

Cardiovascular Risk and APOE ε4 Amplify Domain-specific Cognitive Decline

Evidence from the Southeast Asian BIOCIS Study

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INTRODUCTION

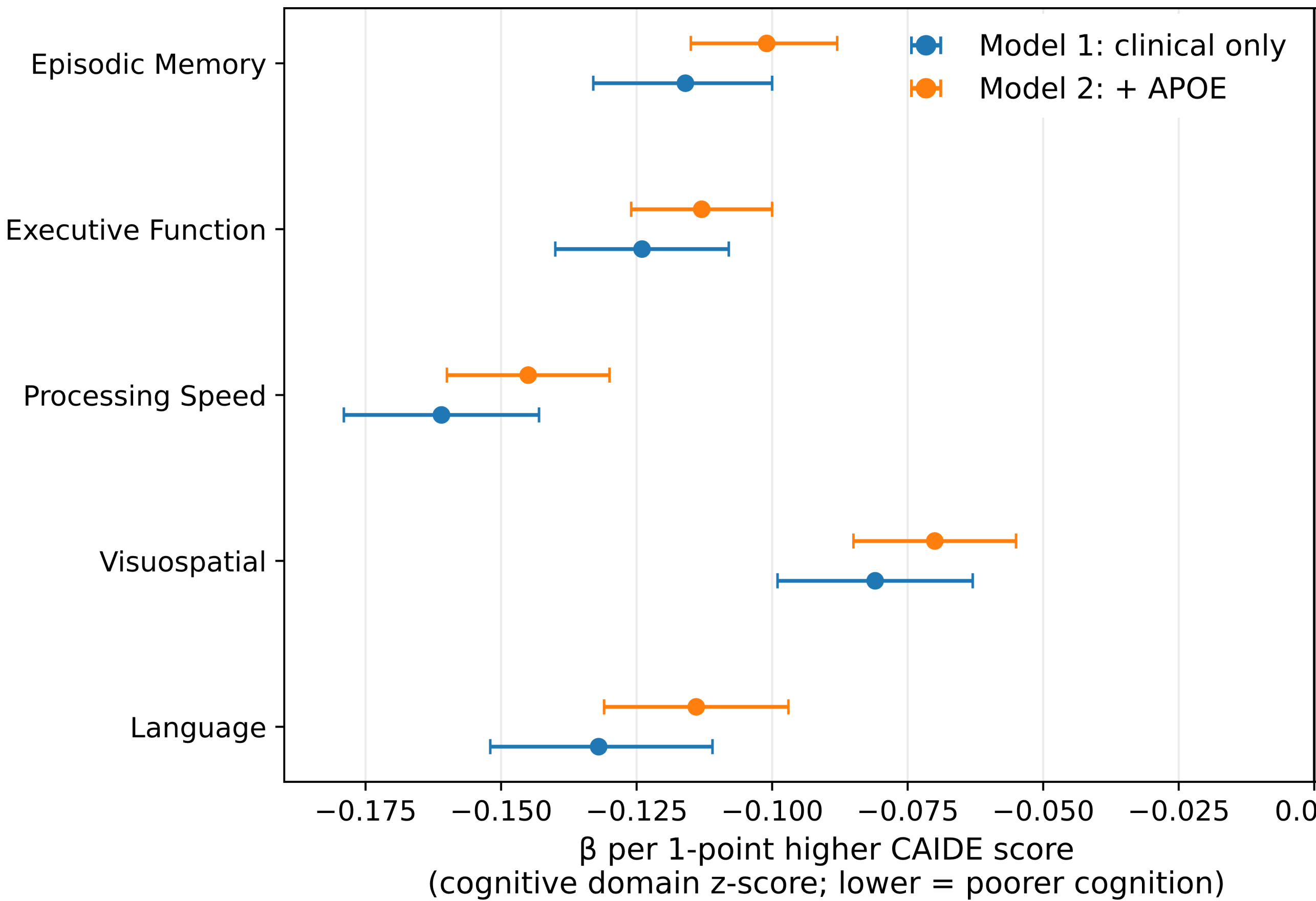
Cardiovascular risk and genetic susceptibility independently predict cognitive decline, but their synergistic interaction remains unclear. The CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) model quantifies mid-life cardiometabolic burden. We investigated whether CAIDE scores associate with cognitive domains, whether incorporating *APOE* genotype improves model performance, and whether associations differed by *APOE* ε4 status or age.

