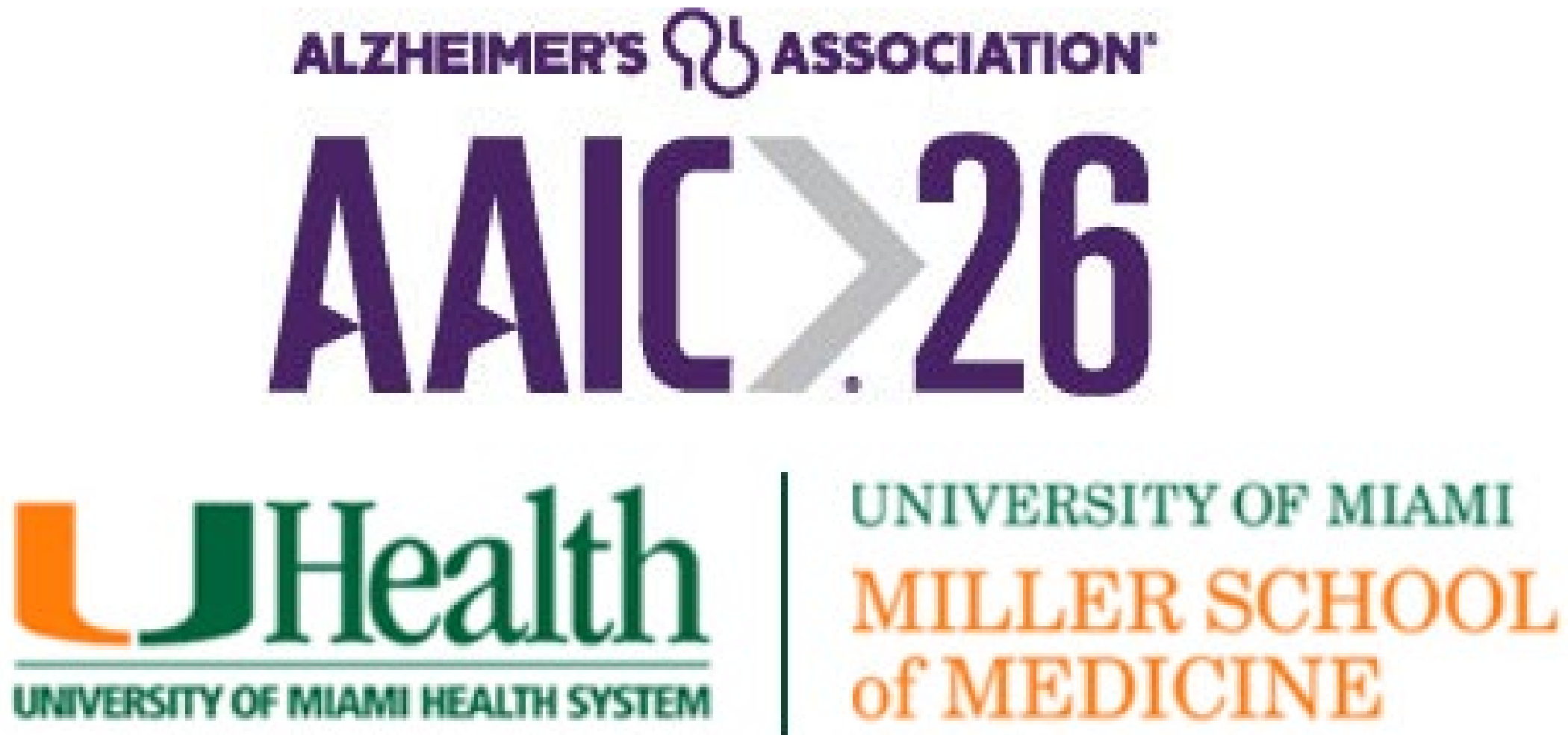


Blood DNA methylation signature of cognitive reserve moderates the association between CSF tau pathology and memory in prodromal Alzheimer’s disease

