Tailoring plasma p-Tau217 cutoffs for diagnostic performance across cognitive stages

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ABSTRACT

Background: Plasma biomarkers, particularly phosphorylated tau (p-tau) 217, have emerged as minimally invasive and accessible alternatives to positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) analysis for Alzheimer's disease (AD) diagnostics. However, the diagnostic performance of p-tau217 across diverse cognitive and demographic subgroups remains underexplored.

Objective: This study aimed to assess the diagnostic utility of plasma p-tau217 using a double cutoff approach in a large, diverse cohort, with a focus on subgroup analyses based on cognitive status, age, sex, body mass index (BMI), and *APOE* ε4 carrier status.

Methods: Plasma p-tau217 levels were analyzed in cognitively unimpaired (CU) and cognitively impaired (CI) individuals. Double cutoffs for p-tau217 levels were selected to classify participants into amyloid-negative, intermediate, and amyloid-positive groups. Diagnostic performance metrics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were evaluated across subgroups, and tailored cutoff strategies were explored for specific populations.

Results: The optimal cutoffs differed between CU and CI groups, reflecting the need for stage-specific thresholds. In the CI group, diagnostic accuracy was consistently high across all subgroups, meeting confirmatory test standards with sensitivity and specificity ≥90%. In the CU group, the appropriate standards varied by subgroup. *APOE* ε4 carriers and individuals aged ≥65 years met only triaging standards, while participants aged <65 years required alternative cutoffs to improve sensitivity to 85.0% and maintain specificity at 95.7%.

Conclusion: Plasma p-tau217 demonstrated robust diagnostic accuracy across CI subgroups and highlighted the importance of tailored cutoff thresholds for CU populations. These

findings support the integration of plasma p-tau217 into clinical workflows for AD diagnostics, emphasizing its potential for early detection and risk stratification.

Abbreviations

AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; BMI, body mass index; APOE, apolipoprotein E; CU, cognitively unimpaired; CI, cognitively impaired; PPV, positive predictive value; NPV, negative predictive value; Aβ, amyloid-beta; MCI, mild cognitive impairment; DAT, dementia of Alzheimer's type; MRI, magnetic resonance imaging; rdcCL, regional direct comparison Centiloid; ROC, receiver operating characteristic; AUC, area under the curve

1. BACKGROUND

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles [1-3]. Recent advancements in plasma biomarkers have transformed the diagnostic landscape of AD by offering minimally invasive and accessible alternatives to traditional methods such as positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) analysis [4-7]. Among these biomarkers, phosphorylated tau (p-tau) 217 has emerged as a particularly promising tool for detecting Aβ pathology with high accuracy while also reflecting tau pathology to a significant extent [8-12]. Its strong concordance with PET imaging for both Aβ and tau pathologies makes it a valuable candidate for integration into clinical workflows, providing a scalable and less invasive alternative to PET- and CSF-based diagnostic approaches.

To ensure clinical applicability, plasma biomarker tests must meet specific performance criteria. Confirmatory tests require a sensitivity and specificity of at least 90%, ensuring diagnostic accuracy equivalent to CSF-based tests [13]. Triaging tests, in contrast, prioritize sensitivity (≥90%) with slightly lower specificity (75–85%), minimizing false negatives and ensuring that most individuals with Aβ pathology are identified [13]. Additionally, a two-cutoff approach has been proposed to classify individuals into Aβ-negative, intermediate, and Aβ-positive groups [14, 15]. The intermediate group is typically defined as those with plasma biomarker levels falling between two thresholds, with the intermediate category capped at 15–20% of the tested population. This approach plays a critical role in addressing the overlap often observed in plasma biomarker results, which lack a clear bimodal distribution [16].

