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RESEARCH ARTICLE

Equivalence of plasma p-tau217 with cerebrospinal fluid in the diagnosis of Alzheimer's disease

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Abstract

INTRODUCTION: Plasma biomarkers are promising tools for Alzheimer's disease (AD) diagnosis, but comparisons with more established biomarkers are needed.

METHODS: We assessed the diagnostic performance of p-tau$_{181}$, p-tau$_{217}$, and p-tau$_{231}$ in plasma and CSF in 174 individuals evaluated by dementia specialists and assessed with amyloid-PET and tau-PET. Receiver operating characteristic (ROC) analyses assessed the performance of plasma and CSF biomarkers to identify amyloid-PET and tau-PET positivity.

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RESULTS: Plasma p-tau biomarkers had lower dynamic ranges and effect sizes compared to CSF p-tau. Plasma p-tau$_{181}$ (AUC = 76%) and p-tau$_{231}$ (AUC = 82%) assessments performed inferior to CSF p-tau$_{181}$ (AUC = 87%) and p-tau$_{231}$ (AUC = 95%) for amyloid-PET positivity. However, plasma p-tau$_{217}$ (AUC = 91%) had diagnostic performance indistinguishable from CSF (AUC = 94%) for amyloid-PET positivity.

DISCUSSION: Plasma and CSF p-tau$_{217}$ had equivalent diagnostic performance for biomarker-defined AD. Our results suggest that plasma p-tau$_{217}$ may help reduce the need for invasive lumbar punctures without compromising accuracy in the identification of AD.

KEYWORDS
Alzheimer's disease, amyloid-β, CSF, PET, plasma, p-tau, tau

Highlights

- p-tau$_{217}$ in plasma performed equivalent to p-tau$_{217}$ in CSF for the diagnosis of AD, suggesting the increased accessibility of plasma p-tau$_{217}$ is not offset by lower accuracy.
- p-tau biomarkers in plasma had lower mean fold-changes between amyloid-PET negative and positive groups than p-tau biomarkers in CSF.
- CSF p-tau biomarkers had greater effect sizes than plasma p-tau biomarkers when differentiating between amyloid-PET positive and negative groups.
- Plasma p-tau$_{181}$ and plasma p-tau$_{231}$ performed worse than p-tau$_{181}$ and p-tau$_{231}$ in CSF for AD diagnosis.

1 | INTRODUCTION

Diagnosis of Alzheimer's disease (AD) based on clinical criteria is challenging. Highly specialized centers misdiagnose AD in approximately 15%–30% of cases[1,2] and the rate of misdiagnosis in primary care settings is estimated to be even greater.[3] Correspondingly, cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers of amyloid-β and tau are increasingly used in the diagnosis of AD,[4] as inclusion criteria for clinical trials,[5,6] and will be necessary when determining eligibility for disease-modifying therapies.[7]

Blood-based biomarkers of phosphorylated tau (p-tau) show strong correlations with PET, CSF, and post-mortem measurements of AD pathology.[8–18] Due to lower cost and invasiveness compared to PET and CSF, blood biomarkers may provide accessible and scalable diagnostic tools for AD, provided they display comparable diagnostic performance.[19–21] The recently proposed Alzheimer's Association appropriate use recommendations for AD blood biomarkers highlight the need to assess equivalence and/or non-inferiority of plasma biomarkers with respect to more established AD biomarkers.[22] Here, we compare the performance of plasma p-tau$_{181}$, p-tau$_{217}$, and p-tau$_{231}$ with CSF p-tau$_{181}$, p-tau$_{217}$, and p-tau$_{231}$ head-to-head for the identification of amyloid-PET positivity and biologically-defined AD.

2 | METHODS

2.1 | Participants

We assessed 174 individuals from the Translational Biomarkers of Aging and Dementia (TRIAD)[23] cohort: 27 young adults, 76 cognitively unimpaired (CU) older adults, and 71 cognitively impaired (CI) individuals. All participants had CSF assessments of p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$, plasma assessments of p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$, as well as amyloid-PET with [^{18}F]AZD4694 and tau-PET with [^{18}F]MK6240. Evaluations of participants included a review of their medical history and an interview with the participant and their study partner, a neurological examination by a physician and a neuropsychological examination. Participants were approached consecutively and data was collected prospectively. CU individuals had no objective cognitive impairment and a Clinical Dementia Rating (CDR) score of 0. CI individuals had subjective and/or objective cognitive impairment and a CDR score of 0.5, 1 or 2. Participants were excluded from this study if they had systemic conditions which were not adequately controlled through a stable medication regimen. Other exclusion criteria were active substance abuse, recent head trauma, recent major surgery, or MRI/PET safety contraindications. This study was conducted in accordance to the Standards for Reporting of Diagnostic

Accuracy (STARD) guidelines. The study was approved by the Montreal Neurological Institute PET working committee and the Douglas Mental Health University Institute Research Ethics Board. Written informed consent was obtained for all participants. The complete study protocol can be accessed by contacting the investigators.

2.2 | CSF and plasma biomarker quantification

Collection of CSF samples has been reported previously.[24] All p-tau residues measured from CSF were quantified in the Clinical Neurochemistry Laboratory, University of Gothenburg by scientists blinded to participant clinical and biomarker information. CSF concentrations of p-tau$_{181}$ and p-tau$_{217}$ were quantified using a custom single molecule array (Simoa; Simoa HD-X instruments, Quanterix, Billerica, Massachusetts, USA) assay,[25] and CSF p-tau$_{231}$ was measured using an enzyme-linked immunosorbent assay (ELISA) assay, as described previously.[26] Blood samples were collected following previously described protocols.[11] Plasma p-tau$_{181}$ and plasma p-tau$_{231}$ were also measured in the Clinical Neurochemistry Laboratory, University of Gothenburg, by scientists blinded to participant clinical and biomarker information. Both plasma biomarkers were assessed using an in-house Simoa method, as described previously.[13,27] Plasma p-tau$_{217}$ concentrations were measured using a Simoa assay developed by Janssen[28,29] by scientists blinded to clinical and biomarker data.

