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RESEARCH ARTICLE

# Influence of cognitive impairment and race on plasma p-Tau$_{217}$ in two diverse cohorts

**Ashima Nayyar**[1,2] | **Mei-ling Li**[1,2] | **Victor Sotelo**[1,2] | **Guibin Su**[1,2] | **Isabelle Hwang**[1,2] | **Milota Kaluzova**[1] | **Mini Jomartin**[1] | **Michelle Migut**[1,2] | **Hilary Grosso Jasutkar**[1] | **Karlyndsay Sitterley**[1] | **Karthik J. Kota**[1,2] | **William T. Hu**[1,2]

[1]Department of Neurology, Rutgers-Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

[2]Center for Healthy Aging Research, Institute for Health, Health Care Policy, and Aging Research, Rutgers Biomedical and Health Sciences, New Brunswick, New Jersey, USA

**Correspondence**
William T. Hu, MD, PhD, FAAN, Department of Neurology, Rutgers-Robert Wood Johnson Medical School, 125 Paterson Street, Suite 6200, New Brunswick, NJ 08901, USA.
Email: william.hu@rutgers.edu

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## Abstract

**INTRODUCTION:** Factors influencing plasma Alzheimer's disease (AD) biomarkers remain incompletely understood. Here we evaluated Fujirebio plasma p-Tau$_{217}$ in two diverse cohorts among whom 91% underwent cerebrospinal fluid (CSF) analysis.

**METHODS:** Non-Hispanic White (NHW, $n$ = 113), Black/African American (B/AA, $n$ = 66), and Chinese American (ChA, $n$ = 38) participants recruited from two universities were included. We examined if plasma p-Tau$_{217}$ correlated with CSF and clinical factors, differed between racial groups, and associated with novel CSF proteins.

**RESULTS:** CSF p-Tau$_{181}$ strongly correlated with CSF p-Tau$_{217}$ ($R^2 = 0.912$) which moderately correlated with plasma p-Tau$_{217}$ ($R^2 = 0.694$). Plasma p-Tau$_{217}$ levels were higher with greater cognitive impairment but lower in B/AA than NHW participants even after adjusting for CSF p-Tau$_{181}$. This resulted in greater positive predictive value for NHW than B/AA participants, and could be mediated by complement or lysosomal pathways.

**DISCUSSION:** Severity of cognitive impairment and race both influence plasma p-Tau$_{217}$ levels beyond race-associated differences in CSF p-Tau$_{181}$.

KEYWORDS
biomarkers, cerebrospinal fluid, complement, CSF, dementia, ethnicity, mild cognitive impairment, tau

## Highlights

- Cognitive impairment associates with plasma p-Tau$_{217}$ independent of CSF biomarkers.
- Black/African Americans had lower plasma p-Tau$_{217}$ than non-Hispanic White Americans.

- CSF p-Tau$_{181}$ could not explain lower plasma p-Tau$_{217}$ in Black/African Americans.
- Plasma p-Tau$_{217}$ difference results in more false positive cases according to race.
- Novel CSF processes were associated with race-related plasma p-Tau$_{217}$ difference.

## 1 | BACKGROUND

Objective biomarkers for Alzheimer's disease (AD) can greatly enhance its early detection and treatment. Currently established biomarkers include cerebrospinal fluid (CSF) levels of core AD proteins (A$\beta$42, A$\beta$40, t-Tau, and p-Tau$_{181}$) and substrate-specific positron emission tomography (PET) targeting amyloid and tau aggregates.[1] Blood-based biomarkers for AD have long been championed as accessible and convenient[2], but their broader adaptation in the past has been limited by suboptimal performance or reproducibility.[3–6] More recently, mass spectrometry-based approaches[7] or highly sensitivity immunoassays[8] have improved the detection of AD-related protein levels in blood. The latest generation of blood-based AD biomarkers have been found to strongly associate with *post mortem* AD neuropathologic changes[9], discriminate between tau PET profiles[9] yet better correlate with amyloid PET[10–12], and predict subsequent cognitive decline in the asymptomatic AD stage.[13] At the same time, their real-world applicability has often fallen short of these promising group-level epidemiological findings, with potential confounds from renal clearance, cardiovascular co-morbidities[14,15], and potential blood–brain barrier (BBB) disruption in the setting of non-AD neurodegeneration[16] and progressive dementia.[17] While plasma p-Tau$_{217}$ may better predict brain AD neuropathologic changes than plasma p-Tau$_{181}$, insufficient number of participants having CSF p-Tau$_{217}$ measures using widely available assays in prior studies makes comparison of two phosphorylated forms of tau difficult to interpret.

We were the first to report lower CSF levels of AD-related tau biomarkers (t-Tau, p-Tau$_{181}$) in older Black/African American (B/AA) than non-Hispanic White (NHW) adults[18], and this has now been replicated in older[19], middle-aged[20], and younger[21] adults. This phenomenon was not observed until a sufficient number of diverse participants were recruited into modern AD biomarker research, and poses a direct challenge to the equitable application of AD fluid biomarkers for older B/AA adults and potentially Hispanic, Asian, and other populations yet to regularly participate in AD biomarker research. This is because a threshold for CSF t-Tau or p-Tau$_{181}$ determined in a largely NHW population would under-estimate the number of B/AA adults with AD neuropathologic changes. The reason for these differences remains unknown, although differences are variably associated with alternate inflammatory pathways following amyloid deposition to social determinants of health. Because p-Tau$_{217}$ represents another threonine site phosphorylated on tau, we hypothesize that p-Tau$_{217}$ levels would also differ between B/AA and NHW adults. Based on promising findings related to plasma p-Tau$_{217}$ across analytical platforms, cohorts, and even racial/ethnic groups[11,22], we evaluated its performance and examined its relationship with established CSF AD biomarkers and demographic/clinical variables in two well-characterized diverse cohorts.

## 2 | METHODS

### 2.1 | Ethical conduct of study

This study was approved by the Rutgers University and Emory University Institutional Review Boards. Written informed consents were previously obtained from all participants in accordance with the Declaration of Helsinki and the Belmont report for the long-term storage and future analysis of samples.