Plasma p-tau217 levels are influenced by cognitive status and demographic factors, necessitating a tailored approach to diagnostic thresholds. Cognitively unimpaired (CU)

individuals represent an earlier stage of AD, where amyloid pathology dominates and tau pathology remains minimal. In contrast, cognitively impaired (CI) individuals typically exhibit both amyloid and tau pathologies at more advanced disease stages [17, 18]. These differences underscore the need for cognitive stage-specific thresholds. Plasma p-tau217 levels are also shaped by demographic and clinical factors such as age, sex, body mass index (BMI), and *APOE* ε4 carrier status [19, 20]. These subgroup-specific factors can influence the optimal diagnostic cutoffs needed to maintain accuracy across diverse populations [21, 22]. Tailoring thresholds to cognitive stages and demographic factors are essential to maximize the diagnostic utility of plasma p-tau217.

In the present study, we aimed to assess the diagnostic performance of plasma p-tau217 using a double cutoff approach in a large, diverse cohort with varying cognitive statuses, including subgroup analyses of demographic and clinical factors. Specifically, we sought to: (1) evaluate the optimal cutoffs for CU and CI groups, (2) investigate the consistency of diagnostic performance across demographic and clinical subgroups, and (3) explore the utility of alternative thresholds for improving accuracy in specific subgroups.

2. METHODS

2.1. Study population

Participants were recruited from the Korea-Registries to Overcome dementia and Accelerate Dementia (K-ROAD) project, a multicenter nationwide initiative involving 25 hospitals, with Samsung Medical Center serving as the core center from 2016 to 2024 [23]. We analyzed a total of 2,607 individuals who underwent both plasma p-tau217 testing and amyloid PET imaging. For this study, we included participants from two groups: cognitively unimpaired (CU, n=636) and cognitively impaired (CI, n=1,971), with the CI group

consisting of individuals diagnosed with mild cognitive impairment (MCI, n=1,396) or dementia of the Alzheimer's type (DAT, n=575). Detailed diagnostic criteria and inclusion/exclusion criteria for study participants are provided in the Supplementary Methods.

2.2. Brain magnetic resonance imaging acquisition

All participants underwent brain magnetic resonance imaging (MRI) at their respective centers, following a standardized imaging protocol. This protocol included 3-dimensional (3D) T1 turbo field echo sequences and fluid attenuated inversion recovery (FLAIR) imaging, using a 3.0-T MRI scanner. T1-weighted images were obtained with an isotropic voxel size of 1 mm^3 on all MRI machines. All images were reviewed at Samsung Medical Center. The median time between Aβ PET imaging and plasma collection was 4 days, with an interquartile range of 0–69 days.

2.3. Aβ PET imaging acquisition and analysis

All participants underwent Aβ PET imaging with 18F-florbetaben or 18F-flutemetamol, according to the manufacturer's imaging guidelines. We then quantified Aβ uptake using the global MRI-based regional direct comparison Centiloid (rdcCL) method [24]. Aβ positivity on PET was defined using a global MRI-based rdcCL threshold of 20. All imaging analyses were conducted at the Alzheimer's Disease Convergence Research Center at SMC. The detailed protocol for PET imaging, quantification and obtaining Aβ PET cutoff points is described in the Supplementary Methods.

2.4. Plasma collection and plasma biomarker assays

We obtained 8 mL of blood from each participant, placed the sample into a 0.5 M EDTA-containing tube, and mixed it for 5 minutes. Plasma was extracted from the blood sample after centrifugation (1300 ×g, 4 °C) for 10 minutes and dispensed into 5 or 10 vials at a volume of 0.3 mL each. All plasma samples were stored frozen at −75 °C until analysis. This process complied with the manual for human resource collection and registration of the National Biobank of the Republic of Korea.

The frozen plasma samples were shipped to the Department of Psychiatry and Neurochemistry, University of Gothenburg, for analysis. These samples were thawed on wet ice and centrifuged at 500 ×g for 5 min at 4°C. Plasma p-tau217 levels were measured using the commercial ALZpath p-tau217 Single molecule array (Simoa®) assay at the University of Gothenburg.

