



UCL



UK Dementia
Research Institute



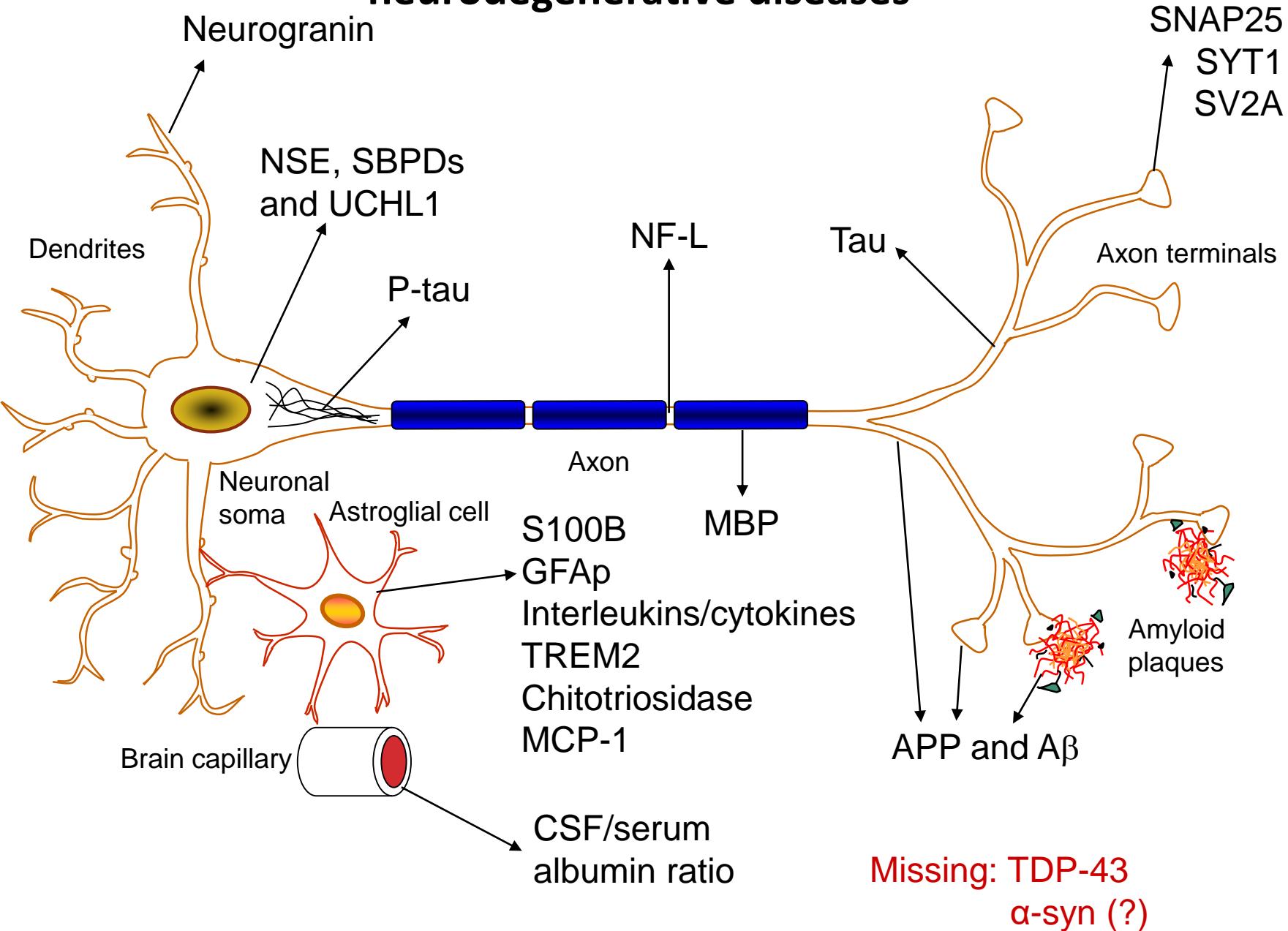
UNIVERSITY OF GOTHENBURG

Biomarker studies

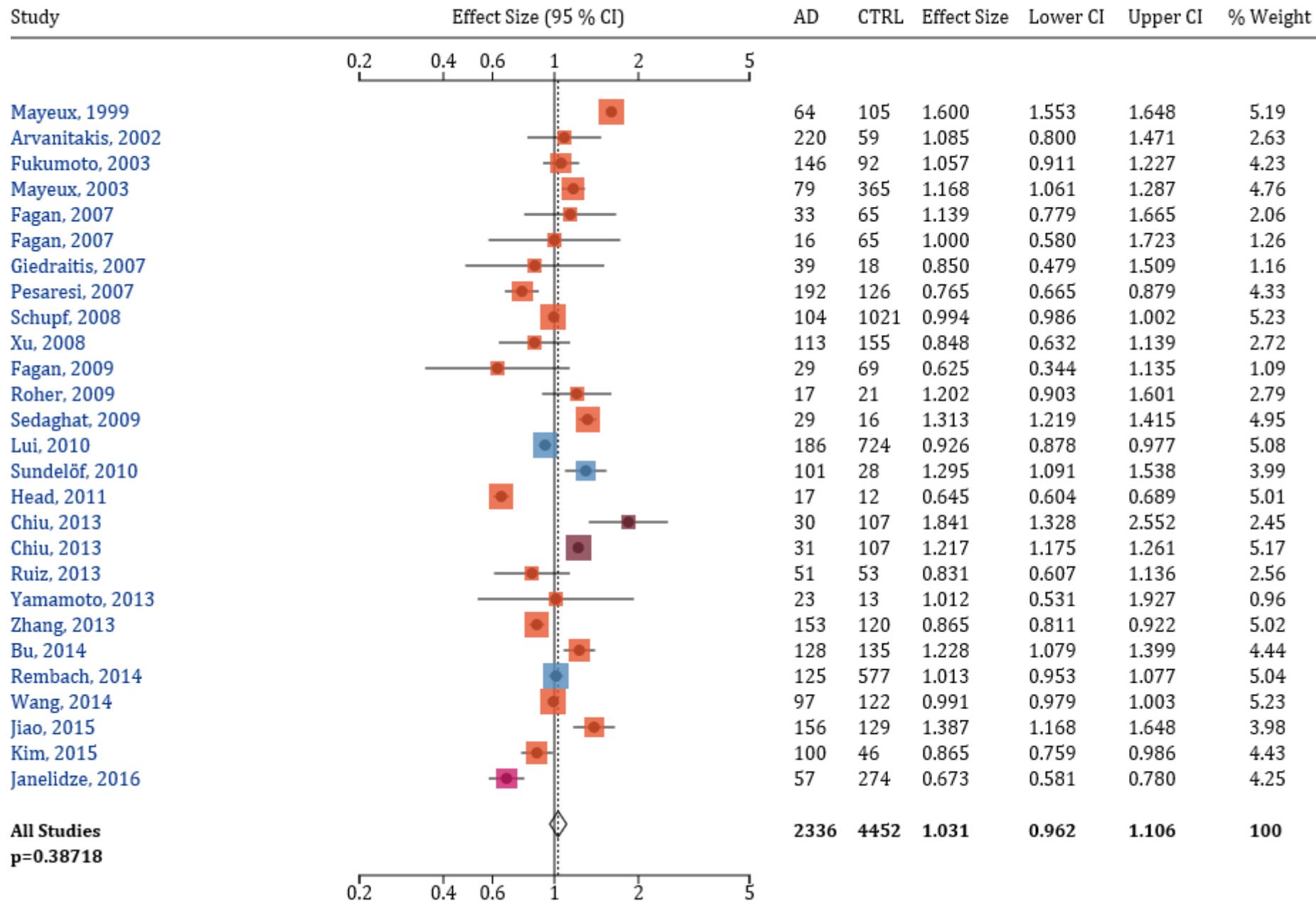
Henrik Zetterberg, MD, PhD
Department of Psychiatry and Neurochemistry,
University of Gothenburg, Sweden;
Institute of Neurology, UCL, UK

The Sahlgrenska Academy

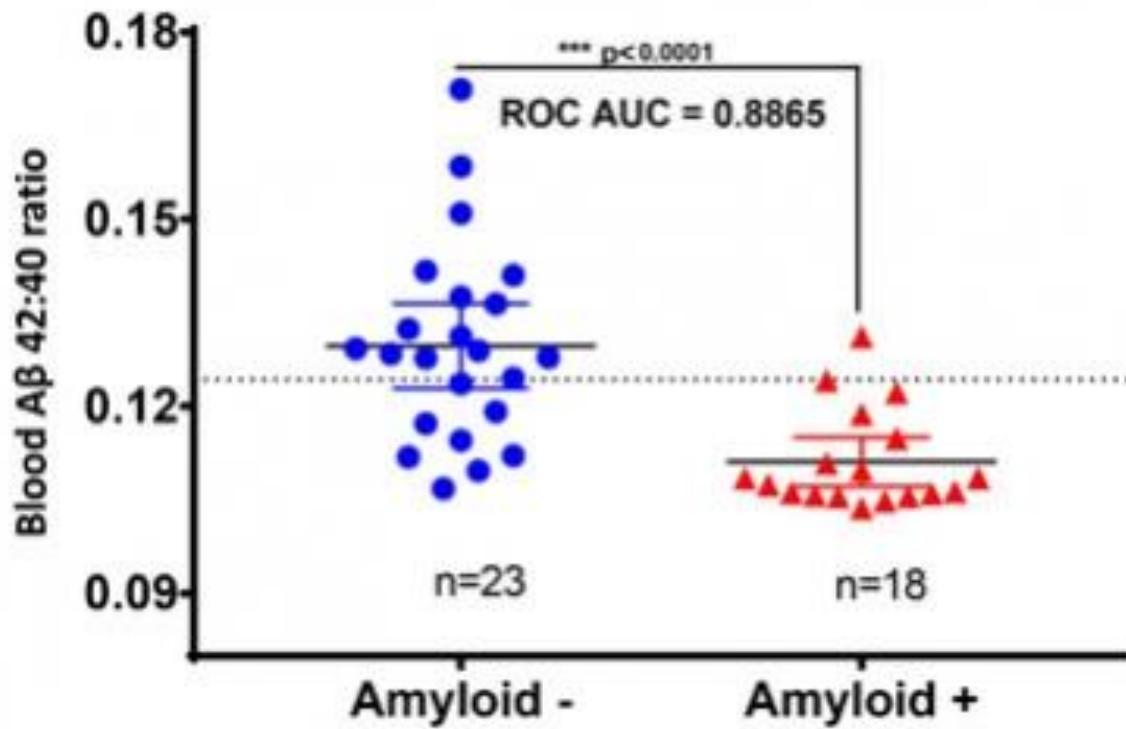
Fluid biomarker candidates of potential relevance to neurodegenerative diseases

