State of Science on ADRD Biomarkers and Comorbidities

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ALZHEIMER'S DIAGNOSIS
IN OLDER ADULTS WITH CHRONIC CONDITIONS

Wake Forest University
School of Medicine

ADVOCATE HEALTH

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- I have **no conflicts** for this presentation

Blood-based biomarkers (BBMs)

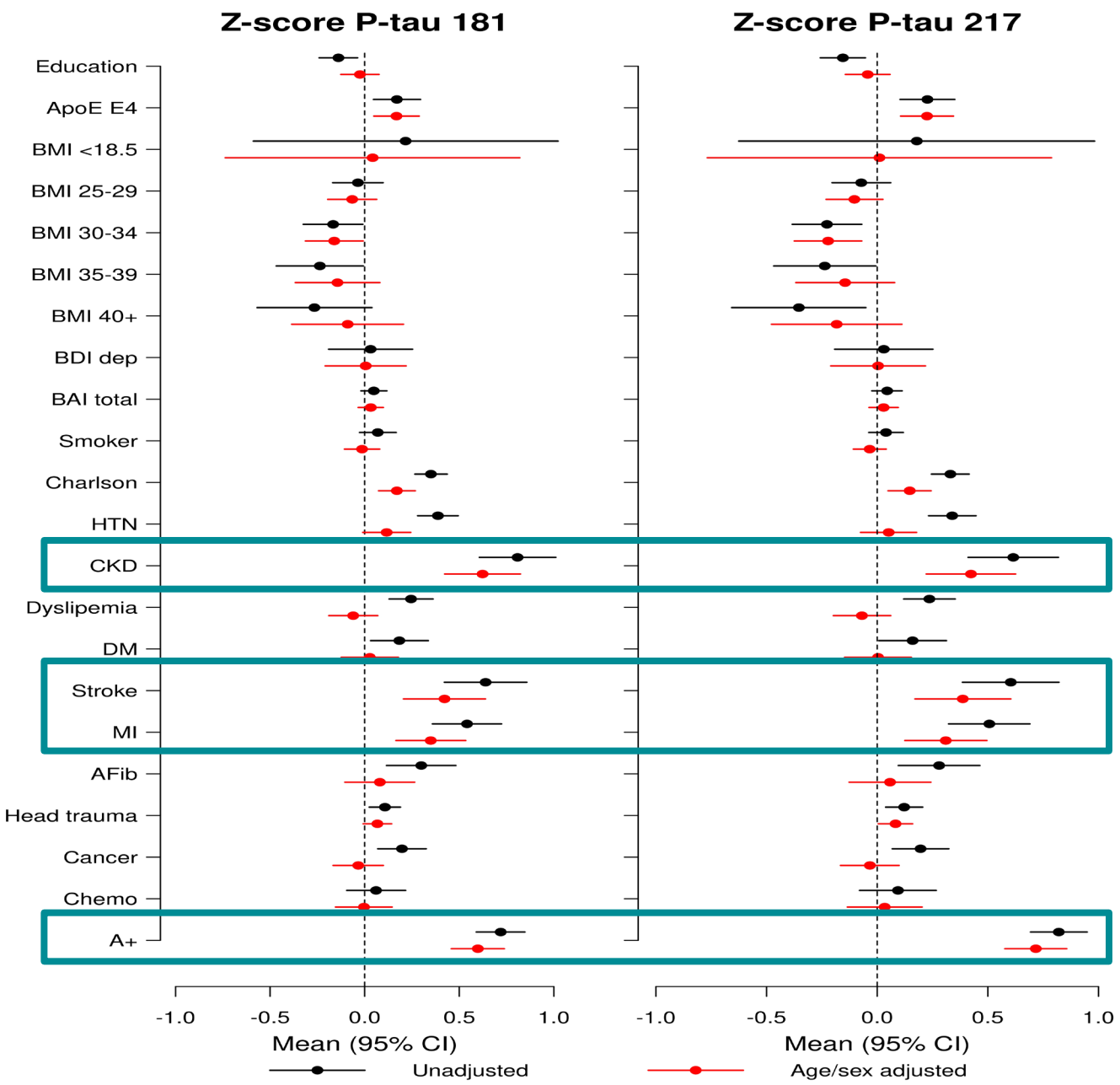
- Many causes of cognitive impairment
  - Utilizing biomarkers can help elucidate underlying etiology
- Limitations of PET and CSF for widespread AD diagnosis
  - Cost, invasiveness, feasibility, accessibility
- Technological advances have led to measurement of low concentrations of AD proteins in blood
- Multiple studies show the potential clinical utility of plasma measures of amyloid-beta 40 and 42 and phosphorylated tau as biomarkers of AD pathology
  - Some assays are available clinically (immunoassays are reimbursable)
- Most studies to date have focused on clinical, white, younger and higher SES populations
  - Urgent need to understand how the blood markers perform in heterogenous, diverse populations and what factors might affect their interpretation at the population level

