

Analysis of longitudinal trajectories of Alzheimer's disease related biomarkers using NULISaseq



Giovanna T. Evans, Yang An, Murat Bilgel, Tuğçe Duran, Michael R. Duggan, Cassandra O. Blew, Susan M. Resnick, Keenan A. Walker



Introduction

Our study examined the trajectories of plasma proteins relative to the onset and progression of amyloid deposition. By leveraging longitudinal blood samples and brain amyloid positron emission tomography (PET) scans from the Baltimore Longitudinal Study of Aging (BLSA), the present study examined trajectories of a broad set of neurodegenerative, immune, synaptic, and vascular plasma proteins relative to amyloid onset and progression.

Methods

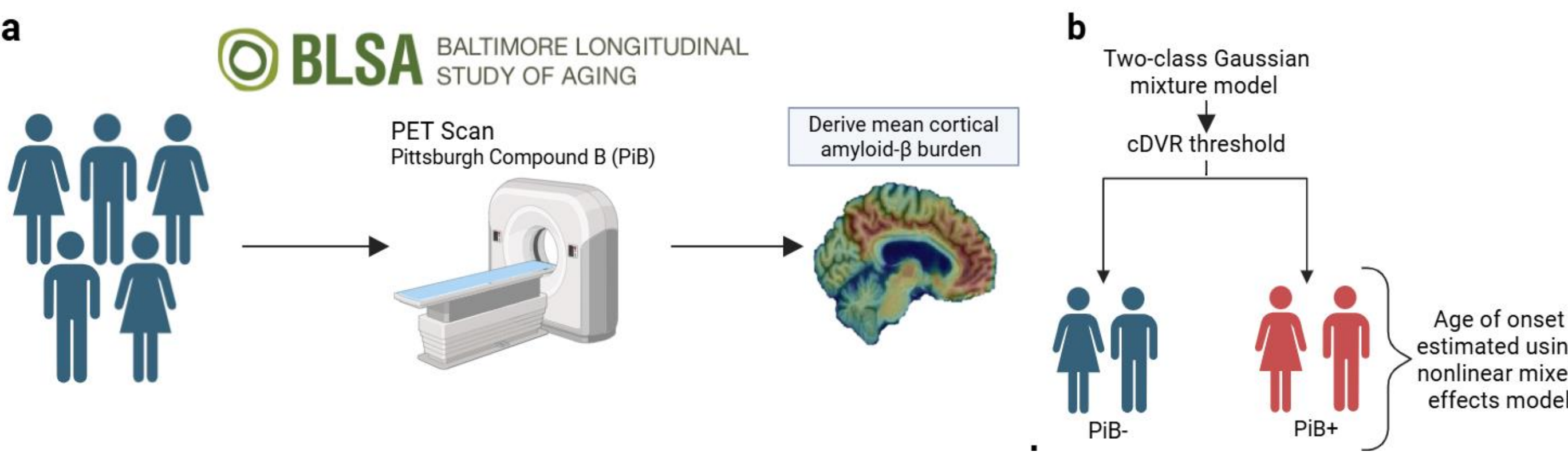


Figure 1. Study design (a-b). (a) 225 subjects from the BLSA underwent longitudinal positron emission tomography (PET) using the radiotracer Pittsburgh Compound B (PiB). Distribution volume ratio (DVR) and mean cortical amyloid burden were subsequently calculated and mean cortical DVR (cDVR) values were harmonized. (b) A two-class Gaussian mixture model was fitted to baseline mean cDVR data, and the cDVR threshold was estimated, which classified participants into PiB- and PiB+ groups based on their last visits. Age of onset for PiB+ participants was estimated using a nonlinear mixed effects model.

