

Cumulative Risk Burden Predicts Blood-based Biomarker Levels And Accelerated Trajectories In Cognitively Unimpaired Older Adults

Michelle Yang Li¹, Paulina Tolosa-Tort¹, Margo B Heston¹, Philip Insel¹, Shea J Andrews¹

¹The University of California, San Francisco

Background

Blood-based biomarkers offer minimally invasive and cost-effective mediums to measure preclinical AD pathology [1-3]. Prior work has established *APOE* $\epsilon 4$, polygenic risk, and lifestyle factors as independent contributors to biomarker levels and AD risk [4].

Gap: The cumulative effect of genetic, familial, and modifiable lifestyle risk burden on plasma biomarker levels and trajectories in cognitively unimpaired (CU) adults is unknown.

Study question: Does a higher composite AD risk burden predict elevated biomarker levels and accelerated biomarker accumulation over time?

Hypothesis: Higher cumulative risk burden is associated with elevated plasma biomarkers and accelerated biomarker trajectories over time.

Methods

Cohort: PREVENT-AD participants with plasma biomarker and genetic data (N=285; 71% female; age 63.1 $\pm$ 5.1 years; follow-up 7.3 $\pm$ 2.6 years; 99% Caucasian) [5]

- Risk Factors:**
- APOE* $\epsilon 4$ carrier status
 - PRS (74 SNPs from Bellenguez et al. 2022 GWAS [6])
 - CogDrisk (14/16 original risk factors used; spans demographic, clinical, and lifestyle domains) [7]
 - LIBRA2 (11/15 original risk factors used; spans clinical and lifestyle modifiable factors) [8]
 - Family history of AD in first-degree relatives (FDRs)

Plasma Biomarkers: AB42/40, GFAP, NfL, ptau181, ptau217, ptau217/AB42

- Composite risk burden score (0-4):** Constructed from binary AD indicators:
- APOE* $\epsilon 4$ carrier status
 - High polygenic risk score (Top quartile)
 - AD family history (2+ first-degree relatives with AD)
 - High polyexposure score (1 SD $\geq$ mean)

Statistical analyses: Multivariable linear regression; linear mixed effects models

APOE $\epsilon 4$ is the strongest predictor of biomarker levels

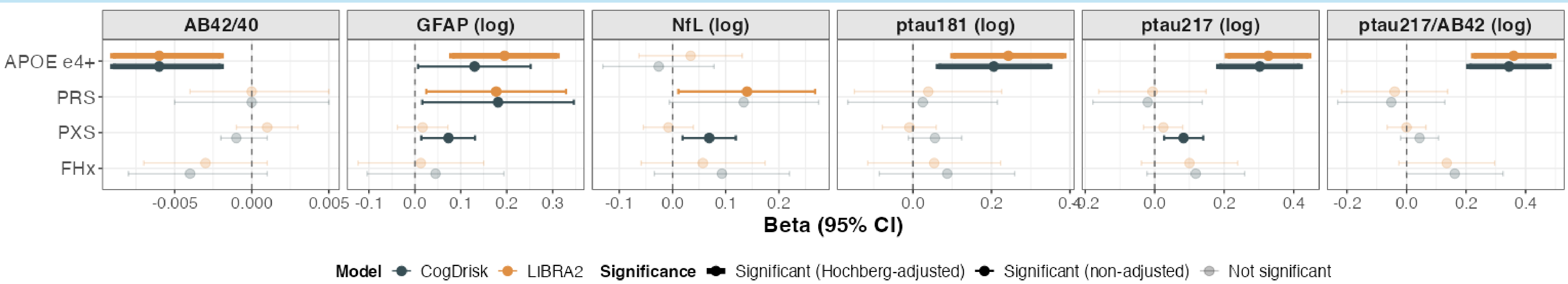


Figure 1. Composite AD risk burden components associations with plasma biomarker levels. Multivariable linear regression; LIBRA2-based model additionally adjusted for age, sex, and education. Cohort: PREVENT-AD (N=285). PRS, polygenic risk score. PXS, polyexposure risk score. FHx, family history.

