

Multi-marker Plasma Endotyping Identifies Divergent Cognitive Decline Pathways In Community-dwelling Older Adults: The Shape Cohort

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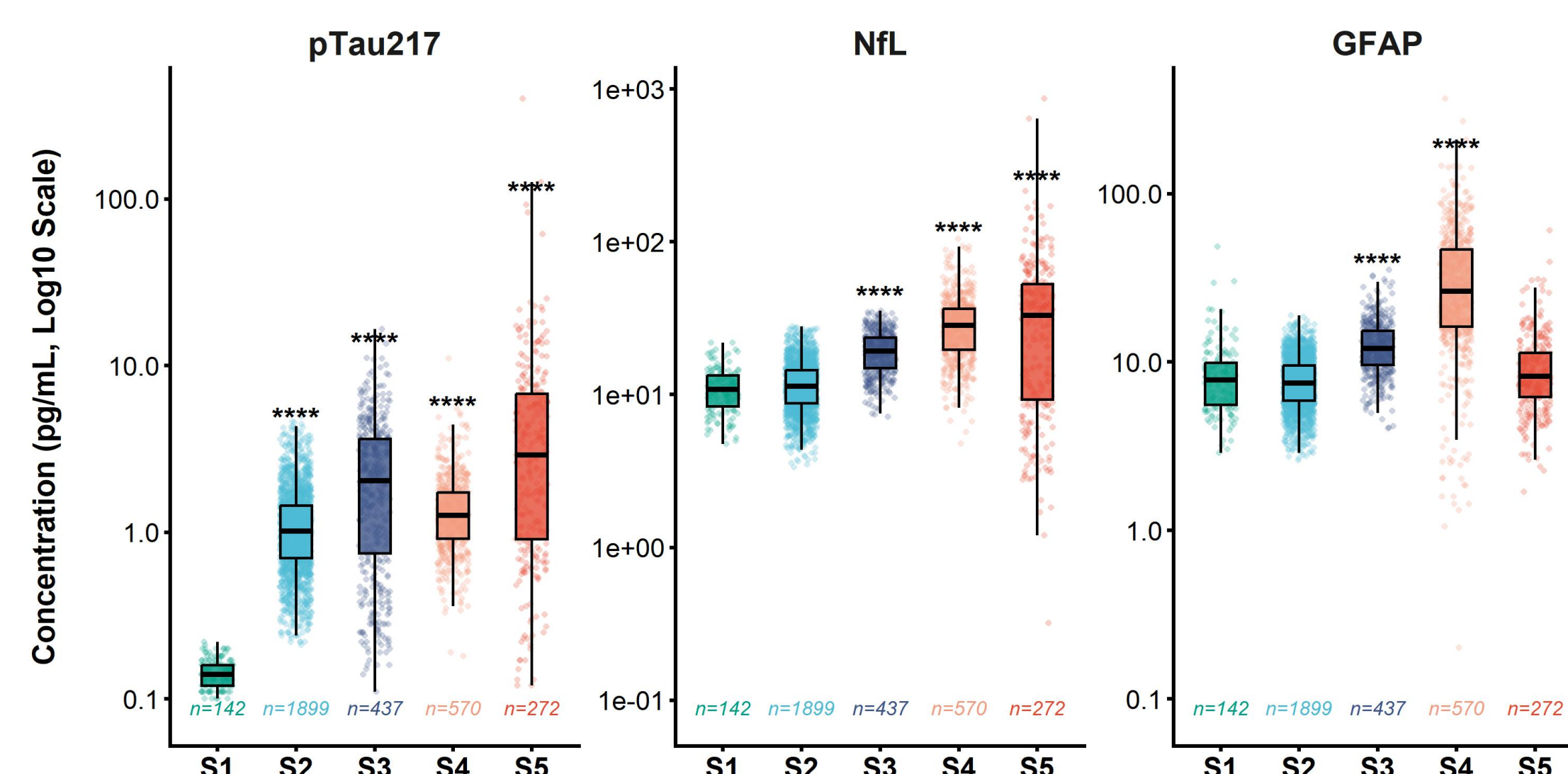
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background