### 2.2 | Diversity, equity, and inclusion

Two cohorts were included in the study (Table 1). The Rutgers University cohort consists of older Chinese American (ChA), B/AA, and NHW adults recruited through the Center for Healthy Aging Research, Cognitive Neurology and AD Clinic, and the greater New Jersey area between 2021 and 2024 through direct outreach and community partnerships. In particular, B/AA recruitment was facilitated via a community-based outreach coordinator and consultation with the local National Association for the Advancement of Colored People; ChA recruitment was conducted via culturally and linguistically appropriate materials and presentations by native Mandarin speakers. The previously described Emory University cohort[18] included older B/AA and NHW adults recruited through the AD Research Center, Cognitive Neurology Clinic, and the greater Atlanta area between 2013 and 2015 through direct outreach, community partnerships, and leadership by non-NHW researchers. All authors are women, People of Color, or both.

### 2.3 | Participant characterization

All Rutgers and Emory participants underwent detailed clinical, neuropsychological, and magnetic resonance imaging (MRI) analysis, with Mini-Mental State Examination (MMSE) scores available only in the Emory cohort. Race/ethnicity was by self-report. All B/AA and NHW participants underwent cerebrospinal fluid (CSF) and non-fasting plasma sample collection between 8AM and noon on the same day, with CSF donation an optional component for the ChA participants due to our more recent engagement with this group. Diagnosis of normal cognition (NC), mild cognitive impairment (MCI), AD dementia, or

**RESEARCH IN CONTEXT**

1. **Systematic review**: We reviewed the literature using traditional sources (e.g., PubMed, Google Scholar; keywords: biomarkers, tau, blood/plasma, Alzheimer's disease [AD], and related terms). Elevated plasma p-Tau$_{217}$ is strongly associated with cerebral amyloid and tau positron emission tomography (PET) positivity, *post mortem* Alzheimer's disease (AD), reduced renal clearance, and cardiovascular diseases. Only two studies included sufficient number of Black/African American (B/AA) participants, but neither had sufficient number with cerebrospinal fluid (CSF) p-Tau$_{181}$ which is known to be lower in B/AA than non-Hispanic White (NHW) participants.
2. **Interpretation**: We showed very strong correlation between p-Tau$_{181}$ and p-Tau$_{217}$ in the CSF, and each moderately correlated with plasma p-Tau$_{217}$. In two independent cohorts, we also found plasma p-Tau$_{217}$ to associate with clinical diagnosis and B/AA race independent of CSF p-Tau$_{181}$, potentially compounding racial disparities linked to tau biomarkers.
3. **Future directions**: Further work is needed to equitably apply plasma p-Tau$_{217}$ and identify factors underlying reported racial disparities.

non-AD dementia was derived through a consensus process. Non-AD dementia participants included two patients with dementia with Lewy bodies (CSF positive for a-synuclein RT-QuIC) and four patients with behavioral variant frontotemporal dementia (bvFTD; two with *GRN* mutations and two with CSF not consistent with AD). *Apolipoprotein E* (*APOE*) genotyping was performed at Center for Applied Genomics (Children's Hospital of Philadelphia) for Rutgers participants and at Emory for Emory participants.

## 2.4 | CSF and plasma collection and processing

CSF was collected into 15 mL polypropylene tubes via 24-gauge atraumatic needle and syringe aspiration between 8AM and noon. Emory CSF samples were immediately inverted several times, aliquoted (500 µL), and frozen at −80°C. Rutgers CSF samples were centrifuged 600 × *g* at room temperature for cellular studies[23], and supernatants were then inverted, aliquoted (500 µL), and frozen at −80°C until analysis. For each participant, 20 mL of non-fasting whole blood was drawn into $K_2$-EDTA tubes and immediately centrifuged at 2400 rpm for 15 min at 4°C to derive plasma which was aliquoted (500 µL) and frozen at −80°C until analysis.

## 2.5 | CSF and plasma biomarker analysis

CSF levels of Aβ42, t-Tau, and p-Tau$_{181}$ were previously measured in Emory participants using the AlzBio3 assay (Fujirebio Diagnostics Inc, Malvern, PA) on the bead-based Luminex platform (Austin, TX), with a threshold of t-Tau/Aβ42 ≥ 0.39 for AD neuropathologic changes.[24] Additional biomarkers previously measured in this cohort included CSF levels of Aβ40 (INNOTEST, Fujirebio Diagnostics, Malvern, PA), neurofilament light chain (NfL; NF-light, Uman Diagnostics, Umeå, Sweden)[18], neurogranin (Ng), complement-related proteins (C3, C3b, C1q, and C4), and 15 inflammatory proteins including soluble trigger receptor expressed on myeloid cells 2 (sTREM2) and soluble tumor necrosis factor receptors 1 and 2 (sTNFR1, sTNFR2; MilliporeSigma, Burlington, MA)[20].

CSF levels of Aβ40, Aβ42, t-Tau, and p-Tau$_{181}$ were measured in Rutgers participants using the automated Lumipulse G1200 platform (Fujirebio Diagnostics Inc, Malvern, PA)[25] with a threshold of t-Tau/Aβ42 ≥0.58 for AD neuropathologic changes converted from AlzBio3-based threshold. For Lumipulse, our laboratory achieves median intermediate precision of 4.2% for Aβ40, 6.4% for Aβ42, 6.2% for t-Tau, and 4.5% for p-Tau$_{181}$ across calibrator and cartridge lots. In a subset of this cohort ($n$ = 44), CSF levels of NfL, Ng, sTNFR1, sTNFR2, complement-related proteins, and other inflammatory proteins were measured using aptamer-based assays (SomaLogic, Boulder, CO) as part of a larger multi-center biomarker study (1084 analytes in 350 participants; Hu, unpublished)[23].

All plasma p-Tau$_{217}$ levels were measured using Lumipulse G1200 (Fujirebio Diagnostics Inc, Malvern, PA) following manufacturer's protocol. Plasma samples were thawed on ice, vortexed for 10-15 seconds, and then centrifuged at 2000 × *g* for 5 min at room temperature. For CSF p-Tau$_{217}$, a preliminary experiment using five CSF samples and various dilutions (1:10, 1:20, 1:50, and 1:100) determined the optimal dilution of 1:50 for using the plasma-based assay. For participants in the CSF-plasma p-Tau$_{217}$ correlation, CSF samples were thawed, diluted in distilled water before loading onto Lumipulse for analysis.

