Factors beyond AD pathophysiology that affect the concentration and interpretation of diagnostic AD blood biomarkers

MCI SYMPOSIUM, 2026-04-24

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New solutions introduce new challenges!

Example from the not so ancient history:

Highly sensitive troponin assays arrived, leading to a change in how myocardial infarction (MI) was defined[1], compared with “CK-MB era”

[1]Thygesen et al. JACC. 2012

- Increased sensitivity → individuals with no myocardial ischemia have elevated troponin (*e.g.,* septicemia, atrial fibrillation).
- Do they have MI? No! Context!

Agewall et al. Eur Heart J. 2011

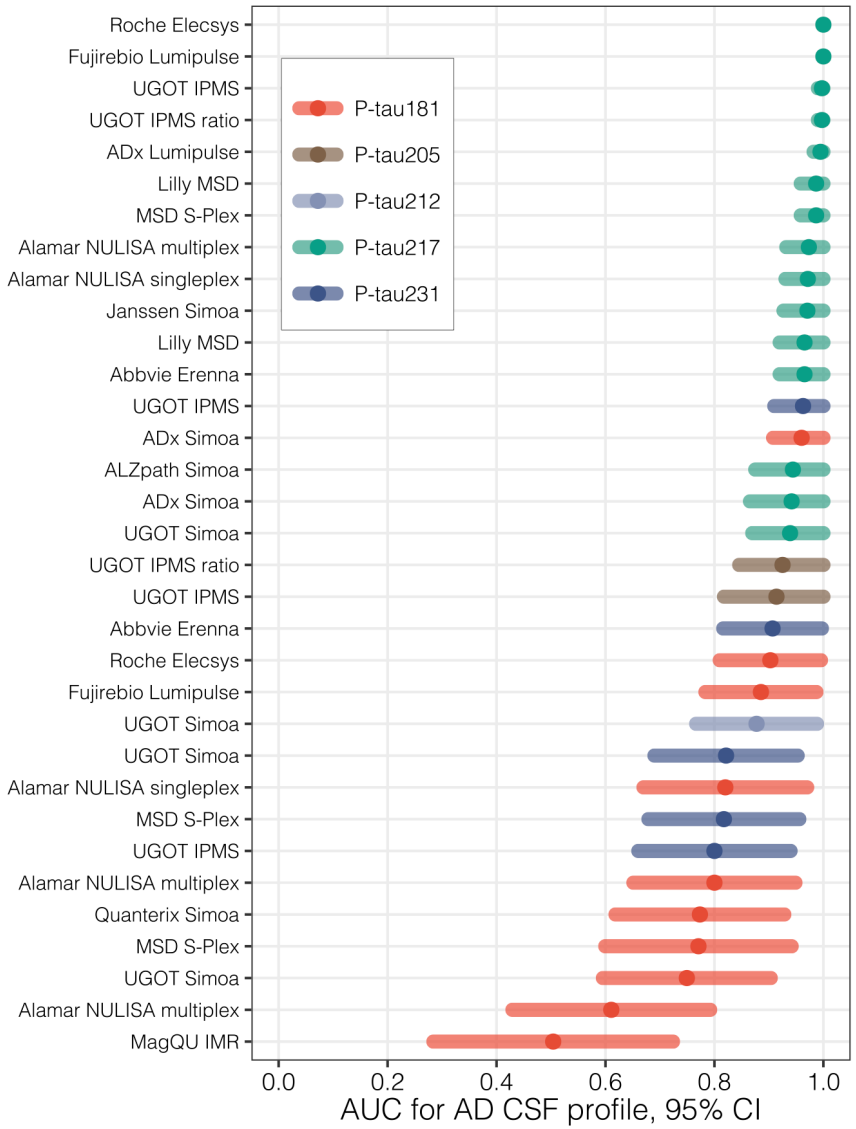
Macrotroponin, troponin in complex with antibodies, lead to stable false elevations of troponin in several % of individuals

Wittfooth et al. Circulation. 2025

Plasma p-tau217 is a highly performing test



- Plasma P-tau217 performs best across assay platforms in separating individuals with/without an AD CSF profile + cognitive impairment
- "Round-robin" study of candidate methods.



Ashton NJ, Keshavan A, Brum WS, et al. The Alzheimer's Association Global Biomarker Standardization Consortium (GBSC) plasma phospho-tau Round Robin study. *Alzheimers Dement*. 2025;21(2):e14508. doi:10.1002/alz.14508

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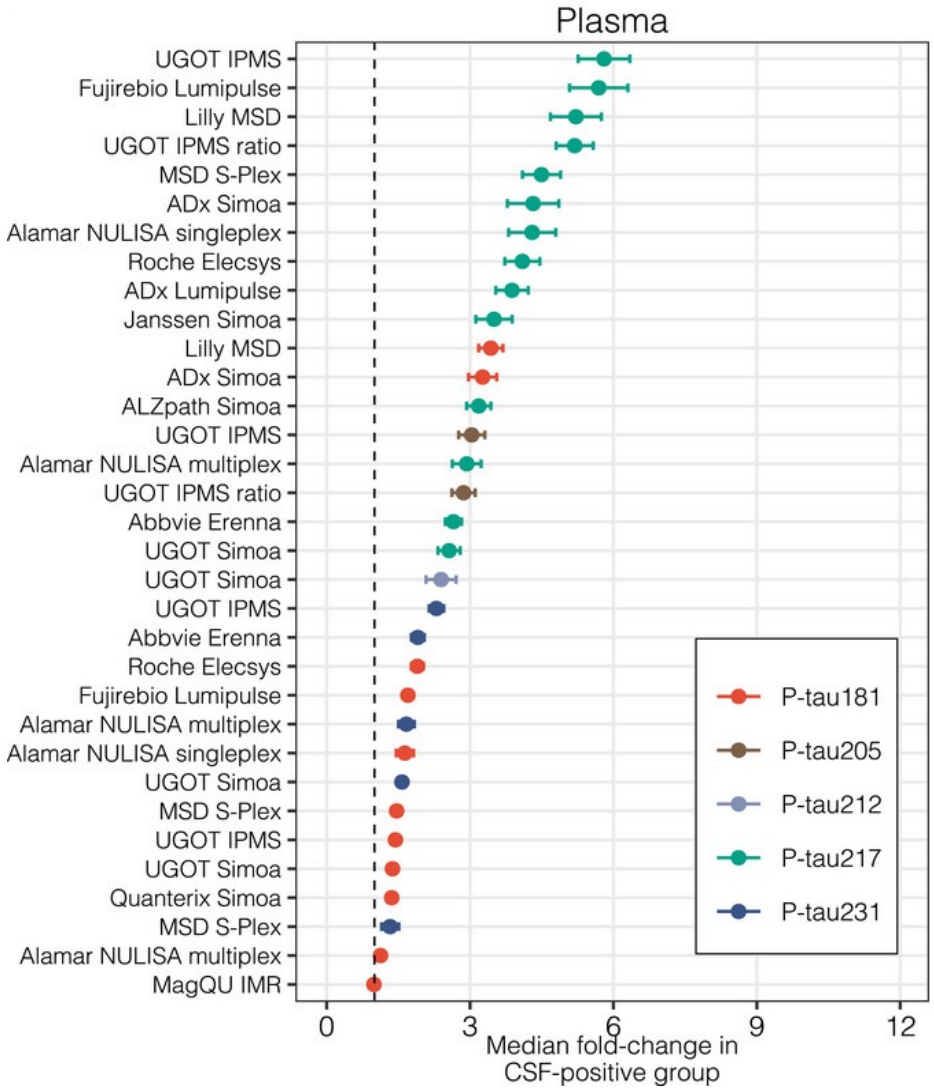

