

1 Background

- Brain hypometabolism (FDG-PET) is a hallmark of Alzheimer's disease progression.
- FDG-PET predicts neurodegeneration and cognitive decline but is expensive and not widely accessible.
- Plasma proteins may provide minimally invasive biomarkers that reflect cerebral metabolic dysfunction.
- Identifying these proteins could improve disease staging and prognosis.

Objective: Identify plasma proteins associated with FDG-PET metabolism and determine whether they predict future cognitive decline.

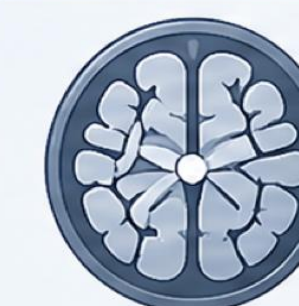
2 Methods



86 individuals with MCI or mild-to-moderate AD from the TRACK-AD cohort



Plasma sampling and quantification of 324 proteins (NULISA CNS & Inflammation panels)



FDG-PET acquisition and AD-signature ROI SUVR estimated with FreeSurfer



Annual follow-up for up to 2 years with cognitive assessments

Elastic-Net regression with stability selection (bootstrapping)

- 80% selection threshold

Stepwise linear regression (BIC criterion) + age and sex

Significant predictors combined ("protein load") and tested for future cognitive status and decline

Outcomes



FDG-PET SUVR (AD-signature ROI)



Cognitive performance (MMSE)



Functional status (CDR-Sum of Boxes)



