

Brain-derived p-tau50 as a fluid biomarker of a master phosphorylation site propagating tau hyperphosphorylation in Alzheimer's disease

Anna L. Wojdala¹, Ingolf Lachmann², Hans Heijst¹, Azzam Aladdin¹, Everard G.B. Vijverberg³, Charlotte E. Teunissen¹

¹ Neurochemistry Laboratory, Amsterdam UMC, Amsterdam, Netherlands, ² Roboscreen GmbH, Leipzig, Germany, ³ Alzheimer Center Amsterdam, Amsterdam UMC, Amsterdam, Netherlands

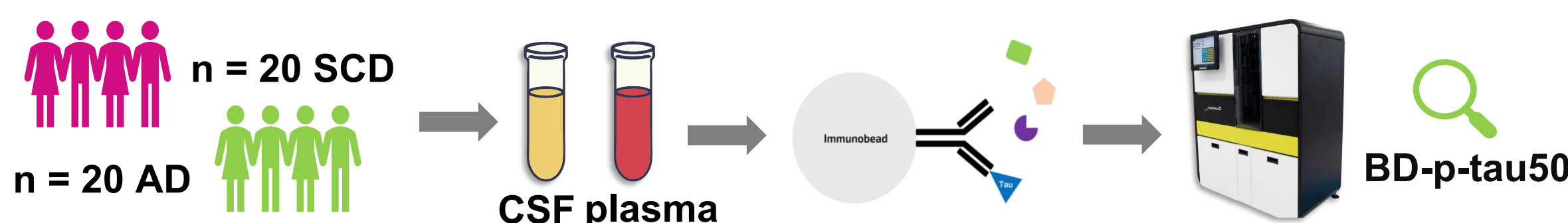
BACKGROUND

Several phosphorylated tau proteoforms (p-tau) were shown to provide a high diagnostic potential as Alzheimer's disease (AD) cerebrospinal fluid (CSF) and blood biomarkers. However, biomarkers reflecting initiation and propagation of the tau phosphorylation at multiple sites are not yet available. Recent mechanistic report (Ref: Stefanoska K et al., Sci Adv, 2022) identified **p-tau50** as one of the master sites, governing **progressive tau hyperphosphorylation at multiple other sites**.

AIM

We aimed to evaluate the AD biomarker potential of brain-derived p-tau50 (BD-p-tau50) in CSF and blood plasma.

METHODS



From the Amsterdam Dementia Cohort, we enrolled n=20 participants with AD at the stage of dementia (AD-dem, CSF A+/T+) and n=20 age- and sex-matched control participants with subjective cognitive decline (SCD, CSF A-/T-) (Table 1.). Paired CSF and plasma samples underwent pre-analytical tau enrichment via magnetic bead immunoprecipitation (Neuro IP-Kit, Roboscreen, Germany). 10x diluted IP eluates were measured on the HD-XTM platform (Quanterix, USA) with a **Simoa® immunoassay specifically detecting BD-p-tau50** (mAbs 2B8 & 15E3, Roboscreen, Germany).

Table 1. Demographic table.

Characteristic	AD-dem N = 20 ¹	SCD N = 20 ¹	p-value ²
Sex (female)	10 / 20 (50%)	10 / 20 (50%)	>0.9
Age (years)	67.2 (61.8, 71.3)	65.1 (63.9, 70.3)	0.7
MMSE	24.5 (20.5, 26.0)	28.0 (26.0, 29.0)	<0.001
CSF BD-p-tau50 (pg/mL)	155 (115, 223)	86 (76, 101)	<0.001
Plasma BD-p-tau50 (pg/mL)	1.10 (0.57, 1.55)	0.39 (0.19, 0.79)	0.001

MMSE: Mini-mental state examination. 1 Median (Q1-Q3). 2 χ^2 and Mann Whitney U test.

RESULTS

CSF and plasma BD-p-tau50 levels:

- **did not correlate with each other** ($\rho=0.26$, ns)
- significantly **correlated** with available **CSF (p-tau181, t-tau, A β 42)** and **plasma (p-tau217, NFL, GFAP)** biomarkers (Fig.1).
- were significantly **elevated in AD-dem vs. SCD group** (CSF: $p<0.0001$, plasma $p=0.0012$; Fig.2).
- **enabled discrimination between the clinical groups** (CSF: AUC 0.91 95%CI 0.82-1.00; Plasma: AUC 0.81, 95%CI 0.67-0.95, Fig.3).