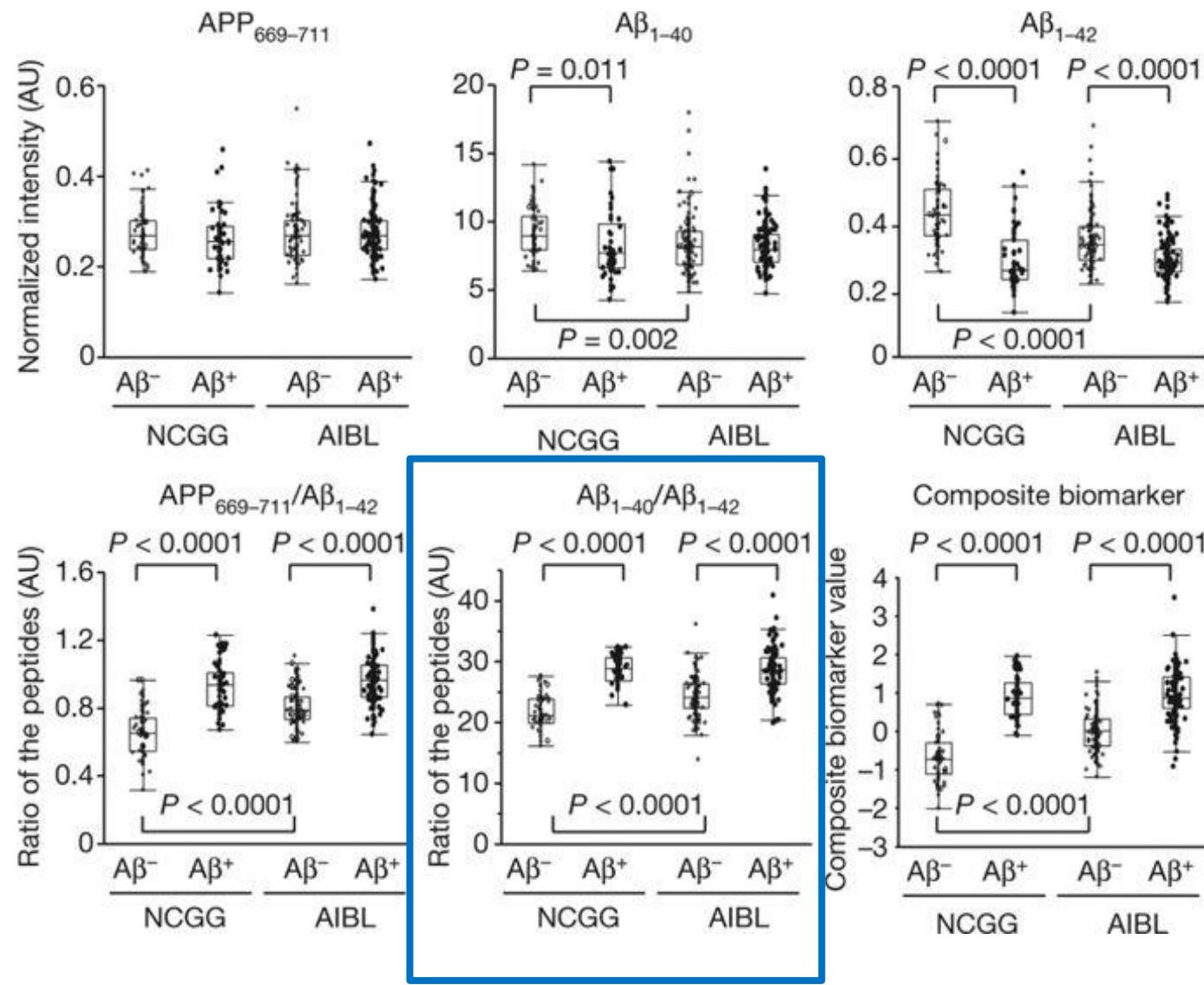


Historically, plasma A β could show any result



Ovod – A&D, 2017

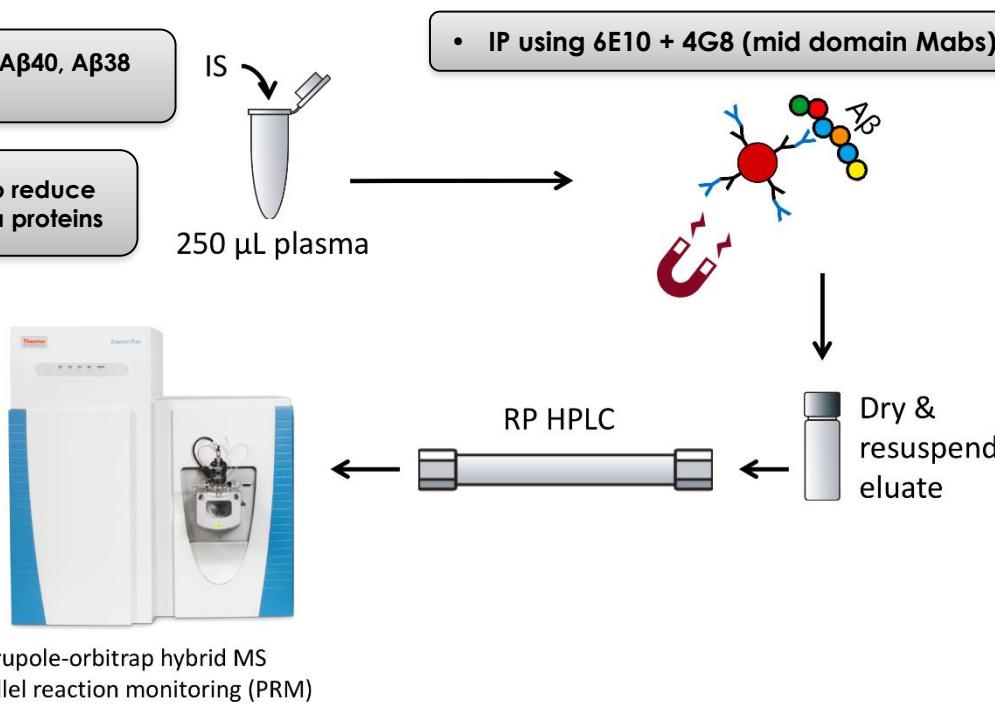




Optimized method for plasma A β by IP-MS/MS

- Recombinant ^{15}N labelled A β 42, A β 40, A β 38 as internal standard

- Plasma treated with Triton X100 to reduce matrix effects - binding to plasma proteins



Coefficients of variation for Quality Control (QC) samples

	pg/mL	CV
A β ₁₋₃₈	21	5 %
A β ₁₋₄₀	262	2 %
A β ₁₋₄₂	25	12 %

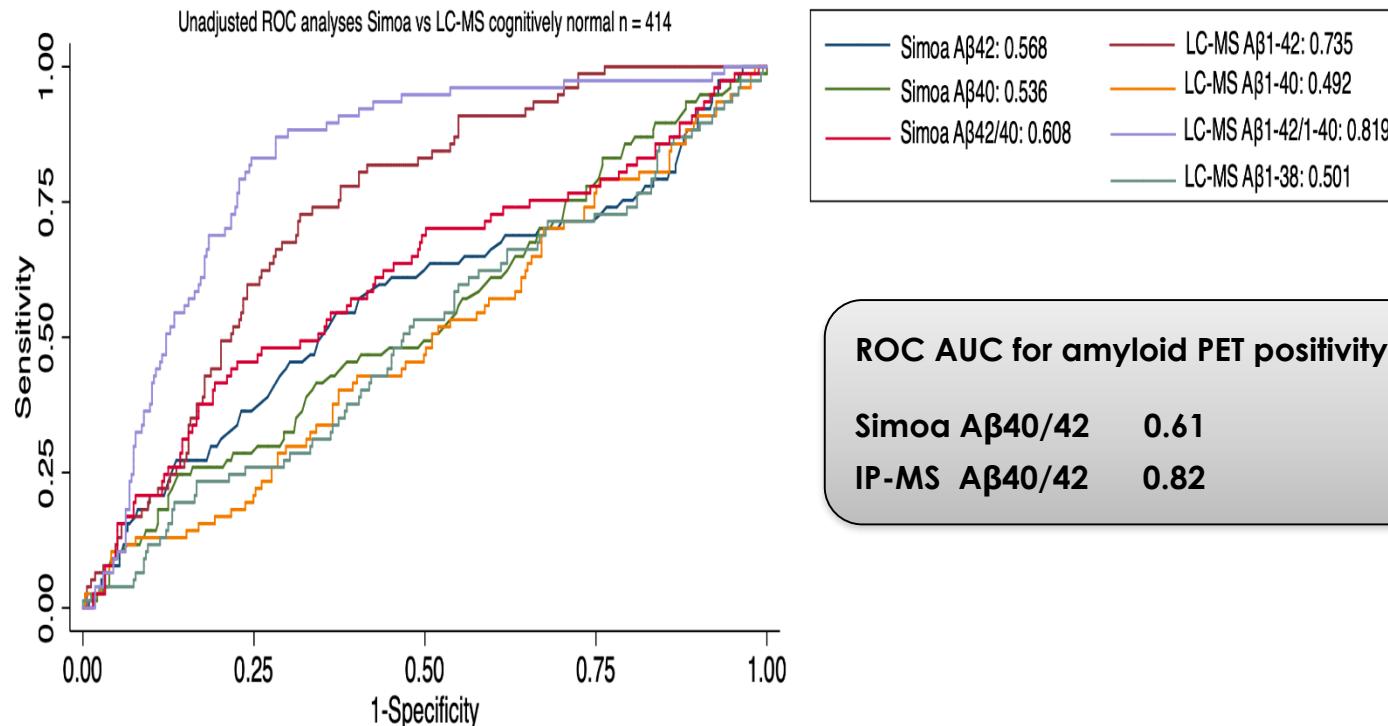
→ Levels of A β 42 and A β 40 in plasma can be measured in 250 μL of plasma with high precision
Also A β 38 and A β -3 to 40 (APP 669-711) can be quantified

Plasma A β in the Insight46 cohort

Study design: Insight46 - epidemiological study people born 1946 (n= 414 cognitively unimpaired)

APOE genotype, neuropsych testing, amyloid PET

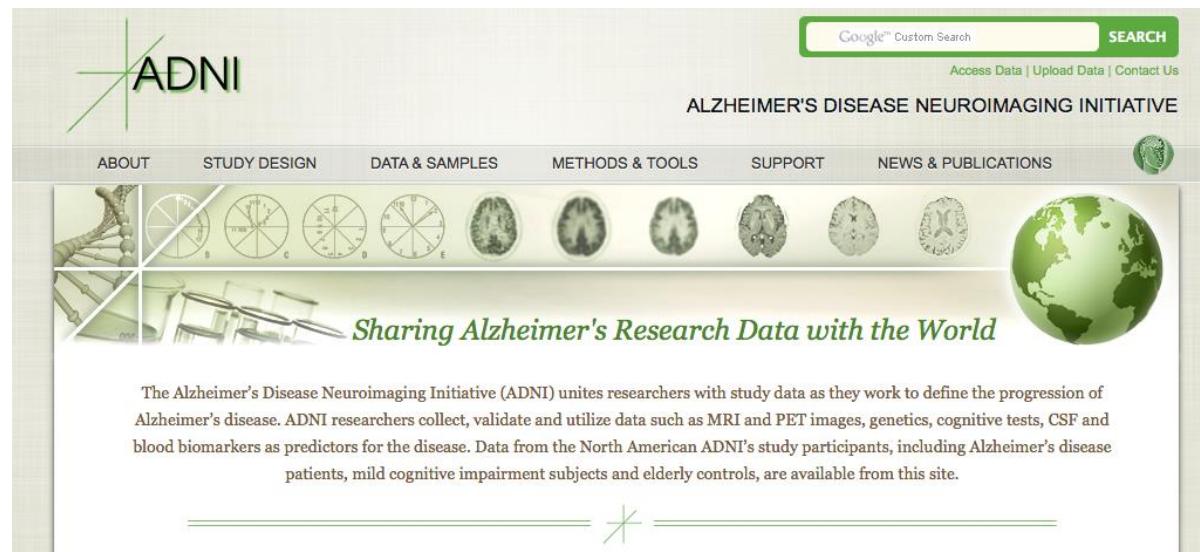
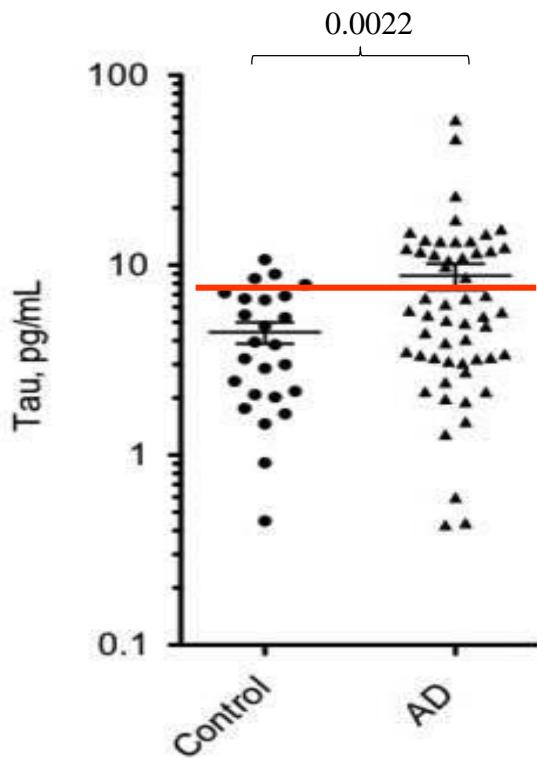
Plasma A β 42, A β 40/42 using immunoassay (Simoa) and IP LC-MS/MS