Considerations of comorbidities and BBMs

3 potential explanations for how comorbidities can impact the interpretation of ADRD BBMs:

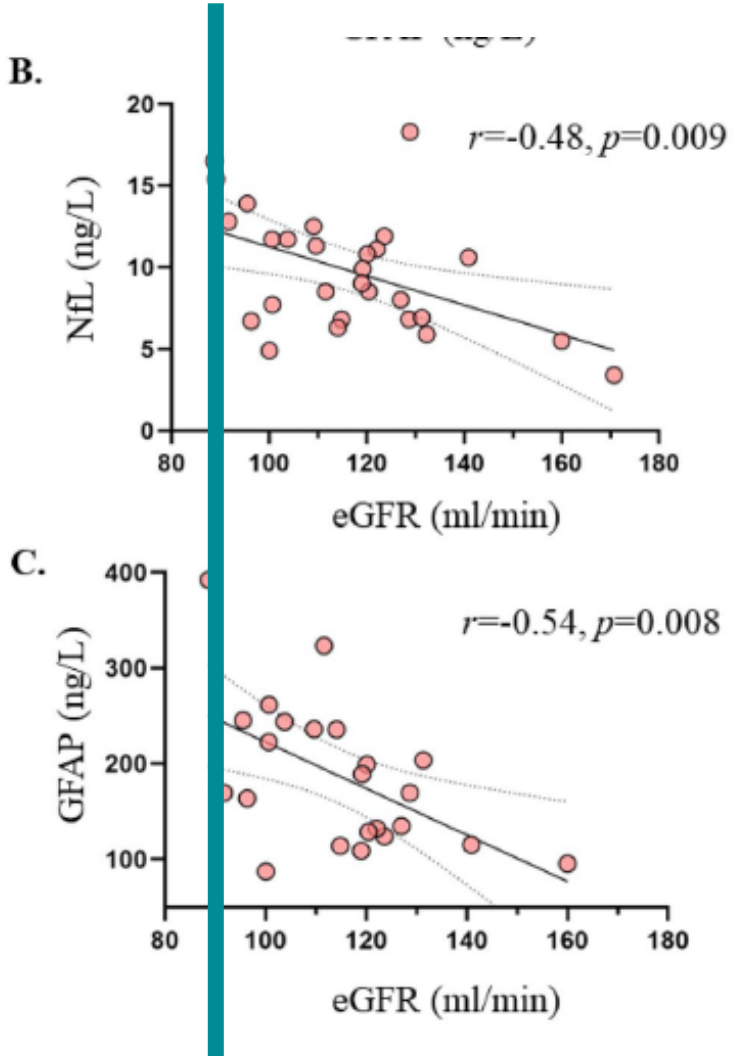
1. Risk factors for ADRD
2. Physiologically cause increase or decrease in BBMs
3. Both