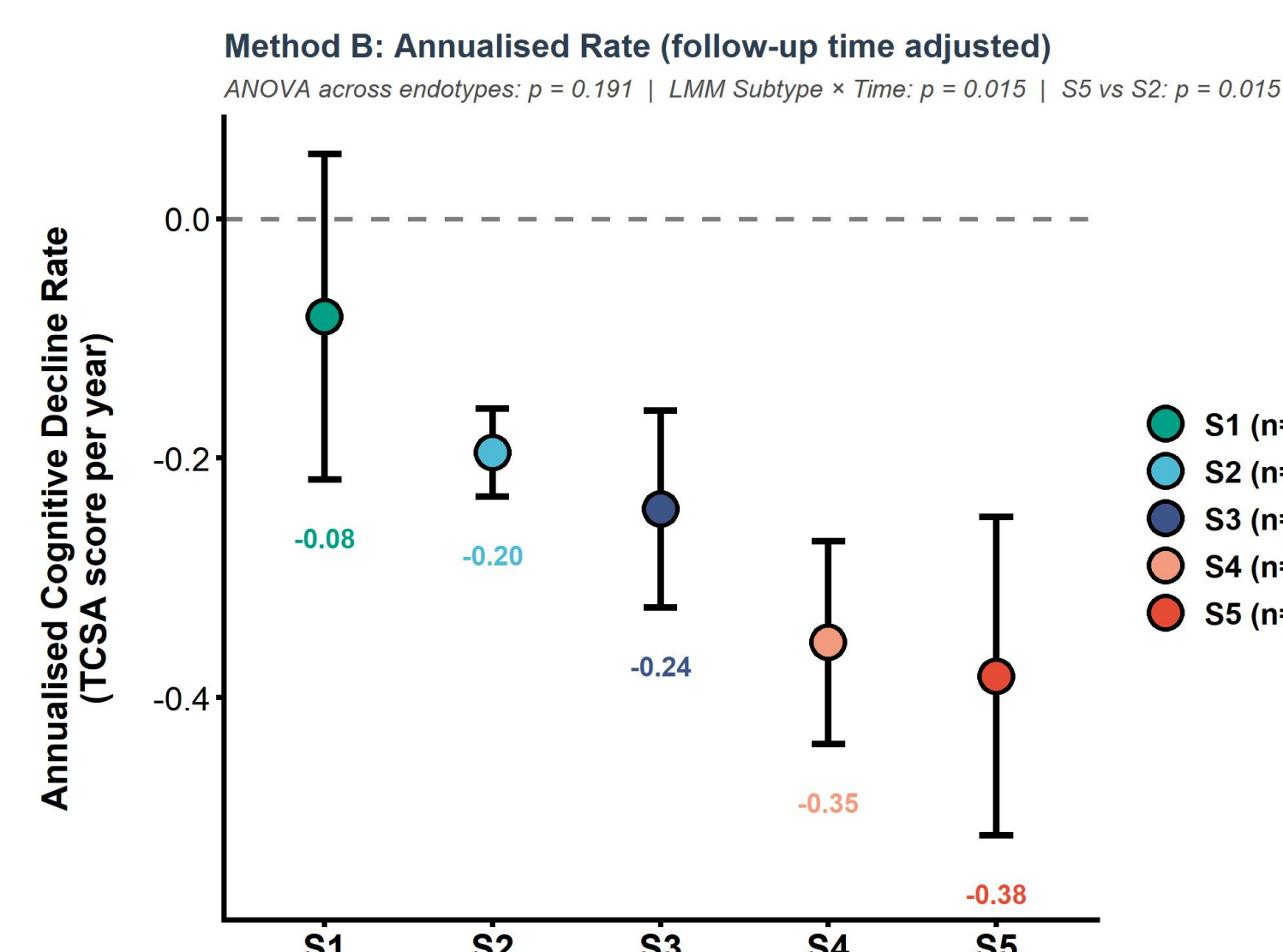
Cognitive decline in community-dwelling older adults is biologically heterogeneous, yet most screening strategies rely on single biomarkers such as plasma p-Tau217. Plasma phosphorylated tau-217 (p-Tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) capture complementary dimensions of tau pathology, neuronal injury, and glial reactivity. Whether multi-marker endotyping can identify biologically distinct high-risk subgroups with divergent mechanistic profiles remains unclear.

Methods

We analysed 3,320 community-dwelling older adults from the SHAPE cohort (Shanghai, 2021-2025). Plasma p-Tau217, NfL, and GFAP were quantified using Simoa technology. Unsupervised Gaussian mixture modelling (GMM) was applied to identify latent biological endotypes. Differences in APOE ε4 carrier frequency and peripheral metabolic comorbidities were compared across endotypes. Longitudinal cognitive trajectories were evaluated using linear mixed-effects models on repeated TCSA-P scores. Multivariable logistic regression assessed associations between endotype membership and cognitive impairment at follow-up, with progressive adjustment for age, sex, education, APOE ε4, hypertension, diabetes, and dyslipidaemia.



* vs S1 (Dunn posthoc, BH-adjusted); *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. Kruskal-Wallis: pTau217 p<0.001; NfL p<0.001; GFAP p<0.001