2.5. Stratification by potential influencing factors affecting plasma p-tau217 level

We first evaluated the diagnostic accuracy of plasma p-tau217 in participants classified into the cognitively impaired (CI) and cognitively unimpaired (CU) groups and investigated potential factors influencing plasma biomarker levels, including age, sex, BMI status, and *APOE* ε4 allele carrier status. Subgroup analyses were performed within the CI and CU groups based on these factors to assess variations in the diagnostic accuracy of plasma p-tau217 across different demographic and clinical characteristics, where age was dichotomized at 65 years, BMI status was categorized into obese (≥25) and non-obese (<25) groups according to the Asia-Pacific BMI criteria, and *APOE* ε4 carriers were defined as individuals with ε2/ε4, ε3/ε4, or ε4/ε4 genotypes.

2.6. Double cutoffs and their diagnostic accuracy

The double cutoff points for cognitively impaired participants were obtained using receiver operating characteristic (ROC) curve analysis. Initial sensitivity and specificity thresholds were set at 95% to acquire crude low and high cutoffs, respectively. The values around crude cutoffs to the nearest 0.05 pg/mL were chosen as the potential cutoff candidates for lower and higher cutoffs, intended to increase robustness of the cutoffs. The diagnostic accuracy of all possible cutoff combinations generated from potential candidate values were calculated, and the combination with the best accuracy (mean value of sensitivity and specificity) was chosen as the final cutoffs. The same procedure was done for cognitively unimpaired participants.

The accuracy of the originally determined double cutoffs for each group were recalculated in subgroups stratified by age, sex, BMI, and *APOE* ε4 carrier status.

2.7. Statistical Analysis

The demographic and clinical characteristics were presented as means and standard deviations for continuous variables and as numbers (percentages) for categorical variables. Considering its non-linearity, median and interquartile ranges were presented for plasma p-tau217 level. Outliers exceeding 3 standard deviations in the log-transformed value of plasma p-tau217 were excluded from the analysis. The areas under the ROC curve (AUCs) of the CI and CU groups were obtained, and the 95% confidence intervals for performance metrics of cutoffs in strata based cognitive groups and additional factors were calculated using bootstrapping with 1,000 resampled datasets. Statistical analysis was executed using SAS

version 9.4 (SAS Institute Inc, Cary, NC) and R 4.4.2 (Vienna, Austria; http://www.R-project.org/).

3. RESULTS

3.1. Baseline characteristics of the study population

The baseline characteristics of the study population are summarized in Table 1. Among cognitively impaired (CI) participants (N = 1,971) and cognitively unimpaired (CU) participants (N = 636), the mean age was 71.7 and 70.1 years, respectively, with 21.3% and 25.2% under 65 years. Females comprised 63.0% of the CI group and 64.5% of the CU group. The mean BMI was 23.5 in the CI group and 24.0 in the CU group, with obesity (BMI $\geq$ 25 kg/m^2) observed in 27.6% and 34.0%, respectively. *APOE* ε4 carriers accounted for 44.0% of the CI group and 25.5% of the CU group, while amyloid positivity was found in 63.7% and 26.6%, respectively.

Table 1. Baseline characteristics of participants

Characteristics	CU (N = 636)	CI (N = 1,971)
Age, mean (SD)	70.1 (8.2)	71.7 (8.8)
Age < 65, n (%)	160 (25.2%)	419 (21.3%)
Female, n (%)	410 (64.5%)	1241 (63.0%)
Years of education, mean (SD)	11.4 (4.7)	10.6 (4.8)
BMI, mean (SD)	24.0 (2.9)	23.5 (3.2)
Obese (BMI $\geq$ 25 kg/m^2), n (%)	214 (34%)	542 (27.6%)
APOE ε4 carrier, n (%)	162 (25.5%)	868 (44.0%)

Characteristics	CU (N = 636)	CI (N = 1,971)
Cognitive stage (MCI / DAT), n (%)	Not Applicable	1,396 (70.8%) / 575 (29.2%)
Amyloid positivity (rdcCL > 20), n (%)	169 (26.6%)	1256 (63.7%)
Plasma p-tau217 (pg/mL), median (IQR)	0.275 (0.23)	0.750 (0.87)

CU: Cognitively unimpaired; CI: Cognitively impaired; SD: Standard deviation; n: Number of individuals; BMI: Body mass index; *APOE*: Apolipoprotein E; MCI: Mild cognitive impairment; DAT: Dementia of Alzheimer's type; rdcCL: regional direct comparison Centiloid; IQR: interquartile range

3.2. Overall diagnostic performance of double cutoffs in CI and CU groups

The area under the ROC curve was 0.935 (95% CI 0.927 – 0.953) in the CI group and 0.917 (95% CI 0.889 – 0.944) in the CU group.

