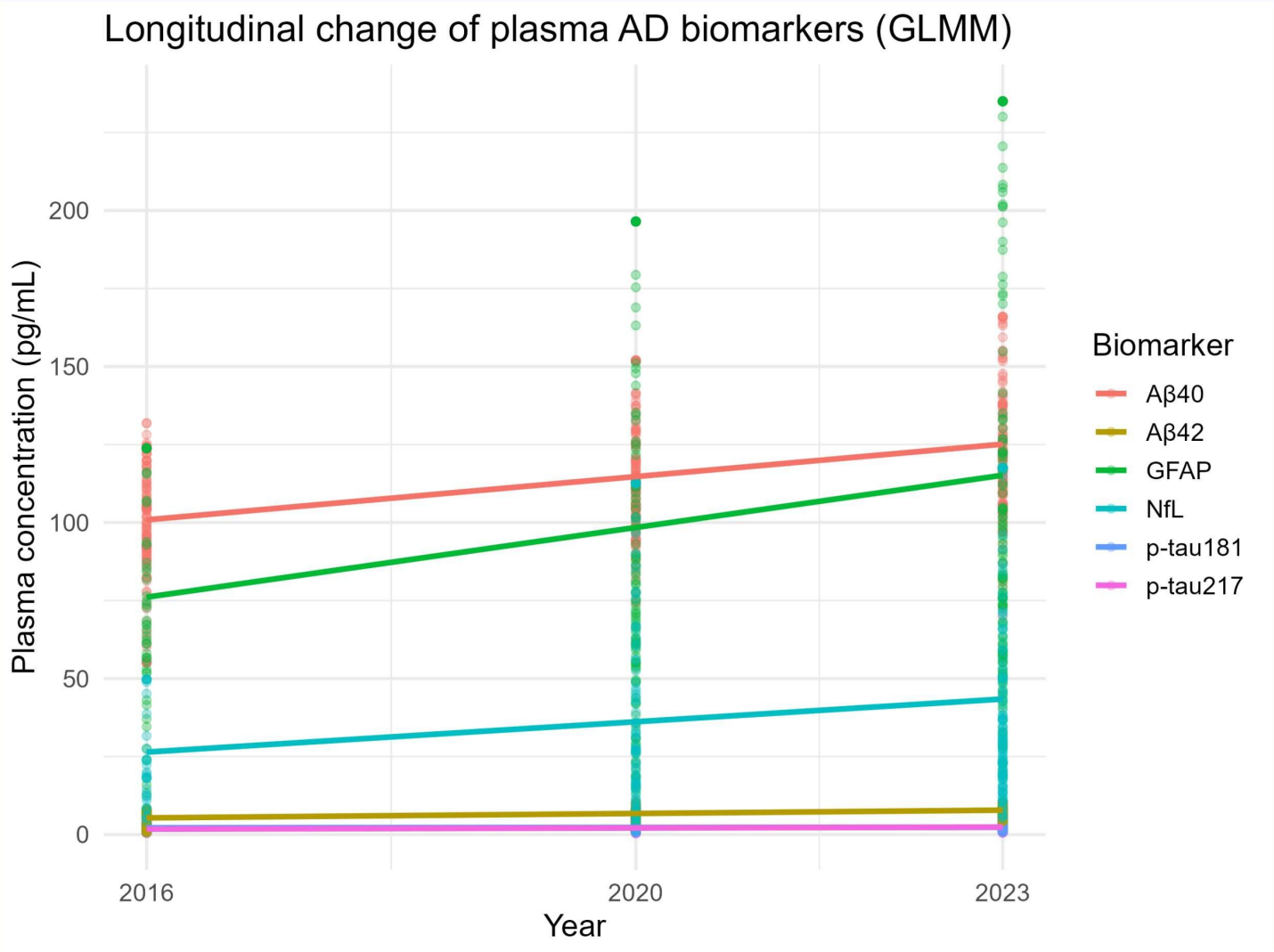


Longitudinal Trajectories Of AD Plasma Biomarkers And Related Factors In Cognitively Normal Adults: A Cohort Study

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- Longitudinal plasma p-tau217, Aβ40/42, GFAP and NfL show significant annual elevations in cognitively normal older adults, while p-tau181 has no obvious longitudinal change.
- Older age is associated with higher levels of almost all plasma AD biomarkers; APOE ε4 genotype specifically elevates Aβ42 concentrations.
- Worse cognitive performance (lower MMSE) correlates with elevated GFAP and NfL, reflecting early astrocytic and neuronal injury in preclinical AD.

INTRODUCTION	METHODS	Results	Conclusions
Alzheimer's disease (AD) is characterized by dynamic changes in multiple biological pathways over time. Longitudinal evaluation of AD-related biomarkers is essential for understanding disease progression and identifying early pathophysiological changes. However, population-based studies integrating multiple biomarkers with extended follow-up periods among cognitively normal adults remain limited.	This longitudinal analysis was based on a population-based cohort in rural China, including 127 cognitively normal participants with plasma biomarker assessments conducted at three time points between 2016 and 2023. Plasma biomarkers included p-tau217, p-tau181, Aβ40, Aβ42, GFAP, and neurofilament light chain (NfL). Generalized linear mixed-effects models were applied to evaluate longitudinal biomarker trajectories. All models were adjusted for baseline age, sex, years of education, APOE ε4 carrier status and cognitive performance assessed by the Mini-Mental State Examination (MMSE).	- Distinct longitudinal trajectories were observed across the biomarkers. Five of the six biomarkers demonstrated significant increases over time (all $P<0.001$), whereas the annual change for p-tau181 was not statistically significant ($P=0.122$). - Specifically, p-tau217 ($\beta=0.09$), Aβ40 ($\beta=3.46$), and Aβ42 ($\beta=0.35$) increased over time. Similarly, GFAP ($\beta=5.58$) and NfL ($\beta=2.43$) showed pronounced upward trends. - Baseline age was positively associated with five of six biomarkers (all $P<0.05$, except Aβ42). Longitudinal change of plasma AD biomarkers (GLMM)  - APOE ε4 status was associated with Aβ42 levels (non-carriers: $\beta=3.19$ $P=0.001$; heterozygous carriers: $\beta=2.76$ $P=0.002$), with ε4 homozygotes set as the reference group. - Lower MMSE scores were associated with higher GFAP ($\beta=-2.43$ $P=0.041$) and NfL ($\beta=-2.13$ $P=0.009$). - Male sex was associated with lower GFAP ($\beta=-21.12$, $P=0.003$), and higher education was associated with higher GFAP ($\beta=1.14$, $P<0.001$).	Our findings demonstrate broadly similar longitudinal patterns among plasma AD biomarkers, with most markers showing progressive increases over time. These results underscore the importance of considering demographic, genetic, and cognitive factors when interpreting long-term biomarker trajectories in aging populations.
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