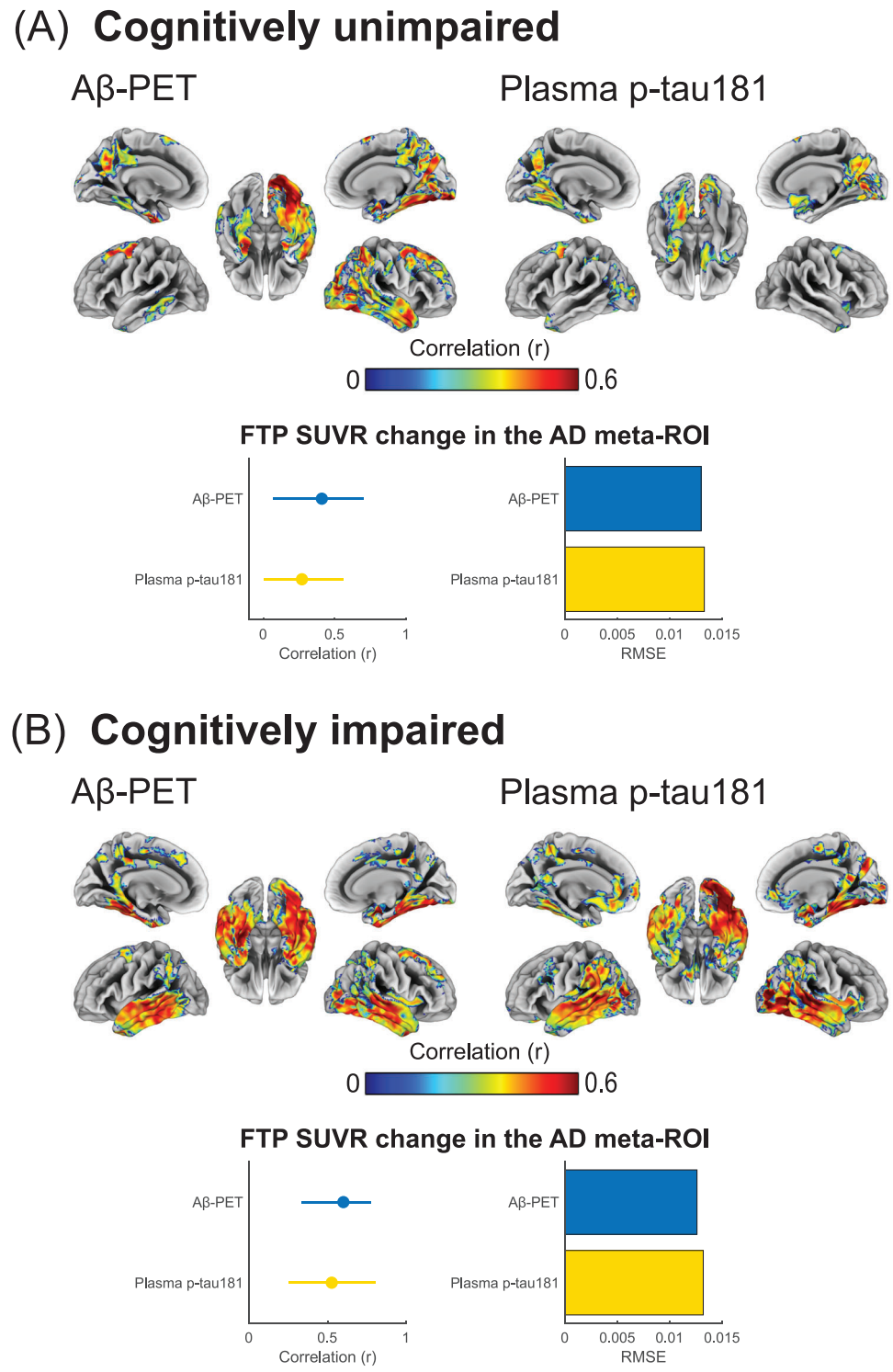

FIGURE 2 Associations of baseline amyloid beta positron emission tomography (Aβ-PET) and baseline plasma phosphorylated tau (p-tau)181 with [^{18}F]flortaucipir (FTP) standardized uptake value ratio (SUVR) annualized change for (A) cognitively unimpaired and (B) cognitively impaired individuals in Cohort 2. Brain surface renderings depict Pearson correlation coefficients adjusted for age and sex (r) representing the strength of the association between the different biomarkers and FTP SUVR change in each brain region. The right upper panel represents age- and sex-adjusted Pearson correlation coefficients (r), along with *P* values, for the association between the biomarkers and FTP SUVR change in the AD meta-ROI. Regression coefficients are reported in Table S12 in supporting information. RMSE is the root mean squared error for the prediction of FTP SUVR change by a linear model with the biomarker as predictor and age and sex as covariates. RMSE was estimated using leave-one-out cross-validation. Voxel-wise statistical maps were thresholded using more lenient cluster-forming thresholds of $P < .05$ (uncorrected) at the voxel level and further thresholded at the cluster level by restricting results to clusters with a number of voxels higher than the expected number of voxels as predicted using random field theory