Factors associated with plasma P-tau181 and P-tau217



Mielke MM, et al. Nature Medicine 2022

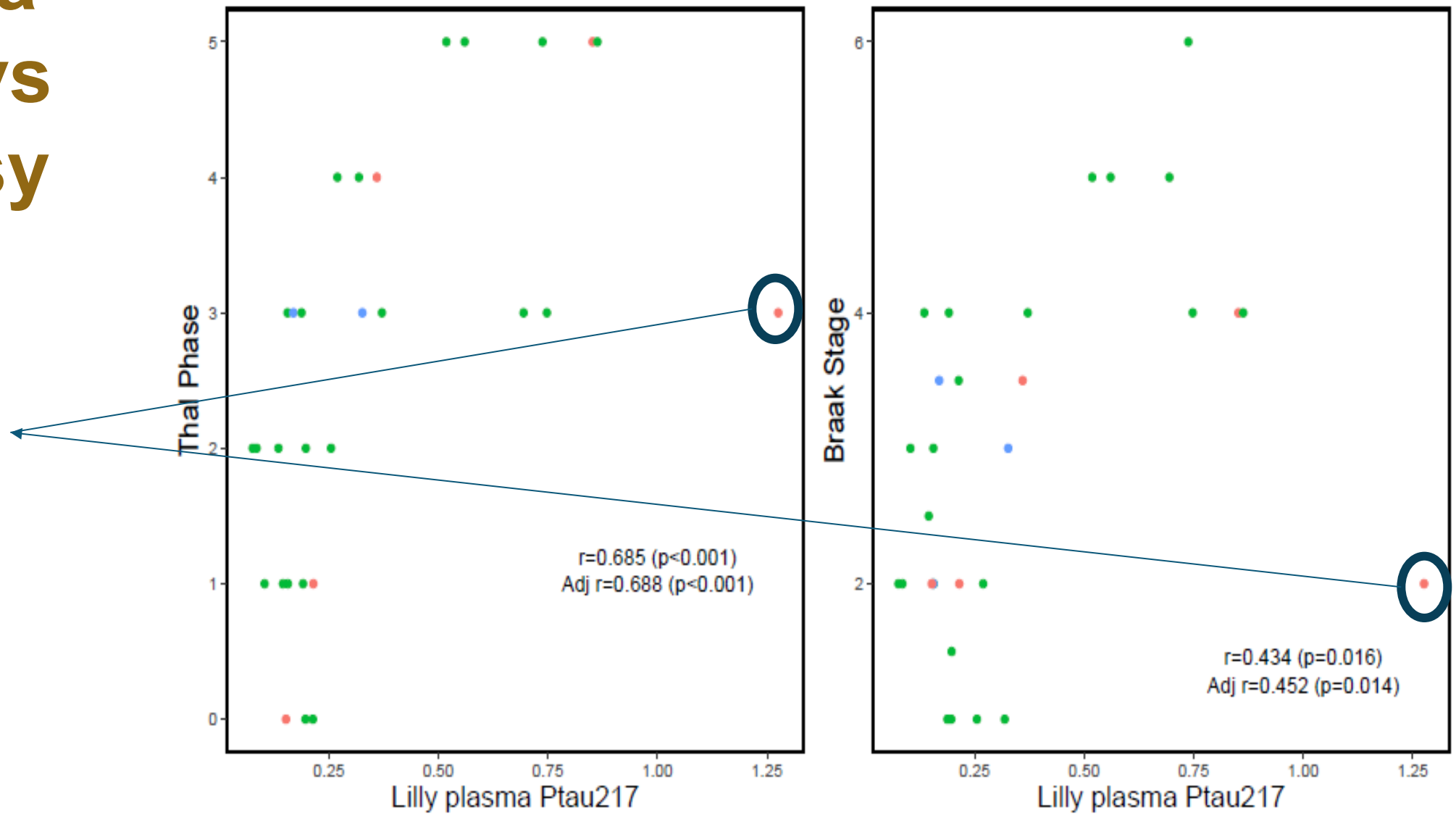
NfL and GFAP related to eGFR



Rebelos E et al. Scientific Reports 2022

Plasma P-tau vs autopsy

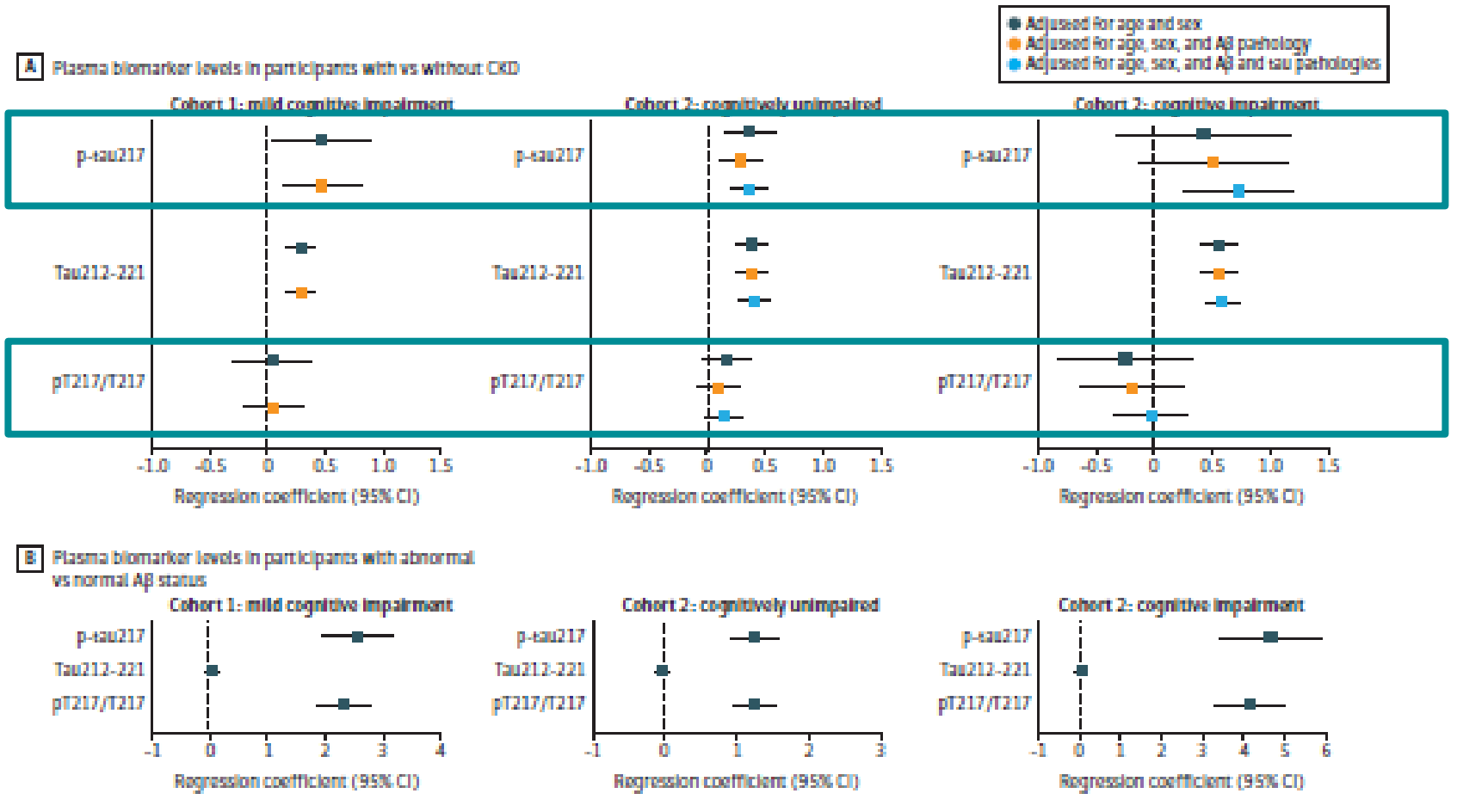
Serum creatinine=3.7



Murray M & Mielke MM, unpublished

Mitigating effects of CKD for interpretation

Figure 1. Associations of Plasma of Phosphorylated Tau (p-tau) 217, Tau212-221, and pT217/T217 With Chronic Kidney Disease (CKD) and Amyloid-β (Aβ) Status