Plasma but not CSF BD-p-tau50 levels shown significant negative **correlation with MMSE** ($p=0.013$, Fig.4).



Fig.1. CSF and plasma biomarker correlations assessed in the total cohort. Spearman correlation analysis.

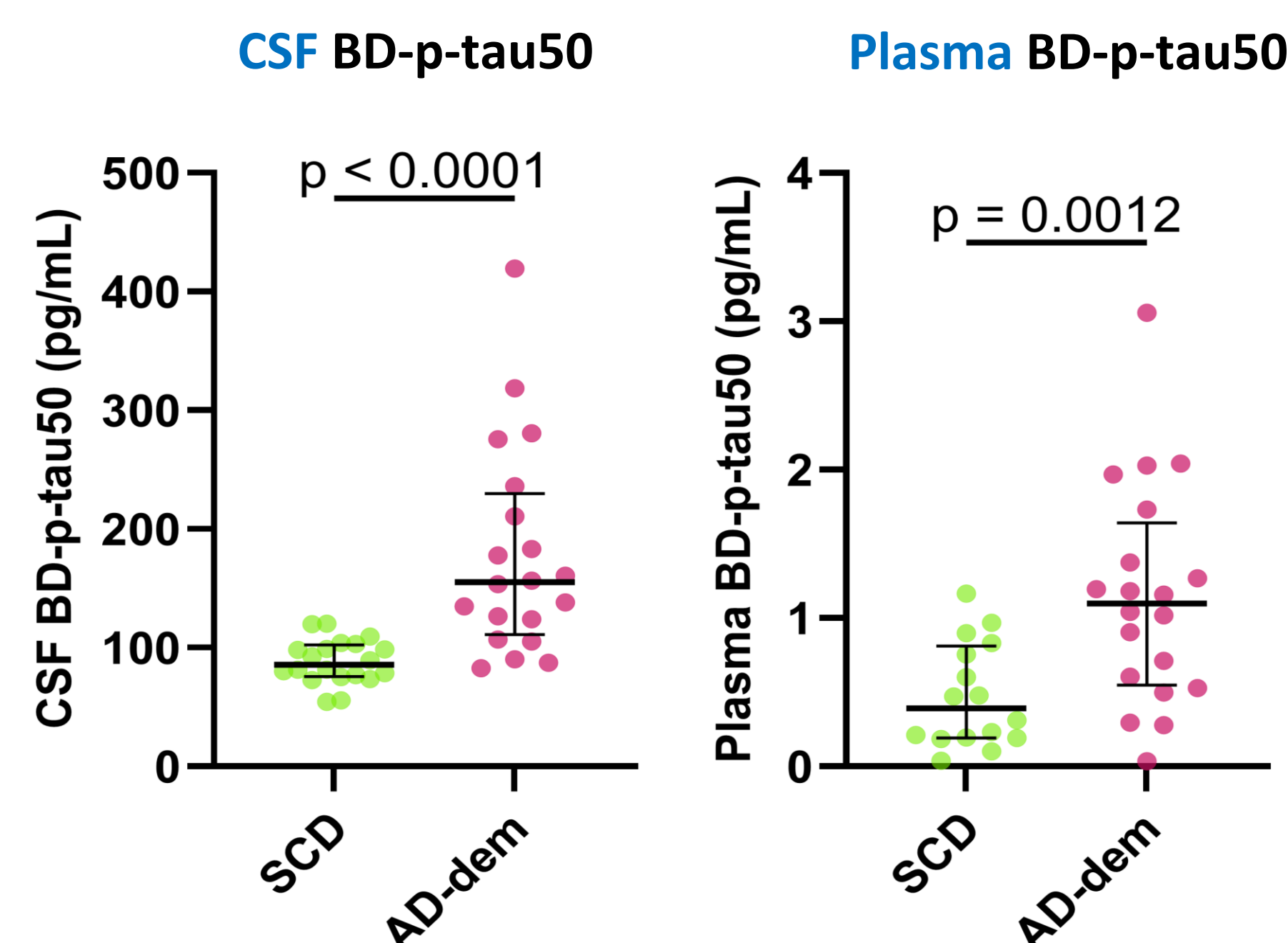


Fig.2. Elevated CSF and plasma BD-p-tau50 levels in AD vs. SCD group. Mann-Whitney U test. Horizontal bars: median and IQR.