Abnormality for CSF biomarkers was determined using a support vector classification model differentiating amyloid-PET positive from amyloid-PET negative individuals as reported previously.[30] The thresholds selected had the least distance from the ideal discriminator (0, 1) and maximized the true positive rate while minimizing the false negative rate. This approach resulted in a threshold of 427.9 pg/ml for p-tau$_{181}$, 10.45 pg/ml for p-tau$_{217}$ and 16.34 pg/ml for p-tau$_{231}$. Nearly identical CSF biomarker classifications were observed when using thresholds for CSF abnormality derived from the mean +2 SD of amyloid-PET negative CU older adults: 428.6 pg/ml for p-tau$_{181}$, 11.9 pg/ml for p-tau$_{217}$ and 15.8 pg/ml for p-tau$_{231}$. Abnormality for plasma biomarkers was predefined in accordance with appropriate use recommendations.[22] A threshold of 15.085 pg/ml was employed for plasma p-tau$_{181}$ and a threshold of 17.652 pg/ml was employed for plasma p-tau$_{231}$.[31] A threshold of 0.083 pg/ml was employed for the Janssen plasma p-tau$_{217}$ assay based on the same methods used for p-tau$_{181}$ and p-tau$_{231}$ thresholds. Predefined abnormality thresholds were only employed in analyses assessing the individual-level agreement between plasma and CSF p-tau biomarkers.

2.3 | PET imaging acquisition and processing

[^{18}F]AZD4694 PET and [^{18}F]MK6240 PET scans were acquired with a brain-dedicated Siemens High Resolution Research Tomograph (HRRT). [^{18}F]AZD4694 PET images were acquired 40–70 min after bolus injection and reconstructed on a four-dimensional volume with three frames (3 × 600s), as previously described.[32] [^{18}F]MK6240 PET images were acquired at 90-110 min after bolus radiotracer injection and reconstructed on a four-dimensional volume with four frames (4 × 300s).[2] A 6-min transmission scan with a rotating ^{137}Cs point source followed each PET acquisition for attenuation correction. PET images were corrected for decay, motion, dead time, random, and scattered coincidences. T1-weighted MRIs were acquired at the Montreal Neurological Institute on a 3T Siemens Magnetom using a standard head coil. They underwent correction for non-uniformity and field-distortion and were processed using an in-house pipeline. PET images were automatically registered to the T1-weighted image space, and the T1-weighted images were linearly and non-linearly registered to the Montreal Neurological Institute (MNI) reference space. To minimize interference of meningeal spillover, [^{18}F]MK6240 images were meninges-striped in native space before they were transformed and blurred, as described previously.[33] [^{18}F]AZD4694 standardized uptake value ratio (SUVR) maps were calculated using the whole cerebellum gray matter as the reference region and [^{18}F]MK6240 SUVR maps were generated using the inferior cerebellar grey matter as a reference region. Spatial smoothing allowed the PET images to achieve an 8-mm full-width at half-maximum resolution.

Amyloid-β SUVR from a neocortical region of interest (ROI) for each participant was estimated by averaging the SUVR from the precuneus, prefrontal, orbitofrontal, parietal, temporal, and cingulate cortices,[32] with amyloid-β positivity defined as an [^{18}F]AZD4694 above 1.55.[32] The SUVR from the temporal meta-ROI, a composite mask commonly used as a summary measure of tau-PET, was calculated

RESEARCH IN CONTEXT

1. **Systematic Review**: Literature was reviewed using traditional sources (PubMed and Google scholar), as well as meetings and presentations. Several recent observational studies have reported high performance of plasma phosphorylated tau (p-tau) for Alzheimer's disease (AD). The Alzheimer's Association appropriate use criteria for blood-based biomarkers highlight that blood biomarker performance must be compared to more established CSF biomarkers before clinical implementation. The most relevant cross-sectional studies on p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$ are cited in this manuscript.
2. **Interpretation**: Plasma p-tau$_{181}$ and plasma p-tau$_{231}$ performed significantly worse than p-tau$_{181}$ and p-tau$_{231}$ in cerebrospinal fluid (CSF). In contrast, plasma p-tau$_{217}$ performed equivalent to CSF p-tau$_{217}$ for the identification of amyloid-PET positivity and for biological AD.
3. **Future Directions**: Multicenter studies, which invariably have less tightly controlled pre-analytical protocols are needed to assess performance of plasma p-tau$_{217}$ in real-world settings. Furthermore, assessing p-tau$_{217}$ performance in more diverse populations is needed.

TABLE 1 Demographic characteristics of the sample.

