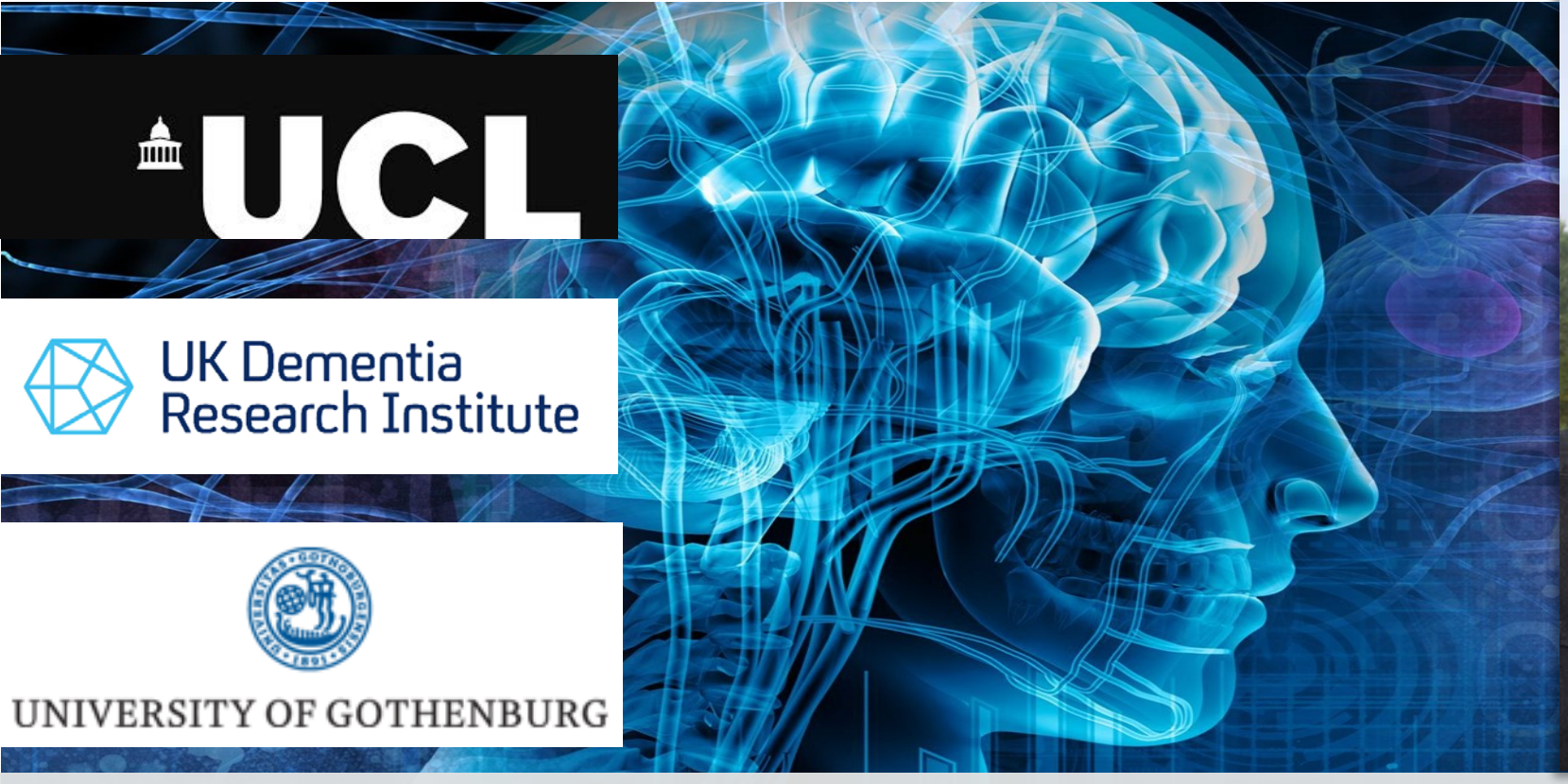
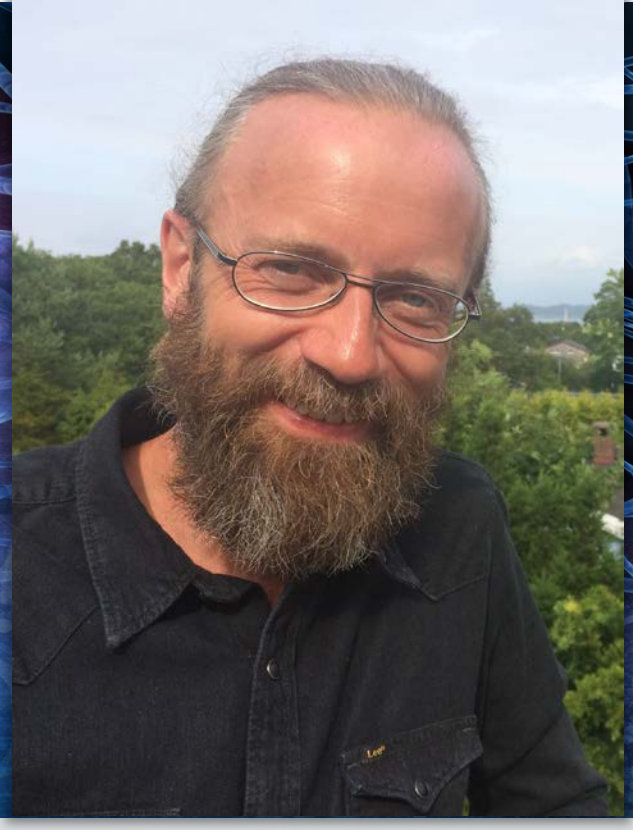
UCL

UK Dementia Research Institute

UNIVERSITY OF GOTHENBURG





Keynote 3: Integration of Biomarkers and Quantitative Modeling - Plasma

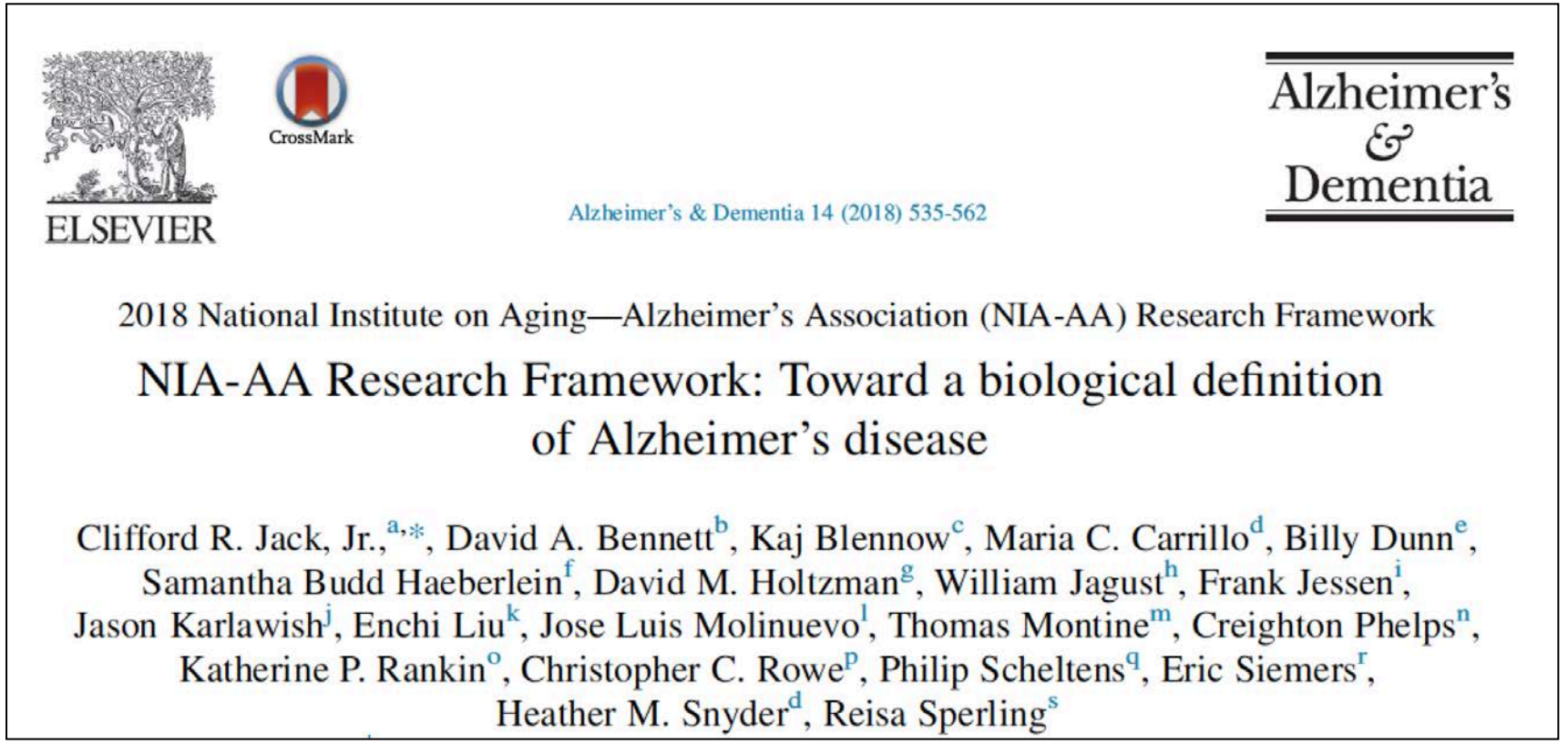
October 27, 2020

Henrik Zetterberg, Professor University of Gothenburg & University College London

CONFIDENTIAL

CRITICAL PATH INSTITUTE 15 YEARS

CPAD CRITICAL PATH FOR ALZHEIMER'S DISEASE CRITICAL PATH INSTITUTE



Alzheimer's & Dementia 14 (2018) 535-562

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

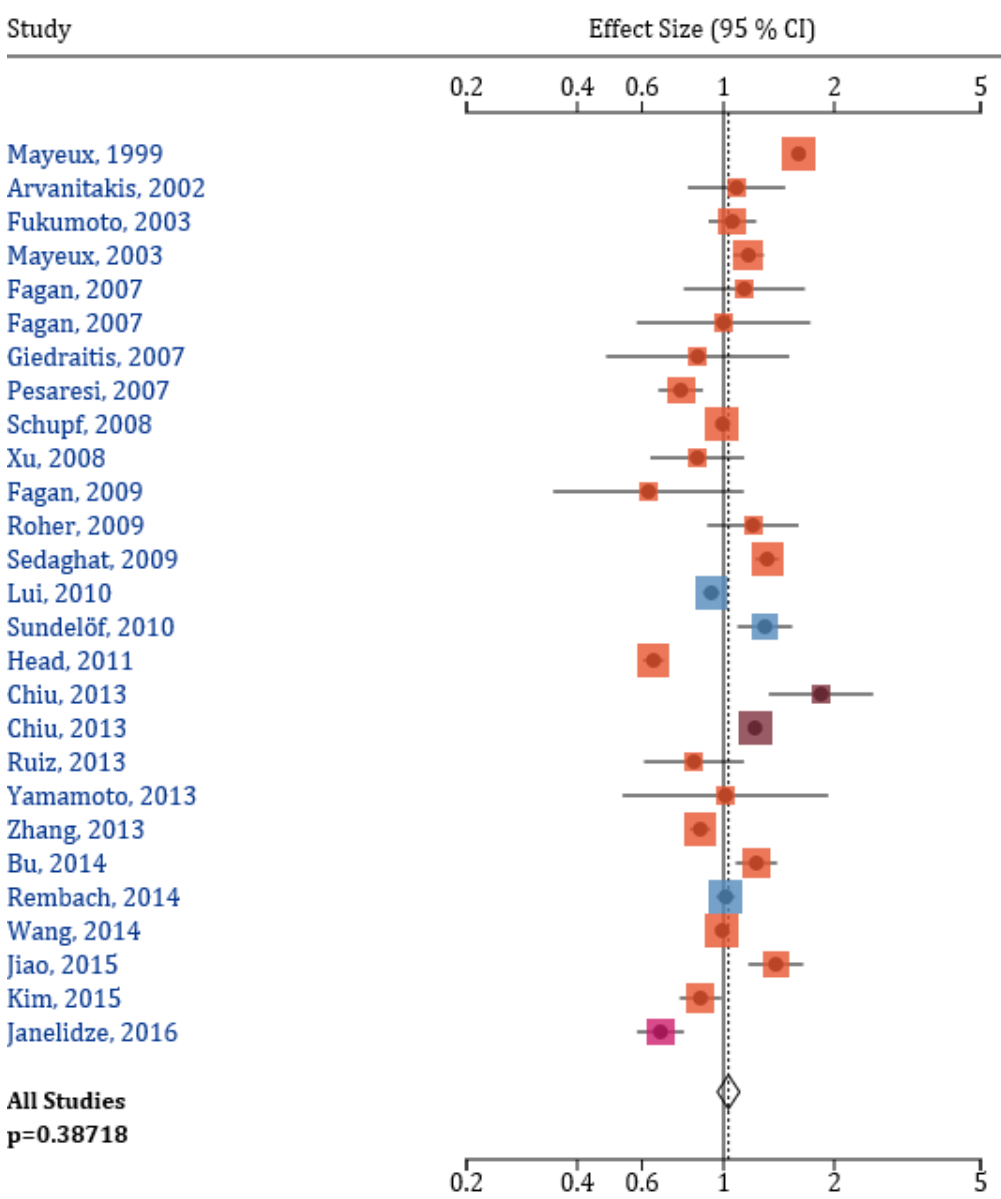
Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Biomarkers for A/T/N

- Amyloid = CSF Aβ42/Aβ40 ratio and amyloid PET
- Tau = Tau PET (CSF P-tau as a predictive marker?)
- Neurodegeneration = CSF neurofilament light, MRI, FDG-PET

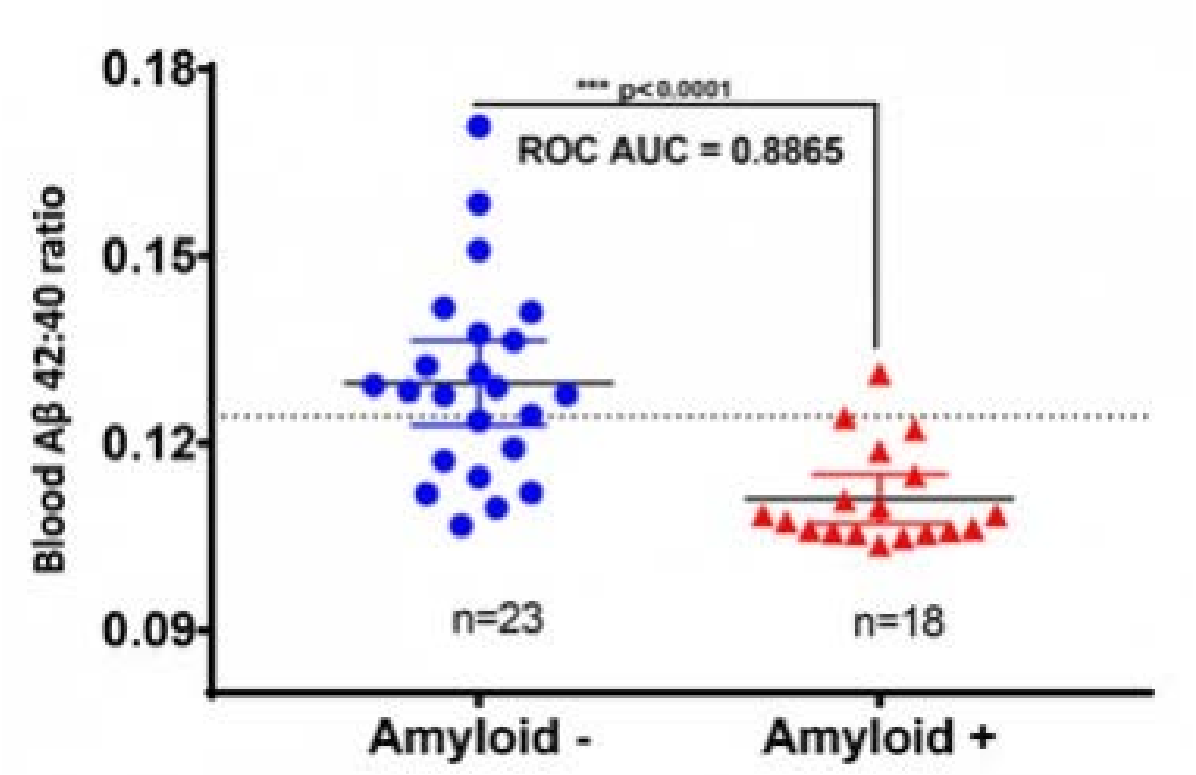
Can this be measured in blood?