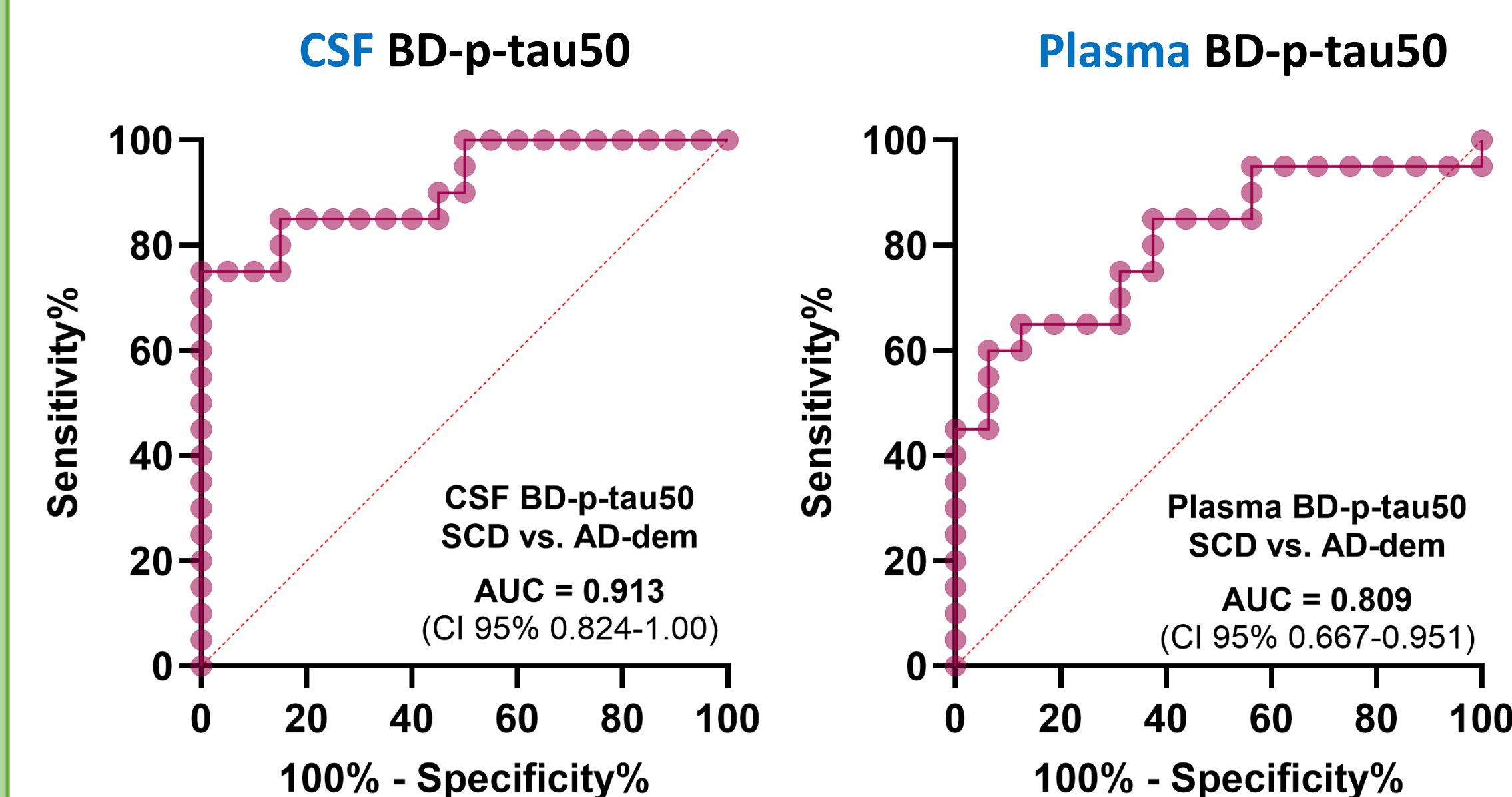


Fig.3. Area Under the Curve (AUC) for discrimination between SCD and AD groups via CSF and plasma BD-p-tau50. ROC analysis.

