

Astroglial reactivity is associated with longitudinal cortical microstructural change in asymptomatic adults at risk of AD

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Introduction

- Amyloid-β and tau pathology can be detected years before symptom onset, but they do not fully explain why some individuals show faster downstream tissue injury than others.^{1,2}
- Glial reactivity may be a biological modifier shaping the link from early AD pathology to neurodegeneration.^{3,4}
- Cortical mean diffusivity (cMD) is a sensitive marker of microstructural tissue integrity and may detect subtle cortical injury before overt atrophy.⁵

AIM

Test whether glial reactivity contributes to associations between AD pathology and longitudinal cortical micro- and macrostructural changes in preclinical AD.

Methods

Participants

- 299 cognitively unimpaired participants with baseline CSF/plasma biomarkers and longitudinal MRI from the ALFA+ cohort

AD pathology

- CSF Aβ42/40 ratio → **A** status
 - CSF p-tau181 → **T1** status
- Previously validated cut-offs⁶

Glial biomarkers⁷

- **Astroglial:** plasma GFAP, CSF YKL-40, CSF s100B
 - **Microglial:** CSF sTREM2
- Log-transformed. Outliers: 3 x IQR removed

Demographics

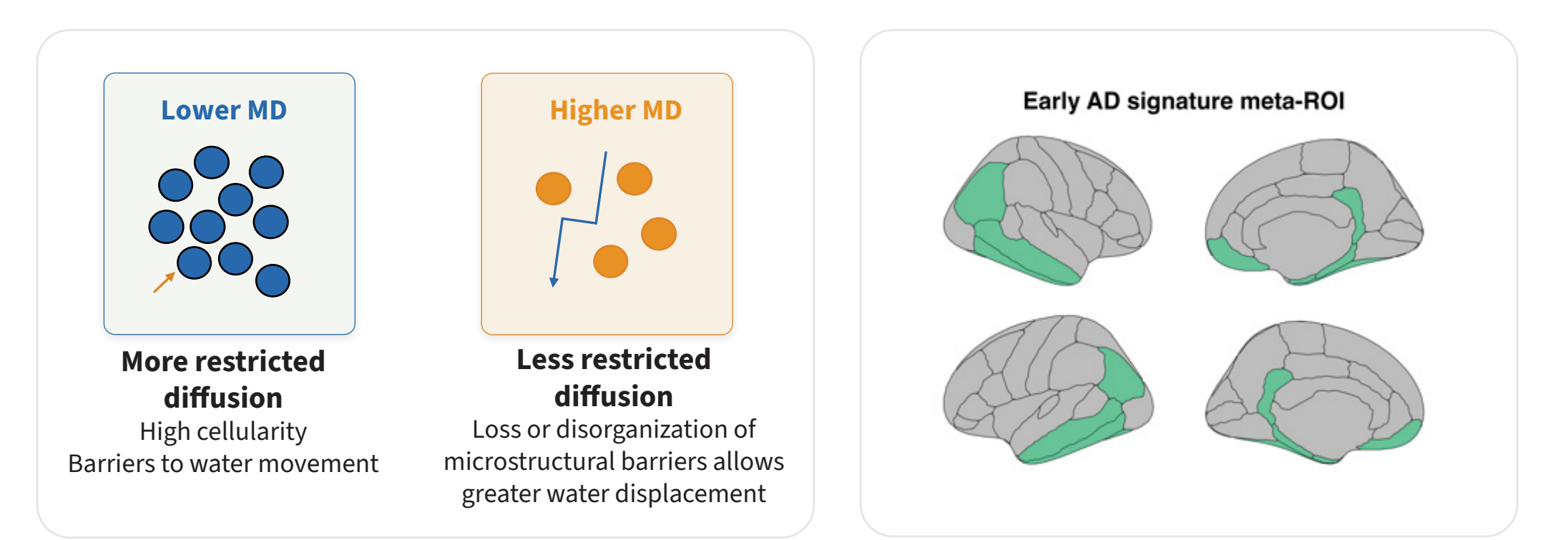
	A-T-	A+T-	A+T+	Total
	n=197	n=77	n=25	n=299
Sex, m	73 (37.1%)	33 (42.9%)	7 (28.0%)	113 (37.8%)
Age, y	60.0 (4.4)	61.2 (4.9)	64.0 (4.5)	60.6 (4.7)
Education, y	13.6 (3.4)	13.9 (3.6)	11.5 (3.4)	13.5 (3.5)
MMSE	29.1 (0.9)	29.4 (0.9)	28.9 (1.4)	29.2 (1.0)
APOE ε4 carrier	82 (41.6%)	64 (83.1%)	14 (56.0%)	160 (53.5%)
Follow-up time, y	6.3 (1.2)	6.0 (1.3)	5.7 (1.4)	6.2 (1.2)

