

Background

- Plasma glial fibrillary acidic protein (GFAP) is a marker of astrocytic activation strongly associated with cerebral amyloid-beta (A β) pathology.¹
- GFAP has been classified as a biomarker of neuroinflammation in the 2024 Alzheimer's Association criteria for AD diagnosis and staging.²
- Whether GFAP independently predicts tau pathology, neurodegeneration, and cognitive decline beyond its relationship with A β remains unclear.
- Anti-A β therapies (lecanemab, donanemab) reduce plasma GFAP proportional to plaque clearance, suggesting A β accumulation may drive GFAP elevation.³
- Here, we investigated whether GFAP independently predicts AD progression using convergent longitudinal data from HABS (Harvard Aging Brain Study: in vivo plasma and imaging) and ROSMAP (Religious Orders Study/Memory and Aging Project: postmortem histopathology and transcriptomics).

Methods

Study Participants

- HABS** (n = 355): Prospective cohort of cognitively unimpaired older adults
- Plasma GFAP (MSD platform) at baseline
- In vivo A β : Baseline ¹¹C-PiB PET cortical composite
- Outcomes: Longitudinal ¹⁸F-flortaucipir tau PET (inferior temporal cortex), MRI hippocampal volume, PACC5 composite

- ROSMAP** (n = 610): Longitudinal prospective cohort with autopsy, mixed cognitive status (CU to dementia)
- Brain GFAP mRNA expression (bulk RNA-seq, DLPFC)
- Postmortem A β and tau: Quantitative immunohistochemistry (IHC)
- Outcomes: Quantitative tau IHC, longitudinal global cognitive slope