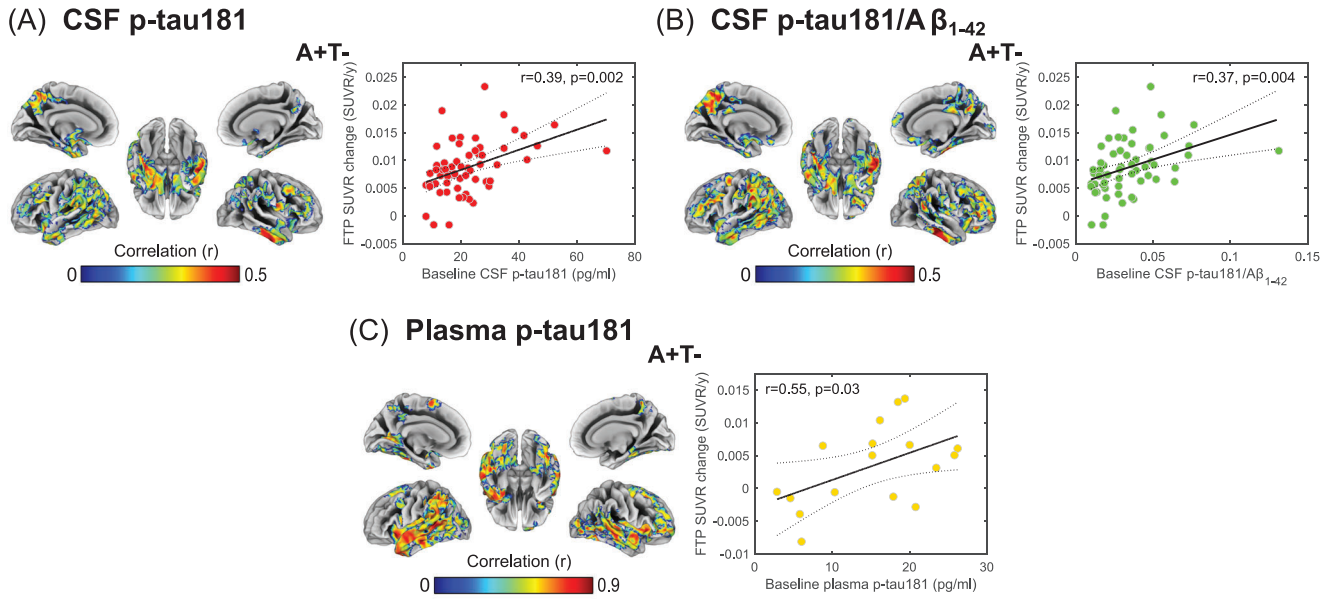

FIGURE 3 Associations of baseline cerebrospinal fluid (CSF) phosphorylated tau (p-tau)181 and baseline CSF p-tau181/amyloid beta $(A\beta)_{1\text{-}42}$ (Cohort 1), and baseline plasma p-tau181 (Cohort 2) with [^{18}F]flortaucipir (FTP) standardized uptake value ratio (SUVR) annualized change in Aβ-positive individuals with normal baseline tau-positron emission tomography (PET; A+T−). Solid lines represent regression lines describing univariable (non-adjusted) associations; dotted lines represent 95% confidence intervals. Pearson correlation coefficients adjusted for age and sex (r), along with *P*-values (*P*), represent the strength of the association between the different biomarkers and FTP SUVR change. Regression coefficients are reported in Table S13 in supporting information. Voxel-wise statistical maps were thresholded using more lenient cluster-forming thresholds of $P < .05$ (uncorrected) at the voxel level and further thresholded at the cluster level by restricting results to clusters with a number of voxels higher than the expected number of voxels as predicted using random field theory