Data are expressed as mean and standard deviation or number of participants (n) and percentage (%). A-T+ individuals were excluded from analysis. Follow-up range: 2.7 - 8.8 years. Abbreviations: APOE, apolipoprotein; MMSE, Mini Mental State Examination.

Methods

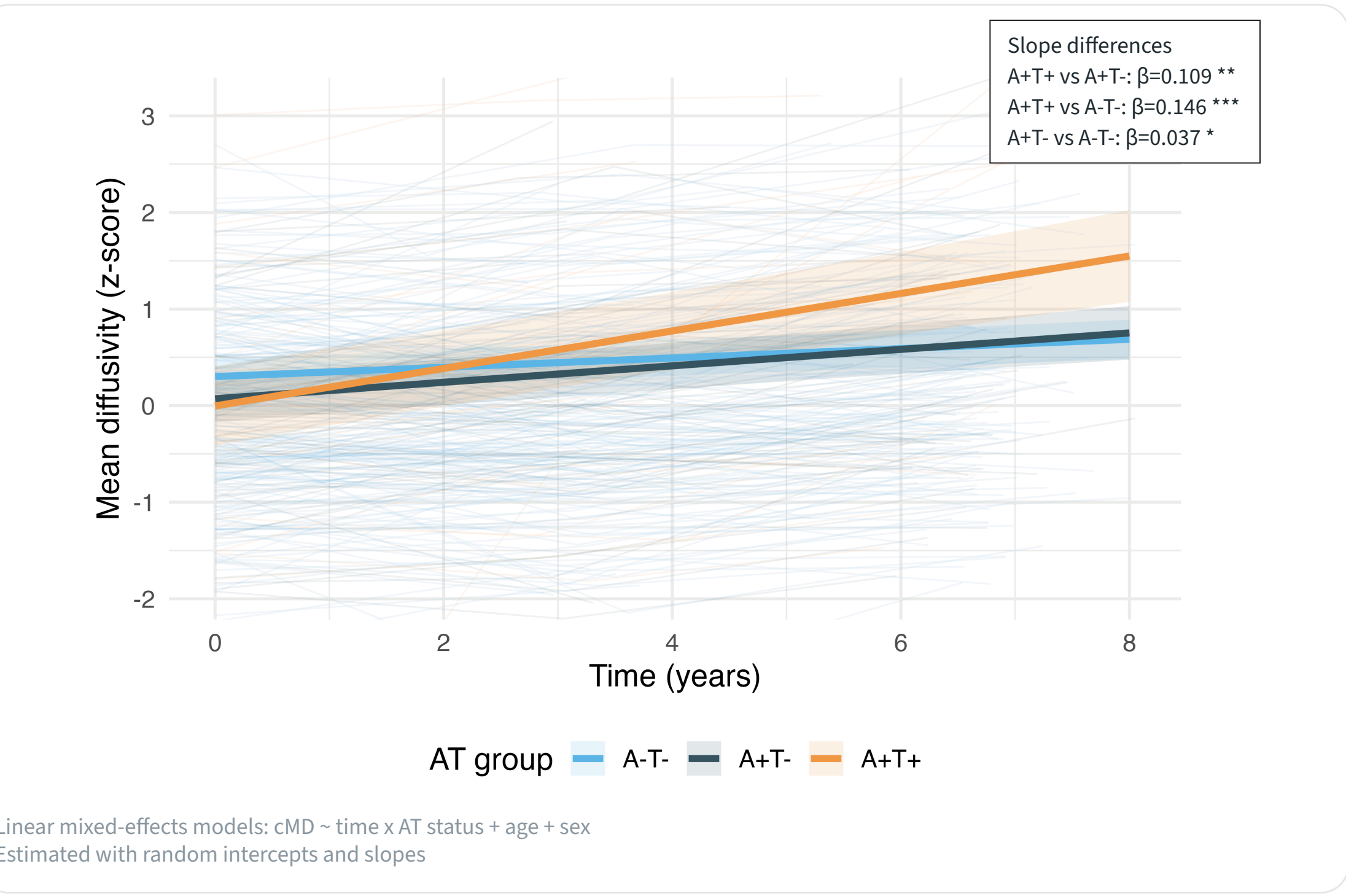
Imaging outcome

- Cortical mean diffusivity was derived with DONSURF⁸
- Projects diffusion metrics onto each subject’s cortical surface
- Averaged within an early AD cortical meta-ROI⁹

