Temporal dynamics and biological variability of Alzheimer biomarkers: discordance with PET imaging

Jihwan Yun, MD, PhD[1]; Daeun Shin, MD, MSc[2]; Eun Hye Lee, MD, PhD [2]; Jun Pyo Kim, MD, PhD [2]; Hongki Ham, MSc[2,6,8,9]; Yuna Gu, MSc[2,7]; Min Young Chun, MD, PhD[3,4]; Sung Hoon Kang, MD, PhD[5]; Hee Jin Kim, MD, PhD[2,6,7,8]; Duk L. Na, MD, PhD[2,10]; Chi-Hun Kim, MD, PhD[11]; Ko Woon Kim, MD, PhD[12]; Si Eun Kim, MD, PhD[13]; Yeshin Kim, MD, PhD[14]; Jaeho Kim, MD, PhD[15]; Na-Yeon Jung, MD, PhD[16]; Yeo Jin Kim, MD, PhD[17]; Soo Hyun Cho, MD, PhD[18]; Henrik Zetterberg, MD, PhD[19,20,21,22,23,24]; Kaj Blennow, MD, PhD[19,20,25,26]; Fernando Gonzalez-Ortiz[19,20]; Nicholas J Ashton[19,27,28,29]; Joseph Therriault, PhD[30,31]; Nesrine Rahmouni, MSc[30,31] ; Pedro Rosa-Neto, MD, PhD[30,31,32,33]; Michael W. Weiner, MD, PhD[33]; Sang Won Seo, MD, PhD [2,6,7,8,9*]; and Hyemin Jang, MD, PhD[34*] on behalf of the K-ROAD study groups

[1]Department of Neurology, Soonchunhyang University Bucheon Hospital, Gyeonggi-do, South Korea

[2]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam-gu, Seoul, South Korea

[3]Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea

[4]Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin, South Korea

[5]Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea

[6]Alzheimer's Disease Convergence Research Center, Samsung Medical Center, Seoul, South Korea

[7]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, South Korea

[8]Department of Digital Health, SAIHST, Sungkyunkwan University. Seoul, South Korea

[9]Department of Intelligent Precision Healthcare Convergence, Sungkyunkwan University, Suwon, South Korea

[10]Happymid Clinic, Seoul, South Korea

[11]Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, South Korea

[12]Department of Neurology, Jeonbuk National University Medical School and Hospital, Jeonju, Korea

[13]Department of Neurology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, Korea.

[14]Department of Neurology, Kangdong Sacred Heart Hospital, Seoul 05355, Republic of Korea.

[15]Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea

[16]Department of Neurology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Korea

[17]Department of Neurology, Kangwon National University College of Medicine, Chuncheon-si, Gangwon-do, Korea.

[18]Department of Neurology, Chonnam National University Medical School and Chonnam National University Hospital, Gwangju, Korea.

[19]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

[20]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden

[21]Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

[22]UK Dementia Research Institute at UCL, London, UK

[23]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China

[24]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53792, USA

[25]Paris Brain Institute, ICM, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France

[26]Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, and Department of Neurology, Institute on Aging and Brain Disorders, University of Science and Technology of China and First Affiliated Hospital of USTC, Hefei, P.R. China

[27]King's College London, Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Clinical Neuroscience Institute, London, United Kingdom

[28]NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation, London, United Kingdom

[29]Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger,

Norway

[30]McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Le Centre Intégré Universitaire de Santé et de Services Sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal

[31]Department of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada

[32]Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania

[33]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California, USA

[34]Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, South Korea

[*]These two authors contributed equally to this article as co-corresponding authors

Jihwan Yun, ORCID: 0000-0002-2436-4947

Daeun Shin, ORCID: 0000-0003-4834-1026

Eun Hye Lee, ORCID: 0000-0002-4206-6214

Jun Pyo Kim, ORCID: 0000-0003-4376-3107

Hongki Ham, ORCID: 0009-0002-0806-6453

Yuna Gu, ORCID: 0009-0007-3200-3977

Min Young Chun, ORCID: 0000-0003-3731-6132

Sung Hoon Kang, ORCID: 0000-0002-2481-0302

Hee Jin Kim, ORCID: 0000-0002-3186-9441

Duk L. Na, ORCID: 0000-0002-0098-7592

Chi-Hun Kim, ORCID: 0000-0001-8167-4530

Ko Woon Kim, ORCID: 0000-0002-4564-9714

Si Eun Kim, ORCID: 0000-0003-0429-5486

Yeo Jin Kim, ORCID: 0000-0002-6564-3774

Jaeho Kim, ORCID: 0000-0003-3770-2359

Na-Yeon Jung, ORCID: 0000-0002-8265-9508

Yeshin Kim, ORCID: 0000-0002-4643-5478

Soo Hyun Cho, ORCID: 0000-0002-4262-1468

Henrik Zetterberg, ORCID: 0000-0003-3930-4354

Kaj Blennow, ORCID: 0000-0002-1890-4193

Fernando Gonzalez-Ortiz, ORCID: 0000-0001-7897-9456

Nicholas J Ashton, ORCID: 0000-0002-3579-8804

Joseph Therriault, ORCID: 0000-0002-7826-4781

Nesrine Rahmouni, ORCID: 0009-0004-3081-8468

Pedro Rosa-Neto, ORCID: 0000-0001-9116-1376

Michael W. Weiner, ORCID: 0000-0002-0144-1954

Sang Won Seo, ORCID: 0000-0002-8747-0122

Hyemin Jang, ORCID: 0000-0003-3152-1274

Address for correspondence:

Corresponding author 1: Hyemin Jang, MD, PhD

Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

101 Daehak-ro, Jongno-gu, Seoul, 03080, South Korea

Tel.: +82-2-2072-4802, E-mail: hmjang57@snu.ac.kr

Corresponding author 2: Sang Won Seo, MD, PhD

Department of Neurology, Sungkyunkwan University School of Medicine, Samsung Medical Center, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea

Tel.: +82-2-3410-6147, Fax: +82-2-3410-0052, E-mail: sangwonseo@empal.com

Conflicts of interest:

The authors have no potential conflicts of interest to disclose.

Word count (main text): 2,976 words

Number of figures and tables: 3 figures, 2 tables

Key Points

Question What are the characteristics and clinical consequences of plasma biomarkers and Aβ or tau PET discordance?

