



Liver-metabolic stress and APOE ε4 in Relation to Alzheimer pathology and memory impairment

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INTRODUCTION

Metabolic dysregulation and hepatic injury have been implicated in cognitive ageing, but their links to memory, amyloid pathology, and potential modification by APOE ε4 remain insufficiently characterized. We examined whether lipid-/metabolism-related indices and a liver fibrosis marker are associated with cognitive performance and cortical amyloid burden, and whether these associations differ by APOE ε4 status.

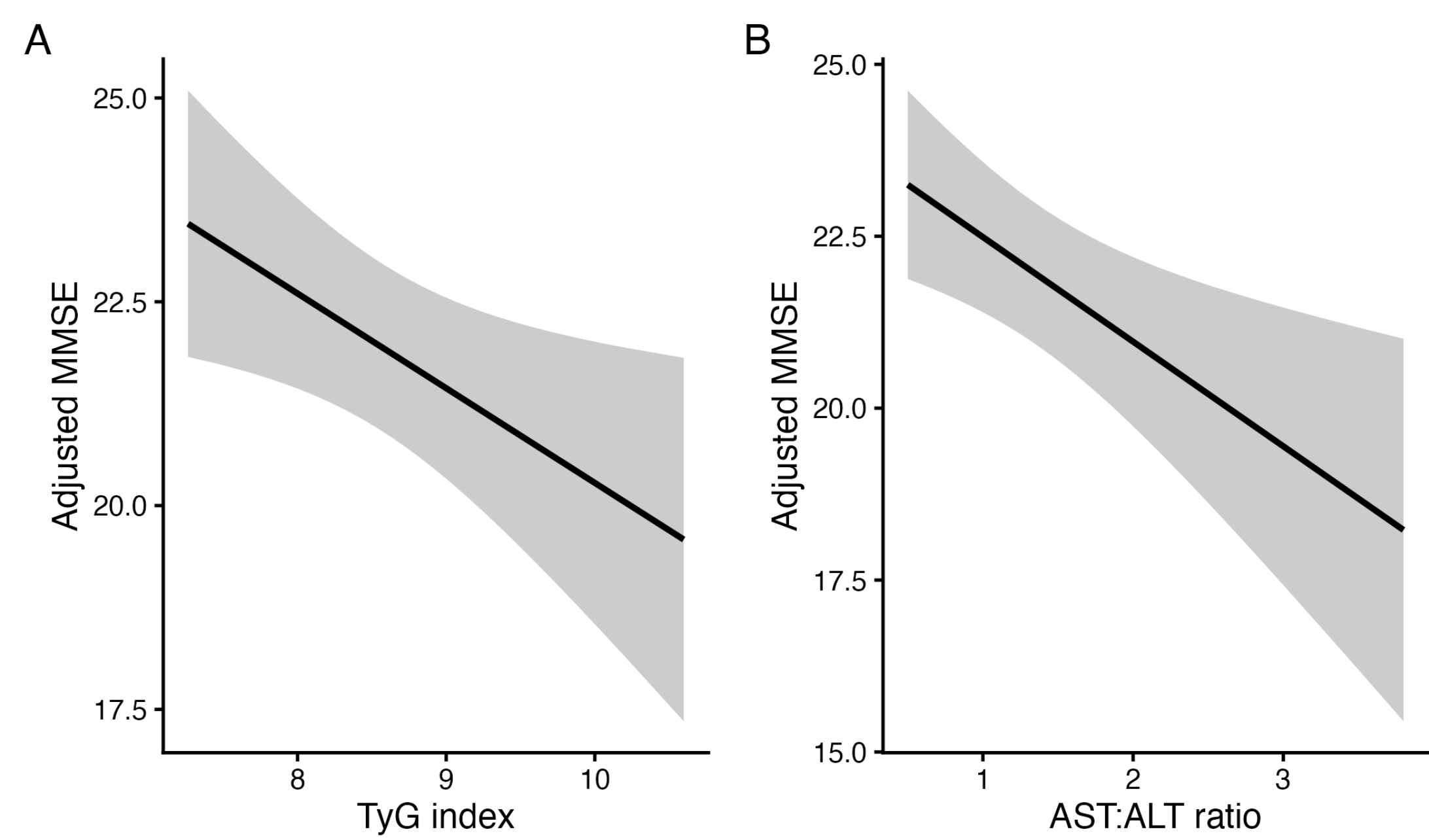


FIGURE 2 Associations of liver–metabolic stress markers with global cognitive function. Partial effect plots illustrating the adjusted associations of the TyG index (left) and AST/ALT ratio (right) with MMSE scores from multivariable linear regression models. Solid lines indicate model-predicted values and shaded areas indicate 95% confidence intervals.

METHODS

We conducted a cross-sectional analysis of older adults in the Dementia Platform Korea Trial-Ready Cohort (DPK-TRR). Global cognition was assessed with the Mini-Mental State Examination (MMSE) and domain-level cognition with CERAD-K and SNSB-II. Using routine laboratory data, we calculated the triglyceride-glucose (TyG) index, AST/ALT ratio, and FIB-4 stage; APOE ε4 carrier status was determined by genotyping. In a subset who underwent amyloid PET, cortical amyloid burden was summarized as SUVR. Multivariable regression models evaluated TyG and AST/ALT ratio as primary predictors and tested the FIB-4 × APOE ε4 interaction, adjusting for age, sex, education, hypertension, diabetes, and dyslipidemia.