→ Plasma A β 42 and A β 40/42 ratio by IP-MS/MS show high concordance with brain amyloidosis

Plasma tau in Alzheimer's disease

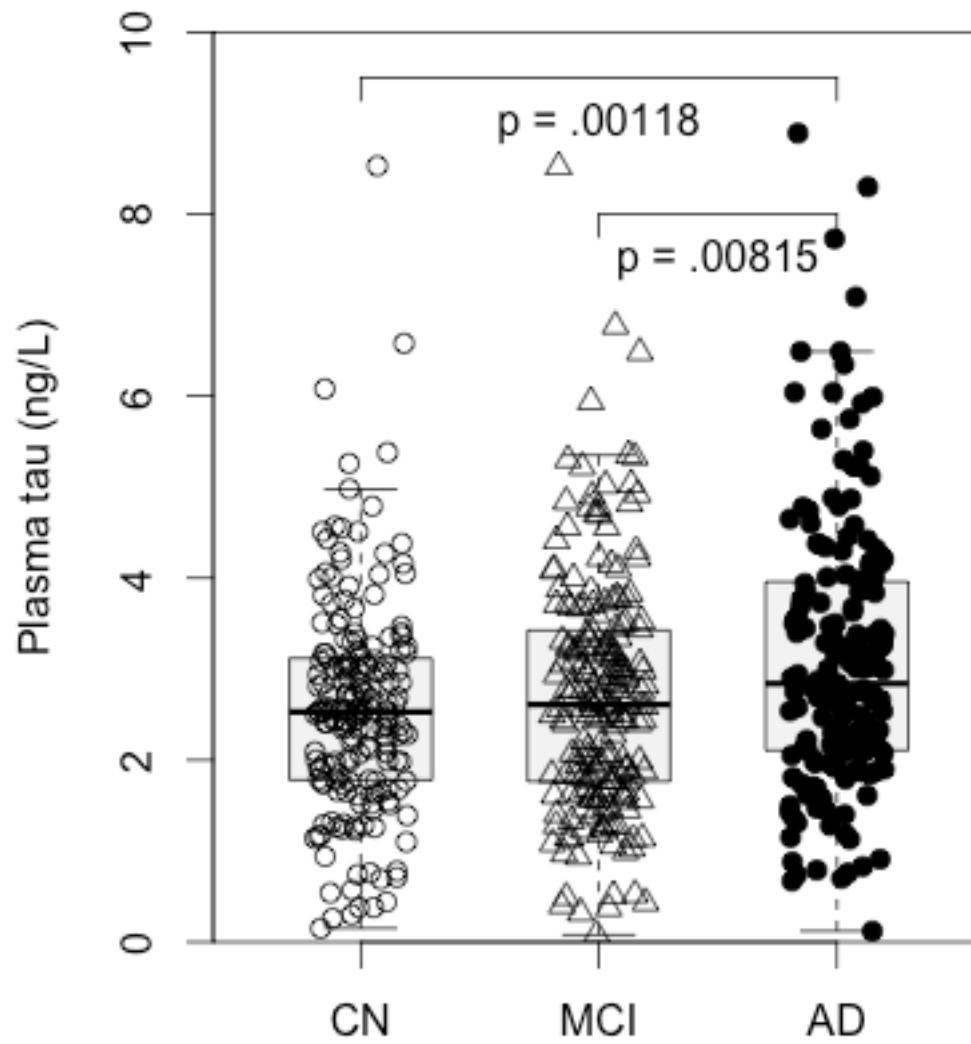
AD dementia n= 54
Healthy controls n= 25



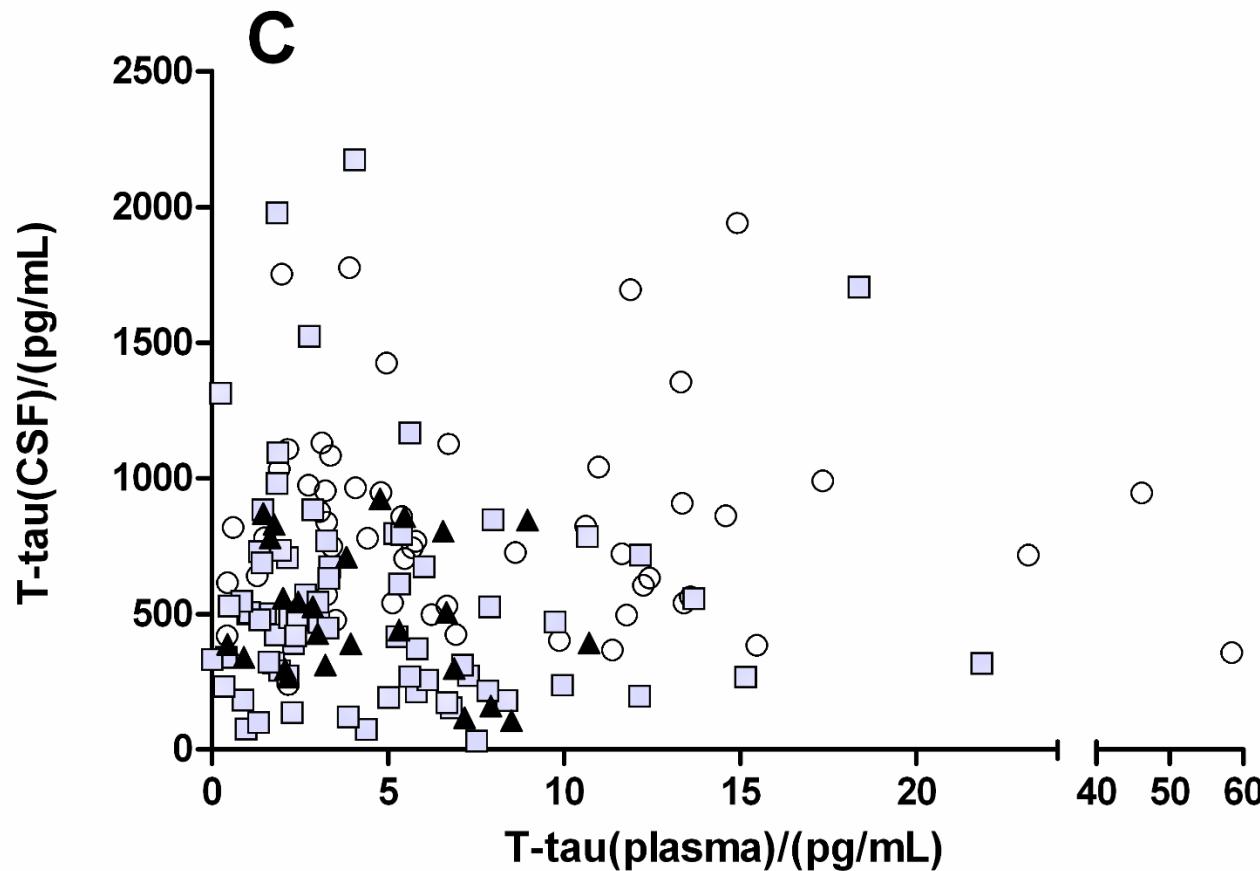
>400 plasma samples from:

Normal elderly (4-7 years follow-up)
Mild cognitive impairment
AD dementia

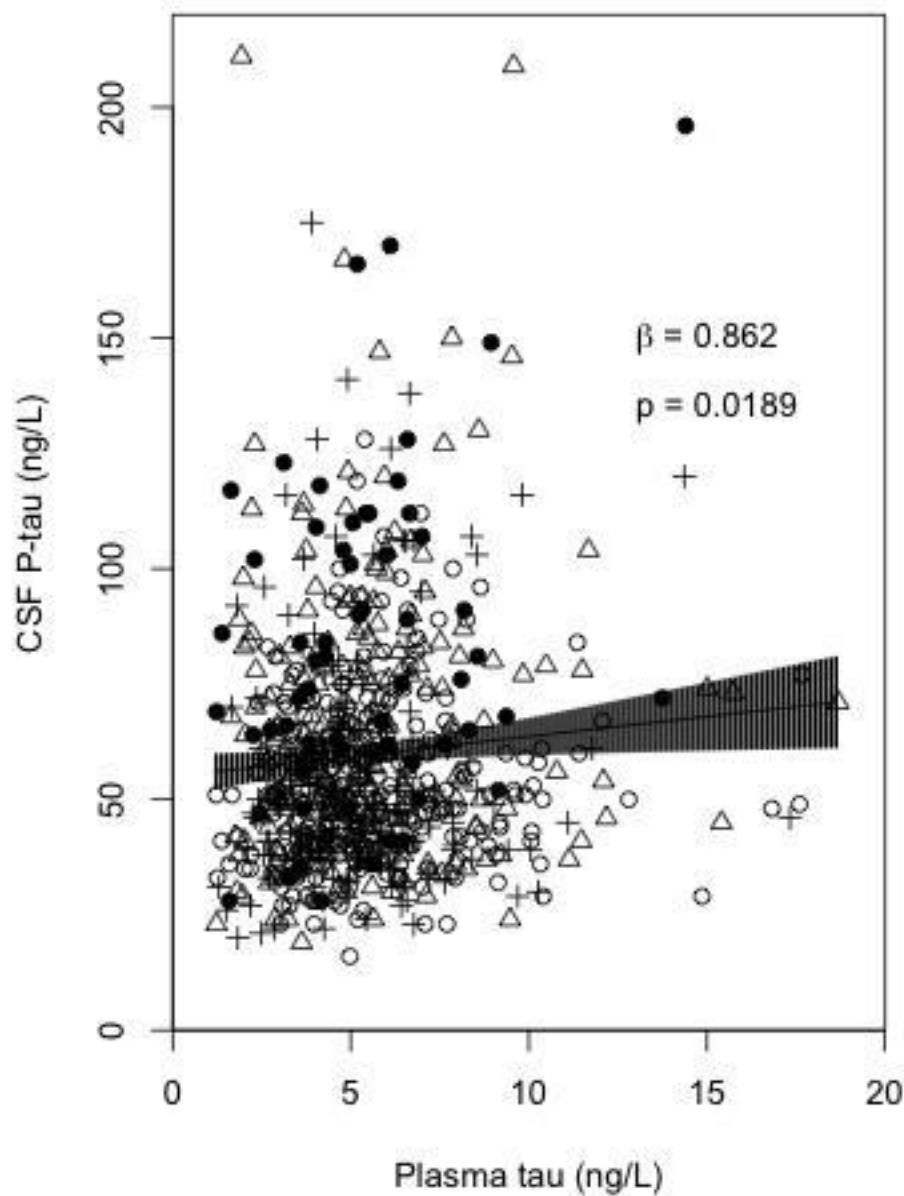
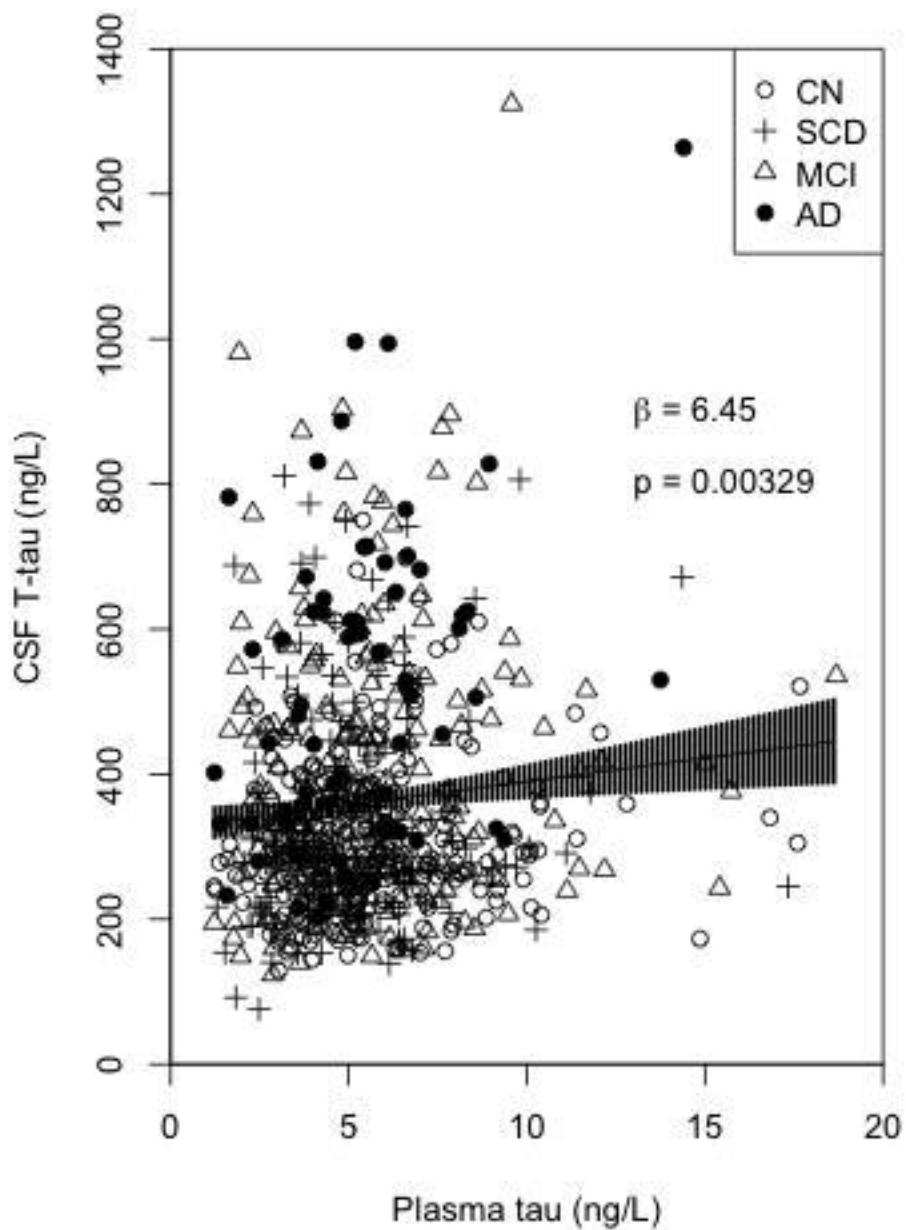
Plasma tau in ADNI



