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Introduction

→ Plasma phosphorylated tau at threonine 217 (p-tau217) is a robust marker of Alzheimer's disease (AD) pathology and progression. However, individuals positive for p-tau217 show substantial clinical heterogeneity, suggesting the influence of modifying biological processes.

→ We previously showed that plasma glial fibrillary acidic protein (GFAP) abnormality is key to unleashing A β effects on tau phosphorylation in preclinical AD.

→ However, whether astrocyte reactivity continues to shape the downstream impact of tau phosphorylation as disease progresses beyond the preclinical stage remains unknown.

To investigate whether plasma GFAP modifies the association between p-tau217 and clinical progression.

Methods

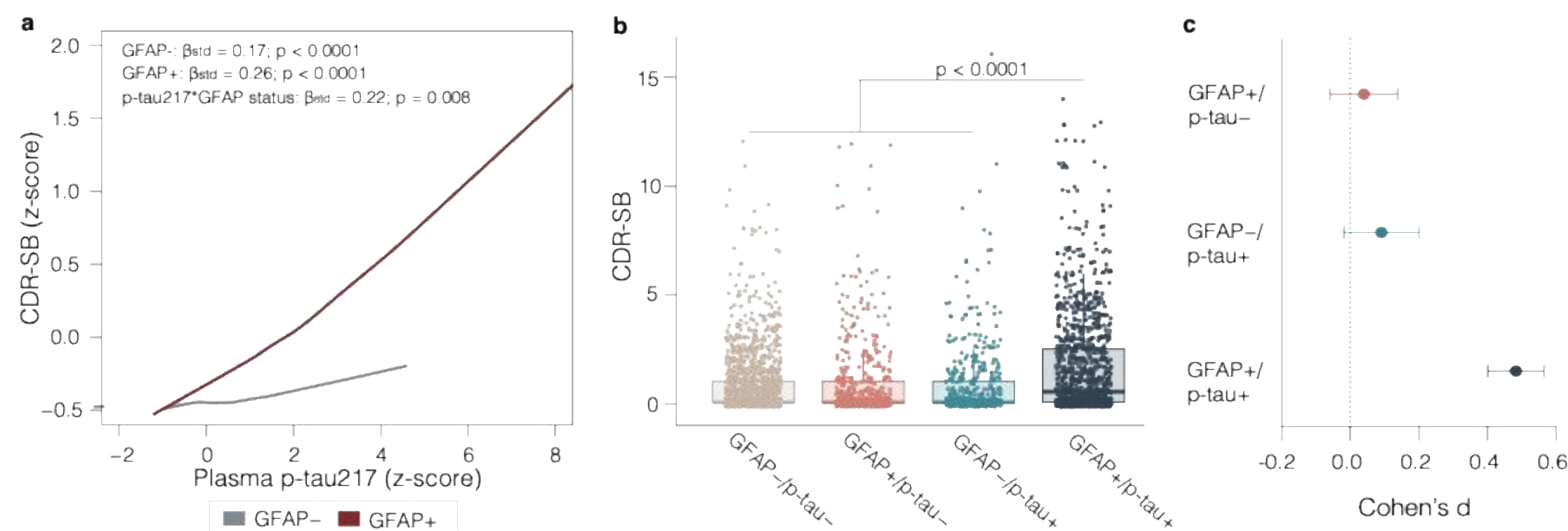
3,041 individuals from six independent cohorts:
1,982 cognitively unimpaired
1,419 cognitively impaired

