



Plasma brain derived phospho-tau: from pre-clinical to clinical cohorts



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Ashvini Keshavan^{1,2}, Katharine Wiltshire^{1,2}, William Coath³, David M Cash^{1,2}, Kirsty Lu^{1,2}, Melanie Hart^{4,5}, Michael P Lunn^{4,6}, Amanda Heslegrave², Henrik Zetterberg^{2,3,7,8,9,10,11,12}, Jonathan M Schott^{1,2}

1. Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of Neurology, London, United Kingdom. 2. UK Dementia Research Institute at UCL, London, United Kingdom. 3. Department of Medicine, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, United States of America. 4. Neuroimmunology & CSF Laboratory, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust (UCLH) Queen Square London, United Kingdom. 5. Department of Neuroinflammation, UCL Queen Square Institute of Neurology, London, United Kingdom. 6. MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom. 7. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden. 8. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. 9. Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong Special Administrative Region, China. 10. Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, United States of America. 11. Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States of America. 12. Centre for Brain Research, Indian Institute of Science, Bengaluru, India

Key message

In symptomatic individuals, plasma brain-derived tau phosphorylated at threonine 217 (BD-ptau217) discriminated CSF AD status better than p-tau217. In asymptomatic individuals, though BDp-tau217 performed better in detecting tau deposition outside the mesial temporal lobe (Braak 3-6) on tau PET, both biomarkers had similar cross-sectional associations with cognitive performance on the pre-clinical Alzheimer's cognitive composite (PACC).

Background

We compared the performance of BDp-tau217 with p-tau217 in detecting CSF-defined AD in ADAPT stage 1 (a symptomatic cohort), and in detecting tau PET positivity and correlations with cognitive performance in Insight 46 (the neuroscience sub-study of the 1946 British birth cohort: a cognitively asymptomatic cohort) at age 76-79

Methods: ADAPT

- EDTA plasma from symptomatic individuals was assayed by ALZpath Simoa p-tau217 (Quanterix), Lumipulse p-tau217 (Fujirebio) and NULISA BDP tau217 (quantitative single-plex and 5-plex, Alamar)
- Inter-biomarker correlations were examined by Spearman rho; median fold change (FC) and robust median average deviation-normalized effect sizes (ES) computed.
- ROC analysis was undertaken against reference standard: paired CSF. AD: Lumipulse A β 42/40 $\leq$ 0.065. Non-AD A β 42/40>0.065.
- 95% sensitivity and 95% specificity cut-points were used to derive intermediate percentage (IP), overall accuracy (OA), negative (NPV) and positive predictive value (PPV).

Methods: Insight 46

- EDTA plasma from asymptomatic individuals at age 76-79 was assayed by NULISA panel CNSv2 in an interim dataset of those with contemporaneous tau PET data (Freesurfer-derived Braak regions assigned +/- by Gaussian mixture (99th centile) modelling; inferior cerebellar grey matter reference region).
- ROC analysis assessed concordance of single biomarkers (p-tau181, p-tau217, p-tau231 and BD counterparts) with tau PET positivity (Braak 3-6) and *post hoc* De Long tests compared areas under the curve (AUC).
- Linear regression examined biomarker associations with PACC, adjusted for age, sex, APOE E4 carrier status, childhood cognition, social class and educational attainment.

Results: ADAPT

- Demographic details are summarized in **Table 1**. Prevalence of CSF AD status was 61.8%. In those diagnosed with clinical AD (n=135), 9.4% had MCI, 28.9% had mild dementia, and 28.9% had moderate dementia (17.6% MMSE not available).
- All p-tau217 and BD-ptau217 were highly correlated (**Figure 1**) but BD p-tau217 had higher median fold changes and robust normalized effect sizes (**Figure 2a-d**) and significantly higher AUC than either p-tau217 assay in CSF AD vs non-AD individuals (**Table 2**).
- Comparing performance of 95% sensitivity and 95% specificity cut-points, the intermediate range was lower for BDp-tau217 (**Table 2**)

