

Plasma biomarkers of Alzheimer’s disease in a community-based sample: Associations with amyloid burden and the influence of renal function

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Background

- Plasma biomarkers have been extensively evaluated in clinical settings and show high promise as large-scale screening tools for identifying individuals at risk of amyloid-beta (A β) accumulation.^{1,2}
- In particular, recently developed brain-derived p-tau (BD-p-tau) isoforms demonstrate strong performance in detecting brain A β deposition^{3,4} and appear less prone to confounding by medical comorbidities, such as renal dysfunction,⁴ than conventional plasma biomarkers.
- However, the ability of plasma biomarkers to reflect brain A β burden remains understudied in heterogeneous, community-based cohorts that more closely represent real-world populations than clinic-based cohorts.

Aim

To examine (i) the associations of total and brain-derived Alzheimer’s disease plasma biomarkers with brain A β burden, and (ii) whether renal function modifies these associations in a community-based, racially and ethnically diverse sample of cognitively unimpaired (CU) individuals.

Methods

Study Participants and Measurements

- 546 CU Hispanic, Non-Hispanic Black, and Non-Hispanic White adults.
- As a measure of renal function, estimated glomerular filtration rate (eGFR) was derived using the 2012 Chronic Kidney Disease Epidemiology Collaboration cystatin C equation, considering cystatin C, age, and sex.
- Chronic kidney disease (CKD) stages were categorized as normal/high kidney function (eGFR $\geq$ 90 mL/min/1.73 m²); mildly decreased kidney function (eGFR 60–89 mL/min/1.73 m²); and moderately/severely decreased kidney function or failure (eGFR<60 mL/min/1.73 m²).

Plasma A β 38, A β 40, A β 42, ACHE, BACE1, BASP1, BD-p-tau181, BD-p-tau217, CD63, IGFBP7, KLK6, MAPT-tau, PSEN1, total p-tau181, p-tau217, p-tau231, SFRP1 were measured with **NULISaseq CNS Disease Panel 120** 

Brain A β burden was quantified as global standardized uptake value ratio (SUVR) using ¹⁸F-Florbetaben positron emission tomography (PET).

Statistical analysis

- Spearman correlation analysis to explore the relationship between plasma biomarkers and global A β SUVR, unadjusted and adjusted for eGFR
- Bidirectional stepwise linear regression to identify a parsimonious set of plasma biomarkers associated with global A β SUVR
- Interaction analysis to test whether the associations between identified plasma biomarkers and global A β SUVR were modified by CKD stage
- Exploratory analysis: Stepwise logistic regression to identify a parsimonious set of plasma biomarkers associated with A β PET positivity
- Sensitivity analysis: (i) Stepwise linear regression with adjustment for age; (ii) the least absolute shrinkage and selection operator (LASSO) for biomarker selection

Conclusions

In a diverse, community-based sample of CU adults, **BD-p-tau217** emerged as the plasma biomarker **most strongly associated with brain A β deposition**. **This association was attenuated in the presence of moderately/severely decreased kidney function or failure**, but not in mildly decreased kidney function. **IGFBP7** and **BACE1** were identified as **novel plasma biomarker candidates for brain A β deposition**, which require replication in independent cohorts.