- A β PET
- Plasma p-tau217 (AlzPath)
- Plasma GFAP (Quanterix)
- CDR-SB

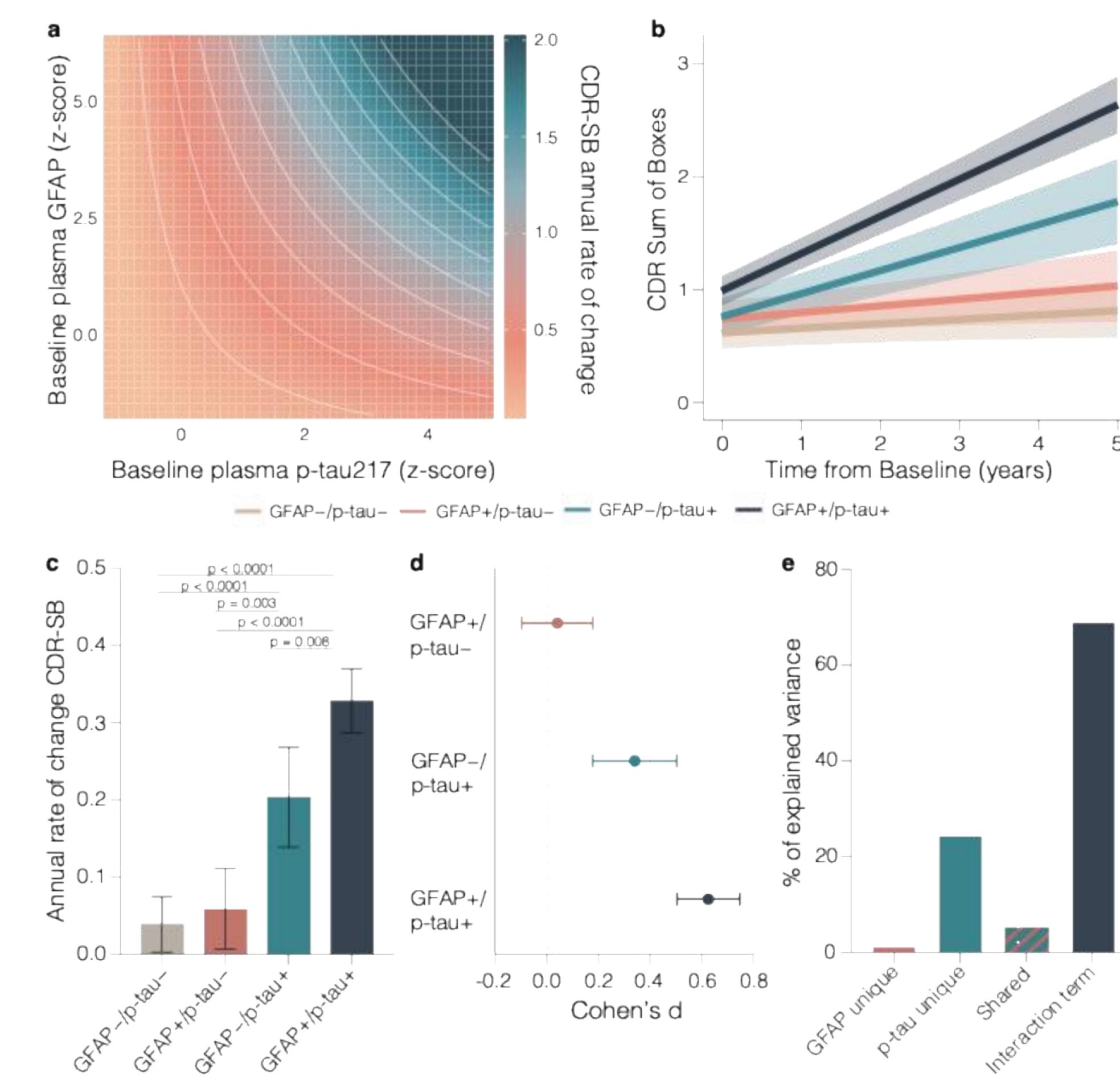
- Participants were classified into four biomarker groups based on GFAP and p-tau217 positivity.
- Cross-sectional associations with cognitive severity were examined using linear regression and ANCOVA.
- Longitudinal cognitive trajectories over five years were modeled using linear mixed-effects models.
- Variance partitioning decomposed biomarker-attributable variance in individual-level annual CDR-SB change rates.
- Time to clinical worsening (CDR-SB increase ≥ 0.5 points) was assessed using Kaplan-Meier survival analysis and Cox proportional hazards regression

