

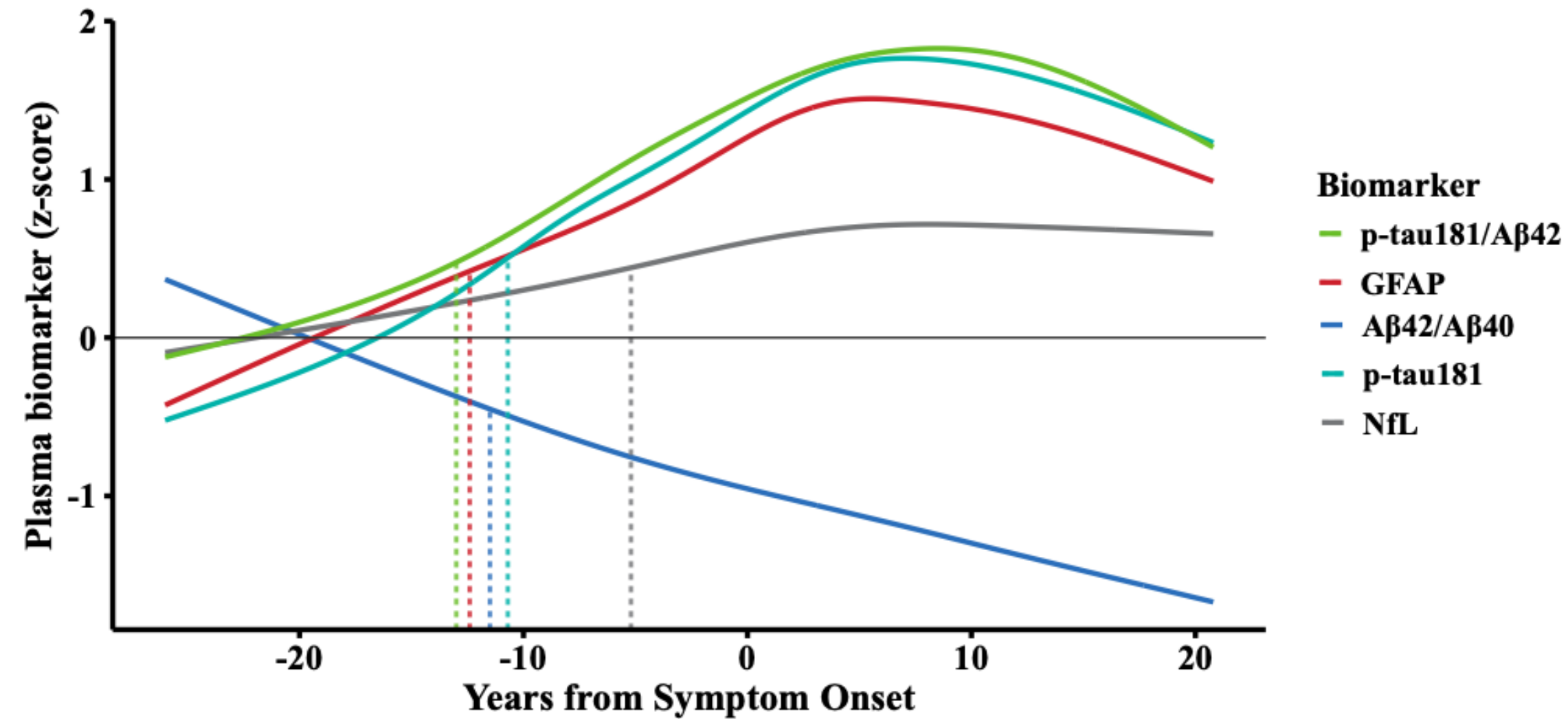
Plasma biomarker trajectories across Alzheimer’s clinical onset: a 17-year prospective study

Siqi Xie¹, Yumei Liang¹, Abhay Moghekar², Marilyn Albert², Jianping Jia¹, for the BIOCARD Study team

¹Innovation Center for Neurological Disorders and Department of Neurology, National Clinical Research Center for Geriatric Diseases, Xuanwu Hospital, Capital Medical University, Beijing, China

²Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Plasma biomarkers can detect Alzheimer’s disease-related pathological changes more than a decade before clinical symptom onset, providing a non-invasive and scalable approach for early detection and intervention.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS
Long-term trajectories of plasma biomarkers relative to clinical symptom onset in Alzheimer’s disease (AD) remain scarce. AD features a prolonged preclinical phase, with a cascade of pathological changes initiating decades prior to the onset of clinical symptoms. Because plasma tests are significantly more accessible, cost-effective, and less invasive than cerebrospinal fluid (CSF) or neuroimaging methods, they create unprecedented opportunities for scalable screening, making it crucial to understand how these markers evolve across the disease course.	We analyzed 17-year longitudinal data from 195 initially cognitively unimpaired participants in the BIOCARD study. Plasma biomarker trajectories were modeled as a function of years from the estimated onset of mild cognitive impairment symptoms using generalized additive mixed models. This approach allowed us to analyze the longitudinal trajectories for key biomarkers including the Aβ42/Aβ40 ratio, p-tau181, p-tau181/Aβ42, NfL, GFAP, sTREM2, and YKL-40.	For participants who progressed to amyloid-positive mild cognitive impairment (MCI), plasma p-tau181/Aβ42 diverged from stable controls earliest, at approximately 13.0 years before symptom onset. This initial change was sequentially followed by abnormalities in GFAP at 12.4 years, Aβ42/Aβ40 at 11.5 years, p-tau181 at 10.7 years, and NfL at 5.2 years before symptom onset. In contrast, individuals who developed amyloid-negative MCI exhibited abnormalities only in GFAP at 10.8 years before onset and YKL-40 at 0.9 years after symptom onset.  Fig. Temporal sequence of significant plasma biomarker changes in AD progressors	We establish a clinically anchored temporal map of plasma AD biomarkers, demonstrating their ability to detect pathological changes more than a decade before clinical symptom onset. These biomarkers offer a scalable approach for identifying at-risk individuals for early intervention. REFERENCES Xie S, Liang Y, Pang Y, et al. Plasma biomarker trajectories across Alzheimer’s clinical onset: a 17-year prospective study. <i>Alz Res Therapy</i>. 2026;18(1). doi:10.1186/s13195-026-02045-0 CONTACT Siqi Xie, xiesqi@mail.ccmu.edu.cn Jianping Jia, jiajp@vip.126.com  ALZHEIMER’S ASSOCIATION AAIC>26