temporal: r = 0.22, *P* = .11). At follow-up, nine A+T− participants progressed to T+. Both baseline CSF p-tau181 (b = 0.06, *P* = .03) and CSF p-tau181/$A\beta_{1\text{-}42}$ (b = 32.6, *P* = .05) were associated with faster progression rates to T+.

In a similar manner, in Cohort 2, higher plasma p-tau181 levels were associated with faster FTP SUVR change rates among A+T− participants (Figure 3C). Baseline plasma p-tau181 levels showed weaker but positive correlations with FTP SUVR change in entorhinal and inferior temporal ROIs, though these associations did not reach statistical significance (Figure S5). Associations in the AD meta-ROI were largely unchanged when adjusting for baseline FTP SUVR (r = 0.58, *P* = .03), baseline Centiloid (r = 0.54, *P* = .05), or clinical diagnosis (r = 0.51, *P* = .07). Three A+T− individuals progressed to T+ at follow-up. No statistically significant association between baseline plasma p-tau181 levels and progression rates to T+ was found (b = 0.39, *P* = .31).

3.3 | Implications for clinical trials

We estimated required samples sizes to detect a 25% reduction in tau accumulation by using CSF biomarkers as "stand-alone" test for inclusion. Participant enrollment based on CSF p-tau181/$A\beta_{1\text{-}42}$ alone systematically yielded the highest tau accumulation rates and lowest sample sizes at highly similar screening failure rates compared to Aβ-PET (Table 2, Tables S8 and S9 in supporting information). This result did not change when including outlier subjects with strong longitudinal decreases in FTP SUVR (Table S10 in supporting information).

Finally, we evaluated reductions in the number of required biomarker tests (i.e., required Aβ-PET scans or lumbar punctures) in clinical trials by using plasma p-tau181 for prescreening of biomarker positivity (see Figure S8 in supporting information for the rest of the CSF biomarkers). Among CU individuals, plasma p-tau181 more accurately identified subjects above 68 CL-based cut-points than subjects above the standard cut-point of 24.4 CL for Aβ positivity (Figure 4A and 4B, left panels, Aβ-PET: Δ area under the curve [AUC] = 0.05, 95% confidence interval [CI: −0.03 to 0.13]; CSF p-tau181/$A\beta_{1\text{-}42}$: ΔAUC = 0.08, 95% CI [0.00 to 0.17]). As such, increases in biomarker positivity prevalence after prescreening were higher using 68 CL-based cut-points (Figure 4A and 4B, mid panels), resulting in reductions of ≈50% in the number of required Aβ-PET scans or CSF p-tau181/$A\beta_{1\text{-}42}$ assessments (Figure 4B, right panel). In the CI group, plasma p-tau181 identified biomarker-positive individuals with moderate accuracy (Figure 4C, left panel) and increased biomarker positivity prevalence after prescreening, with reductions of ≈20% in the number of required biomarker tests (Figure 4C, mid and right panels).

4 | DISCUSSION

Here, we analyzed the associations of CSF biomarkers and plasma p-tau181 with longitudinal tau accumulation as measured with tau-PET

TABLE 2 Estimated sample sizes per arm required to detect a 25% reduction of PET-measured tau accumulation in the temporal AD meta-ROI in a hypothetical two-arm placebo-controlled trial, with $\alpha = 0.05$ (one-sided) at 80% power

