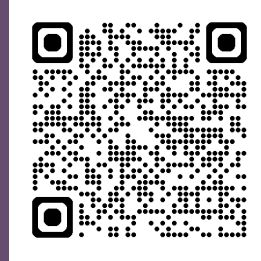


Genetic architecture of Alzheimer’s disease–related plasma biomarkers

Estimating unique and shared genetic effects using a multivariate twin design

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1 Introduction

Plasma biomarkers offer a scalable and affordable way to assess pathological changes. Alzheimer’s disease–related plasma biomarkers have been investigated in relation to other biomarkers, such as amyloid PET, but their interrelationships and the factors underlying these associations have received less attention.

Family designs allow disentangling genetic and environmental contributions to phenotypic variance, and a multivariate approach enables decomposition of phenotypic correlations into genetic and environmental components. Despite the relevance of phosphorylated tau in AD, only one previous study estimating the multivariate heritability of AD-related plasma biomarkers has included p-tau217, along with our previous study on the univariate heritability of p-tau217^{1,2}. These studies have yielded heritability estimates of 0.56 and 0.41–0.42^{1,2}.

We studied the **multivariate heritability of Alzheimer’s disease–related plasma biomarkers Aβ42/Aβ40, p-tau181, p-tau217, NfL and GFAP with classical twin design.**

2 Methods

The cross-sectional TWINGEN study included participants from the older Finnish Twin Cohort study³. Participants were 65–85 years old, and they were included irrespective of their co-twin’s participation. Individuals with a diagnosis of dementia-causing neurodegenerative disease were excluded. The data were gathered across Finland in 2023.

Plasma biomarkers were quantified with Simoa HD-X Analyzer. We used the Blom transformation to obtain rank-based inverse normalized biomarker values and regressed them on age and sex. Prior to model fitting, we calculated the phenotypic intraclass correlations (ICC) for MZ and DZ twin pairs.

First, we fitted an ACE model and compared it to a saturated model. Then, we fitted AE, CE and E sub-models by fixing the 1) C, 2) A and 3) C and A variance matrices to 0 and compared each sub-model to the full ACE model with likelihood ratio tests and Akaike information criteria (AIC) to select the best fitting model. We used full information maximum likelihood for model fitting and estimated the variance-covariance matrices freely.