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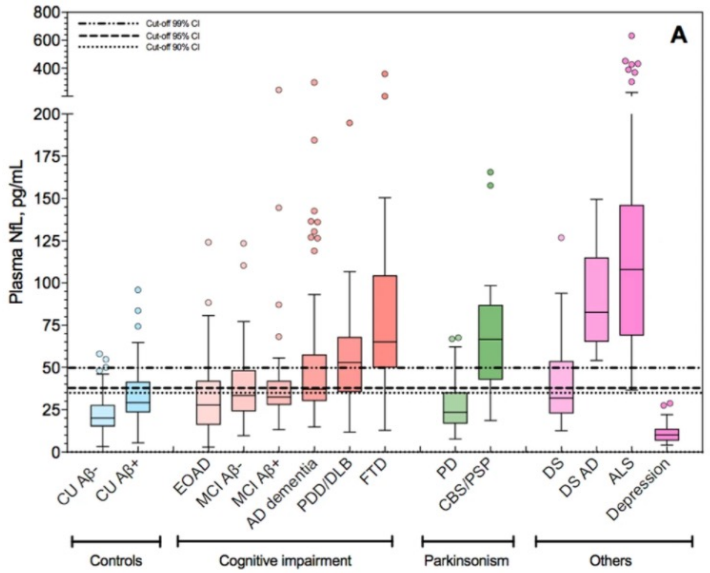
Neurofilament light (NfL) is sensitive, dynamic but disease agnostic

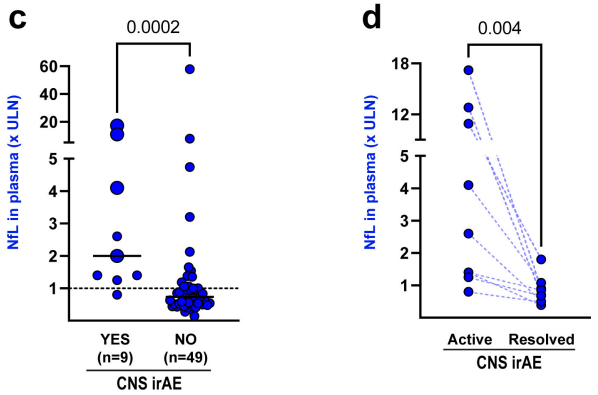


Ashton et al. Nat Commun. 2021

Plasma NfL altered on group level in most neurodegenerative diseases

Concentrations of S100B and neurofilament light chain in blood as biomarkers for checkpoint inhibitor–induced CNS inflammation

Sara Bjursten,[a,b,*] Zhiyuan Zhao,[a,b,c] Hifaa Al Remawi,[a,b] Marie Studahl,[d,e] Ankur Pandita,[a,b,c] Joel Simrén,[f,g] Henrik Zetterberg,[f,g,h,i,j] Anna-Carin Lundell,[k] Anna Rudin,[k] Lars Ny,[a,b] and Max Levin[a,b,c]

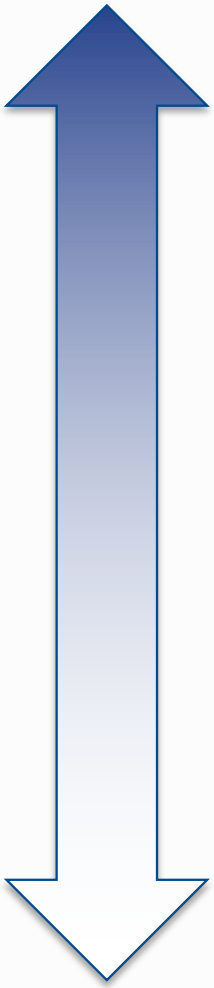


Bjursten et al. eBioMedicine. 2024

Response to therapy in both acute and chronic conditions

New solutions introduce new challenges!

Factors beyond AD pathophysiology and neuronal damage that affect plasma P-tau217 and NfL



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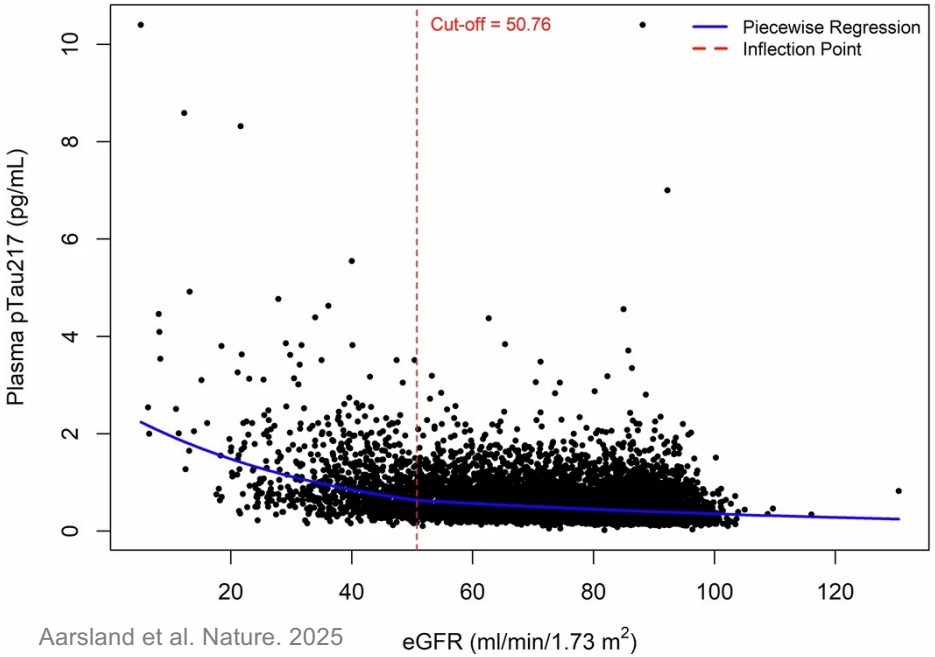
Rare/Not clinically relevant

Low glomerular filtration rate (GFR) is associated with reduced clearance of blood biomarkers



Aarsland et al. Nature. 2025

GFR matters, but the group level effect of amyloid pathology on p-tau217 is much stronger. In individual cases around cutoffs or with very low GFR, it may have an effect. Probabilistic interpretation!