	Young (*N* = 27)	CU OA (*N* = 76)	CI (*N* = 71)	Overall (*N* = 174)
Sex				
Female, *n* (%)	16 (59.3%)	43 (56.6%)	37 (52.1%)	96 (55.2%)
Male, *n* (%)	11 (40.7%)	33 (43.4%)	34 (47.9%)	78 (44.8%)
Age, years				
Mean, (SD)	24.4 (2.58)	70.5 (7.82)	68.7 (7.84)	62.6 (17.2)
Education, years				
Mean, (SD)	17.1 (2.32)	14.9 (3.40)	14.9 (3.30)	15.3 (3.30)
APOE ε4 status				
Non-carriers, *n* (%)	20 (74.1%)	52 (68.4%)	39 (54.9%)	111 (61.7%)
Carriers, *n* (%)	7 (25.9%)	24 (31.6%)	32 (45.1%)	64 (36.2%)
MMSE				
Mean, (SD)	29.8 (0.506)	29.1 (0.943)	25.2 (5.26)	27.7 (3.94)
Neocortical [^{18}F]AZD4694 SUVR				
Mean, (SD)	1.20 (0.07)	1.48 (0.39)	1.92 (0.61)	1.61 (0.54)
Temporal meta-ROI [^{18}F]MK6240 SUVR				
Mean, (SD)	0.82 (0.07)	0.86 (0.155)	1.43 (0.80)	1.09 (0.59)

Abbreviations: APOE ε4, apolipoprotein epsilon 4; CI, cognitively impaired; CU, cognitively unimpaired; MMSE, Mini-Mental State Examination; OA, older adult; ROI, region of interest; SD, standard deviation; SUVR, standardized uptake value ratio.

from the entorhinal, parahippocampal, amygdala, fusiform, inferior, and middle temporal cortices, as previously described,[34] with positivity defined as SUVRs above 1.24.[35] Individuals were deemed to have biomarker-defined AD if they had positive amyloid-PET and tau-PET scans.[36]

2.4 | Statistical analyses

Statistical analyses were performed in R v4.1.1 and GraphPad Prism v9. Normality of p-tau biomarkers was evaluated using Anderson-Darling tests. Because plasma and CSF biomarkers did not meet criteria for normality, they were log-transformed for parametric *t*-tests between amyloid-PET positive and negative groups. Effect sizes of amyloid-PET positive and negative group differences were determined using Cohen's *d*. We also looked at the mean fold-change between amyloid-PET positive and negative groups for all CSF and plasma p-tau biomarkers. Bland-Altman analyses assessed the agreement between measurements from plasma and CSF. Area under the receiver operating characteristic (ROC) curve values were calculated for all plasma and CSF p-tau biomarkers. Two reference standards were evaluated for ROC analyses: (i) abnormal amyloid-PET (regardless of tau-PET status; indicating either Alzheimer's pathologic change or biological AD) and (ii) abnormal amyloid-PET and tau-PET, indicating biological AD.[36] Sensitivity, specificity, positive predictive value, and negative predictive value were also calculated for each p-tau biomarker. We selected PET biomarkers as the reference standard instead of clinical diagnosis in accordance to the biological definition of AD.[36] We tested differences in area under the ROC curve using DeLong's test with the pROC package in R.

3 | RESULTS

3.1 | Participants

Demographic and clinical characteristics of all individuals in the study are reported in Table 1. The mean (SD) age of all participants was 62.6 (17.2) and 55% were female. No differences in age ($p = 0.17$), years of education ($p = 0.99$) or sex distribution ($p = 0.59$) were observed between CU older adults and the CI group. The CI group had higher composite amyloid-PET SUVRs ($p < 0.0001$) and higher temporal tau-PET SUVRs ($p < 0.0001$).

3.2 | Comparison of CSF and plasma p-tau differences according to amyloid-PET status

Density and box plots displaying the distribution of p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$ in CSF and plasma are presented in Figure 1. Plasma p-tau$_{181}$ and p-tau$_{231}$ had considerably greater overlap between amyloid-PET positive and amyloid-PET negative participants compared to evaluations in CSF. Plasma p-tau$_{181}$ and plasma p-tau$_{231}$ had effect sizes approximately 50% of those in CSF when comparing amyloid-PET positive and negative groups, while p-tau$_{217}$ in plasma had an effect size 84% of that of p-tau$_{217}$ in CSF. Moreover, plasma

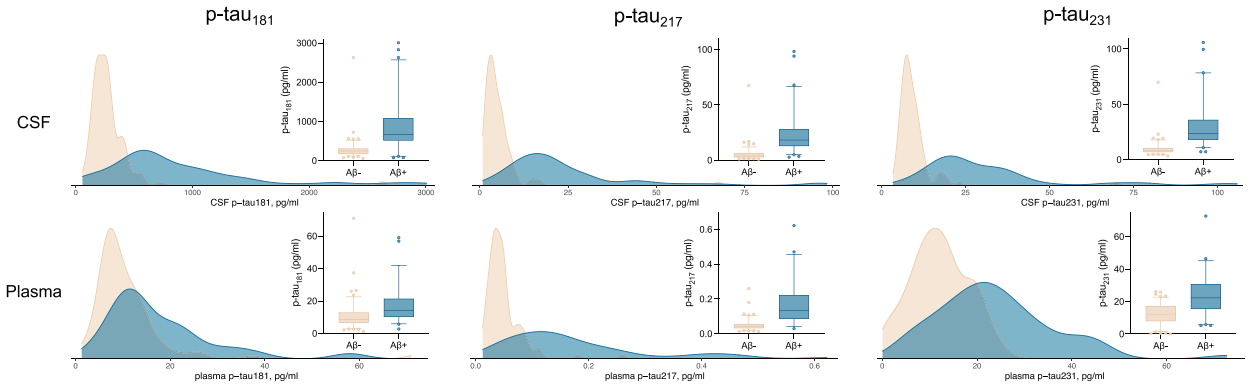

FIGURE 1 Distributions of CSF and plasma p-tau181, 217, and 231 by amyloid-PET status. Density plots represent the continuous distribution of CSF (top) and plasma (bottom) biomarkers of p-tau$_{181}$ (left), p-tau$_{217}$ (middle), and p-tau$_{231}$ (right). Beige indicates amyloid-PET negative participants, and blue indicates amyloid-PET positive participants. Boxplots are also presented for each biomarker, where lines indicate 95% confidence intervals and individual circles are data points that lie outside 95% confidence intervals. Plasma p-tau$_{181}$ and p-tau$_{231}$ had considerably greater overlap between amyloid-PET positive and amyloid-PET negative participants compared to evaluations in CSF. CSF p-tau$_{181}$ and CSF p-tau$_{231}$ had significantly greater effect sizes when differentiating between amyloid-PET positive and amyloid-PET negative participants compared to plasma (Table 2). CSF and plasma p-tau$_{217}$ had similar degrees of overlap and similar effect sizes to distinguish amyloid-PET positive and amyloid-PET negative participants. All comparisons were significant at $p < 0.0001$.