Historically, plasma Aβ could show any result

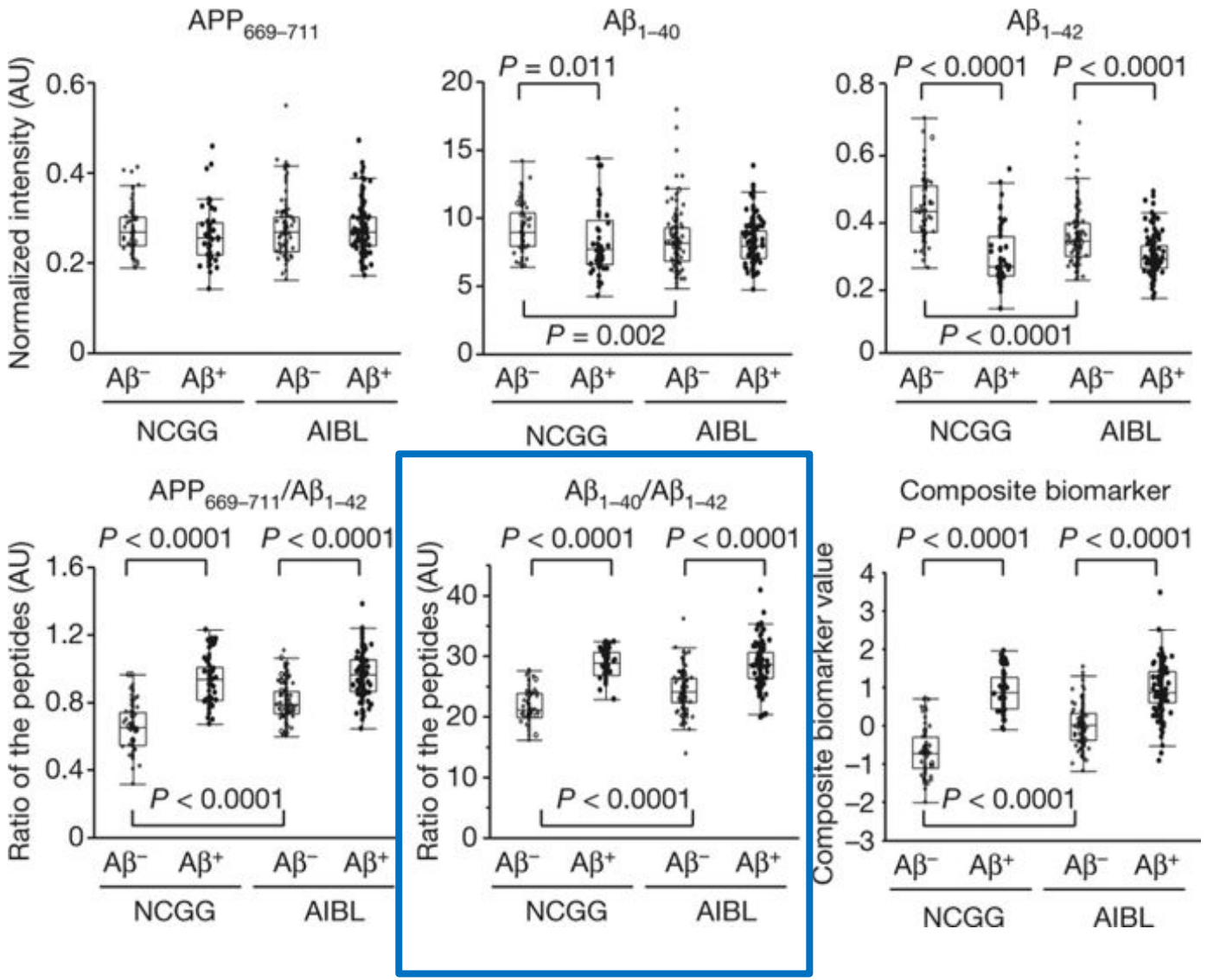


Study	AD	CTRL	Effect Size	Lower CI	Upper CI	% Weight
Mayeux, 1999	64	105	1.600	1.553	1.648	5.19
Arvanitakis, 2002	220	59	1.085	0.800	1.471	2.63
Fukumoto, 2003	146	92	1.057	0.911	1.227	4.23
Mayeux, 2003	79	365	1.168	1.061	1.287	4.76
Fagan, 2007	33	65	1.139	0.779	1.665	2.06
Fagan, 2007	16	65	1.000	0.580	1.723	1.26
Giedraitis, 2007	39	18	0.850	0.479	1.509	1.16
Pesaresi, 2007	192	126	0.765	0.665	0.879	4.33
Schupf, 2008	104	1021	0.994	0.986	1.002	5.23
Xu, 2008	113	155	0.848	0.632	1.139	2.72
Fagan, 2009	29	69	0.625	0.344	1.135	1.09
Roher, 2009	17	21	1.202	0.903	1.601	2.79
Sedaghat, 2009	29	16	1.313	1.219	1.415	4.95
Lui, 2010	186	724	0.926	0.878	0.977	5.08
Sundelöf, 2010	101	28	1.295	1.091	1.538	3.99
Head, 2011	17	12	0.645	0.604	0.689	5.01
Chiu, 2013	30	107	1.841	1.328	2.552	2.45
Chiu, 2013	31	107	1.217	1.175	1.261	5.17
Ruiz, 2013	51	53	0.831	0.607	1.136	2.56
Yamamoto, 2013	23	13	1.012	0.531	1.927	0.96
Zhang, 2013	153	120	0.865	0.811	0.922	5.02
Bu, 2014	128	135	1.228	1.079	1.399	4.44
Rembach, 2014	125	577	1.013	0.953	1.077	5.04
Wang, 2014	97	122	0.991	0.979	1.003	5.23
Jiao, 2015	156	129	1.387	1.168	1.648	3.98
Kim, 2015	100	46	0.865	0.759	0.986	4.43
Janelidze, 2016	57	274	0.673	0.581	0.780	4.25
All Studies	**2336**	**4452**	**1.031**	**0.962**	**1.106**	**100**
p=0.38718						

Ovod – A&D, 2017

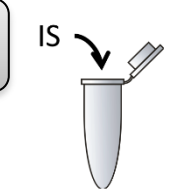

0.18
0.15
0.12
0.09
Blood Aβ 42:40 ratio
**** p<0.0001
ROC AUC = 0.8865
n=23
n=18
Amyloid -
Amyloid +

Nakamura – Nature, 2018

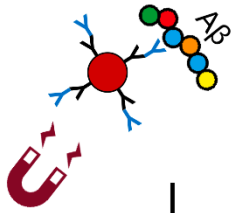


Optimized method for plasma Aβ by IP-MS/MS

- Recombinant ^{15}N labelled Aβ42, Aβ40, Aβ38 as internal standard
- Plasma treated with Triton X100 to reduce matrix effects - binding to plasma proteins



- IP using 6E10 + 4G8 (mid domain Mabs)



Quadrupole-orbitrap hybrid MS
- parallel reaction monitoring (PRM)

RP HPLC

Dry & resuspend eluate

Coefficients of variation for Quality Control (QC) samples

	pg/mL	CV
$Aβ_{1-38}$	21	5 %
$Aβ_{1-40}$	262	2 %
$Aβ_{1-42}$	25	12 %

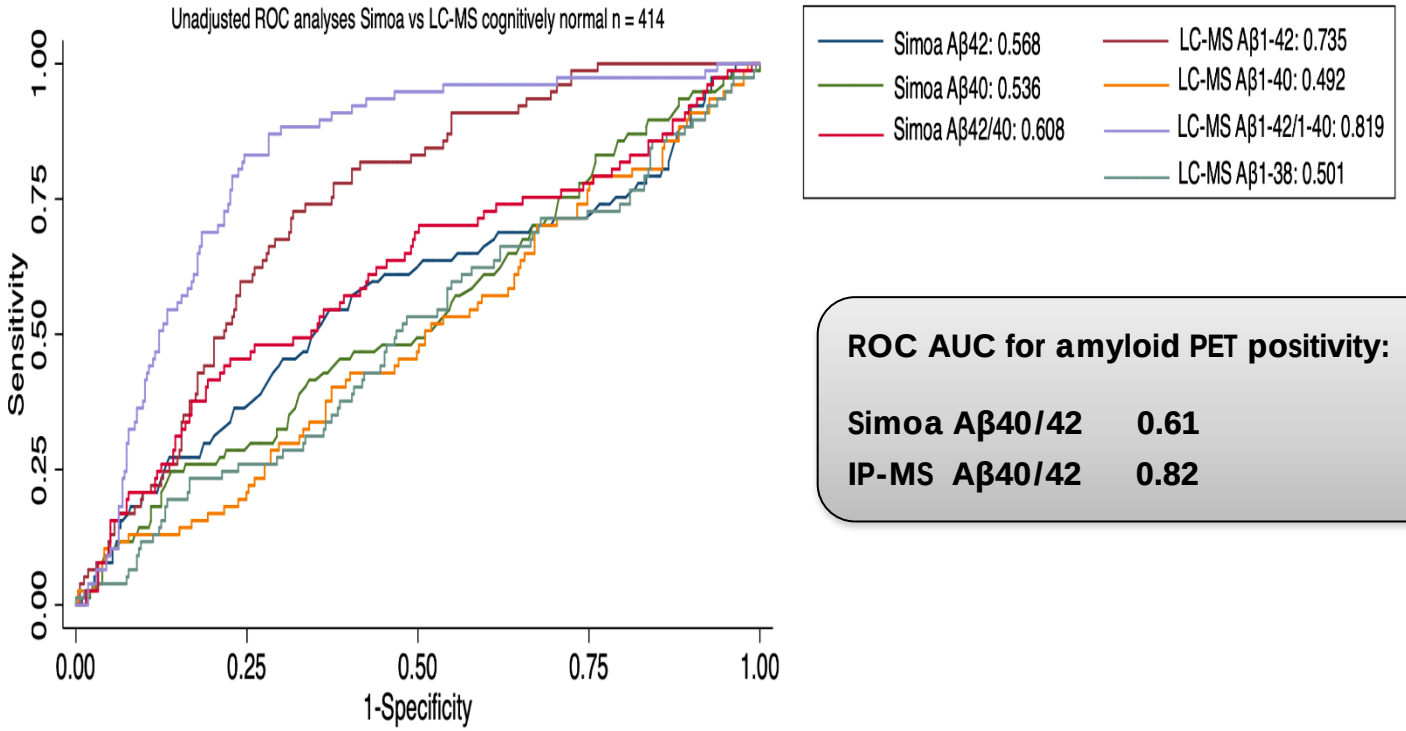
➔ **Levels of Aβ42 and Aβ40 in plasma can be measured in 250 uL of plasma with high precision**
Also Aβ38 and Aβ -3 to 40 (APP 669-711) can be quantified

Plasma Aβ in the Insight46 cohort

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

***APOE* genotype, neuropsych testing, amyloid PET**

Plasma Aβ42, Aβ40/42 using immunoassay (Simoa) and IP LC-MS/MS

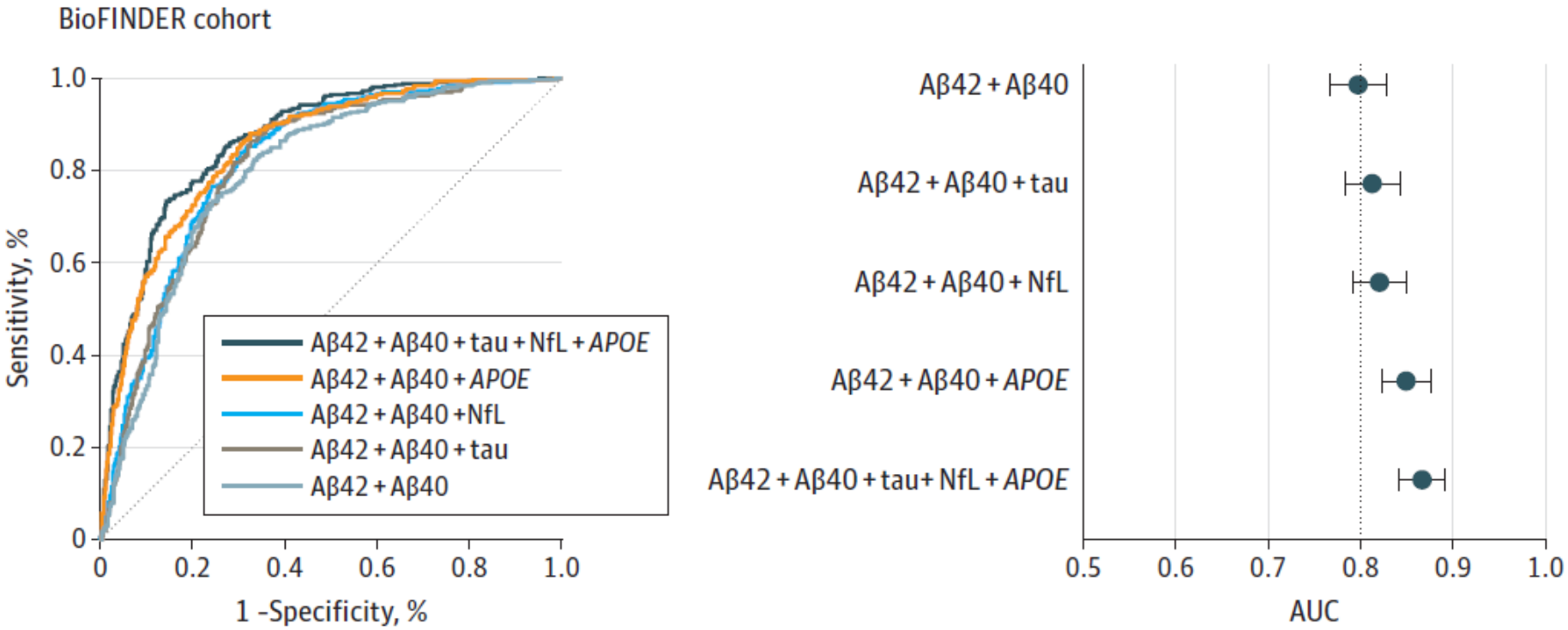


ROC AUC for amyloid PET positivity:

Simoa Aβ40/42	**0.61**
IP-MS Aβ40/42	**0.82**

➔ **Plasma Aβ42 and Aβ40/42 ratio by IP-MS/MS show high concordance with brain amyloidosis**

The Elecsys prototype assay for plasma Aβ40 and Aβ42 – Diagnostic performance for detecting Aβ positivity (determined by CSF)



Palmqvist *et al*. JAMA Neurol 2019

Plasma p-tau181 as a biomarker for tau pathology in AD

Tatebe et al. Molecular Neurodegeneration (2017) 12:63
DOI 10.1186/s13024-017-0206-8

Molecular Neurodegeneration

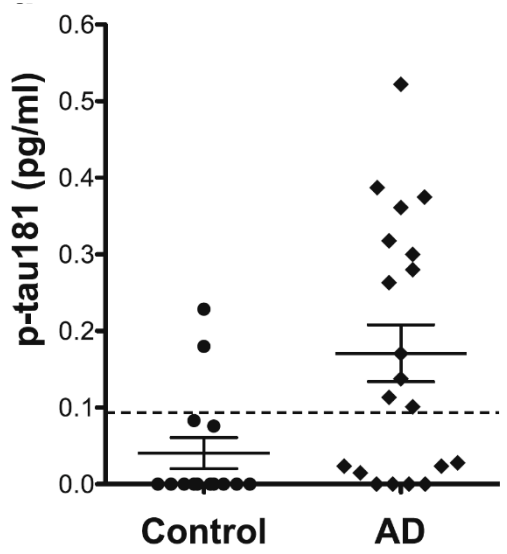
RESEARCH ARTICLE Open Access

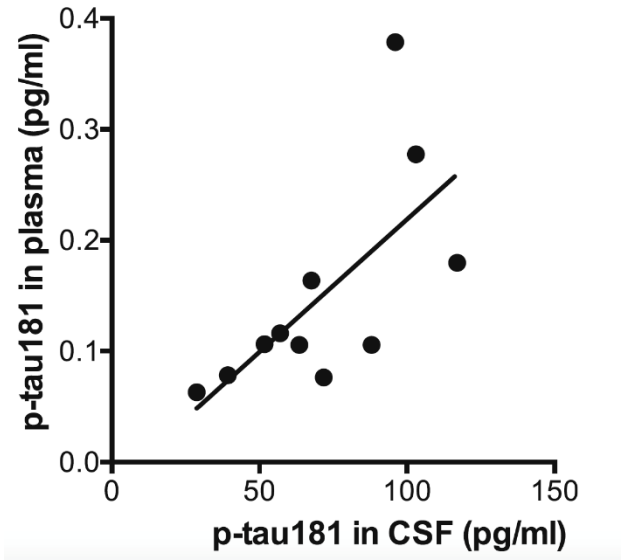
Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome

Harutsugu Tatebe[1,2], Takashi Kasai[1], Takuma Ohmichi[1], Yusuke Kishi[3], Tomoshi Kakeya[3], Masaaki Waragai[4], Masaki Kondo[1], David Allsop[5] and Takahiko Tokuda[1,6*]

Plasma p-tau181 measured by a modified version of the Quanterix Simoa T-tau assay

Cohort: **15 controls**
20 AD dementia





➔ **Plasma P-tau181 a candidate blood biomarker for AD**

➔ **Good correlation between plasma and CSF levels – reflects brain pathophysiology**

➔ **Lack of analytical sensitivity to measure all samples (even in AD patients)**

Lilly Research Lab MSD method for plasma P-tau181

ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-9

Alzheimer's & Dementia

Featured Article

Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography

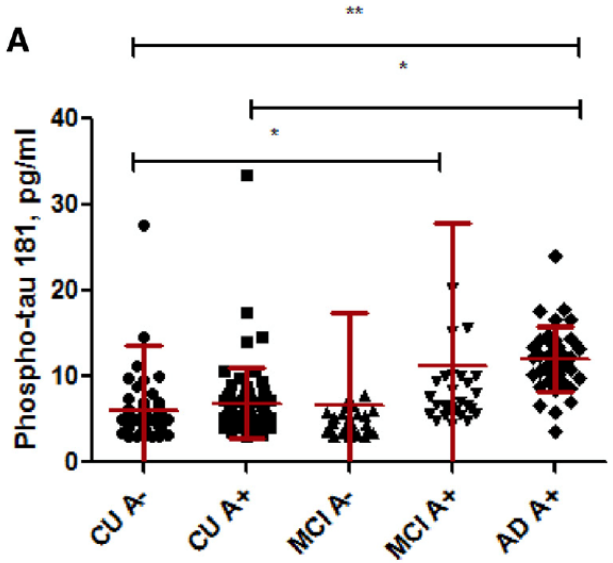
Michelle M. Mielke[a,b,*], Clinton E. Hagen[c], Jing Xu[d], Xiyun Chai[d], Prashanthi Vemuri[e], Val J. Lowe[e], David C. Airey[d], David S. Knopman[b], Rosebud O. Roberts[a,b], Mary M. Machulda[f], Clifford R. Jack, Jr.[e], Ronald C. Petersen[a,b], Jeffrey L. Dage[d]

Plasma p-tau181 (AT270) – MSD
Plasma total tau (T-tau) – Simoa

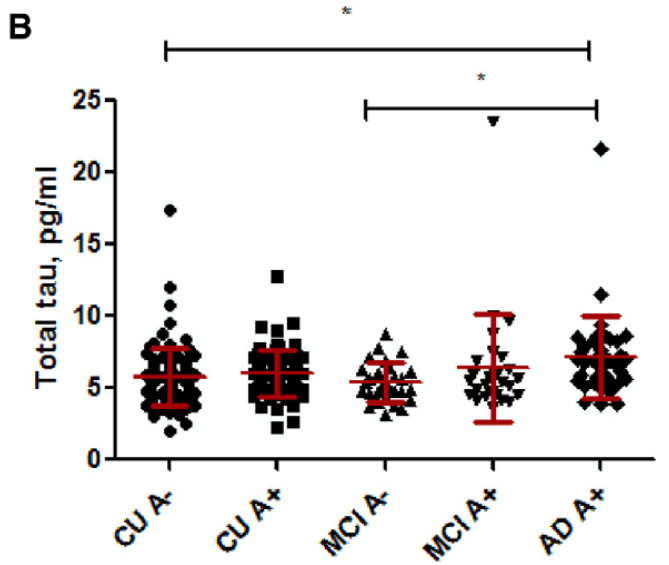
Cohort: 172 cognitively unimpaired
57 MCI
40 AD dementia

Stratification by amyloid PET

AUC 0.803 for amyloid PET+



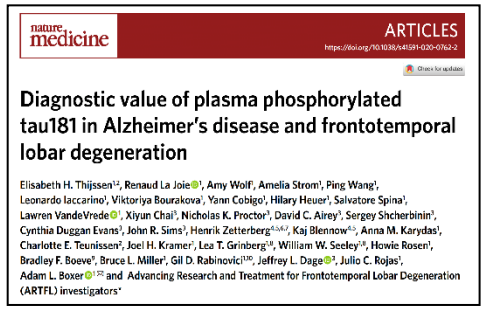
AUC 0.598 for amyloid PET+



➔ **MSD assay for P-tau181 show promise as a candidate blood biomarker for AD**

➔ **Simoa assay for T-tau show poor discriminatory power (as before)**

Large clinical studies on the Lilly MSD plasma P-tau181 method – UCSF and ARTFL cohorts


nature medicine ARTICLES

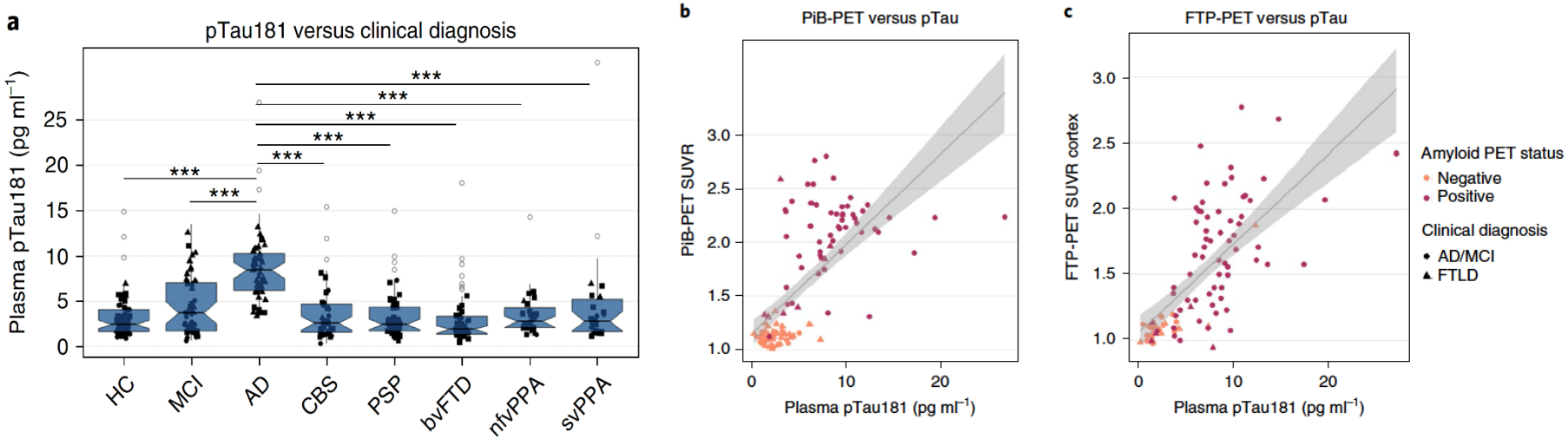
Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration

Elisabeth H. Thijssen[1,2], Renaud La Joie[1], Amy Wolf[1], Amelia Strom[1], Ping Wang[1], Leonardo Iaccarino[1], Viktoriya Bourakova[1], Yann Cobigo[1], Hillary Heuer[1], Salvatore Spina[1], Lawren VandeVrede[1], Xiyun Chai[1], Nicholas K. Proctor[1], David C. Airey[1], Sergey Shcherbinin[1], Cynthia Duggan Evans[1], John R. Sims[1], Henrik Zetterberg[4,5,6,7], Kaj Blennow[4,5], Anna M. Karydas[1], Charlotte E. Teunissen[2], Joel H. Kramer[1], Lea T. Grinberg[1,8], William W. Seeley[1,9], Howie Rosen[1], Bradley F. Boeve[9], Bruce L. Miller[1], Gil D. Rabinovici[1,10], Jeffrey L. Dage[3], Julio C. Rojas[1], Adam L. Boxer[1,11] and Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) investigators*

Plasma p-tau181 (AT270) – MSD

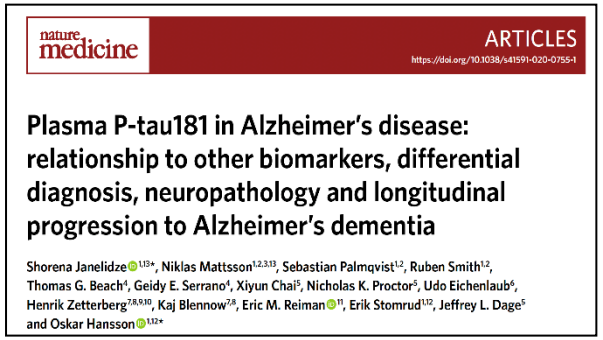
Cohort of 362 cases with AD, MCI, tauopathies and healthy controls

Amyoid (PiB) and tau (FTP) PET



- ➔ **P-tau181 assay differentiated AD from clinical (AUC 0.89) and autopsy-confirmed (AUC 0.88) FTD**
- ➔ **Plasma P-tau181 identified amyloid PET positive cases regardless of clinical diagnosis and correlated with cortical tau deposition measured by flortaucipir (FTP) PET**
- ➔ **Plasma P-tau181 may be a useful screening tool for AD-type tau pathology**

Large clinical studies on the Lilly MSD plasma P-tau181 method – BioFinder cohort


nature medicine ARTICLES
https://doi.org/10.1038/s41591-020-0755-1

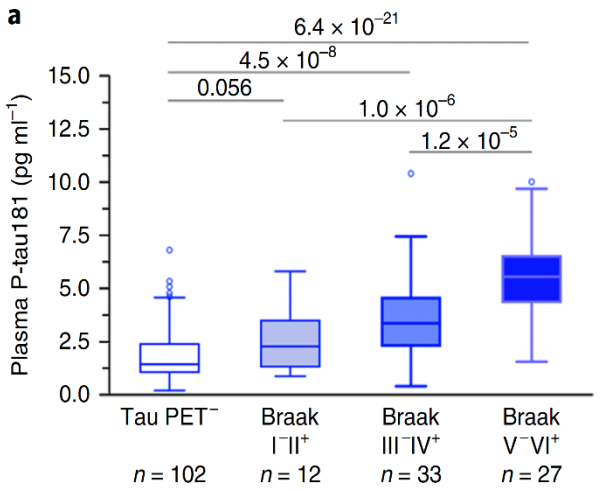
Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia

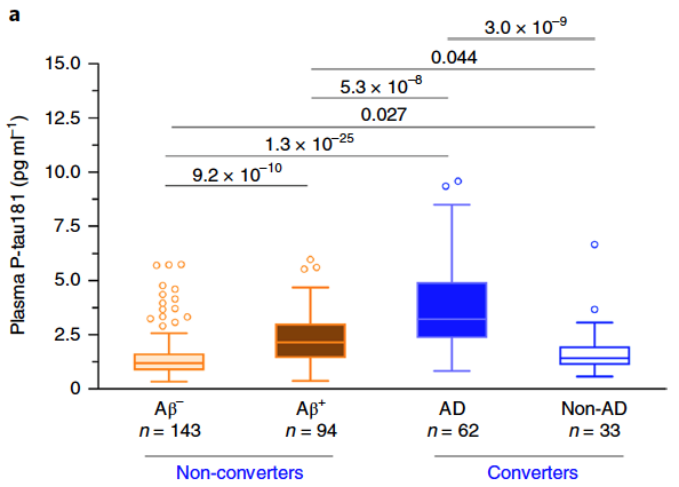
Shorena Janelidze[1,13*], Niklas Mattsson[1,2,3,13], Sebastian Palmqvist[1,2], Ruben Smith[1,2], Thomas G. Beach[4], Geidy E. Serrano[4], Xiyun Chai[5], Nicholas K. Proctor[5], Udo Eichenlaub[6], Henrik Zetterberg[7,8,9,10], Kaj Blennow[7,8], Eric M. Reiman[11], Erik Stomrud[1,12], Jeffrey L. Dage[5] and Oskar Hansson[1,12*]