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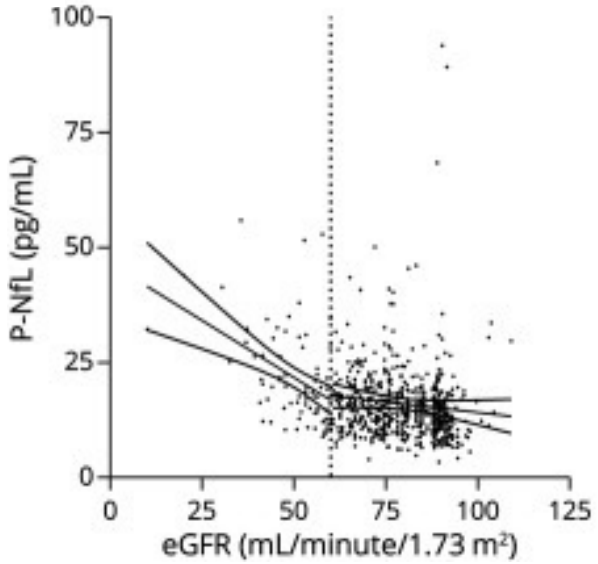
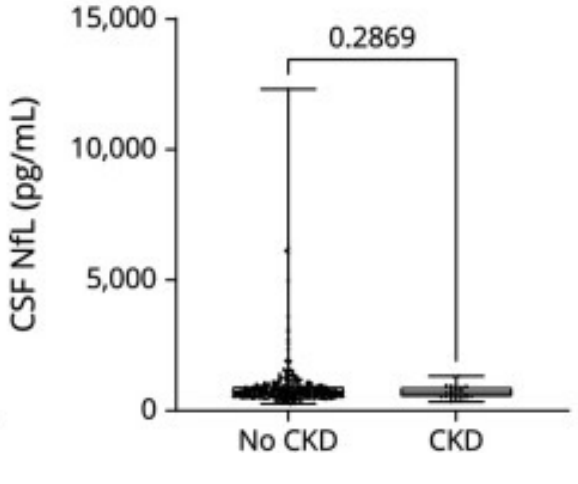
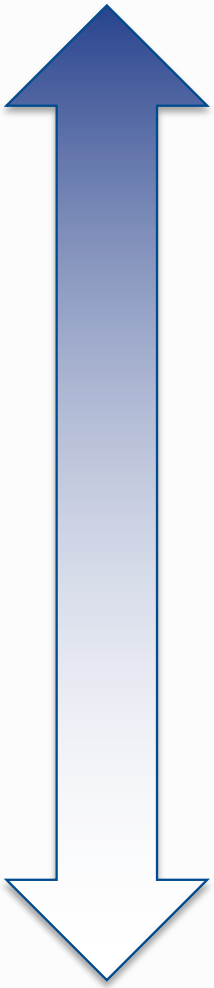


Dittrich et al. Neurology. 2023



Dittrich et al. Neurology. 2023

GFR matters for NfL, and should be interpreted in the clinical context it is used. Not seen with CSF NfL. Probabilistic interpretation!



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Rare/Not clinically relevant

Should clinical cutoffs for blood biomarkers be *APOE*-dependent?

2014

Original Investigation

Apolipoprotein E Genotype and the Diagnostic Accuracy of Cerebrospinal Fluid Biomarkers for Alzheimer Disease

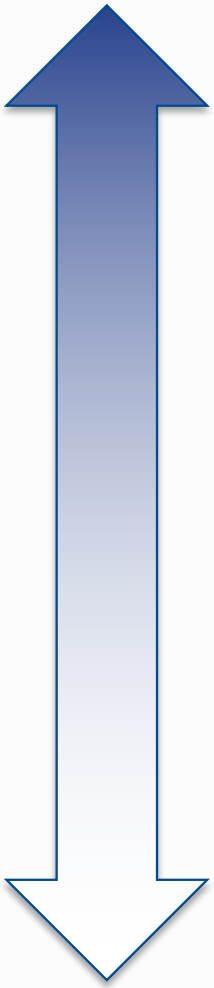
Ronald Lautner, MD; Sebastian Palmqvist, MD, PhD; Niklas Mattsson, MD, PhD; Ulf Andreasson, PhD; Anders Wallin, MD, PhD; Erik Pålsson, PhD; Joel Jakobsson, PhD; Sanna-Kaisa Herukka, BM, MSc, PhD; Rikard Owenius, PhD; Bob Olsson, PhD; Harald Hampel, MD; Dan Rujescu, MD, PhD; Michael Ewers, PhD; Mikael Landén, MD, PhD; Lennart Minthon, MD, PhD; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD; Oskar Hansson, MD, PhD; for the Alzheimer's Disease Neuroimaging Initiative

CONCLUSIONS AND RELEVANCE Cerebrospinal fluid levels of Aβ42 are strongly associated with the diagnosis of AD and cortical Aβ accumulation independent of *APOE* genotype. The clinical cutoff for CSF levels of Aβ42 should be the same for all *APOE* genotypes.