Clinical trajectory Stable vs. Progressors

3 Results

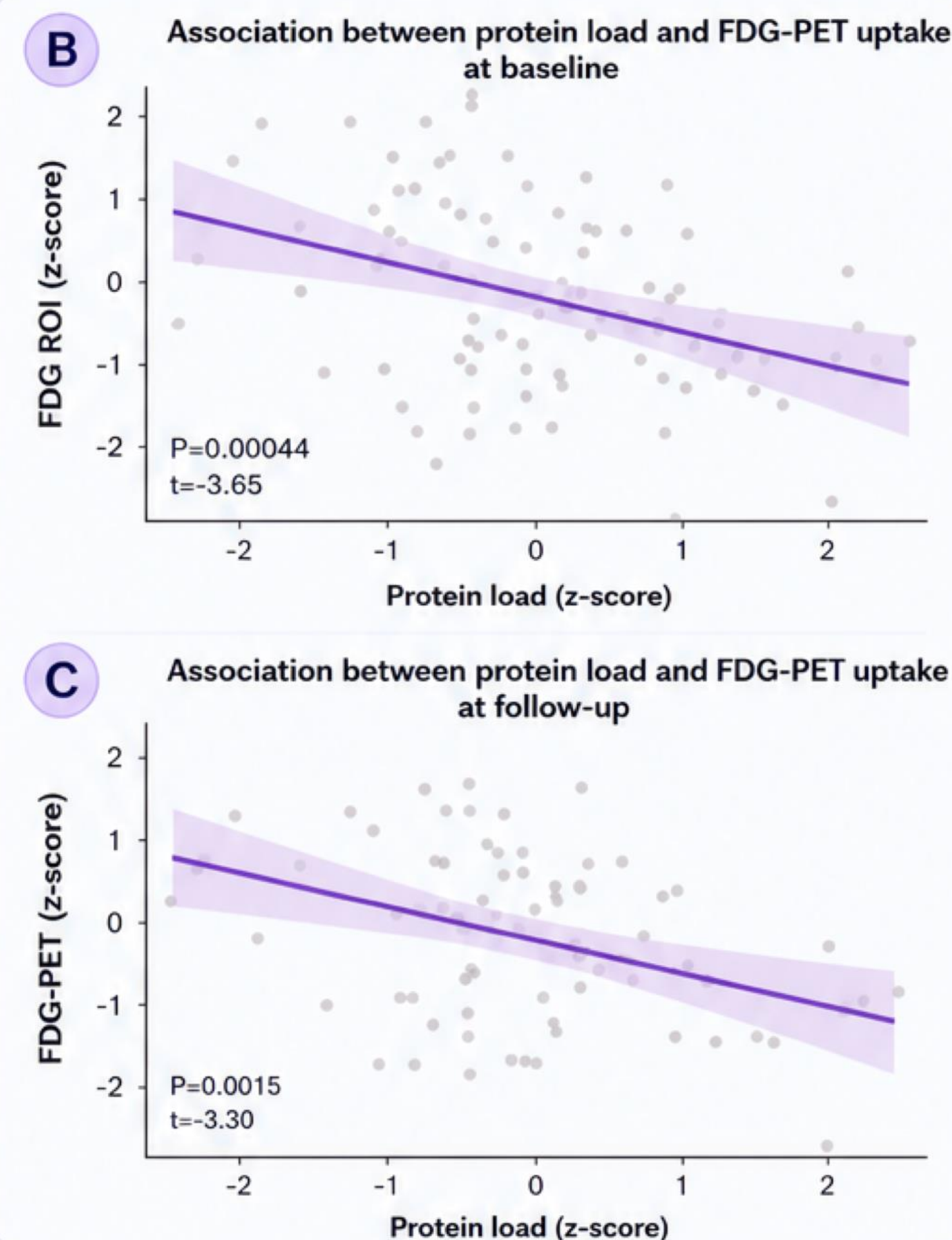
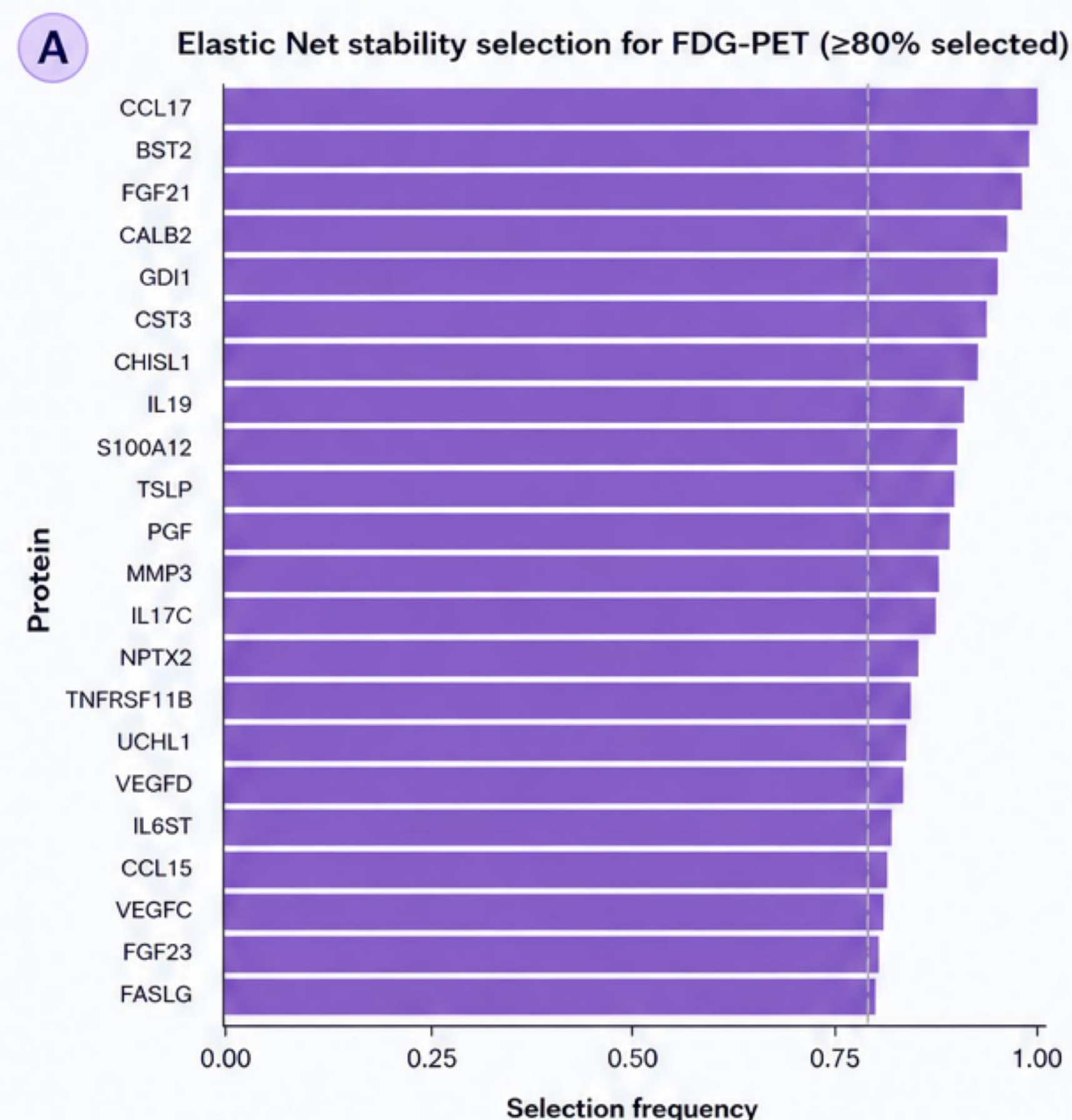