Plasma tau in Alzheimer's disease – no correlation to CSF...

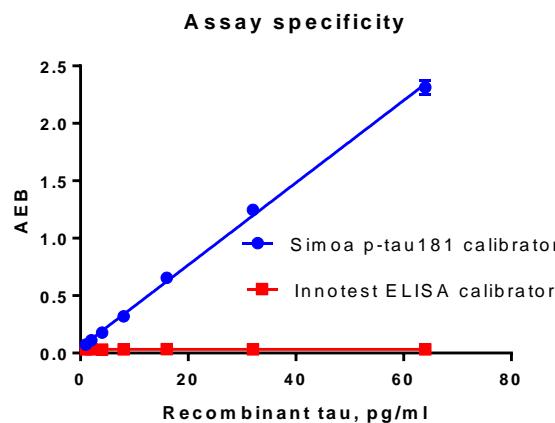
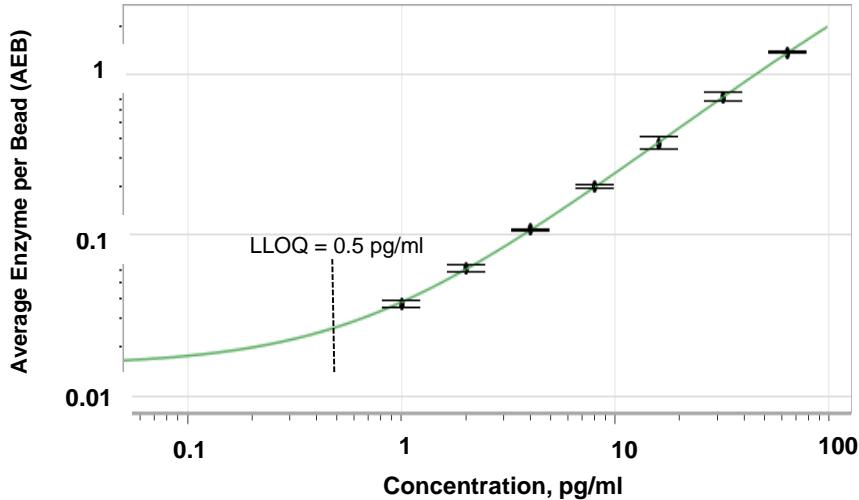


Plasma tau in ADNI



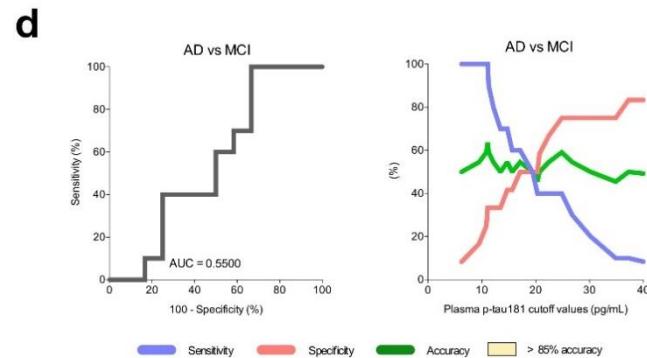
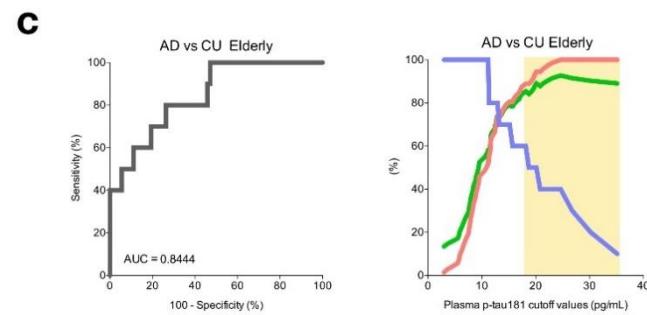
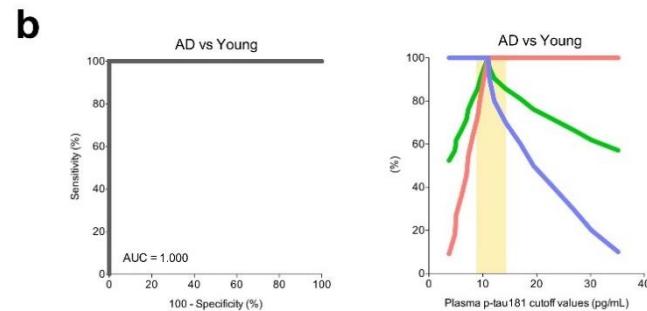
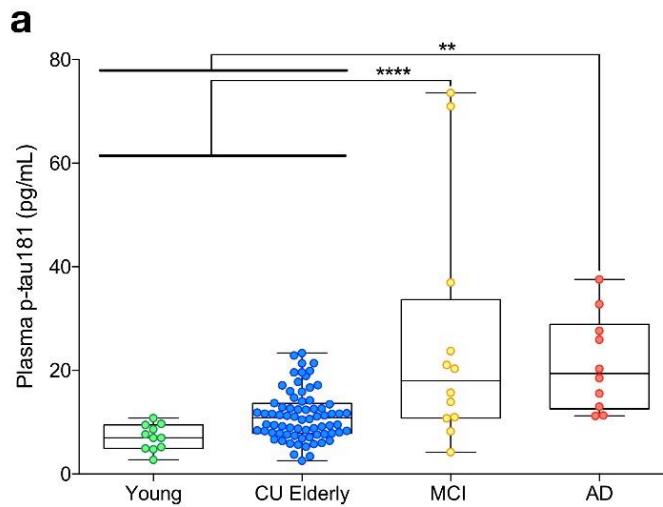
Plasma P-tau181 in Alzheimer's disease and related disorders

In house Simoa assay

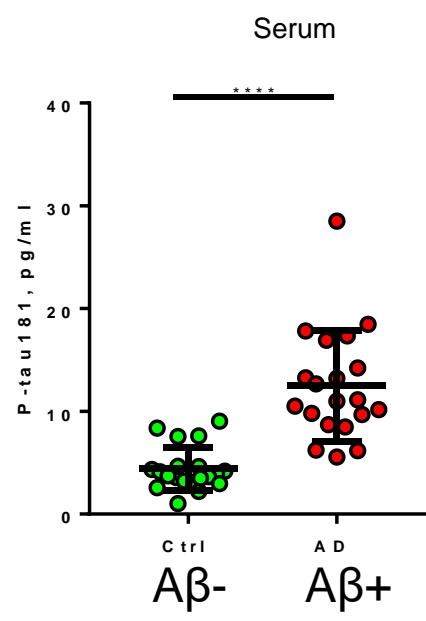
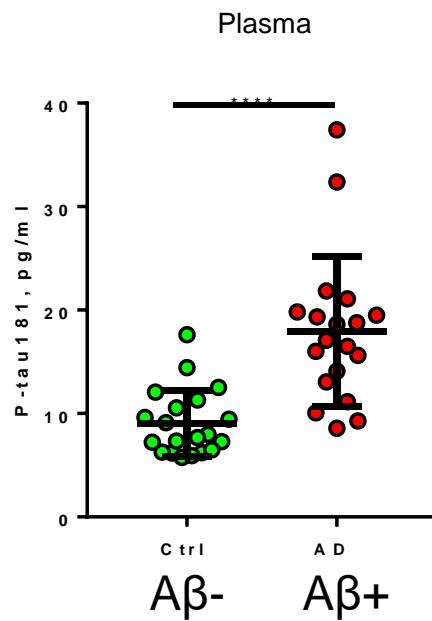