2026

- Higher P-tau217 in *APOE ε4* carriers, but attenuated after adjusting for amyloid status[1]
- Plasma p-tau217 cut-offs should generally *not* be *APOE* genotype dependent
- A positive plasma p-tau217 in homozygous *APOE ε4* carriers strongly predictive of amyloid pathology

[1]Mielke et al. Nat Med. 2022



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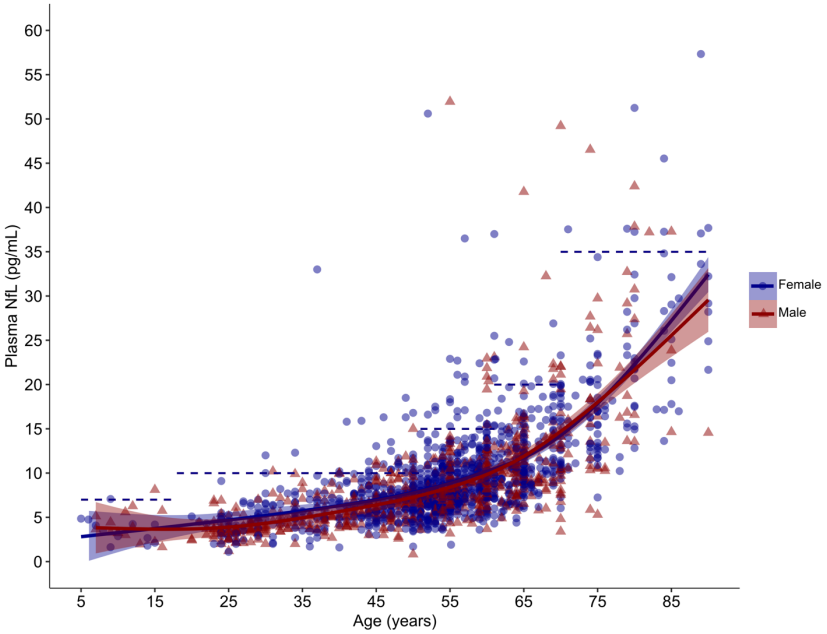
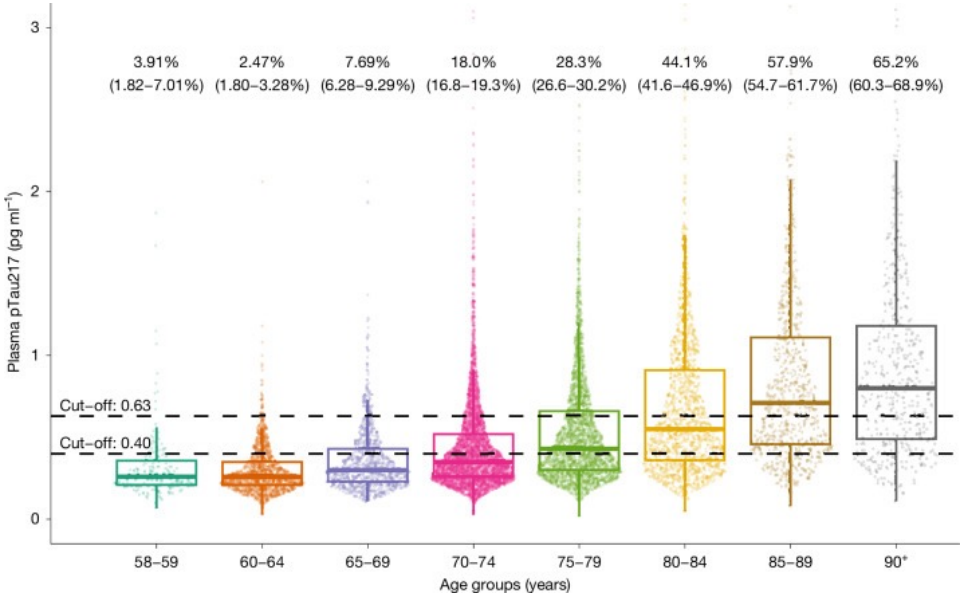
Age and their influence on NfL and P-tau217?



Simrén et al. Brain Commun. 2021



Aarsland et al. Nature. 2025

NfL in plasma moderately influenced by age. Increases about 3-4% per year in apparently healthy adults.

P-tau217 also increases with age

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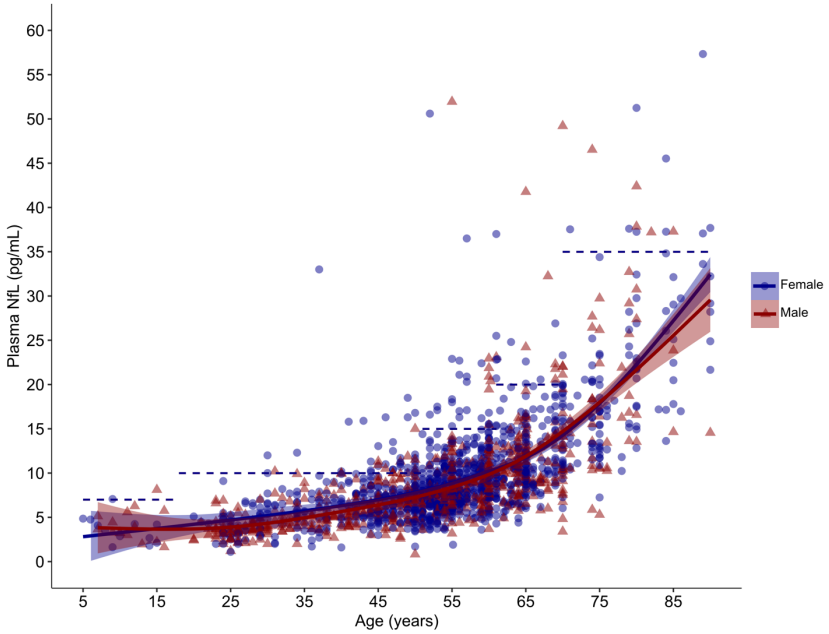

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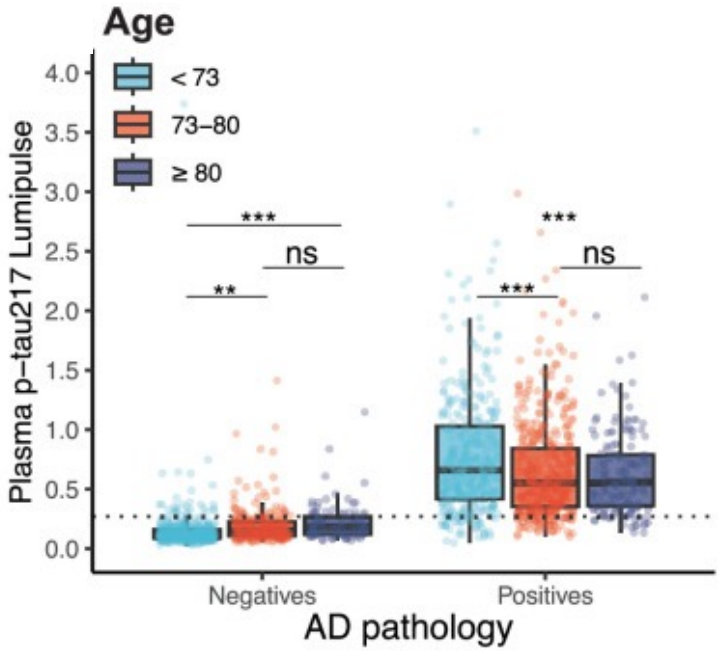
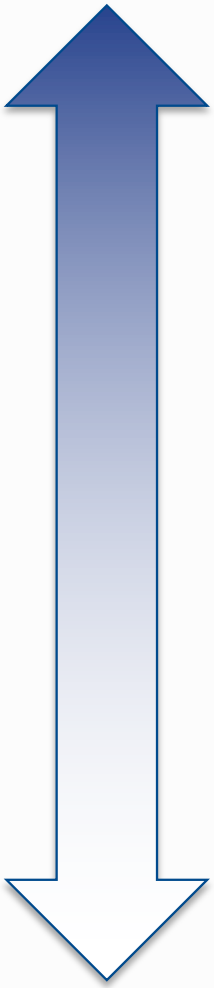