Target group	Biomarker cut-point	Tau accumulation rate, SUVR/y (95% confidence interval)	Screening failure rate, %	Sample size needed per arm, N (95% confidence interval)
CU, 24.4 CL-based cut-points				
Aβ-PET	24.4 CL	0.022 (0.013–0.031)	48 (38–59)	369 (239–1027)
CSF $A\beta_{1\text{-}42}$	921 pg/mL	0.027 (0.017–0.036)	53 (42–63)	269 (185–649)
CSF p-tau181	24.8 pg/mL	0.023 (0.012–0.035)	60 (50–70)	418 (240–1593)
CSF p-tau181/$A\beta_{1\text{-}42}$	0.0206	0.027 (0.018–0.036)	52 (41–62)	259 (183–598)
CU, 68 CL-based cut-points				
Aβ-PET	68 CL	0.031 (0.019–0.044)	76 (66–85)	181 (117–507)
CSF $A\beta_{1\text{-}42}$	687 pg/mL	0.033 (0.018–0.049)	76 (66–85)	233 (138–815)
CSF p-tau181	32.3 pg/mL	0.038 (0.021–0.055)	83 (74–90)	148 (90–470)
CSF p-tau181/$A\beta_{1\text{-}42}$	0.0391	0.040 (0.024–0.056)	77 (68–85)	169 (109–474)
CI, 24.4 CL-based cut-points				
Aβ-PET	24.4 CL	0.033 (0.017–0.049)	31 (21–44)	390 (223–1501)
CSF $A\beta_{1\text{-}42}$	MCI: 981 pg/mL AD: 888 pg/mL	0.028 (0.013–0.044)	30 (20–42)	452 (239–2211)
CSF p-tau181	MCI: 21.3 pg/ml AD: 21.5 pg/mL	0.032 (0.017–0.047)	37 (26–50)	323 (191–1119)
CSF p-tau181/$A\beta_{1\text{-}42}$	MCI: 0.0218 AD: 0.0299	0.035 (0.020–0.050)	30 (20–42)	307 (188–981)

Notes: Trial duration was assumed 24 months, with tau-PET performed every 12 months. Sample sizes were estimated for three different target groups for clinical trials: CU individuals with standard Aβ positivity (24.4 CL-based cut-points), CU individuals with high Aβ burden (68 CL-based cut-points), and CI individuals with standard Aβ positivity (24.4 CL-based cut-points). Tau accumulation rates were estimated as the fixed time effect of the linear mixed model used to estimate sample sizes. See Methods S8 for a detailed description of the algorithms used for the estimation of sample sizes and 95% confidence intervals.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CI, cognitively impaired; CL, Centiloid; CSF, cerebrospinal fluid; CU, cognitively unimpaired; FTP, [^{18}F]flortaucipir; PET, positron emission tomography; ROI, region of interest; SUVR, standardized uptake value ratio.

imaging, and further investigated potential implications of the use of these markers for recruitment in clinical trials that use longitudinal tau-PET as outcome. Our results indicate that fluid biomarkers are significantly associated with PET-measured tau accumulation, showing, in the case of CSF biomarkers, similar predictive performance compared to Aβ-PET. Further, we demonstrated that p-tau181 elevations in CSF and blood were associated with tau accumulation in A+T− individuals, suggesting that elevations of these markers may precede early tau aggregation. From a clinical trial perspective, our findings suggest that participant enrollment based on CSF p-tau181/$A\beta_{1\text{-}42}$ would result in comparable required sample sizes to trial inclusion based on Aβ-PET, with similar screening failure rates. Moreover, we demonstrated that prescreening with plasma p-tau181 may result in significant reductions in the number of required PET scans or lumbar punctures for clinical trials, particularly for inclusion of CU individuals with high amyloid burden (> 68 CL-based cut-points) indicative of high rates of tau accrual.[38] Together, our findings highlight the potential of fluid biomarkers for predicting tau pathology progression in AD and contribute to increase the battery of biomarkers that might be used for participant selection in clinical trials of tau-targeting therapies that use longitudinal tau-PET as endpoint.