TRIAD 'discovery' cohort

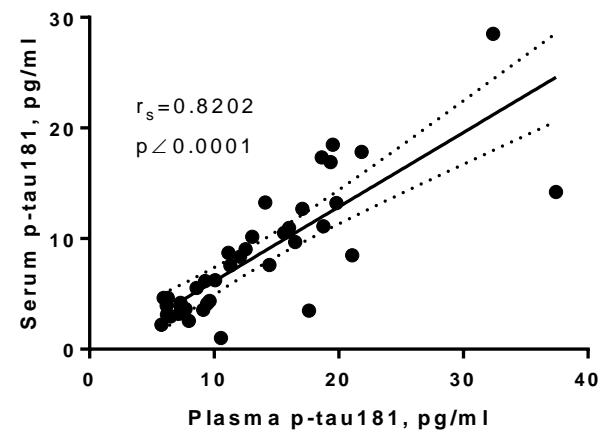
Plasma P-tau181 increased in MCI and AD



Plasma and serum p-tau181 are accurate predictors of biologically defined AD



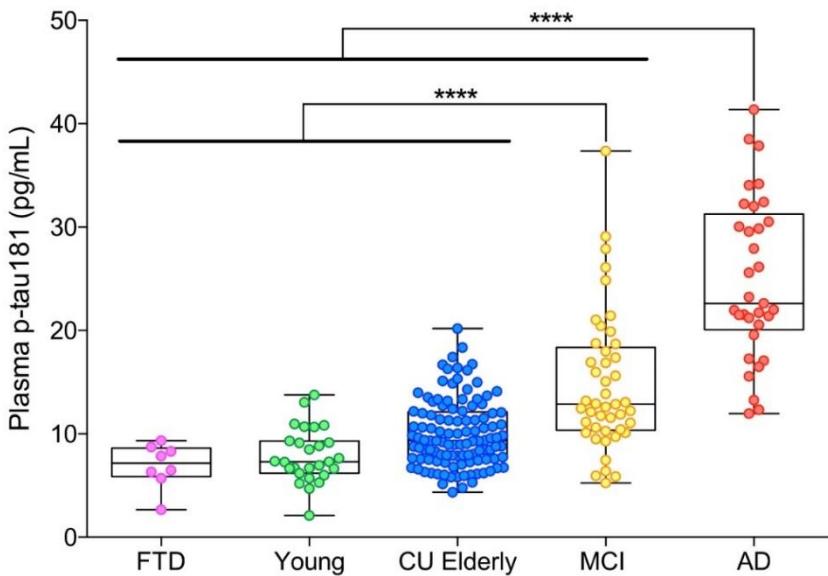
Plasma and serum are both suitable for p-tau181 analysis



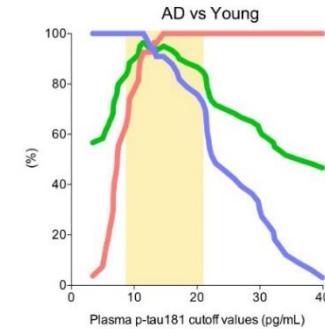
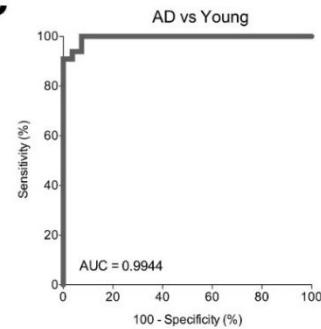
TRIAD validation cohort

P-tau181 in relation to clinical diagnoses

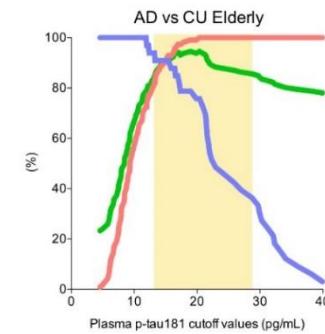
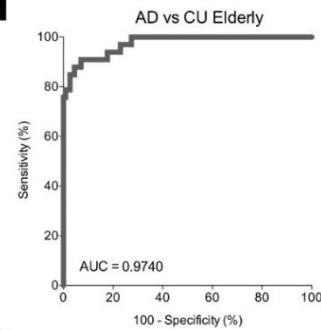
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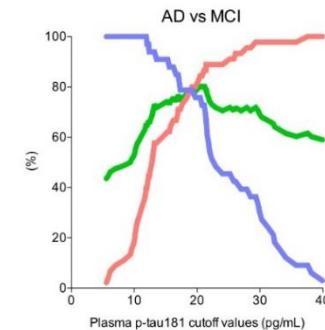
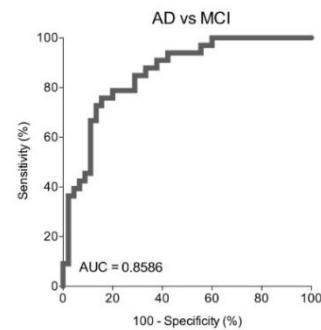
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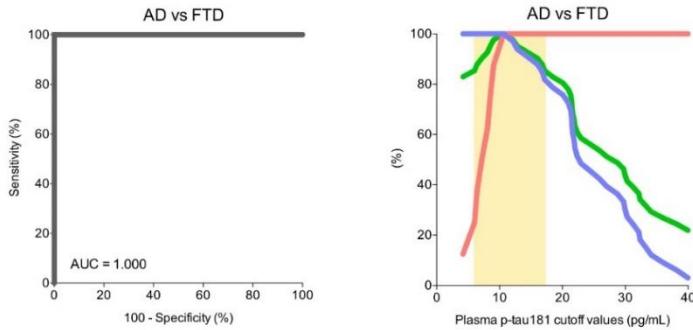
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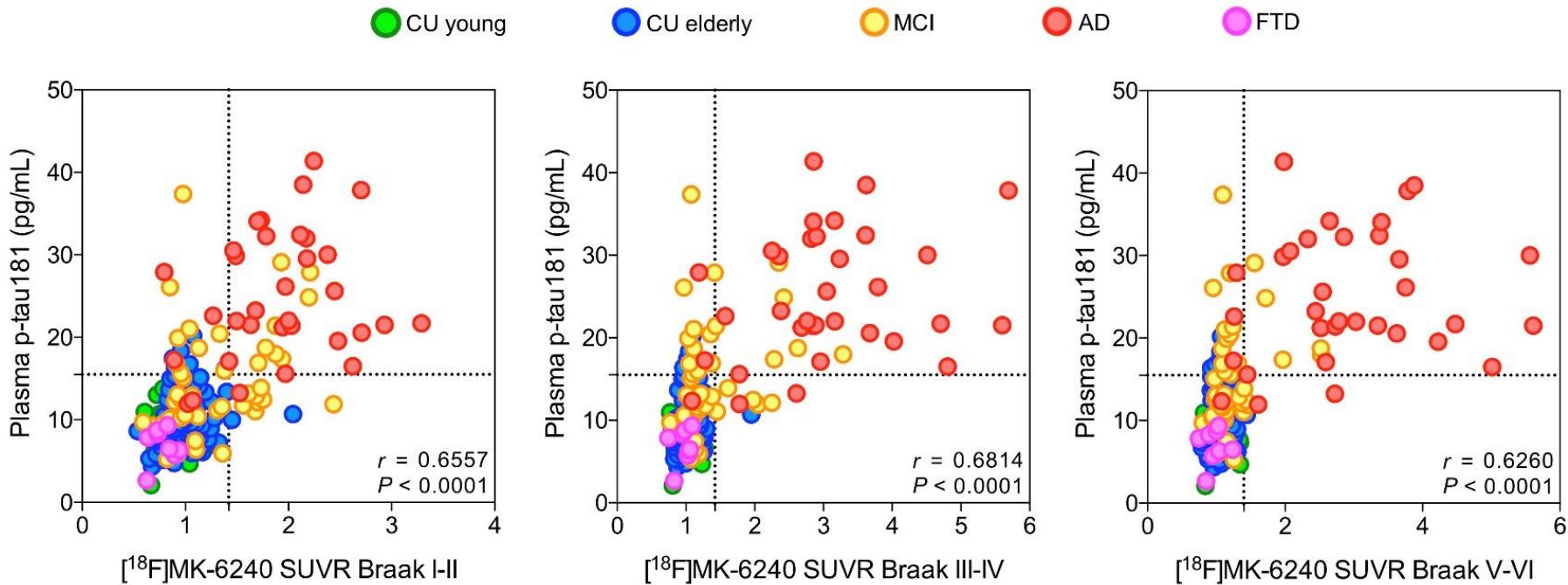


b



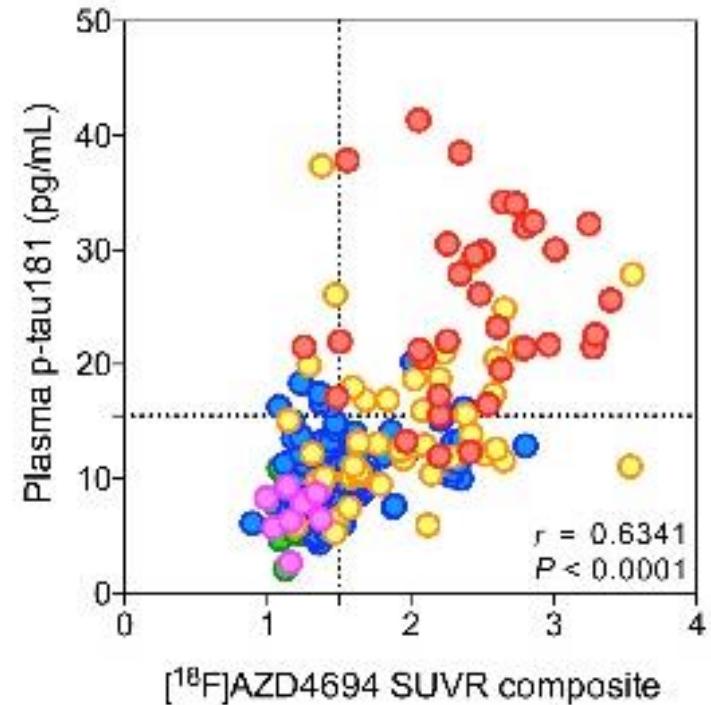
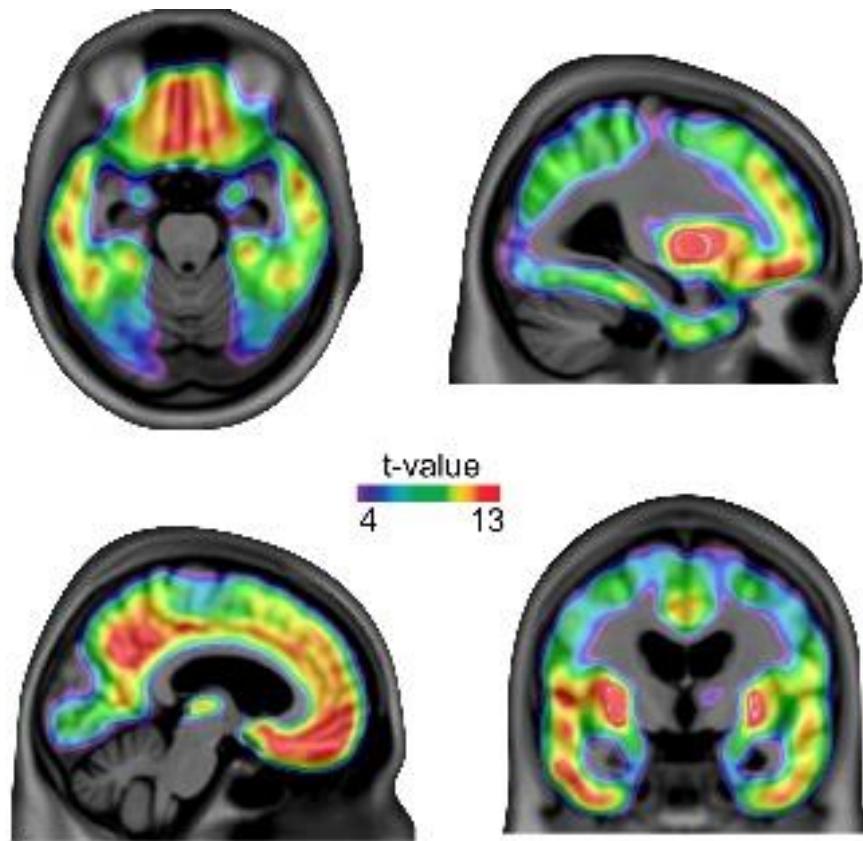
Legend:
 █ Sensitivity █ Specificity █ Accuracy █ > 85% accuracy