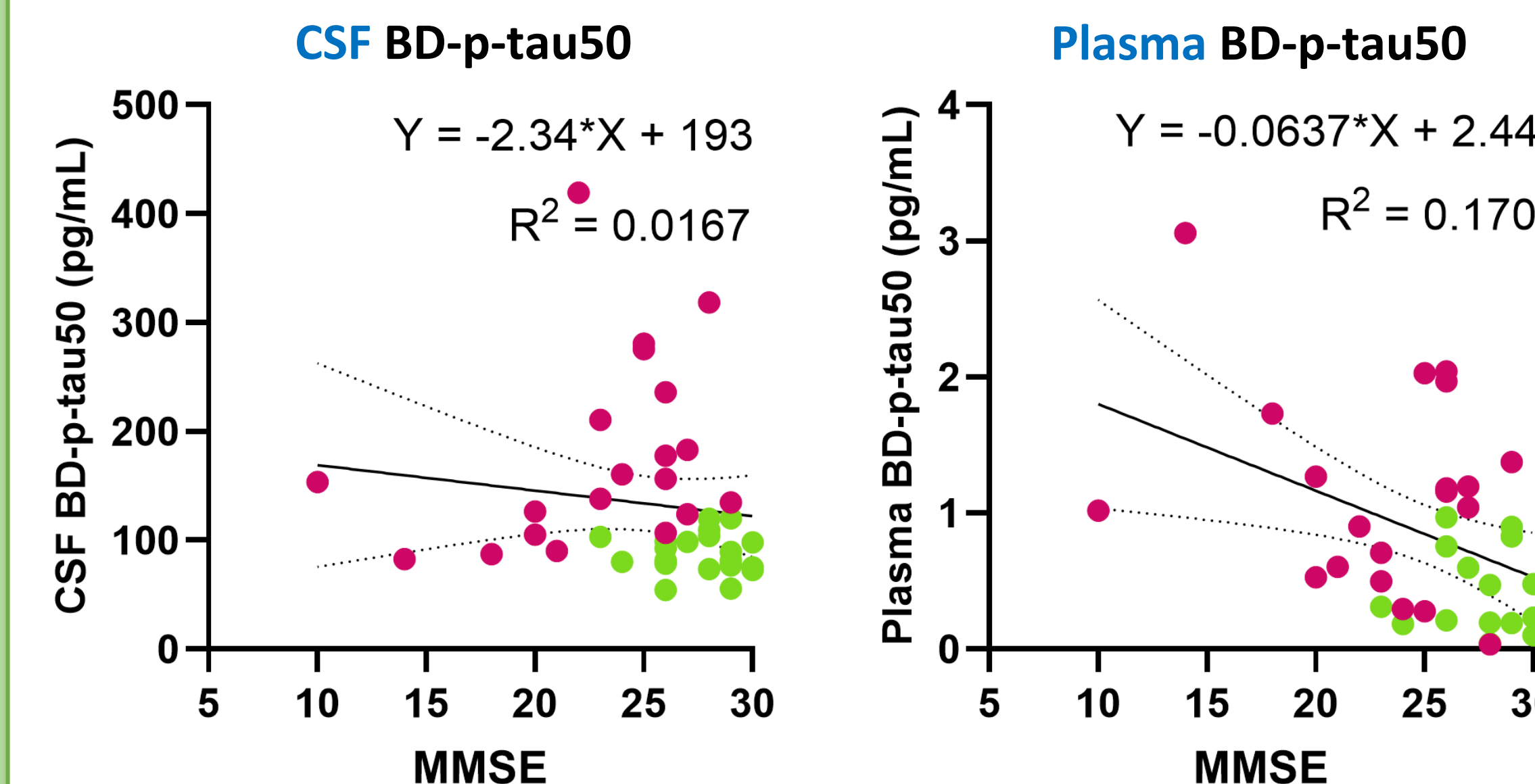


Fig.4. Negative correlation of CSF and plasma BD-p-tau50 levels with cognitive score (MMSE). Linear regression. Pink: AD, green: SCD.

CONCLUSIONS

BD-p-tau50 shows strong **AD biomarker potential**, as measured in both **CSF and blood**. We hypothesize that upon further testing, BD-p-tau50 could present as a particularly **sensitive indicator of early AD pathology**, with levels peaking at the incipient stage of the disease. The ongoing measurements across larger cohorts, encompassing preclinical AD stage, will elucidate its trajectory across the AD continuum, also in relation to established p-tau markers.