The diagnostic accuracy of plasma p-tau217 using the double cutoff approach was evaluated separately in cognitively impaired (CI) and cognitively unimpaired (CU) groups. In the CI group, applying the low cutoff of 0.40 pg/mL and high cutoff of 0.70 pg/mL resulted in a sensitivity of 95.2%, specificity of 91.6%, and an intermediate group size of 16.1% (Figure 1). Positive and negative predictive values (PPV and NPV) were 95.0% and 91.9%, respectively. For the CU group, the low cutoff of 0.30 pg/mL and high cutoff of 0.45 pg/mL achieved a sensitivity of 90.6%, specificity of 91.7%, and an intermediate group size of 19.9%, with PPV and NPV of 80.4% and 96.3%, respectively (Figure 2).

3.3. Effect of covariates on diagnostic accuracy of double cutoffs

We further evaluated the diagnostic performance of plasma p-tau217 across subgroups stratified by age, sex, BMI, and *APOE* ε4 carrier status in both CI and CU groups. The double cutoff approach in the cognitively impaired (CI) group showed sensitivity and

specificity exceeding 90% across all subgroups, with the intermediate risk group remaining below 20%, meeting the Global CEO Initiative's confirmatory test standards [13] (Figure 1). Specifically, for age subgroups, sensitivity, specificity, and intermediate risk were 97.1%, 96.5%, and 9.5% for participants aged <65 years, and 94.6%, 90.1%, and 17.8% for those aged ≥65 years. By sex, males showed 95.5% sensitivity, 89.5% specificity, and a 15.9% intermediate risk proportion, while females exhibited 94.9%, 93.0%, and 16.1%, respectively. For BMI, non-obese participants had 96.0% sensitivity, 90.6% specificity, and 15.9% intermediate risk, compared to 92.5%, 93.5%, and 16.6% in obese individuals. *APOE* ε4 carriers had 96.5% sensitivity, 90.6% specificity, and 18.5% intermediate risk, while non-carriers had 93.3%, 91.7%, and 14.1%.

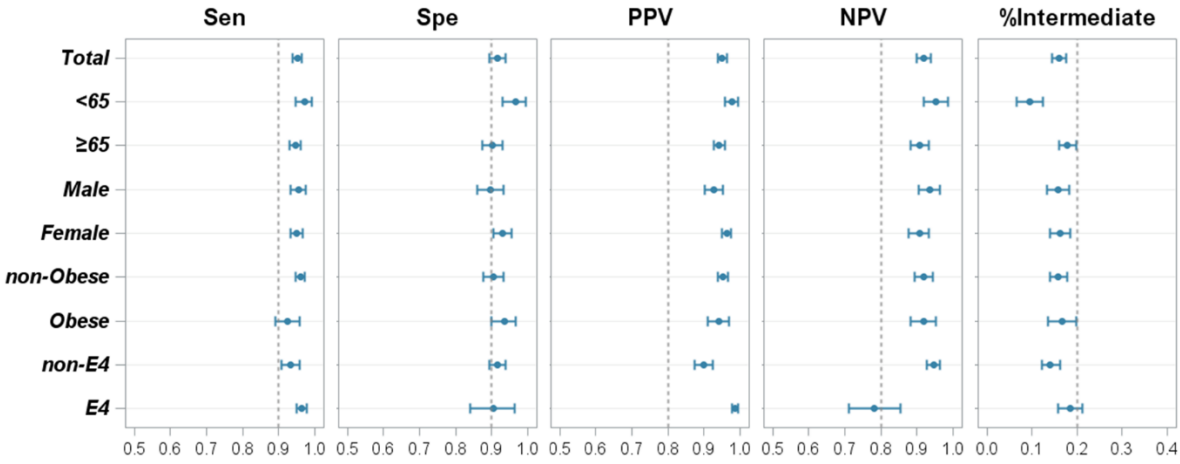

Figure 1. Overall diagnostic performance and subgroup-specific accuracy of plasma p-tau217 in CI group. The diagnostic performance metrics (sensitivity, specificity, PPV, NPV, and percentage of intermediate group) for plasma p-tau217 using double cutoffs of 0.4 and 0.7, analyzed across different subgroups (age, sex, BMI, and *APOE* ε4 status) within CI group. CI: cognitively impaired; Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value.