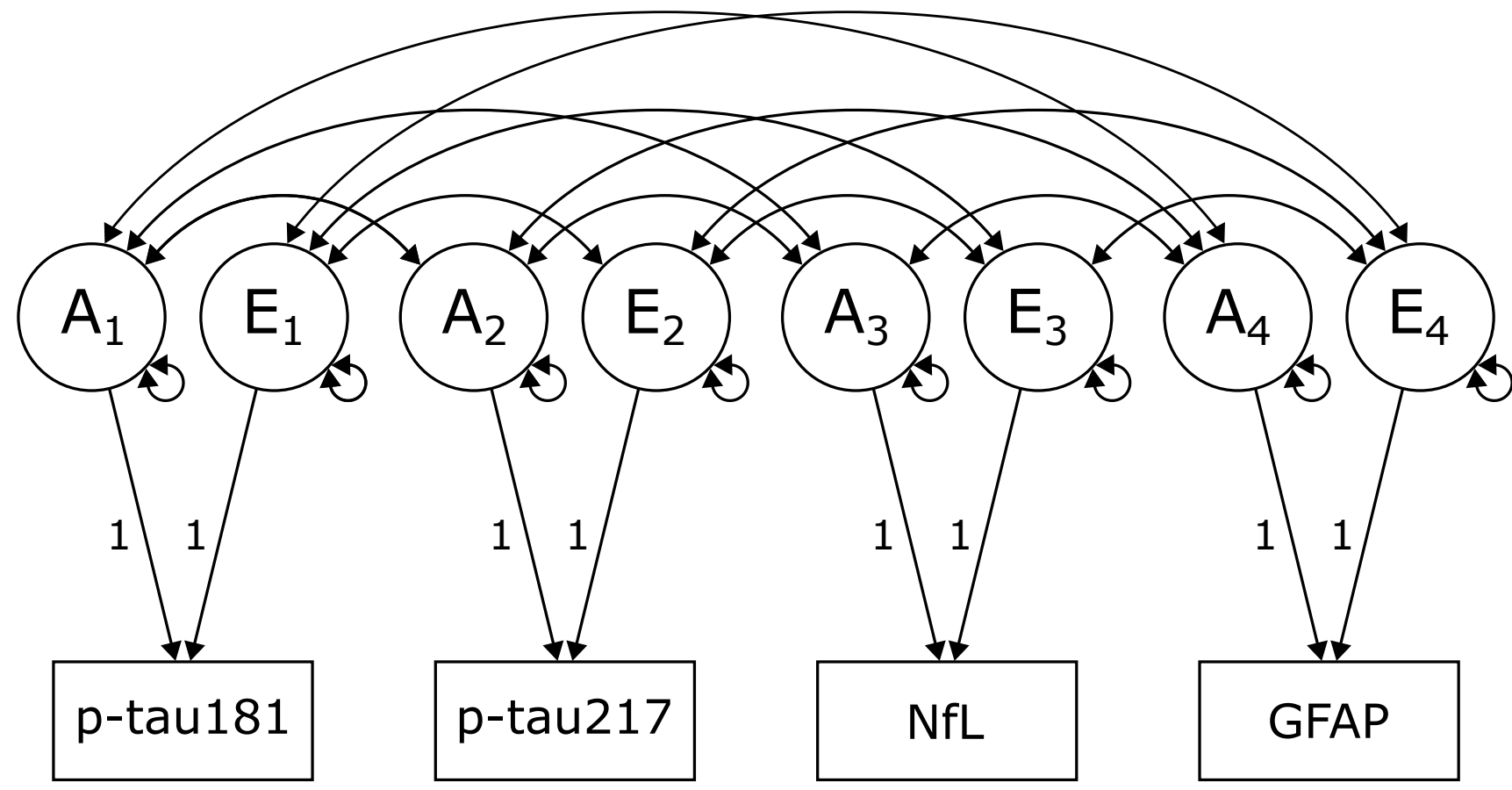


Figure 1. Multivariate AE model.