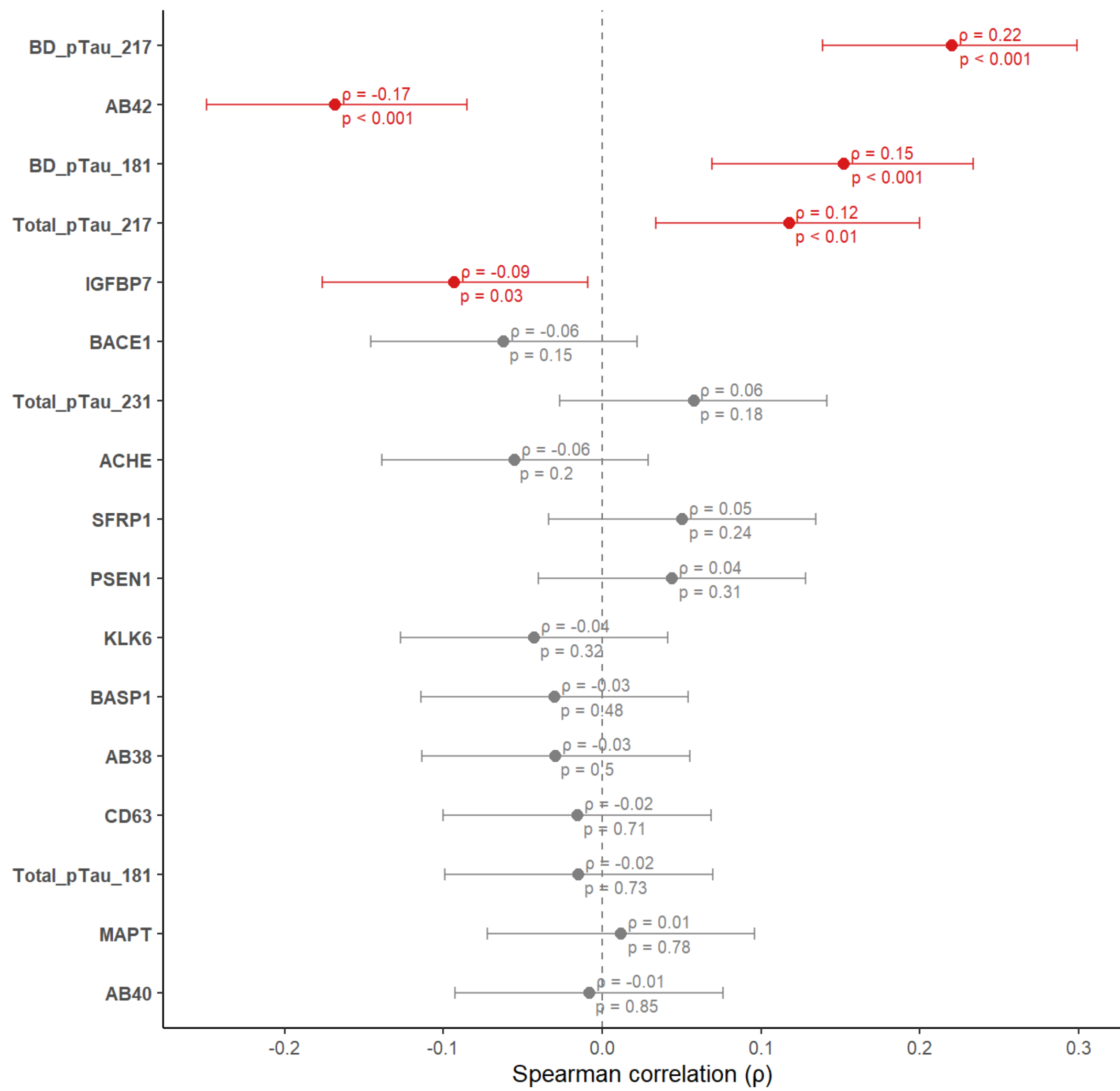
Results

Table 1 Characteristics of the entire sample and stratified by chronic kidney disease stage