TABLE 2 p-tau biomarker means, mean fold-change, statistical tests, and effect sizes between amyloid-PET positive and negative groups.

	Aβ−	Aβ+	Fold-change	Comparison *t*-value	*p*-Value	Effect size
CSF p-tau$_{181}$	285.0	870.4	2.05	9.12	<0.0001	1.53
Plasma p-tau$_{181}$	10.6	17.8	0.68	5.03	<0.0001	0.83
CSF p-tau$_{217}$	5.391	23.64	3.39	14.05	<0.0001	2.24
plasma p-tau$_{217}$	0.0496	0.1736	2.5	10.83	<0.0001	1.88
CSF p-tau$_{231}$	9.57	30.60	2.20	13.87	<0.0001	2.29
Plasma p-tau$_{231}$	12.28	24.25	0.97	6.57	<0.0001	0.99

Note: p-tau biomarker means are reported in pg/ml. *t*-tests were carried out using log-transformed p-tau biomarker data. Effect sizes are reported as Cohen's d.
Abbreviation: CSF, cerebrospinal fluid; PET, positron emission tomography.

p-tau$_{217}$ had a greater effect size than CSF p-tau$_{181}$ when comparing amyloid-PET positive and negative groups. A similar pattern was observed for fold-changes, in which plasma p-tau$_{181}$ and p-tau$_{231}$ biomarkers had lower fold-changes than did CSF biomarkers, with p-tau$_{217}$ having the smallest difference between plasma and CSF. Plasma p-tau$_{217}$ also had higher fold-changes than did CSF p-tau$_{181}$ and CSF p-tau$_{231}$. CSF and plasma p-tau$_{217}$ had similar degrees of overlap and similar effect sizes to distinguish amyloid-PET positive and amyloid-PET negative participants. All comparisons were significant at $p < 0.0001$. A summary of fold-changes, statistical comparisons and effect sizes between amyloid-PET positive and negative groups for all p-tau biomarkers is reported in Table 2.

3.3 | Relationship between CSF and plasma p-tau concentrations

Scatterplots representing z-scored p-tau biomarker concentrations from plasma and CSF in the same individuals are presented in Figure 2A. For all p-tau biomarkers, plasma p-tau concentrations were lower in magnitude when CSF concentrations were high, and this pattern was the least pronounced for plasma p-tau$_{217}$ (p-tau$_{181}$: $y = 0.388x + 0.010$; p-tau$_{217}$: $y = 0.575x + 0.016$; p-tau$_{231}$: $y = 0.489–0.005$). Bland-Altman plots displaying the agreement between plasma and CSF p-tau biomarkers are presented in Figure 2B. For all p-tau biomarkers, data points outside the upper and lower limits of agreement were more likely to be found at higher concentrations. Lower concentrations of p-tau had values closely centered around 0 in Bland-Altman analyses, indicating very high agreement between p-tau measurements in CSF and plasma at low concentrations, particularly for p-tau$_{217}$.

Next, we assessed the agreement between dichotomized p-tau biomarkers in CSF and plasma (i.e., plasma−/CSF−, plasma+/CSF−, plasma−/CSF+ and plasma+/CSF+). To avoid circularity, we employed predefined thresholds of abnormality.[22] Scatterplots representing p-tau biomarker concentrations from CSF and plasma are presented in Figure 2C, with dashed lines indicating predefined thresholds. For p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$, agreement between two negative