Findings Among AD plasma biomarkers, p-tau 217 showed the highest concordance with Aβ and tau PET. P-tau 217/Aβ PET discordant cases exhibit distinctive features affecting p-tau 217 concentration. P-tau 217+/Aβ PET- displayed worse imaging, clinical features, and trajectory compared to p-tau 217-/Aβ PET-. Tau/PET discordant cases and the p-tau 217-/tau PET- group exhibited no significant differences regarding medical comorbidities or clinical outcomes.

Meaning Plasma biomarker/PET discordance has significant implications for clinical outcomes. Plasma biomarker biological variability should be considered when interpreting these discrepancies.

Abstract

Importance: Understanding the characteristics of discordance between plasma biomarkers and positron emission tomography (PET) results in Alzheimer's disease (AD) is crucial for accurate interpretation of findings.

Objectives: To compare 1) medical comorbidities affecting plasma biomarker concentrations, 2) imaging and clinical features, and 3) cognitive changes between plasma biomarker and PET discordant and concordant cases.

Design: A cross-sectional study performed between 2016 and 2023

Setting: A multi-center study

Participants: Individuals with unimpaired cognition, mild cognitive impairment, or Alzheimer's-type dementia, who had both β-amyloid (Aβ) PET imaging and plasma biomarkers. A subset of participants also underwent tau PET imaging.

Exposures: Participants were categorized into four groups based on their plasma and PET biomarker results: Plasma-/PET-, Plasma+/PET-, Plasma-/PET+, and Plasma+/PET+.

Main Outcomes and Measures: Clinical characteristics were compared between the four groups, focusing on the discordant groups.

Results: A total of 2,611 participants, of whom 124 additionally underwent tau PET, were included. The mean age was 71.2 years, and 63.4% were females. Among the plasma biomarkers, p-tau 217 exhibited the highest concordance rate with Aβ (2,326/2,571, 90.5%) and tau (100/120, 83.3%) PET. The p-tau 217+/Aβ PET- group was older (70.0 vs.75.8; *P* <.001) with a higher prevalence of hypertension, DM, and chronic kidney disease compared to the p-tau 217-/Aβ PET- group (25.0% vs. 36.8%; 14.7% vs. 26.3%; 2.0% vs. 11.2%, *P*< .001 for all). Body mass index was higher in p-tau 217-/Aβ PET+ than in p-tau 217+/Aβ PET+ (24.1±2.8 vs. 23.1±3.1; *P*

= .001). The p-tau 217+/Aβ PET- group had lower hippocampal volume (2979.1 ± 545.8 vs. 2555.4 ± 576.9; *P* <.001) and worse clinical trajectory compared to p-tau 217-/Aβ PET- (β=-0.5341; *P* <.001). In contrast, tau PET discordant cases did not show significant differences in medical comorbidities or clinical outcomes compared to the p-tau 217-/tau PET- group. Only the p-tau 217+/tau PET+ group demonstrated faster cognitive deterioration compared to the p-tau 217-/tau PET- group (β= -1.655; *P* <.001).

Conclusions and Relevance: The mechanisms underlying the discordance between plasma biomarkers and PET findings may be multifaceted, underscoring the need to consider the temporal dynamics and biological variability of plasma biomarkers.

Introduction

Recent advances in biochemical technology have facilitated the detection of plasma biomarkers reflective of various Alzheimer's disease (AD) pathologies, including beta-amyloid (Aβ), hyperphosphorylated tau, neuroinflammation, and neurodegeneration.[1-3] Specifically, both plasma Aβ42/40 and phosphorylated-tau (p-tau) species have demonstrated high accuracy for predicting Aβ positron emission tomography (PET) positivity. Additionally, p-tau epitopes have shown good to excellent performances in predicting tau uptakes on PET.[4-6] Among these, p-tau217 has attracted significant attention due to its superior efficacy compared to other biomarkers.[7-11] Several studies indicated that p-tau217 is independently associated with both Aβ and tau PET and mediates the association between Aβ and tau, suggesting that it is involved in Aβ-dependent tau accumulation.[8,12,13]

Previous research has suggested that the discordance between fluid biomarkers and PET imaging might be related to temporal mismatch. Specifically, fluid biomarkers detect the soluble form of Aβ, which appears before the insoluble form of fibrillar Aβ that is detected by Aβ PET. Alternatively, medical comorbidities that could affect plasma biomarker concentrations might contribute to plasma and PET discordance. In fact, chronic kidney disease (CKD) and increased body mass index (BMI) could contribute biologically to increased and decreased plasma biomarker concentrations, respectively. Furthermore, discordance between plasma biomarkers and PET might vary according to types of pathologies that the plasma biomarkers and PET are reflecting. With a requirement for the clinical integration of various plasma biomarkers for AD, a thorough understanding of the characteristics and consequences of discordances between each plasma biomarker and PET imaging is crucial to accurately interpret biomarker test results. Furthermore, this investigation

may provide insight into the temporal dynamics and clinical variability of plasma biomarkers in research and clinical practice.

Therefore, in the present study, we aimed to investigate the frequency of discordance between plasma biomarkers and PET imaging of Aβ and tau. Additionally, we compared clinical characteristics, including medical comorbidities that affect the concentration of plasma biomarkers; imaging and clinical features; and cognitive trajectories, between plasma biomarker and PET discordant and concordant cases.

Methods

Participants

The study included 2,611 individuals from the Korea Registries to Overcome dementia and Accelerate Dementia research cohort (K-ROAD).[14] The participants comprised cognitively unimpaired (CU) individuals, and individuals with mild cognitive impairment (MCI) and dementia of Alzheimer's type (DAT). Cognitively Unimpaired (CU) individuals were recruited from both the general population and a memory clinic using the same criteria. Cognitively Impaired (CI) individuals were recruited from a specialized center. The detailed diagnostic criteria and processes are described in eMethods 1.

This study was approved by the institutional review board of Samsung Medical Center (No. 2021-02-135). All participants provided written informed consent to participate in the study, and data were collected according to the Declaration of Helsinki.