Results

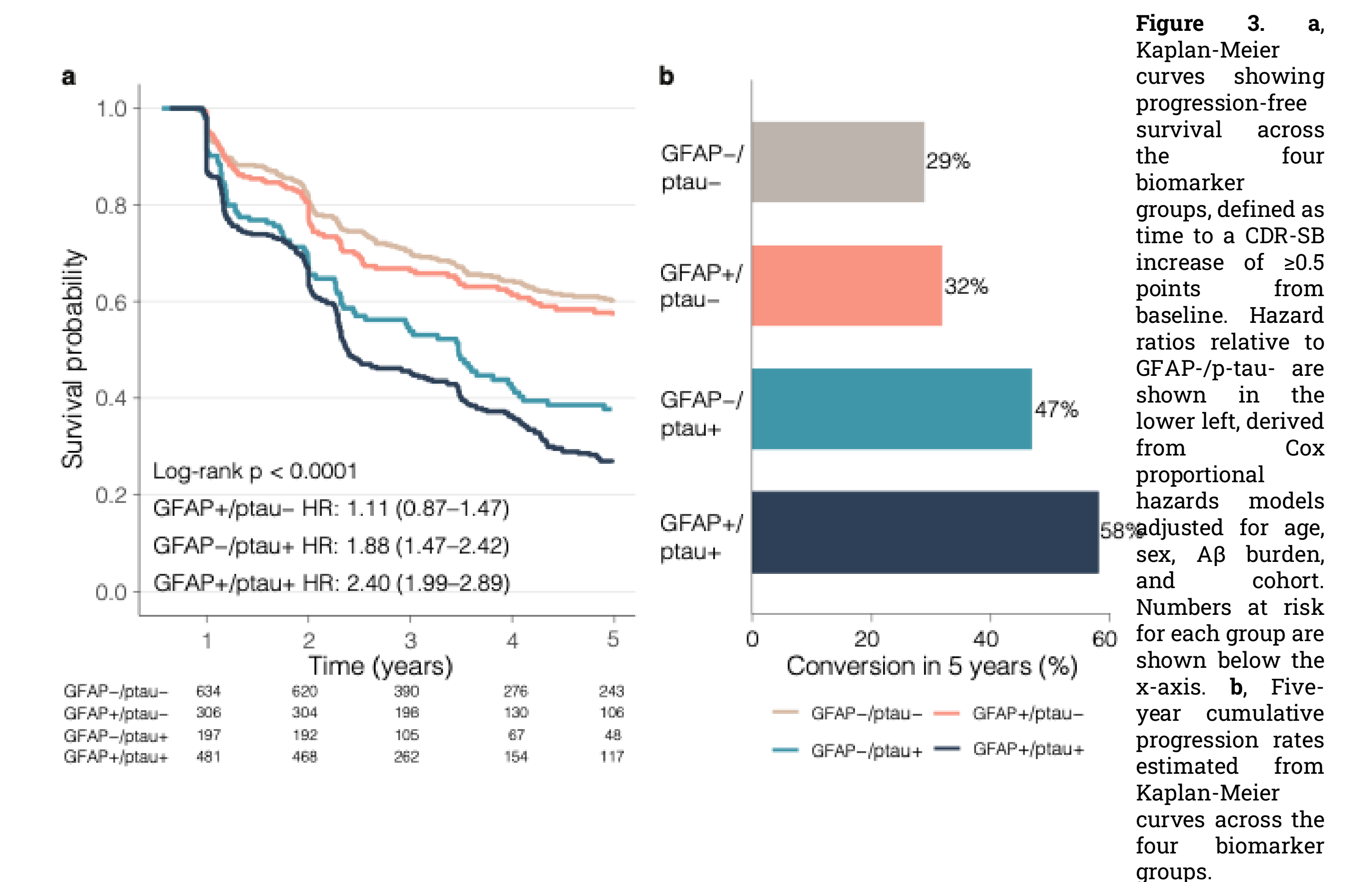
GFAP amplifies the effect of p-tau217 on cognition



GFAP and p-tau217 interact to predict cognitive trajectories



GFAP and p-tau217 jointly determine clinical progression



Conclusions

This study establishes plasma GFAP as a clinically significant modulator of cognitive outcomes across the AD continuum. The finding that astrocyte reactivity amplifies the clinical impact of p-tau217 at both cross-sectional and longitudinal levels and independently accelerates conversion risk even among tau-positive individuals, positions astrocyte reactivity not merely as an early upstream signal, but as an ongoing and dynamic determinant of AD-related clinical severity. Together, these findings extend prior preclinical observations, with direct implications for disease prognostication and the selection of individuals in clinical trials and practice.

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