Figure 1. A) Elastic Net regression with 1,000 bootstrap resamples was used to identify plasma proteins robustly associated with FDG-PET ROI uptake (precuneus, cingulate and temporal cortices) after accounting for multicollinearity. Bars show the selection frequency (dashed line) were considered reliably associated with FDG-PET and carried forward to subsequent regression analyses. B,C) A linear regression model for each protein, reflecting how often the predictor was retained across bootstrap models. Proteins exceeding the 80% stability threshold (was used to examine the relationship between protein load and FDG-PET uptake at baseline and follow-up (adjusted for age and sex). Scatter points show the regression line (with 95% confidence band) illustrating the significant negative associations between higher protein load and lower FDG-PET signal. Protein load and FDG values were standardized (z-scores) to facilitate interpretation.

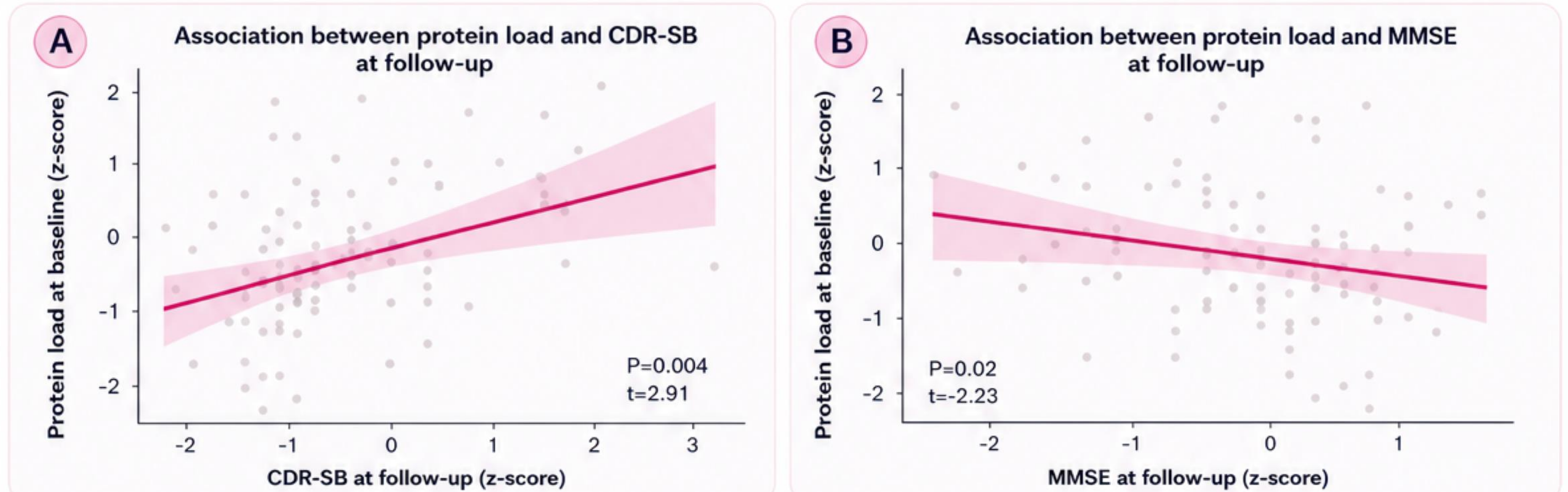


Figure 2. A linear regression model was used to examine the relationship between protein load and CDR-Sum of Boxes (A) and MMSE (B) at follow-up (adjusted for age, sex and time between visits). Scatter points show the regression line (with 95% confidence band) illustrating the significant associations between variables, with values standardized (z-scores) to facilitate interpretation.