Table 1: ADAPT (symptomatic cohort) demographic details

Variable	All (n = 257)	CSF AD (n = 159)	CSF non-AD (n = 98)	p
Mean age at sampling (s.d.), years	63.3 (7.3)	64.1 (6.7)	61.9 (8.1)	0.024
Male sex, n (%)	153 (59.5)	80 (50.3)	73 (74.5)	0.0001
Serum creatinine (IQR), mL/min/m ²	74 (63–87) n = 62	72 (63, 84) n = 35	77 (63, 90) n = 27	0.335
Ethnicity				0.496
White	112 (43.1)	66 (41.5)	46 (46.9)	
Black	19 (7.3)	11 (6.9)	7 (7.1)	
Asian	5 (1.9)	3 (1.9)	2 (2.0)	
Other	5 (1.9)	5 (3.1)	0	
Not stated/known	119 (45.8)	74 (46.5)	43 (43.9)	

Figure 1: ADAPT (symptomatic cohort) biomarker correlations (Spearman rho; n=257)

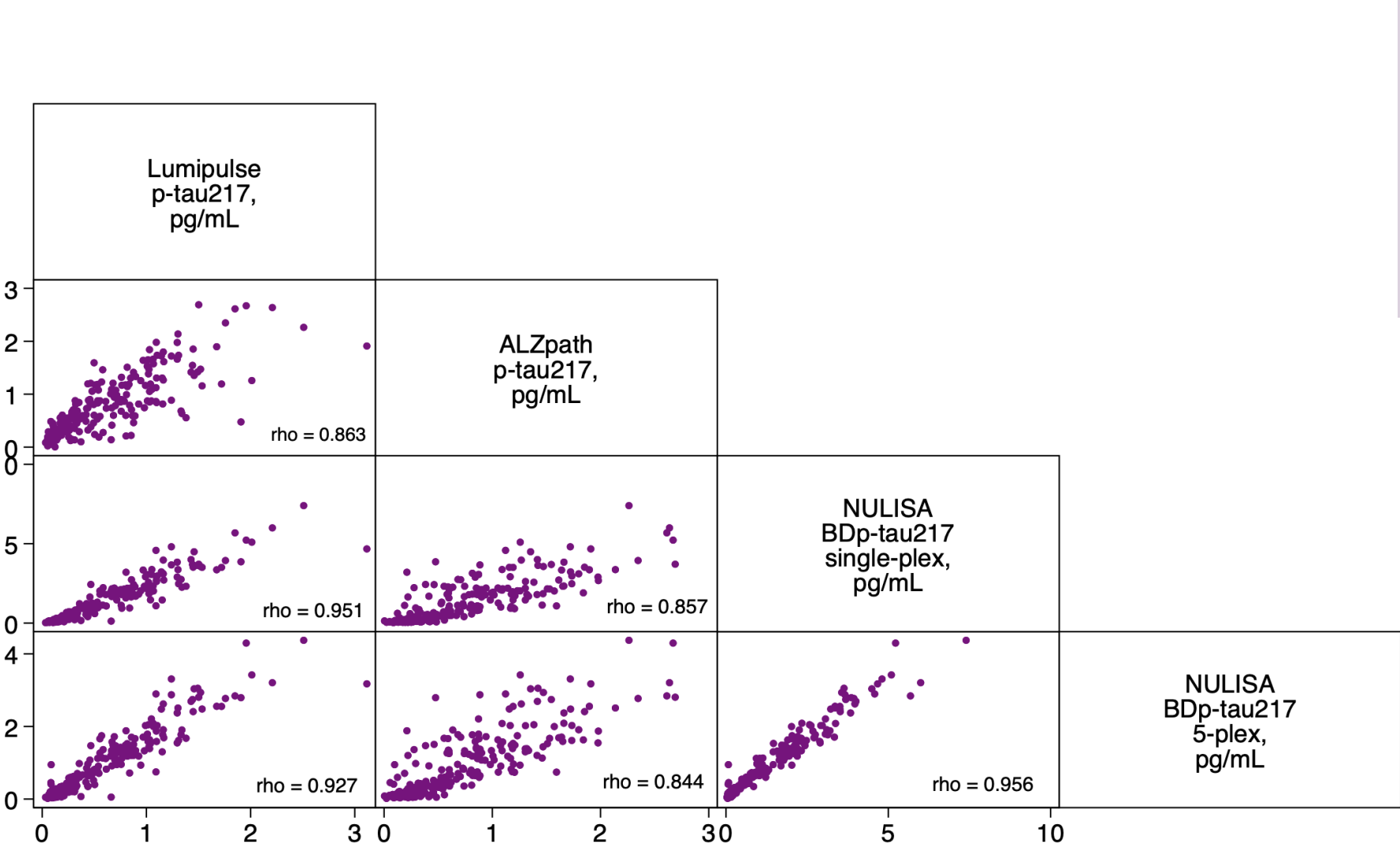
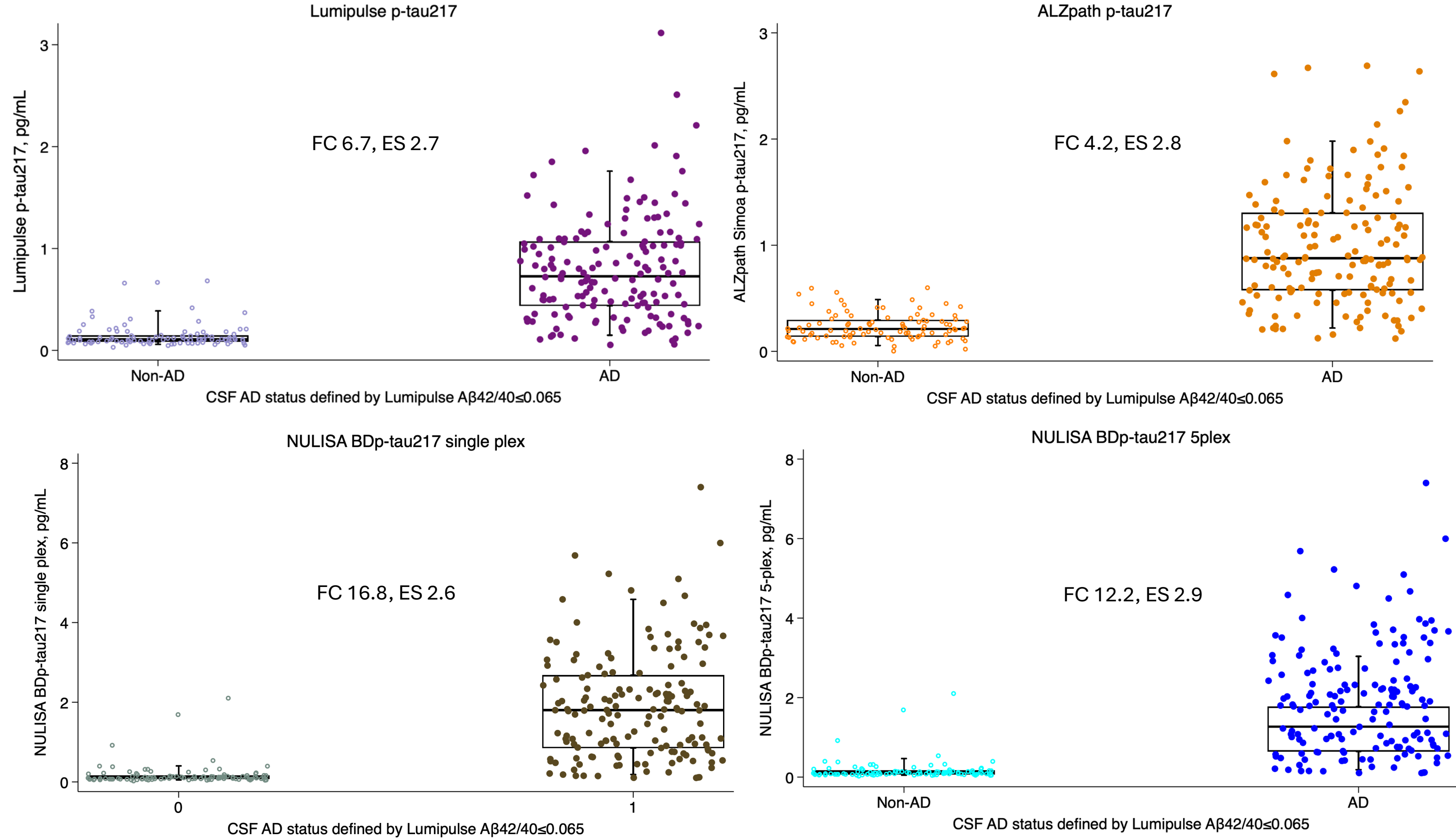