Plasma p-tau181 (AT270) – MSD

Cohort of 589 cases with AD, MCI, non-AD neurodegenerative disorders and controls

Amyloid (flutemetamol) and tau (FTP) PET





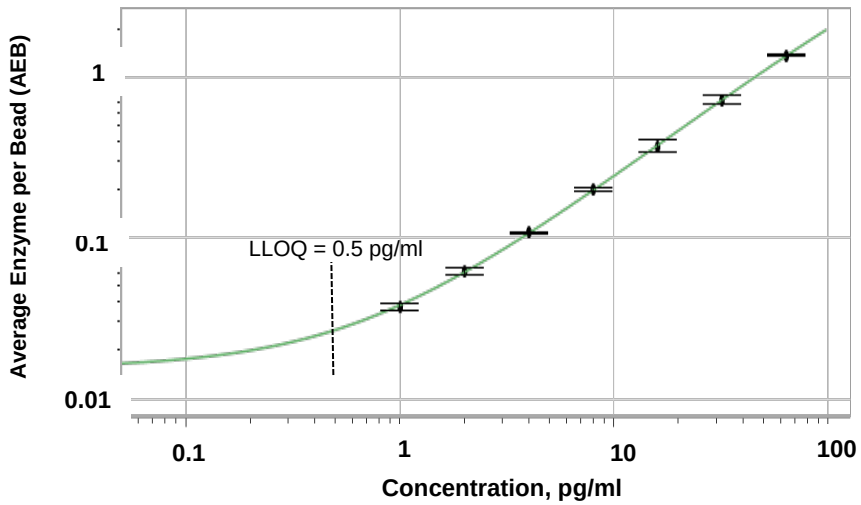
➔ **Increased plasma P-tau181 with higher Braak stages**

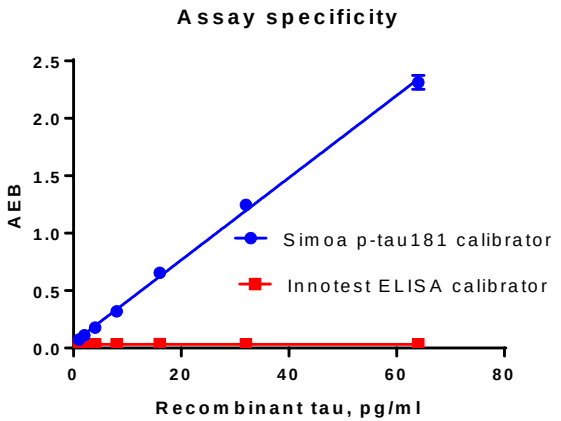
➔ **High baseline P-tau181 in controls and MCI cases predicts progression to AD dementia**

➔ **Further support for the usefulness of plasma P-tau181 as a biomarker for AD-type tau pathology**