RESULTS

Characteristic	Overall	Non-carrier	APOE ε4 carrier
Age, years	58.2 (10.7)	58.3 (10.6)	57.4 (10.8)
Female sex (n/%)	1,215 (63%)	981 (62%)	234 (67%)
Ethnicity (n/%)			
Chinese	1,697 (88%)	1,403 (89%)	294 (84%)
Malay	77 (4.0%)	54 (3.4%)	23 (6.6%)
Indian	101 (5.2%)	84 (5.3%)	17 (4.8%)
Education, years	15.0 (3.5)	15.0 (3.6)	15.0 (3.3)
CAIDE Model 1 score (0-15)	4.9 (2.3)	4.9 (2.3)	4.8 (2.3)
CAIDE Model 2 score (0-18)	6.0 (2.7)	5.7 (2.6)	7.5 (2.7)
MoCA raw Score (0-30)	25.8 (3.0)	25.8 (3.0)	25.8 (3.2)

Table 1. Baseline characteristics of participants by APOE ε4 carrier status.
Values are mean ± SD or n (%). APOE ε4 carriers were defined as participants with at least one ε4 allele.
CAIDE Model 1 includes clinical cardiovascular risk factors; CAIDE Model 2 additionally incorporates APOE genotype.

Figure 1. Higher CAIDE scores were associated with poorer cognitive performance.



References

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2. Leow, Y. J., Chen, C., Chua, T. L., Mah, K. K., Ng, A., Tan, B. Y., Tan, J., Lim, Y. Y., Lee, F. H. E., Kandiah, N., & BIOCIS Study Group. (2024). Biomarkers and Cognition Study, Singapore (BIOCIS). *The Journal of Prevention of Alzheimer's Disease*.

METHODS

Cross-sectional analyses included 1,927 participants from a multi-ethnic Singapore cohort (BIOCIS Study). CAIDE Model 1 (clinical only; range 0-15) and Model 2 (clinical + *APOE*; range 0-18) were compared. Linear regressions estimated associations between CAIDE and MoCA score and five cognitive domain z-scores (episodic memory, executive function, processing speed, visuospatial, language), adjusting for race. Interaction terms assessed effect modification by APOE ε4 and age tertiles.

APOE improved model fit

Incorporating APOE genotype improved the explanatory performance of CAIDE models, particularly for processing speed, where adjusted R² increased from **0.164 to 0.185**.

Figure 2. CAIDE associations were steeper in APOE ε4 carriers for MoCA and episodic memory.