Aβ PET acquisition and quantification

Each participant underwent Aβ PET scan using either ^{18}F-florbetaben or ^{18}F-flutemetamol PET, following the manufacturer's imaging guidelines. Aβ uptake was quantified using the regional direct comparison Centiloid (rdcCL) method, which was developed in a previous study.[15] Aβ PET positivity was defined using a global magnetic resonance imaging (MRI)-based rdcCL threshold of 25.5. The detailed guidelines and methods for analyses are described in eMethods 2.

Tau PET acquisition and quantification

A series of scans were conducted 80 min after administering a typical 280 MBq dose of ^{18}F-flortaucipir. For tau uptake analysis, temporal meta-regions of interest (ROIs) were defined, encompassing the entorhinal cortex, amygdala, fusiform gyrus, parahippocampal gyrus, and the inferior and middle temporal gyri. A tau PET positivity threshold was set at an SUVR of 1.38 in these ROIs, which is two standard deviations above the mean SUVR of the same regions in Aβ PET- CU participants. The detailed guidelines and methods for analyses are described in eMethods 3.

Plasma collection and processing

Blood was drawn and laced in tubes containing 0.5 M ethylenediaminetetraacetic acid (eMethods 4). The samples were centrifuged at 1300×*g* for 10 min, separated into 0.3 mL-vial, and then stored at -75 ºC. The interval between plasma collection and Aβ PET scan ranged from 0 to 69 days, with a mean of 4 days. The plasma samples were maintained at a temperature of -70 ºC during transportation to the Department of Psychiatry and Neurochemistry at the University of Gothenburg, where they were subsequently analyzed. Upon arrival, the

samples were thawed on wet ice and centrifuged at 500×*g* for 5 min at 4 ºC. The plasma Aβ40 and Aβ42 were measured using the Neurology 4-Plex E kit (Quanterix, Billerica, MA, USA). The concentrations of plasma p-tau 181 and p-tau 231 were assessed using Simoa assays developed by the University of Gothenburg. The p-tau 217 levels were measured using the commercial ALZpath kit. All measurements were conducted by analysts who were blinded to the clinical backgrounds, and a single batch of reagents was utilized in one experimental session. The intra-assay variability for these biomarker tests was maintained below 10%.

Definition of abnormal plasma Aβ 42/40 and p-tau biomarkers cutoff

To determine the plasma biomarker thresholds for Aβ and tau PET positivity, logistic regression analyses were conducted in the same cohort, followed by receiver operating characteristic analyses to identify the cut-off values that maximize the Youden index, thereby optimizing the balance between sensitivity and specificity. The plasma biomarker cutoffs for Aβ PET positivity were 0.060 for Aβ 42/40, 6.22 for p-tau 181, 0.46 for p-tau 217, and 8.35 for p-tau 231. The cutoffs for tau PET positivity were 0.058 for Aβ 42/40, 8.06 for p-tau 181, 0.92 for p-tau 217, and 10.6 for p-tau 231. The plasma biomarker levels according to Aβ and tau PET positivity and the ROC results are described in **eFigure 1** and **eTable 1**.

Brain MRI and hippocampal volume assessment

All participants underwent 3D T1 turbo field echo imaging with sagittal slice thickness of 1.0 mm with a 50% overlap. The hippocampal volume (HV) was measured using an automated hippocampus segmentation method that combined a graph cut algorithm with an atlas-based segmentation and morphological opening as

previously described.[16]

Other measurement variables

The medical records and/or reliable informants provided information regarding the status of vascular risk factors, including hypertension, diabetes mellitus (DM), hyperlipidemia, ischemic stroke, and CKD. The BMI and systolic/diastolic blood pressure (SBP/DBP) were obtained from the medical records. The laboratory findings including low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1c), and estimated glomerular filtration rate (eGFR) within seven days from the date of plasma sampling were collected from medical records of participants.

Longitudinal Follow-up

A subset of 1,872 who underwent two or more assessments employing mini–mental state examination (MMSE) was included in the MMSE longitudinal analysis, while 1,686 participants were included in Clinical dementia rating sum of boxes (CDR-SB) analysis. Retrospective and prospective MMSE and CDR-SB scores were obtained relative to the time of blood sampling. The mean follow-up period was 3.63 (range 0.5 to 21.4) years and 3.10 (range 0.5 to 17.4) years for the MMSE and CDR-SB analyses, respectively.

External validation using two independent cohorts

For external validation, we utilized data from the TRIAD (N=274) and ADNI (N=378) cohorts, with detailed procedures described in **eMethods 5**. Briefly, in TRIAD, Aβ PET positivity was defined by a global ^{18}F-AZD4694 SUVR of 1.55, (24 Centiloids), and tau PET positivity by a ^{18}F-MK6240 PET temporal meta-ROI SUVR

threshold of 1.18. In ADNI, Aβ PET positivity was defined by a global ^{18}F-flortaucipir SUVR threshold of 1.11 (22.5 Centiloids), while tau PET positivity was defined by ^{18}F-flortaucipir meta-temporal ROI SUVR threshold of 1.34. Both cohorts used SIMOA for p-tau217 measurements, with TRIAD employing University of Gothenburg assays and ADNI using the Quanterix platform. Plasma p-tau217 cutoffs for Aβ and tau PET positivity were established using ROC analyses, maximizing the Youden index. Thus, we validated the main analyses in both cohorts and the combined cohort (K-ROAD + TRIAD + ADNI) based on p-tau217/PET concordance. However, data of vascular risk factors and comorbidities were unavailable in the ADNI cohort.

Statistical analysis

Participants were categorized into four groups according to plasma and PET positivity (plasma-/PET−, plasma+/PET−, plasma-/PET+, and plasma+/PET+). The concordance rate was defined as the proportion of participants with matching plasma and results (either plasma-/PET− or plasma+/PET+) for amyloid or tau, relative to the total number of participants analyzed. Clinical characteristics—including biological factors and biomarker profiles—were compared between discordant and concordant groups (plasma−/amyloid or tau PET− vs. plasma+/amyloid or tau PET− and plasma−/ amyloid or tau PET+ vs. plasma+/ amyloid or tau PET+) using independent samples t-test and Kruskal–Wallis tests for continuous variables and chi-square and Fisher's exact tests for categorical variables. Linear mixed model analysis was used to investigate whether the four groups exhibited different cognitive trajectories, with fixed effects that included age, *APOE* ε4 carrier status, group, time, and the group by time interaction term. A random-effects model was used to account for repeated measures among participants. Subgroups with fewer than 10 participants were

excluded from the analysis due to the limited sample size. A false discovery rate (FDR) of 0.05 was used to correct for multiple comparisons. All tests were two-sided, and statistical significance was set at $P < .05$. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R (version 4.3.2) and R studio (version 2023.12.0+369).