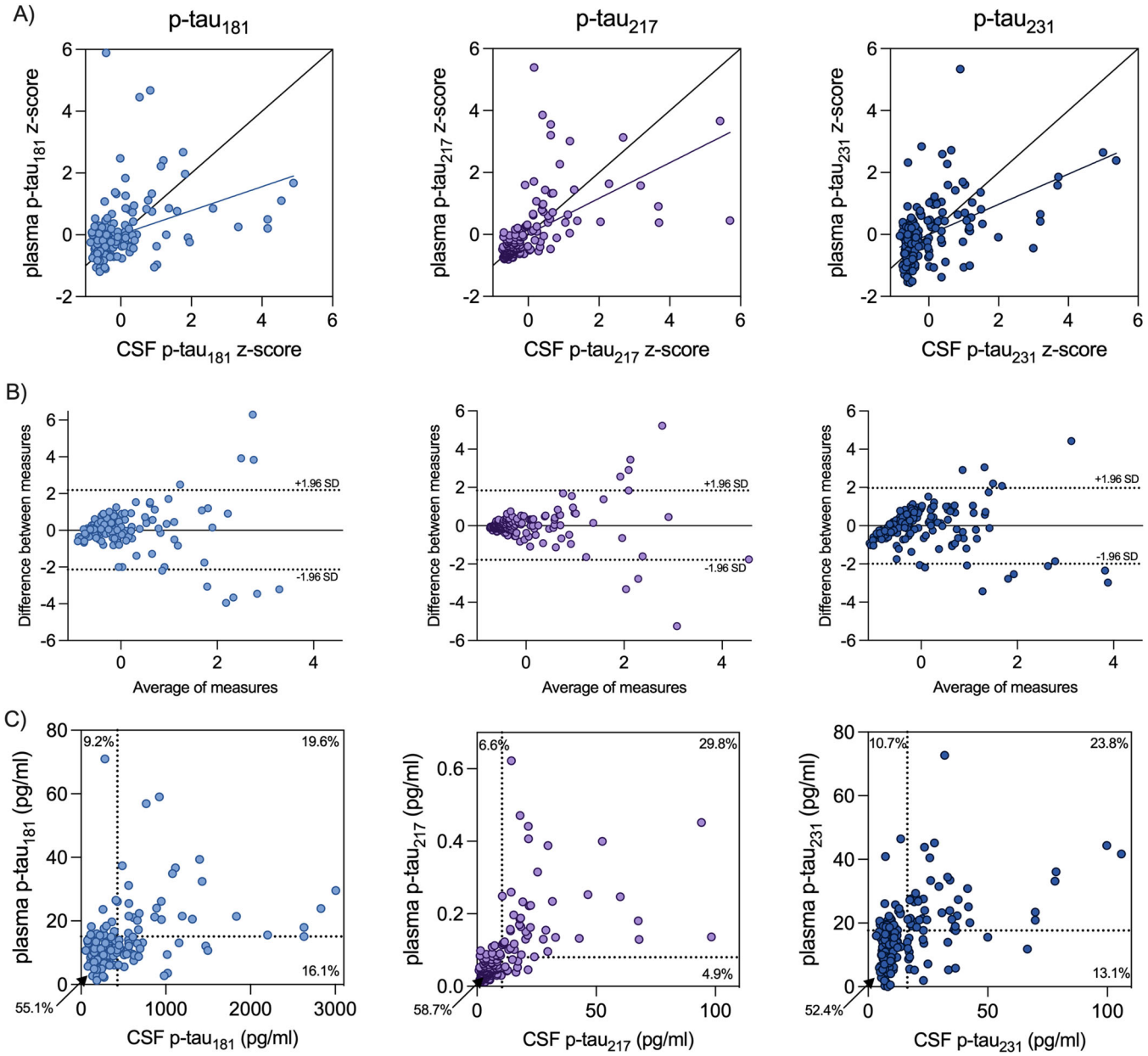

FIGURE 2 Relationship between CSF and plasma p-tau concentrations. (A) Black lines of origin along the horizontal depict a theoretical linear relationship between variables without over- or under-estimation. The true line below the origin indicates that plasma p-tau measurements underestimate p-tau concentrations from CSF, a finding observed for p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$. (B) Bland-Altman analysis assessing bias between CSF and plasma measurements. Dashed lines indicate limits of agreement. Z-scores for each biomarker are represented to facilitate comparisons between measurements. (C) Within-subject agreement between classification from CSF and plasma p-tau biomarkers. Cutoff values for plasma biomarkers were determined from independent cohorts, and cutoffs for CSF biomarkers were determined using a support vector classification model (see methods). Of all three p-tau biomarkers investigated, plasma p-tau$_{217}$ had the highest rates of agreement (88.5%), followed by p-tau$_{231}$ (75.0%) and p-tau$_{181}$ (66.7%). Abnormal plasma p-tau in individuals without abnormal CSF p-tau (plasma+/CSF−) was more common than the reverse for all p-tau biomarkers, but was most pronounced for p-tau$_{181}$ and p-tau$_{217}$.

biomarkers was the most common outcome. For p-tau$_{181}$, we observed agreement between plasma and CSF classifications in 74.7% of cases (55.1% plasma−/CSF− and 19.8% plasma+/CSF+) and disagreement in 25.3% of cases (9.2% plasma+/CSF− and 16.1% plasma−/CSF+). Significantly higher agreement was observed for p-tau$_{217}$, with agreement between plasma and CSF classifications in 88.5% of cases (58.7% plasma−/CSF− and 29.8% plasma+/CSF+) and disagreement in 11.5% of cases (6.6% plasma+/CSF− and 4.9% plasma−/CSF+). The individuals who were plasma/CSF p-tau$_{217}$ discordant were similar in terms of age (mean: 72 years), sex (44% male) and amyloid-PET positivity rate (33% positive) as compared to the rest of the non-young adult sample. There were no plasma/CSF p-tau$_{217}$ discordant individuals with