Palmqvist et al. Nat Med. 2025

Most important driver of increasing P-tau217 with age is AD pathology



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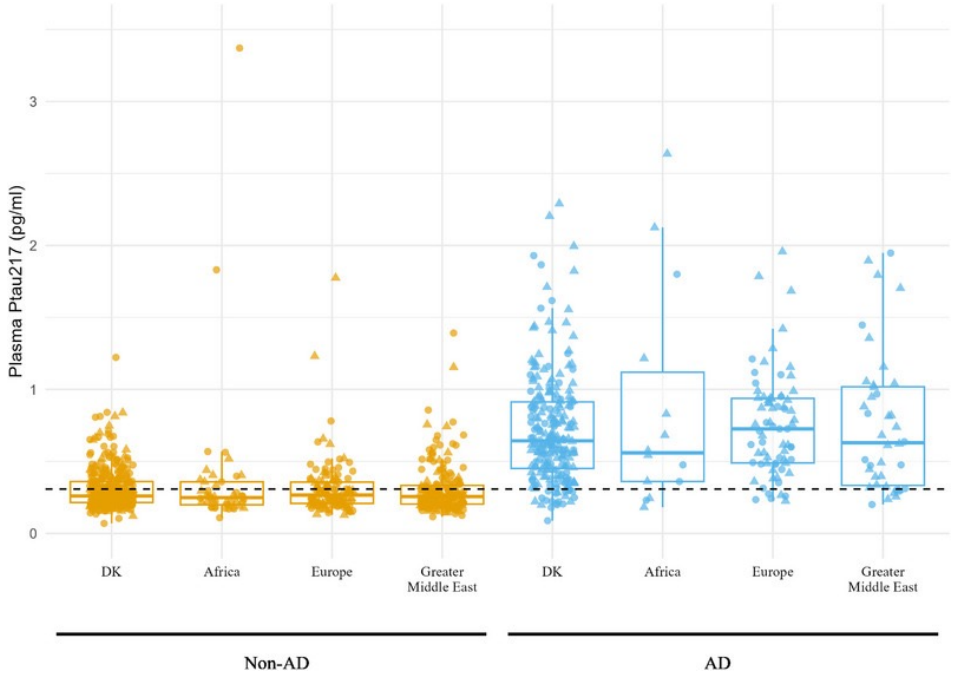
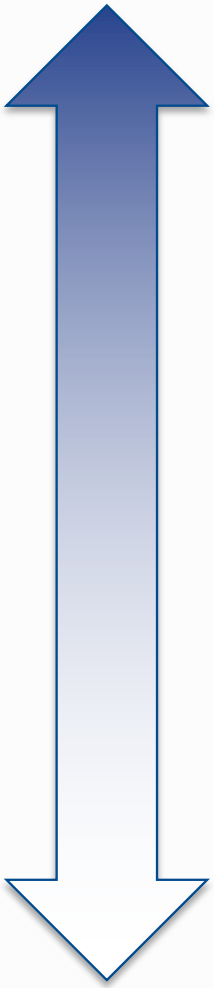
Rare/Not clinically relevant

Ethnic background does not affect concentration or accuracy of plasma P-tau217

- Scarcity of well-designed studies comparing the effect of ethnic background on high-performing blood biomarker assays
- Social determinants of health likely important for group-level differences that may be seen
- Important that these studies compare the performance to a reference standard
- Based on available data, unlikely that ethnic background is *important* for clinical interpretation



Kjaegaard et al. Alzheimers Dement. 2025



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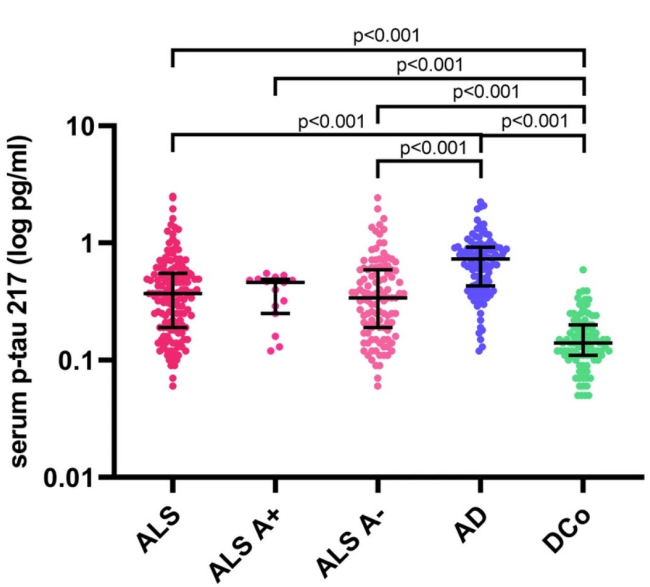
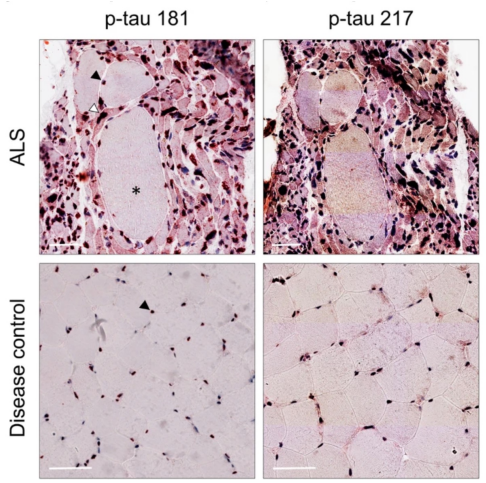
Rare/Not clinically relevant