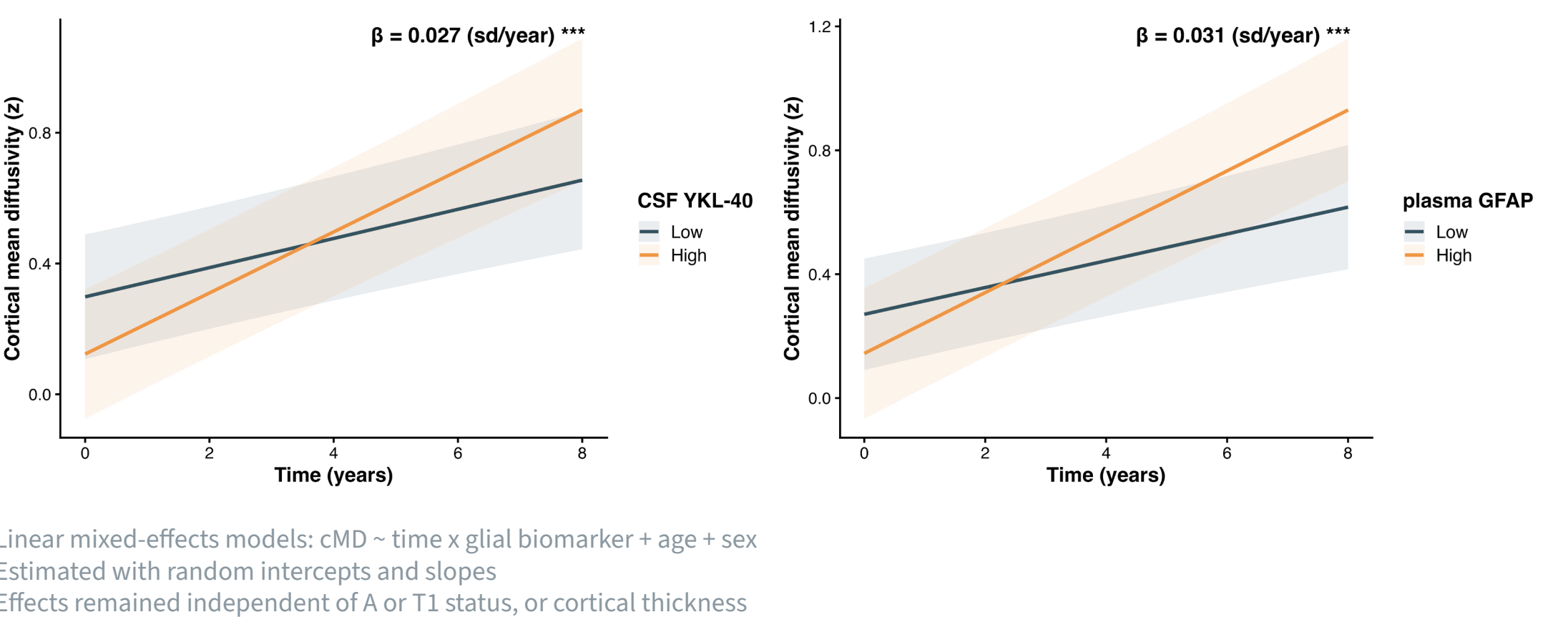


Results

Cortical MD increased fastest in A+T+ individuals