TRIAD validation cohort
Plasma p-tau181 correlates with MK-6240 tau PET



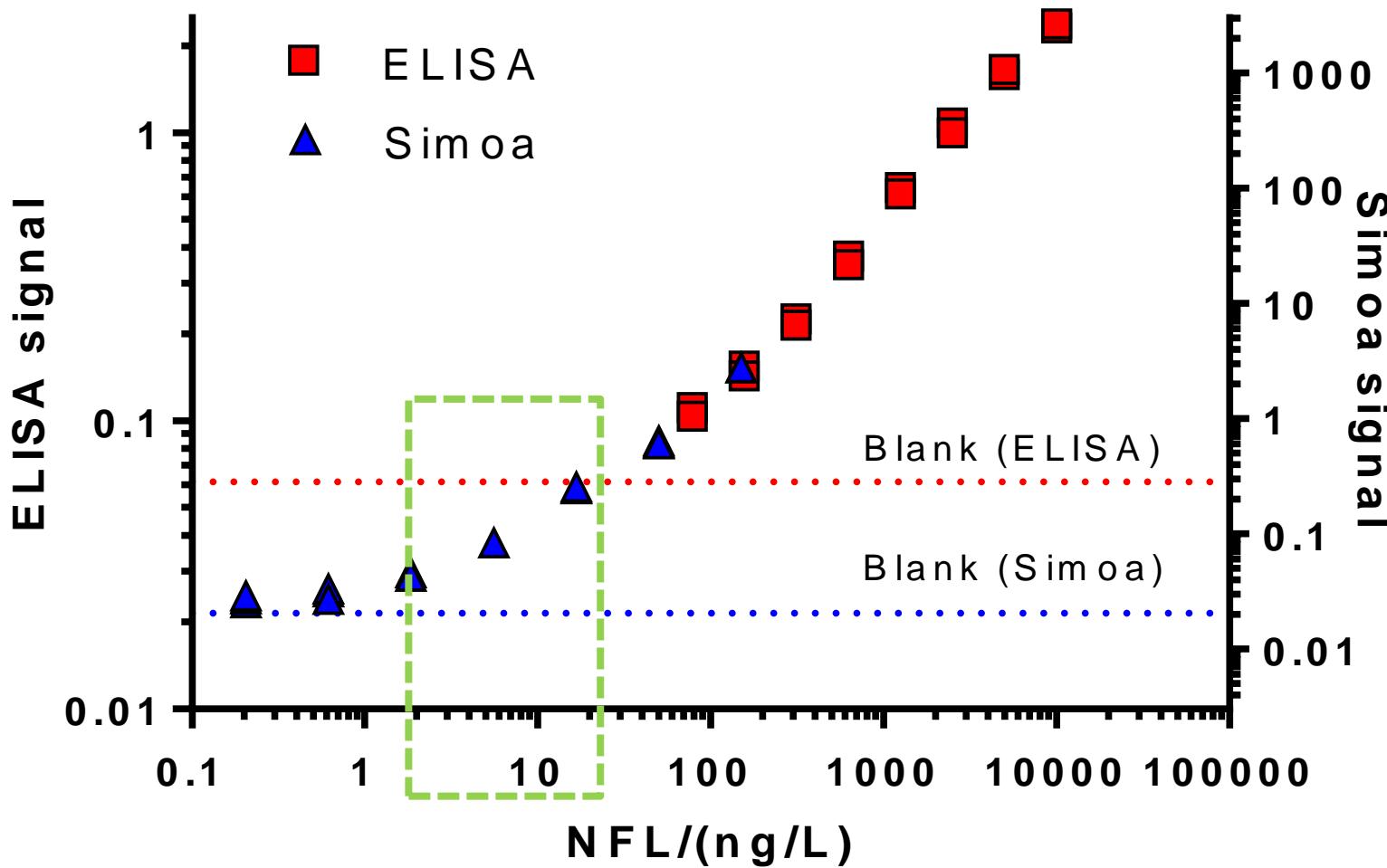
TRIAD validation cohort

P-tau181 correlates with AZD4694 amyloid PET



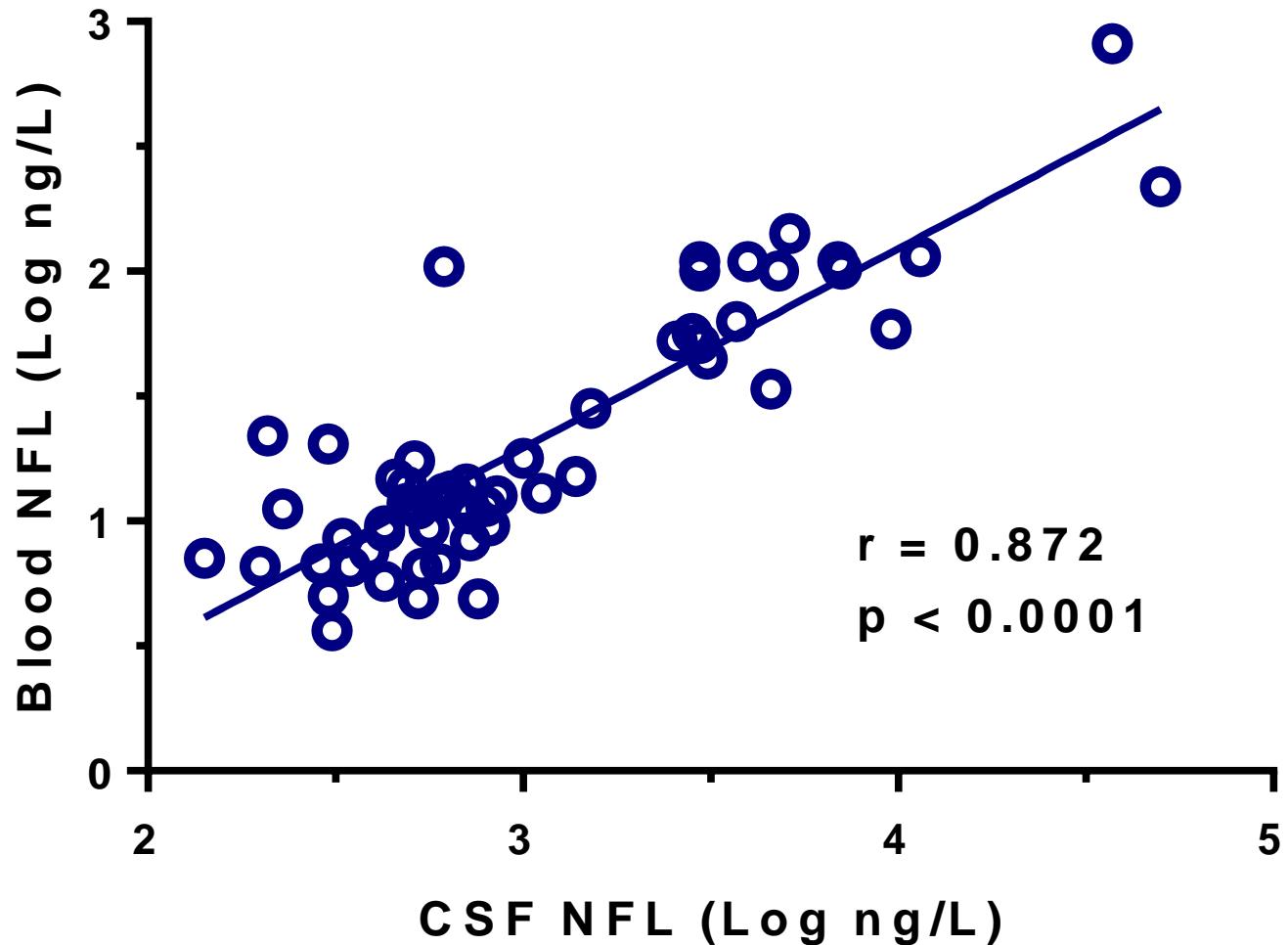
Karikari *et al.*, unpublished

NfL - ELISA vs. Simoa

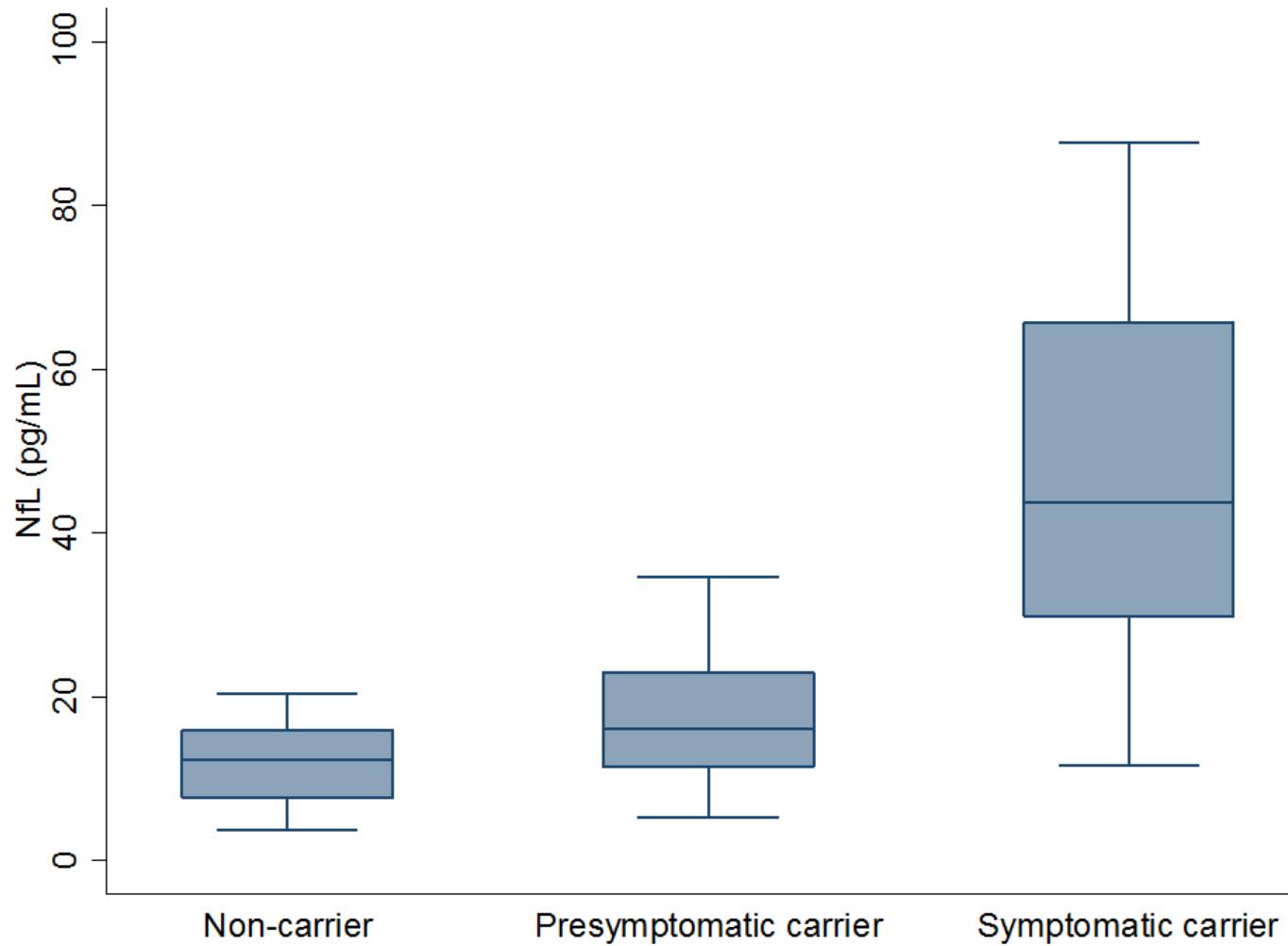