Increase in plasma (but not CSF) P-tau217 is seen in ALS





Abu-Rumeileh et al. Nat Commun. 2025

P-tau increased in plasma but not CSF in ALS

Higher P-tau in ALS may be related to peripheral denervation

Peripheral amyloid pathology is associated with high p-tau217 and p-tau181

nature medicine

Brief Communication https://doi.org/10.1038/s41591-026-04272-2

Blood phosphorylated tau elevation as a biomarker in immunoglobulin light chain and transthyretin amyloidosis

Received: 25 June 2025

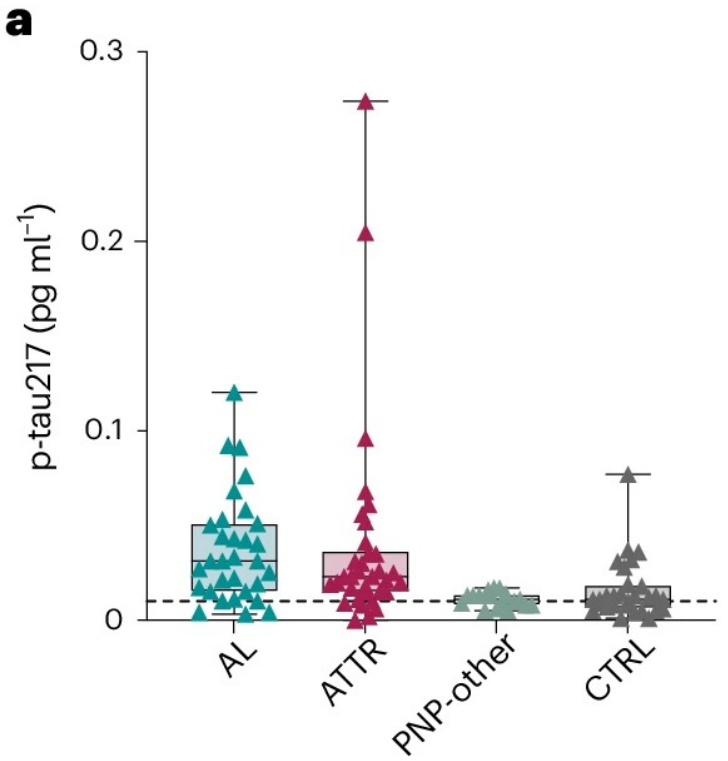
Accepted: 5 February 2026

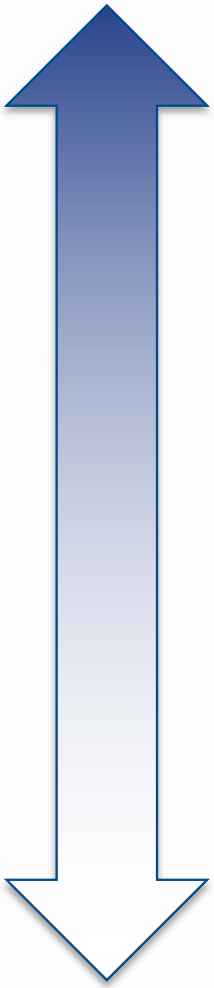
Published online: 11 March 2026

Check for updates

Stephan A. Kaeser[1,2,11], Stephanie A. Schultz[3,4,11], Anna Hofmann[1,2,11], Lisa M. Häsler[1,2], Ying Xu[1,2], Marius Lambert[1,2], Ulrike Obermüller[1,2], Kathrin Brockmann[1,5], Johan Bijzet[6], Hans Nienhuis[7] ✉, Mario Nuvolone[8,9], Laura Obici[9], Giovanni Palladini[8,9] ✉, Ute Hegenbart[10], Stefan O. Schönland[10] ✉ & Mathias Jucker[1,2] ✉

- P-tau is elevated transthyretin (ATTR) amyloidosis and immunoglobulin light chain (AL) amyloidosis
- Peripheral amyloid may also trigger P-tau release from peripheral nerves





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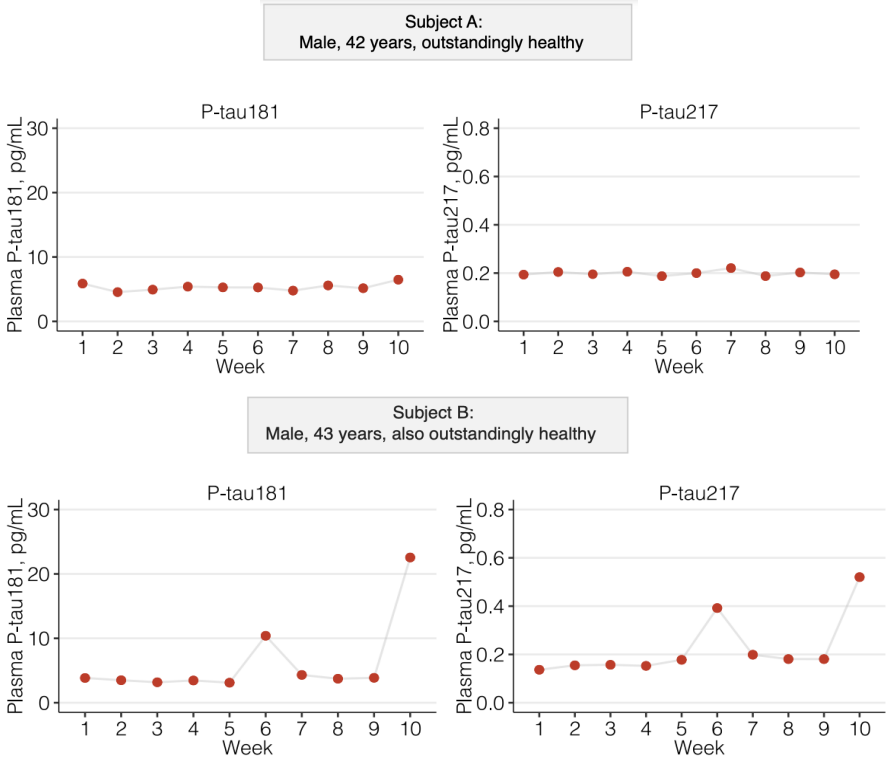
Rare/Not clinically relevant

Rarely there is no clear reason, or analytical issues

Biological variation over 10 weeks in healthy adults



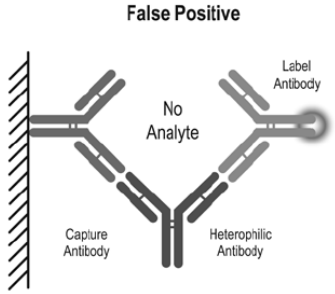
Brum et al. Alzheimers Dement. 2023

Rarely heterophilic antibodies → unusually high p-tau217 when using immunoassays

Received: 2 October 2025 | Revised: 12 November 2025 | Accepted: 23 November 2025
DOI: 10.1002/alz.71045
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION
SHORT REPORT