To assess the impact of BBB permeability on the relationship between CSF and plasma p-Tau$_{217}$, CSF and plasma albumin were measured in 36 Rutgers participants using a bromocresol green-based BCG albumin assay kit (Cat# MAK-124, Millipore Sigma, Burlington, MA, USA) following the manufacturer's protocol (absorbance at 620 nm). The Albumin Quotient (Q-Alb) was calculated as the ratio of CSF albumin (mg/dL) to plasma albumin (g/dL).

## 2.6 | Intermediate precision analysis for plasma p-Tau$_{217}$

To determine intermediate precision for plasma p-Tau$_{217}$ between adjacent aliquots, we identified 13 Rutgers participants with six frozen aliquots of plasma representing a range of CSF p-Tau$_{181}$ concentrations. Plasma p-Tau$_{217}$ levels for these samples were measured in

**TABLE 1** Participants included in the current study.

| Parameter | Rutgers ($n = 98$) | | | | Emory ($n = 123$) | |
|---|---|---|---|---|---|---|
| Race | ChA ($n = 38$) | B/AA ($n = 11$) | NHW ($n = 44$) | Other ($n = 5$) | B/AA ($n = 55$) | NHW ($n = 68$) |
| Women (%) | 19 (50%) | 10 (91%) | 24 (54%) | 4 (80%) | 29 (53%) | 39 (57%) |
| Age, median (IQR) | 67 (64, 73) | 70 (64, 74) | 68 (62, 73) | 72 (62, 82) | 68 (64, 73) | 69.5 (65, 76) |
| Education, median (IQR) | 18 (16, 18) | 16 (14, 18) | 16 (13, 18) | 17 (10, 18) | 16 (14, 18) | 16 (14, 18) |
| Having ≥1 *APOE* e4 allele | 10 (27%) | 3 (27%) | 17 (39%) | 1 (20%) | 29 (53%) | 35 (51%) |
| Diagnosis | | | | | | |
| NC | 27 | 2 | 13 | 0 | 23 | 28 |
| MCI | 9 | 4 | 16 | 2 | 23 | 25 |
| AD dementia | 2 | 4 | 8 | 3 | 9 | 15 |
| Other dementia | 0 | 1 | 7 | 0 | 0 | 0 |
| CSF analysis[a] | 18 (47%) | 11 (100%) | 45 (100%) | 100% | 55 (100%) | 68 (100%) |
| Aβ42, mean (SD) | 656 (385) | 543 (191) | 622 (292) | 537 (433) | 214 (117) | 207 (148) |
| t-Tau, mean (SD) | 327 (236) | 453 (356) | 453 (251) | 419 (181) | 47.7 (31.7) | 71.5 (47.8) |
| p-Tau$_{181}$, mean (SD) | 50.4 (41.2) | 73.4 (62.0) | 63.9 (40.1) | 66.2 (36.9) | 17.8 (9.4) | 25.6 (12.6) |
| Plasma p-Tau$_{217}$, mean (SD) | 0.16 (0.22) | 0.34 (0.46) | 0.37 (0.29) | 0.27 (0.20) | 0.22 (0.28) | 0.27 (0.28) |

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; B/AA, Black/African American; ChA, Chinese American; CSF, cerebrospinal fluid; IQR, interquartile range; MCI, mild cognitive impairment; NC, normal cognition; NHW, non-Hispanic White.

[a]CSF analysis performed using Lumipulse for Rutgers participants, and AlzBio3 assays on Luminex for Emory participants. All biomarker concentrations are reported in pg/mL. Other race/ethnicity in Rutgers cohort: Hispanic ($n = 2$), Asian Indian ($n = 1$), Japanese ($n = 1$), and Filipino ($n = 1$) American participants.

the morning and in the afternoon on three separate days by two experienced Lumipulse operators.

## 2.7 | Statistical analysis

All statistical analysis was performed in IBM SPSS 29.0 (Aramonk, NY). To determine intermediate precision within the same day, coefficients of variation (CV, in %) were calculated for each day's AM and PM run of 13 samples across 3 days, and the average concentrations and pair-wise %CV values were plotted to generate the intra-day precision profile. To determine intermediate precision across days, average concentrations and overall %CV were calculated separately for AM and PM runs.

For relationships between plasma p-Tau$_{217}$ and CSF p-Tau measured at different threonine epitope (181 vs. 217) and by different assay platforms (Lumipulse vs. Luminex), we compared the correlation between plasma p-Tau$_{217}$ and (1) CSF p-Tau$_{217}$ measured by Lumipulse in 72 Rutgers participants (same analyte, same platform); (2) CSF p-Tau$_{181}$ in 79 Rutgers participants measured by Lumipulse (different analyte, same platform); and (3) CSF p-Tau$_{181}$ in 123 Emory participants measured by Luminex (different analyte, different platform).

To determine factors associated with plasma p-Tau$_{217}$, continuous variables were examined if normally distributed (age, CSF, Aβ42) or after transformation if not normally distributed ($\log_{10}$-transformation for t-Tau, p-Tau$_{181}$, p-Tau$_{217}$; square root transformation for MMSE in the Emory cohort). For linear regression models of transformed CSF or plasma p-Tau$_{217}$, categorical variables (gender, race/ethnicity, having ≥1 *APOE* ε4 allele, diagnosis, chronic renal failure [CRF], congestive heart failure [CHF]) were entered as fixed factors, and continuous variables (age, CSF Aβ42, p-Tau$_{181}$) were entered as co-variates, with stepwise removal of variables. Variance inflation factors (VIFs) were also determined in models for p-Tau$_{217}$ to account for collinearity between clinical diagnosis and biomarkers in the Rutgers cohort; between clinical diagnosis, MMSE, and biomarkers in the Emory cohort. MMSE was introduced in the Emory cohort to determine if a screening test – without clinicians and additional testing – could account for the effect of diagnosis. Diagnostic performance of plasma p-Tau$_{217}$ was evaluated through receiver operating characteristics (ROC) curve analysis in the Rutgers sample first, with abnormal CSF t-Tau/Aβ42 or Aβ42/Aβ40 as the outcome. A threshold optimizing sensitivity and specificity was chosen via Youden's index, and the same numerical threshold was validated separately in NHW and B/AA Emory participants.