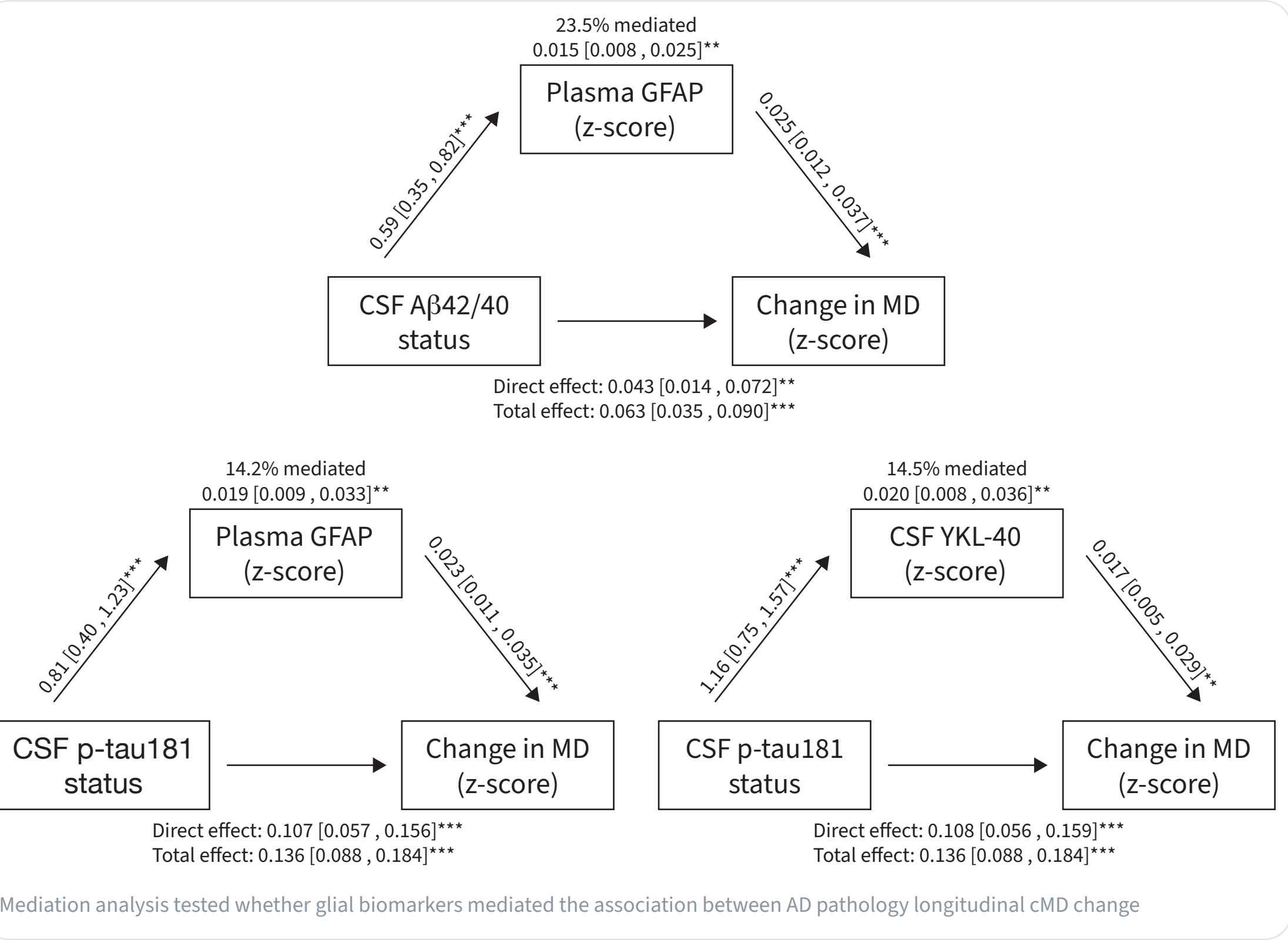


Higher plasma GFAP and CSF YKL-40 levels were associated with faster cortical MD increase