UGOT Simoa assay for blood p-tau181

In house Simoa assay

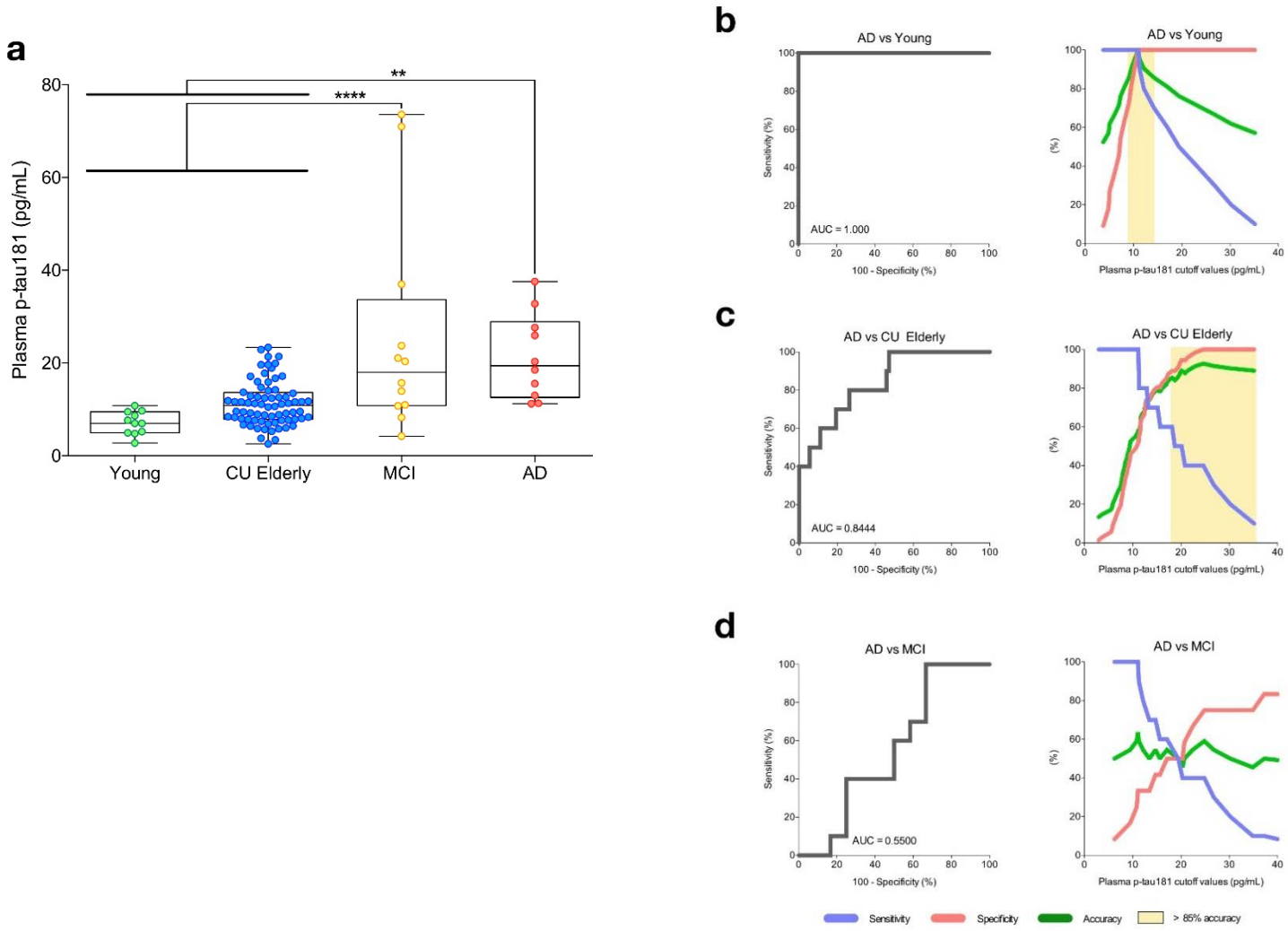




Karikari *et al*., Lancet Neurol, 2020

TRIAD ‘discovery’ cohort

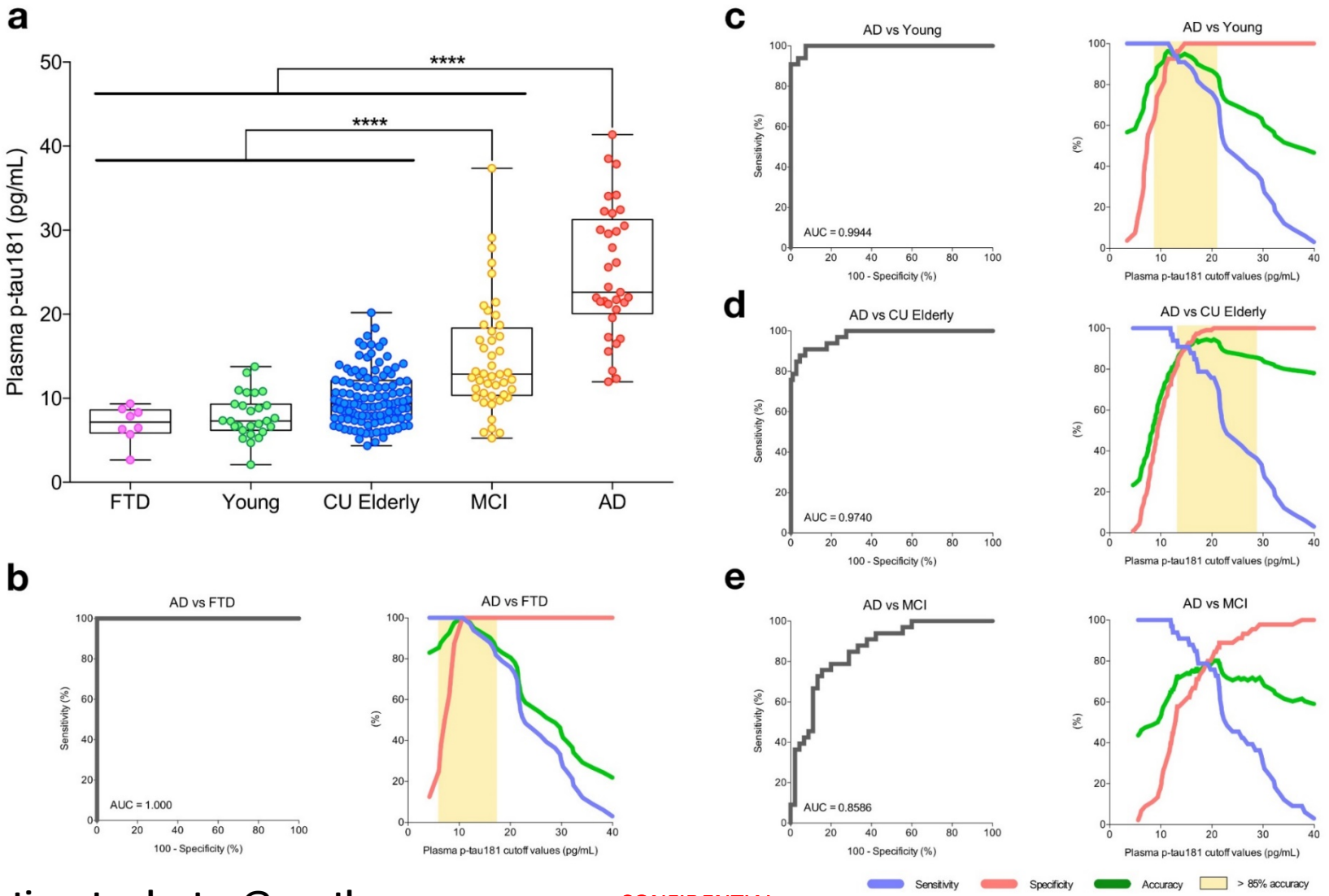
Plasma P-tau181 increased in MCI and AD



Karikari *et al*., Lancet Neurol, 2020

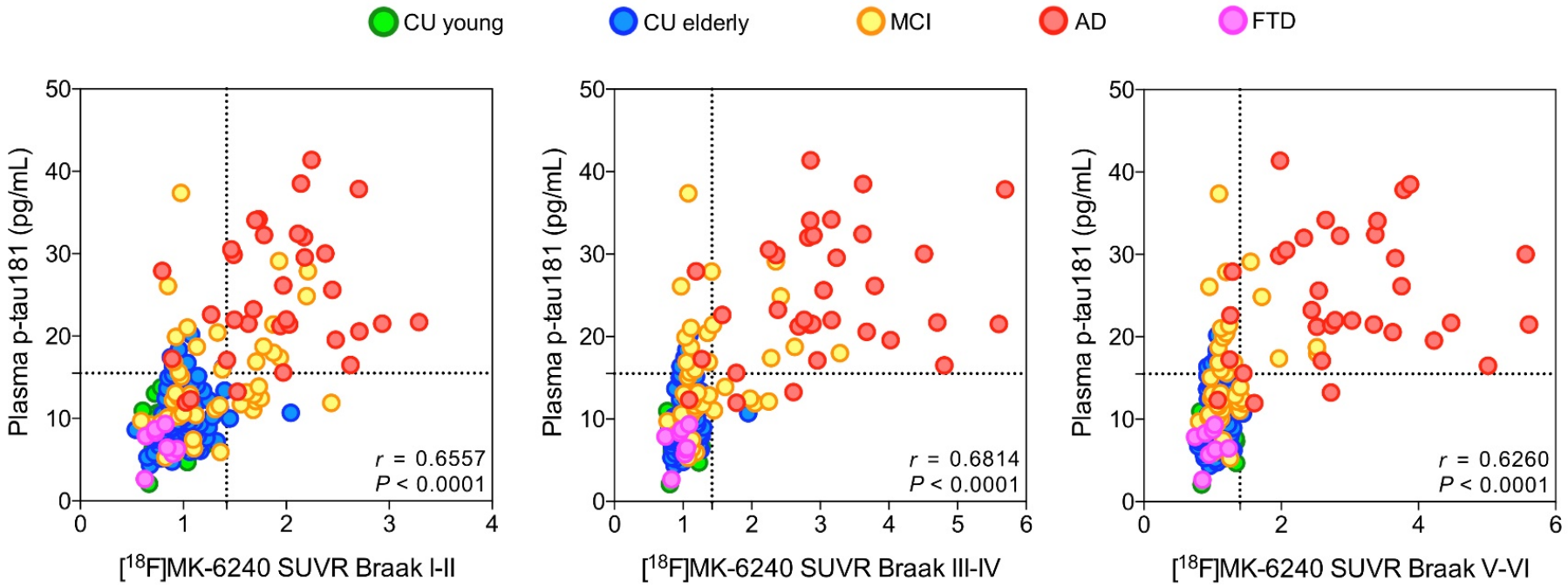
TRIAD validation cohort

P-tau181 in in relation to clinical diagnoses



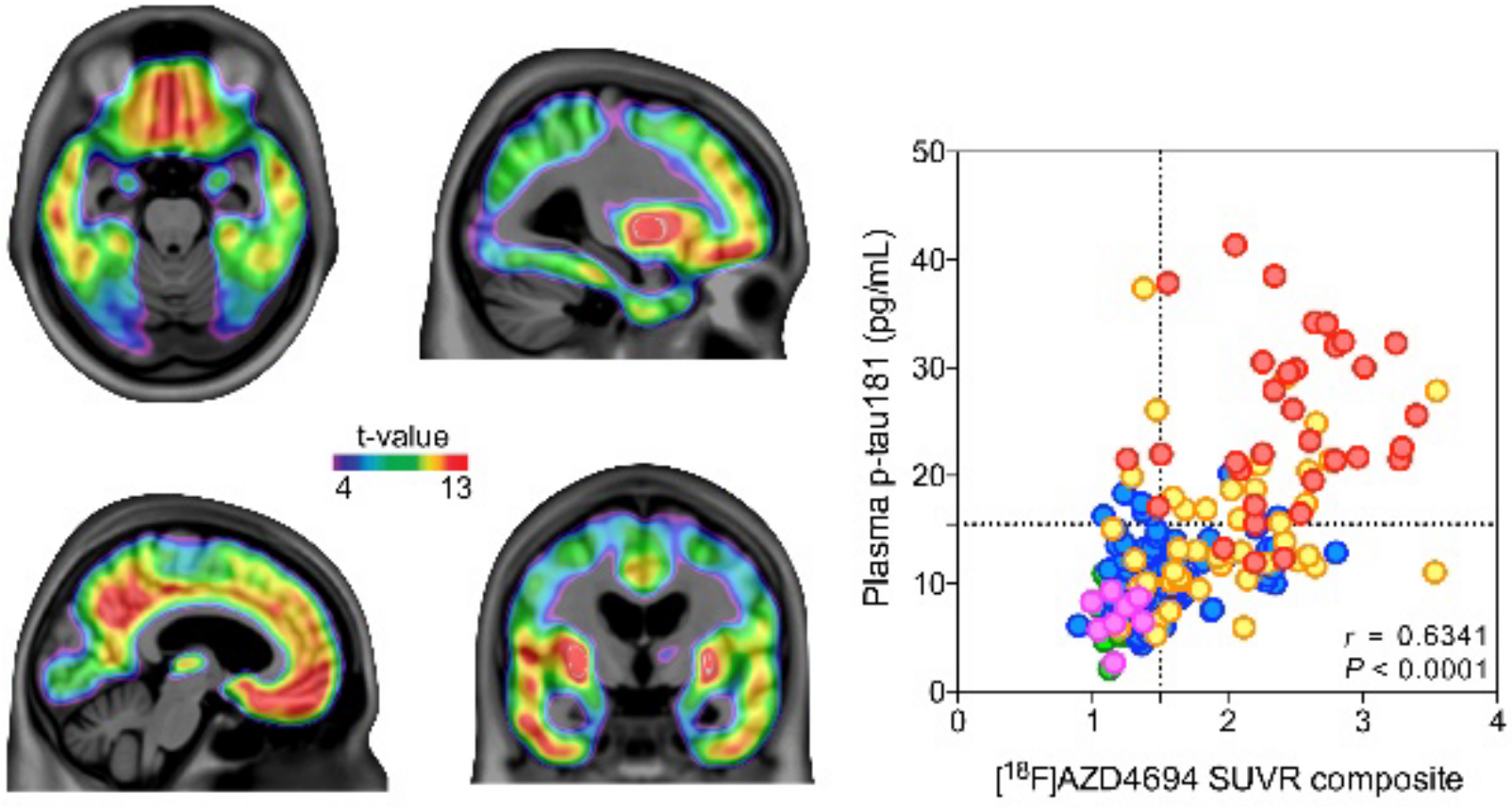
TRIAD validation cohort

Plasma p-tau181 correlates with MK-6240 tau PET

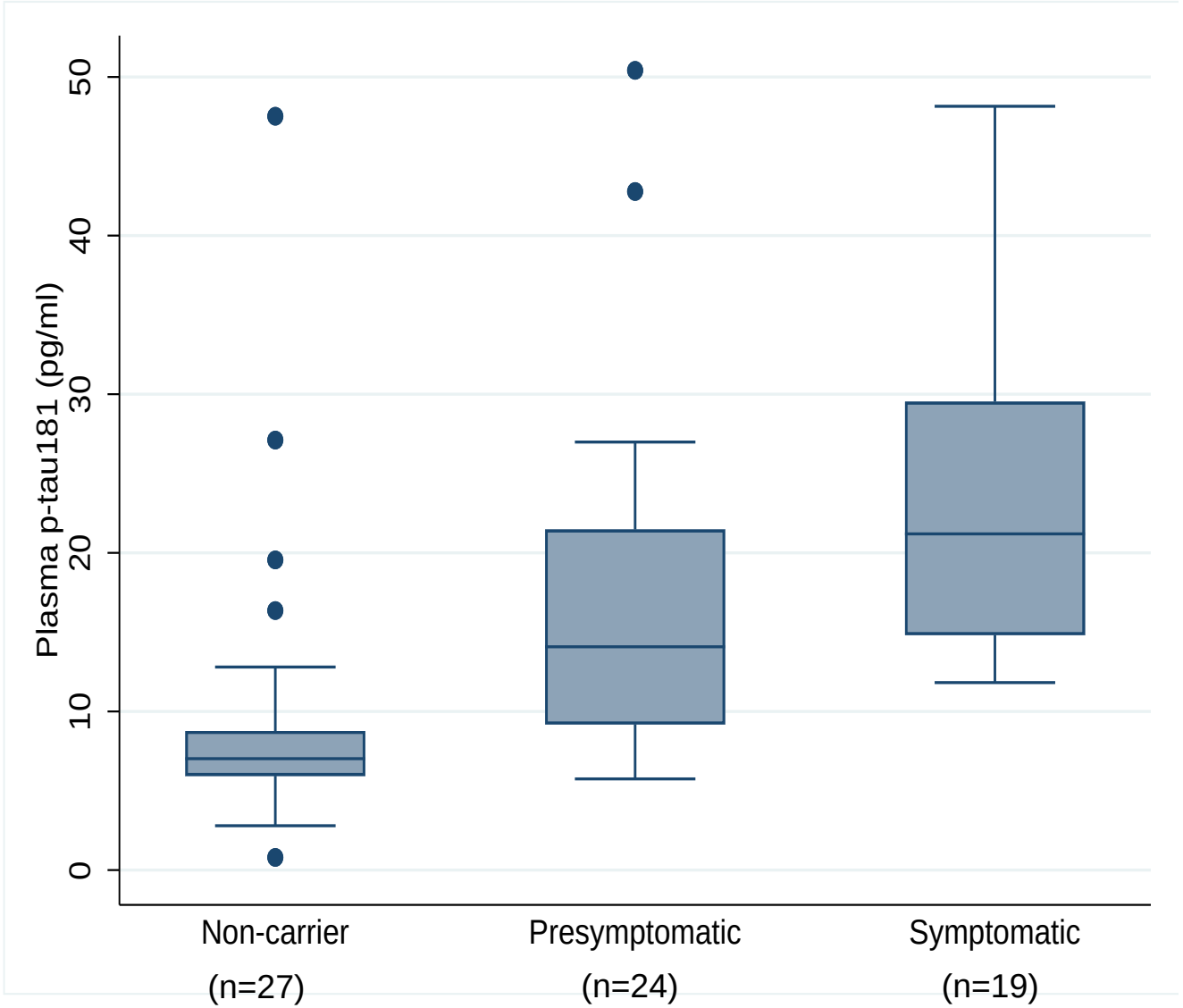


TRIAD validation cohort

P-tau181 correlates with AZD4694 amyloid PET

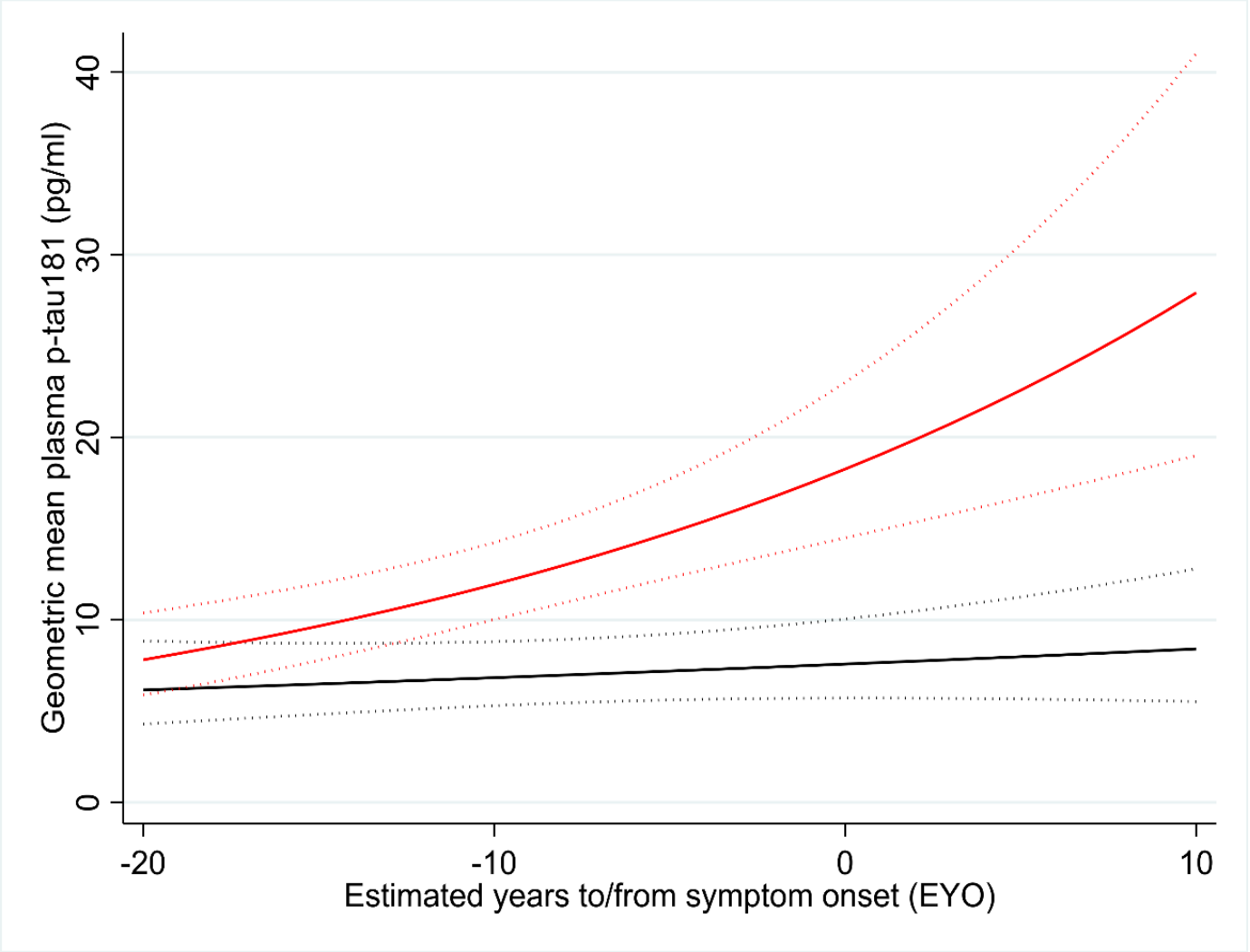


Plasma P-tau181 in familial Alzheimer's disease

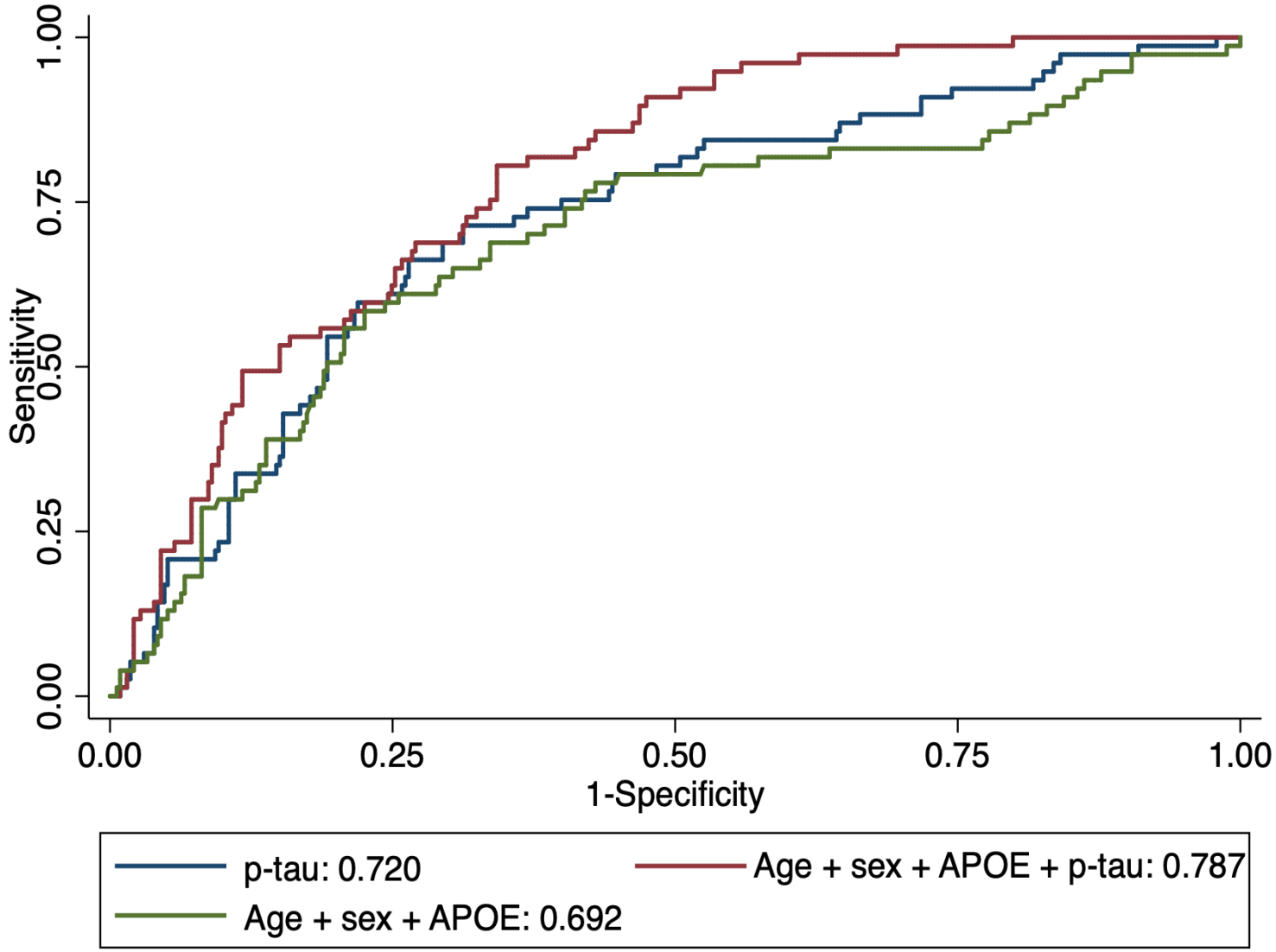


O´Connor A *et al*., Mol Psychiat 2020