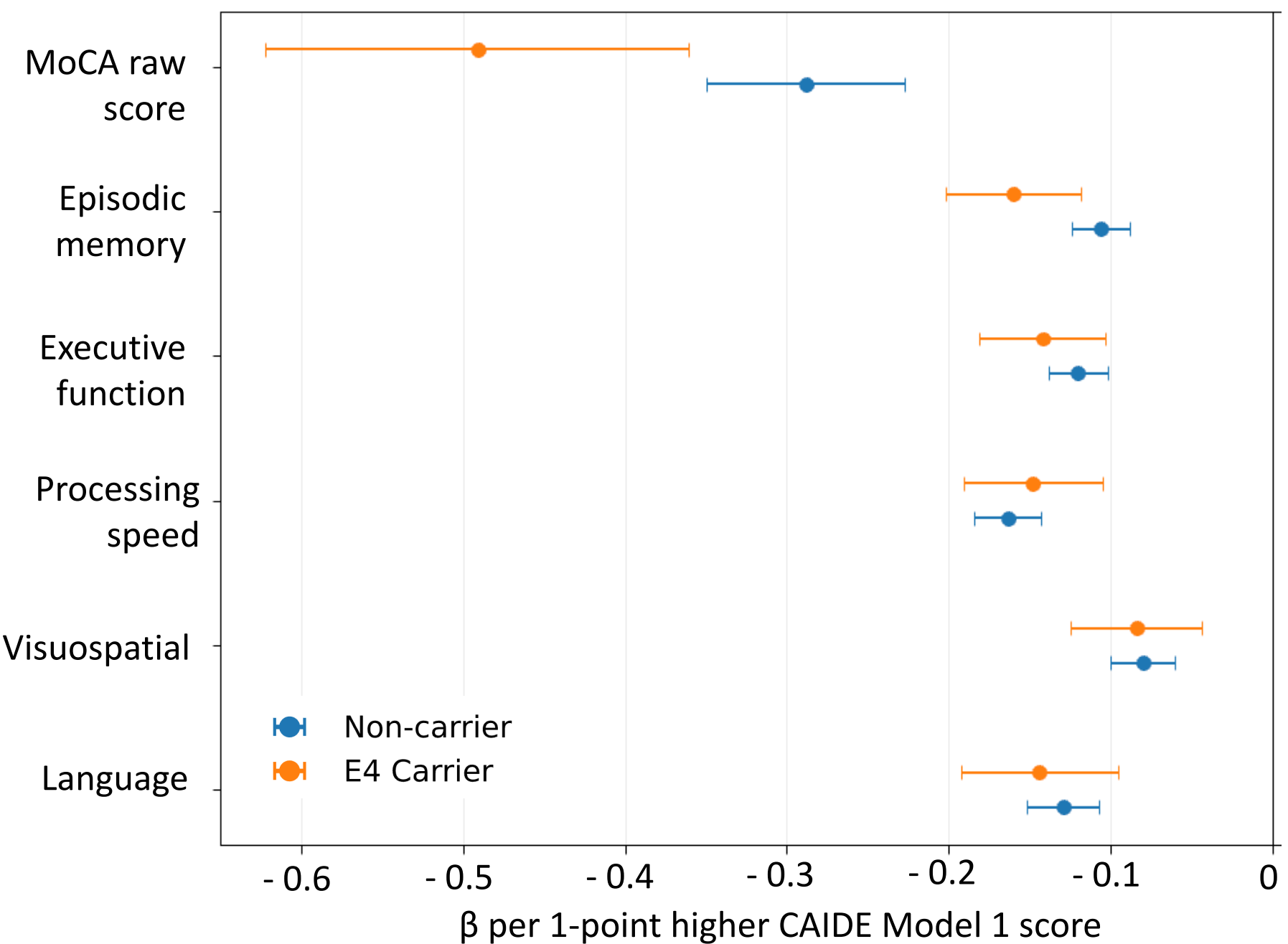
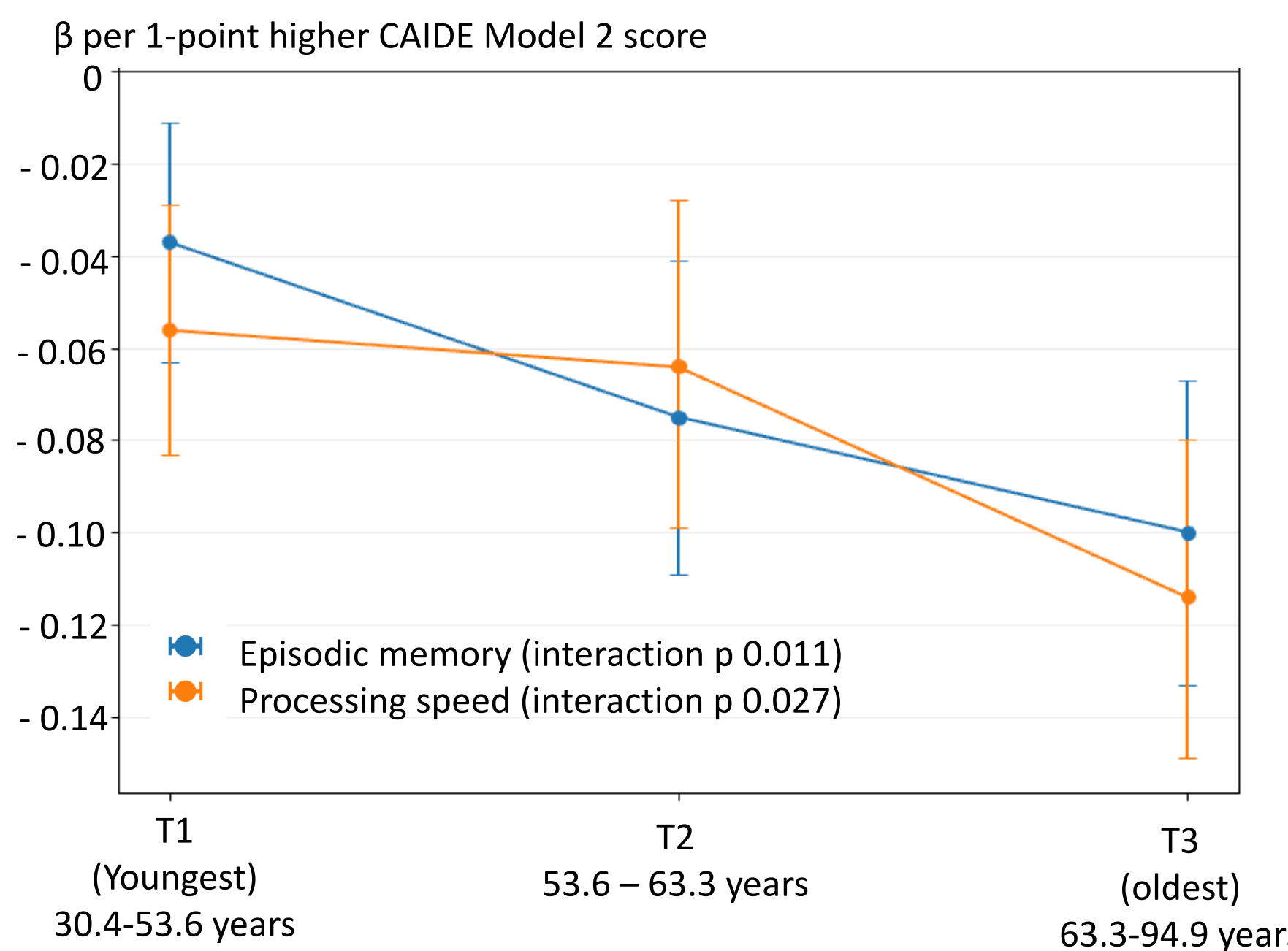


Figure 3. CAIDE associations strengthened across age tertiles for episodic memory and processing speed.



- Higher CAIDE cardiovascular risk scores were associated with poorer global and domain-specific cognitive performance.
- APOE ε4 carriers showed steeper CAIDE associations for MoCA and episodic memory.
- Associations with episodic memory and processing speed strengthened across age tertiles.

CONCLUSIONS

- Higher cardiovascular risk burden was associated with poorer cognitive performance across domains.
- APOE ε4 carriers showed greater vulnerability to cardiovascular risk, particularly for MoCA and episodic memory.
- Older adults showed stronger CAIDE associations with episodic memory and processing speed.
- Dementia prevention may benefit from integrating cardiovascular risk, APOE genotype, and age-based stratification.

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