Variable	Entire Sample N = 541	Normal/high kidney function n = 174	Mildly decreased kidney function n = 286	Moderately/severely decreased kidney function or failure n = 81	p value
Age, mean $\pm$ SD, years	64.2 $\pm$ 3.2	63.2 $\pm$ 2.9	64.5 $\pm$ 3.1	65.4 $\pm$ 3.3	<.001
Education, mean $\pm$ SD, years	12.0 $\pm$ 4.1	12.6 $\pm$ 3.7	11.8 $\pm$ 4.3	11.5 $\pm$ 4.0	.053
Women, no. (%)	351 (64.9)	113 (64.9)	190 (66.4)	48 (59.3)	.473
Hispanic, no. (%)	344 (63.6)	113 (64.9)	184 (64.3)	47 (58.0)	.354
Non-Hispanic Black, no. (%)	120 (22.2)	33 (19.0)	68 (23.8)	19 (23.5)	
Non-Hispanic White, no. (%)	77 (14.2)	28 (16.1)	34 (11.9)	15 (18.5)	
APOE- ϵ 4 carrier, no. (%)	189 (34.9)	53 (30.5)	109 (38.1)	27 (33.3)	.243
Global A β SUVR, mean $\pm$ SD	1.2 $\pm$ 0.1	1.2 $\pm$ 0.1	1.2 $\pm$ 0.1	1.2 $\pm$ 0.10	.107
A β -positive, no. (%)	85 (15.7)	23 (13.2)	50 (17.5)	12 (14.8)	.474
Cystatin C, mean $\pm$ SD	1.1 $\pm$ 0.4	0.8 $\pm$ 0.1	1.0 $\pm$ 0.08	1.5 $\pm$ 0.9	<.001
eGFR, mean $\pm$ SD	78.7 $\pm$ 17.8	98.1 $\pm$ 5.8	75.1 $\pm$ 7.9	49.7 $\pm$ 10.9	<.001

eGFR = Estimated glomerular filtration rate. A β -positive status was defined by a global A β SUVR $\geq$ 1.25.

Figure 1 Spearman correlation (unadjusted) of NULISaseq biomarkers and brain A β burden



These correlations remained significant after eGFR adjustment, with plasma BD-p-tau217 (p<.001), BD-p-tau181 (p<.001), and total p-tau217 (p<.001) evidencing positive correlations, and plasma A β 42 (p<.001) and IGFBP7 (p=.015) evidencing negative correlations with global A β SUVR.

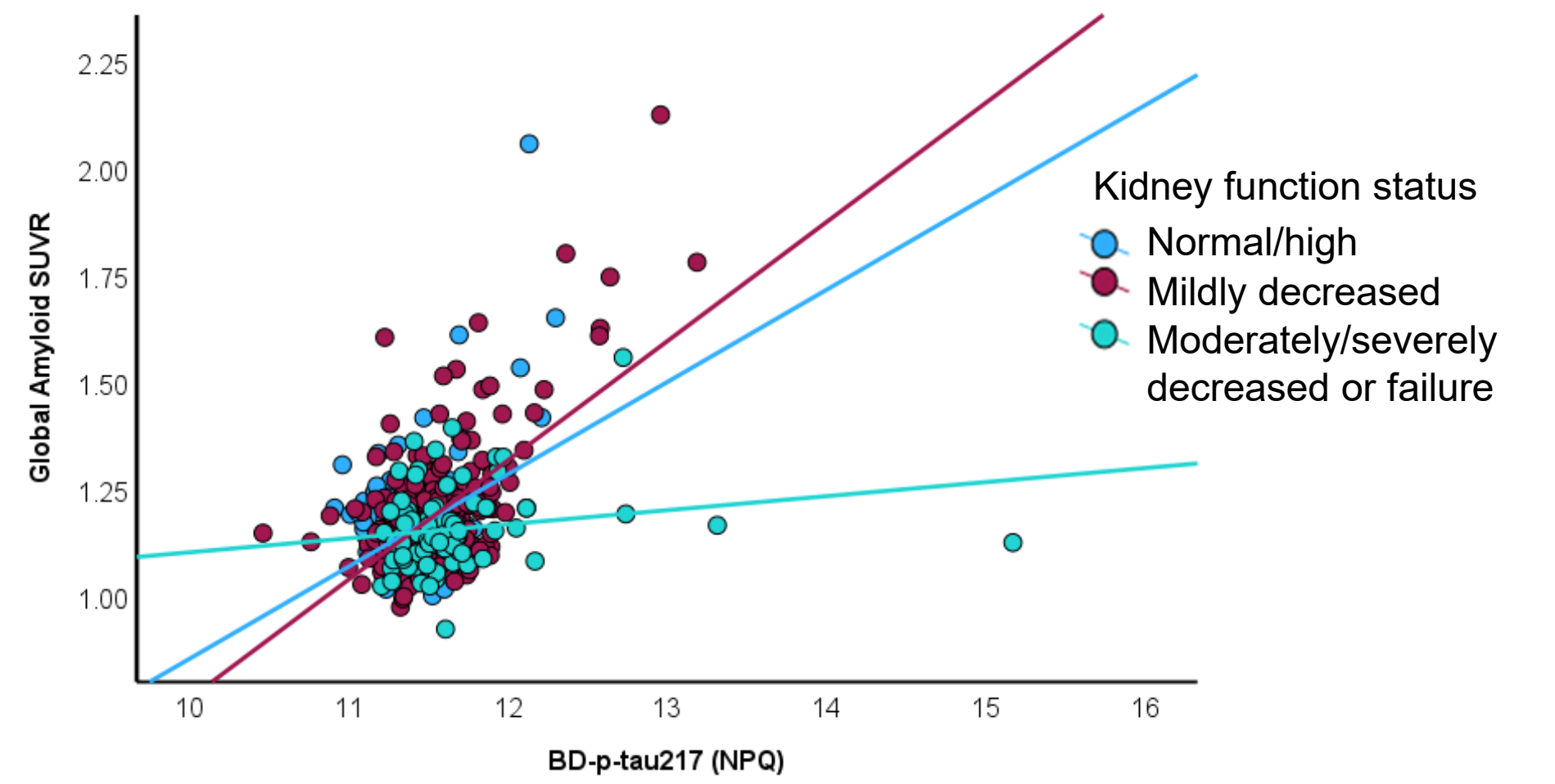
Table 2 Stepwise selection of plasma biomarkers associated with A β SUVR