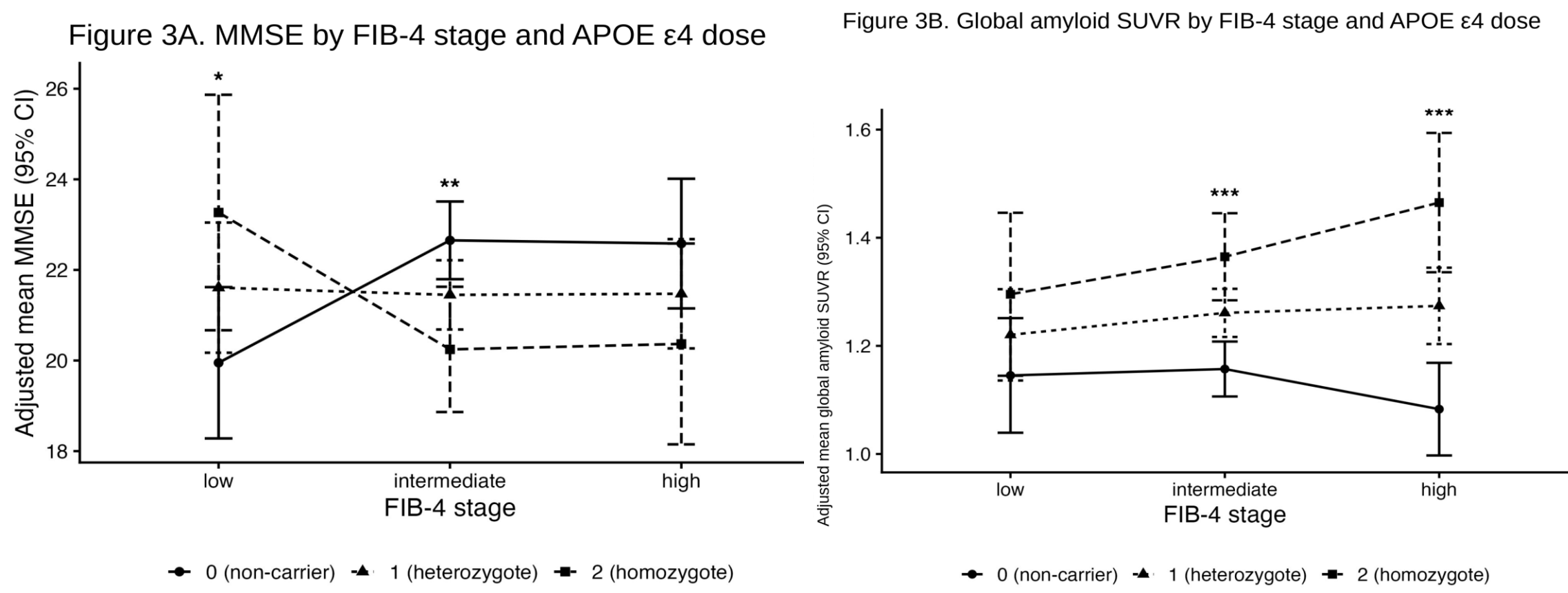


FIGURE 3 Interactive effects of FIB-4 stage and APOE ε4 genotype group on global cognition and cortical amyloid burden. (A) Adjusted estimated marginal means (EMMs) of MMSE scores across FIB-4 stages (low, intermediate, high) by APOE ε4 genotype group (non-carrier, heterozygote, homozygote). (B) Adjusted EMMs of global amyloid PET SUVR across FIB-4 stages by APOE ε4 genotype group. Error bars represent 95% confidence intervals.