LLoD = 0.26 ng/L; LLoQ = 1.95 ng/L

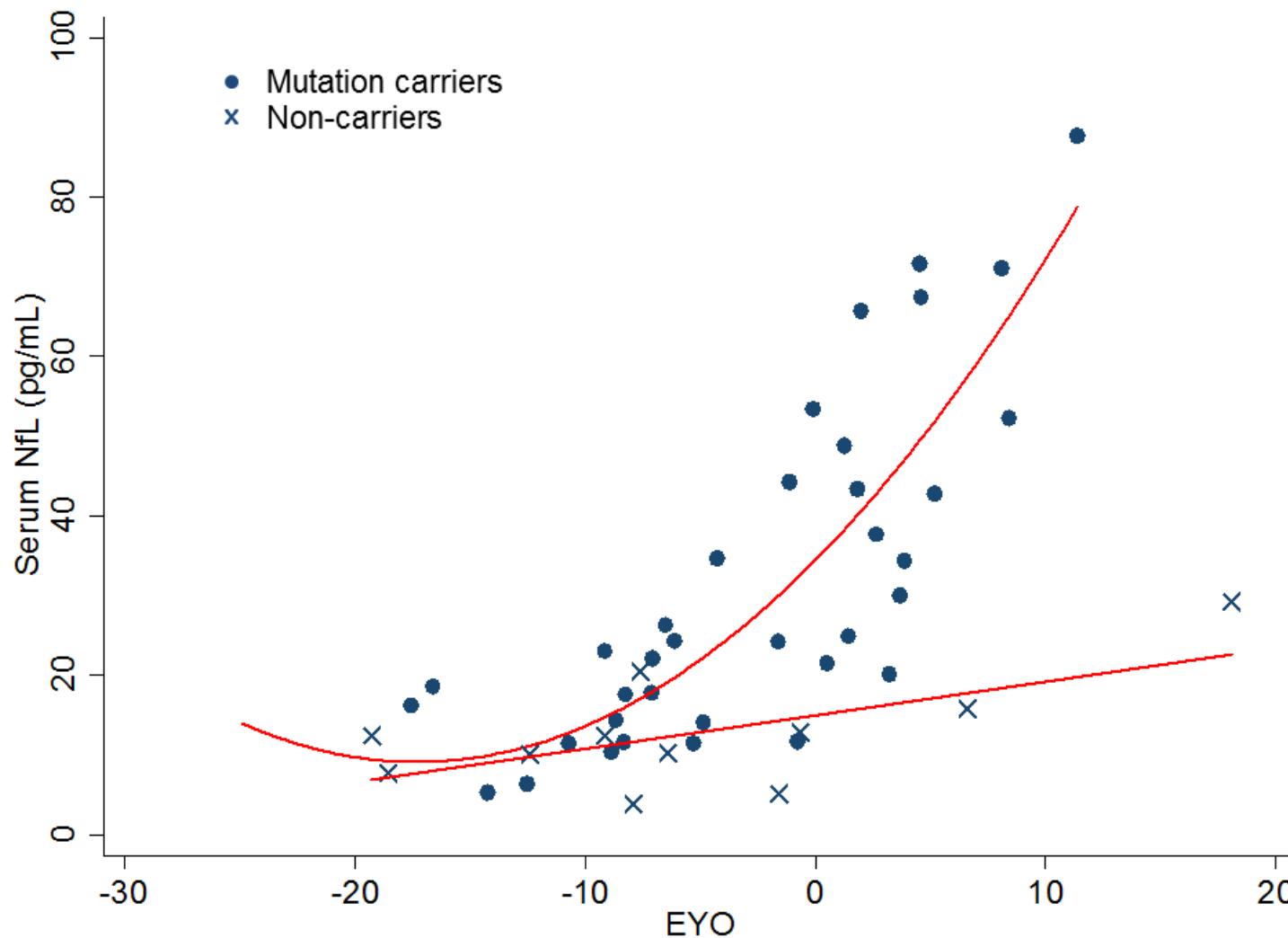
Plasma NfL correlates with CSF NfL



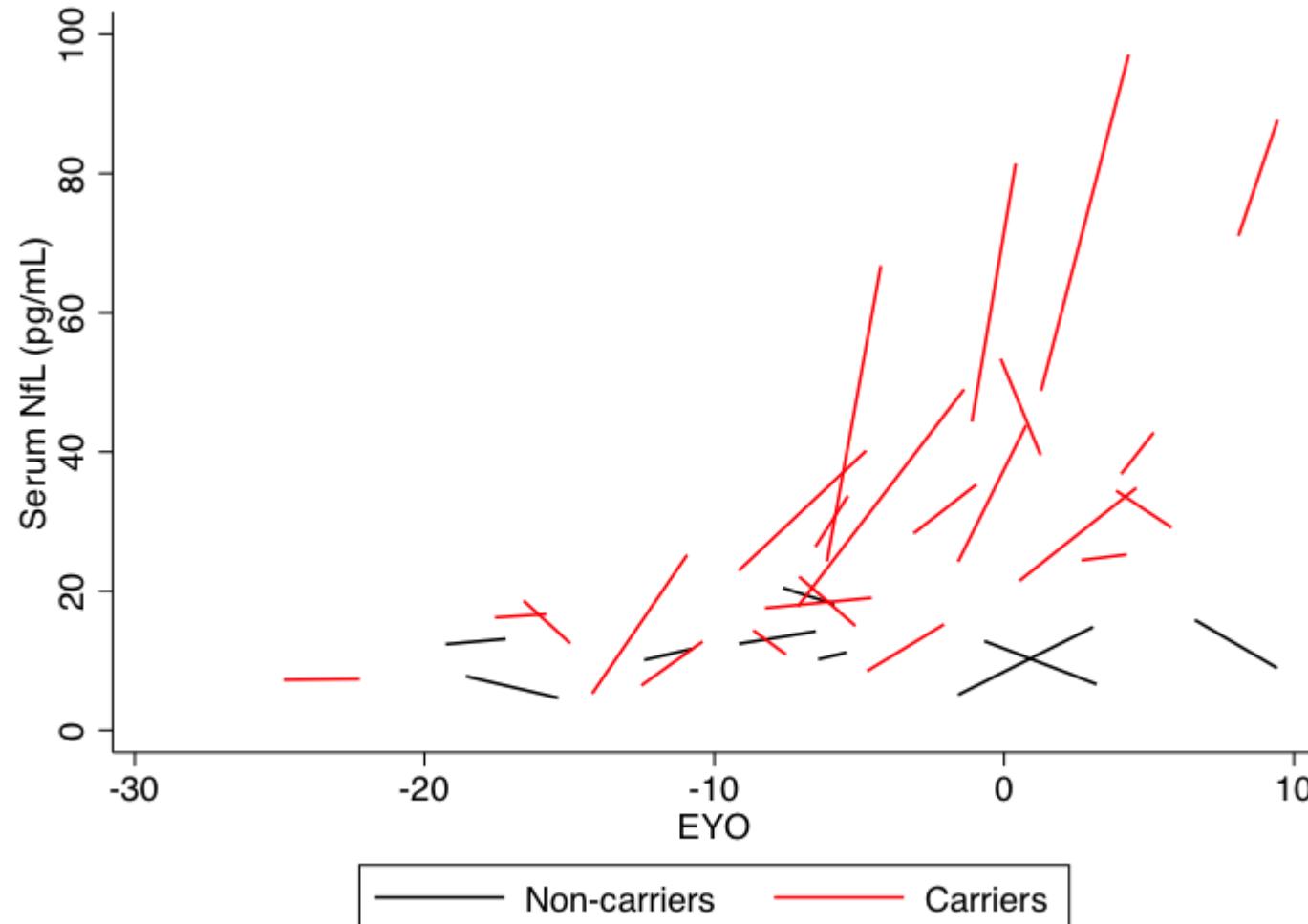
Plasma NfL in familial Alzheimer's disease



Plasma NfL in familial Alzheimer's disease

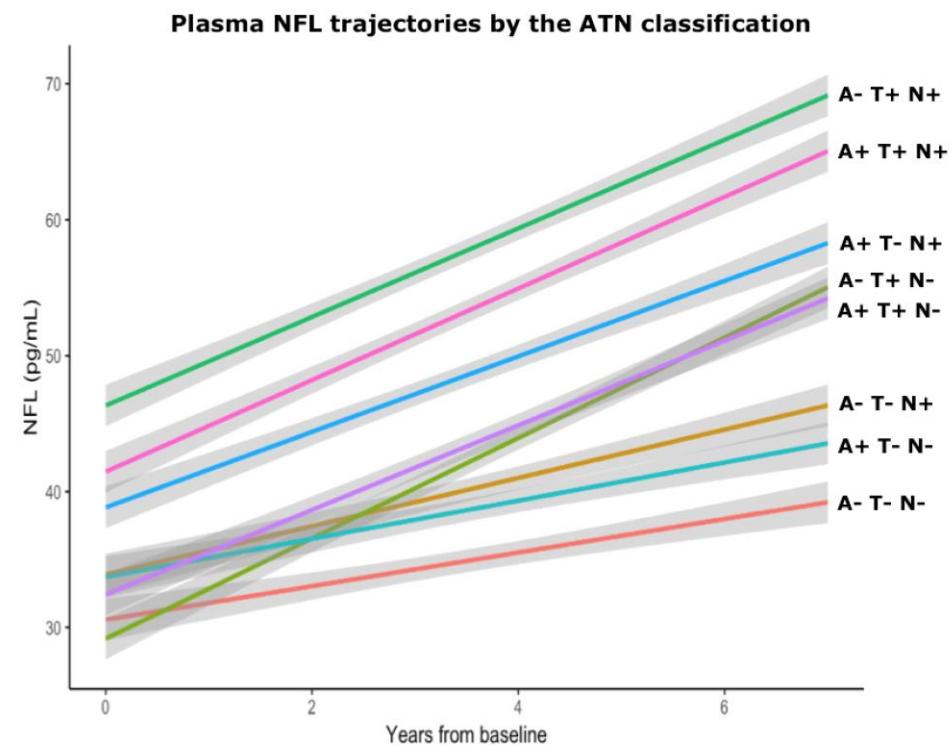
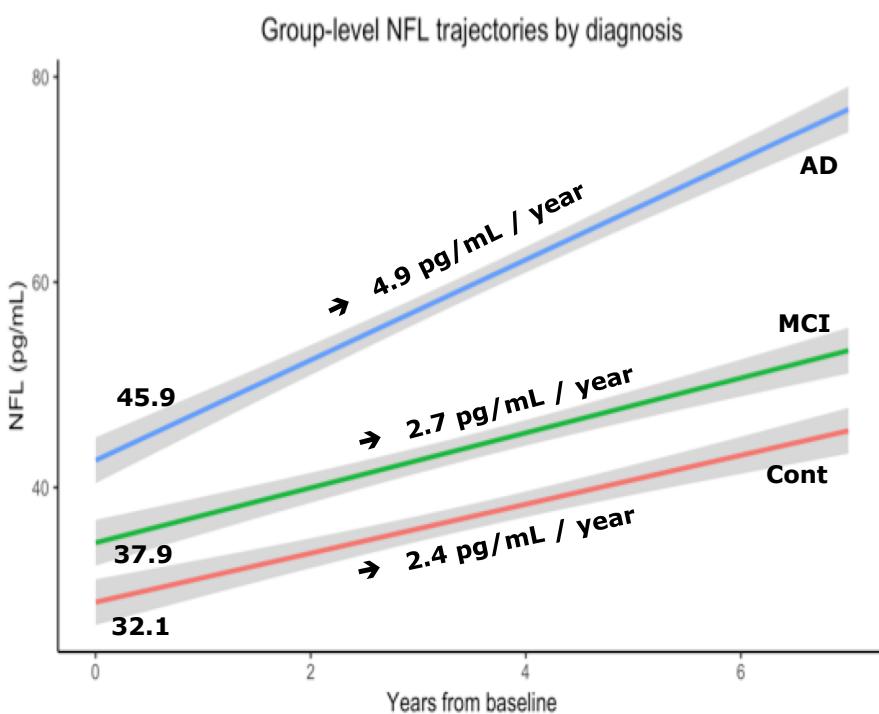


