Biological and methodological factors underlying a continuous amyloid CSF/PET imbalance model and its association with longitudinal cognition

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Background

- Discordance between CSF and PET Aβ occurs in 10-20% of the AD *continuum*
- Biomarker discordance might reflect the imbalance between soluble and aggregated Aβ pools
- To date, models characterizing discordance have been suboptimal (i.e., dichotomizing discordance)

Aims

1) To develop a continuous measure of Aβ CSF/PET imbalance
2) To investigate biological and methodological factors that contribute to imbalance
3) To examine the predictive value of imbalance on cognition

Methods

Sample
Discovery 261 CU and 561 CI ADNI participants
Validation 326 CU and 57 MCI AMYPAD-PNHS participants

Continuous CSF/PET imbalance model (aim 1)
Hyperbolic regression models between CSF-Aβ42 and global amyloid-PET (CL). Standardized residuals as **Aβ-aggregation scores** (negative = more soluble relative to aggregated Aβ, positive = more aggregated relative to soluble Aβ).

Statistical analyses (aim 2 and 3)
Linear regression models predicting Aβ-aggregation score
- Methodological factors (Δt CSF-PET & ventricular volume)
- Demographics (age, sex, education, APOE-ε4 alleles)
- CSF biomarkers (p-tau, t-tau, Aβ38, Aβ40)
- Vascular burden (WMH volumes)

Adjusted for a model-derived measure of Aβ-progression and ventricular volume. Models of CSF biomarkers and vascular burden were additionally adjusted for age, sex, APOE-ε4 alleles.

Linear regressions and mixed models were performed to predict cognition with Aβ-aggregation scores, covarying for age, sex, education, APOE-ε4 alleles, ventricular volume, and Aβ-progression

Demographics

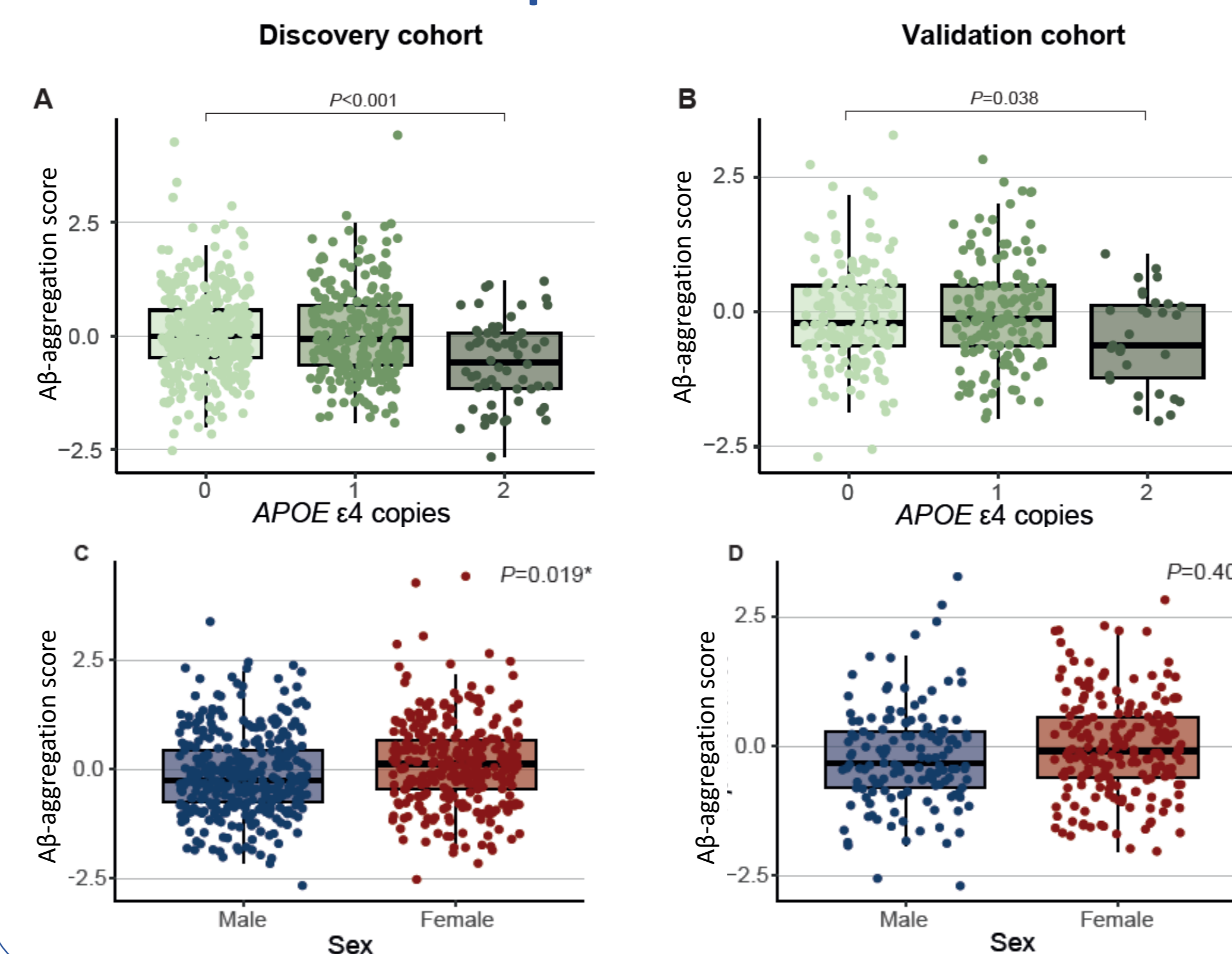|	Discovery cohort	Validation cohort
N	822	383
Age	73.0 (7.4)	65.2 (6.9)
Female, n (%)	384 (46.7)	224 (58.5)
Years of education	16.3 (2.6)	14.6 (3.8)
MMSE score	27.6 (2.6)	28.9 (1.5)
Missing, n (%)	0 (0.0)	17 (4.4)
APOE-ε4 copies, n (%)		
0	451 (54.9)	189 (49.3)
1	293 (35.6)	159 (41.5)
2	78 (9.5)	33 (8.6)
Missing, n (%)	0 (0.0)	2 (0.5)
Interval CSF/PET (days)	0.19 (17.1)	95.3 (123.6)
CSF-Aβ42,*	1200 (631)	-0.6 (1.3)
Global amyloid (CL)	40.3 (44.1)	17.4 (27.8)

