The Journal of Prevention of Alzheimer's Disease 13 (2026) 100472

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Association of plasma p-tau and p-tau/Aβ ratio with Alzheimer's pathology

Xuhui Chen [a,b,#], Mingxing Jiang [c,d,#], Laihong Zhang [e,f], Jiayi Zhu [e,g], Anqi Li [e,h], Zhengbo He [e,f], Xin Zhou [e,i], Yalin Zhu [e,h], Chen Zhang [a], Cong Wang [a], Mingxu Li [j], Yiying Wang [e], Xinyue Ma [e], Binhui Liu [e], Rong Ma [e], Yipeng Jin [e], Xiang Fan [k], Zhen Liu [e], Tengfei Guo [e,*], Yong-An Sun [a,**], Guoyu Lan [e,*]

[a] Department of Neurology, Peking University First Hospital, Beijing 100034, China
[b] Department of Neurology, Peking University Shenzhen Hospital, Shenzhen 518132, China
[c] Shenzhen Medical Academy of Research and Translation, Shenzhen 518132, China
[d] Westlake University, Hangzhou 310024, China
[e] Institute of Neurological and Psychiatric Disorders, Shenzhen Bay Laboratory, Shenzhen 518132, China
[f] School of Life Science and Technology, Harbin Institute of Technology, Harbin 150001, China
[g] School of Biology and Biological Engineering, South China University of Technology, Guangzhou 510641, China
[h] Division of Life Science, The Hong Kong University of Science and Technology, Hong Kong 999077, China
[i] School of Biomedical Engineering, Hainan University, Haikou 570228, China
[j] Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China
[k] Department of Medical Imaging, Peking University Shenzhen Hospital, Shenzhen 518132, China

ARTICLE INFO

Keywords:
Plasma biomarker
P-tau
B-amyloid
Alzheimer's disease
Brain atrophy
Cognitive decline

ABSTRACT

Background: Plasma phosphorylated tau (p-tau) and β-amyloid (Aβ) are promising biomarkers for Alzheimer's disease (AD). However, it remains unclear whether combining p-tau with Aβ provides better predictive performance than using p-tau alone.
Objectives: To evaluate the predictive utility of plasma p-tau and Aβ combinations for AD-related pathology, brain atrophy, and cognitive decline.
Design, setting, and participants: This study included 352 participants from the Greater-Bay Area Healthy Aging Brain Study (GHABS) cohort in China, classified into 227 Aβ-negative and 125 Aβ-positive individuals.
Measurements: Participants underwent Aβ positron emission tomography (PET) and plasma biomarker assessments. Plasma concentrations of p-tau181, p-tau217, p-tau231, Aβ42, and Aβ40 were quantified on the Quanterix HD-X and Lumipulse G1200 platform.
Results: Among the individual plasma p-tau variants, p-tau217 consistently outperformed p-tau181 and p-tau231. The combination of p-tau biomarkers (p-tau181, p-tau217, and p-tau231) with Aβ42 or the Aβ42/40 ratio further improved discrimination between Aβ+/CU (cognitively unimpaired) and Aβ-/CU individuals. Both p-tau/Aβ42 and p-tau/(Aβ42/40) exhibited slightly stronger or comparable associations with Aβ PET burden, baseline and longitudinal measures of hippocampal atrophy, AD-typical cortical thinning, and cognitive decline, relative to p-tau alone.
Conclusions: The head-to-head comparisons indicate that p-tau217 is the most robust biomarker among the variants tested, and p-tau/Aβ ratios perform comparably or slightly better than p-tau alone in reflecting AD pathology, potentially providing complementary information for early detection and monitoring of disease progression.

List of abbreviations: ad, alzheimer's disease; Aβ, β-amyloid; Ci, cognitive impaired; Ci, confidence interval; Csf, cerebrospinal fluid; Cu, cognitively unimpaired; Ghabs, greater-bay-area healthy aging brain study; Glm, generalized linear models; Lc–ms, liquid chromatography-mass spectrometry; Moca-basic, montreal cognitive assessment basic; MCI, Mild Cognitive Impairment; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography; p-tau, Phosphorylated Tau; rHCV, residual Hippocampal Volume; ROI, Region of Interest; SD, Standard Deviation; SUVR, Standardized Uptake Value Ratio.

* Corresponding author at: Institute of Neurological and Psychiatric Disorders, Shenzhen Bay Laboratory, No.5 Kelian Road, Shenzhen 518132, China.
** Corresponding author at: Peking University First Hospital, Xishiku Street, Xicheng District, Beijing 100034, China.
E-mail addresses: tengfei.guo@szbl.ac.cn (T. Guo), sya@bjmu.edu.cn (Y.-A. Sun), langy@szbl.ac.cn (G. Lan).
# These authors contributed equally.

https://doi.org/10.1016/j.tjpad.2025.100472
Received 12 October 2025; Received in revised form 10 December 2025; Accepted 16 December 2025
Available online 1 January 2026

1. Introduction

Alzheimer's disease (AD), the leading cause of dementia, poses a growing global health challenge in the context of aging populations worldwide [1,2]. It is neuropathologically characterized by the accumulation of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles consisting of hyperphosphorylated tau protein [3,4]. Early detection of these AD hallmarks before overt cognitive impairment is essential for identifying at-risk individuals suitable for disease-modifying therapies [5].

Over the past decade, blood-based biomarkers have emerged as promising tools for detecting and monitoring AD-related pathological changes [6,7]. Compared with cerebrospinal fluid (CSF) testing or positron emission tomography (PET) imaging, plasma biomarkers provide a scalable and cost-effective alternative suitable for large-scale screening and longitudinal tracking [8]. Currently, the most well-established plasma biomarkers include the Aβ42/40 ratio [9–11] and phosphorylated tau (p-tau) variants [12–15]. Blood-based biomarker trajectories demonstrate that plasma Aβ42/40 and p-tau217 abnormalities are among the earliest detectable changes [11,16,17]. These alterations are closely associated with subtle cerebral Aβ deposition. Liquid chromatography-mass spectrometry (LC–MS) assays have reported high concordance between plasma Aβ42/40 and Aβ PET positivity [11,18]. However, the modest dynamic range of plasma Aβ42/40 decline can limit its diagnostic accuracy, especially in early disease stages. In contrast, several novel immunoassays targeting specific p-tau epitopes, such as p-tau181, p-tau217, and p-tau231, exhibit strong associations with AD pathophysiology. Notably, assays incorporating p-tau217 show particularly high accuracy in detecting Aβ pathology, even in asymptomatic individuals [19]. Evidence from independent cohorts has shown that the diagnostic performance of plasma p-tau217 is comparable to that of CSF AD biomarkers [20,14]. Therefore, the revised criteria of AD frameworks recognize plasma p-tau217 assays with a minimum accuracy of 90 % for detecting Aβ PET abnormality in the intended-use population as acceptable biomarkers [3].

Recently, the United States Food and Drug Administration (FDA) has approved the Lumipulse plasma p-tau217/Aβ42 ratio and Roche plasma p-tau181 assays as commercially available tools for AD diagnosis in clinical practice, expanding the panel of clinically validated plasma biomarkers. Emerging evidence suggests that combining p-tau with Aβ measures may further improve diagnostic performance compared to p-tau alone [13,21–23]. However, widespread adoption of these biomarkers requires a better understanding of their associations with AD pathological alterations to yield more informative biomarker combinations. As these tests expand into global clinical practice, comparisons between the leading automated platforms, such as Quanterix's Simoa and Fujirebio's Lumipulse systems, become necessary. These platforms employ different immunoassay technologies, which may have varying systematic biases and analytical sensitivities. Therefore, determining their agreement is crucial for ensuring accurate interpretation across various settings and confirming the equivalence of biomarker results, regardless of the platform used.

