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BIOMARKERS

POSTER PRESENTATION

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BIOMARKERS (NON-NEUROIMAGING)

Head-to-Head Comparison of Four Plasma Phosphorylated Tau 217 Biomarkers

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Abstract

Background: We assessed the efficacy of four plasma phospho-tau217 (p-tau217) biomarkers in a head-to-head comparison, and against two clinically available CSF biomarkers for Alzheimer's disease (AD).

Method: Samples were analyzed from 1009 individuals from the Swedish BioFINDER-2 cohort (Table 1). We included the following biomarkers: %p-tau217$_{WashU}$, p-tau217$_{WashU}$ (both mass-spectrometry), p-tau217$_{Lilly}$, p-tau217$_{Janssen}$ (both immunoassays), CSF p-tau181 and p-tau181/Aβ42 (Elecsys). Biomarker correlations were assessed using linear regression models. Their discriminative accuracy for global Aβ- and temporal meta-ROI tau-PET status was evaluated with receiver operating characteristic (ROC) curves. Area under the curve (AUC) values from two ROC curves were compared with DeLong tests. Linear regression models with continuous Aβ- and tau-PET measures were performed. Participants were grouped into PET-positive quartiles, which were compared with t-tests. Effect sizes (Cohen's D (CD))

were calculated between PET-positive/negative groups, and between neighboring quantiles.

Result: All plasma biomarkers were correlated ($0.62 \geq R_{adj}^2 \geq 0.92$, Figure 1). %p-tau217$_{WashU}$ showed the significantly largest effect size for both Aβ-PET status and tau-PET status ($CD_{A\beta\text{-PET}}=1.635$, $CD_{Tau\text{-PET}}=1.828$) compared to the other biomarkers (all $p_{FDR} < 0.05$). p-tau217$_{Janssen}$ had a lower plasma effect size ($CD_{A\beta\text{-PET}}=1.313$; $CD_{Tau\text{-PET}}=1.590$), but not significantly different from p-tau217$_{Lilly}$. Although all plasma biomarkers showed high AUCs (0.90-0.95) for Aβ-PET positivity, %p-tau217$_{WashU}$ was the highest, performing significantly better than all other biomarkers including CSF p-tau181/Aβ42$_{Elecsys}$ (all $p_{FDR} < 0.01$) (Figure 2A). A similar pattern was observed for tau-PET where %p-tau217$_{WashU}$ also performed significantly better than all other biomarkers except for p-tau217$_{WashU}$ (all $p_{FDR<}0.01$) (Figure 2A). With continuous PET measures, %p-tau217$_{WashU}$ showed the highest R_{adj}^2 compared to the other biomarkers for Aβ-PET and tau-PET (Figure 2B). In this context, all plasma ptau217 markers performed better that CSF ptau181$_{Elecsys}$. Compared to CSF p-tau181/Aβ42$_{Elecsys}$, p-tau217$_{Lilly}$ and p-tau217$_{WashU}$ performed similarly whereas %p-tau217$_{WashU}$ performed significantly better. Quantile grouping revealed that all biomarkers showed significant differences when distinguishing between negatives and early-stage positives for both Aβ-PET and tau-PET, with %p-tau217$_{WashU}$ consistently having the significantly largest effect size (Figure 2C). For tau-PET, plasma biomarkers distinguished better between disease stages compared to CSF.

Conclusion: When predicting Aβ- and tau-PET load, both mass-spectrometry and immunoassay methods detecting plasma p-tau217 perform similarly to an FDA-approved CSF test, with %p-tau217$_{WashU}$ performing even better.