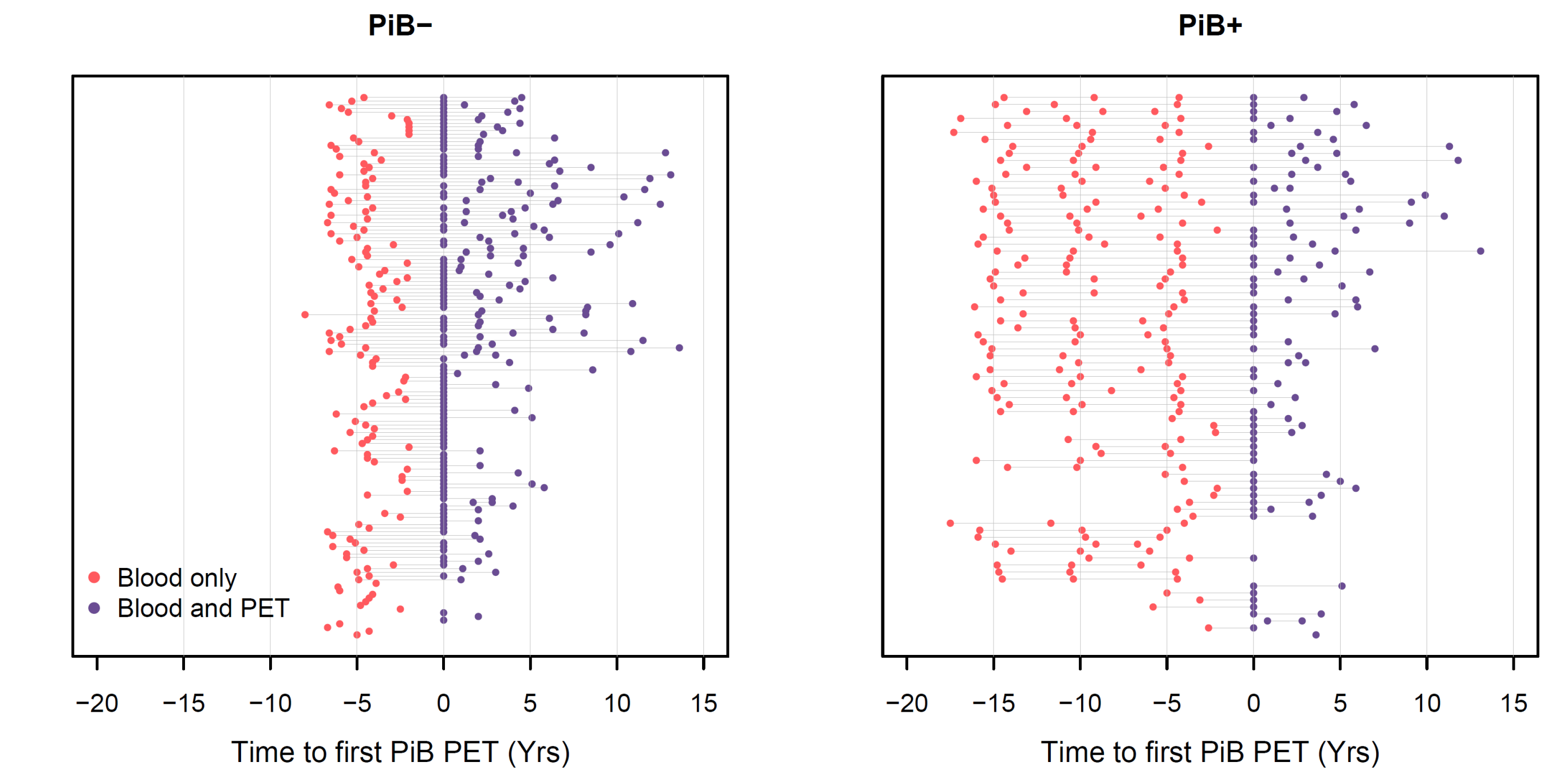


Figure 2. Study design (c). (c) PiB PET subjects (lines) and visits (dots) plotted against time to first PiB PET scan for PiB- (amyloid-) and PiB+ (amyloid+) subjects.