In this study, we comprehensively investigated the change in three plasma p-tau biomarkers (p-tau181, p-tau217, and p-tau231) and their corresponding ratios to Aβ42, Aβ40, and Aβ42/40 across the AD continuum using two fully automated platforms, Quanterix HD-X and Lumipulse G1200. We further assessed their associations with brain Aβ and tau accumulations, neurodegeneration, and cognitive decline in a well-characterized Chinese population of older adults. This study aims to determine the analyte stability and performance of different plasma p-tau/Aβ ratios and p-tau alone in detecting and monitoring AD-related pathology and cognitive decline.

2. Methods

2.1. Participants

This study utilized data from the Greater-Bay Area Healthy Aging Brain Study (GHABS) (ClinicalTrials.gov ID: NCT06183658), a longitudinal and prospective cohort study launched by the Shenzhen Bay Laboratory in May 2021 [24]. Detailed recruitment, exclusion, and inclusion criteria of the GHABS cohort have been reported previously [24]. All participants completed cognitive assessments, genetic screening, and blood sample collection. Some of them further underwent baseline and longitudinal Aβ PET, tau PET, and magnetic resonance imaging (MRI) scans every 2 years. Participants were classified as cognitively unimpaired (CU), mild cognitive impairment (MCI), or dementia following the standard protocol of the Alzheimer's Disease Neuroimaging Initiative (ADNI) [25]. In this study, cognitively impaired (CI) was defined as individuals with MCI or dementia. This study was approved by the Institutional Review Board of Shenzhen Bay Laboratory, and all participants who met the inclusion requirements signed a written informed consent.

2.2. Plasma biomarker measurements

Plasma concentrations of p-tau181^{QX}, Aβ42^{QX}, and Aβ40^{QX} were measured using commercial immunoassays on the Quanterix HD-X platform (pTau-181 V2 Advantage Kit, #103714; Neuro 4-Plex Reagent kit, #103670). Plasma p-tau217^{GOT} and p-tau231^{GOT} were determined using in-house single molecular arrays (SIMOA) developed at the University of Gothenburg. Additional measurements of plasma p-tau217^{Fuji}, Aβ42^{Fuji}, and Aβ40^{Fuji} were performed on the Lumipulse G1200 platform (Fujirebio). All biomarkers were tested in a double-blind manner at Shenzhen Bay Laboratory (Shenzhen, China).

2.3. MRI and PET imaging processing

Details on descriptions of MRI and PET imaging procedures in GHABS have been reported previously [24]. The structural MRI images were collected on 3.0T scanners and segmented into different cortical and subcortical regions of interest (ROIs) using Freesurfer (version 7.2.0). The estimated intracranial volume was used to adjust bilateral hippocampal volume (HCV), and then the residual HCV (rHCV) was obtained by calculating the difference between raw HCV and the expected HCV [4]. Temporal-metaROI cortical thickness was calculated as an area-weighted average of mean cortical thickness in AD-signature atrophy brain regions, including entorhinal, fusiform, inferior temporal, and middle temporal cortices [26].

Aβ PET imaging was performed with two tracers [^{18}F]-D3FSP (FSP) [27] or [^{18}F]-florbetapir (FBP) [28], and tau PET imaging was performed with [^{18}F]-flortaucipir (FTP) [29]. PET imaging was coregistered to their corresponding T1 structural MRI scans, and regional uptake values were extracted from 68 Freesurfer-defined cortical ROIs defined by the Desikan-Killiany atlas. A composite standardized uptake value ratio (SUVR) for Aβ burden was calculated from AD summary cortical regions, including frontal, cingulate, parietal, and temporal regions [30], with the brainstem used as a reference for FSP [27] or the whole cerebellum for FBP [31]. The accumulation of cortical tau tangles was evaluated using the SUVR in temporal meta-ROI regions, including the entorhinal, parahippocampal, fusiform, amygdala, and inferior temporal and middle temporal regions, with the inferior cerebellum serving as the reference [32]. The cutoff of Aβ PET positivity was defined as composite SUVR $>$ 0.78 for FSP or $>$ 1.11 for FBP [33]. The cutoff of tau PET positivity was defined as temporal meta-ROI FTP SUVR $>$ 1.27 [34].

2.4. Statistical analysis

All statistical analyses were conducted in R version 4.4.2 (The R Foundation for Statistical Computing). Demographics and clinical characteristics of participants are summarized as mean (Standard Deviation (SD)) or number (%). Comparisons between Aβ-negative (Aβ-) and Aβ-positive (Aβ+) groups were conducted by using Wilcoxon rank-sum tests or Fisher's exact test at the significance level of $p < 0.05$ unless otherwise noted. Plasma biomarkers were $\log_{10}$-transformed before parametric analyses. We first compared the difference in plasma biomarker levels across different Aβ PET positivity and cognitive status groups using generalized linear models (GLM), adjusted for age and sex. The effect size estimates between groups were further computed using Cohen's d, with absolute values shown. To further examine biomarker changes along Aβ plaque burden, participants with FSP PET were stratified by composite SUVR: Aβ- individuals were defined as Q0 reference (n = 167), while Aβ-positive individuals (n = 106) were divided into SUVR quartiles (Q1–Q4). We evaluated the correlation between plasma biomarkers with Aβ PET and tau PET, as well as baseline levels and longitudinal changes of hippocampal volume, cortical thickness, and cognitive function using Pearson's r correlation. These associations were further assessed by using GLM models, adjusted for age and sex (education was additionally controlled for cognitive outcomes).

3. Results

3.1. Demographics

This study included 352 participants from the GHABS cohort who underwent Aβ PET imaging, comprising 227 Aβ- and 125 Aβ+ individuals. Among them, 142 participants further underwent tau PET scans. Plasma biomarkers were available for all participants, including $Aβ42^{QX}$, $Aβ40^{QX}$, p-tau181^{QX}, p-tau217^{GOT}, and p-tau231^{GOT}. A subset of 255 participants was additionally analyzed using Lumipulse plasma assays ($Aβ42^{Fuji}$, $Aβ40^{Fuji}$, and p-tau217^{Fuji}) for sensitivity validation. Demographic and clinical characteristics are summarized in Table 1 and Table S1. The mean age of all participants was 67.5 years, with comparable sex distributions between Aβ− and Aβ+ groups. Regarding cognitive status, 82.8 % of Aβ- participants were CU, while 62.4 % of Aβ+ participants were diagnosed with CI. Additionally, 143 participants underwent longitudinal structural MRI scans with a mean follow-up duration of 1.26 years, and 214 underwent longitudinal cognitive assessments with a mean follow-up duration of 1.43 years.

Table 1
Demographic characteristics of participants.