Plasma NfL in familial Alzheimer's disease – longitudinal data



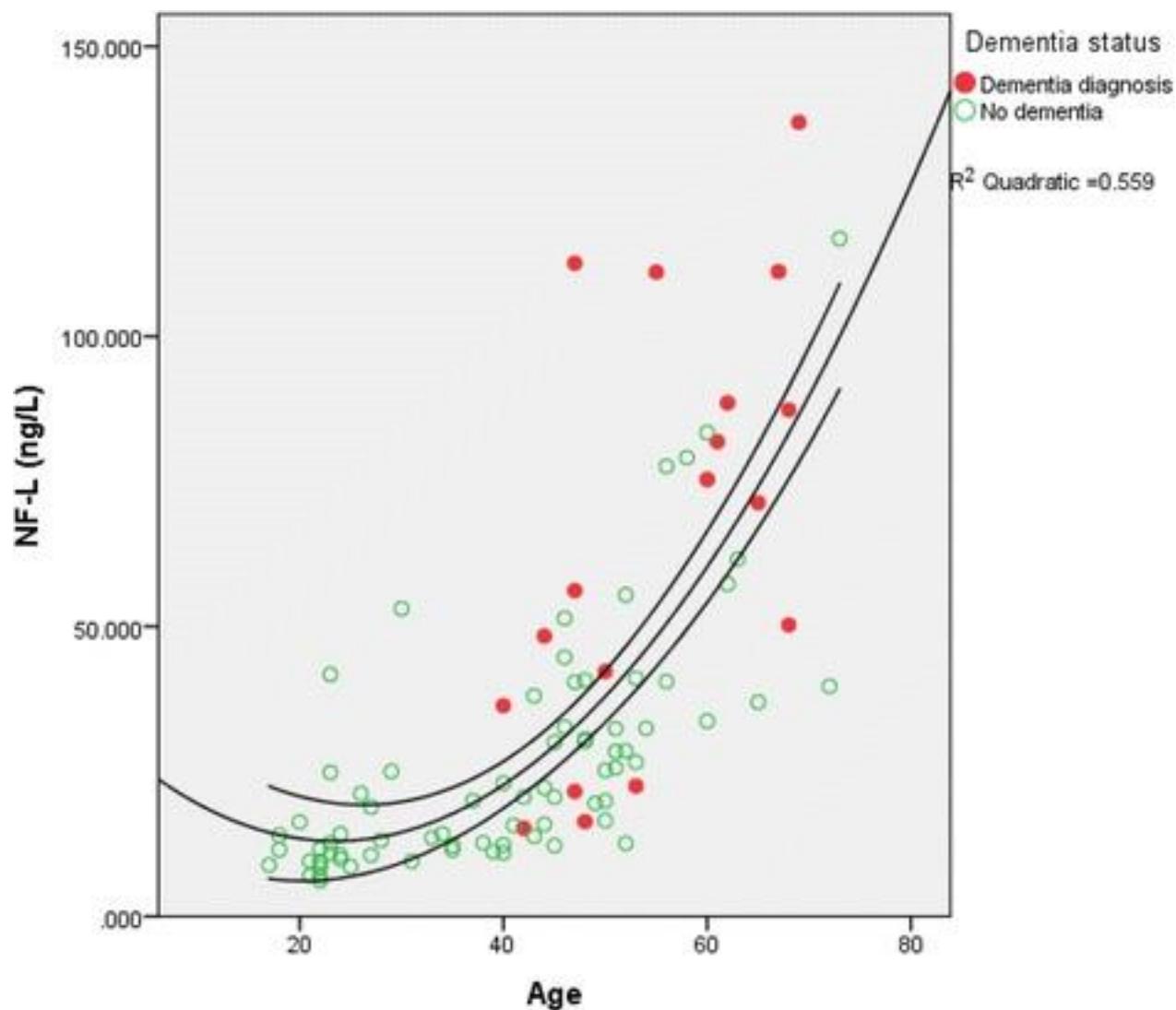
Longitudinal plasma NFL in the ADNI study

- All ADNI patients: CU controls (n= 401), MCI (n= 855) and AD dementia (n= 327)
- Baseline + up to 11 year longitudinal data, in total 4326 samples
- In-house Simoa for plasma NFL: Uman antibodies + bovine NFL calibrator Gisslén et al, EBioMed 2016

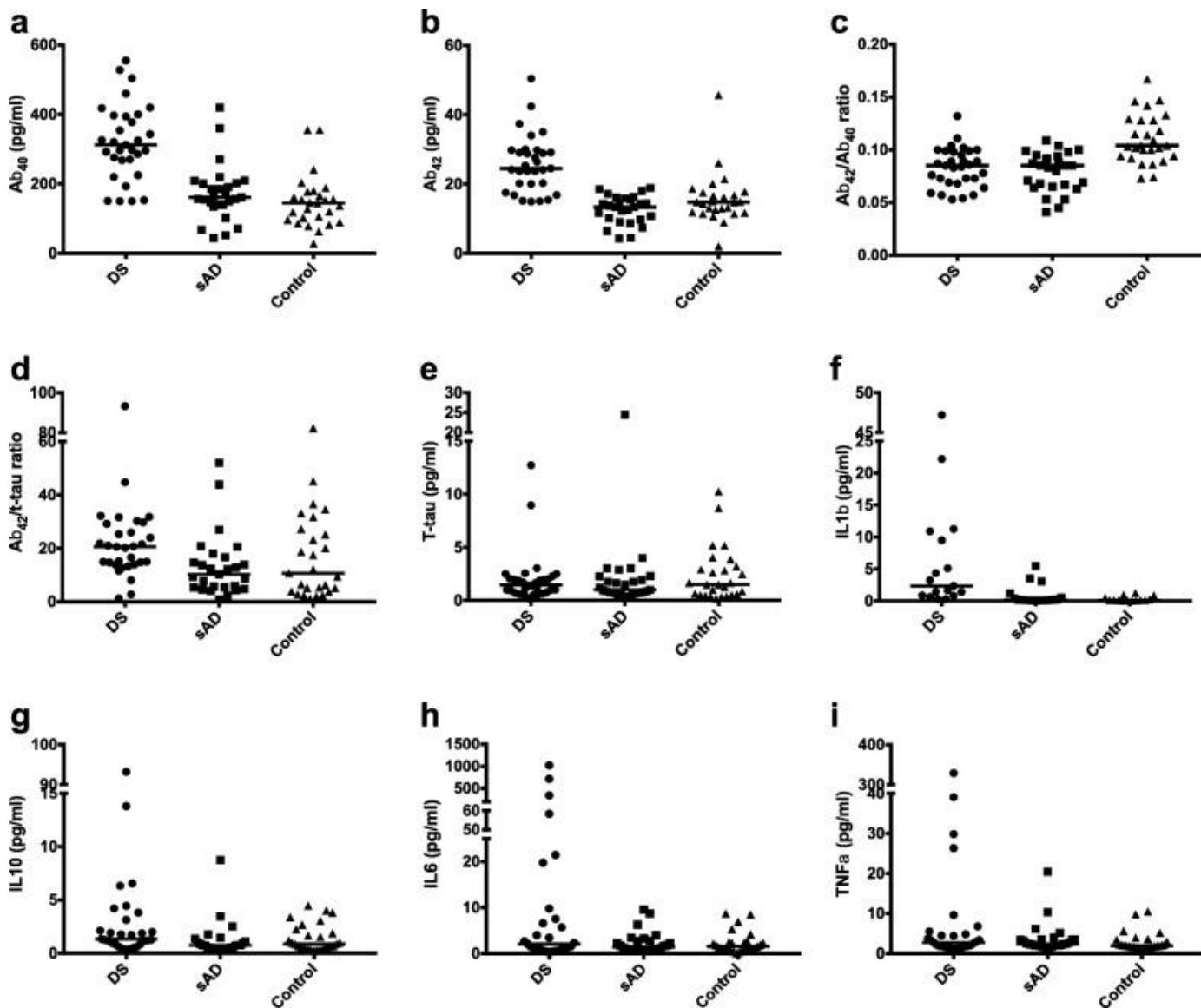


- Plasma NFL can track neurodegeneration throughout the AD continuum
- Serum NFL may be useful to monitor downstream drug effects on intensity of neurodegeneration

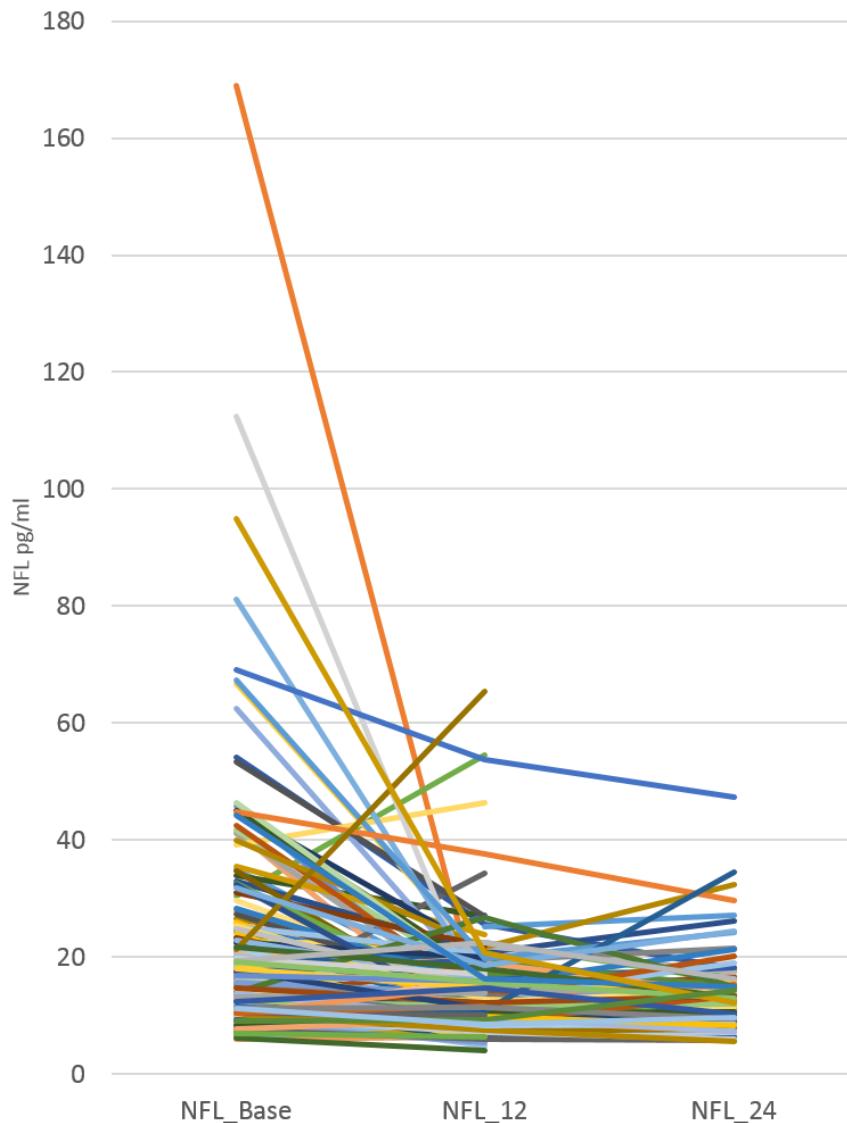
Plasma NfL in Down individuals



Plasma AD biomarkers in Down



Serum NfL in multiple sclerosis – before and after treatment with natalizumab



Unpublished

Conclusions - blood biomarkers

- Promising results for plasma A β (plaque pathology)
- Less promising results (current assays) for plasma total-tau (a predictive marker of AD-type neurodegeneration or a neuronal response to amyloid marker?)
- Very promising results for plasma P-tau181 (a predictive marker of AD-type tangle pathology + a neuronal response to amyloid marker?)
- Promising results for plasma/serum NfL (neurodegeneration)

Thanks!!



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