Plasma P-tau181 in familial Alzheimer's disease

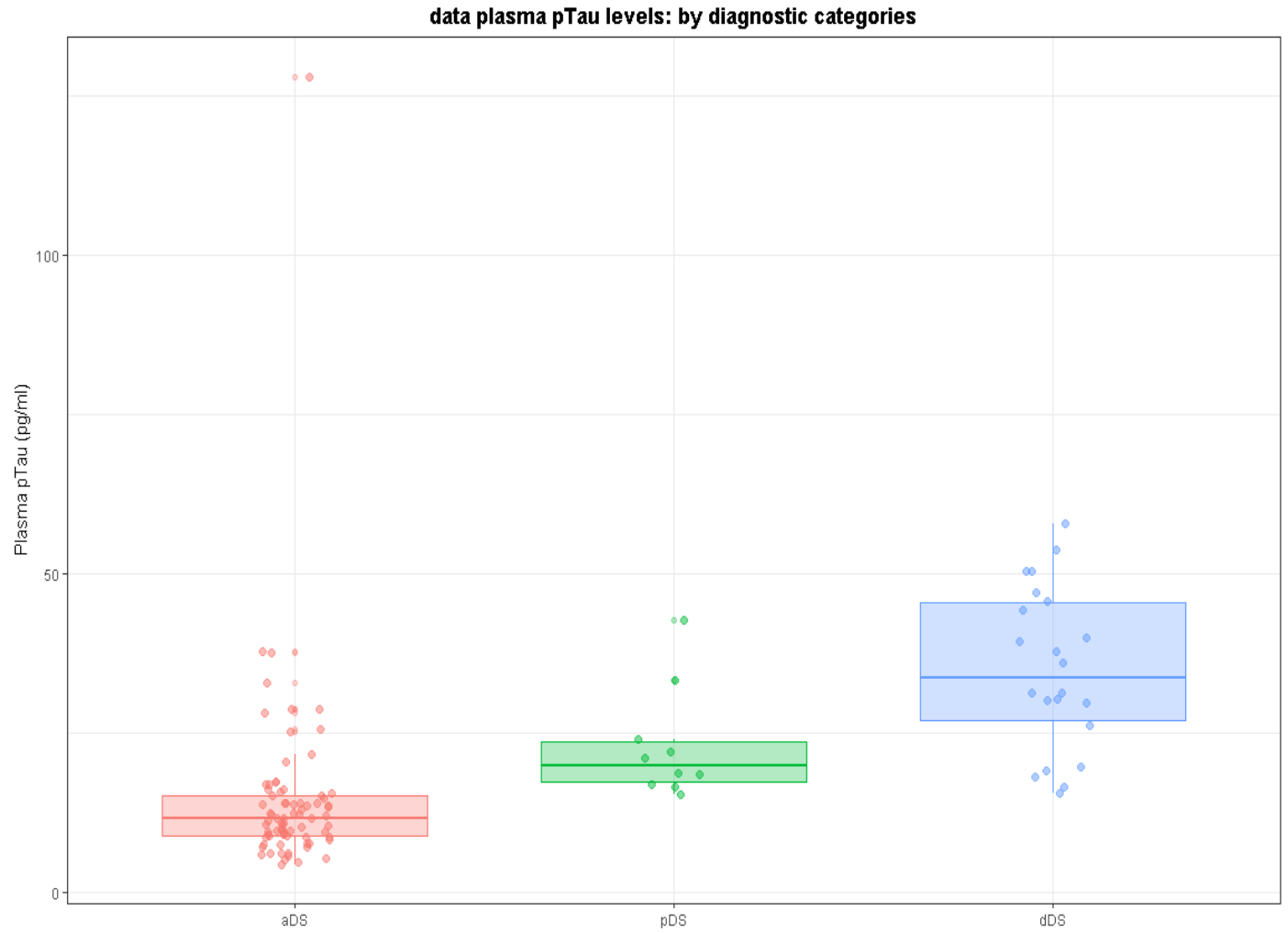


Plasma P-tau181 in the 1946 cohort – plasma p-tau181 as a pre-screening tool for amyloid status



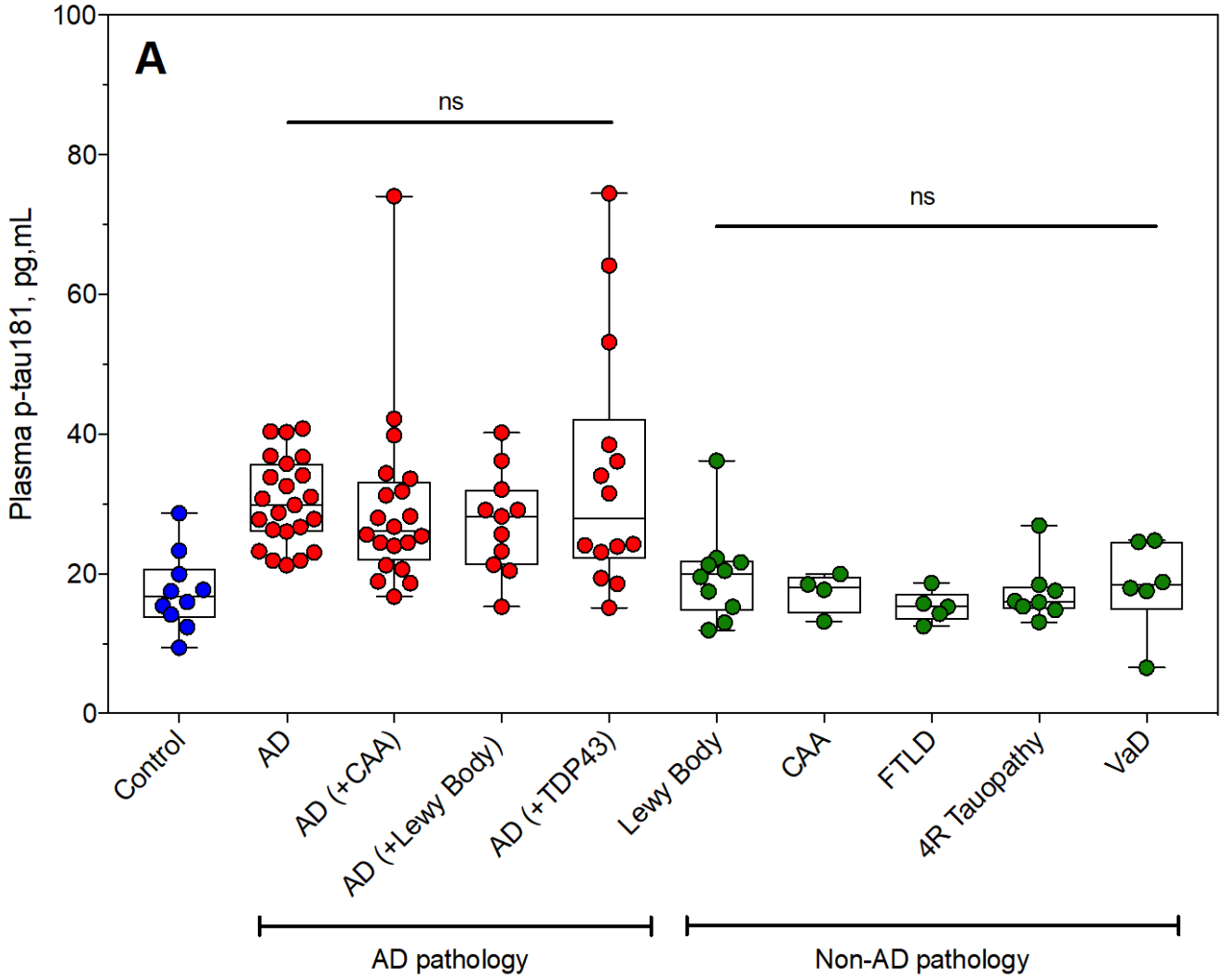
Keshavan *et al*., unpublished

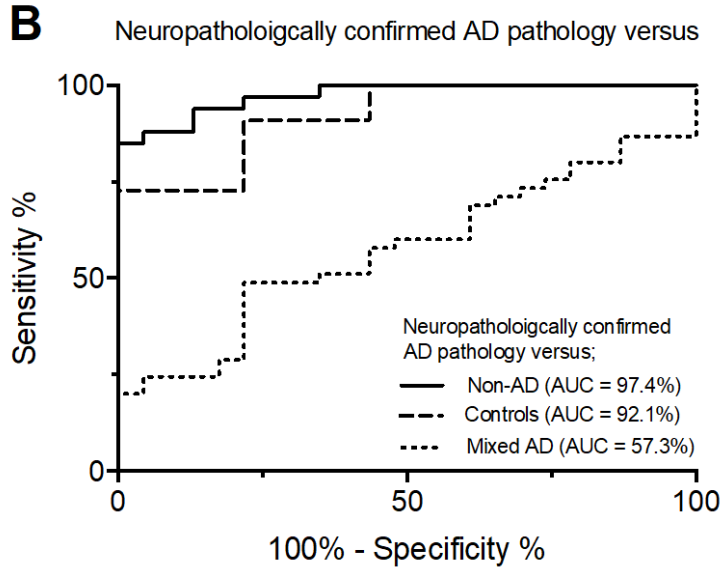
Plasma P-tau181 in Down syndrome

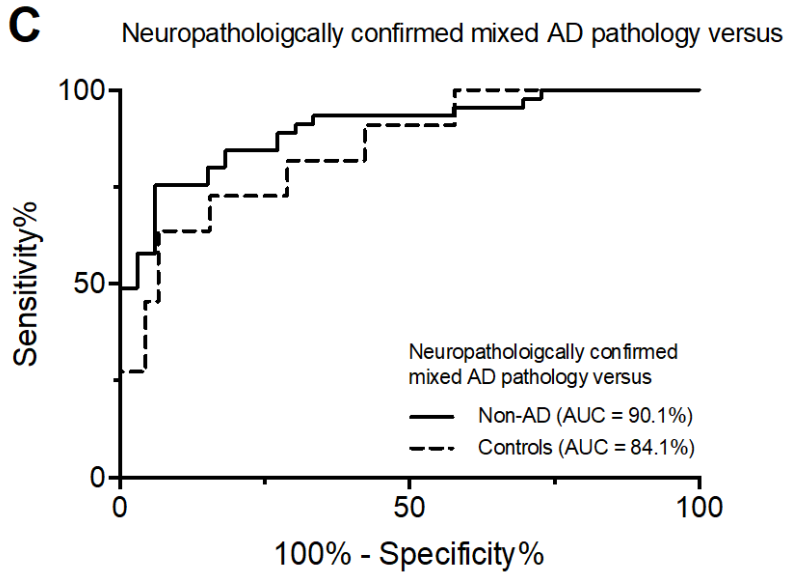


Fortea *et al*., 2020, unpublished

Plasma P-tau181 – neuropathological validation







Lantero Rodriguez J *et al*. *Acta Neuropath. 2020*

JAMA | Original Investigation

Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders

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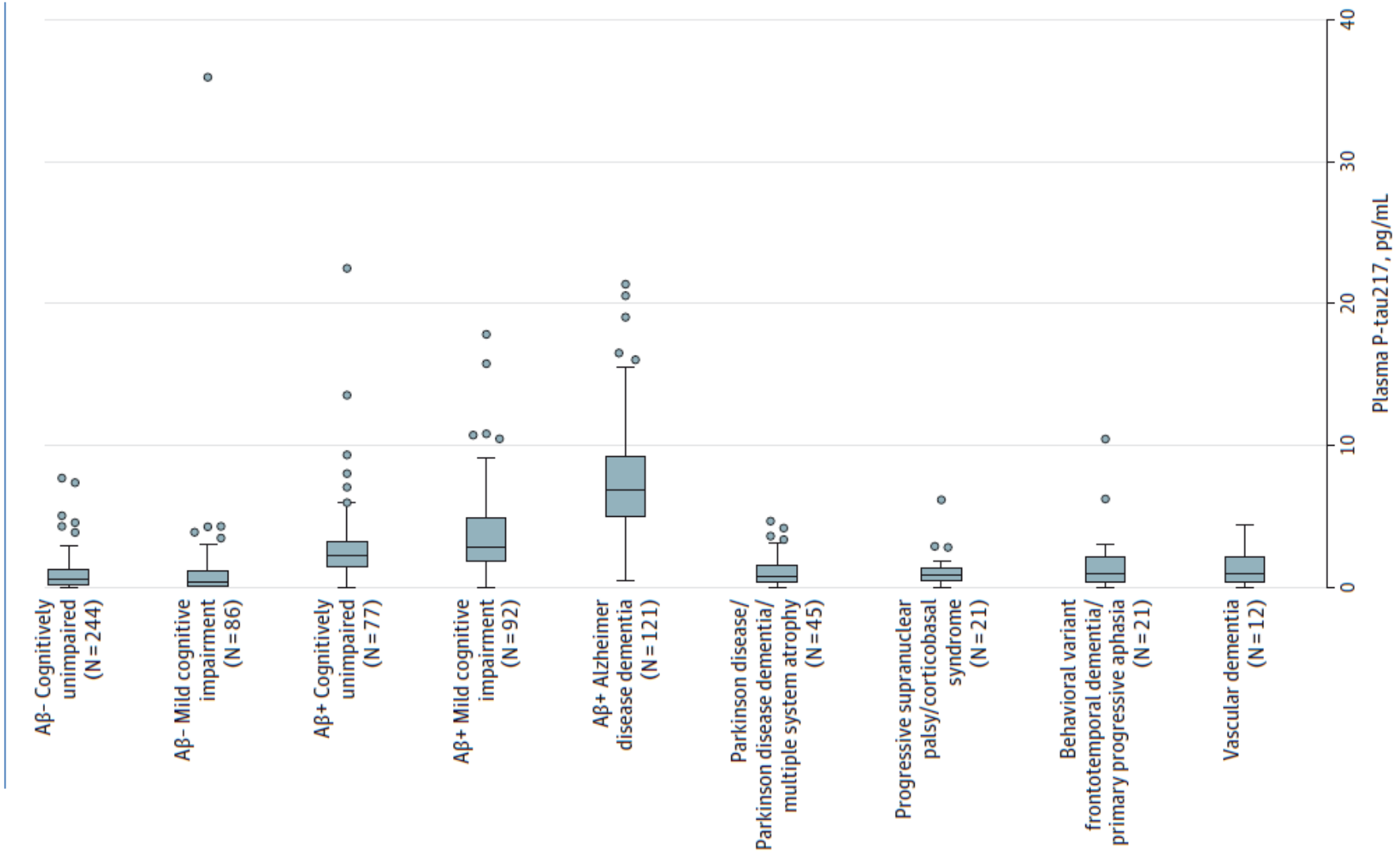
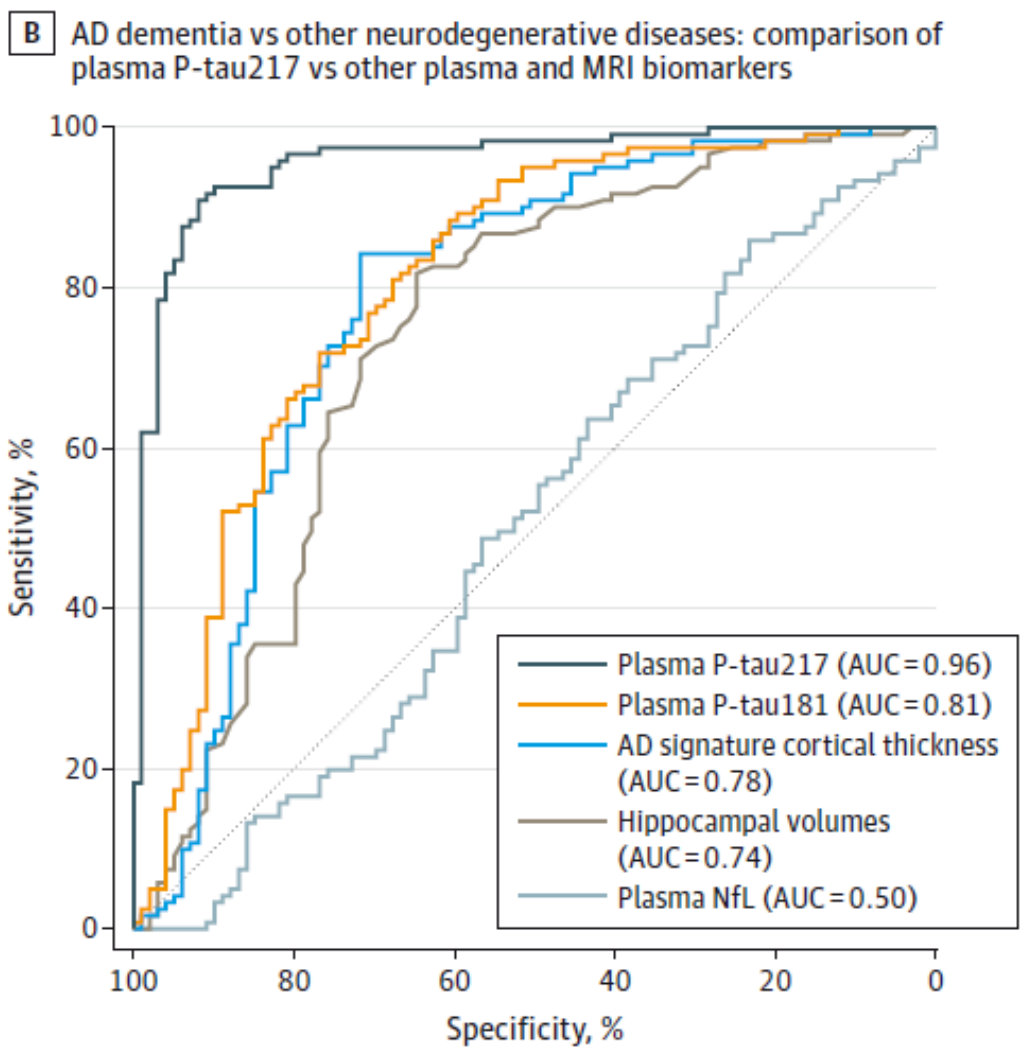
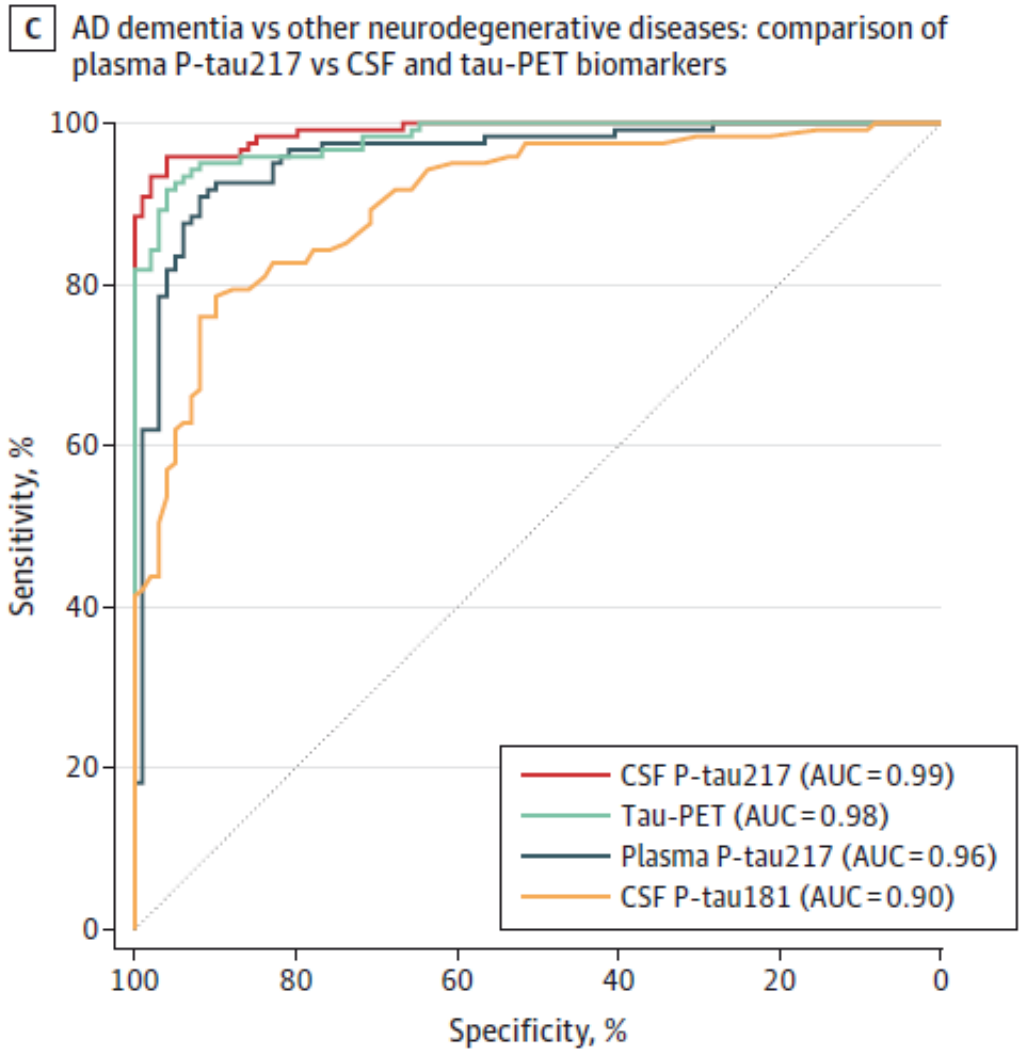
Palmqvist *et al*., 2020, JAMA