Results

Characteristics of study participants

A total of 2,611 participants (mean age: 71.2 years; women: 63.4%) were included in the plasma/Aβ PET discordance study (**eTable 2**). The proportions of CU, MCI, and DAT were 24.4% (n=636), 52.4% (n=1,369), and 23.2% (n=606), respectively. A subset of participants (n=124) was included in the plasma/tau PET discordance study (**eTable 2**). Characteristics of study participants included in longitudinal analyses are described in **eTable 3 & 4**. The associations between vascular risk factors, comorbidities, p-tau217 levels, and longitudinal MMSE changes are detailed in eResults1.

Discordance of plasma biomarkers with Aβ PET

Plasma p-tau 217 exhibited the highest concordance rate of 90.5% with Aβ PET (**Figure 1A**), followed by p-tau 231 (77.4%), 181 (77.1%), and the Aβ 42/40 ratio (76.0%) (**eFigure 3A1-3**). The p-tau 217+/Aβ PET- group was older compared to the other groups, and had higher prevalence of hypertension, DM, hyperlipidemia, and CKD, with the lowest eGFR compared to p-tau 217-/Aβ PET- group ($P < .05$, for all) (**Table 1**). The p-tau 217-/Aβ PET+ group had a higher BMI than that of the p-tau

217+/Aβ PET+ group (*P* = .001). The p-tau 217+/Aβ PET+ group exhibited the most rapid cognitive deterioration including MMSE and CDR-SB (**Figure 1B**). Among the discordant groups, the p-tau 217+/Aβ PET- group demonstrated a faster decline than that in the p-tau 217-/Aβ PET- group (**Figure 1B**).

Details of a sensitivity analysis and the subgroup analyses based on age, cognitive stage, and other dementia types are provided in eResults2.

Discordance of plasma biomarkers with tau PET

P-tau 217 exhibited the highest concordance rate of 83.1% with Tau PET (**Figure 2A**), followed by p-tau 181 (77.2%), 231 (71.2%), and the Aβ 42/40 ratio (64.3%) (**eFigure 3B1-3**). The pairwise comparison of age and major vascular risk factors showed no statistically significant differences across the groups (**Table 2**). The p-tau 217+/tau PET+ group demonstrated the fastest cognitive deterioration including MMSE and CDR-SB, while the discordant groups did not exhibit significant differences in cognitive trajectories compared to the p-tau 217-/tau PET- group (**Figure 2B**).

External validation using independent cohorts

Concordance rates between pTau217 and Aβ PET were high as 86.9% in TRIAD and 81.4% in ADNI (**Figure 1A**). In both, the p-tau217+/Aβ PET- group was the oldest, consistent with K-ROAD. In TRIAD, the p-tau217+/Aβ PET- group had a higher prevalence of hypertension and lower eGFR than the p-tau217-/Aβ PET- group ($P < 0.05$) (Table 1). In both cohorts, p-tau217+/Aβ PET+ group showed the fastest cognitive decline, and p-tau217+/Aβ PET- also had faster CDR-SB decline than p-tau217-/Aβ PET- in ADNI (**Figure 1B**). Combining cohort confirmed faster

cognitive decline in p-tau217-/Aβ PET+ compared to p-tau217-/Aβ PET- (**Figure 3A**).

Plasma p-tau217 and tau PET concordance rates were 84.7% in TRIAD and 75.9% in ADNI (**Figure 2A**). The p-tau217+/tau PET- group was older than the p-tau217-/tau PET- group (Table 2). Again, p-tau217+/tau PET+ showed the fastest decline (**Figure 2A**). Combining cohort confirmed faster decline in p-tau217-/tau PET+ compared to p-tau217-/tau PET- (**Figure 3B**).

When considering all three biomarkers, the plasma+/Aβ PET+/tau PET+ group had the most rapid cognitive decline (**Figure 3C**).

Discussion

The present study aimed to investigate the characteristics of discordance between plasma biomarkers and PET reflecting AD pathologies in terms of medical comorbidities and clinical outcomes. Our findings revealed that in the case of Aβ PET, p-tau 217 and PET discordant groups had distinctive medical comorbidities that may influence the p-tau 217 concentration compared to the concordant groups. Furthermore, the p-tau 217+/Aβ PET- group exhibited worse clinical outcomes compared to the p-tau 217-/Aβ PET- group. In contrast, tau PET discordant cases did not exhibit significant differences in medical comorbidities or clinical outcomes compared to the p-tau 217-/tau PET- group. However, after combining the three Tau PET cohorts, the p-tau217-/tau PET+ group showed a faster decline than the tau PET- group. Taken together, these findings suggest that the mechanisms underlying discordance between plasma biomarkers and PET reflecting AD pathologies may be heterogeneous, underscoring the importance of considering the temporal dynamics

and biological variability of plasma biomarkers in research and clinical practice.

Our conclusion that the mechanisms underlying the discordance between p-tau epitopes and Aβ PET may be heterogeneous could be explained by some of our findings. Specifically, the p-tau 217+/Aβ PET- group was older with a higher prevalence of vascular risk factors or medical comorbidities including hypertension, DM, and CKD compared to the p-tau 217-/Aβ PET- group, which might contribute biologically to increased discordance rates. It has been reported that age and CKD reduce total blood volume and the clearance rate of proteins, which may potentially lead to an increase in plasma biomarker levels.[17,18] Despite these findings, the p-tau217+/Aβ PET- group demonstrated worse clinical outcomes compared to the p-tau217-/Aβ PET- group, which may be explained by a temporal mismatch between p-tau217 and Aβ PET. The soluble form of the biomarker, reflected by p-tau217, likely appears earlier in the disease process than the insoluble form seen on PET, contributing to the more severe clinical outcomes. In fact, a recent study suggested that peak relative changes in p-tau epitopes might occur earlier than those in Aβ-PET uptake, suggesting that p-tau epitopes might precede Aβ-PET uptake.[19] There is a possibility that advanced age and vascular risk factors in the p-tau217+/Aβ PET- group may contribute to faster cognitive decline. However, our data showed no significant effects of vascular comorbidities on cognitive trajectories (eTable5), supporting the temporal mismatch explanation. Furthermore, in both younger and older age groups, the p-tau217+/Aβ PET- group consistently showed faster cognitive decline compared to the p-tau217-/Aβ PET- group (eFigure6).