False positive plasma p-tau217 results associated with heterophilic antibody interference: A potential clinical pitfall

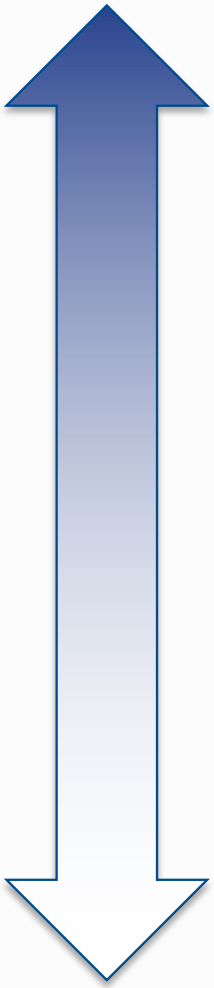
Alicia Algeciras-Schimnich | J Paul Theobald | Daniel J. Figdore | Susan Ashrafzadeh Kian | Joshua A. Bornhorst



Morton. Australian Journal of General Practice. 2014

Rarely there is no clear reason, or analytical issues

Aβ42 may add analytical variability with limited incremental value



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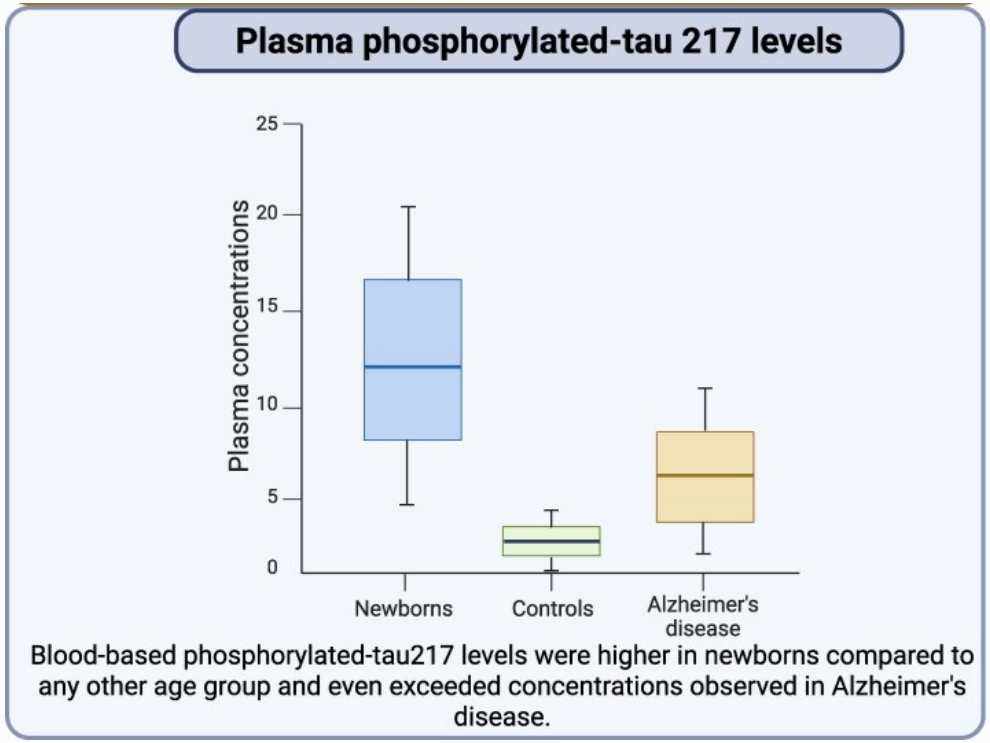
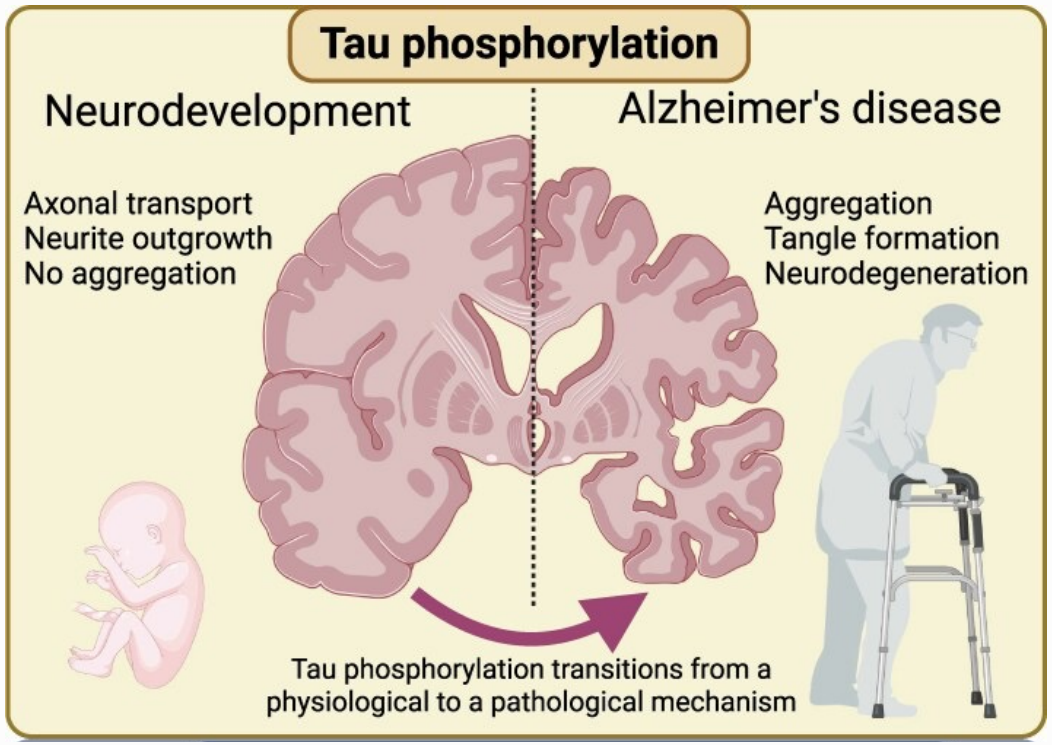
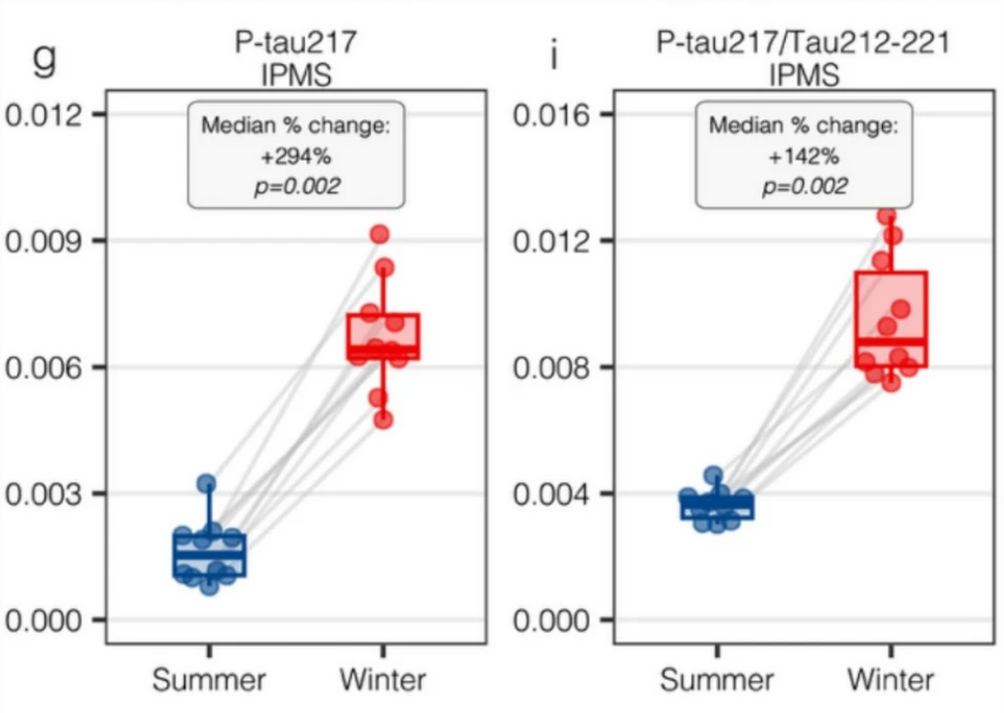