Higher composite AD risk burden is broadly associated with elevated blood-based biomarker levels

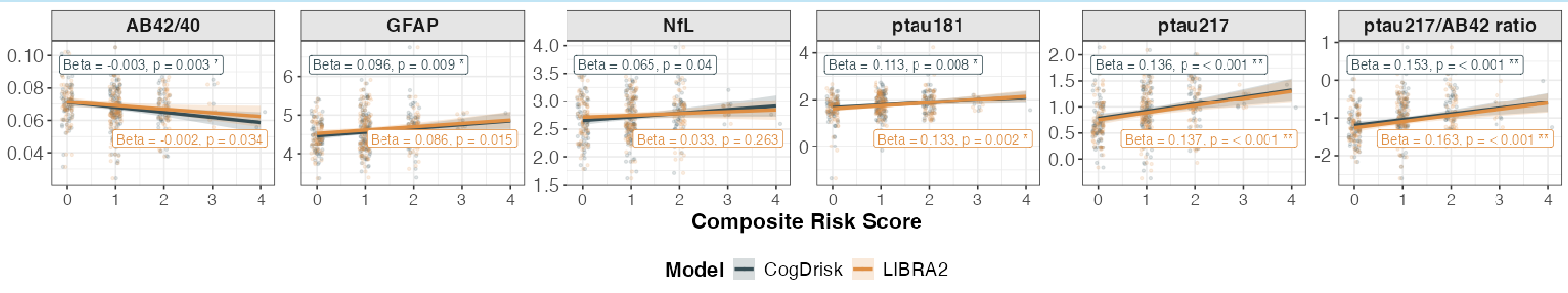


Figure 2. Composite AD risk burden score and plasma biomarker levels. Simple linear regression; LIBRA2-based model additionally adjusted for age, sex, and education. Cohort: PREVENT-AD (N=285).

Higher composite AD risk burden is associated with accelerated ptau₁₈₁ accumulation over time

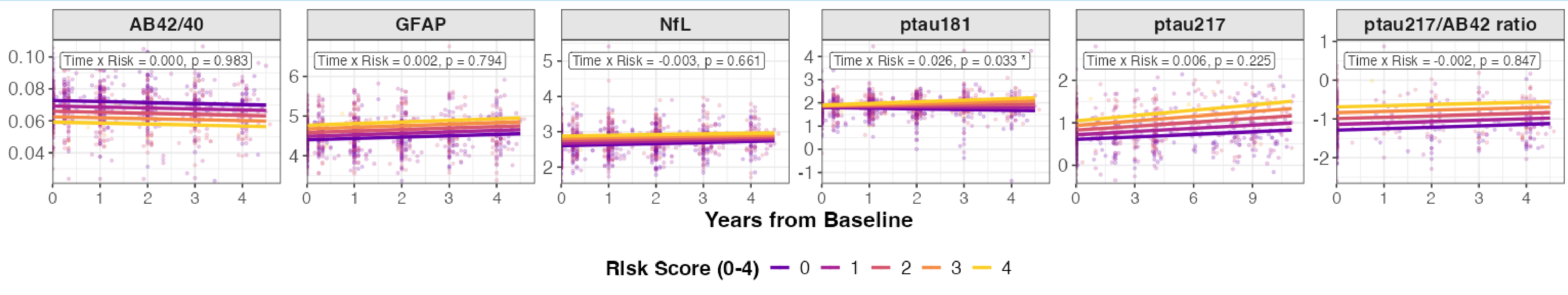


Figure 3. Predicted plasma biomarker trajectories by CogDrisk-based composite AD risk score. Linear mixed-effects model with random slopes and random intercepts. Cohort: PREVENT-AD (N=285).

Conclusion: Cumulative AD risk burden is broadly associated with plasma biomarker levels and specifically predicts accelerated ptau181 accumulation in cognitively unimpaired older adults, supporting structured composite risk profiling as a framework for AD risk stratification.

References

[1] Blennow K, Zetterberg H. 2018 Mar 13;62(3):1125–40.
[2] Nakamura A, et al. Nature. 2018 Feb;554(7691):249–54.
[3] Schindler SE. Continuum. 2022 Jun;28(3):822–33.
[4] Andrews SJ, et al. Alzheimer's & Dementia. 2025 Nov;21(11):e70826.
[5] Tremblay-Mercier J, et al. NeuroImage: Clinical. 2021;31:102733.

[6] Bellenguez C, et al. Nat Genet. 2022 Apr;54(4):412–36.
[7] Anstey KJ, et al. Alz & Dem Diag Ass & Dis Mo. 2022 Jan;14(1):e12336.
[8] Rosenau C, et al. Neurology. 2025 Nov 25;105(10):e214312.