	All (n = 352)	Aβ- (n = 227)	Aβ+ (n = 125)	p-values
Age	67.5 (7.46)	66.8 (6.72)	68.8 (8.81)	0.032
Sex, female	214 (60.8)	134 (59.0)	80 (64.0)	0.425
Education	12.5 (3.9)	13.3 (3.6)	11.0 (3.9)	< 0.001
Diagnose, CU/CI	235/117	188/39	47/78	
APOE ε4, carrier	117 (33.2)	51 (22.5)	66 (52.8)	< 0.001
Cortical Thickness	2.70 (0.15)	2.74 (0.10)	2.64 (0.20)	< 0.001
Residual HCV	−0.44 (1.05)	−0.09 (0.73)	−1.08 (1.23)	< 0.001
MoCA	23.1 (6.3)	25.5 (3.5)	18.6 (7.8)	< 0.001
Plasma $Aβ42^{QX}$	5.34 (1.39)	5.61 (1.43)	4.86 (1.17)	< 0.001
Plasma $Aβ40^{QX}$	91.3 (19.3)	90.4 (20.4)	93.0 (17.2)	0.110
Plasma p-tau217^{GOT}	5.3 (3.1)	3.8 (1.6)	7.9 (3.5)	< 0.001
Plasma p-tau231^{GOT}	15.0 (5.4)	13.1 (4.0)	18.4 (5.9)	< 0.001
321 participants had plasma p-tau181^{QX}				
Plasma p-tau181^{QX}	2.45 (1.23)	1.96 (0.73)	3.31 (1.45)	< 0.001
255 participants had Lumipulse plasma biomarkers				
Plasma $Aβ42^{Fuji}$	25.8 (4.8)	27.0 (4.4)	23.3 (4.5)	< 0.001
Plasma $Aβ40^{Fuji}$	269.3 (40.6)	264.7 (40.2)	278.5 (40.1)	0.020
Plasma p-tau217^{Fuji}	0.210 (0.27)	0.095 (0.037)	0.451 (0.375)	< 0.001
273 participants had D3FSP Aβ PET and 113 FBP Aβ PET				
D3FSP Aβ PET SUVR	0.80 (0.15)	0.71 (0.04)	0.96 (0.14)	< 0.001
FBP Aβ PET SUVR	0.73 (0.11)	0.68 (0.03)	0.91 (0.09)	< 0.001
142 participants had Tau PET				
Tau PET SUVR	1.32 (0.39)	1.12 (0.05)	1.57 (0.47)	< 0.001

Data are presented as numbers (%) or mean (SD).
Abbreviations: CI = Cognitive Impaired, CU = Cognitive Unimpaired, p-tau = Phosphorated tau, HCV = Hippocampl Volume, MoCA = Montreal Cognitive Assessment, SUVR = Standardized Uptake Value Ratio, SD = Standard deviation.

3.2. Comparisons of plasma p-tau biomarkers and their ratio across the AD continuum

We first compared the levels of individual plasma p-tau biomarkers and their corresponding ratios to Aβ species across different Aβ positivity and cognitive status groups. In terms of p-tau alone, all variants—p-tau181^{QX}, p-tau231^{GOT}, p-tau217^{GOT}, and p-tau217^{Fuji}—were significantly higher in both Aβ+/CU and Aβ+/CI groups compared to Aβ-/CU (Fig. 1). Notably, p-tau217^{GOT} and p-tau217^{Fuji} showed larger effect sizes than p-tau181^{QX} and p-tau231^{GOT}. For the combinations of plasma p-tau with Aβ peptides, all biomarkers in ratios were also higher in Aβ+/CU and Aβ+/CI, with the most pronounced effects observed for p-tau217-based ratios. Among CU individuals, p-tau ratios to Aβ42 or Aβ42/40 yielded larger effect size differences compared to p-tau alone. Specifically, in the Aβ+/CU group, the effect sizes relative to p-tau alone increased by 58.7 % for p-tau231^{GOT}/Aβ42 and 60.9 % for p-tau231^{GOT}/(Aβ42/40) (Fig. 1B), followed by 44.2 % for p-tau181^{QX}/Aβ42 and 53.8 % for p-tau181^{QX}/(Aβ42/40) (Fig. 1A), and last with 21.5 % for p-tau217^{GOT}/Aβ42 and 15.9 % for p-tau217^{GOT}/(Aβ42/40) (Fig. 1C). Similar improvements were observed with Lumipulse plasma assays: p-tau217^{Fuji}/Aβ42 and p-tau217^{Fuji}/(Aβ42/40) showed increases of 20.9 % and 16.3 %, respectively (Fig. 1D). When participants were stratified by Aβ PET SUVR quartiles (Q0–Q4), all plasma p-tau biomarkers showed significantly higher levels from Q2 to Q4 groups, with p-tau217^{GOT} and p-tau217^{Fuji} exhibiting the greatest effect sizes (Fig. S1). Similarly, when expressed as ratios to Aβ42 or Aβ42/40, the effect sizes relative to Q0 further increased, particularly in the Q2 group. These results suggest that combining Aβ42 and Aβ42/40 may improve the sensitivity of p-tau to subtle cerebral Aβ deposition, particularly in preclinical AD, with the most pronounced effect observed for p-tau217.

3.3. Associations of plasma p-tau biomarkers and their ratios with cerebral Aβ and tau accumulations

Next, we evaluated the association between plasma p-tau biomarkers and PET measures of cortical Aβ and tau aggregations. All p-tau biomarkers, both alone and as ratios to Aβ species, were significantly associated with cortical Aβ burden measured by FSP and FBP PET (Fig. 2A-B). p-tau217^{GOT} and p-tau217^{Fuji} correlated most strongly with Aβ PET, outperforming p-tau181^{QX} and p-tau231^{GOT}, regardless of cognitive status. When combining p-tau with Aβ42 or Aβ42/40, the ratios incorporating p-tau217 exhibited the strongest correlations with Aβ PET, which was comparable to p-tau217 alone. Additionally, these combinations further strengthened the correlations for p-tau181^{QX} and p-tau231^{GOT}. Concerning tau aggregations, p-tau217^{GOT} and p-tau181^{QX} showed similar correlation strengths with temporal-metaROI tau PET, and both were slightly stronger than p-tau231^{GOT} but weaker than p-tau217^{Fuji} (Fig. 2C). The strength of correlations with tau PET did not significantly alter depending on whether individual p-tau or their ratios to Aβ species were used. Overall, in contrast to p-tau alone, their combinations with Aβ42 or Aβ42/40 generally exhibit comparable or