We also found that the p-tau217-/Aβ PET+ group had a higher BMI compared to the p-tau217+/Aβ PET+ group, which could contribute to the increased discordance rates. This is likely because higher BMI decreases p-tau217

concentrations by increasing total blood volume.[20-22] Additionally, while Aβ positivity in the p-tau217-/Aβ PET+ group may be incidental due to age or the early stages of AD, their younger age compared to the p-tau217+/Aβ PET- group suggests that they are more likely in the early stages of AD. Comparison of the p-tau217-/Aβ PET+ and p-tau217+/Aβ PET+ group revealed differences in Aβ uptake, tau PET positivity (16.7% vs. 69.6%), hippocampal volumes, MMSE, and CDR-SB scores (Table1 and eFigure 4), indicating that the p-tau217+/Aβ PET+ group is more advanced. The steepest MMSE decline in the p-tau217+/Aβ PET+ group further supports its more advanced stage of AD.

Our study found that p-tau217 had the highest concordance rate with tau PET scans (83.1%) among several plasma biomarkers. No significant differences were observed in clinical outcomes between discordant groups and the p-tau217-/tau PET- group. In external validation, p-tau217 and tau PET concordance rates were confirmed to be 84.7% in the TRIAD cohort and 75.9% in the ADNI cohort. The p-tau217+/tau PET+ group consistently exhibited the fastest cognitive decline across cohorts. Moreover, combining the Tau PET cohorts revealed that the p-tau217-/tau PET+ group experienced a more rapid cognitive decline compared to the p-tau217-/tau PET- group, underscoring the value of integrating plasma and PET biomarkers for predicting disease progression. These relatively benign characteristics of the p-tau 217-/tau PET+ group suggest that some of these patients may have Primary Age-Related Tauopathy (PART). However, given that 90% of the group is Aβ positive, PART alone cannot fully explain the observed discordance.

The present study has several strengths. We included a large cohort that underwent plasma biomarker testing and Aβ PET imaging as well as extensive biological factors affecting plasma biomarker levels and validated the findings using

external cohorts. Nevertheless, this study possesses some limitations. First, pathological verification was lacking. Although we proposed the possibility of other pathologies in the discordant cases, we did not confirm their presence. Second, the study participants underwent Aβ PET using different types of tracers. Although the diversity of tracer types could affect the proportions of Aβ positivity, we consider that this bias is minimal given the very high correlations between Aβ PET tracers[23], and we used the CL method for harmonization. Third, the small sample size in the tau PET study was initially thought to cause nonsignificant differences in cognitive decline, but after combining the multiple tau PET cohorts, the p-tau217-/tau PET+ group showed a faster decline than the tau PET- group. Fourth, the present study did not include data on socioeconomic factors and other variables that could potentially affect plasma biomarkers. Finally, in non-AD participants, medical comorbidities and cognitive trajectories between p-tau217/PET concordant/discordant groups were less distinct, likely due to underlying co-pathologies. Therefore, caution is needed when generalizing these findings to non-AD populations (eTable 10 & 11 and eFigure8).

In summary, our study suggests that the mechanisms underlying the discordance between plasma biomarkers and PET reflective of AD pathologies may be heterogeneous. As such, our findings highlight the significance of temporal dynamics of plasma biomarkers in research and clinical practice.

Acknowledgement

Author contributions

JY, SS, and HJ conceptualized and designed the study and drafted the manuscript. JY, SS, and HJ accessed and verified the data. DS, EL, JK, MC, SK, HK, DLN, CK, KK, SK, YK, JK, NJ, YK, SC, JT, NR, PRN and MWW acquired the data. HH and YG contributed to data curation and analysis. SS and HJ interpreted the data, with JY handling statistical analysis. Funding was obtained by HZ, KB, SS, and HJ. The manuscript was revised by SS, and HJ and HJ supervised the study.
All authors contributed to the final manuscript and were involved in the decision to submit for publication.

Data sharing

The anonymized data for the analyses presented in this report are available upon request from the corresponding authors.

Funding

HZ is a Wallenberg scholar and a distinguished professor at the Swedish Research Council supported by grants from the Swedish Research Council (#2023-00356, #2022-01018, and #2019-02397), European Union’s Horizon Europe research and innovation program under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C, and #ADSF-24-1284328-C), Bluefield Project, Cure Alzheimer’s Fund, Olav Thon Foundation, Erling-Persson Family Foundation, Familjen Rönströms Stiftelse,

Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and the UK Dementia Research Institute at UCL (UKDRI-1003).

KB is supported by the Swedish Research Council (#2017-00915 and #2022-00732), Swedish Alzheimer Foundation (#AF-930351, #AF-939721, #AF-968270, and #AF-994551), Hjärnfonden, Sweden (#FO2017-0243 and #ALZ2022-0006), Swedish state under the agreement between the Swedish government and the County Councils, ALF-agreement (#ALFGBG-715986 and #ALFGBG-965240), European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236), Alzheimer's Association 2021 Zenith Award (ZEN-21-848495), Alzheimer's Association 2022–2025 Grant (SG-23-1038904 QC), La Fondation Recherche Alzheimer (FRA), Paris, France, Kirsten and Freddy Johansen Foundation, Copenhagen, Denmark, and Familjen Rönströms Stiftelse, Stockholm, Sweden.