3 Results

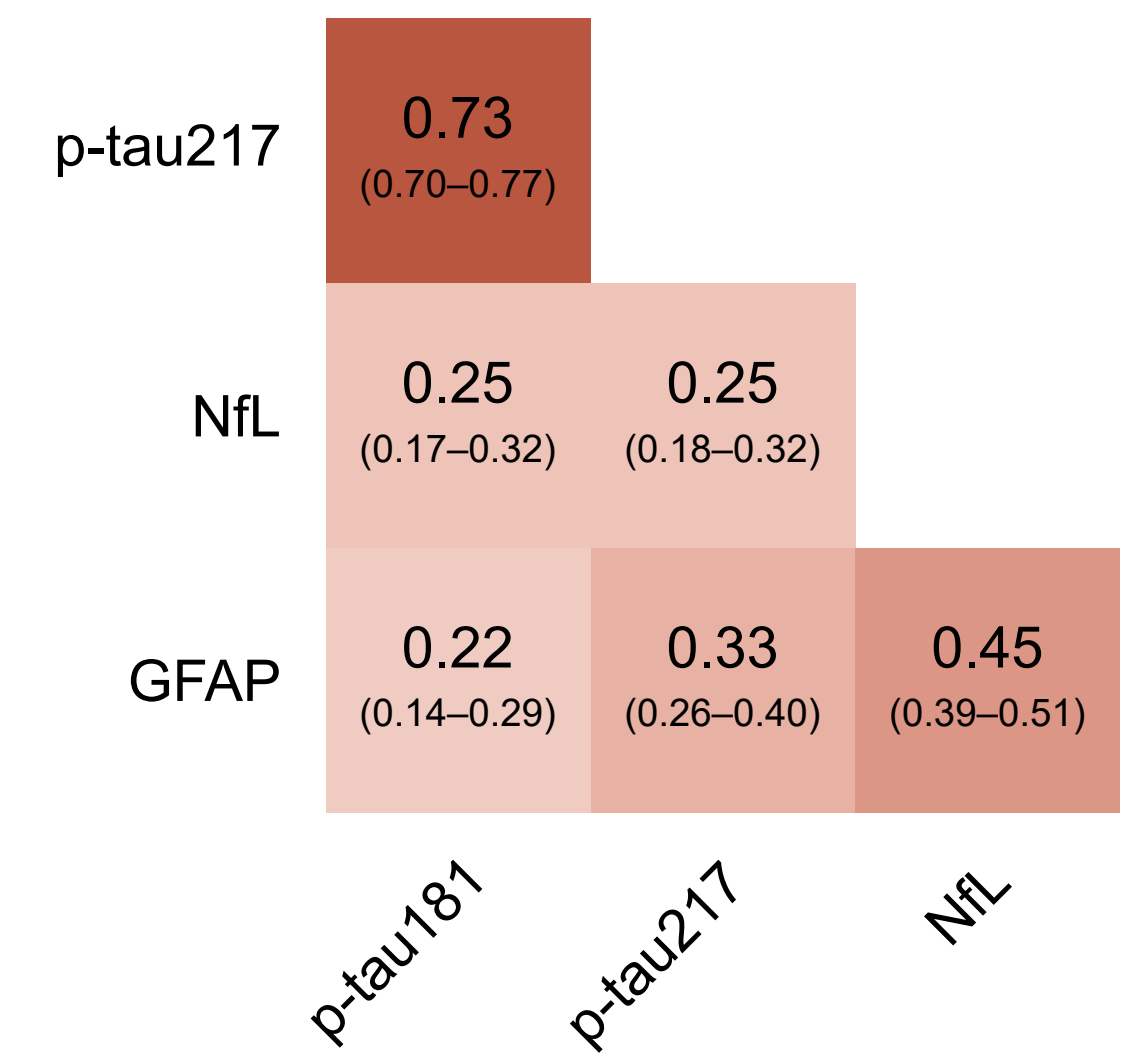


Figure 2. Model-implied phenotypic pairwise correlation estimates.