Table 2: ADAPT (symptomatic cohort) AUC for CSF AD status and performance with 95% sensitivity and 95% specificity cut-points (n=257)

Model	AUC	Lower 95% CI	Upper 95% CI	AIC	95% sensitivity Lower cutpoint, pg/ml	95% specificity Upper cutpoint, pg/ml	Intermediate (%)	Negative predictive value (95% CI)	Positive predictive value (95% CI)	Accuracy of test for individuals classified as low or high (%)
Age + Sex	0.673	0.605	0.741	325	0.150	0.387	18.7	90.2 (81.7–95.7)	96.1 (91.1–98.7)	93.8
Lumipulse p-tau217	0.947	0.919	0.974	157	0.221	0.488	23.0	85.7 (74.6–93.3)	96.3 (91.6–98.8)	93.4
ALZpath p-tau217	0.940	0.914	0.967	151	0.187	0.402	8.2	90.7 (82.5–95.9)	97.3 (93.3–99.3)	94.9
BDptau217 NULISA single plex	0.966*	0.944	0.987	143	0.189	0.460	13.6	90.5 (82.1–95.8)	96.4 (91.7–98.8)	94.1
BDptau217 NULISA 5-plex	0.960*	0.938	0.982	143	0.150	0.387	18.7	90.2 (81.7–95.7)	96.1 (91.1–98.7)	93.8

Logistic regression model fits were evaluated by Akaike Information Criteria (AIC). The statistical significance of differences in under the ROC curves (AUC) were compared by De Long tests. * p<0.05 for comparison of BDp-tau217 models with Lumipulse p-tau217 model.