Avid Radiopharmaceuticals, Inc., a wholly owned subsidiary of Eli Lilly and Company, enabled the use of the 18F-flortaucipir tracer by providing a precursor, but did not provide direct funding and was not involved in data analysis or interpretation

SS is supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare and Ministry of science and ICT, Republic of Korea (grant number: RS-2022-KH127756), a grant of the Korea Dementia Research Project through the Korea Dementia Research Center (KDRC), funded by the Ministry of Health &

Welfare and Ministry of Science and ICT, Republic of Korea (RS-2020-KH106434), Future Medicine 20*30 Project of the Samsung Medical Center [#SMX1240561], the "Korea National Institute of Health" research project (2024-ER1003-00), the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2019R1A5A2027340) and Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (MSIT) (No.RS-2021-II212068, Artificial Intelligence Innovation Hub)
HJ is supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare and Ministry of science and ICT, Republic of Korea (grant number: RS-2022-KH125667) and a grant of the Korea Dementia Research Project through the Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (RS-2020-KH107436)

Declaration of interest

HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has delivered lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, 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). KB has served as a consultant and was on advisory boards for Abbvie, AC Immune, ALZPath, AriBio,

BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served on data monitoring committees for Julius Clinical and Novartis; has delivered lectures, produced educational materials, and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai, and Roche Diagnostics, 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.

Table 1. Clinical Characteristics of P-tau 217/Aβ PET Concordant and Discordant Groups

	K-ROAD						TRIAD cohort						ADNI cohort					
	p-tau217 -/Aβ PET- (N = 1,073)	p-tau217 +/ Aβ PET - (N = 152)	*P* value	p-tau217 -/ Aβ PET + (N = 93)	p-tau217 +/ Aβ PET + (N = 1,253)	*P* value	p-tau217 -/Aβ PET- (N = 152)	p-tau217 +/ Aβ PET - (N = 13)	*P* value	p-tau217 -/ Aβ PET + (N = 23)	p-tau217 +/ Aβ PET + (N = 86)	*P* value	p-tau217 -/Aβ PET- (N = 186)	p-tau217 +/ Aβ PET - (N = 35)	*P* value	p-tau217 -/ Aβ PET + (N = 35)	p-tau217 +/ Aβ PET + (N = 122)	*P* value
Demographics																		
Age, years	70.0 ± 8.8	75.8 ± 7.2	<.001	71.5 ± 7.0	71.7 ± 8.6	0.793	60.0 ± 19.4	71.3 ± 11.3	0.005	69.2 ± 10.7	68.8 ± 8.2	0.837	71.7 ± 6.7	78.7 ± 6.6	<.001	72.7 ± 5.4	76.4 ± 7.2	0.006
Sex, female, n (%)	666 (62.1)	82 (53.9)	0.067	63 (67.7)	822 (65.6)	0.759	98 (64.5%)	5 (38.5%)	0.119	16 (69.6%)	52 (60.5%)	0.577	94 (50.5%)	17 (48.6%)	0.977	22 (62.9%)	51 (41.8%)	0.045
Education, years	10.9 ± 4.8	10.3 ± 5.3	0.176	10.8 ± 4.3	10.6 ± 4.7	0.91	15.6 ± 3.4	15.0 ± 3.8	0.533	14.5 ± 4.2	15.1 ± 3.0	0.524	16.4 ± 2.8	17.3 ± 2.6	0.061	16.1 ± 2.4	16.1 ± 2.6	0.94
APOE ε4 carriers, n (%)	175 (16.4)	27 (17.9)	0.722	44 (47.3)	769 (61.5)	0.009	42 (27.6%)	2 (16.7%)	0.626	10 (43.5%)	49 (57.0%)	0.358	38 (20.4%)	6 (17.1%)	0.829	17 (48.6%)	66 (54.1%)	0.7
Diagnosis																		
CU/MCI/DAT, n (%)	453/546/74 42.2/50.9/6.9	30/98/24 19.7/64.5/15.8	<.001	33/48/12 35.5/51.6/12.9	117/652/484 9.3/52.0/38.6	<.001	134/17/1 (88.2/11.2/0.7)	6/5/2 (46.2/38.5/15.4)	<.001	(65.2/21.7/13.0)	(27.9/38.4/33.7)	0.004	113/73/0 (60.8/39.2/0.0)	22/10/3 (62.9/28.6/8.6)	<.001	24/8/3 (68.6/22.9/8.6)	50/57/15 (41.0/46.7/12.3)	0.015
Vascular risk factors																		
HTN, n (%)	266 (25.0)	56 (36.8)	0.003	26 (28.6)	374 (30.1)	0.848	48 (33.3%)	10 (83.3%)	0.002	8 (40.0%)	29 (36.2%)	0.959						
DM, n (%)	156 (14.7)	40 (26.3)	<.001	9 (9.9)	171 (13.7)	0.379	10 (6.9%)	0 (0.0%)	0.741	2 (10.0%)	4 (5.0%)	0.752						
Hyperlipidemia, n (%)	270 (25.9)	54 (36.0)	0.012	26 (29.5)	396 (32.2)	0.695												
Lacunar infarction, n (%)	23 (2.2)	3 (2.0)	1	3 (3.3)	31 (2.5)	0.89												
CKD, n (%)	21 (2.0)	17 (11.2)	<.001	1 (1.1)	22 (1.8)	0.941												
BMI, kg/m^2	24.2 ± 3.0	23.9 ± 3.5	0.059	24.1 ± 2.8	23.1 ± 3.1	0.001	26.8 ± 5.3	27.5 ± 5.1	0.679	26.7 ± 4.1	27.0 ± 5.7	0.843						
SBP, mmHg	130.1 ± 17.6	129.4 ± 18.4	0.854	130.8 ± 13.4	128.4 ± 17.7	0.225												
DBP, mmHg	70.3 ± 11.6	67.2 ± 12.7	0.093	70.1 ± 8.5	69.2 ± 10.8	0.408												