To explore additional CSF factors associated with plasma p-Tau$_{217}$, levels of 1084 analytes in the larger Rutgers biomarker study were first examined for normality and $\log_{10}$-transformed if not normally distributed. Raw or $\log_{10}$-transformed values were then analyzed according to principal component analysis (PCA; correlation matrix, Varimax rotation) which derived 102 principal components (PCs). Because of the smaller sample size ($n = 44$), adjustment for multiple comparison was made by identifying only PCs whose correlations with plasma p-Tau$_{217}$ had smaller *p*-value than CSF p-Tau$_{217}$.

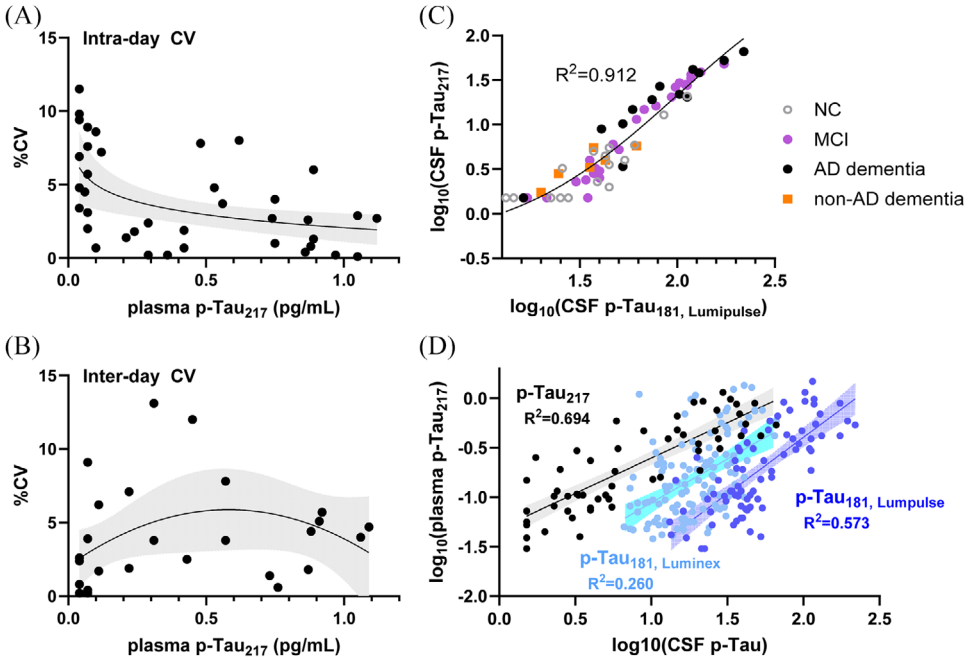


**FIGURE 1** Performance and correlates of the automated plasma p-Tau$_{217}$ assay. Intermediate precision for the assay was determined over six runs (two runs per day for 3 non-consecutive days) for adjacent aliquots from 13 participants. Intra-day (A) and inter-day (B) coefficients of variation (%) are shown in precision profiles. The relationship between CSF p-Tau$_{217}$ and p-Tau$_{181}$ – both measured on the automated assays – was marginally better represented by a sigmoidal than a linear function (C), while plasma p-Tau$_{217}$ levels better correlated with automated CSF p-Tau assay results than CSF p-Tau$_{181}$ measured on the Luminex platform (D). In panel D, each data point represents an individual having plasma p-Tau$_{217}$ measured by Lumipulse, with Rutgers participants having CSF p-Tau$_{217}$ and/or CSF p-Tau$_{181}$ measured by Lumipulse, and Emory participants having CSF p-Tau$_{181}$ measured by Luminex. CSF, cerebrospinal fluid.

## 3 | RESULTS

### 3.1 | Plasma p-Tau$_{217}$ has high intermediate precision within and across days

Plasma p-Tau$_{217}$ levels were measured in 13 samples in two separate runs within the same day across 3 days using adjacent aliquots (78 measurements total). For assays within the same day, precision profile showed maximum CV < 10% at plasma p-Tau$_{217}$ > 0.04 pg/mL, and mean CV < 5% at plasma p-Tau$_{217}$ > 0.24 pg/mL (Figure 1A). For assays done 24 h apart over 3 non-consecutive days, precision profile showed maximum CV < 10% at p-Tau$_{217}$ > 0.45 pg/mL, with upper limit of the 95% confidence interval of the mean CV curve falling below 8% at the same threshold (Figure 1B).

### 3.2 | Relationship between CSF p-Tau$_{181}$, CSF p-Tau$_{217}$, and plasma p-Tau$_{217}$

Analysis of CSF p-Tau$_{181}$ and p-Tau$_{217}$ in 72 Rutgers participants (same biofluid, different antibodies; representing a range of CSF p-Tau$_{181}$ concentrations) showed a very strong linear correlation (adj $R^2 = 0.888, p = 5 \times 10^{-29}$), although a sigmoidal curve was a slightly better fit (adj $R^2 = 0.912$, Figure 1C). Plasma p-Tau$_{217}$ was not correlated with a measure of BBB permeability (Q-Alb, $p = 0.426$). Multivariate analysis showed that controlling for CSF A$\beta$42 levels modestly improved the overall model (adj $R^2 = 0.944$ with $R^2$ change of 0.056, $p = 4 \times 10^{-10}$; VIF < 1.05 for each). Plasma p-Tau$_{217}$ moderately correlated with CSF p-Tau$_{217}$ (different biofluids, same antibodies; Figure 1D, adj $R^2 = 0.690$, $p = 2.5 \times 10^{-16}$) and p-Tau$_{181}$ (different biofluids and antibodies; adj $R^2 = 0.568$, $p = 1.5 \times 10^{-15}$) measured by Lumipulse, suggesting additional factors to influence plasma p-Tau$_{217}$ levels beyond CSF p-Tau levels when measured on the same platform. By comparison, plasma p-Tau$_{217}$ only weakly correlated with CSF p-Tau$_{181}$ measured by Luminex in the Emory cohort (different biofluids, antibodies, and assay platforms; Figure 1D, adj $R^2 = 0.255$, $p = 1.6 \times 10^{-9}$).