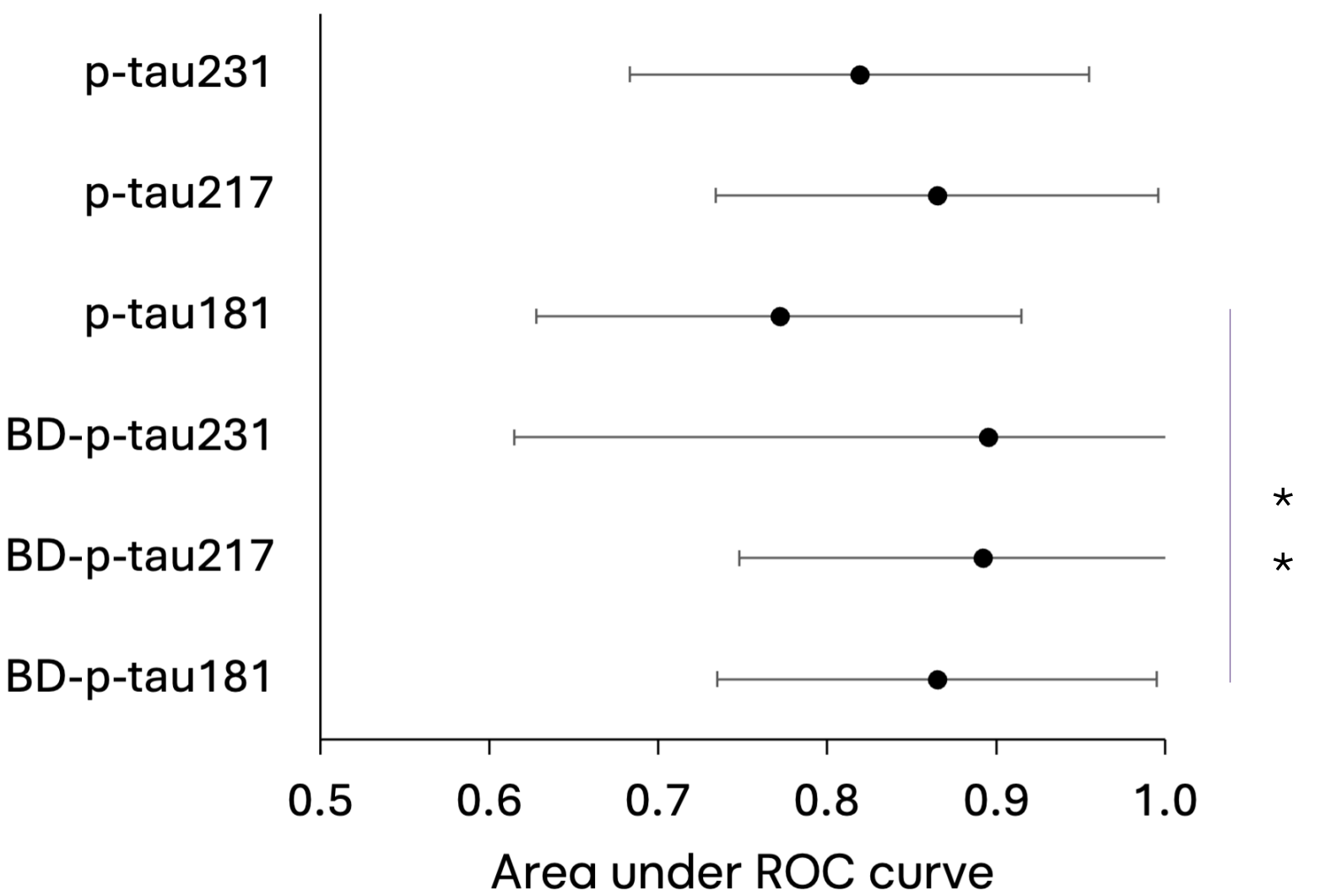
Figure 2: ADAPT (symptomatic cohort) biomarker distributions, median fold changes (FC) & robust standardized effect sizes (ES) by CSF AD status, n=257