Among CU participants, *APOE* ε4 non-carriers met confirmatory test standards, with performance consistent across sex and BMI subgroups (figure 2). *APOE* ε4 carriers and participants aged ≥65 years met only triaging test standards (sensitivity ≥90%, specificity 75−85%). Carriers showed sensitivity of 91.2%, specificity of 84.7%, and an intermediate risk proportion of 21.2%. Participants aged ≥65 years demonstrated sensitivity of 91.8%, specificity of 88.1%, and an intermediate risk proportion of 22.8%. In contrast, participants aged <65 years did not meet either standard, with sensitivity of 81.0%, specificity of 98.4%, and an intermediate risk proportion of 11.3%. To address the sensitivity limitation in participants aged <65 years (81.0%), we performed additional analyses with alternative cutoff ranges. As shown in figure 3, adjustments to lower cutoffs (e.g., 0.30–0.35) improved sensitivity to 85.0% while maintaining specificity at 95.7%, both within acceptable limits. Considering the minimal discrepancy between the low and high cutoffs, we further assessed whether a single cutoff could achieve comparable diagnostic performance. When a single threshold of 0.35 pg/mL for plasma p-tau217 levels was applied, sensitivity was 85.0% and specificity was 95.7%.

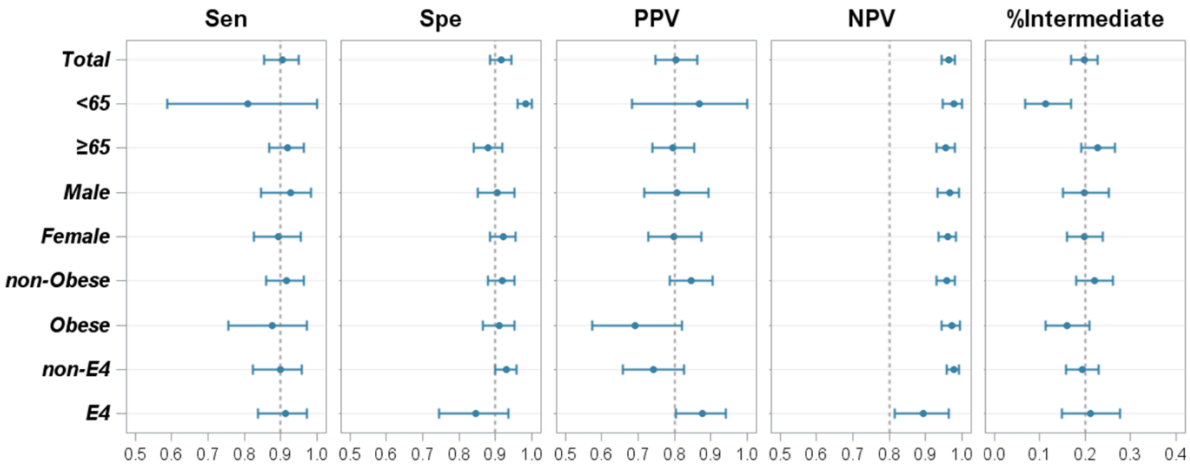

Figure 2. Overall diagnostic performance and subgroup-specific accuracy of plasma p-tau217 in CU group. The diagnostic performance metrics (sensitivity, specificity, PPV, NPV, and percentage of intermediate group) for plasma p-tau217 using double cutoffs of 0.3 and 0.45, analyzed across different subgroups (age, sex, BMI, and *APOE* ε4 status) within CU group. CU: cognitively unimpaired; Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value.