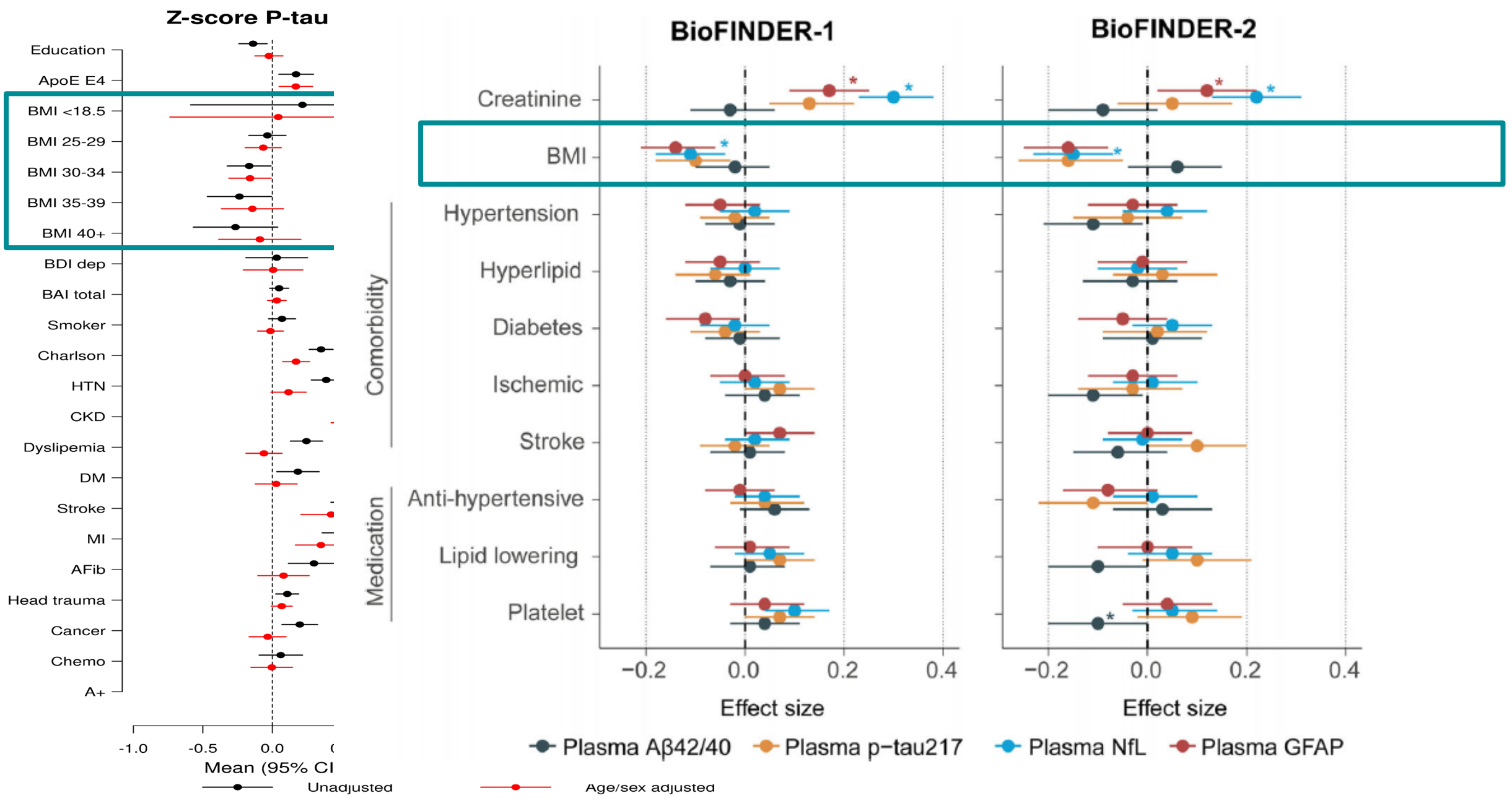


Janelidze S et al. JAMA Neurology 2023

But…Not there yet

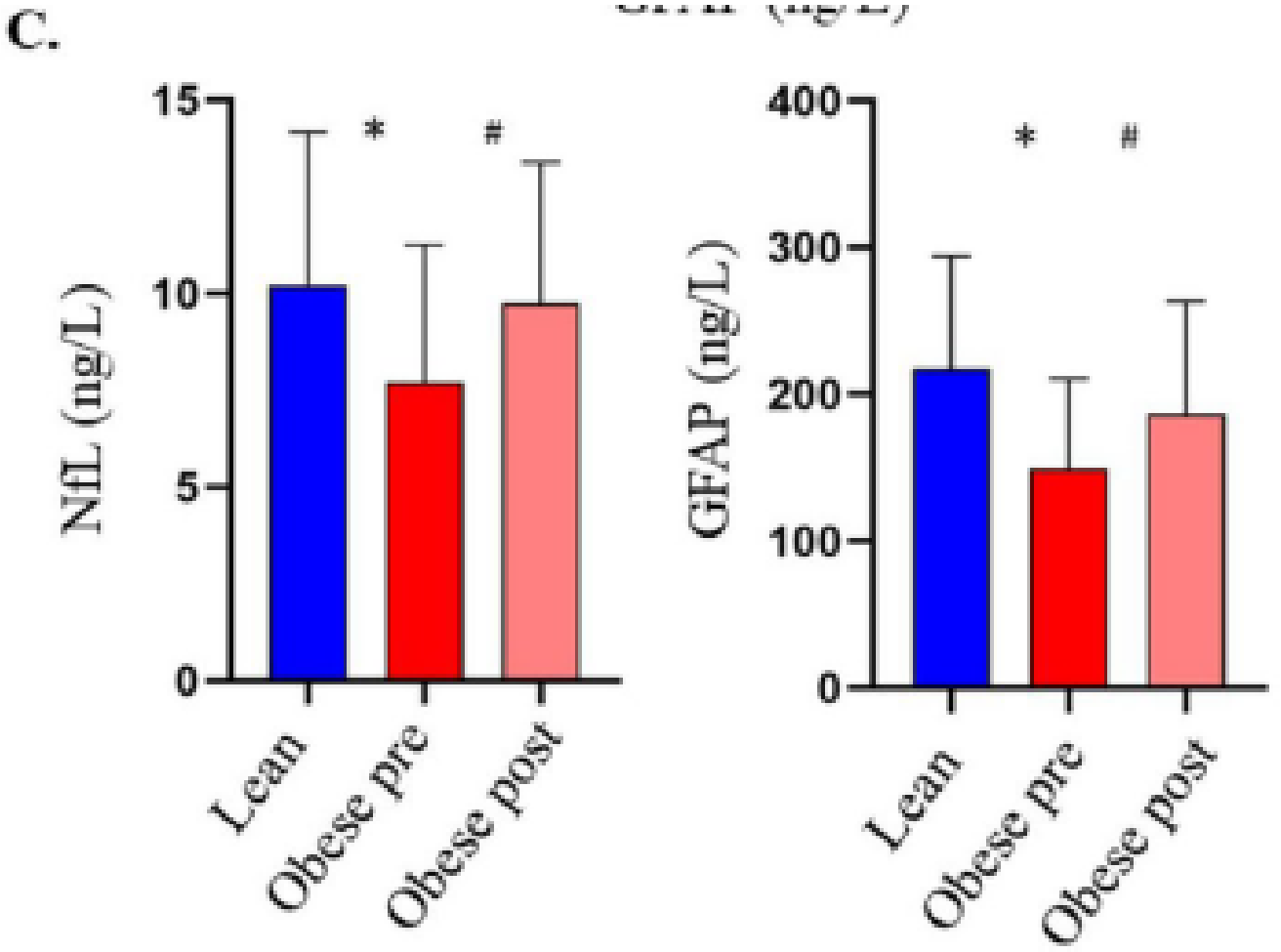
	C_2N %p-tau217					
	All %p-tau217 = 2.929 × eGFR$^{(-0.1989)}$		Amyloid− %p-tau217 = 8.357 × eGFR$^{(-0.6081)}$		Amyloid+ %p-tau217 = 1.084 × eGFR$^{(0.1628)}$	
eGFR	Calculated value	% Change from 60 eGFR (95% CI)	Calculated value	% Change from 60 eGFR (95% CI)	Calculated value	% Change from 60 eGFR (95% CI)
60	1.30	N/A	0.69	N/A	2.11	N/A
50	1.35	+4 (−5 to 13)	0.77	+12 (2–22)	2.05	−3 (−13 to 8)
45	1.37	+6 (−8 to 21)	0.83	+19 (3–38)	2.01	−5 (−19 to 13)
40	1.41	+8 (−11 to 31)	0.89	+28 (4–57)	1.98	−6 (−26 to 18)
30	1.49	+15 (−17 to 59)	1.06	+52 (8–116)	1.89	−11 (−40 to 33)