Though previous reports have investigated the independent contributions of imaging and demographic factors for the prediction of longitudinal tau accumulation in CU and CI individuals,[10,11] the associations of CSF biomarkers with longitudinal FTP change, as well as their relative predictive performance compared to Aβ-PET, remained unexplored. Here, we provide novel evidence suggesting that CSF biomarkers are markedly associated with longitudinal tau accumulation, showing similar predictive performance to Aβ-PET in both the CU and CI groups, particularly for the CSF p-tau181/$A\beta_{1\text{-}42}$ ratio. Plasma p-tau181 was less strongly associated with longitudinal tau accumulation in CU individuals but showed significant associations with tau accrual in the CI group, with similar predictive performance as Aβ-PET. Overall, these findings indicate that the more scalable CSF and plasma biomarkers are useful tools for predicting the progression of aggregated tau.

Another relevant result of our study was that higher p-tau181 levels in CSF or plasma were associated with faster rates of tau accumulation in individuals with elevated Aβ but normal baseline tau-PET signal (A+T−). These results represent the first longitudinal confirmation of the hypothesis raised by previous cross-sectional studies that suggested that elevations in soluble p-tau might precede tangle

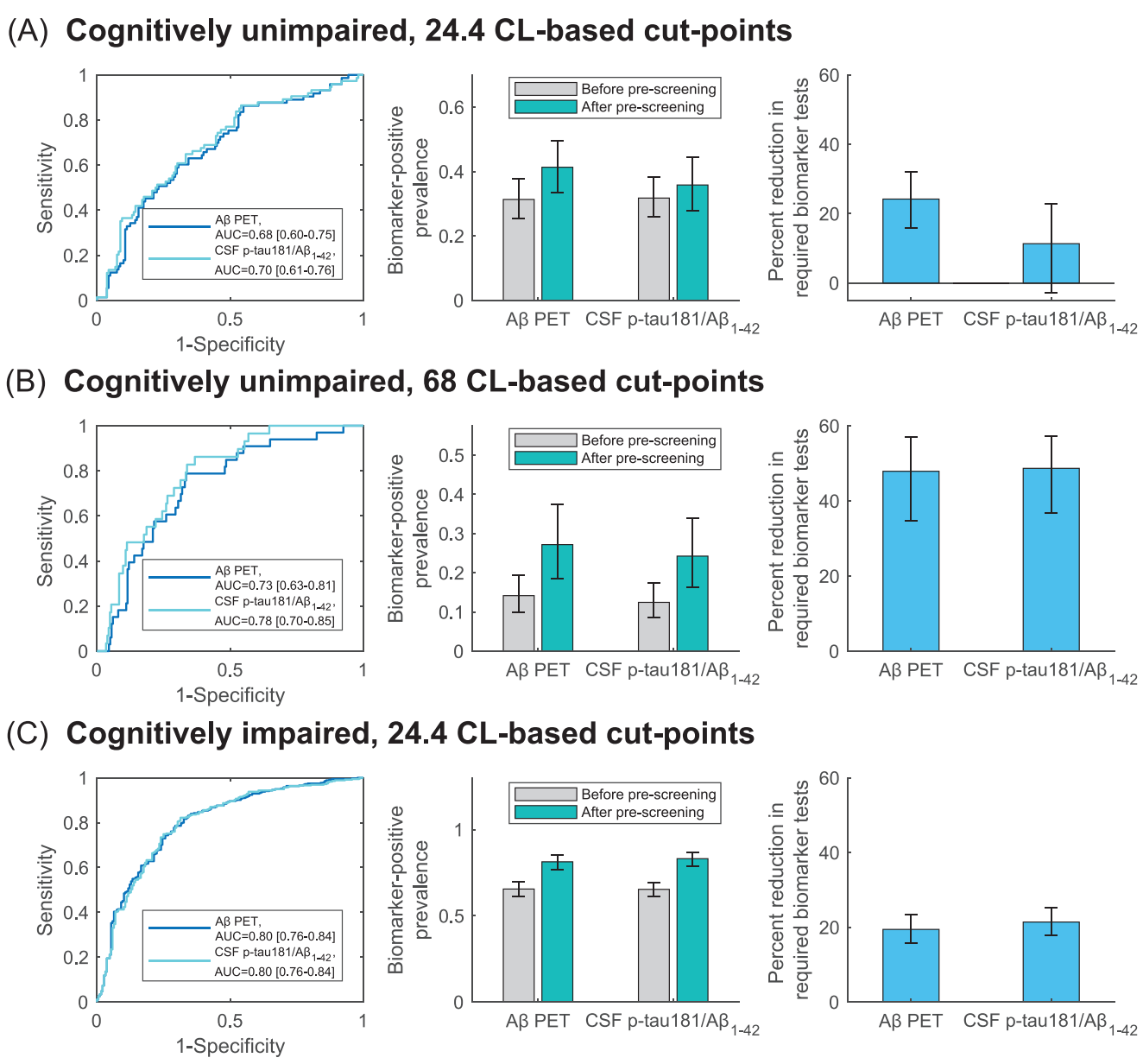

FIGURE 4 Implications of the use of plasma phosphorylated tau (p-tau)181 as a prescreening tool in clinical trials. Prescreening with plasma p-tau181 was analyzed for participant selection based on either amyloid beta positron emission tomography (Aβ-PET) or the cerebrospinal fluid (CSF) p-tau181/A$\beta_{1\text{-}42}$ ratio, in three different scenarios: (A) a trial of cognitively unimpaired (CU) individuals prescreened for standard Aβ positivity (24.4 Centiloid [CL]-based cut-points), (B) a trial of CU individuals prescreened for high Aβ burden (68 CL-based cut-points), and (C) a trial of cognitively impaired (CI) individuals prescreened for standard Aβ positivity (24.4 CL-based cut-points). Left panels represent the discriminative accuracy, quantified as the area under the receiver operating characteristic curve (AUC), of plasma p-tau181 to