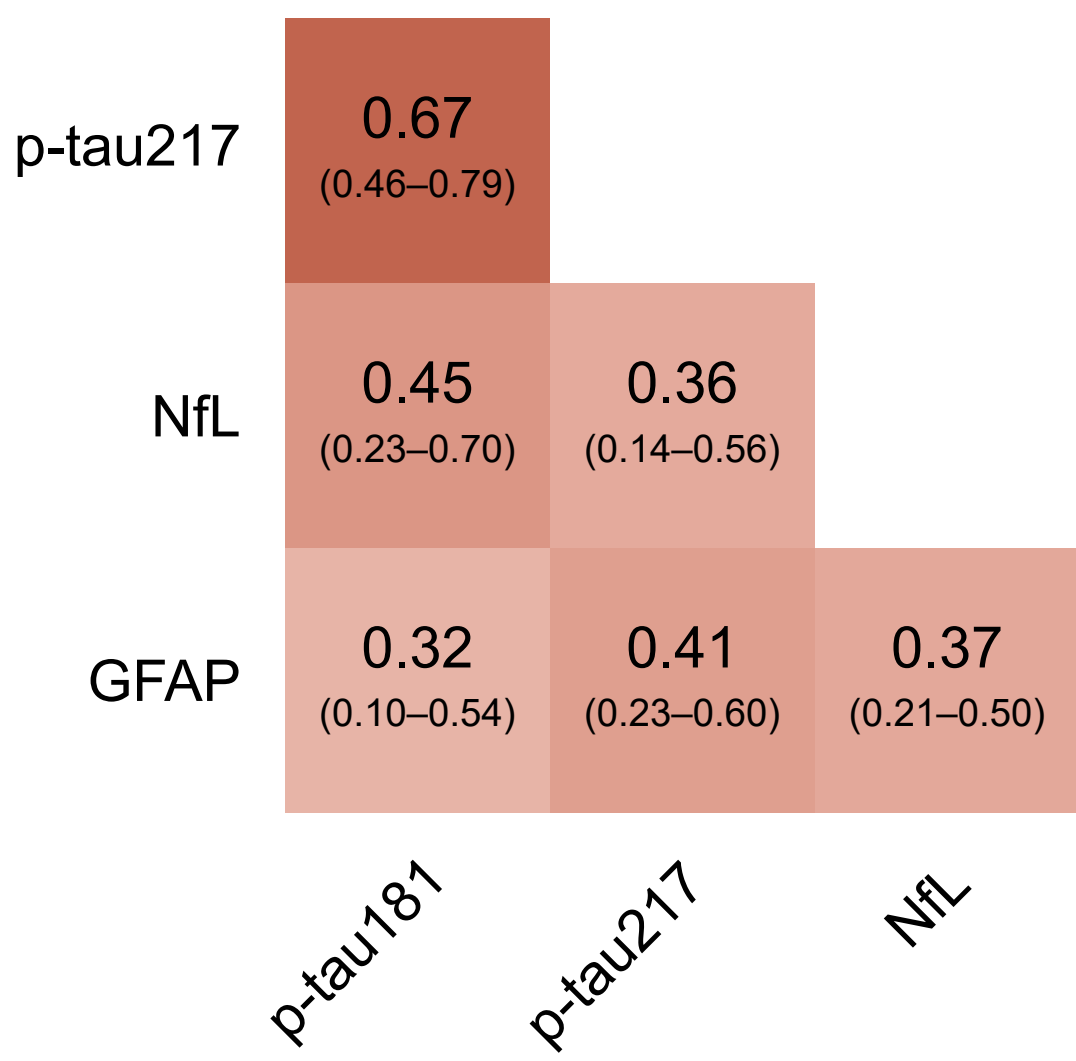


Figure 3. Model-implied estimates for pairwise correlations between the latent additive genetic components, reflecting how much same genes influence the biomarkers.