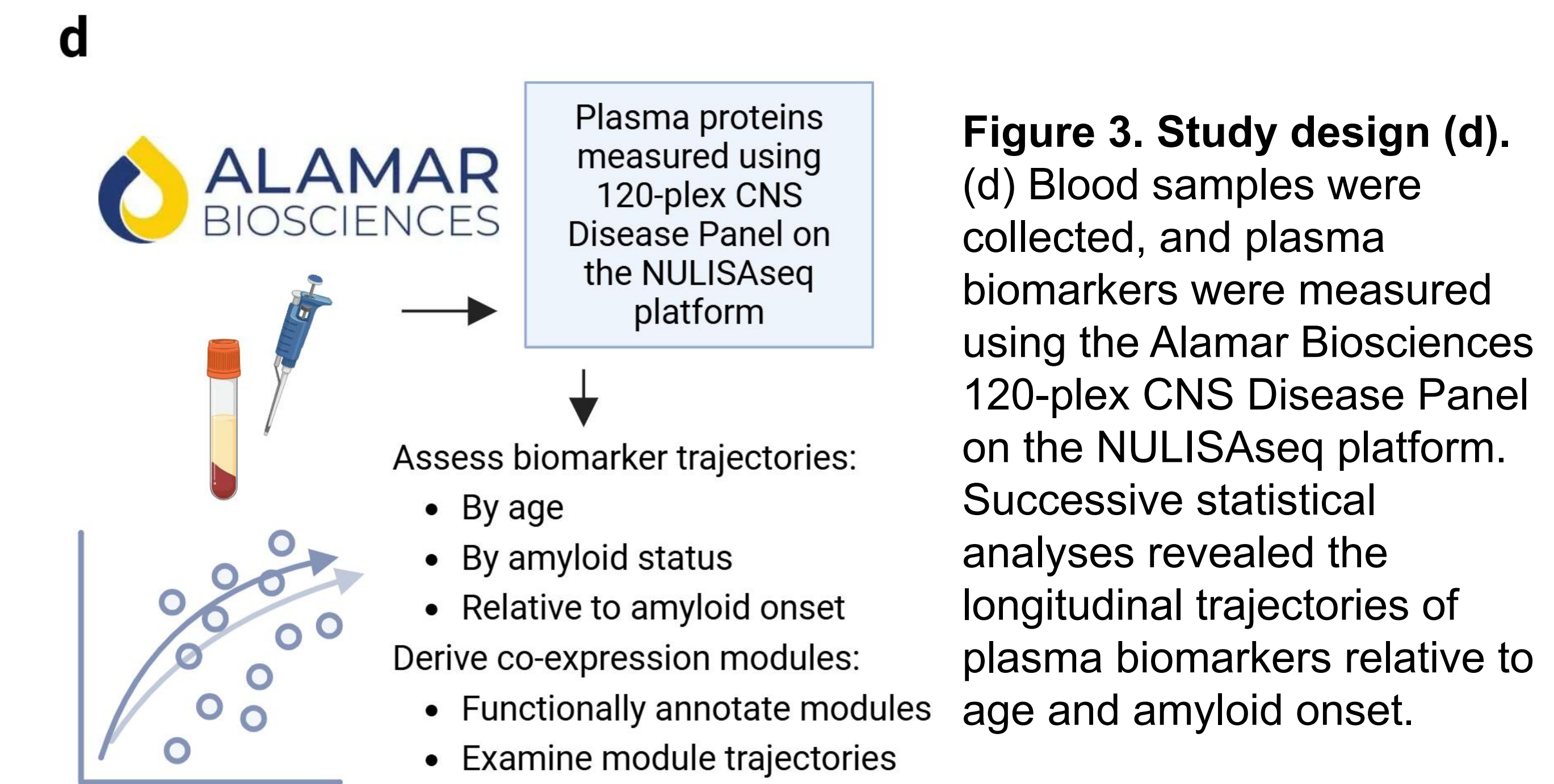


Figure 3. Study design (d). (d) Blood samples were collected, and plasma biomarkers were measured using the Alamar Biosciences 120-plex CNS Disease Panel on the NULISaseq platform. Successive statistical analyses revealed the longitudinal trajectories of plasma biomarkers relative to age and amyloid onset.