identify Aβ-PET–positive or CSF p-tau181/A$\beta_{1\text{-}42}$-positive individuals; quantities between brackets are 95% confidence intervals estimated using bias-corrected and accelerated bootstrap (n = 5000 repetitions). Mid panels represent the prevalence of biomarker-positive individuals before and after prescreening (i.e., among plasma p-tau181–positive subjects) with plasma p-tau181. Error bars represent binomial exact 95% confidence intervals. Right panels represent the percent reduction in the number of required biomarker tests (Aβ-PET or CSF p-tau181/A$\beta_{1\text{-}42}$) in a clinical trial if participants are prescreened with plasma p-tau181. Error bars represent 95% confidence intervals computed using bias-corrected and accelerated bootstrap (n = 5000 repetitions)

aggregation.[19,41,42] The fact that both CSF biomarkers and plasma p-tau181 can anticipate very early AD-related tau aggregation may be relevant for trials using tau-targeting drugs as it opens up the possibility of including A+T− individuals at increased risk of imminent tau accumulation in these trials, halting tau progression at the earliest stages and potentially preventing the subsequent cascade of neurodegeneration and cognitive impairment. Yet, it must be noted that FTP-PET seems to lack the sensitivity to detect early tau pathology (Braak stages I–IV),[43–45] and thus, our findings could have been different using more sensitive tau-PET tracers.

Power analyses comparing Aβ-PET and CSF biomarkers head-to-head demonstrated that trial participant recruitment based on the CSF p-tau181/$A\beta_{1-42}$ ratio yielded comparable sample sizes to Aβ-PET. Remarkably, this result not only holds for the recruitment of CU and CI participants with standard amyloid positivity, but also for CU individuals with high Aβ burden (> 68 CL-based cut-points) previously demonstrated to be at higher risk for longitudinal tau accumulation.[38] Altogether, these results suggest that the use of the CSF p-tau181/$A\beta_{1-42}$ ratio instead of an Aβ-PET scan for participant selection in anti-tau trials is not detrimental in terms of enrichment, yet may dramatically reduce recruitment costs, as the cost of a complete CSF analysis is about 10 to 15 times lower than for an Aβ-PET scan.[46]