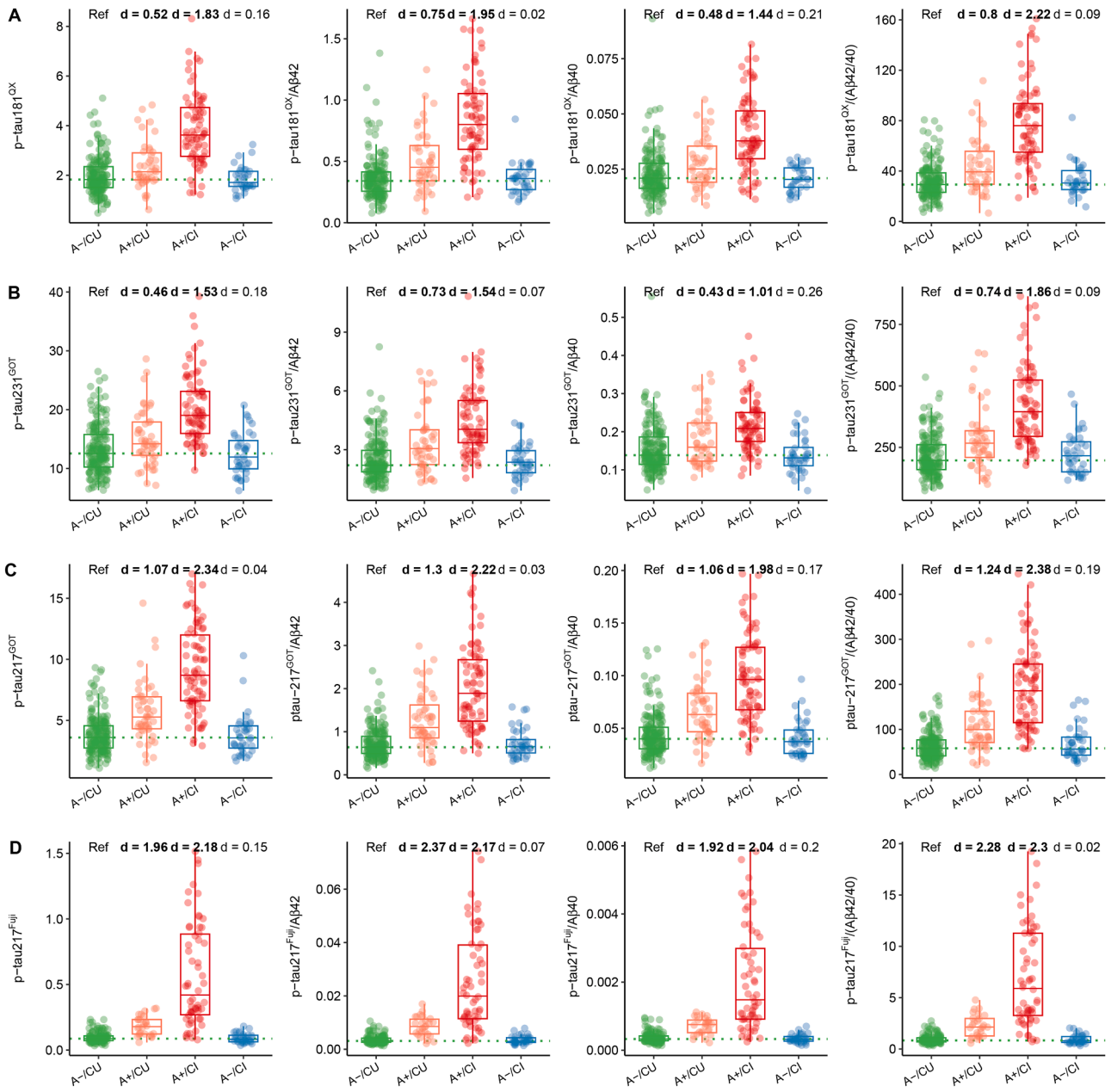

Fig. 1. Comparison of plasma p-tau and p-tau/Aβ ratio across the AD continuum. Plasma levels of p-tau181^{QX} and p-tau181^{QX}/Aβ ratios (A), p-tau231^{GOT} and p-tau231^{GOT}/Aβ ratios (B), p-tau217^{GOT} and p-tau217^{GOT}/Aβ ratios (C), and p-tau217^{Fuji} and p-tau217^{Fuji}/Aβ ratios (D) across groups defined by Aβ positivity and clinical diagnosis. The boxplots depict the median (horizontal bar), IQR (hinges), and 1.5 × IQR (whiskers). Each point represents an individual, and green dashed lines represent the median values of the Aβ– CU group. The Cohen's d values are shown above the bar, and bolded numbers indicate statistical significance ($p < 0.05$) using GLMs, adjusted for age and sex. The exact p-values were corrected for multiple comparisons using the Benjamini–Hochberg approach. A-, Aβ PET negative; *A*+, Aβ PET positive; CU, cognitively unimpaired; CI, cognitively impaired.

slightly stronger associations with Aβ pathology, especially for p-tau181 and p-tau231, but do not influence the association with tau pathology in brains.

3.4. Association of plasma p-tau biomarkers and their ratio with neurodegeneration and cognitive decline

Finally, we explored the performance of plasma p-tau biomarkers in predicting cross-sectional and longitudinal changes in brain structure and cognitive function. As expected, all p-tau biomarkers, used both individually and in ratios, showed significant associations with baseline residual HCV, temporal-metaROI cortical thickness, and MoCA scores, with effects largely maintained in CI individuals (Fig. 3). Two p-tau217 assays and their ratios consistently exhibited the highest strength of these correlations. Moreover, for p-tau181^{QX}, p-tau231^{GOT}, and p-tau217^{GOT}, their ratios to Aβ42 and Aβ42/40 tended to show similar or slightly stronger correlations than the individual biomarkers, whereas the ratios to Aβ40 appeared relatively weaker. In contrast, individual p-tau217^{Fuji} and its ratios showed comparable correlation strengths at baseline. Longitudinally, individual p-tau217^{Fuji} and its ratios exhibited the strongest correlations with the rates of decline in residual HCV, temporal-metaROI cortical thickness, and MoCA scores, followed by p-tau217^{GOT} and p-tau181^{QX}, and p-tau231^{GOT} was the weakest (Fig. 4). For decline rates of residual HCV and MoCA scores, the ratios of p-tau181^{QX}, p-tau231^{GOT}, and p-tau217^{GOT} to Aβ42 and Aβ42/40 showed higher correlations than the individual biomarkers and their ratios to

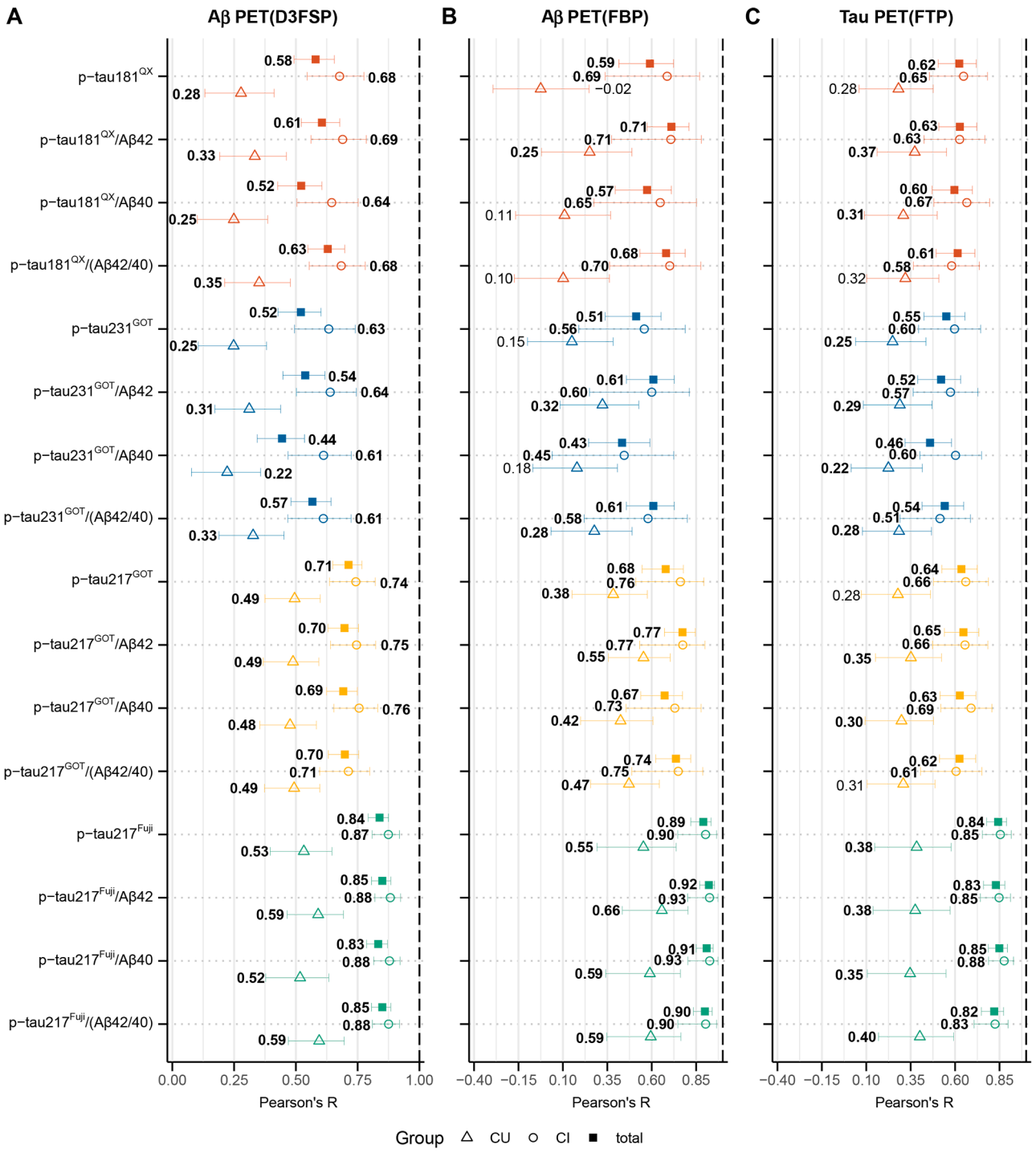

Fig. 2. Associations of plasma p-tau and p-tau/Aβ ratio with cerebral Aβ and tau deposition. Associations of plasma p-tau and p-tau/Aβ ratios with D3FSP Aβ-PET SUVR (A), FBP Aβ-PET SUVR (B), and FTP Tau-PET SUVR (C). The points and error bars represent Pearson's R correlations and 95 % confidence intervals, respectively. Bolded numbers indicate statistical significance ($p < 0.05$) using GLM models, adjusted for age and sex.