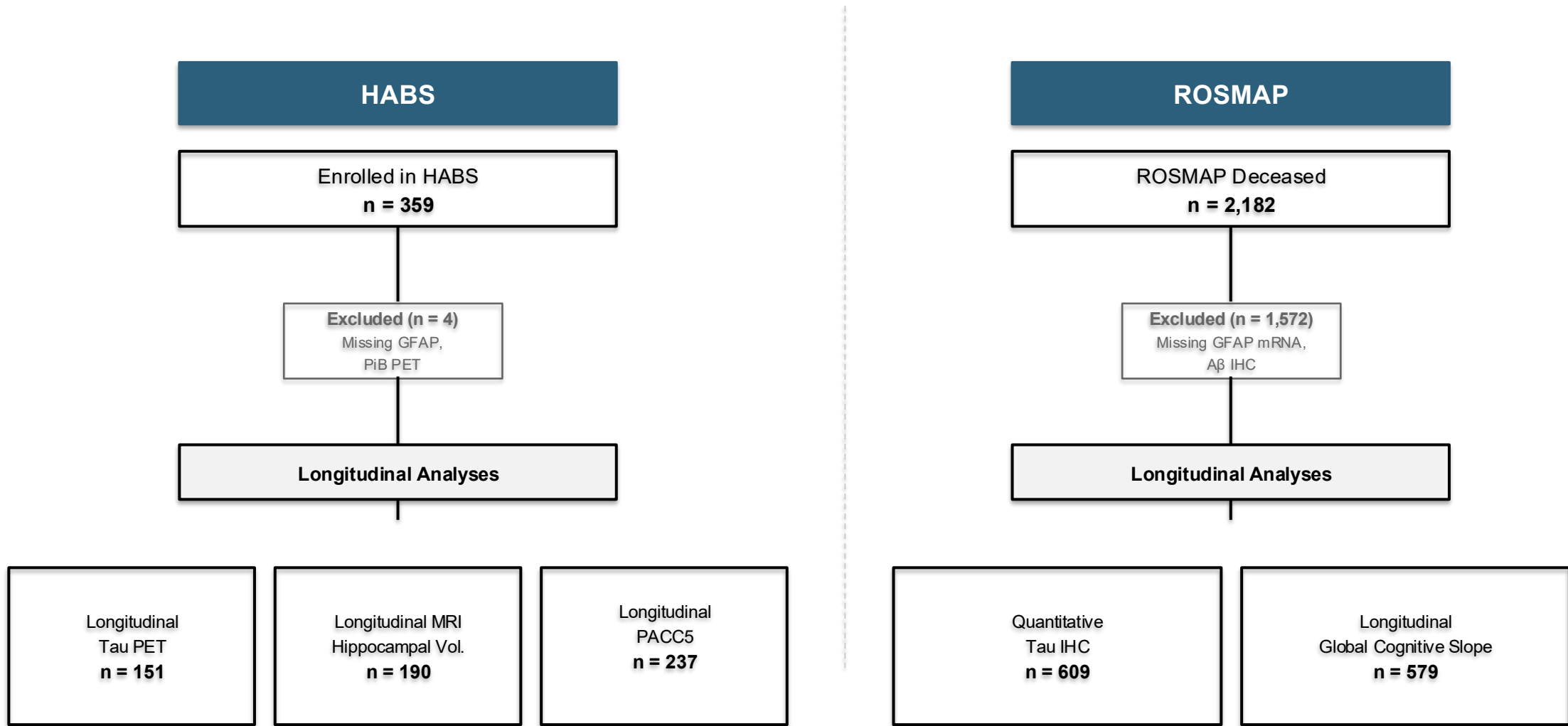
Table 1. Participant Characteristics

Measure	HABS (n = 355)	ROSMAP (n = 610)
Demographics		
Age, years (mean $\pm$ SD)	71 $\pm$ 8.3	81 $\pm$ 7.1 (enrollment) 89 $\pm$ 6.6 (death)
Female, n (%)	222 (63)	396 (65)
Race, n (%)	White 278 (78%) Black 60 (17%) Asian 8 (2%); Other 9 (3%)	White NH 591 (97%) Black NH 8 (1%) Other 11 (2%)
APOE ϵ 4 carrier, n (%)	100 (28)	158 (26)
Cognition		
MMSE, median (IQR)	29 (29–30)	25 (16–28)
Cognitive measure (mean $\pm$ SD)	PACC5: 0 $\pm$ 0.7	GCS: –0.02 $\pm$ 0.09
Biomarkers		
Amyloid, median (IQR)	PiB PET DVR 1.09 (1.06–1.17)	A β IHC, mean % area 1.9 (0.9–3.1)
GFAP, median (IQR)	Plasma GFAP 63.8 (47.7–86.4)	GFAP mRNA, log ₂ 0.08 (–0.15–0.26)
Tau, median (IQR)	Tau PET ITC SUVR 1.33 (1.21–1.39)	Tau IHC, tangles/mm ² 0.13 (0.00–0.48)
Hippocampal volume median (IQR)	7718 (7004–8294)	—
Pathology / Diagnosis		
Elevated A β , n (%)	PiB +ve: 80 (23%) PiB –ve: 275 (77%)	Definite AD: 182 (30%) Probable AD: 212 (35%) Possible AD: 54 (9%) No AD: 162 (27%)
All-cause dementia n (%)	0 (0)	259 (43)

GCS = Global Cognitive Slope; NH = non-Hispanic.

Statistical Analysis

- HABS: Linear mixed-effects models with baseline GFAP $\times$ time interaction
- ROSMAP: Linear regression models
- All variables z-standardized; models adjusted for age and sex (and education for cognitive variables)
- Models run with and without adjustment for A β burden