Lilly MSD plasma P-tau217 across neurodegenerative diseases



Lilly MSD plasma P-tau217 in Alzheimer's disease – compared with other markers, including P-tau181





Plasma P-tau217 vs. P-tau181 – which one is the best?

JAMA paper (Palmqvist *et al*. 2020) favors P-tau217 over P-tau181 with higher AUCs for the former marker for clinical and biomarker-supported AD diagnoses

Evidence that P-tau217 might be more CNS-specific and more specific to "pathological tau phosphorylation" (Barthélemy NR *et al*., J Exp Med. 2020)

But plasma P-tau181 may have similar or higher diagnostic performance against neuropathology:

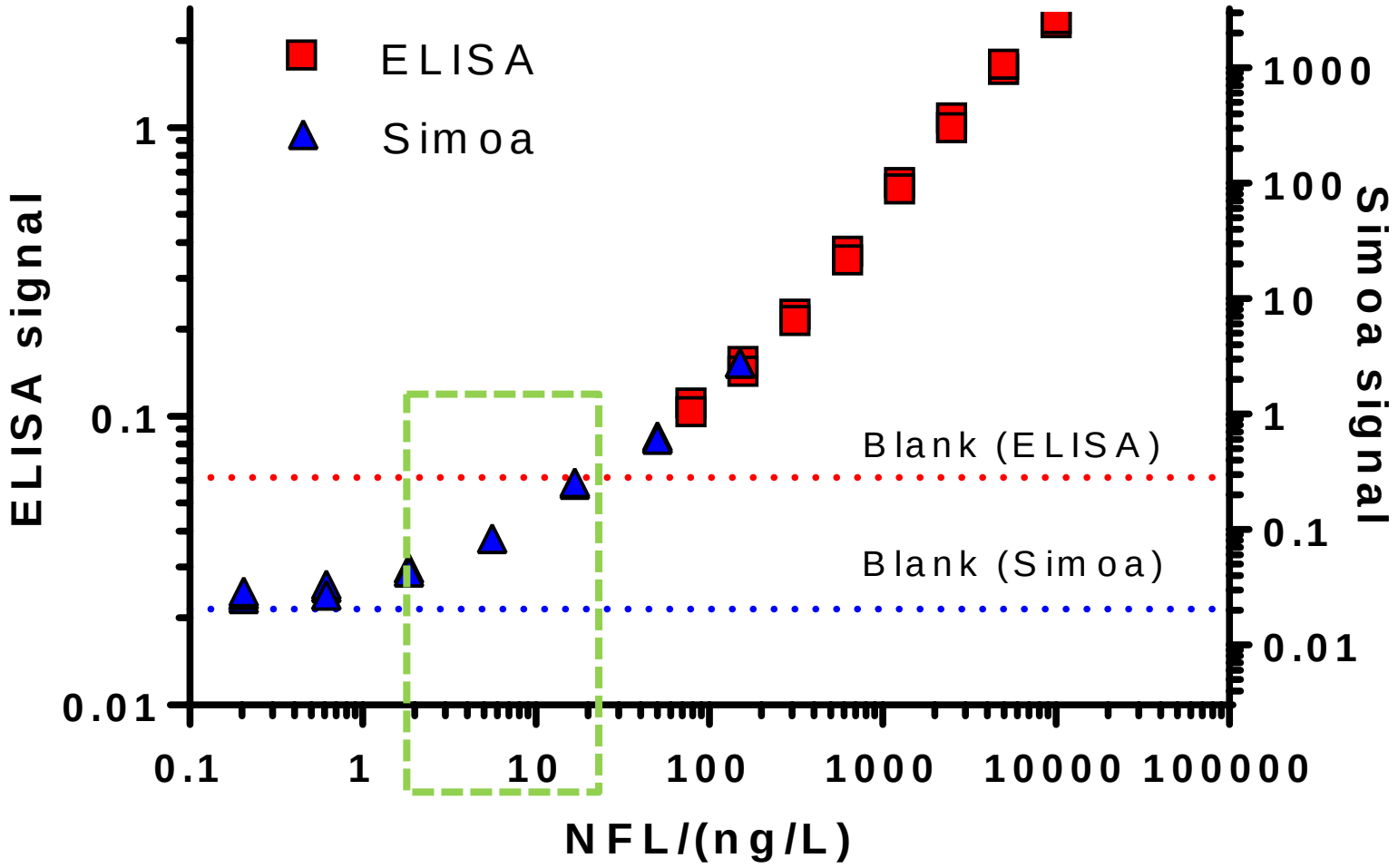
P-tau181 AUC for AD vs. non-AD pathologies: 0.97 (95% CI 0.94-1.00)
(Lantero Rodriquez J *et al*., Acta Neuropathol. 2020)

P-tau217 AUC for AD vs. non-AD pathologies: 0.89 (95% CI 0.81-0.97)
(Palmqvist S *et al*., JAMA 2020)

P-tau217 a little bit harder to measure than P-tau181?