Aβ40. Regarding cortical thinning, only the ratios to Aβ42 and Aβ40 showed slightly elevated correlation coefficients. Overall, the combination of plasma p-tau with Aβ42 or Aβ42/40 appeared to modestly strengthen the associations with neurodegeneration and cognitive decline compared to using p-tau alone.

4. Discussion

In this study, we conducted a head-to-head comparison of three plasma p-tau biomarkers (p-tau181, p-tau231, and p-tau217) and their ratios to Aβ species (Aβ42, Aβ40, and Aβ42/40) across the AD continuum in a well-characterized community-based aging population, using fully automated assays on the Quanterix HD-X and Lumipulse G1200 platforms. Our study found that plasma p-tau217 levels exhibited greater fold increases in Aβ+ groups, and stronger correlations with Aβ-PET, tau-PET, brain atrophy, and cognitive decline when compared to p-tau181 and p-tau231. Critically, when combining with Aβ biomarkers, the p-tau ratio to Aβ42 or Aβ42/40 showed moderately improved ability in distinguishing AD patients from controls and somewhat stronger correlations with Aβ pathology, brain atrophy, and cognitive decline,

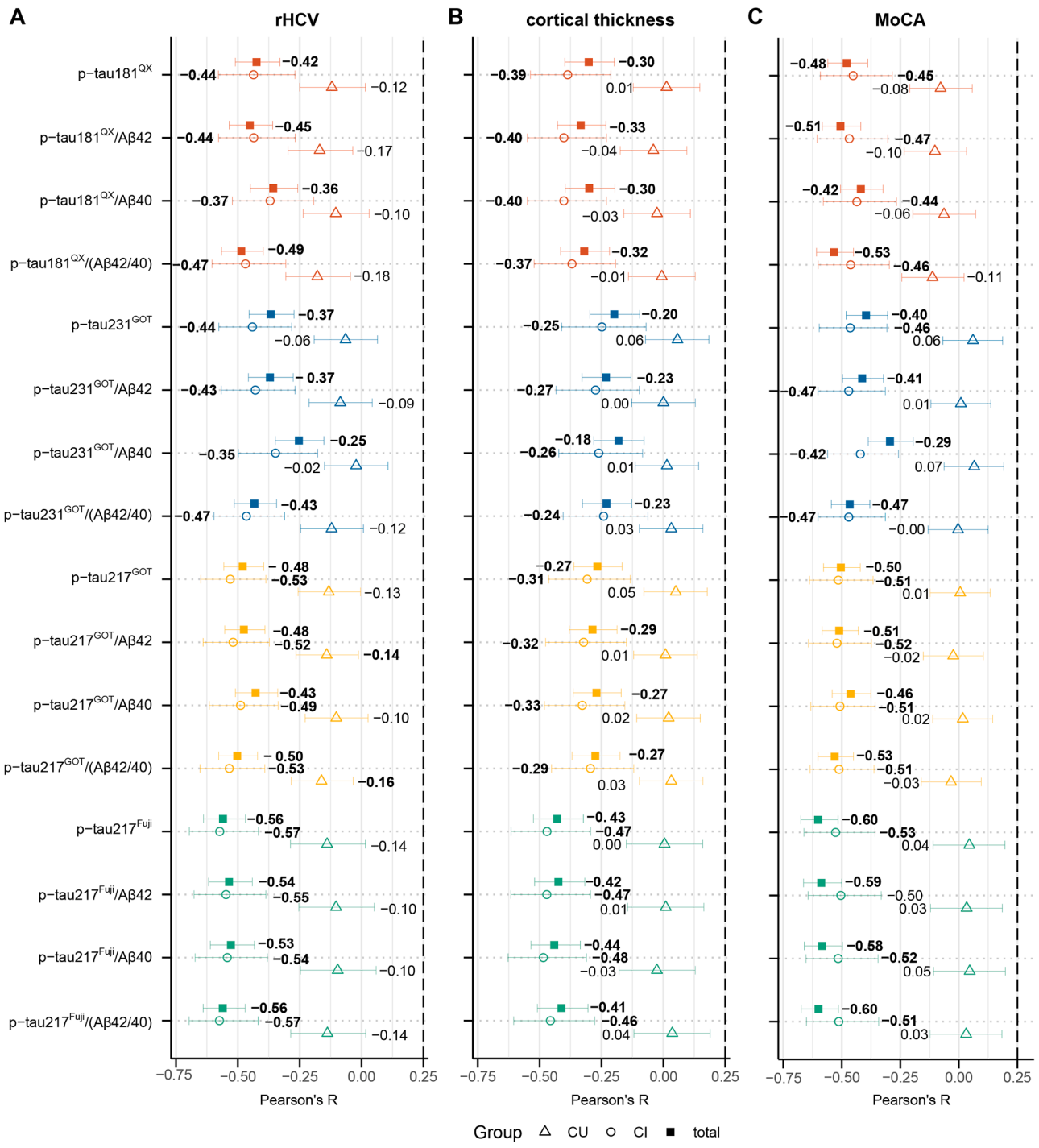

Fig. 3. Associations of plasma p-tau and p-tau/Aβ ratio with baseline brain structure and cognitive function. Associations of plasma p-tau and p-tau/Aβ ratios with baseline rHCV (A), temporal-metaROI cortical thickness (B), and MoCA score (C). The points and error bars represent Pearson's R correlations and 95 % confidence intervals, respectively. Bolded numbers indicate statistical significance ($p < 0.05$) using GLMs, adjusted for age, sex, and education for cognitive outcome. rHCV, residual Hippocampal Volume; MoCA, Montreal Cognitive Assessment.

especially for p-tau181 and p-tau231. Overall, these findings suggest that plasma p-tau/Aβ42 and p-tau/(Aβ42/40) ratios may offer comparable or modestly enhanced utility for reflecting early AD-related pathology and cognitive decline.

Accurate plasma assays, particularly p-tau217 alone or in combination, provide a simple alternative to CSF biomarkers as standalone diagnostic tests for AD, requiring a minimum accuracy of 90 % to identify abnormal Aβ PET in the intended-use population [3]. Our recent work demonstrated that plasma p-tau217 abnormality occurred earlier than other plasma p-tau and non-p-tau variants, along with worsening cortical Aβ plaque deposition [19], which was corroborated in the present study. In blood, the levels of p-tau181, p-tau231, and p-tau217 were all reported to increase in preclinical AD [35,15,36], while the fold changes between individuals with and without Aβ pathology were greater for p-tau217 relative to p-tau181 and p-tau231 [37–39]. This aligns with our findings that p-tau217 showed an approximately 2-fold higher effect size compared to p-tau181 and p-tau231 among CU individuals. Previous studies have reported that plasma p-tau biomarkers