A novel aspect of our study is the fact that plasma p-tau181 seemed particularly suited for identifying CU individuals with high Aβ burden (> 68 CL-based cut-points, Figure 4B, left panel), who are at increased risk of tau accumulation compared to Aβ-positive subjects with lower Aβ burden.[38] This higher performance is consistent with findings from our previous study on the temporal course of plasma p-tau181, in which we showed that this marker reaches abnormal levels at relatively high burdens of global Aβ pathology.[14] The increased accuracy of plasma p-tau181 for CU individuals with high Aβ burden may have important implications for clinical trials, as the prevalence of CU individuals with high Aβ is relatively low (≈12–15%, Figure 4B, mid panel). Thus, a trial targeting CU individuals with high Aβ (> 68 CL) on Aβ-PET would require 1278 Aβ-PET scans to achieve the sample size estimated in Table 2 but only 666 if participants were prescreened with plasma p-tau181. Assuming a cost of $3000 for an Aβ-PET scan versus $50 for plasma p-tau181 measurement,[20] this would result in a 46% reduction of the associated costs. Biomarker-associated recruitment costs would be dramatically lower if the CSF p-tau181/$A\beta_{1-42}$ ratio is instead used to select these CU individuals with high Aβ burden after prescreening with plasma p-tau181: cost reductions were as high as 95% (assuming a cost of $200 for CSF measurements), which translates into a cost of ≈$192,000 compared to ≈$3,834,000 using Aβ-PET for participant selection and without prescreening. These results highlight the potential of plasma p-tau181 and CSF biomarkers to boost drug research for tau pathology in AD, contributing to minimize screening failures with invasive procedures and to reduce costs of clinical trials.

Our study has several limitations. Sample size was relatively small in Cohort 2, which might have limited our statistical power to detect an association between plasma p-tau181 and longitudinal tau accumulation among CU individuals. Furthermore, the number of A+T− subjects in Cohort 2 and the number of subjects who progressed to T+ at follow-up was limited and thus the analyses involving these participants should be considered exploratory. The limited number of participants in Cohort 2 did not allow for an accurate evaluation of plasma p-tau181 as a standalone test for participant selection in trials with tau-PET outcomes, nor allowed for a comparison with CSF biomarkers. Future comparative studies using larger sample sizes are warranted to evaluate the value of plasma p-tau181 and CSF as standalone biomarkers for sample enrichment. There was a time lag from biofluid collection and baseline tau-PET, which was larger in Cohort 2 because plasma p-tau181 was only available in the latest visits of ADNI2 whereas tau-PET was acquired when individuals were followed up in ADNI3. Though these time intervals might have influenced our findings, key results remained virtually unchanged after adjusting for time interval (see Tables S4, S5, and S7). The present study lacked neuropathological validation of the observed associations between in vivo biomarkers and tau accumulation. Participant selection was based on availability of imaging and fluid biomarkers, which may have introduced some degree of selection bias. Our findings might not extrapolate to more diverse populations with higher prevalence of common comorbidities such as vascular pathology, which might influence tau or Aβ deposition.[47,48]

In conclusion, our study suggests that CSF biomarkers and plasma p-tau181 represent cost-effective predictors of longitudinal tau accumulation as measured by tau-PET, being capable to anticipate future tau aggregation even at very early stages of tau deposition. The use of fluid biomarkers may be an effective strategy for participant inclusion in anti-tau clinical trials, as it resulted in a similar enrichment as for Aβ-PET and in significant reductions of the costs associated with biomarker screening.

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CONFLICTS OF INTEREST

HZ has served on scientific advisory boards and/or as a consultant for Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, CogRx and Red Abbey Labs. KB has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Lilly, MagQu, Prothena, Roche Diagnostics, and Siemens Healthineers. HZ has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, and Biogen. KB has given lectures in symposia sponsored by GEECD/Roche Diagnostics and IFCC/SNIBE. MS has received speaker's fee from Genentech. AM received a travel fellowship for attending AAIC 2021. TKK reports the following patent: Pedersen, J.T.; Karikari, TK; Höglund, K; Blennow, K; Harndal, M.N.; Zetterberg, H. Use of a tau pS396 assay to diagnose tauopathies. Patent: WIPO (PCT) No. WO2020193500A1 https://patents.google.com/patent/WO2020193500A1/en. KB has served on scientific advisory boards and/or as a consultant for Julius Clinical and Novartis. MS has served at scientific advisory boards and/or as a consultant for Servier Pharmaceuticals. HZ is a chair of the Alzheimer's Association Global Biomarker Standardization Consortium and the AA Biofluid-Based Biomarker PIA. HZ is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. AM, TKK, MJG, NJA, JLR, and AS report no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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