### 3.3 | Effects of cognitive impairment and race/ethnicity on plasma p-Tau$_{217}$

Because prior studies have suggested p-Tau$_{217}$ to associate with presence of AD pathologic changes but also clinical dementia, we next examined if clinical diagnosis (NC, MCI, and dementia) was associated with plasma p-Tau$_{217}$ levels. This showed greater plasma p-Tau$_{217}$ levels in participants with AD dementia than those with NC, even after adjusting for CSF p-Tau$_{181}$ levels (Figure 2A). A regression model

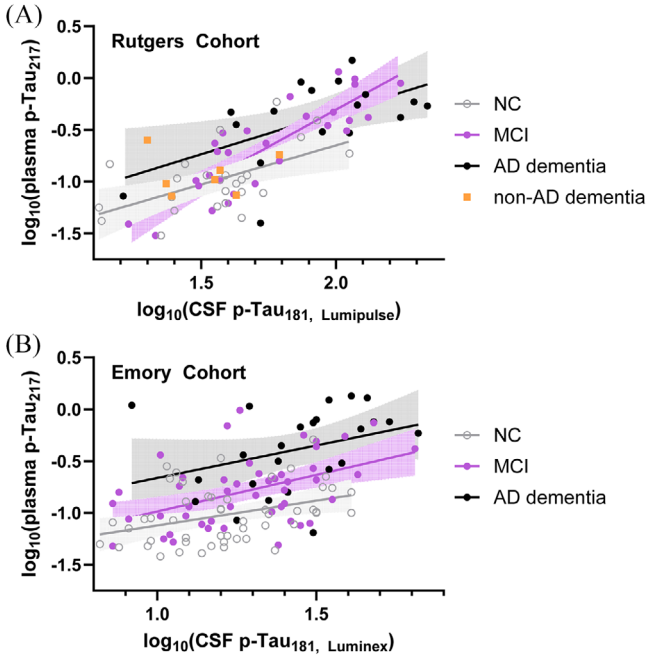


**FIGURE 2** Effect of clinical diagnosis (NC, MCI, AD dementia, non-AD dementia) on plasma p-Tau$_{217}$. Differences according to diagnosis persisted after controlling for CSF p-Tau$_{181}$ levels in the Rutgers (A) and Emory (B) cohorts. AD, Alzheimer's disease; CSF, cerebrospinal fluid; NC, normal cognition; MCI, mild cognitive impairment.

**TABLE 2** Factors influencing plasma p-Tau$_{217}$ levels in the Rutgers cohort ($n = 73$ with complete data; CSF A$\beta$42 Z-transformed according to NC participants' levels).

| Parameter | B (95% confidence interval) | *p*-value |
|---|---|---|
| Constant | **−2.592 (−3.019, −2.165)** | <0.001 |
| $\log_{10}$(CSF p-Tau$_{181,\ Lumipulse}$) | **0.966 (0.731, 1.201)** | <0.001 |
| Z CSF A$\beta$42 | **−0.167 (−0.236, −0.099)** | <0.001 |
| Race/Ethnicity | | |
| NHW | Reference | |
| ChA | 0.018 (−0.119, 0.154) | 0.798 |
| Other Asian American | −0.095 (−0.366, 0.176) | 0.486 |
| Hispanic | **−0.581 (−1.071, −0.091)** | 0.021 |
| B/AA | **−0.216 (−0.385, −0.047)** | 0.013 |
| Diagnosis | | |
| NC | Reference | |
| MCI | 0.077 (−0.062, 0.215) | 0.272 |
| AD dementia | **0.247 (0.056, 0.437)** | 0.012 |
| Non-AD dementia | 0.020 (−0.188, 0.228) | 0.848 |
| Having ≥1 *APOE* ε4 allele | −0.119 (−0.238, 0) | 0.050 |

*Note*: Coefficients and confidence intervals are bolded if $p < 0.05$.
Abbreviations: AD, Alzheimer's disease; B/AA, Black/African American; ChA, Chinese American; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; NC, normal cognition; NHW, Non-Hispanic White.

incorporating demographic (age, sex, and race/ethnicity), clinical (diagnosis, *APOE* ε4 carrier status, CRF, and CHF), and biomarker (CSF p-Tau$_{181}$ and A$\beta$42, both measured by Lumipulse) variables showed greater plasma p-Tau$_{217}$ levels to associate with greater CSF p-Tau$_{181}$ levels and lower CSF A$\beta$42 levels (each linked to AD neuropathologic changes) as well as clinical AD dementia diagnosis ($p = 0.012$, Table 2). While neither CRF ($n = 6$, $p = 0.422$) nor CHF ($n = 1$, $p = 0.857$) influenced plasma p-Tau$_{217}$ levels ($p = 0.422$), B/AA race ($n = 11$; observed power of 0.874) – but not ChA ethnicity ($n = 18$) – was associated with lower plasma p-Tau$_{217}$ levels ($p = 0.013$). This difference in B/AA participants was surprising as we expected the race-associated difference to be already accounted by CSF p-Tau$_{181}$ levels in the model. Because of the small number of B/AA participants in the Rutgers cohort, we sought to replicate these findings in a cohort with similar numbers of B/AA and NHW participants.