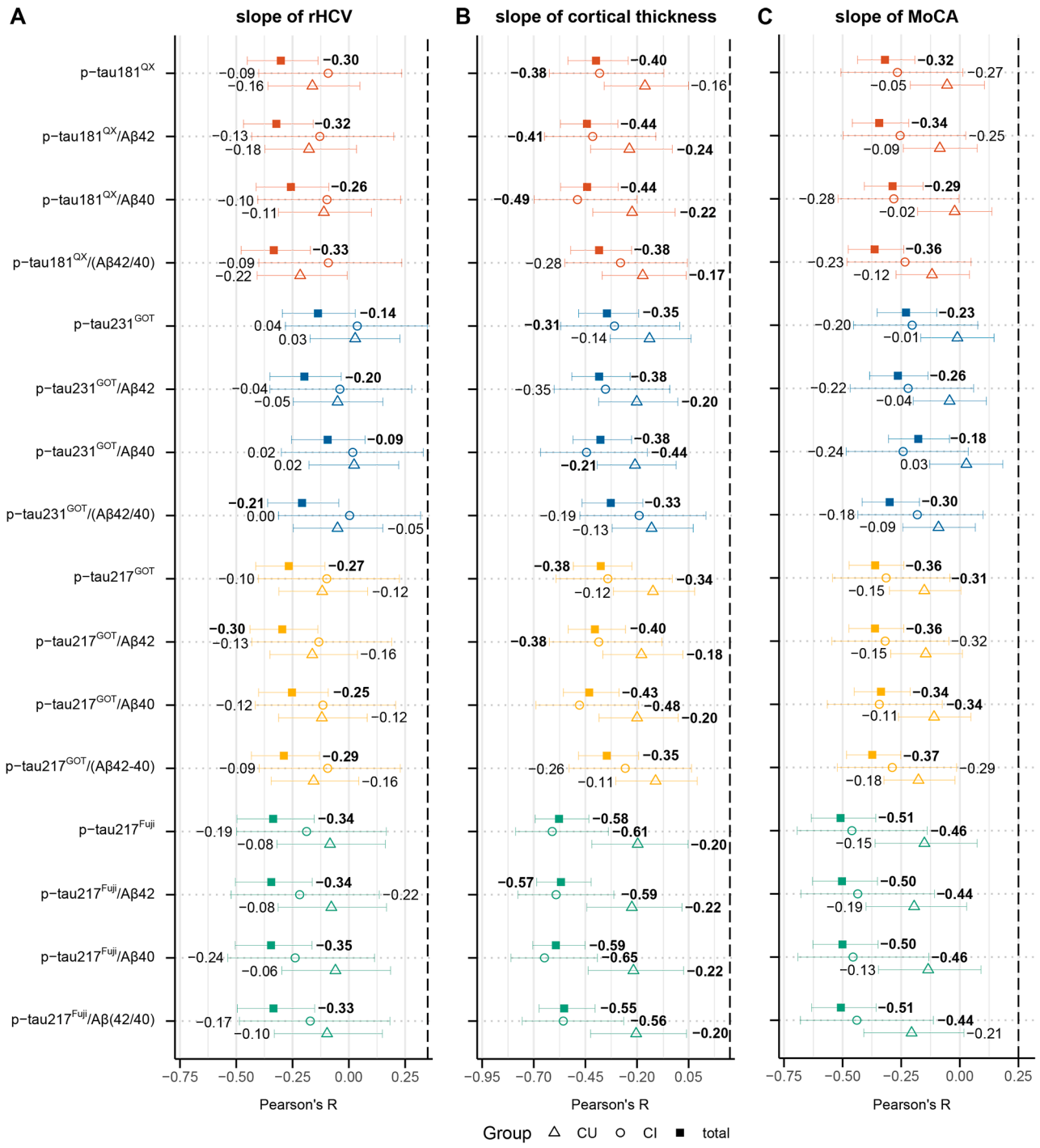

Fig. 4. Associations of plasma p-tau and p-tau/Aβ ratio with longitudinal brain atrophy and cognitive decline. Associations of plasma p-tau and p-tau/Aβ ratios with slopes of rHCV (A), temporal-metaROI cortical thickness (B), and MoCA score (C). The points and error bars represent Pearson's R correlations and 95 % confidence intervals, respectively. Bolded numbers indicate statistical significance ($p < 0.05$) using GLMs, adjusted for age, sex, and education for cognitive outcome. rHCV, residual Hippocampal Volume; MoCA, Montreal Cognitive Assessment.

are capable of detecting both amyloid-β and tau pathologies in AD [40–42]. In line with these reports, our results demonstrated that plasma p-tau biomarkers, as well as their ratios to Aβ biomarkers, are significantly associated with brain amyloid-β and tau burdens across both CU and CI participants, with p-tau217 showing the strongest correlations. These results support that plasma p-tau217 serves as a highly sensitive and predictive biomarker for early AD pathology.

Additionally, we observed that Lumipulse plasma p-tau217 exhibited stronger associations with Aβ-PET, tau-PET, brain atrophy, and cognitive decline compared to ALZpath p-tau217. Similarly, the effect sizes of Aβ42 and Aβ42/40 measured by Lumipulse assays in Aβ+/CU were also higher than those measured by Quanterix assays (Fig. S2). These findings suggest that the Lumipulse immunoassays may provide robust performance and sensitivity in detecting AD-related pathological changes, potentially offering added value for both research and clinical applications. However, these findings require further validation in diverse cohorts.

Several studies have demonstrated that plasma p-tau to Aβ42 ratios

outperform individual biomarkers in identifying preclinical AD and predicting disease progression [43–46]. In line with these findings, our study showed that combining plasma p-tau with Aβ42 or the Aβ42/40 ratio may modestly enhance the detection of AD pathology, especially for p-tau181 and p-tau231. Nevertheless, the addition of Aβ40 alone provides no further benefit, which may be due to the relatively small dynamic range of plasma Aβ40 and its limited association with amyloid plaque burden. The ratios of p-tau/Aβ42 likely integrate distinct but complementary pathological signals. Decreases in Aβ42 and Aβ42/40 indicate amyloid deposition, and increases in p-tau levels reflect Aβ-related tau hyperphosphorylation [47,48]. Although plasma Aβ changes are modest in early disease stages, leading to substantial overlap between individuals with and without pathology [18,49], the incorporation with p-tau biomarkers, which tend to respond earlier and more strongly to Aβ pathology, may help increase pathological contrast and modestly improve early diagnostic performance. While these findings support the clinical value of ratio-based biomarkers such as p-tau217/Aβ42, their implementation in real-world settings is not without challenges. Practical use of the p-tau217/Aβ42 ratio requires careful attention to pre-analytical sample handling. Studies show that although p-tau217 remains stable at room temperature and under refrigeration, Aβ42 and Aβ40 degrade rapidly, requiring immediate freezing of samples unless testing is performed within six hours of collection [50]. Therefore, standardization of assay protocols, including sample collection, storage, and processing procedures, will be essential for broader clinical translation.

A major strength of this study is that we systematically evaluated both established and emerging plasma p-tau biomarkers—including p-tau181, p-tau231, and p-tau217—individually and in combination with Aβ-related markers (Aβ42, Aβ40, and the Aβ42/40 ratio), enabling a comprehensive assessment of their performance in detecting AD-related pathology. Our study directly compared multiple p-tau isoforms and their respective ratios with diverse Aβ species, providing a more nuanced understanding of their relative performance in detecting early-stage AD. Furthermore, the use of two widely available platforms, Quanterix HD-X and Lumipulse G1200, also enhances the translational relevance of our findings by demonstrating consistency and potential applicability in varied clinical and laboratory settings. Building on our findings that provide a better understanding of the associations between plasma biomarker measurements and AD pathology, future studies should directly compare the diagnostic performance of p-tau and p-tau/Aβ ratios for classifying key pathological stages (such as Aβ abnormality) across diverse clinical cohorts, especially in preclinical AD. It is essential for determining the optimal biomarker or combination for specific clinical practice and for informing the development of standardized diagnostics across various platforms.