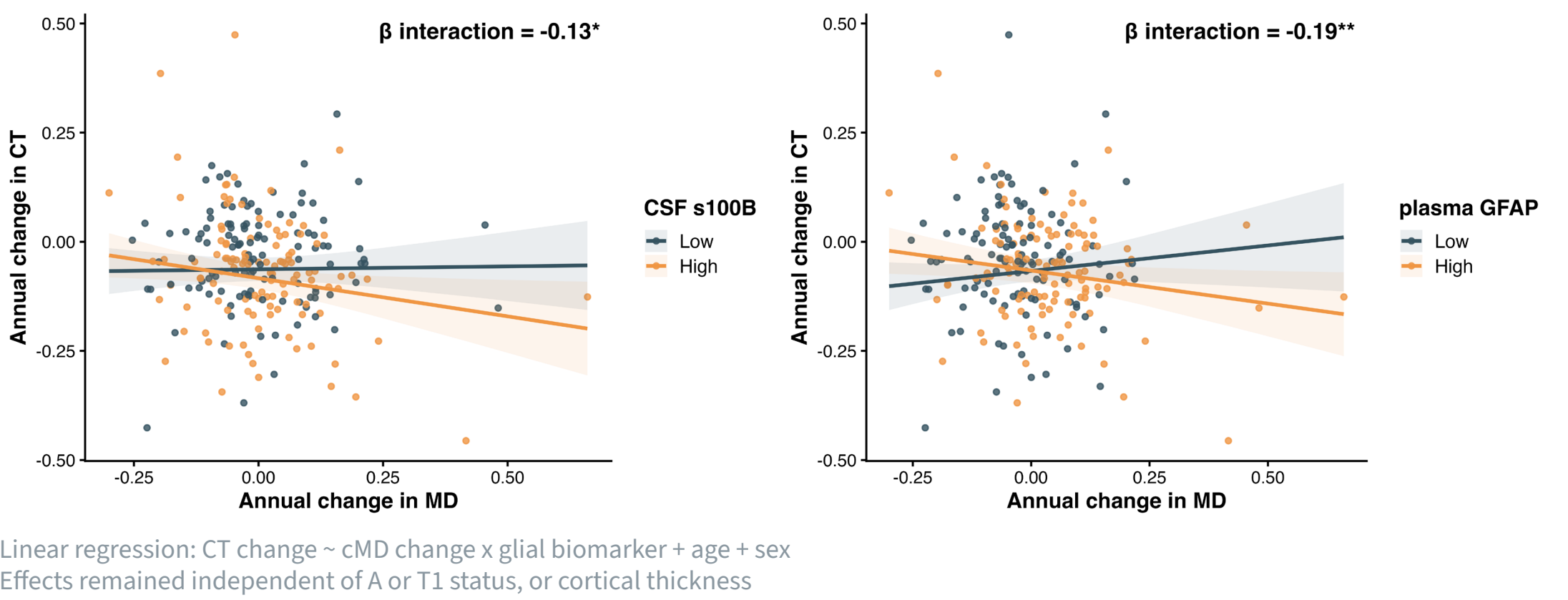


Results

Astroglial biomarkers partly explain AD pathology-related cMD change



Microstructural change is linked to cortical thinning only when astroglial reactivity is high



Conclusion

- Astroglial reactivity is associated with longitudinal cortical microstructural change in CU individuals.
- Increased astroglial reactivity may link early AD pathology to longitudinal cortical microstructural changes.
- And influence the extent to which microstructural alterations progress towards downstream atrophy.
- Astrocyte-related pathways may be relevant therapeutic targets alongside anti-amyloid and anti-tau strategies in prevention trials.
- Replication in an independent cohort is ongoing.