## 3.4 | Replicating effects of cognitive impairment and race on plasma p-Tau$_{217}$

In the Emory cohort, we first validated that a clinical diagnosis of AD dementia ($p < 0.001$) but also now a diagnosis of MCI ($p = 0.002$) to associate with greater plasma p-Tau$_{217}$ levels after controlling for CSF p-Tau$_{181}$ levels (Figure 2B). When clinical diagnosis, history of CRF, history of CHF, MMSE, *APOE* genotype, race, and CSF AD biomarkers were entered into a regression model, B/AA participants continued to show lower plasma p-Tau$_{217}$ levels than NHW participants (observed power of 0.509) beyond the race-associated difference in CSF p-Tau$_{181}$ levels. The inclusion of MMSE diminished the impact of clinical diagnosis, suggesting that incorporating a simple screening test may diminish the role of formal diagnosis in interpreting plasma p-Tau$_{217}$.

Since CSF A$\beta$42 will not be available in most instances when plasma p-Tau$_{217}$ is used to predict CSF p-Tau, our models suggest plasma p-Tau$_{217}$ to better predict the p-Tau$_{181}$/A$\beta$42 ratio than p-Tau$_{181}$ levels alone. Substituting the ratio's individual components in the model by the ratio did not diminish the impact of race ($p = 0.020$ and $p = 0.010$ for B/AA race in the two cohorts, data not shown).

## 3.5 | Race-related impact of using plasma p-Tau$_{217}$ to screen for abnormal CSF AD biomarkers

We additionally examined if a plasma p-Tau$_{217}$ threshold derived in the Rutgers cohort was applicable to the Emory cohort. ROC curve analysis showed plasma p-Tau$_{217}$ ≥ 0.150 (Youden's index of 0.848) in the Rutgers cohort to identify elevated CSF t-Tau/A$\beta$42 with sensitivity of 90.5% and specificity of 94.3% (AUC = 0.940, Figure 3A). Applying this threshold in the Emory cohort resulted in sensitivity of 90.3% and specificity of 81.1% for NHW participants, but only sensitivity of 73.7% and specificity of 72.5% for B/AA participants (Figure 3A). Performance of plasma p-Tau$_{217}$ to identify decreased CSF A$\beta$42/A$\beta$40 was also better in NHW than B/AA participants (Figure 3B). When the two cohorts

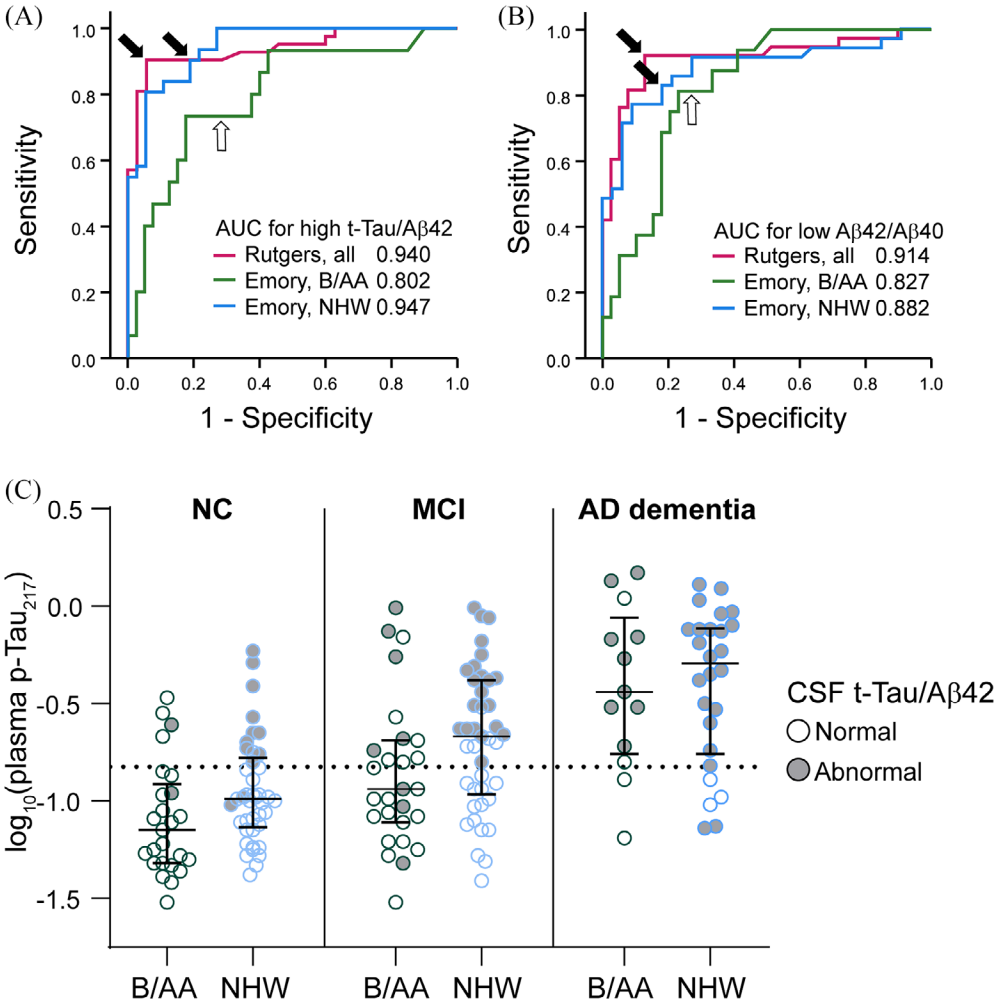


**FIGURE 3** Impact of a plasma p-Tau$_{217}$ threshold developed from a diverse cohort. ROC curve analysis of plasma p-Tau$_{217}$ for elevated CSF t-Tau/Aβ42 (A) or reduced Aβ42/Aβ40 (B) in the mixed Rutgers cohort (red line), B/AA Emory participants (dark green line), and NHW Emory participants (blue line; AUC). Filled arrows indicate the optimal p-Tau$_{217}$ threshold derived in the Rutgers and applied to the NHW Emory participants, and empty arrow indicates the same threshold applied to the B/AA Emory participants. When examined according to diagnosis and core CSF AD biomarker status (t-Tau/Aβ42 in (C), the same threshold had greater positive predictive value in NHW than B/AA participants. AD, Alzheimer's disease; AUC, area under the curve; B/AA, Black/African American; CSF, cerebrospinal fluid; NHW, non-Hispanic White; ROC, receiver operating characteristics.

were analyzed together, plasma p-Tau$_{217}$ of 0.150 showed slightly better overall accuracy in NHW than B/AA participants (87% vs. 77%, $p = 0.145$), but a much higher positive predictive value (PPV) in NHW than in B/AA (87% vs. 58%, $p = 0.003$). Using p-Tau$_{217}$ to identity decreased Aβ42/Aβ40 gave a similar outcome (85% vs. 65%, $p = 0.04$, Figure 3B).