Several limitations should be acknowledged. First, a subset of participants lacked p-tau217^{Fuji} data due to sample availability or assay constraints, which may have introduced bias or reduced statistical power in some comparisons. Second, longitudinal PET data were not available, limiting our ability to track dynamic changes in Aβ and tau aggregations and to examine the temporal relationships between plasma biomarkers and disease progression. Third, the follow-up duration in our cohort was relatively short, restricting our ability to fully assess the predictive value of these biomarkers for long-term cognitive decline and clinical conversion. Finally, the variability of plasma biomarkers is influenced by residual confounding factors [51,52], such as vascular pathology and kidney dysfunction, beyond the demographics and clinical covariates adjusted for in this study. These factors should be noted in future observational studies. Thus, these findings should be further validated in larger and independent populations, especially those with longitudinal plasma and neuroimaging biomarker data. Moreover, our study focused on a Han Chinese aging population, which may limit the generalizability of our findings to individuals of other races or ethnicities, as plasma biomarkers may exhibit population-specific variation.

In conclusion, this study suggests that plasma p-tau217 is the most robust biomarker for AD-related pathological changes, outperforming plasma p-tau181 and p-tau231. The combinations with Aβ42 or the Aβ42/40 ratios may enhance the utility of p-tau in distinguishing Aβ deposition, neurodegeneration, and cognitive decline, particularly for p-tau181 and p-tau231. Our head-to-head comparisons underscore the potential relevance of plasma p-tau biomarkers, particularly when used in combination with Aβ42 or the Aβ42/40 ratio, as a sensitive and scalable biomarker for detecting early AD pathology, providing complementary information for early diagnosis and monitoring.

Statement of ethics

All the GHABS participants provided informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and subsequent revisions.

Funding

This study was funded by the National Key Research and Development Program of China (2023YFC3605400 to T.G.), National Natural Science Foundation of China (Grant No. 82301380 to G.L., 82422027, U24A20340 and 82171197 to T.G., 12231018, 82401397 to Y.S.), Science and Technology Innovation 2030- Major Project (2021ZD0201805, 2021ZD0201800 to Y.S.), Guangdong Basic and Applied Basic Science Foundation for Distinguished Young Scholars (Grant No. 2023B1515020113 to T.G.), the Shenzhen Science and Technology Program (Grant No. RCYX20221008092935096 to T.G.), Shenzhen Medical Research Fund (Grant No. A2403016 to G.L.), Shenzhen Bay Laboratory (Grant No. S241101004–1 to T.G.).

Declaration of generative AI and AI-assisted technologies in the writing process

I have not used any AI at all.

Supplementary material

Supplemental material can be found online.

Data availability

The data used in the current study were obtained from the GHABS cohort. Derived data is available from the corresponding author on request by any qualified investigator, subject to a data use agreement.

CRediT authorship contribution statement

Xuhui Chen: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Mingxing Jiang:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Laihong Zhang:** Investigation. **Jiayi Zhu:** Investigation. **Anqi Li:** Investigation. **Zhengbo He:** Investigation. **Xin Zhou:** Investigation. **Yalin Zhu:** Conceptualization. **Chen Zhang:** Investigation. **Cong Wang:** Investigation. **Mingxu Li:** Investigation. **Yiying Wang:** Investigation. **Xinyue Ma:** Investigation. **Binhui Liu:** Investigation. **Rong Ma:** Investigation. **Yipeng Jin:** Investigation. **Xiang Fan:** Investigation. **Zhen Liu:** Investigation. **Tengfei Guo:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Yong-An Sun:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Guoyu Lan:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank all the participants and staff of the GHABS research group (clinical trials No. NCT06183658) for their immense contributions to data collection. The Shenzhen Bay Laboratory supercomputing center supported the imaging processing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100472.

