

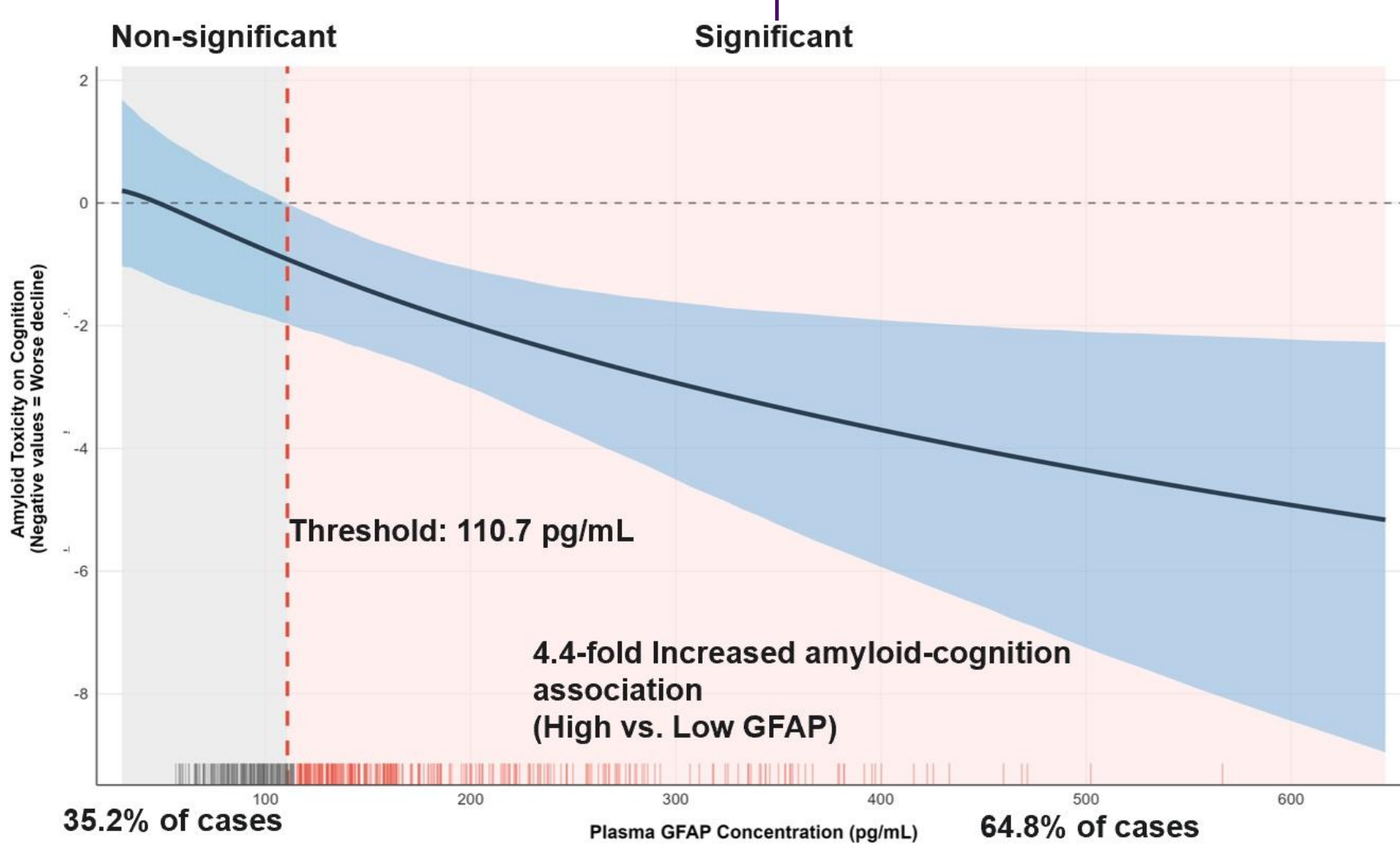
APOE Genotype Shapes Distinct Pathogenic Cascades and Identifies a GFAP Threshold for Precision Anti-amyloid Therapy Stratification

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- APOE separates AD into tau-driven, inflammation-gated, and protective cascade patterns.
- In $\epsilon 3/\epsilon 3$ carriers, GFAP >110.7 pg/mL marks a 4.4-fold stronger amyloid-cognition association for treatment stratification.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Plasma biomarkers are reshaping AD diagnosis and treatment monitoring. Clinical gap: the same amyloid burden may not carry the same cognitive meaning across APOE genotypes. Aim: test whether APOE modifies biomarker-cognition coupling and whether GFAP identifies an actionable inflammatory threshold.	C-PAS cohort: 2,677 participants; age 68.1 +/- 8.1 years; 63.9% female. PET validation subset: 995 participants. Measures: plasma Abeta42/40, p-tau217, GFAP, NfL; ACE-III cognition. Models: mixed models, relative importance, moderated mediation, and Johnson-Neyman analysis. Adjustment: age, sex, and education.	 Distinct cascades: $\epsilon 3/\epsilon 4$ cognition was mainly tau-driven; p-tau217 RI = 29.4%. Inflammation-gated $\epsilon 3/\epsilon 3$: GFAP amplified Abeta-tau by 55% (p = 0.005) and tau-cognition by 183% (p = 0.007). Protective $\epsilon 2/\epsilon 3$ pattern: GFAP negatively moderated the Abeta-tau link (p = 0.016). Threshold: GFAP 110.7 pg/mL; above it, amyloid-cognition coupling was 4.4-fold stronger.	APOE changes the pathway, not just biomarker level. High-GFAP $\epsilon 3/\epsilon 3$ carriers may be a priority group for amyloid-directed treatment stratification. Low-GFAP $\epsilon 3/\epsilon 3$ carriers may need alternative approaches and longitudinal validation before clinical deployment.	Selected references 1. Jack CR Jr, et al. <i>Alzheimers Dement.</i> 2024;20:5143-5169. doi:10.1002/alz.13859 2. Yamazaki Y, et al. <i>Nat Rev Neurol.</i> 2019;15:501-518. doi:10.1038/s41582-019-0228-7 3. Bellaver B, et al. <i>Nat Med.</i> 2023;29:1775-1781. doi:10.1038/s41591-023-02380-x 4. Benedet AL, et al. <i>JAMA Neurol.</i> 2021;78:1471-1483. doi:10.1001/jamaneurol.2021.3671 5. van Dyck CH, et al. <i>N Engl J Med.</i> 2023;388:9-21. doi:10.1056/NEJMoa2212948
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