TABLE 2 Associations of TyG index and AST: ALT ratio with global cognition, memory domains, and amyloid burden.

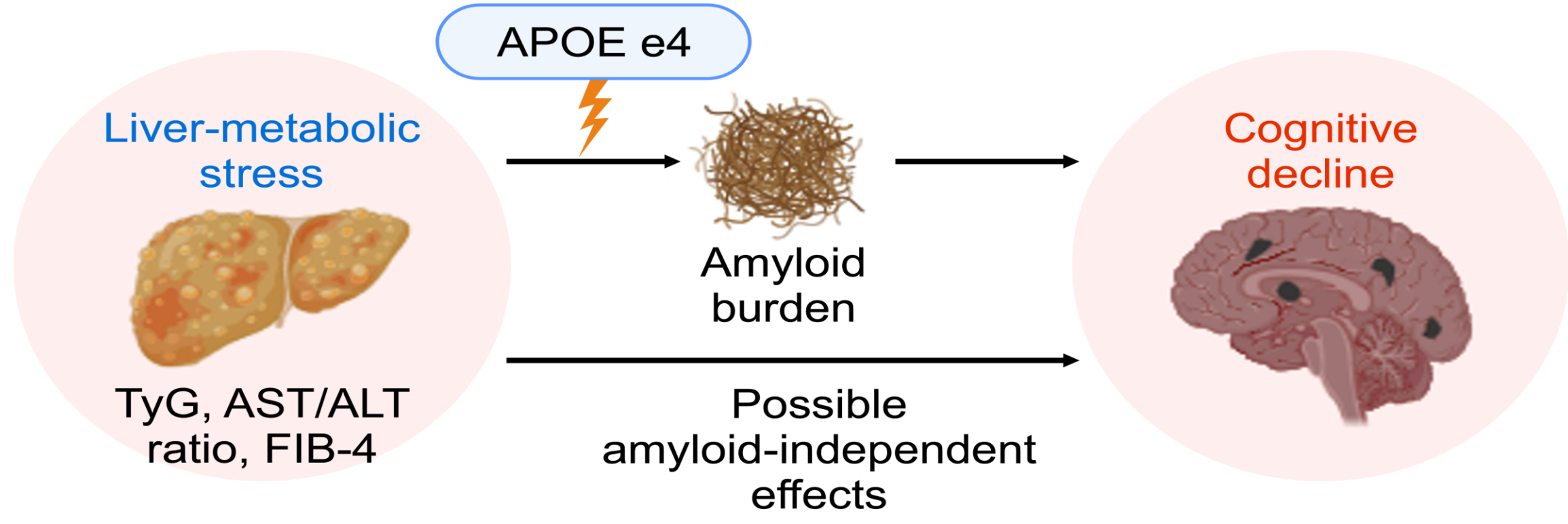
Characteristic	MMSE global			SNSB-II memory z			CERAD delayed recall z			Amyloid PET SUVR		
	β (95% CI)	95% CI	p-value	β (95% CI)	95% CI	p-value	β (95% CI)	95% CI	p-value	β (95% CI)	95% CI	p-value
TyG	−1.13	−2.11, −0.16	0.022*	−0.31	−0.68, −0.05	0.087	−0.29	−0.52, −0.06	0.012*	−0.03	−0.09, 0.03	0.3
AST: ALT ratio	−1.4	−2.1, −0.39	0.007*	−0.37	−0.83, 0.09	0.113	0.00	−0.21, 0.22	0.98	−0.02	−0.08, 0.04	0.57