Gonzalez-Ortiz et al. Brain Commun. 2025

Context is important when interpreting any clinical chemistry test

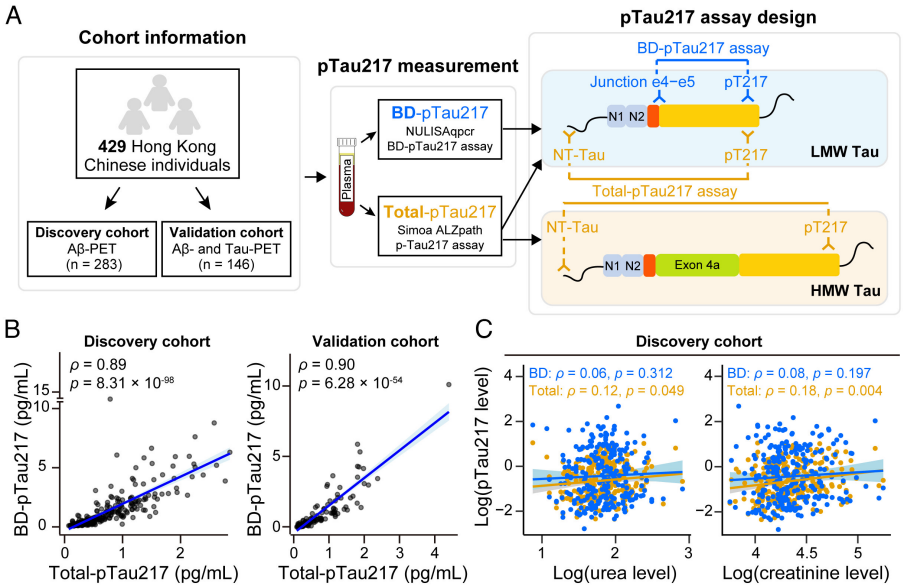
Hibernating bears have very high plasma P-tau217



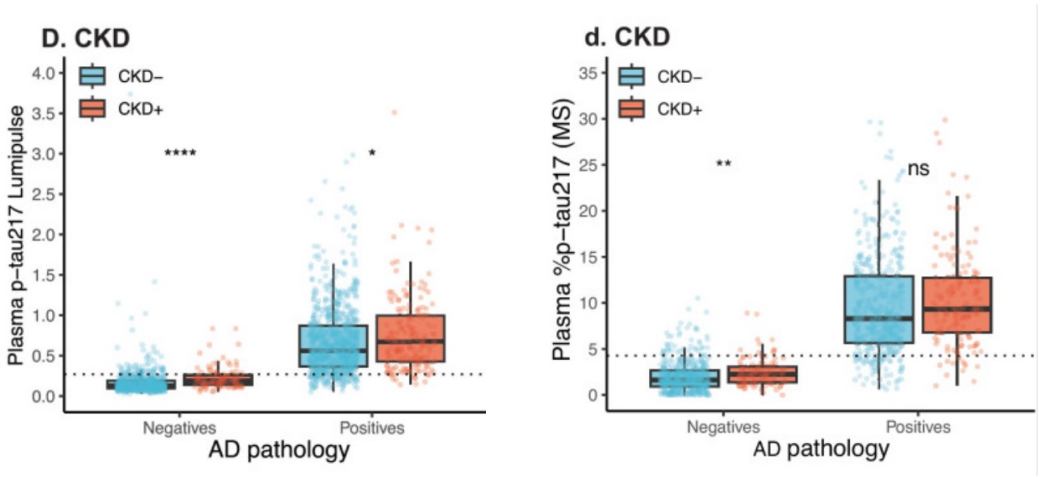
Brum et al. Acta Neuropathol. 2025

"If you find high plasma P-tau217 in a bear, it's more likely that it's hibernating than that it has Alzheimer's disease"

How do we mitigate these issues?



Jiang et al. PNAS. 2026



Palmqvist et al. Nat Med. 2025

Increase specificity to capture only CNS-specific forms

Normalize for variability in tau secretion and clearance

Conclusions

- Interpreting p-tau217 and other blood biomarkers require consideration of the clinical context, and comorbid diseases.
- Regardless, AD pathophysiology is the strongest predictor of P-tau217 concentrations in appropriate clinical contexts.
- Plasma NfL concentration and variability is seemingly more influenced by age, likely partly due to the absence of a reference standard that can explain this increase
- Ethnic background and *APOE* genotype do not meaningfully seem to affect P-tau217 concentrations independently of AD pathophysiology.
- **Finally, if one knows the pitfalls of p-tau217 and NfL, they are highly useful clinical chemistry tests likely to solve a lot more problems than they create!**



Thank you for listening!

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