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Background

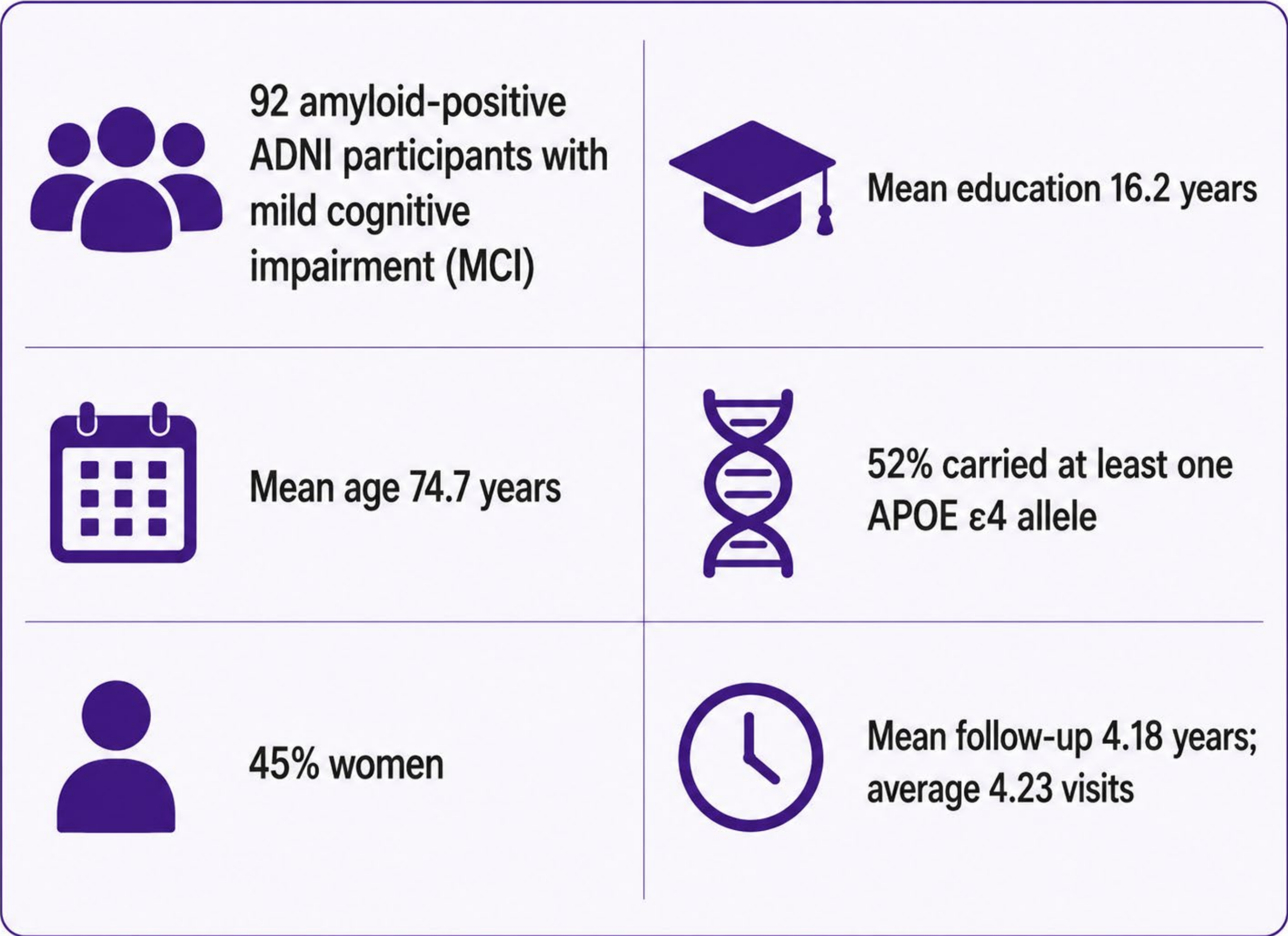
- Cognitive reserve (CR) reflects variability in cognitive adaptability that modifies the impact of Alzheimer’s disease (AD) pathology on cognition.
- We operationalized CR as memory reserve, defined by attenuation of the cerebrospinal fluid (CSF) phosphorylated tau (pTau181)-memory association.
- DNA methylation (DNAm) is influenced by both genetic and environmental factors, including lifestyle factors (e.g., smoking, diet, and exercise), which have been shown to contribute to CR.
- Our goal is to identify blood DNAm loci involved in memory reserve.