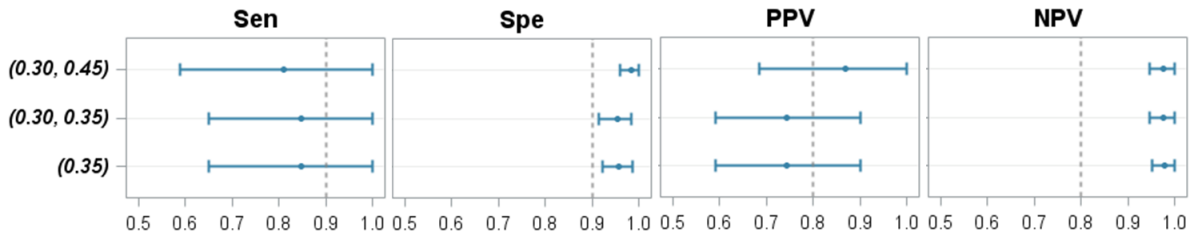

Figure 3. Diagnostic performance of plasma p-tau217 in CU individuals aged <65 years using different cutoff strategies. CU: cognitively unimpaired; Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value.

4. DISCUSSION

In the present study, we assessed the diagnostic performance of plasma p-tau217 using a double cutoff in a large, diverse cohort with varying cognitive statuses, including subgroup analyses of demographic and clinical factors. Our major findings are as follows: First, the optimal cutoffs differed between CU and CI groups, reflecting the need for cognitive stage-specific thresholds. Second, in the CI group, diagnostic accuracy was consistently high across all subgroups, meeting confirmatory test standards. Third, in the CU group, the appropriate standards varied by subgroup, with some meeting confirmatory standards and others meeting only triaging standards. For participants aged <65 years, alternative cutoff ranges may be needed to improve diagnostic performance. Taken together, these findings highlight the potential of plasma p-tau217 as a reliable confirmatory tool in CI populations and underscore the importance of tailored thresholds for specific CU subgroups. Clinically, these results support the use of plasma p-tau217 for amyloid risk stratification in CI individuals and suggest adjustments to cutoff thresholds to enhance its utility in CU populations.

Our first major finding was that the optimal cutoffs differed between CU and CI groups, with higher thresholds observed in the CI group. This reflects the need for cognitive stage-specific thresholds that account for the underlying pathophysiology. In CU participants, p-tau217 levels are predominantly influenced by amyloid pathology in the earlier stages of disease [25], justifying the use of lower cutoffs. In contrast, CI participants exhibit both amyloid and tau pathology, where p-tau217 shows stronger correlations with tau PET uptake in CI group [12]. The additive effect of these dual pathologies amplifies p-tau217 levels, necessitating higher thresholds to maintain diagnostic accuracy. These findings underscore the importance of tailoring cutoff thresholds to cognitive stages, enhancing the biomarker's ability to distinguish amyloid pathology across the disease continuum.

Our second major finding was that, in the CI group, diagnostic accuracy was consistently high across all subgroups when using a double cutoff approach, with all subgroups meeting confirmatory test standards. Specifically, subgroup analyses showed that applying the same double cutoff thresholds across age, sex, BMI, and *APOE* ε4 subgroups resulted in robust diagnostic performance. This finding is supported by previous studies, including our own, which revealed that factors such as age, sex, BMI, and *APOE* ε4 carrier status influenced plasma p-tau217 levels but had minimal impact on diagnostic accuracy [20]. These results underscore the robustness of plasma p-tau217 as a diagnostic biomarker, consistently maintaining high performance across diverse clinical and demographic subgroups. Its reliability and universal applicability suggest that subgroup-specific cutoffs may not be necessary, simplifying its use for early detection of AD.