Results

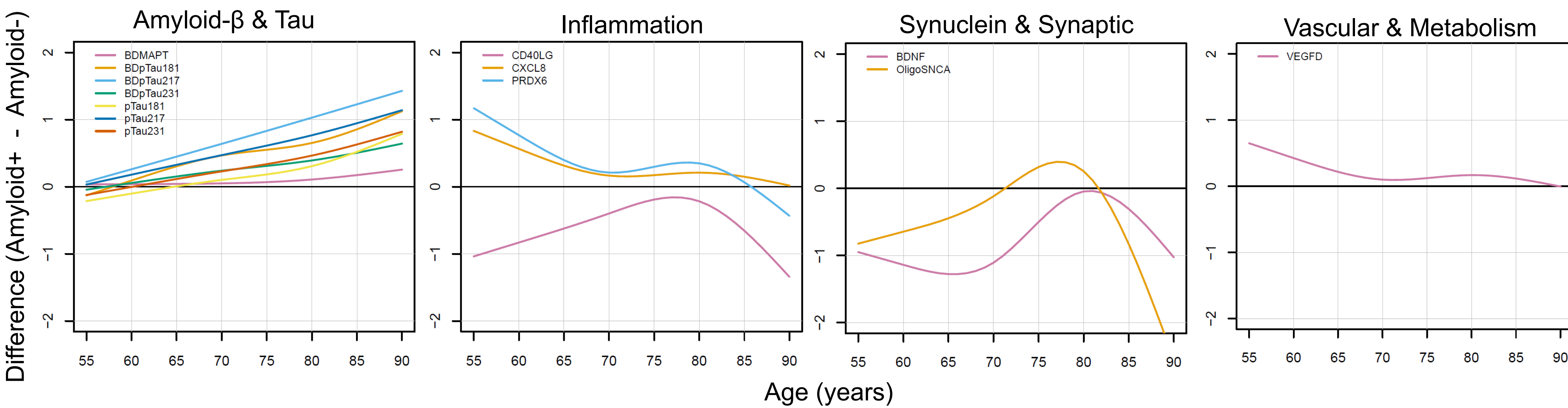


Figure 4. Amyloid- β influences the trajectories of 13 proteins. The differences in protein level and slope between PiB+ and PiB- groups as a function of age.