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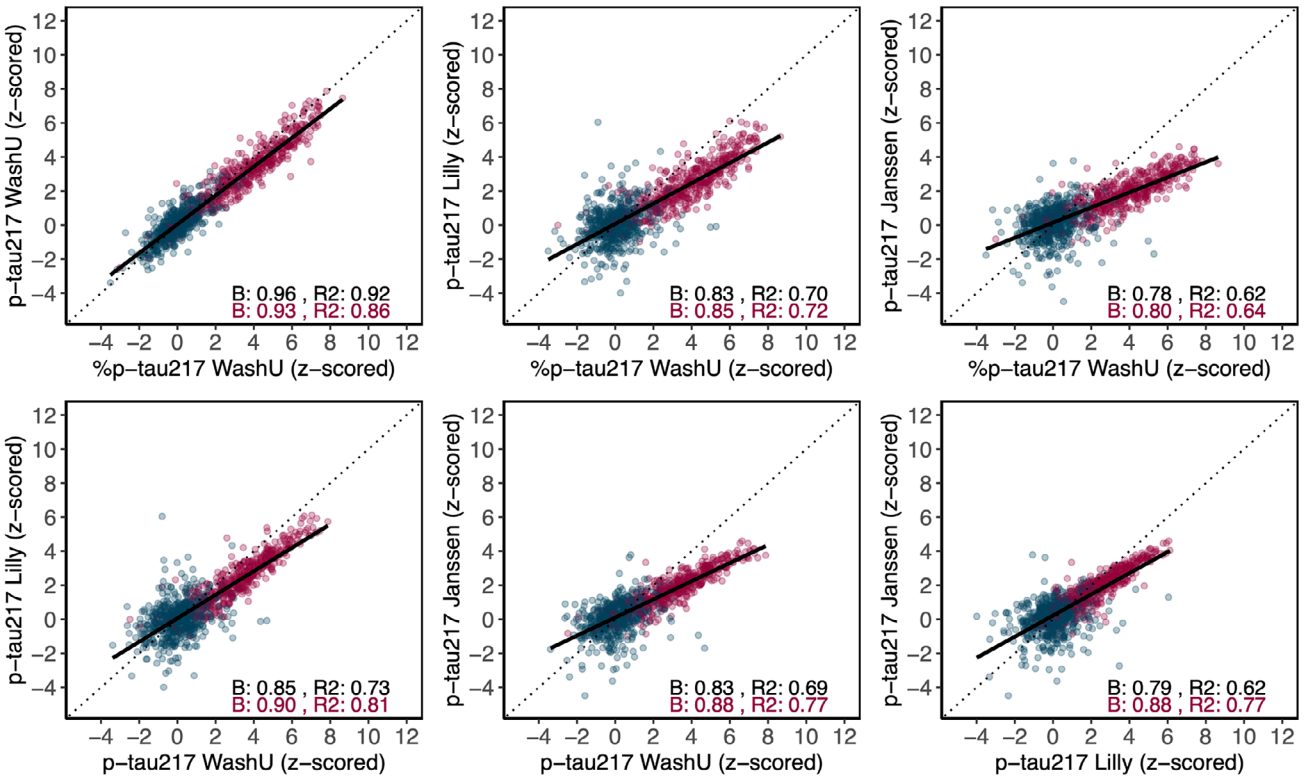
Table 1. Descriptive statistics

	***N* = 1009**
Characteristics	**Mean ± SD (range)**
Age (years)	68.53 ± 12.05 (20.02 - 92.48)
Sex (% female)	530 / 1009 (53%)
Education levels (years)	12.81 ± 3.32 (3 – 36)
MMSE score	26.84 ± 3.77 (6 – 30)
APOE-e4 carrier (% yes)	477 / 1009 (47%)
CSF Aβ-status (% positives)	447 / 1009 (44%)
Cognitively normal / MCI / Dementia (% total)	518 / 256 / 237 (51% / 26% / 23%)
PET	
[^{18}F]flutemetamol PET global Aβ-PET SUVR[1]	1.11 ± 0.30 (0.81 – 2.24)
[^{18}F]RO948 temporal-meta ROI tau-PET SUVR[1]	1.34 ± 0.43 (0.85 - 4.29)
Plasma biomarkers	
%p-tau217 WashU[2]	1.76 ± 1.73 (0.21 – 12.81)
p-tau217 WashU (pg/ml)[3]	4.24 ± 5.00 (0.34 – 40.36)
p-tau217 Lilly (pg/ml)[4]	0.31 ± 0.29 (0.03 – 2.01)
p-tau217 Janssen (pg/ml)[5]	0.07 ± 0.07 (0.00 – 0.47)
CSF biomarkers	
p-tau181 (pg/ml) Elecsys[6]	22.32 ± 2.76 (8.00 - 100.50)
p-tau181/Aβ42 (pg/ml) Elecsys[6]	0.02 ± 0.02 (0.00 – 0.14)

Abbreviations: Aβ = amyloid-beta; *APOE*ε4 = apolipoprotein E genotype (carrying at least one ε4 allele); CSF = cerebrospinal fluid; MCI = mild cognitive impairment; MMSE = mini-mental state examination; PET = positron emission tomography; ROI = region of interest; SUVR = standardized uptake value ratio.

[1]. Participants diagnosed with dementia do not undergo Aβ-PET (missing *n* = 315). Tau-PET is missing for *n* = 38.
[2]. The ratio between p-tau217 and non-phosphorylated tau217 was measured using mass spectrometry developed at Washington University (WashU).
[3]. P-tau217 was measured using mass spectrometry developed at WashU.
[4]. P-tau217 was measured using immunoassays developed by Lilly Research Laboratories (Lilly).
[5]. P-tau217 was measured using Simoa immunoassays by Johnson & Johnson Innovative Medicine, formerly Janssen R&D (Janssen).
[6]. P-tau181 and Aβ42 were measured using Roche Elecsys p-Tau(181P) and β-amyloid(1-42) assays on a Roche cobas 6000 e 601 module (Elecsys).

Figure 1. Correlations between p-tau217 biomarkers.



Note. All beta's reported are standardized. R2 is adjusted. Plasma biomarkers have been $\log_{10}$ transformed and subsequently z-scored to facilitate comparisons. Z-scores were calculated with cognitively unimpaired, Aβ− individuals as reference group.