References

[1] 2025 Alzheimer's disease facts and figures. Alz Dement 2025;21:e70235.
[2] Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. Lancet 2021;397(10284):1577–90.
[3] Jack CR, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: alzheimer's Association Workgroup. Alz Dement 2024;20(8):5143–69.
[4] Guo T, Korman D, Baker SL, Landau SM. Jagust WJ. Longitudinal cognitive and biomarker measurements support a unidirectional pathway in Alzheimer's Disease pathophysiology. Biol Psychiatry 2021;89(8):786–94.
[5] Cummings JL, Teunissen CE, Fiske BK, Le Ber I, Wildsmith KR, Schöll M, et al. Biomarker-guided decision making in clinical drug development for neurodegenerative disorders. Nat Rev Drug Discov 2025;22(8):1–21.
[6] Palmqvist S, Tideman P, Mattsson-Carlgren N, Schindler SE, Smith R, Ossenkoppele R, et al. Blood biomarkers to detect Alzheimer disease in primary care and secondary care. JAMA 2024;332(13):1245–54.
[7] Schindler SE, Galasko D, Pereira AC, Rabinovici GD, Salloway S, Suárez-Calvet M, et al. Acceptable performance of blood biomarker tests of amyloid pathology — Recommendations from the Global CEO Initiative on Alzheimer's Disease. Nat Rev Neurol 2024;20(7):426–39.
[8] Grande G, Valletta M, Rizzuto D, Xia X, Qiu C, Orsini N, et al. Blood-based biomarkers of Alzheimer's disease and incident dementia in the community. Nat Med 2025;30(1):1–9.
[9] Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. Neurology 2019;93(17):e1647–59.
[10] Xiong C, Luo J, Wolk DA, Shaw LM, Roberson ED, Murchison CF, et al. Baseline levels and longitudinal changes in plasma Aβ42/40 among black and white individuals. Nat Commun 2024;15(1):5539.
[11] Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature 2018;554(7691):249–54.
[12] Mielke MM, Dage JL, Frank RD, Algeciras-Schimnich A, Knopman DS, Lowe VJ, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. Nat Med 2022;28(7):1398–405.
[13] Palmqvist S, Warmenhoven N, Anastasi F, Pilotto A, Janelidze S, Tideman P, et al. Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. Nat Med 2025;31(12):2036–43.
[14] Ashton NJ, Brum WS, Di Molfetta G, Benedet AL, Arslan B, Jonaitis E, et al. Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer Disease pathology. JAMA Neurol 2024;81(3):255–63.
[15] Milà-Alomà M, Ashton NJ, Shekari M, Salvadó G, Ortiz-Romero P, Montoliu-Gaya L, et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease. Nat Med 2022;28:1797–801.
[16] Bilgel M, An Y, Walker KA, Moghekar AR, Ashton NJ, Kac PR, et al. Longitudinal changes in Alzheimer's-related plasma biomarkers and brain amyloid. Alz Dementia 2023;19(10):4335–45.
[17] Ashton NJ, Janelidze S, Mattsson-Carlgren N, Binette AP, Strandberg O, Brum WS, et al. Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. Nat Med 2022;28(12):2555–62.
[18] Janelidze S, Teunissen CE, Zetterberg H, Allué JA, Sarasa L, Eichenlaub U, et al. Head-to-Head comparison of 8 plasma amyloid-β 42/40 assays in Alzheimer disease. JAMA Neurol 2021;78(11):1375–82.
[19] Lan G, Wang M, Gonzalez-Ortiz F, Zhang L, Li A, Li B, et al. Comprehensive evaluation of plasma tau biomarkers for detecting and monitoring Alzheimer's disease in a multicenter and multiethnic aging population. Nat Aging 2025;5:1601–18.
[20] Barthélemy NR, Salvadó G, Schindler SE, He Y, Janelidze S, Collij LE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. Nat Med 2024;30:1085–95.
[21] Zhong X, Wang Q, Yang M, Lin G, Yao K, Wu Z, et al. Plasma p-tau217 and p-tau217/Aβ1-42 are effective biomarkers for identifying CSF- and PET imaging-diagnosed Alzheimer's disease: insights for research and clinical practice. Alz Dement 2025;21(2):e14536.
[22] Wang J, Huang S, Lan G, Lai YJ, Wang QH, Chen Y, et al. Diagnostic accuracy of plasma p-tau217/Aβ42 for Alzheimer's disease in clinical and community cohorts. Alz Dement 2025;21(3):e70038.
[23] Niimi Y, Janelidze S, Sato K, Tomita N, Tsukamoto T, Kato T, et al. Combining plasma aβ and p-tau217 improves detection of brain amyloid in non-demented elderly. Alz Res Ther 2024;16:115.
[24] Liu Z, Shi D, Cai Y, Li A, Lan G, Sun P, et al. Pathophysiology characterization of Alzheimer's disease in South China's aging population: for the Greater-Bay-Area Healthy Aging Brain Study (GHABS). Alz Res Ther 2024;16:84.
[25] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI) clinical characterization. Neurology 2010;74(3):201–9.
[26] Sun P, He Z, Li A, Yang J, Zhu Y, Cai Y, et al. Spatial and temporal patterns of cortical mean diffusivity in Alzheimer's disease and suspected non-Alzheimer's disease pathophysiology. Alz Dement 2024;20(10):7048–61.
[27] Li A, Zhao R, Zhang M, Sun P, Cai Y, Zhu L, et al. [18F]-D3FSP β-amyloid PET imaging in older adults and alzheimer's disease. Eur J Nucl Med Mol Imaging 2024;51:3990–4000.
[28] Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011;305(3):275–83.
[29] Fleisher AS, Pontecorvo MJ, Devous MD, Lu M, Arora AK, Truocchio SP, et al. Positron emission tomography imaging with [18 F]flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes. JAMA Neurol 2020;77(7):829–39.
[30] Guo T, Landau SM, Jagust WJ. Detecting earlier stages of amyloid deposition using PET in cognitively normal elderly adults. Neurology 2020;94(14):e1512–24.
[31] Cai Y, Shi D, Lan G, Chen L, Jiang Y, Zhou L, et al. Association of β-amyloid, microglial activation, cortical thickness, and metabolism in older adults without dementia. Neurology 2024;102(7):e209205.
[32] Maass A, Landau S, Baker SL, Horng A, Lockhart SN, La Joie R, et al. Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. Neuroimage 2017;157:448–63.
[33] Sun P, He Z, Chu E, Fan X, Cai Y, Lan G, et al. White matter fractional anisotropy decreases precede hyperintensities in Alzheimer's disease. Cell Rep Med 2025;6:102138.
[34] Cai Y, Du J, Li A, Zhu Y, Xu L, Sun K, et al. Initial levels of β-amyloid and tau deposition have distinct effects on longitudinal tau accumulation in Alzheimer's disease. Alz Res Ther 2023;15:30.
[35] Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma p-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med 2020;26(3):379–86.
[36] Suárez-Calvet M, Karikari TK, Ashton NJ, Lantero Rodríguez J, Milà-Alomà M, Gispert JD, et al. Novel tau biomarkers phosphorylated at T181, T217 or T231 rise in the initial stages of the preclinical Alzheimer's *continuum* when only subtle changes in Aβ pathology are detected. EMBO Mol Med 2020;12(12):e12921.
[37] Mendes AJ, Ribaldi F, Lathuiliere A, Ashton NJ, Janelidze S, Zetterberg H, et al. Head-to-head study of diagnostic accuracy of plasma and cerebrospinal fluid p-tau217 versus p-tau181 and p-tau231 in a memory clinic cohort. J Neurol 2024;271:2053–66.
[38] Santos LE, Mattos P, Pinheiro TL, Silva A, Drummond C, Sudo FK, et al. Performance of plasma biomarkers for diagnosis and prediction of dementia in a Brazilian cohort. Nat Commun 2025;16:2911.
[39] Dulewicz M, Kac PR, Gonzalez-Ortiz F, Karikari TK, Kulczynska-Przybik A, Mroszko B, et al. Different phosphorylated tau isoforms in biochemical diagnosis of Alzheimer's disease. Alz Dement 2024;20(S2):e090819.
[40] Cecchetti G, Agosta F, Rugarli G, Spinelli EG, Ghirelli A, Zavarella M, et al. Diagnostic accuracy of automated Lumipulse plasma pTau-217 in Alzheimer's disease: a real-world study. J Neurol 2024;271:6739–49.
[41] Anastasi F, Fernández-Lebrero A, Ashton NJ, Ortiz-Romero P, Torres-Torronteras J, González-Escalante A, et al. A head-to-head comparison of plasma biomarkers to detect Alzheimer's disease in a memory clinic. Alz Dement 2025;21(2):e14609.
[42] Janelidze S, Bali D, Ashton NJ, Barthelemy NR, Vanbrabant J, Stoops E, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. Brain 2023;146(4):1592–601.
[43] Olvera-Rojas M, Sewell KR, Karikari TK, Huang H, Oberlin LE, Zeng X, et al. Influence of medical conditions on the diagnostic accuracy of plasma p-tau217 and p-tau217/Aβ42. Alzheimer's Dement 2025;21(2):e14430.
[44] Fowler CJ, Stoops E, Rainey-Smith SR, Vanmechelen E, Vanbrabant J, Dewit N, et al. Plasma p-tau181/Aβ1-42 ratio predicts aβ-PET status and correlates with CSF-p-tau181/Aβ1-42 and future cognitive decline. Alz Dement Diagn Assess Dis Monit 2022;14(1):e12375.
[45] Chong JR, Ashton NJ, Karikari TK, Tanaka T, Saridin FN, Reilhac A, et al. Plasma P-tau181 to Aβ42 ratio is associated with brain amyloid burden and hippocampal atrophy in an Asian cohort of Alzheimer's disease patients with concomitant cerebrovascular disease. Alz Dement 2021;17(10):1649–62.
[46] Cousins KAQ, Korecka M, Wan Y, Vulaj A, Brown C, Tropea TF, et al. Comparison of plasma p-tau217/Aβ42, p-tau217, and Aβ42/Aβ40 biomarkers by race to detect Alzheimer's disease. Alz Dement 2025;21(8):e70469.
[47] Mattsson-Carlgren N, Janelidze S, Palmqvist S, Cullen N, Svenningsson AL, Strandberg O, Mengel D, Walsh DM, Stomrud E, Dage JL, et al. Longitudinal

plasma p-tau217 is increased in early stages of Alzheimer's disease. Brain 2020;143 (11):3234–41.
[48] Palmqvist S, Insel PS, Stomrud E, Janelidze S, Zetterberg H, Brix B, et al. Cerebrospinal fluid and plasma biomarker trajectories with increasing amyloid deposition in Alzheimer's disease. EMBO Mol Med 2019;11(11):e11170.
[49] Hansson O, Edelmayer RM, Boxer AL, Carrillo MC, Mielke MM, Rabinovici GD, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alz Dement 2022;18(12):2669–86.
[50] Figdore DJ, Schuder BJ, Ashrafzadeh-Kian S, Gronquist T, Bornhorst JA. Algeciras-Schimnich A. Differences in Alzheimer's disease blood biomarker stability: implications for the use of tau/amyloid ratios. Alz Dement 2025;21(4):e70173.
[51] Bermudez C, Syrjanen JA, Stricker NH, Algeciras-Schimnich A, Kouri N, Kremers WK, et al. Impact of cardiovascular risk factors on plasma biomarkers in prediction of Alzheimer's and cerebrovascular neuropathology. J Prev Alzheimers Dis 2025;12(8):100224.
[52] Dittrich A, Ashton NJ, Zetterberg H, Blennow K, Zettergren A, Simrén J, et al. Association of chronic kidney disease with plasma NfL and other biomarkers of neurodegeneration: the H70 birth cohort study in Gothenburg. Neurology 2023; 101(3):e277–88.