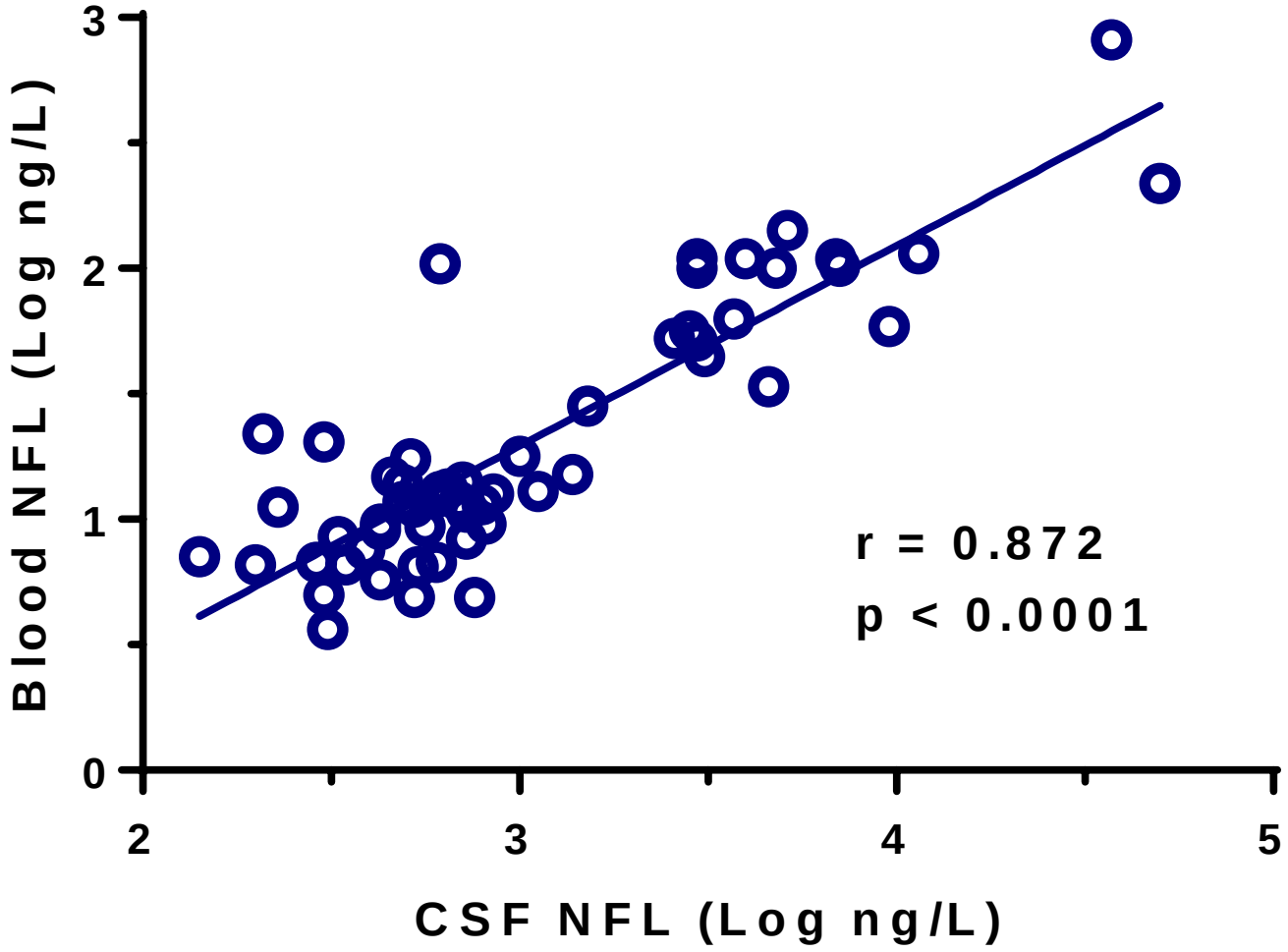
More head-to-head studies needed…

NfL - ELISA vs. Simoa



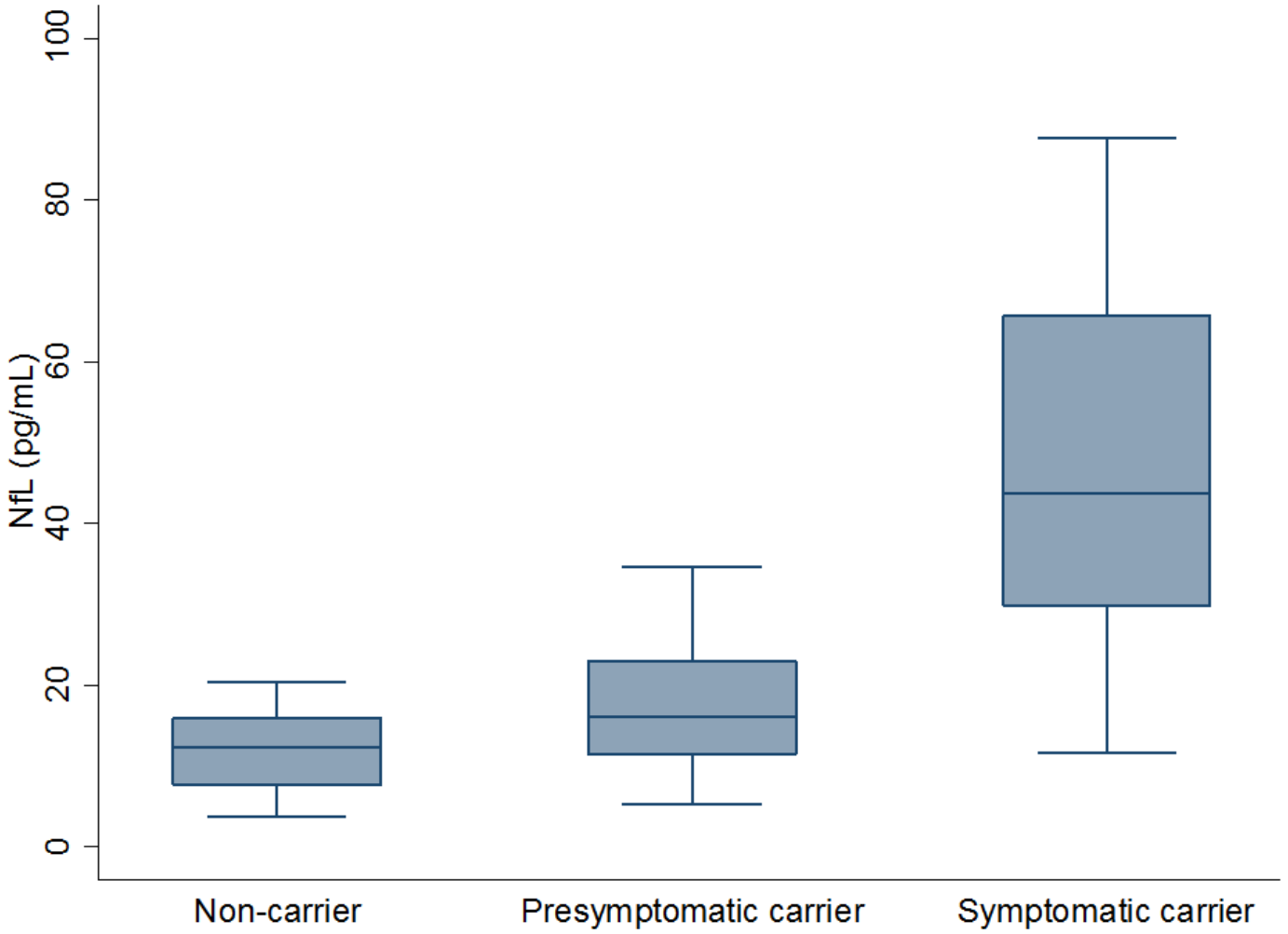
LLoD = 0.26 ng/L; LLoQ = 1.95 ng/L

Plasma NfL correlates with CSF NfL

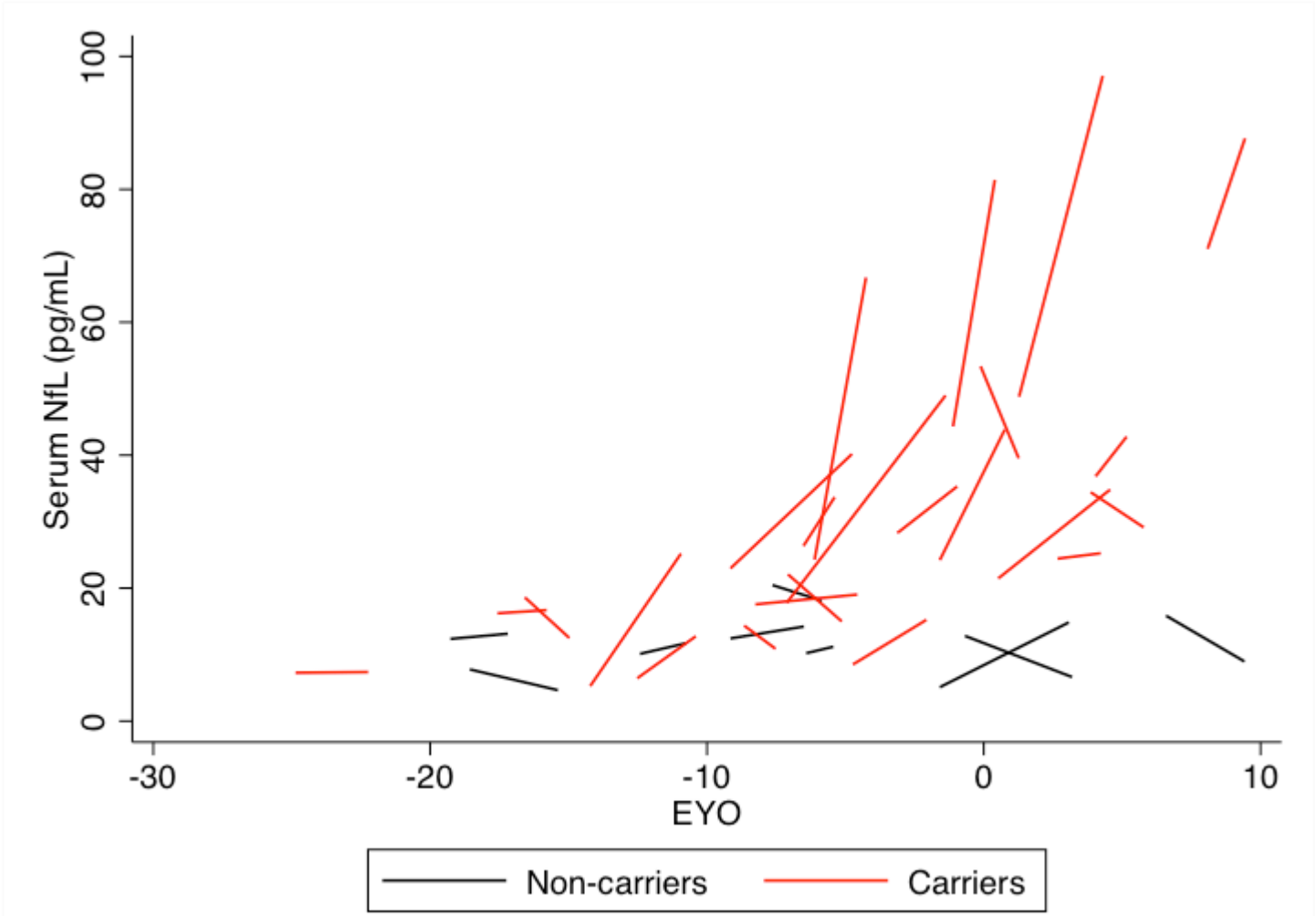


Gisslén et al., 2015

Plasma NfL in familial Alzheimer's disease



Plasma NfL in familial Alzheimer's disease – longitudinal data

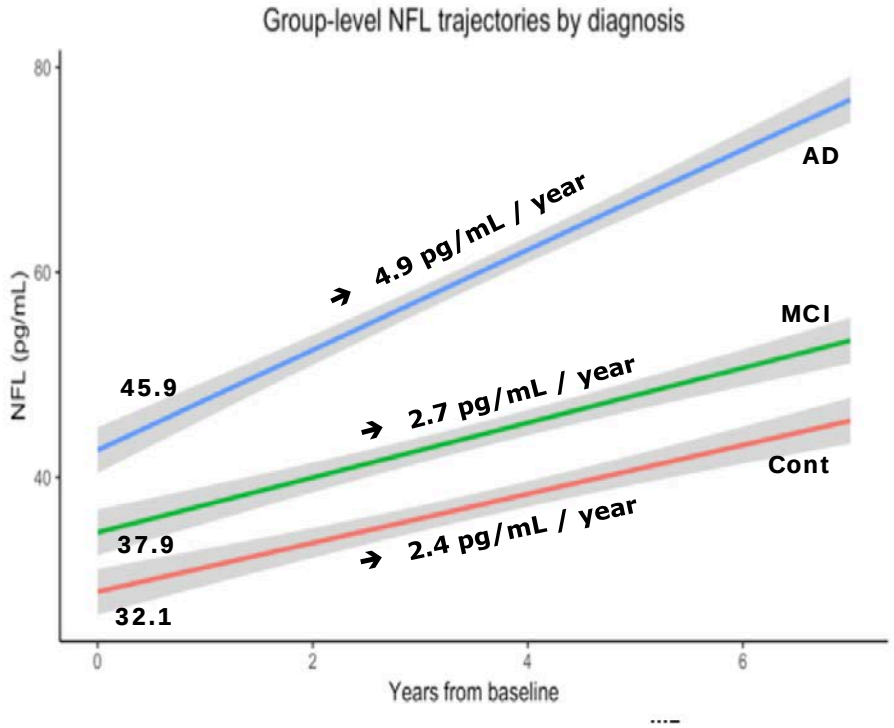


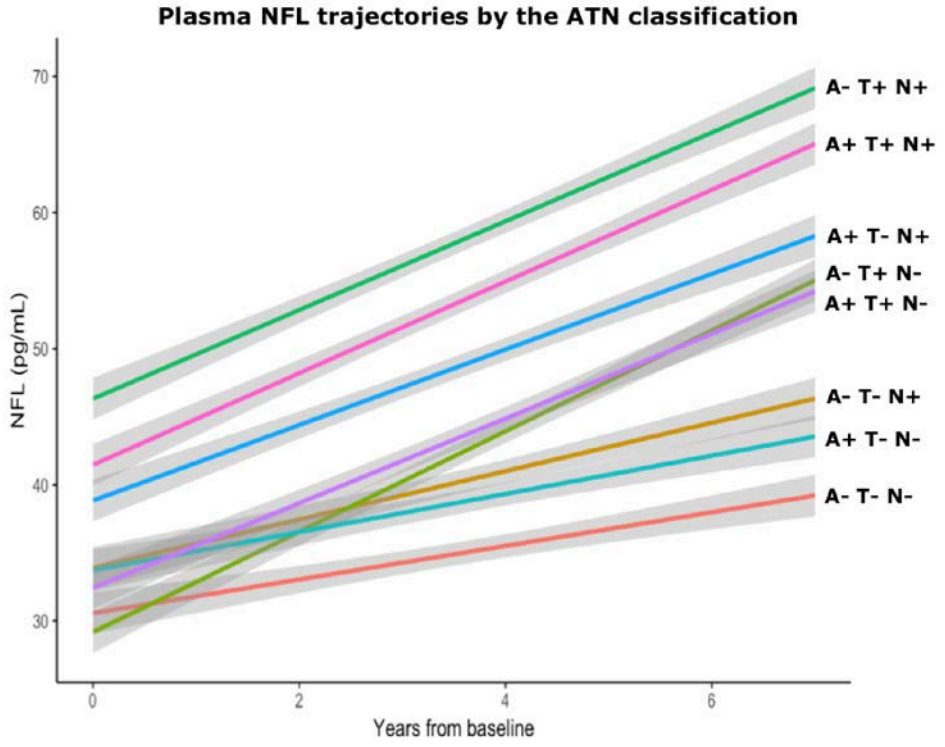
Weston *et al.*, AR&T 2019

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

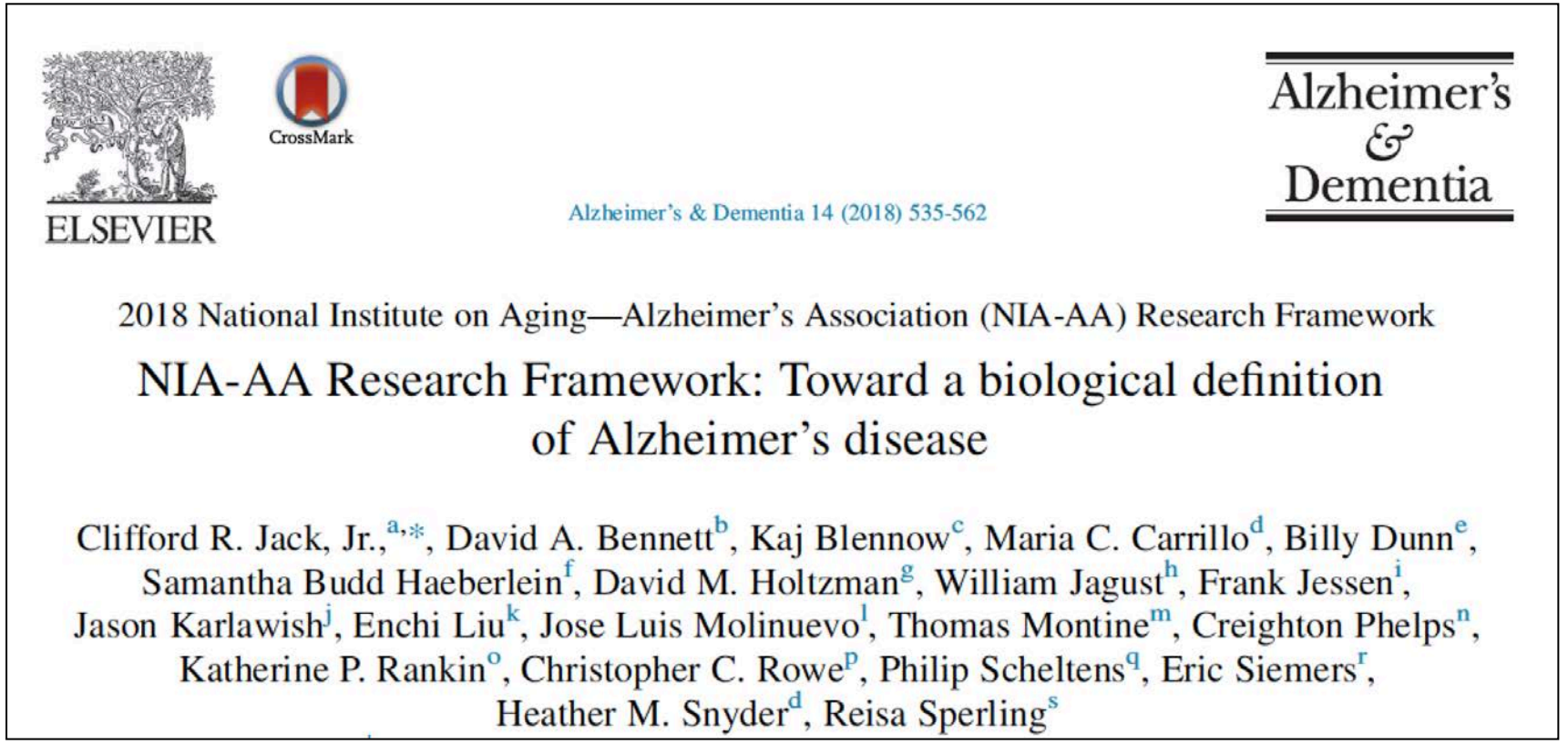
- In-house Simoa for plasma NFL: Uman antibodies + bovine NFL calibrator Gisslén et al, EBioMed 2016





➔Plasma NFL can track neurodegeneration throughout the AD continuum

➔ Serum NFL may be useful to monitor downstream drug effects on intensity of neurodegeneration



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Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

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Biomarkers for A/T/N

- Amyloid = plasma Aβ42/Aβ40 ratio
- Tau = plasma P-tau
- Neurodegeneration = plasma neurofilament light


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