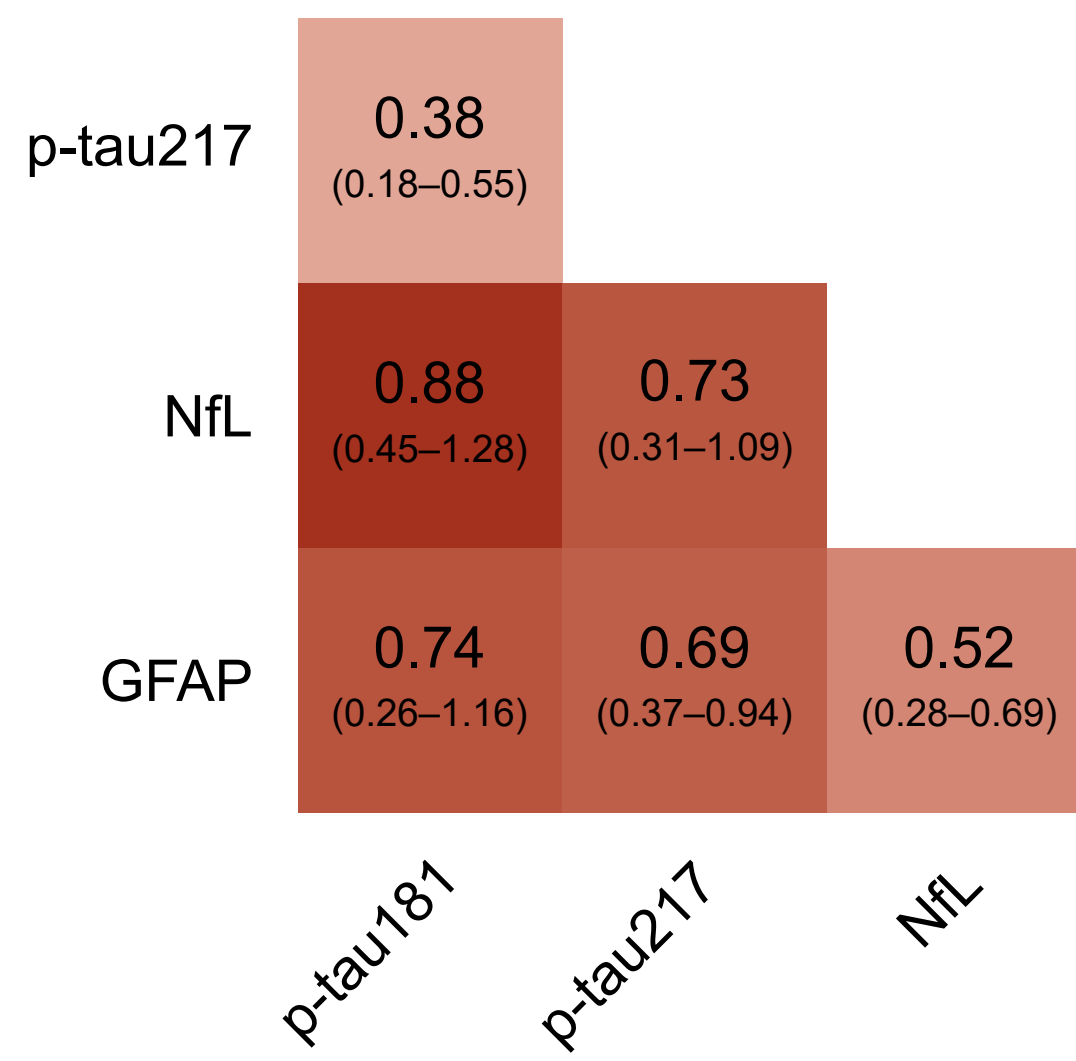


Figure 4. Model-implied estimates for proportions of covariance explained by the genetic correlations, reflecting how much of the covariance is attributable to the shared genetic factors as opposed to shared environmental factors.