Our third major finding was that, in the CU group, the appropriate standards varied by subgroup, with some meeting confirmatory standards, others meeting only triaging standards, and certain subgroups not meeting either. Specifically, *APOE* ε4 non-carriers, males, females, and non-obese individuals met confirmatory standards, consistently achieving high sensitivity, specificity, and low intermediate risk proportions. In contrast, *APOE* ε4 carriers, participants aged ≥65 years, and obese individuals met only triaging standards, with sensitivity exceeding 90% but specificity falling below confirmatory thresholds. Furthermore, participants aged <65 years did not meet either standard under the current cutoffs, likely due to their low amyloid positivity rate (approximately 12.5% in our data) and earlier stage of disease progression, where p-tau217 levels remain lower. In fact, lowering the cutoffs for this subgroup improved diagnostic performance by enhancing sensitivity while maintaining specificity. Notably, a single threshold approach demonstrated robust accuracy in this

subgroup, highlighting the potential for tailored cutoff adjustments to optimize diagnostic outcomes.

One notable strength of this study is its large, well-characterized cohort, which allowed us to examine plasma p-tau217 performance across a wide spectrum of cognitive statuses and demographic factors. However, this study has several limitations. First, the relatively low amyloid positivity rate in CU participants aged <65 years reduced the power to evaluate diagnostic performance in this subgroup comprehensively. Second, the absence of external validation limits the generalizability of findings, particularly regarding the tailored cutoff adjustments proposed. However, this limitation is mitigated by the exceptional size and diversity of our cohort, as well as the use of one of the most widely validated plasma p-tau217 measurement methods, providing a robust foundation for understanding its performance across diverse cognitive statuses and demographic factors. Third, certain clinical conditions, such as chronic kidney disease or severe obesity and underweight, were not analyzed due to the small sample size of these subgroups. However, these conditions represent extreme cases and are unlikely to significantly affect the overall conclusions drawn from this large and diverse cohort. Finally, the study utilized a single platform for plasma p-tau217 measurement, which may impact its comparability to other assays in clinical settings. Nevertheless, this study provides significant insights into the utility of plasma p-tau217 as a diagnostic biomarker, offering a foundation for its integration into clinical workflows. These findings align with the broader goal of optimizing diagnostic strategies for AD.

In conclusion, plasma p-tau217 demonstrated robust diagnostic accuracy in the CI group, establishing its reliability as a confirmatory tool for amyloid pathology across diverse subgroups. In the CU group, the results emphasized the need for tailored thresholds to enhance sensitivity for early disease detection, particularly in younger subgroups. These

findings underscore the utility of plasma p-tau217 as a scalable biomarker for improving AD diagnostics across different stages and populations.

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Conflicts of interest

HZ has served at 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, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, Roche, and WebMD, 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).

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SUPPLEMENTARY MATERIAL

Supplementary Methods

Inclusion criteria

Diagnostic criteria for cognitively unimpaired were as follows: absence of objective cognitive impairment as determined by comprehensive neuropsychological assessment (performance above -1.0 standard deviation (SD) of age- and education-matched norms in memory and above -1.5 SD in other cognitive domains). Mild cognitive impairment (MCI) was diagnosed using the following criteria[1-3]: (1) self-reported cognitive complaints by the individual or their caregiver; (2) objective cognitive impairment in any cognitive domain (below -1.0 SD of age- and education-matched norms in memory or below -1.5 SD in other cognitive domains); (3) absence of significant impairment in activities of daily living; and (4) absence of dementia. Diagnosis of dementia of the Alzheimer type (DAT) followed the National Institute on Aging and Alzheimer's Association (NIA-AA) diagnostic criteria.[4]

Exclusion criteria

Participants with territorial infarctions, cortical stroke, brain tumor, vascular malformation on MRI, White matter hyperintensity (WMH) due to radiation injury, multiple sclerosis, vasculitis, or leukodystrophy were excluded.

Supplementary table 1. Diagnostic accuracy of subgroups in the cognitively impaired group†

	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]	%Intermediate [95% CI]
Total	0.952 [0.939 – 0.964]	0.916 [0.893 – 0.938]	0.950 [0.938 – 0.963]	0.919 [0.898 – 0.938]	16.1% [14.5 – 17.7]
Age < 65	0.971 [0.947 – 0.991]	0.965 [0.930 – 0.993]	0.978 [0.957 – 0.996]	0.953 [0.919 – 0.986]	9.5% [6.7 – 12.4]
Age ≥ 65	0.946 [0.930 – 0.961]	0.901 [0.873 – 0.929]	0.942 [0.927 – 0.958]	0.908 [0.883 – 0.932]	17.8% [15.9 – 19.8]