Outcome: Global A β SUVR			
NULISaseq Biomarker	B (95% CI)	p value	Adjusted R ²
Plasma BD-p-tau217	0.22 (0.19 to 0.25)	<.001	.167
Plasma A β 42	-0.08 (-0.11 to -0.06)	<.001	.265
Plasma IGFBP7	-0.05 (-0.08 to -0.02)	.004	.280
Plasma BACE1	-0.04 (-0.07 to -0.01)	.009	.287

Plasma BD-p-tau217 demonstrated the strongest association with global A β SUVR (**Table 2**) and A β PET positivity (**Table 3**).

Compared with the model including plasma BD-p-tau217 alone, the addition of A β 42, IGFBP7, and BACE1 significantly improved model fit (adjusted R² change=0.120; p<.001, **Table 2**).

Figure 2 Interaction of BD-p-tau217 and CKD stage on brain A β burden



A significant BD-p-tau217-by-CKD stage interaction showed a weaker association between BD-p-tau217 and global A β SUVR in moderately/severely decreased kidney function or failure compared with normal/high kidney function (**Figure 2**).

Table 3 Stepwise selection of plasma biomarkers associated with A β positivity

Outcome: A β PET positivity			
NULISaseq Biomarker	Odds Ratio (95% CI)	p value	Nagelkerke R ²
Plasma BD-p-tau217	23.7 (9.16 to 61.4)	<.001	.101
Plasma A β 42	0.19 (0.10 to 0.35)	<.001	.108
Plasma BACE1	0.26 (0.10 to 0.64)	.003	.213

Compared with the model including plasma BD-p-tau217 alone, the addition of A β 42 and BACE1 significantly improved model fit (Nagelkerke R² change=0.112; p<.001, **Table 3**).

Sensitivity analyses showed that the same plasma biomarkers were selected when (i) adjusting the model for age and (ii) using LASSO method for biomarker selection (data not shown).

REFERENCES: [1] Schindler SE, et al. *Neurology*. 2019; [2] Rissman RA, et al. *Alzheimer’s & Dementia*. 2024; [3] Chong JC, et al. *medRxiv*. Preprint, posted online January 2026; [4] Jiang Y, et al. *Proceedings of the National Academy of Sciences*. 2026.
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