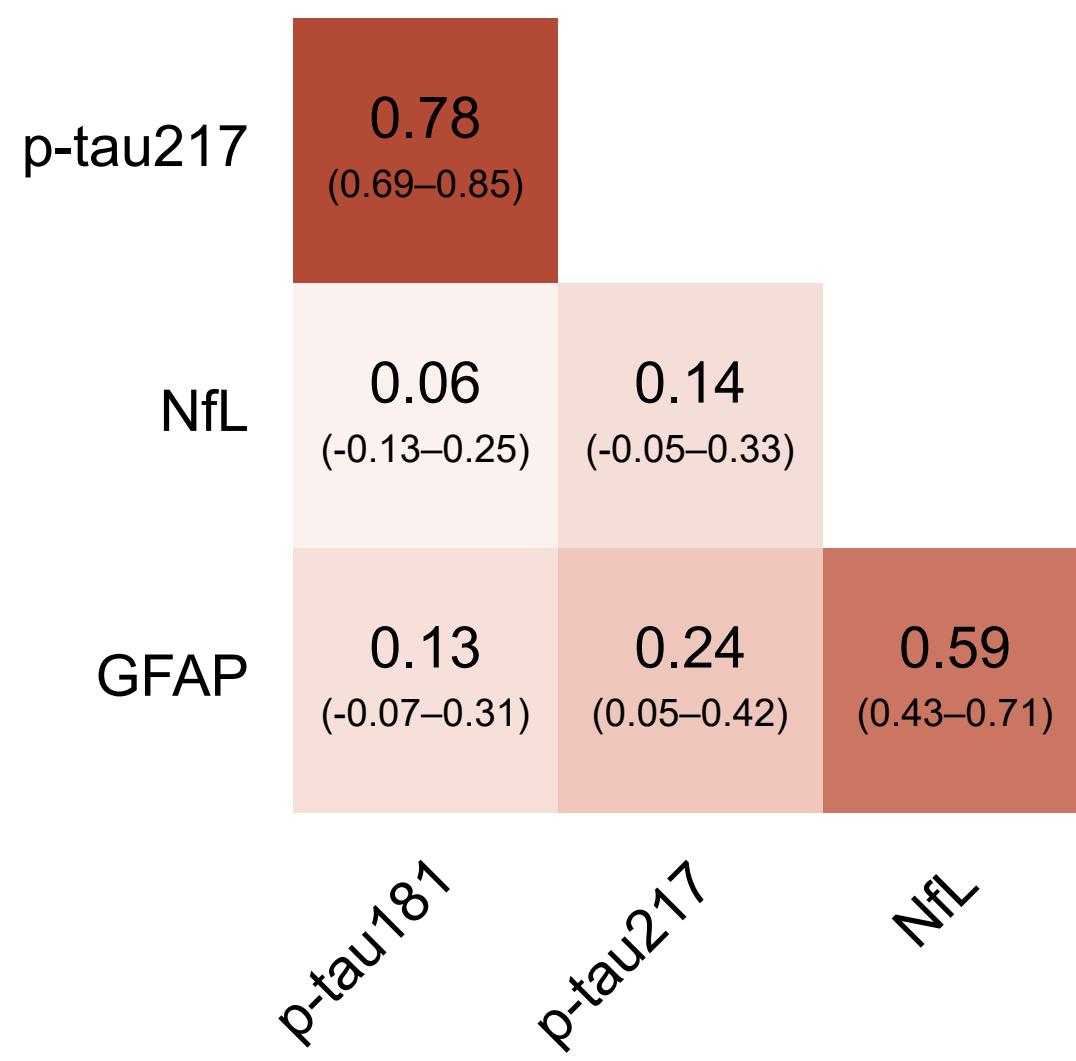


Figure 5. Model-implied pairwise correlation estimates between the latent unique environmental components, reflecting how much the same environmental factors influence the biomarkers.

There were 696 participants, including 153 full twin pairs (80 MZ and 73 DZ). Of the participants, 57.18% were female and 29.21% were APOE ε4 carriers. Mean age (SD) was 76.17 (4.57) years.

We observed higher Aβ42/Aβ40 ICCs for DZ pairs than for MZ pairs, a pattern inconsistent with the assumptions of ACE model, where MZ twin pairs should have higher ICCs in the presence of genetic effects and equal ICCs in the absence of them. Therefore, we excluded Aβ42/Aβ40 from the models.

Table 1. Standardized estimates for additive genetic (A) and unique environmental (E) variance components.

Biomarker	A (95% CI)	E (95% CI)
p-tau181	0.39 (0.22–0.53)	0.61 (0.47–0.78)
p-tau217	0.45 (0.29–0.59)	0.55 (0.41–0.71)
NfL	0.59 (0.46–0.70)	0.41 (0.30–0.54)
GFAP	0.66 (0.54–0.75)	0.34 (0.25–0.46)

First, we fitted the ACE model and compared it to the saturated model with means, variances and covariances freely estimated. The model fit was not significantly worse ($\chi^2_{242} = 46.06$; $p = 0.3079$; $\Delta AIC = -37.94$).

Next, we fit the AE, CE and E sub-models. The AE model did not show statistically significant worsening of fit compared to the ACE model ($\chi^2_{210} = 5.10$, $p = 0.885$; $\Delta AIC = -14.89$), unlike the CE and E sub-models, that fit significantly worse. Subsequently, **the AE model was chosen as the best fitting model** (Figure 1).

The phenotypic associations between plasma biomarkers varied from 0.22 to 0.73 (Figure 2) and the **heritability estimates were 0.39–0.66** (Table 1). Genetic and environmental correlations are presented in Figures 3–5.

4 Conclusion

The heritability of plasma biomarkers p-tau181, p-tau217, NfL and GFAP ranged from 0.39 to 0.66. All biomarkers had pairwise genetic associations, and several, but not all, biomarkers had environmental associations.

The results from our study indicate that in older individuals without a diagnosis of AD, plasma biomarkers reflecting different underlying AD-related pathological changes have **weak to moderate phenotypic associations, and these associations are more driven by genetic than environmental factors**. Interestingly, while p-tau181 and p-tau217 had strong genetic and environmental correlations, neither approached unity, implying unique genes and environmental factors behind these markers, that should be considered for future GWASs and studies on risk factors.

Our results offer insight into disease-specific and progression markers of Alzheimer’s disease and inform future research examining which specific genetic and environmental factors are shared and unique to each plasma biomarker, helping uncover etiological mechanisms underlying Alzheimer’s disease pathology.

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