Male	0.955 [0.932 – 0.975]	0.895 [0.859 – 0.933]	0.927 [0.903 – 0.953]	0.936 [0.904 – 0.963]	15.9% [13.3 – 18.2]
Female	0.949 [0.932 – 0.965]	0.930 [0.903 – 0.955]	0.963 [0.949 – 0.976]	0.907 [0.877 – 0.934]	16.1% [14.1 – 18.4]
Non-obese	0.960 [0.946 – 0.973]	0.906 [0.877 – 0.933]	0.953 [0.939 – 0.966]	0.919 [0.893 – 0.943]	15.9% [14.1 – 17.9]
Obese	0.925 [0.889 – 0.957]	0.935 [0.900 – 0.967]	0.941 [0.910 – 0.969]	0.918 [0.883 – 0.953]	16.6% [13.7 – 19.7]
***APOE* ε4 carrier**	0.965 [0.950 – 0.978]	0.906 [0.841 – 0.965]	0.987 [0.978 – 0.995]	0.781 [0.711 – 0.855]	18.5% [15.9 – 21.2]
***APOE* ε4 non-carrier**	0.933 [0.908 – 0.957]	0.917 [0.893 – 0.939]	0.898 [0.873 – 0.925]	0.946 [0.926 – 0.965]	14.1% [12.2 – 16.1]

†The diagnostic accuracy when applying the double cutoff (low 0.40 pg/mL, high 0.70 pg/mL) in the cognitively impaired group; APOE: Apolipoprotein E; PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval

Supplementary table 2. Diagnostic accuracy of subgroups in the cognitively unimpaired group†

	Sensitivity [95% CI]	**Specificity [95% CI]**	**PPV [95% CI]**	**NPV [95% CI]**	**%Intermediate [95% CI]**
Total	0.906 [0.854 – 0.950]	0.917 [0.885 – 0.944]	0.804 [0.748 – 0.862]	0.963 [0.944 – 0.980]	19.9% [16.9 – 22.8]
Age < 65	0.810 [0.588 – 1.00]	0.984 [0.960 – 1.00]	0.869 [0.684 – 1.00]	0.976 [0.948 – 1.00]	11.3% [6.9 – 16.9]
Age ≥ 65	0.918 [0.868 – 0.964]	0.881 [0.840 – 0.920]	0.795 [0.739 – 0.853]	0.956 [0.929 – 0.981]	22.8% [19.1 – 26.6]
Male	0.926 [0.846 – 0.982]	0.905 [0.851 – 0.953]	0.807 [0.717 – 0.895]	0.967 [0.933 – 0.992]	19.9% [15.0 – 25.2]
Female	0.893 [0.825 – 0.954]	0.921 [0.886 – 0.954]	0.799 [0.727 – 0.874]	0.961 [0.936 – 0.983]	19.8% [16.0 – 23.8]
Non-obese	0.915 [0.860 – 0.963]	0.917 [0.879 – 0.953]	0.845 [0.787 – 0.905]	0.957 [0.931 – 0.981]	22.0% [18.0 – 26.0]
Obese	0.878 [0.758 – 0.972]	0.911 [0.865 – 0.953]	0.693 [0.574 – 0.821]	0.971 [0.943 – 0.993]	15.9% [11.2 – 21.0]
***APOE* ε4 carrier**	0.912 [0.838 – 0.972]	0.847 [0.746 – 0.935]	0.875 [0.803 – 0.942]	0.893 [0.816 – 0.963]	21.2% [14.8 – 27.8]
***APOE* ε4 non-carrier**	0.900 [0.823 – 0.959]	0.929 [0.899 – 0.958]	0.742 [0.659 – 0.827]	0.977 [0.958 – 0.990]	19.4% [15.8 – 23.0]

†The diagnostic accuracy when applying the double cutoff (low 0.30 pg/mL, high 0.45 pg/mL) in the cognitively unimpaired group; *APOE*: Apolipoprotein E; PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval

Supplementary references

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