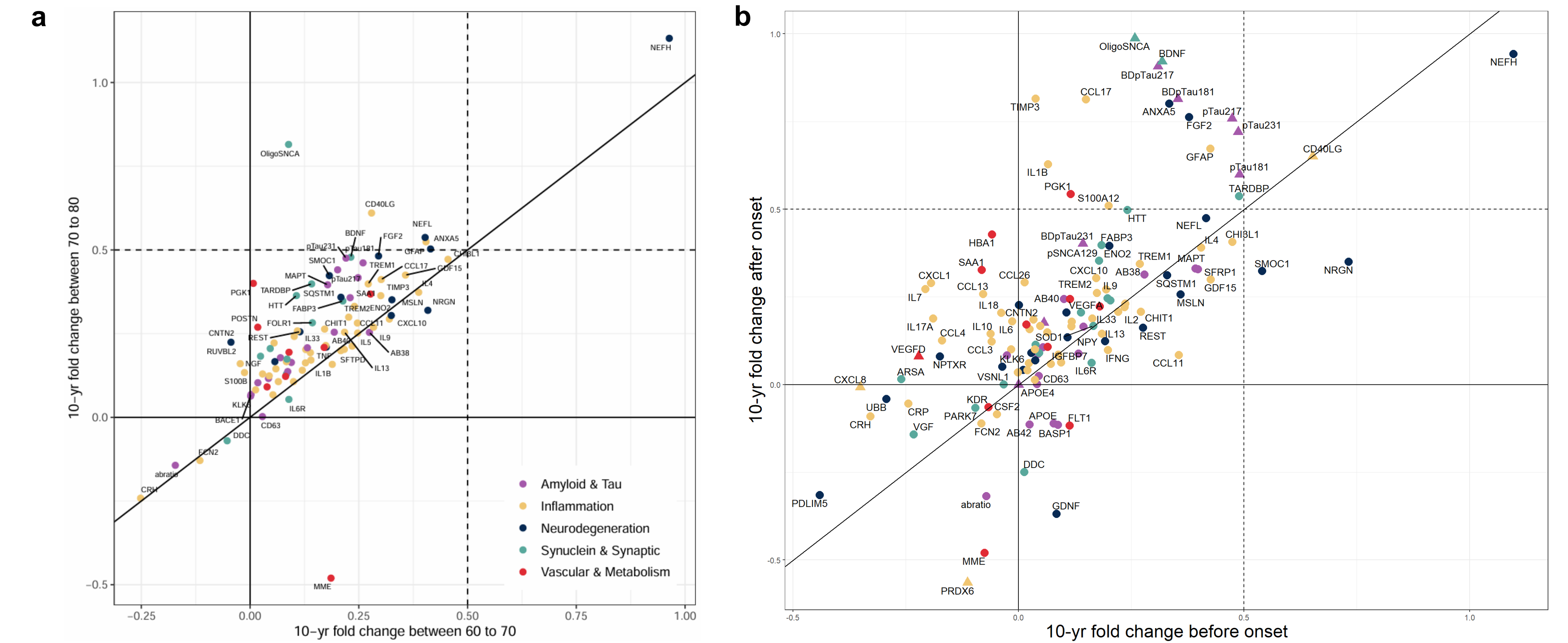


Figure 5. Scatterplots of protein trajectories. (a) Scatter plot of 10-yr fold changes between age 70 to 80 against age 60 to 70. **Triangle symbol** represents biomarkers with significant age effect (FDR $p < 0.05$). (b) Biomarker trajectories relative to amyloid onset. **Triangle symbol** represents biomarkers that also show a significant PiB difference in age trajectories (FDR $p < 0.05$).

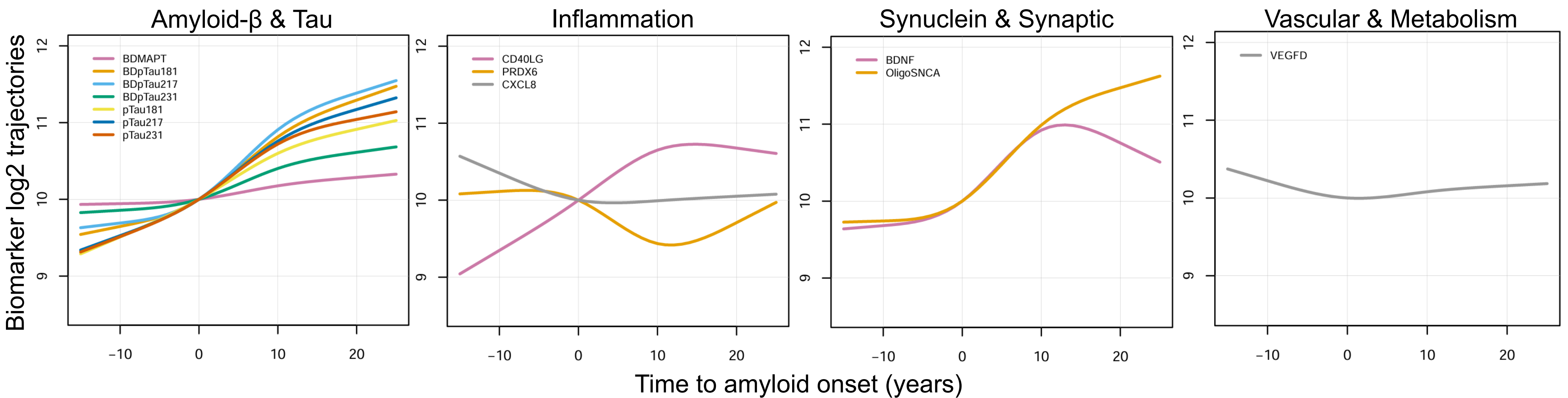


Figure 6. Time to amyloid onset trajectories of 13 proteins. The 13 biomarkers that showed significant PiB status effects on their age trajectories plotted against time to amyloid onset. 11 of the 13 biomarkers had a significant time to amyloid onset effect (gray color represents the non-significant biomarkers).

Conclusions

Examining the trajectories of plasma biomarkers by age, amyloid status, and relative to amyloid onset revealed:

- Many proteins associated with AD and related dementias change with age
- AD pathology may influence the trajectories of inflammatory, vascular, and alpha synuclein proteins
- A subset of inflammatory, vascular, and alpha synuclein proteins are altered a decade or more prior to amyloid onset
- **There is a biologically diverse set of proteins altered in blood both before and immediately after amyloid onset, potentially driving the development of AD pathology**

Acknowledgments: This research was supported by the Intramural Research Program of the NIA. We thank the BLSA participants and staff for their time and efforts put toward the studies.