Results: Insight 46

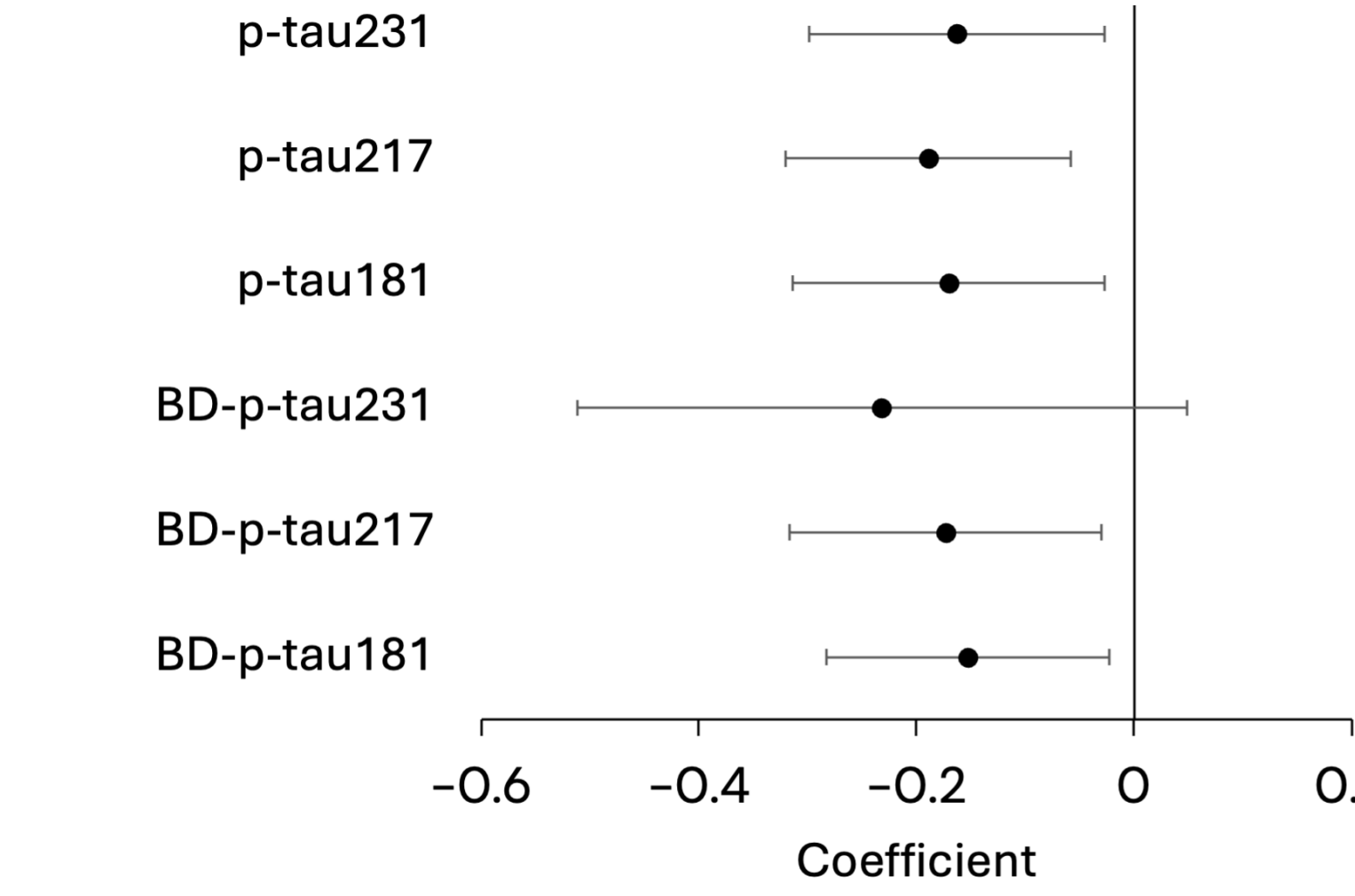
- In 236 individuals with tau PET and NULISA data (mean age 77.3 years, s.d. 1.0; 53.4% male; 29.4% carrying 1 or 2 APOE E4 alleles. 9.7% tau Braak 3-6 +), AUC were significantly higher for BDp-tau217 compared with p-tau217 and for BDp-tau181 compared with p-tau181 (**Figure 3**).
- In 240 individuals with PACC data, higher values of all p-tau and BDp-tau moieties were associated with lower PACC (**Figure 4**).

Figure 3: Insight 46 (asymptomatic cohort) plasma NULISA CNSv2 p-tau biomarker performance for detecting tau PET (Braak 3-6) at age 76-79, n=236



Capped bars indicate 95% CI for the AUC. Asterisks denote statistically significant results for pairwise De Long tests comparing AUC between the BDp-tau form and the respective p-tau form. * p < 0.05, ** p < 0.01

Figure 4: Insight 46 (asymptomatic cohort) plasma NULISA CNSv2 p-tau biomarker associations with pre-clinical Alzheimer cognitive composite at age 76-79, n=240



Linear regression coefficients describe associations with PACC, adjusted for age, sex, APOE E4 carrier status, childhood cognition, social class and educational attainment. Capped bars indicate 95% CI for the coefficients.