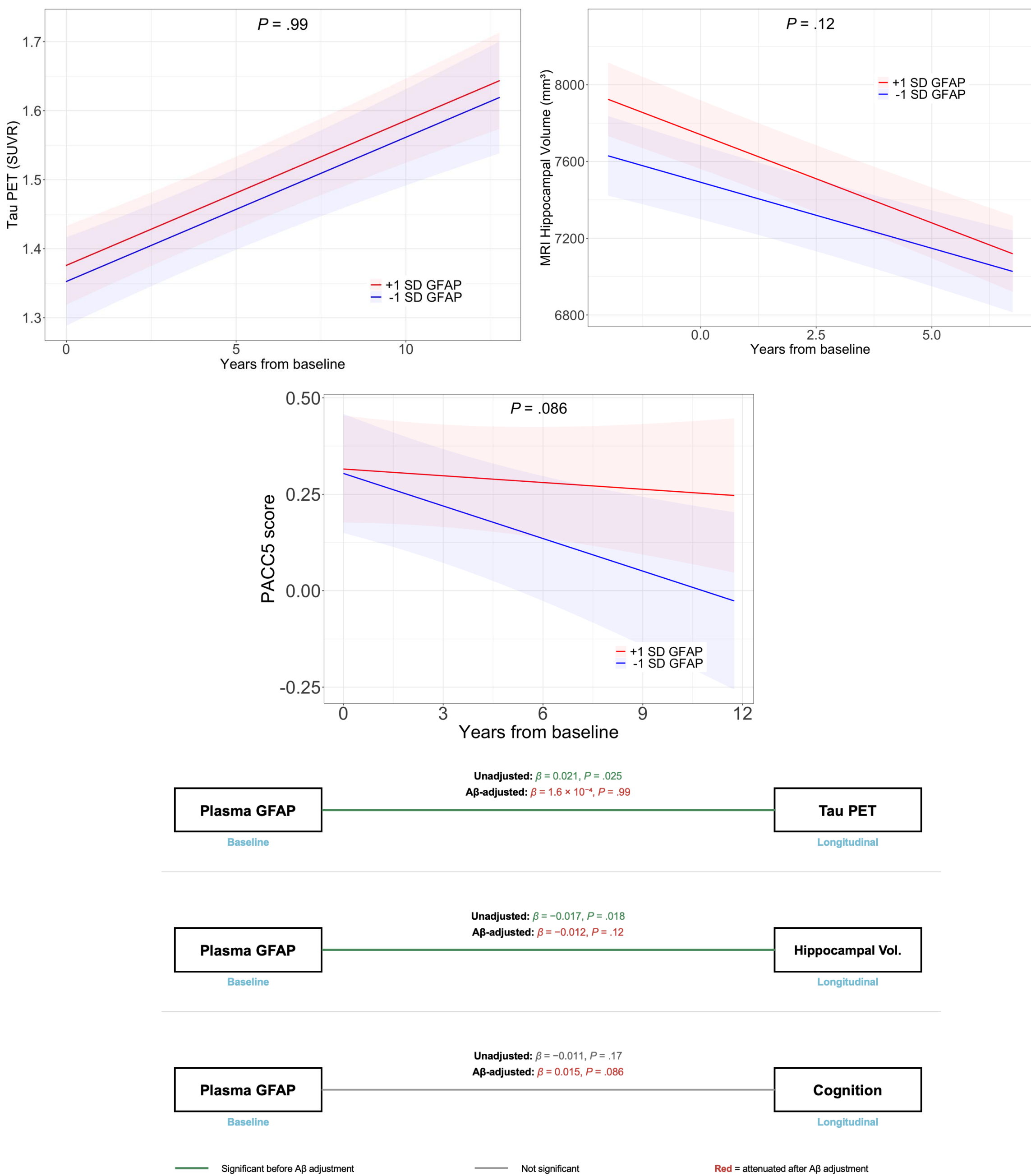


Results: HABS

Does baseline plasma GFAP predict longitudinal tau accumulation, hippocampal atrophy, or cognitive decline?

- (A)** Plasma GFAP predicted **longitudinal tau accumulation** (β = 0.021, P = .025); association fully attenuated after A β adjustment (Figure 1A,D).
- (B)** GFAP predicted **hippocampal volume loss** (β = –0.017, P = .018); attenuated after A β adjustment (Figure 1B,D).
- (C)** GFAP was not associated with **cognitive decline (PACC5)** before or after A β adjustment (Figure 1C,D).

Figure 1. Plasma GFAP and Longitudinal Tau, Atrophy, and Cognition in HABS (After A β Adjustment)