Bornhorst J et al. Neurology 2025



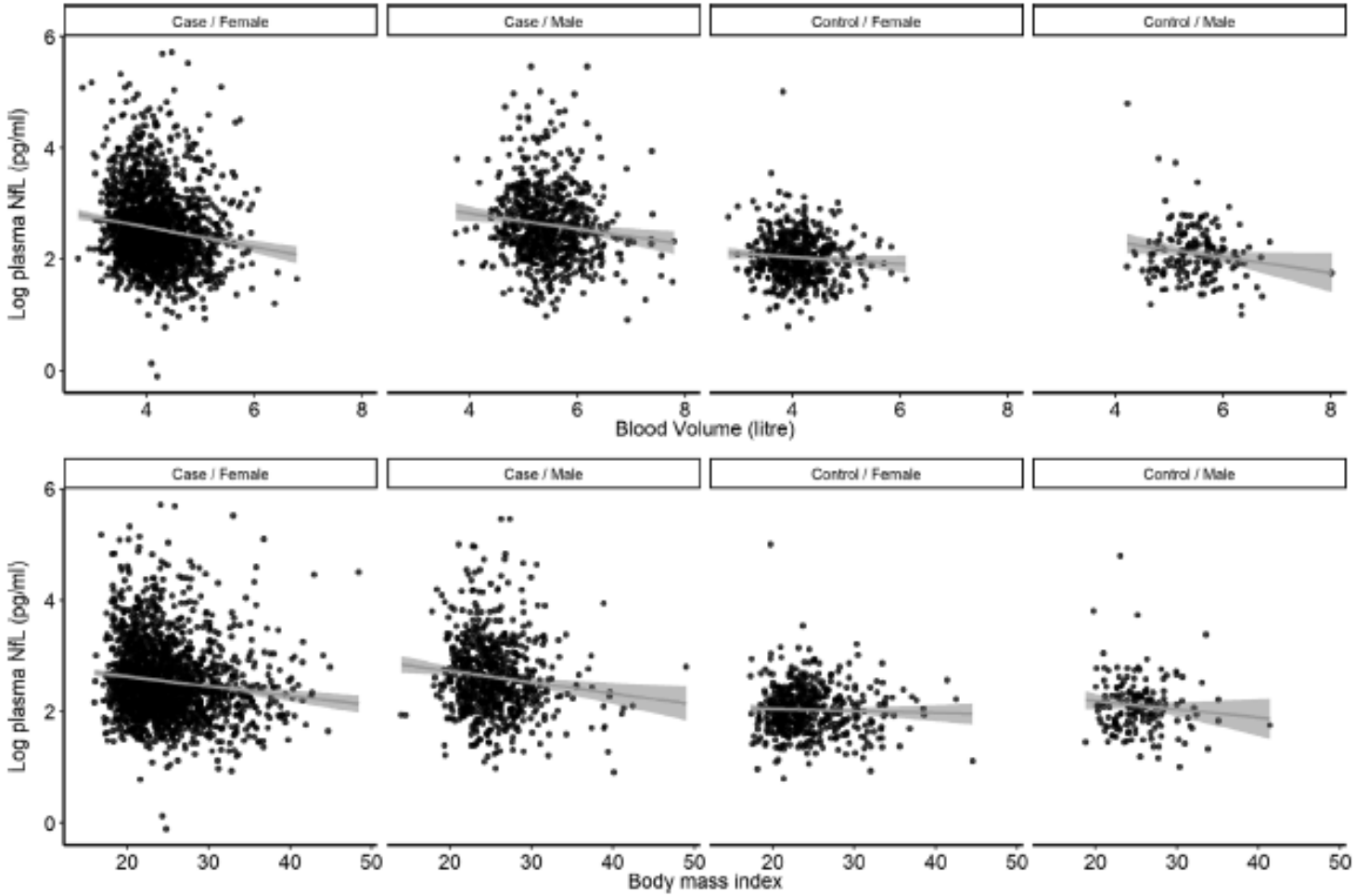
Mielke MM, et al. Nature Medicine 2022; Pichet Binette, et al. Alz Dem 2022