HbA1c, IFCC, %	6.0 ± 0.8	6.2 ± 1.2	0.161	6.1 ± 1.0	5.9 ± 0.7	0.309												
LDL-C, mg/dL	101.5 ± 32.2	93.6 ± 31.8	0.015	103.2 ± 36.2	104.5 ± 31.7	0.571												
eGFR, ml/min	88.0 ± 18.3	70.2 ± 23.5	<.001	88.4 ± 14.9	86.5 ± 19.0	0.317	96.9 ± 15.9	78.1 ± 17.3	0.002	93.3 ± 12.6	89.6 ± 13.8	0.323						
WMH volume, mm^3	1843.9 [424.6;5271.6]	3398.3 [402.0;7372.7]	0.118	2061.5 [398.4;3492.9]	2855.8 [1223.4;7114.6]	0.05												
AD pathology																		
Aβ uptake (Global CL)	1.2 ± 9.6	2.7 ± 12.1	0.199	55.5 ± 30.2	100.4 ± 34.9	<.001	2.7 ± 7.0	12.3 ± 11.5	0.012	59.6 ± 31.4	74.7 ± 27.5	0.026	3.3 ± 10.3	4.6 ± 13.6	0.287	45.6 ± 24.0	74.6 ± 36.1	<.001
Tau SUVR (Meta ROI)	1.2 ± 0.1	1.4 ± 0.4	0.602	1.3 ± 0.2	1.8 ± 0.6	0.032	0.9 ± 0.2	1.3 ± 0.8	0.176	1.2 ± 0.5	1.8 ± 0.9	<.001						
Tau PET Positivity (%)	1 (7.1%)	2 (33.3%)	0.412	1 (16.7%)	64 (69.6%)	0.027	2 (1.3%)	2 (15.4%)	0.026	4 (17.4%)	54 (62.8%)	<.001						
Hippocampal volume, mm^3	2979.1 ± 545.8	2555.4 ± 576.9	<.001	2824.4 ± 623.4	2422.2 ± 549.2	<.001												
MMSE	26.6 ± 3.4	24.6 ± 4.4	<.001	26.1 ± 2.9	22.4 ± 5.1	<.001	29.2 ± 1.3	27.6 ± 2.4	0.033	27.3 ± 4.7	25.6 ± 5.3	0.16	29.0 ± 1.5	28.9 ± 1.6	0.577	28.1 ± 2.5	27.5 ± 2.4	0.157
CDR-SB	1.3 ± 1.7	2.1 ± 2.1	<.001	1.6 ± 1.4	3.5 ± 3.1	<.001	0.3 ± 0.8	1.2 ± 1.6	0.054	1.2 ± 2.4	2.7 ± 3.1	0.035	0.6 ± 0.9	0.8 ± 1.5	0.898	0.9 ± 1.8	1.5 ± 1.7	<.001

Abbreviations: Aβ, β-amyloid; CU, Cognitively Unimpaired; MCI, Mild Cognitive Impairment; DAT, Dementia of the Alzheimer Type; HTN, Hypertension; DM, Diabetes Mellitus; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; AD, Alzheimer's disease; CL, Centiloid; ROI, Regions of Interest; SUVR, Standardized Uptake Value Ratio; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

Values are presented as mean ± standard deviations, number (percentages), and median (interquartile range), appropriately

Table 2. Clinical Characteristics of P-tau 217/Tau PET Concordant and Discordant Groups

	K-ROAD cohort						TRIAD cohort						ADNI cohort					
	p-tau217 -/tau PET- (N = 40)	p-tau217 +/tau PET- (N = 10)	*P* value	p-tau217 -/tau PET+ (N = 10)	p-tau217 +/tau PET+ (N = 60)	*P* value	p-tau217 -/Tau PET- (N = 176)	p-tau217 +/ Tau PET - (N = 34)	*P* value	p-tau217 -/ Tau PET + (N = 7)	p-tau217 +/ Tau PET + (N = 57)	*P* value	p-tau217 -/Tau PET- (N = 166)	p-tau217 +/ Tau PET - (N = 59)	*P* value	p-tau217 -/ Tau PET + (N = 8)	p-tau217 +/ Tau PET + (N = 47)	*P* value
Demographics																		
Age, years	73.3 ± 6.0	74.0 ± 7.2	0.769	70.9 ± 7.3	69.2 ± 9.2	0.57	61.8 ± 18.6	70.9 ± 9.4	<.001	61.7 ± 19.8	67.3 ± 8.0	0.486	74.8 ± 6.6	80.1 ± 7.5	<0.001	80.8 ± 7.1	77.5 ± 7.5	0.251
Sex, female, n (%)	17 (42.5)	6 (60.0)	0.523	7 (70.0)	39 (65.0)	1	114 (64.8%)	18 (52.9%)	0.266	5 (71.4%)	34 (59.6%)	0.847	86 (51.8%)	21 (35.6%)	0.047	4 (50.0%)	24 (51.1%)	1
Education, years	11.4 ± 4.6	10.7 ± 6.2	0.95	10.9 ± 4.1	12.0 ± 4.3	0.415	15.5 ± 3.6	14.9 ± 3.2	0.392	15.3 ± 4.2	15.1 ± 2.7	0.875	16.5 ± 2.8	16.5 ± 2.6	0.909	16.6 ± 2.1	16.0 ± 2.4	0.512
APOE e4 carriers, n (%)	14 (35.0)	7 (70.0)	0.099	6 (60.0)	38 (63.3)	1	50 (28.4%)	11 (33.3%)	0.717	4 (57.1%)	38 (66.7%)	0.937	46 (27.7%)	18 (30.5%)	0.809	2 (25.0%)	27 (57.4%)	0.188
Diagnosis																		
CU/MCI/DAT, n (%)	17/21/2 (42.5/52.5/5.0)	5/3/2 (50.0/30.0/20.0)	0.202	0/4/6 (0.0/40.0/60.0)	4/24/32 (6.7/40.0/53.3)	0.692	150/25/1 (85.2/14.2/0.6)	21/12/1 (61.8/35.3/2.9)	0.005	2/2/3 (28.6/28.6/42.9)	6/21/30 (10.5/36.8/52.6)	0.395	115/46/5 (69.3/27.7/3.0)	39/14/6 (66.1/23.7/10.2)	0.087	3/4/1 (36.5/50.0/12.5)	15/17/15 (21.9/36.2/31.9)	0.524
Vascular risk factors																		
HTN, n (%)	22 (56.4)	6 (60.0)	1	4 (40.0)	26 (44.1)	1	59 (35.5%)	16 (51.6%)	0.136	1 (16.7%)	19 (35.8%)	0.627						
DM, n (%)	13 (33.3)	2 (20.0)	0.666	2 (20.0)	11 (18.6)	1	12 (7.2%)	1 (3.2%)	0.667	1 (16.7%)	2 (3.8%)	0.702						
Hyperlipidemia, n (%)	25 (64.1)	3 (30.0)	0.113	2 (20.0)	28 (47.5)	0.202												
Lacunar infarction, n (%)	4 (10.3)	1 (10.0)	1	1 (10.0)	0 (0.0)	0.31												
CKD, n (%)	0 (0.0)	0 (0.0)	1	0 (0.0)	3 (5.0)	1												
BMI, kg/m^2	24.1 ± 2.9	24.0 ± 3.4	0.747	24.8 ± 4.0	23.4 ± 3.6	0.362	26.9 ± 5.2	26.2 ± 5.9	0.491	29.1 ± 2.5	27.0 ± 5.5	0.409						
SBP, mmHg	134.2 ± 15.2	112.8 ± 32.8	0.256	129.8 ± 17.1	133.6 ± 24.4	0.706												
DBP, mmHg	70.7 ± 15.4	66.0 ± 23.5	0.737	66.7 ± 3.9	71.8 ± 14.1	0.423												
HbA1c, IFCC, %	6.1 ± 1.0	5.3 ± 0.0	1	5.9 ± 0.3	6.2 ± 0.8	0.764												