## 3.6 | Other CSF factors influencing plasma p-Tau$_{217}$ levels

Finally, we explored if other CSF factors influenced plasma p-Tau$_{217}$ levels beyond core AD biomarkers. Common markers of neurodegeneration (NfL, Ng) and neuroinflammation (sTREM2, sTNFR1, and sTNFR2) did not improve the association model between plasma p-Tau$_{217}$ and CSF core AD biomarkers in either cohort (Table S1). Among 102 PCs derived from PCA of 1,086 CSF SomaLogic analytes, 5 showed nominal correlation with plasma p-Tau$_{217}$ at $p < 0.038$ (correlation between plasma and CSF p-Tau$_{217}$; see the Methods section). Regression analysis showed plasma p-Tau$_{217}$ to inversely associate with PC37 and PC7 scores independent of diagnosis, CSF p-Tau$_{181}$, and CSF Aβ42 (Table S2).

An examination of the two PCs showed synaptotagmin 2, ATP synthase subunit b (ATP5F1B), and ADP ribosylation factor like GTPase 2 binding protein (ARL2BP/BART) as top analytes loading positively onto PC37; and multiple lysosomal proteins (cathepsin A, F, V, D; prolylcarboxypeptidase, alpha galactosidase) as top analytes loading positively onto PC7 (Table S3). Two complement proteins (C4a, C3b) also negatively – albeit modestly – loaded onto PC7. Among these proteins, only C3b levels were available in the Emory cohort. Expanding the

**TABLE 3** Factors asscoiated with plasma p-Tau$_{217}$ levels in the Emory cohort of older B/AA and NHW participants, with coefficient, 95% confidence interval, and *p*-value shown for each term (CSF A$\beta$42 values were Z-transformed according to NC participants' levels).

| Parameter | B (95% confidence interval) | *p*-value |
|---|---|---|
| Constant | **1.730 (0.731, 2.729)** | <0.001 |
| Diagnosis | | |
| NC | Reference | |
| MCI | 0.088 (−0.008, 0.183) | 0.071 |
| AD dementia | −0.035 (−0.215, 0.145) | 0.701 |
| Chronic renal insufficiency | **0.682 (0.356, 1.008)** | <0.001 |
| Congestive heart failure | **0.335 (0.067, 0.603)** | 0.015 |
| B/AA race | **−0.091 (−0.181, −0.001)** | 0.048 |
| Having ≥ 1 *APOE* ε4 allele | 0.007 (−0.086, 0.100) | 0.883 |
| MMSE (square root transformed) | **−0.468 (−0.625, −0.310)** | <0.001 |
| log$_{10}$(CSF p-Tau$_{181,\ Luminex}$) | **0.640 (0.430, 0.851)** | <0.001 |
| Z CSF A$\beta$42 | **−0.128 (−0.170, −0.086)** | <0.001 |

*Note*: Coefficients and confidence intervals are bolded if $p < 0.05$.
Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; B/AA, Black/African American; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NC, normal cognition; NHW, non-Hispanic White.

regression analysis from Table 3 to include log$_{10}$(C3b) showed at least some of the additional effect from race to be mediated by introducing a protein from PC7 ($p = 0.038$, Table S4).

## 4 | DISCUSSION

Convenient and effective plasma AD biomarkers have the potential of greatly advancing ready access to early and accurate diagnosis, but nuances can be overlooked in large studies with mixed cohort compositions, enrollment sources, and dementia severity. We showed in one diverse cohort reflecting one regional Northeastern US population a stronger correlation between two related biomarkers (p-Tau$_{217}$ and p-Tau$_{181}$) measured in the same CSF compartment than the same biomarker (p-Tau$_{217}$) measured in two related biofluids (CSF and plasma), which could not be explained by intermediate precision or dynamic range of the assays alone. We further linked greater cognitive impairment to higher but B/AA race to lower plasma p-Tau$_{217}$, and replicated these as well as one novel finding related to CSF non-amyloid/non-tau biomarkers in an independent cohort of B/AA and NHW participants. Importantly, a plasma p-Tau$_{217}$ threshold optimized in a cohort with limited number of B/AA participants (11 out of 98) showed 50% higher PPV in NHW than in B/AA participants. We discuss these findings below.

The origins of plasma AD biomarkers remain unclear, with potential input from the brain via glymphatic clearance, extracellular vesicles, receptor-mediated transport across intact BBB, gross BBB disruption, or a combination of these processes. While a clear understanding of the mechanism giving rise to biomarker changes is not necessary for its validation or clinical application if said biomarker's levels are not readily influenced by common clinical variables, the low signal-to-noise ratio of plasma AD biomarkers (including p-Tau$_{217}$, p-Tau$_{181}$, and A$\beta$42/A$\beta$40) demands greater attention to demographic and clinical factors which predispose to over- or under-detection. Because we were able to confirm the excellent correlation between CSF p-Tau$_{217}$ and CSF p-Tau$_{181}$ using automated assays (one of the first reports to do so), previous reports of better predictive value of p-Tau$_{217}$ over p-Tau$_{181}$[26,27] likely resulted from greater CV using non-automated assays especially given their low concentrations. This excellent correlation also challenges proposed biological differences for AD-related phosphorylation at threonine 181 and 217 derived from assay-based observations.