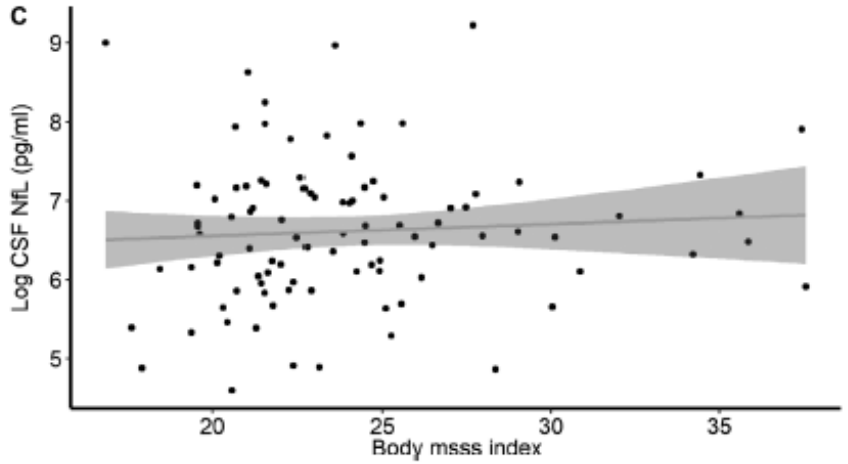
NFL and GFAP related to BMI



Rebelos E et al. Scientific Reports 2022

Plasma, but not CSF, NfL decreases with increasing BMI

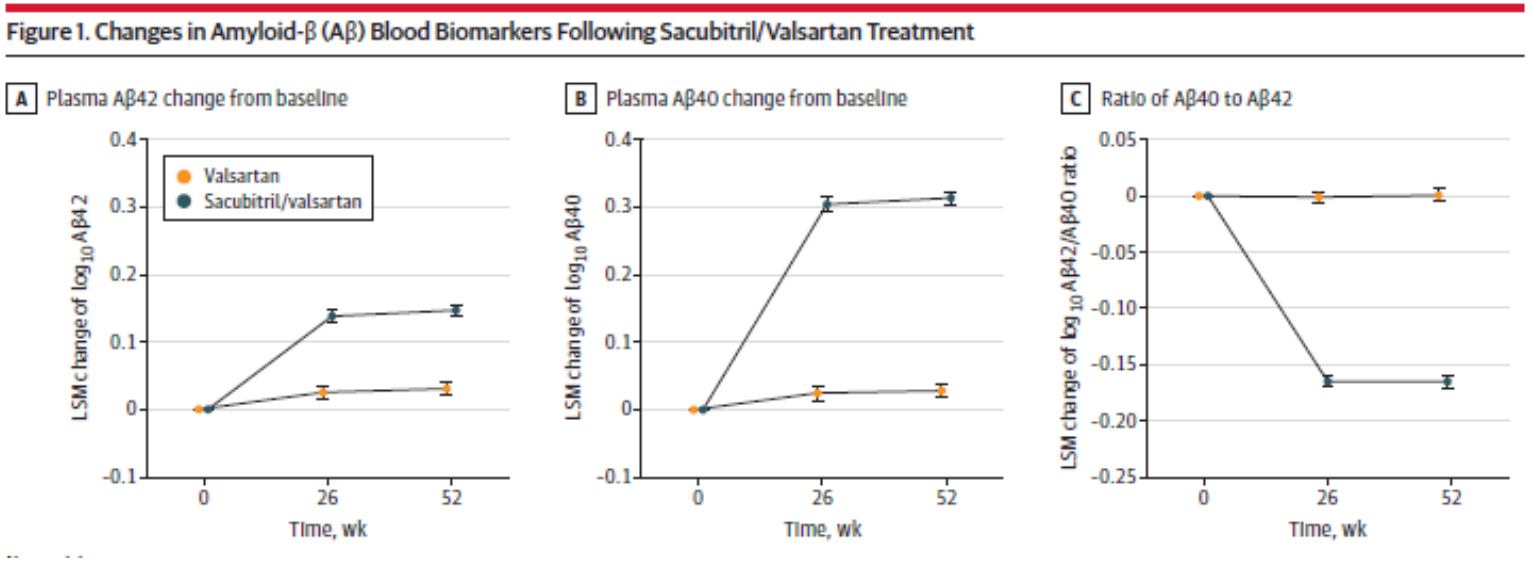




Manouchehrinia A et al. Annals of Clin Trans Neurology 2020

Blood amyloid and cardiac conditions

- Amyloid-beta (Aβ) accumulates in heart of AD patients and induces AD-related cardiac amyloidosis (Troncone L et al. 2016; Schaich CL et al. 2019)
- Higher levels of plasma Aβ40 and Aβ42 associated with incident heart failure (Zhu F et al, 2023)
- Sacubitril (Neprilysin inhibitor + valsartan) lowers plasma Aβ42/40 ratio (Brum WS et al. 2023), but not CSF Aβ42/40 ratio (Langenickel TH et al, 2016)



****No Change in P-tau217**

Diagnostic considerations

AD pathologies begin decades prior to symptoms and increase with age

- Possibility of positive test being incidental
- A blood test in isolation of a clinical assessment for cognitive changes should not be done
- ***Need objective evidence of cognitive impairment***, and not just subjective changes, prior to having a blood test
- We do not yet understand the prognostic value of the blood biomarkers, particularly among asymptomatic individuals or among symptomatic individuals with multiple chronic conditions

Positive blood biomarker test may indicate AD pathology – but the true 'cause' of symptoms?

- Multiple brain pathologies increase with age – '*pure AD' rare in older adults*
- Potential for suboptimal treatment due to disregard for other pathologies
- Continued education to focus on the patient as a whole
- Some individuals with considerable vascular factors may most benefit from treatment of those risk factors
- Other factors important to consider in older adults (e.g., medications, alcohol, sleep apnea, diet/exercise)

Refs: Galasko DR et al. J Alzheimers Dis. 2022; Hampel H et al. Neuron. 2023; Lista S et al. Ageing Res Rev. 2024; Mielke & Fowler, Nat Rev Neurology 2024

Discussion

- CKD increases AD blood-based biomarkers
  - Physiological vs. risk factor
  - Lack of correct interpretation could lead to false positive diagnosis
- Increasing BMI associated with lower levels of biomarkers
  - Unclear how to consider this factor –may need to ascertain recent weight gain or loss and GLP-1 use
- Need further examination of blood amyloid-beta levels in context of cardiac function and medications
- Next step: examine multiple conditions and develop an algorithm
- Although blood AD biomarkers are promising, many questions remain. Yet, they are available and already used in the real-world including primary care
  - While funding is needed to continue discovering new and better biomarkers, funding for how to use and implement in the general population, especially diverse populations, and when is also critical

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Thank you !!

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