TABLE 3 Associations of FIB-4 stage and APOE ε4 dose with cognitive outcomes and amyloid PET SUVR: age-adjusted interaction models.

Characteristic	MMSE global		SNSB-II visuospatial		CERAD visuospatial		Amyloid PET SUVR	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Dose 1 vs 0 (low FIB-4)	3.47 (0.81, 6.12)	0.011*	−0.059 (−1.351, 1.234)	0.929	3.383 (1.378, 5.388)	0.001**	0.080 (−0.081, 0.241)	0.330
Dose 2 vs 0 (low FIB-4)	2.23 (−1.29, 5.75)	0.213	0.256 (−1.460, 1.972)	0.770	2.291 (−0.540, 5.123)	0.112	0.147 (−0.062, 0.357)	0.166
Intermediate × dose1	−4.80 (−7.75, −1.85)	0.001**	0.051 (−1.407, 1.509)	0.945	−3.307 (−5.496, −1.118)	0.003**	0.040 (−0.138, 0.218)	0.661
High × dose1	−4.26 (−7.74, −0.78)	0.017*	0.670 (−1.086, 2.425)	0.454	−2.969 (−5.462, −0.476)	0.020*	0.160 (−0.048, 0.368)	0.132
Intermediate × dose2	−4.54 (−8.52, −0.55)	0.026*	−0.449 (−2.395, 1.496)	0.650	−2.092 (−5.241, 1.058)	0.192	0.046 (−0.191, 0.283)	0.703
High × dose2	−4.62 (−9.28, 0.04)	0.052	0.851 (−1.602, 3.303)	0.496	−0.633 (−4.090, 2.824)	0.718	0.205 (−0.070, 0.481)	0.144

RESULTS

Higher TyG index and AST/ALT ratio were independently associated with lower MMSE scores (TyG: β = −1.13, p = 0.022; AST/ALT ratio: β = −1.40, p = 0.007). Higher TyG index was also associated with poorer episodic memory performance, particularly on CERAD delayed recall (β = −0.29, p = 0.012), whereas the association with SNSB-II memory did not reach statistical significance. FIB-4 stage showed an APOE ε4-dependent interaction pattern for cognitive outcomes. At higher FIB-4 stages, APOE ε4-associated cognitive differences were attenuated or reversed, particularly for MMSE and CERAD visuospatial performance. In the amyloid PET subset, TyG index and AST/ALT ratio showed no clear main associations with cortical amyloid burden. However, amyloid PET SUVR tended to diverge across APOE ε4 groups at higher FIB-4 stages, with higher SUVR in groups with greater ε4 burden.



CONCLUSION

Metabolic indices (TyG and AST/ALT ratio) were associated with global cognition and episodic memory. FIB-4 stage showed an APOE ε4-dependent cross-over pattern for global and visuospatial cognition. In the amyloid PET subset, SUVR tended to diverge across APOE ε4 groups at higher FIB-4 stages, with higher SUVR in groups with greater ε4 burden. These findings support a brain–liver–metabolic pathway in which hepatic fibrosis and metabolic stress may contribute to cognitive vulnerability and Alzheimer-related pathological heterogeneity.

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