Methods

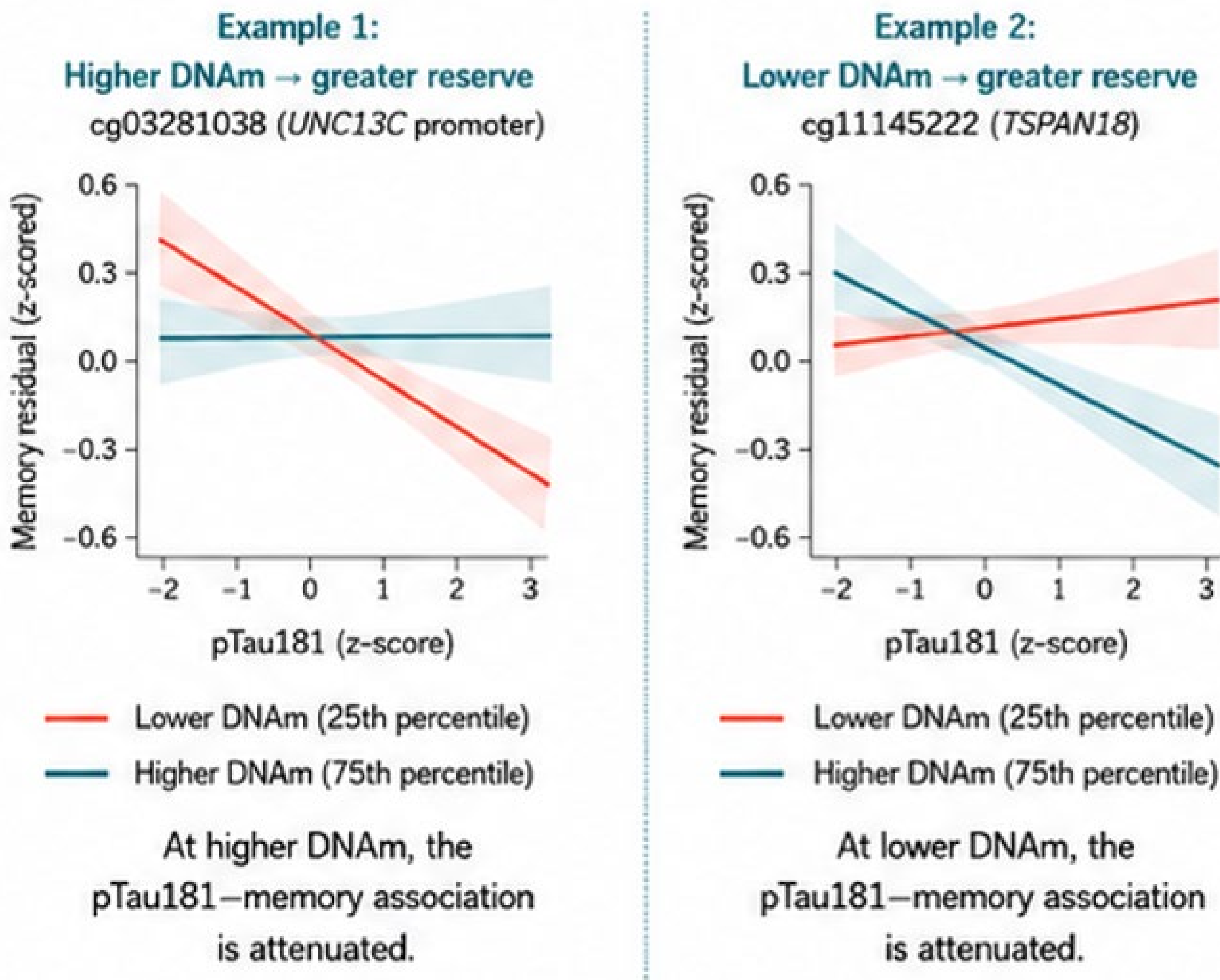
- 1 Blood DNAm + CSF pTau181 + PHC_MEM measured at same visit
- 2 Memory residualized for age, sex, APOE ε4, and immune cell proportions
- 3 Test genome-wide interaction model across 776,649 CpGs after QC
- 4 Identify DMRs with comb-p
- 5 Build methylation reserve score (MRS)
- 6 Test MRS against longitudinal memory decline in 88 participants with follow-up