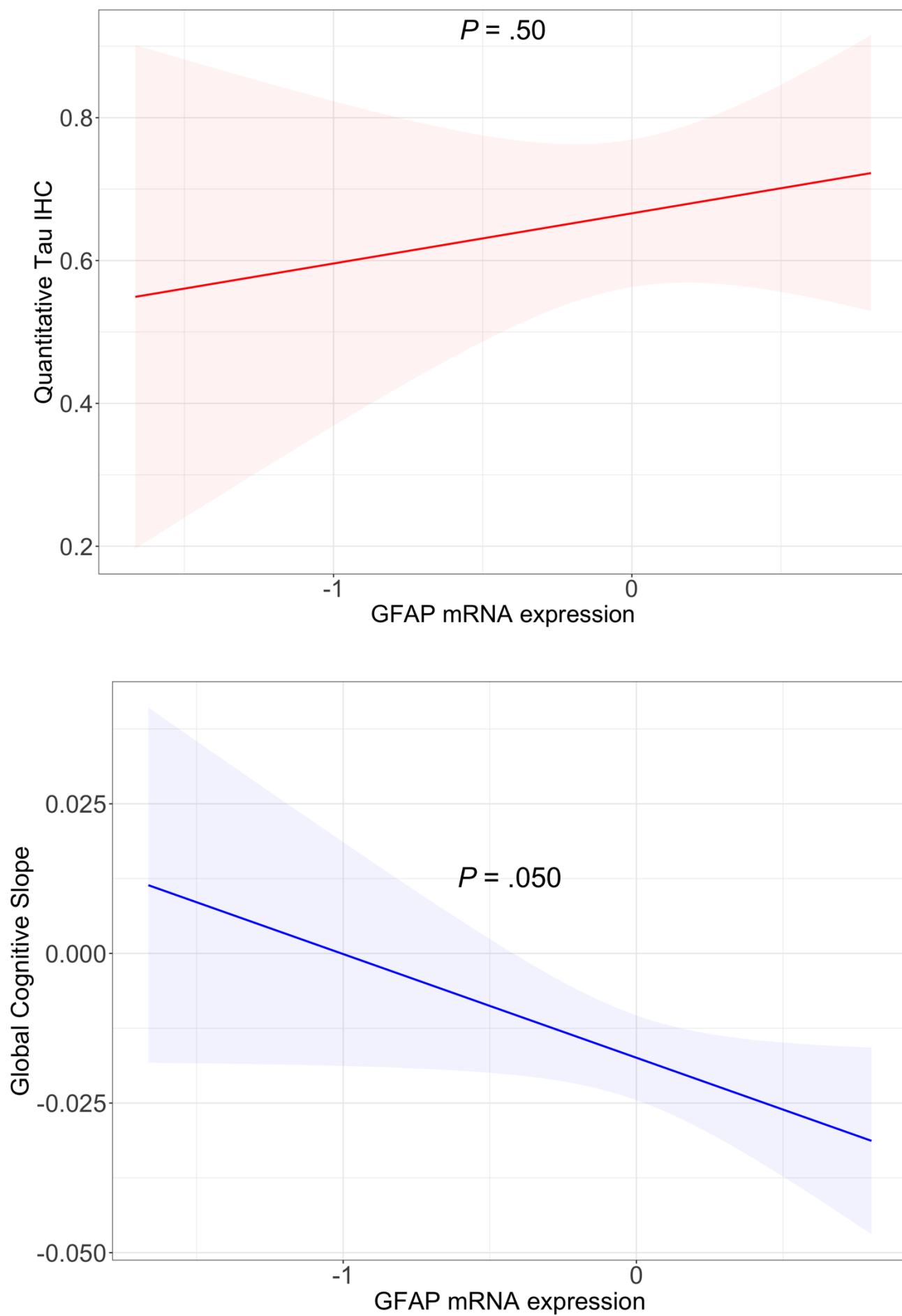


Results: ROSMAP

Does brain GFAP mRNA predict postmortem tau pathology or longitudinal cognitive decline?

- (A)** GFAP mRNA predicted **postmortem tau pathology** (β = 0.10, P = .012); association fully attenuated after A β adjustment (Figure 2A).
- (B)** GFAP mRNA predicted **longitudinal cognitive decline** (β = –0.12, P = 2.5 $\times$ 10^{–3}); attenuated to borderline after A β adjustment (P = .050) (Figure 2B).

Figure 2. GFAP mRNA and Tau Pathology and Cognition in ROSMAP (After A β Adjustment)



Conclusions

- GFAP does not independently predict tau pathology, neurodegeneration, or cognitive decline beyond A β burden in either cohort.
- GFAP elevation reflects amyloid-associated astrocytic activation rather than independently driving disease progression.
- GFAP serves as a complementary index of amyloid burden alongside pTau217 but may not provide independent prognostic information beyond existing amyloid markers.
- Future studies should examine whether GFAP retains independent prognostic value in specific clinical subgroups or larger cohorts and whether GFAP reflects clinically significant neuroinflammatory states.

References

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