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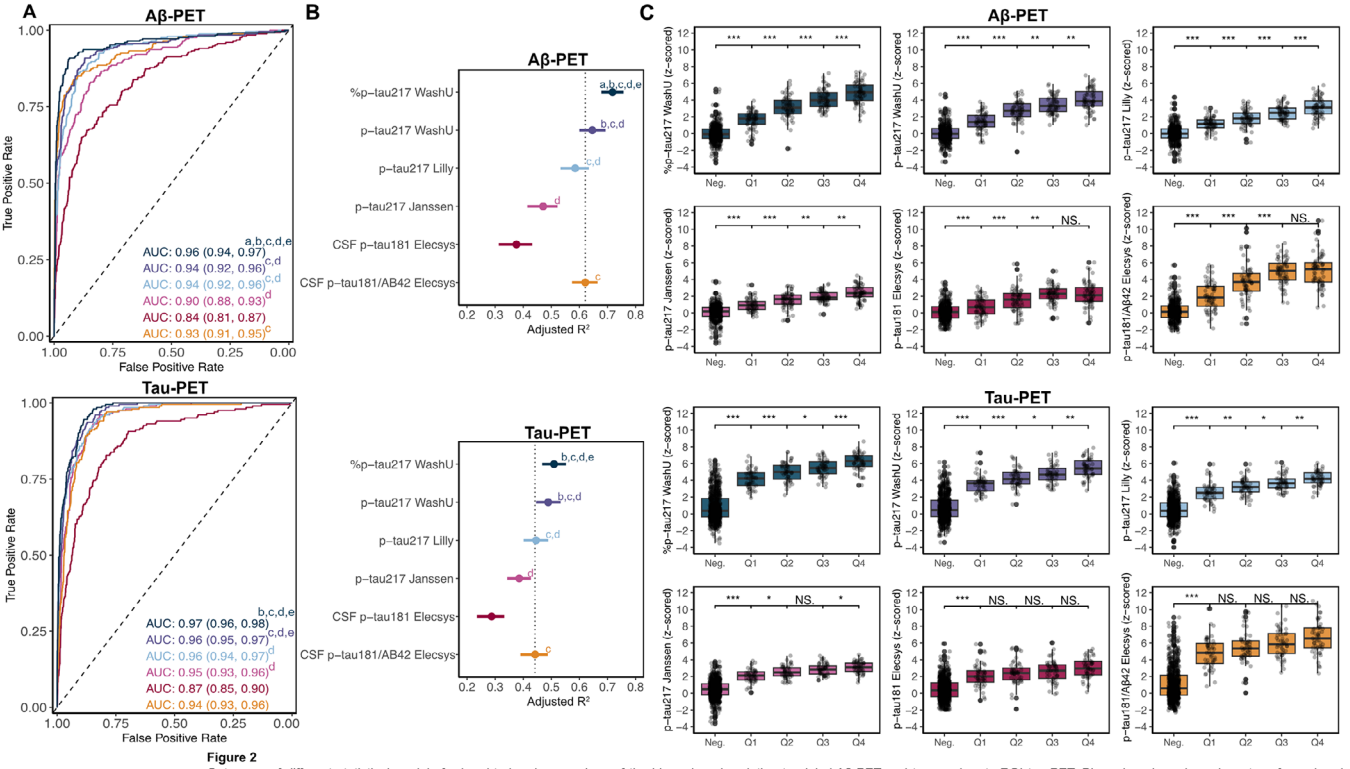

Figure 2

Outcomes of different statistical models for head-to-head comparison of the biomarkers in relation to global Aβ-PET and temporal meta-ROI tau-PET. Biomarkers have been $\log_{10}$ transformed and subsequently z-scored using cognitively unimpaired CSF Aβ-negative individuals as reference group to facilitate comparisons. **A)** AUCs corresponding to logistic regression models with Aβ- and tau-PET as binary outcomes, with 95% CIs, controlled for age and sex. DeLong tests were carried out to compare AUCs, which were subsequently FDR corrected (Benjamini-Hochberg Procedure). **B)** R_{adj}^2 with 95% CIs corresponding to linear regression models controlled for age and sex. R_{adj}^2 for each model was bootstrapped 500 times from which t-distributions were derived and subtracted from each other for each comparison to examine whether R_{adj}^2 differed significantly. Comparisons were subsequently FDR corrected. The dotted line represents the R_{adj}^2 of the FDA-approved diagnostic biomarkers to facilitate comparisons. **C)** Quantiles were calculated using PET-negative individuals as the reference group, respectively for Aβ-PET (top) and tau-PET (bottom). Differences in Cohen's *D* between groups are reported below each graph. Cohen's *D* between biomarkers was compared with bootstrapping methods, using a similar approach to R_{adj}^2. Abbrevations: Aβ = amyloid-beta; AUC; area under the curve; CIs = confidence intervals; CSF = cerebrospinal fluid; FDR = false discovery rate; PET = positron emission tomography.

*** corresponds to p<0.001; ** corresponds to p < 0.01; * corresponds to p < 0.05.

[a] significantly different than p-tau217$_{WashU}$; [b] significantly different than p-tau217$_{Lilly}$; [c] significantly different than p-tau217$_{Janssen}$; [d] significantly different than CSF p-tau181$_{Elecsys}$; [e] significantly different than CSF p-tau181/Aβ42$_{Elecsys}$ (all p_{FDR} <0.05).