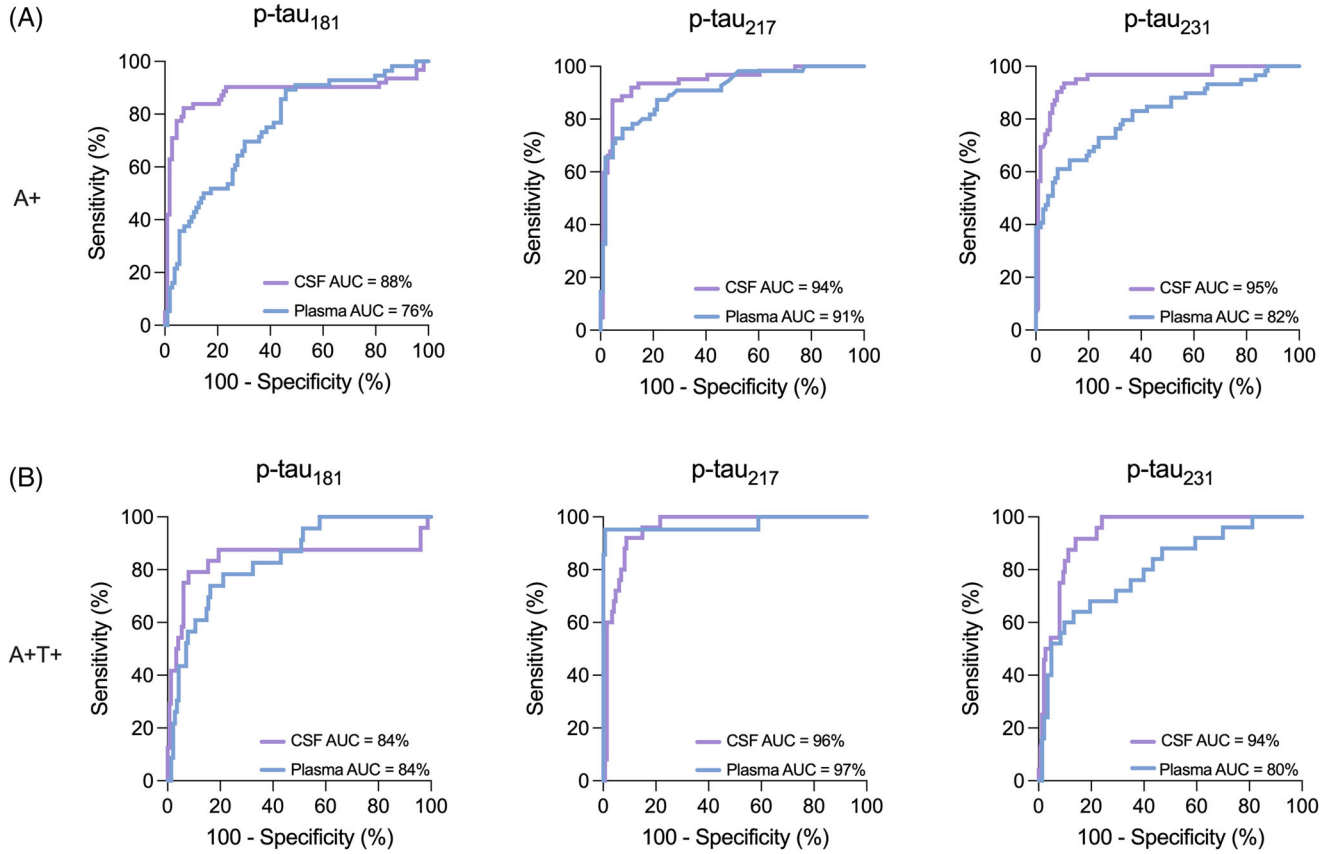

FIGURE 3 Discriminative accuracy of CSF and plasma p-tau for amyloid-PET positivity and for biological AD defined by PET. (A) ROC curves displaying discriminative accuracy of CSF (purple lines) and plasma (blue lines) for amyloid-PET positivity. DeLong's test revealed that plasma p-tau$_{181}$ and plasma p-tau$_{231}$ performed significantly worse than CSF, whereas no difference was observed for p-tau$_{217}$. Plasma p-tau$_{217}$ also outperformed plasma p-tau$_{181}$ and plasma p-tau$_{231}$ for the identification of amyloid-PET positivity. (B) ROC curves displaying discriminative accuracy of CSF (purple lines) and plasma (blue lines) for concurrent amyloid-PET positivity and tau-PET positivity. DeLong's test revealed that plasma p-tau$_{231}$ performed significantly worse than CSF, whereas no difference was observed for p-tau$_{217}$ and p-tau$_{181}$. Plasma p-tau$_{217}$ also had higher discriminative accuracy than plasma p-tau$_{181}$ and plasma p-tau$_{231}$ for the identification of biological AD (A+T+). The summary of all statistical comparisons is reported in Table 3 and Table S1. AD, Alzheimer's disease; ROC, receiver operating characteristic.

CDR 1 or greater, or with tau-PET positivity. A summary of the demographic, clinical and biomarker information for CSF/plasma p-tau217 discordant cases is provided in Table S1. For p-tau$_{231}$, we observed agreement between plasma and CSF classifications in 76.2% of cases (52.4% plasma−/CSF− and 23.8% plasma+/CSF+) and disagreement in 23.8% of cases (10.7% plasma+/CSF− and 13.1% plasma−/CSF+).

3.4 | Diagnostic performance of CSF versus plasma p-tau biomarkers

ROC curves of plasma and CSF p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$ differentiating between amyloid-PET positive and amyloid-PET negative participants are displayed in Figure 3A. For p-tau$_{181}$, CSF had significantly higher performance than plasma in distinguishing between amyloid-PET positive and negative participants ($p = 0.01$) and CSF p-tau$_{231}$ outperformed plasma p-tau$_{231}$ in distinguishing between amyloid-PET positive and negative participants ($p < 0.0001$). However, plasma p-tau$_{217}$ and CSF p-tau$_{217}$ did not have significantly different diagnostic performance for amyloid-PET positivity ($p = 0.23$). ROC curves of plasma and CSF p-tau$_{181}$, p-tau$_{217}$ and p-tau$_{231}$ differentiating between participants with and without biological AD (defined as amyloid-PET and tau-PET positivity) are displayed in Figure 3B. CSF and plasma p-tau$_{181}$ had nearly identical diagnostic performance for biological AD ($p = 0.99$). No differences were observed between CSF and plasma p-tau$_{217}$ in the diagnostic performance of biological AD ($p = 0.60$). CSF p-tau$_{231}$ had significantly higher performance than plasma p-tau$_{231}$ for the identification of biological AD ($p = 0.002$). A summary of all AUC values, 95% confidence intervals and outcomes of statistical comparisons are displayed in Table 3. Next, we compared plasma p-tau$_{217}$ to p-tau$_{181}$ and p-tau$_{231}$ in both CSF and plasma using De Long's test. In the identification of amyloid-PET positivity, plasma p-tau$_{217}$ outperformed both plasma p-tau$_{181}$ ($p < 0.0001$) and plasma p-tau$_{231}$ ($p = 0.02$) and did not perform significantly differently from CSF p-tau$_{181}$ ($p = 0.32$) or CSF p-tau$_{231}$ ($p = 0.11$). In the identification of biological AD, plasma p-tau$_{217}$ also outperformed both plasma p-tau$_{181}$ ($p = 0.007$) and plasma p-tau$_{231}$ ($p = 0.005$) and did not perform significantly differently from CSF p-tau$_{181}$ ($p = 0.12$) or CSF p-tau$_{231}$

TABLE 3 Area under the curve comparisons for plasma and CSF biomarkers for the identification of amyloid-PET positivity and biological Alzheimer's disease.