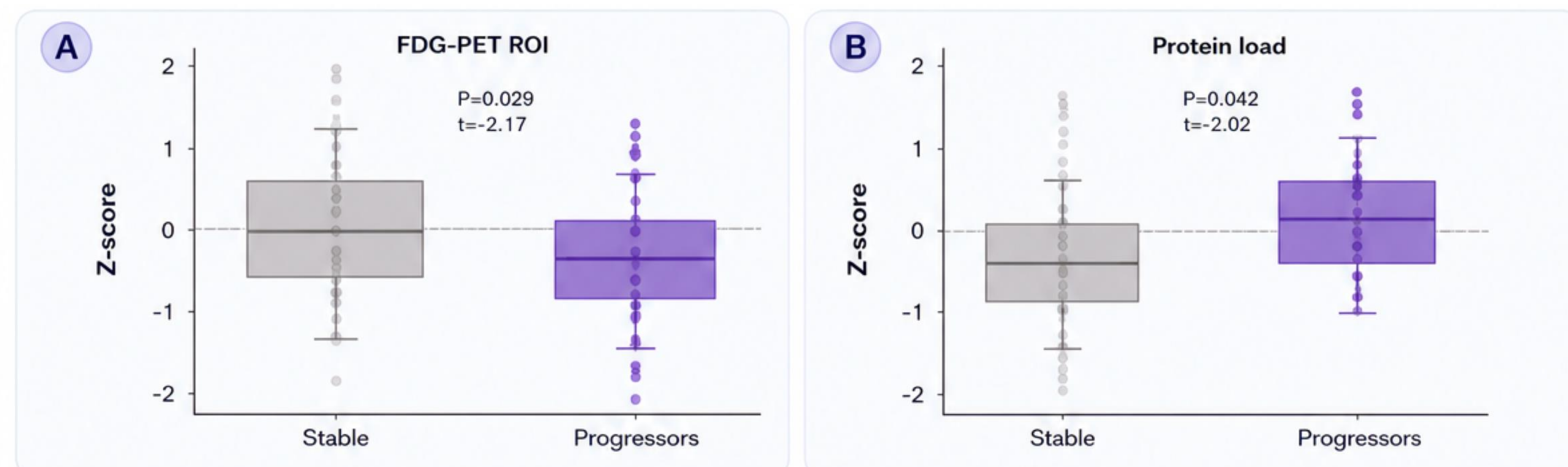


Figure 3. Boxplots show standardized (z-score) FDG-PET (A) and protein load (B) for individuals who remained cognitively stable compared with those who declined clinically (Progressors). Progressors exhibited lower FDG-PET uptake and higher protein load levels relative to stable participants, with individual data points overlaid to illustrate within-group variability.

4 Conclusion

We identified three immune-related plasma proteins—CCL17, CHI3L1, and PGF—that were independently associated with cerebral glucose metabolism in CI individuals with AD. Biologically, these proteins reflect complementary pathological processes implicated in AD, including chronic neuroinflammation and astrocyte activation (CHI3L1), neurovascular dysfunction and vascular remodeling (PGF), and adaptive/peripheral immune signaling (CCL17).

Their combined signal was associated with both baseline and longitudinal FDG-PET uptake, predicted subsequent cognitive and functional decline, and distinguished patients with progressive disease from clinically stable individuals. These findings suggest that converging immune and vascular pathways contribute to cerebral metabolic dysfunction during AD progression.

Overall, our results support the potential of blood-based immune biomarkers as minimally invasive surrogates of cerebral metabolic impairment, providing complementary information for disease staging, prognostication, and the development of precision medicine approaches in Alzheimer's disease.

5 Acknowledgments



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