Results

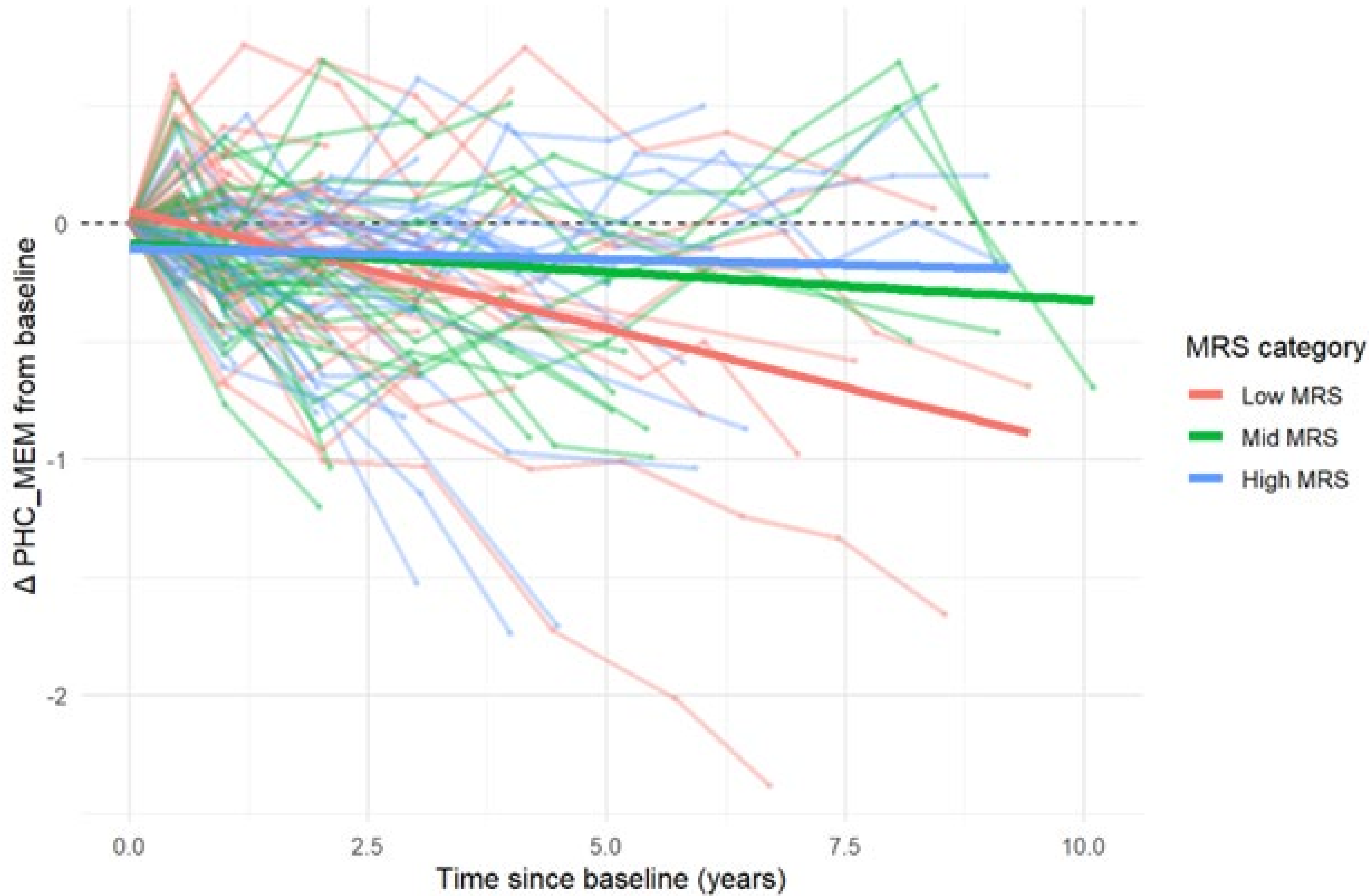
Study Cohort



$$\text{Memory residual} = \alpha + \beta \cdot \text{pTau181} + \tau \cdot \text{DNAm} + \gamma \cdot (\text{DNAm} \times \text{pTau181}) + \epsilon$$



Higher MRS is associated with slower memory decline



Conclusions

- Blood DNAm may capture biologically meaningful variation in memory reserve.
- In amyloid-positive MCI, a DNAm-based methylation reserve score attenuated tau-related memory impairment and was associated with slower subsequent memory decline

Support



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Nothing to disclose

Reference

Lukacsovich et al. (2026) Blood DNA methylation signature of cognitive reserve moderates the association between CSF tau pathology and memory in prodromal Alzheimer’s disease. *Alzheimer’s & Dementia: Translational Research & Clinical Intervention* 12:e70257