	Amyloid-PET positivity				Biological AD			
	Plasma	CSF	95% CI of difference	*p*-Value	Plasma	CSF	95% CI of difference	*p*-Value
p-tau$_{181}$	76% (68%–83%)	87% (81%–95%)	0.03–0.23	0.01	84% (76%–92%)	84% (72%–97%)	−0.15–0.15	0.99
p-tau$_{217}$	91% (86%–96%)	94% (91%–98%)	−0.02–0.08	0.23	97% (92%–100%)	96% (93%–99%)	−0.03–0.05	0.60
p-tau$_{231}$	82% (75%–89%)	95% (92%–99%)	0.06–(−0.21)	0.00005	94% (90%–97%)	80% (70%–90%)	0.05–0.25	0.002

Note: AUCs were compared using DeLong's test.
Abbreviation: AD, Alzheimer's disease; CI, confidence interval; CSF, cerebrospinal fluid; PET, positron emission tomography.

($p = 0.68$). A summary of outcomes of statistical comparisons of plasma p-tau$_{217}$ with p-tau$_{181}$ and p-tau$_{231}$ in CSF and plasma is displayed in Table S2. Sensitivity, specificity and predictive values are reported in Table S3.

4 | DISCUSSION

This study evaluated the diagnostic performance of plasma p-tau biomarkers in comparison to CSF p-tau biomarkers for AD. We report that while plasma p-tau$_{181}$ and plasma p-tau$_{231}$ performance was inferior to their CSF counterparts, plasma p-tau$_{217}$ had statistically indistinguishable diagnostic performance from CSF p-tau$_{217}$ for the identification of amyloid-PET positivity and biological AD. While all plasma p-tau biomarkers reported lower p-tau concentrations than in CSF, rates of agreement between plasma and CSF p-tau biomarkers were high, especially for p-tau$_{217}$. Taken together, our study suggests that plasma p-tau$_{217}$ can help reduce the need for lumbar punctures in the differential diagnosis of AD and when determining eligibility for disease-modifying therapeutics.

AD is the leading cause of dementia globally,[37] and accessible and affordable tests to diagnose AD are urgently needed.[38] Plasma biomarkers show tremendous promise in this regard due to their comparatively lower cost and minimally-invasive nature. However, their performance in relation to more established biomarkers needs to be evaluated in greater detail before they can be implemented. In our study, we compared the effect sizes of plasma and CSF p-tau biomarkers for differentiating between amyloid-PET positive and negative participants. Plasma p-tau$_{181}$ and plasma p-tau$_{231}$ had significantly smaller effect sizes between amyloid-positive and amyloid-negative groups compared to CSF assays for p-tau$_{181}$ and p-tau$_{231}$. Similarly, plasma p-tau$_{181}$ and plasma p-tau$_{231}$ had smaller fold-changes between amyloid-PET groups than did CSF biomarkers. However, plasma p-tau$_{217}$ and CSF p-tau$_{217}$ had similar effect sizes in differentiating between amyloid-PET groups. We also observed that plasma p-tau biomarkers had lower dynamic range compared CSF p-tau, an effect more pronounced at higher concentrations of CSF p-tau. While this suggests plasma p-tau biomarkers may perform less optimally as biomarkers of disease progression, their diagnostic accuracy will be helpful for identifying individuals eligible for PET scanning to stage disease severity,[39] evaluate AD clinic-pathological relationships,[40] and to determine eligibility for disease-modifying therapies.[5–7,41] In this connection, dichotomized plasma p-tau$_{217}$ had excellent (88.5%) agreement with CSF p-tau$_{217}$ status. The agreement between plasma and CSF assessments of p-tau$_{217}$ was notably higher than the agreement between CSF and plasma p-tau$_{181}$ (74.7%) and p-tau$_{231}$ (76.2%). The lack of plasma/CSF p-tau$_{217}$ discordance in individuals with CDR 1 or greater or with tau-PET positivity suggests that these biomarkers are reliable for detecting AD pathology in advanced disease. In contrast, the higher rates of discordance in asymptomatic and tau-PET negative individuals highlights the limitations in detecting very early disease (subtle amyloid-β abnormality) as well as the potential for false positives. In our study, p-tau$_{217}$ plasma−/CSF+ discordant cases were more likely to be amyloid-β positive than plasma+/CSF− cases, further supporting the numerically higher (but not statistically different) AUC for identifying amyloid-PET positivity of CSF p-tau$_{217}$. While all biomarker dichotomization techniques are subject to analytical idiosyncrasies, plasma biomarker results have non-negligible false positive and false negative rates and should be interpreted with caution.[31,42] However, it is also important to consider that false positive or false negative results are also possible with CSF assays, which places some limitations in their use as reference standards for the plasma/CSF comparisons this study. In fact, although p-tau$_{181}$ and p-tau$_{231}$ performed better in CSF than in plasma, their imperfect agreement of CSF with PET reference standards highlights their limitations as reference standards. Despite this, the excellent individual-level agreement between dichotomized CSF and plasma p-tau$_{217}$, as well as the low proportion of participants outside Bland-Altman limits of agreement suggest plasma p-tau$_{217}$ may help circumvent the need for invasive lumbar punctures. Taken together, these studies suggest that plasma p-tau$_{217}$ has high correspondence with CSF biomarkers, and is a strong candidate for future prospective clinical implementation studies.