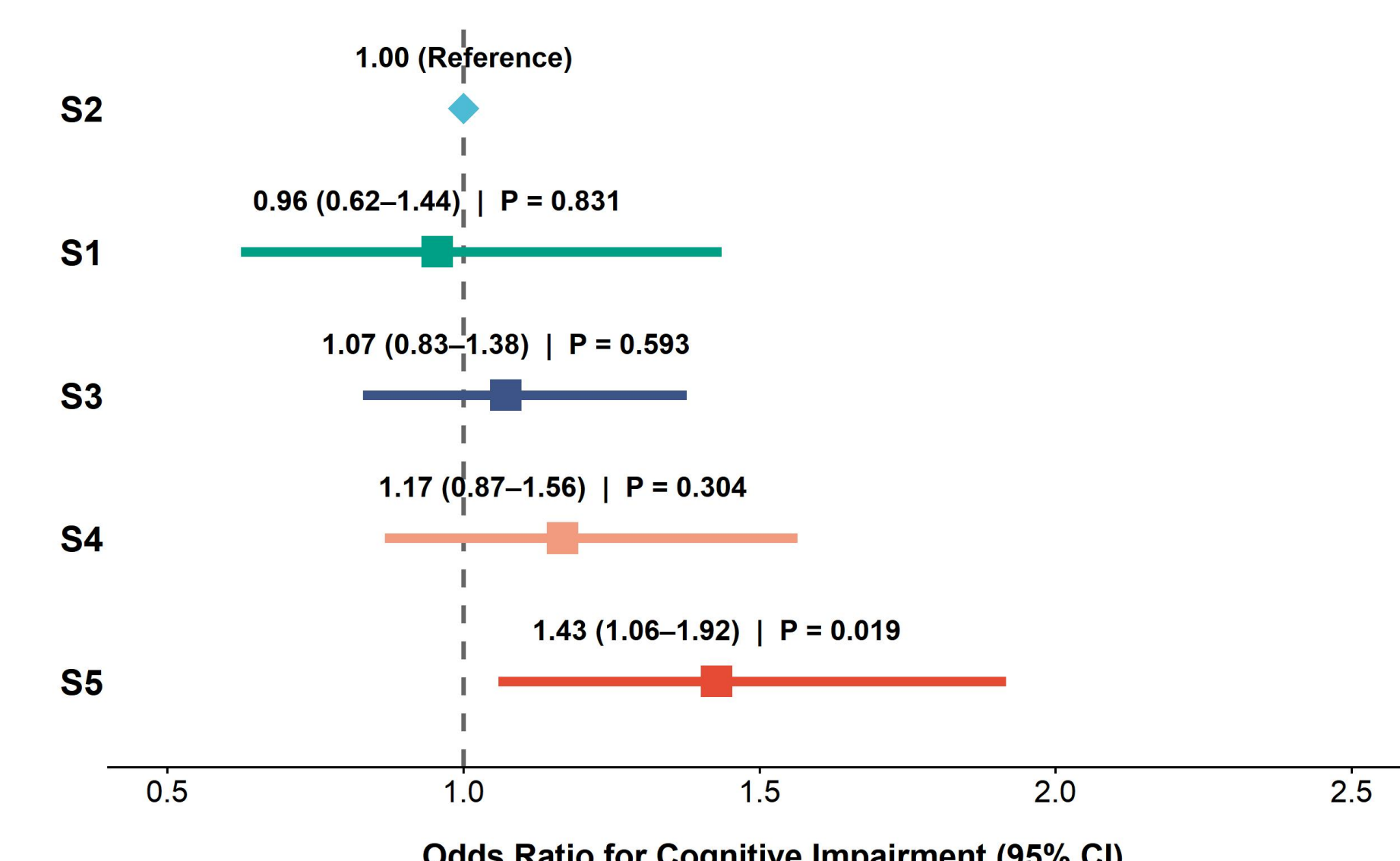
Error bars: mean ± SE of annualised decline rate (TCSA/year). Annualised rate = (Follow-up score - Baseline score) / follow-up years. Adjusted for age, sex, and education (LMM).

Results

GMM identified five endotypes. Two high-risk groups showed similar annualised cognitive decline rates but divergent risk architectures. The tau-predominant endotype (S5; n=272) exhibited markedly elevated p-Tau217, the highest NfL, and the highest APOE ε4 carrier frequency (34.6%); it remained significantly associated with cognitive impairment after full adjustment (OR=1.43, 95% CI: 1.06-1.92, P=0.019). The GFAP-predominant endotype (S4; n=570) showed the highest GFAP, elevated NfL, the lowest APOE ε4 frequency (6.1%), and the heaviest cardiometabolic burden (hypertension 63.7%, diabetes 27.6%); its cognitive risk was substantially attenuated after metabolic adjustment (OR=1.17, 95% CI: 0.87-1.56, P=0.304). Within S4, increasing metabolic comorbidity showed a significant dose-response relationship with GFAP and NfL levels.

Conclusion

Multi-marker plasma endotyping identified at least two biologically distinct high-risk cognitive decline pathways: one driven by endogenous genetic susceptibility and tau pathology, and another driven by peripheral cardiometabolic burden and glial reactivity. These findings support multi-marker stratification to improve identification of heterogeneous cognitive risk in community settings.



S2 = reference (OR = 1.00). Adjusted for age, sex, education, APOE ε4, hypertension, type 2 diabetes mellitus, and dyslipidaemia. Dyslipidaemia did not differ across endotypes (p = 0.619) and did not attenuate risk estimates.