This is not the first report to identify common factors influencing measured p-Tau levels and thus performance as a screening tool for AD pathology or AD risks[11,14,15,27], but significant influences from severity of cognitive impairment on plasma p-Tau$_{217}$ in two separate cohorts suggests comparisons between the usual participants with and without dementia may over-estimate the value of plasma p-Tau$_{217}$ as a fluid biomarker. The conflation of severity markers (often non-specific across neurodegenerative disease types) with etiologic biomarkers is not new in AD, but is increasingly overlooked in cohort studies. Whereas neurodegeneration is often cited *post hoc* to account for this performance inflation (i.e., more AD neuropathology leads to more neurodegeneration), we did not find their typical markers (NfL, Ng) to influence plasma p-Tau$_{217}$ levels. Because we cannot consistently account for the accuracy of clinical cognitive assessment in diverse populations, appropriate determination of novel biomarkers' performance against core AD biomarkers should be ideally carried out in people having similar degrees of cognitive impairment (e.g., MCI) from different etiologies (AD vs. suspected non-amyloid pathology) to eliminate the confounds from diagnostic mislabels.

The impact of B/AA race on plasma p-Tau$_{217}$ again emphasizes the importance of enrolling diverse participants in biomarker studies. One previous study found plasma p-Tau$_{217}$ to potentially have greater race-associated differences than plasma p-Tau$_{181}$,[27] but did not formally assess its predictive accuracy due to the small number of B/AA adults with autopsy- or amyloid PET-confirmed AD ($n = 9$). The more recent Bio-Hermes study including 103 older B/AA adults (27 amyloid PET positive) found them to have significantly lower plasma p-Tau$_{181}$ and p-Tau$_{217}$ levels than older NHW adults.[11] However, only 11 out of 1001 (1%) Bio-Hermes participants had paired CSF p-Tau measurements. Because of the consistently reported difference in CSF p-Tau$_{181}$ levels between B/AA and NHW older adults[18–21,28], omission of CSF p-Tau$_{181}$ leaves open the possibility that lower plasma p-Tau$_{217}$ merely corresponds to the lower CSF p-Tau levels. Across the two cohorts presented here, we analyzed plasma p-Tau$_{217}$ in 69 older B/AA participants (40 or 58% with low CSF A$\beta$42, 100% with paired CSF p-Tau$_{181}$), confirming plasma p-Tau$_{217}$ as a fluid marker with racial disparities beyond a carry-over from race-associated CSF tau-related biomarker disparities[18–21,28], as inclusion of CSF p-Tau$_{181}$ was insufficient to eliminate the effect of race on plasma p-Tau$_{217}$. This is regardless of

whether CSF p-Tau$_{181}$ was measured by bead-based assays in a semi-automated (Luminex, Emory cohort) or fully-automated (Lumipulse, Rutgers cohort) format, although p-Tau$_{181}$ levels measured by the two platforms have a linear relationship.[29] In contrast, we[25] and others[29] have reported a non-linear relationship in CSF A$\beta$42 levels measured by the two platforms at high concentrations.

Notwithstanding the mounting evidence, researchers have so far not identified a solution to address CSF tau-related racial disparities 7 years after our initial report.[18] Here we found that differences in some CSF proteins (e.g, cathepsins, C3b) may begin to elucidate mechanisms by which tau-related protein levels differ according to race. From the perspective of hypothesis generation, one putative mechanism has to do with lysosomes' role in tau processing. Because tau peptides undergo C-terminal truncation in the lysosome before secretion into the CSF and interstitial fluid (ISF)[30–33], the inverse relationship between secreted lysosomal cathepsin proteins (PC7) and p-Tau$_{217}$ could translate into greater lysosomal dysfunction in B/AA participants. This can result from social determinants of health such as environmental toxic exposure (including mercury[34] and air pollution[35]), or an upstream mechanism hypothesized to underlie other B/AA health disparities such as *APOL1*-associated kidney disease (associated with leaky lysosomes).[36–39] For the latter hypothesis, complications of endothelial disease and lower tau secretion would each correlate with lysosomal dysfunction without diminishing the role of AD neuropathologic changes in B/AA brain health.[40,41] Similarly, synaptotagmin 2 (top loading analyte for PC37) negatively regulates lysosomal exocytosis[42–44] beyond its better-known function in synaptic vesicle release. These hypotheses should be prospectively tested in cohorts with sufficient B/AA participants taking into account *APOL1* variants, plasma lysosomal proteins, and plasma p-Tau$_{217}$. Plasma lysosomal protein levels – which already predict renal functions without the need for race-based adjustments[45] – should also be prospectively tested to adjust for race-based differences in plasma p-Tau$_{217}$ levels.

While we present a study using automated assays with high intermediate precision in two diverse cohorts, this study has several limitations. Not all ChA participants had CSF for paired analysis, and we did not have a sufficient number of older Hispanic or non-Chinese Asian participants to generalize our findings to these groups. None of the participants had amyloid or tau PET, even though core CSF AD biomarkers have consistently shown high correspondence with amyloid PET. We also could not assess the longitudinal implication for plasma p-Tau$_{217}$ differences in B/AA participants due to the cross-sectional nature of these studies, although future longitudinal studies might be challenging with the increasing use of anti-amyloid therapies. The two cohorts shared many clinical and biomarker assessments, but the more extensive aptamer-based proteomic analysis was only available in a subset of Rutgers participants and MMSE was only available in Emory participants. Finally, we did not have sufficient matching information to adequately account for the influence on plasma p-Tau$_{217}$ from social determinants of health, but these findings – if further replicated – can be tested in subsequently recruited cohorts having more detailed social characterization.

In conclusion, plasma p-Tau$_{217}$ is a potentially powerful clinico-biological marker which can greatly accelerate the usual AD diagnostic process. At the same time, measuring p-Tau species in blood cannot circumvent the disparities long known to exist in CSF t-Tau and p-Tau$_{181}$ measurements, and the race-associated effect on p-Tau levels may be further compounded in plasma. Extreme caution thus should be exercised when applying plasma p-Tau$_{217}$ to B/AA adults for the purpose of clinical or trial screening, and an informed consent process to minimize mental and financial distress may be necessary to mitigate such biomarker-related disparities.

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## CONFLICT OF INTEREST STATEMENT

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## CONSENT STATEMENT

Written informed consents were previously obtained from all participants in accordance with the Declaration of Helsinki and the Belmont report for the long-term storage and future analysis of samples.

## ORCID

*William T. Hu* https://orcid.org/0000-0003-4862-6777

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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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