LDL-C, mg/dL	89.3 ± 33.0	139.5 ± 26.2	0.111	91.3 ± 33.1	96.7 ± 32.8	1											
eGFR, ml/min	83.7 ± 14.0	81.7 ± 10.8	0.53	94.4 ± 20.3	86.1 ± 20.2	0.406	96.0 ± 15.9	86.5 ± 16.9	0.009	94.9 ± 8.0	90.0 ± 13.0	0.419					
WMH volume, mm^3	2133.1 [480.3;6164.9]	2778.5 [854.1;6503.6]	0.897	1228.3 [814.1;1750.4]	2413.5 [483.3;4863.6]	0.26											
AD pathology																	
Aβ uptake (Global CL)	56.4 ± 54.0	84.0 ± 48.4	0.181	87.7 ± 43.5	103.2 ± 34.6	0.416	10.3 ± 21.9	46.0 ± 29.8	<.001	46.4 ± 48.4	81.8 ± 28.4	0.103	11.3 ± 21.8	49.6 ± 37.7	<0.001	23.2 ± 28.4	87.6 ± 37.2	<0.001
Amyloid positivity, n (%)	25 (62.5%)	8 (80.0%)	0.502	9 (90.0%)	58 (96.7%)	0.904	23 (13.1%)	26 (76.5%)	<.001	4 (57.1%)	55 (96.5%)	0.004	37 (22.3%)	44 (74.6%)	<0.001	4 (50.0%)	44 (93.6%)	0.004
Tau uptake (meta-ROI SUVR)	1.2 ± 0.1	1.3 ± 0.1	0.158	1.7 ± 0.3	2.2 ± 0.5	0.01	0.9 ± 0.1	1.0 ± 0.1	0.001	1.9 ± 0.7	2.3 ± 0.9	0.209	1.2 ± 0.1	1.2 ± 0.1	0.361	1.4 ± 0.1	1.7 ± 0.5	<0.001
Hippocampal volume, mm^3	2813.0 ± 509.0	2704.1 ± 503.4	0.665	2239.6 ± 561.9	2296.5 ± 594.9	0.895											
MMSE	25.8 ± 4.1	25.4 ± 4.2	0.722	23.0 ± 4.3	20.2 ± 6.4	0.236	29.1 ± 1.2	28.7 ± 1.6	0.113	23.0 ± 8.1	23.8 ± 5.7	0.741	28.8 ± 1.7	28.3 ± 1.8	0.046	26.8 ± 3.0	24.5 ± 5.5	0.274
CDR-SB	1.5 ± 1.6	2.6 ± 2.3	0.038	4.1 ± 3.0	4.8 ± 4.2	0.946	0.3 ± 0.7	0.6 ± 1.0	0.116	3.2 ± 3.9	3.8 ± 3.3	0.659	0.5 ± 1.0	0.8 ± 1.4	0.105	2.2 ± 2.4	3.1 ± 3.8	0.533

Abbreviations: Aβ, β-amyloid; CU, Cognitively Unimpaired; MCI, Mild Cognitive Impairment; DAT, Dementia of the Alzheimer Type; HTN, Hypertension; DM, Diabetes Mellitus; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; AD, Alzheimer's disease; CL, Centiloid; ROI, Regions of Interest; SUVR, Standardized Uptake Value Ratio; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

Figure Legends

Figure 1. Concordance of plasma p-tau217 and Aβ PET (A) and cognitive trajectory (B) according to p-tau217/Aβ PET discordance in three cohorts Including (1) K-ROAD, (2) TRIAD and (3) ADNI

The cognitive trajectories across the four groups using linear mixed-effect models with fixed effects including age, *APOE* ε4 carrier status, group, time, and group by time interaction term.

Abbreviations: Aβ, β-amyloid; PET, positron emission tomography; MCI, mild cognitive impairment; DAT, dementia of the Alzheimer type; CU, cognitively unimpaired; MMSE, Mini-Mental State Examination; CDR_SB, Clinical Dementia Rating-Sum of Boxes

Figure 2. Concordance of plasma p-tau217 and tau PET (A) and cognitive trajectory (B) according to p-tau217/tau PET discordance in three cohorts including (1) K-ROAD, (2) TRIAD and (3) ADNI

The cognitive trajectories across the four groups using linear mixed-effect models with fixed effects including age, *APOE* ε4 carrier status, group, time, and group by time interaction term.

Abbreviations: Aβ, β-amyloid; PET, positron emission tomography; MCI, mild cognitive impairment; DAT, dementia of the Alzheimer type; CU, cognitively unimpaired; MMSE, Mini-Mental State Examination; CDR_SB, Clinical Dementia Rating-Sum of Boxes

Figure 3. Cognitive trajectory according to p-tau217 and PET discordance including (A) Aβ PET, (B) tau PET and (C) Aβ PET & tau PET in combining the cohorts (K-ROAD, TRIAD and ADNI)

The cognitive trajectories across the four groups using linear mixed-effect models with fixed effects including age, *APOE* ε4 carrier status, cohort, group, time, and group by time interaction term.

Abbreviations: Aβ, β-amyloid; PET, positron emission tomography; MMSE, Mini-Mental State Examination; CDR_SB, Clinical Dementia Rating-Sum of Boxes

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