While several recent studies have performed head-to-head assessments of the diagnostic performance of different plasma biomarkers,[43–45] few studies compared the performance of multiple plasma and CSF biomarkers collected in the same individuals. Comparisons in the diagnostic performance of p-tau biomarkers indicated that plasma p-tau$_{181}$ and p-tau$_{231}$ performed inferior to CSF p-tau$_{181}$ and p-tau$_{231}$ in the identification of amyloid-PET positivity and biological AD (A+T+). In contrast, plasma p-tau$_{217}$ showed equivalent performance to CSF p-tau$_{217}$ (and to CSF p-tau$_{181}$ and CSF p-tau$_{231}$). Plasma

p-tau$_{217}$ also outperformed plasma p-tau$_{181}$ and plasma p-tau$_{231}$ in the identification of amyloid-PET positivity and biological AD. Our results are in agreement with several recent studies reporting high diagnostic accuracy of plasma p-tau$_{217}$ for AD,[15,16,18,44,46] suggesting it may have an important role in the differential diagnosis of the etiology of cognitive impairment.

Currently, plasma biomarkers are conceptualized as screening biomarkers and not as diagnostic biomarkers.[37] Two-step testing, in which a positive screening test is followed up with a more specific (and often more costly or invasive) test is a common practice in medicine.[42] This strategy increases the specificity of the screening test while limiting the use of the more costly and invasive test.[42] Pending replication in other research cohorts and population-based studies, our results suggest that plasma p-tau$_{217}$ may have strong enough performance to be used in combination with clinical evaluation for the diagnosis of AD. However, due to the variability and matrix interference inherent to plasma biomarker measurements, several important questions remain concerning the interpretation of plasma biomarkers at the individual-level. Prospective studies with pre-established cutoffs are needed to evaluate the robustness of plasma biomarkers,[47] especially for those with small fold-changes between patients and controls, or amyloid-PET positive and negative cases.[19] Multicenter studies assessing changes in diagnostic management and diagnostic confidence in relation to plasma AD biomarkers will be useful for determining their future clinical role.

The Alzheimer's Association appropriate use recommendations for blood biomarkers highlighted the need for studies of non-inferiority compared with more established AD biomarkers.[22] Because plasma p-tau$_{217}$ met criteria for equivalence, we did not investigate non-inferiority of plasma p-tau$_{217}$, as an equivalent test is by definition non-inferior.[48,49] Non-inferiority studies are one-sided in nature, seeking to determine whether a new intervention is not worse (within a pre-specified margin) than a more established intervention and are undertaken when a new intervention is more accessible, less costly, or less toxic, in which some degree of lower efficacy or accuracy is acceptable.[50] In our study, the diagnostic performance of plasma p-tau$_{217}$ was indistinguishable from CSF p-tau$_{181}$, CSF p-tau$_{217}$, and CSF p-tau$_{231}$. Pending replication in more diverse settings, these results suggest that plasma p-tau$_{217}$'s advantages in terms of accessibility, scalability, and cost-effectiveness are not offset by lower diagnostic accuracy. While our study was not designed or powered to detect superiority, the numerically higher effect sizes, fold-changes and AUCs of plasma p-tau$_{217}$ over CSF p-tau$_{181}$ and CSF p-tau$_{231}$ suggest future studies should investigate the superiority of plasma p-tau$_{217}$ over other CSF AD biomarkers. Overall, our results contribute to recent blood-based AD biomarker studies by providing evidence of equivalent diagnostic performance of plasma p-tau$_{217}$ with high-performance CSF biomarkers for the identification of amyloid-PET positivity and for biological AD.

Our results should be considered in the context of several limitations. First, as a single-center study, the consistency and stability of handling of blood and CSF samples was more tightly controlled than can be achieved in multicenter studies. A better understanding of how variability and bias of blood measurements affect plasma p-tau quantification will be essential before widespread clinical use is possible.[19] A second limitation is that the TRIAD cohort is a highly selected research sample, and blood biomarker performance needs to be compared to CSF in more heterogeneous samples with medical comorbidities such as chronic kidney disease which can affect plasma p-tau concentrations.[46,51] Similarly, the demographic make-up of the TRIAD cohort is not representative of the populations at risk for dementia in North America or globally, and studies in more representative populations are needed to support the generalizability of this study.[52] In this connection, greater characterization of plasma biomarker performance is needed in oldest-old populations, who have higher rates of biological AD as well as comorbid medical conditions. Future studies should also investigate the performance of plasma biomarkers in relation to clinical disease severity. Furthermore, as the armamentarium of plasma biomarkers continues to expand, it is important to emphasize that the present study evaluated p-tau$_{181}$ and p-tau$_{231}$ assays from the University of Gothenburg and p-tau$_{217}$ from Janssen which have highly similar but not identical performance to other assays targeting the same analytes.[44] Finally, while the reference standards in this study were established PET imaging thresholds, replication with neuropathological assessments is desirable.

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CONFLICT OF INTEREST STATEMENT

Pedro Rosa-Neto has served at scientific advisory boards and/or as a consultant for Roche, Novo Nordisk, Eisai, and Cerveau radiopharmaceuticals. Henrik Zetterberg has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). Kaj Blennow has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. All other authors report no disclosures. Author disclosures are available in the supporting information.

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