* Raw values are shown for the discovery cohort, z-scores for the validation cohort

Continuous model of CSF/PET imbalance
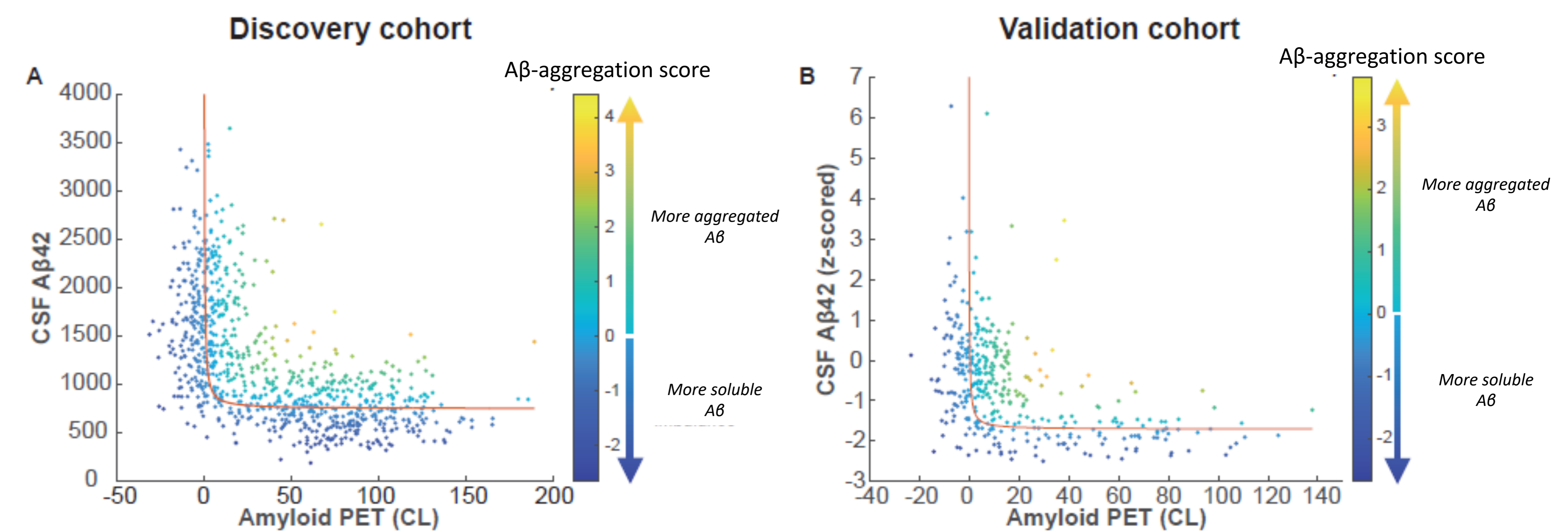
Adequate model fit in both cohorts (R²=0.94) illustrates the applicability across heterogeneous datasets. A wide range of Aβ-aggregation scores are observed across the hyperbolic model, indicating that imbalance permeates the entire Aβ accumulation process, with a similar Aβ-aggregation range across cohorts

## *APOE*-ε4 carriership and sex are associated with Aβ-aggregation scores

In the discovery cohort, Aβ-aggregation was negatively related to carrying 2 *APOE*-ε4 alleles (**A.** β=-0.56), and male sex (**C.** β=-0.18). In addition, a lower Aβ-aggregation score was associated with larger ventricles and lower concentrations of CSF biomarkers (not shown).

Results of *APOE* (**B.** β=-0.41) and CSF biomarkers were replicated in the validation cohort.

Aβ-aggregation score predicts longitudinal cognition

At baseline, higher Aβ-aggregation scores were predictive of better cognitive performance in both cohorts.
Higher Aβ-aggregation scores were predictive of slower cognitive decline over time on MMSE in the discovery cohort (**A.** β=0.13) and on a categorical fluency test in the validation cohort (**B.** β=0.04).
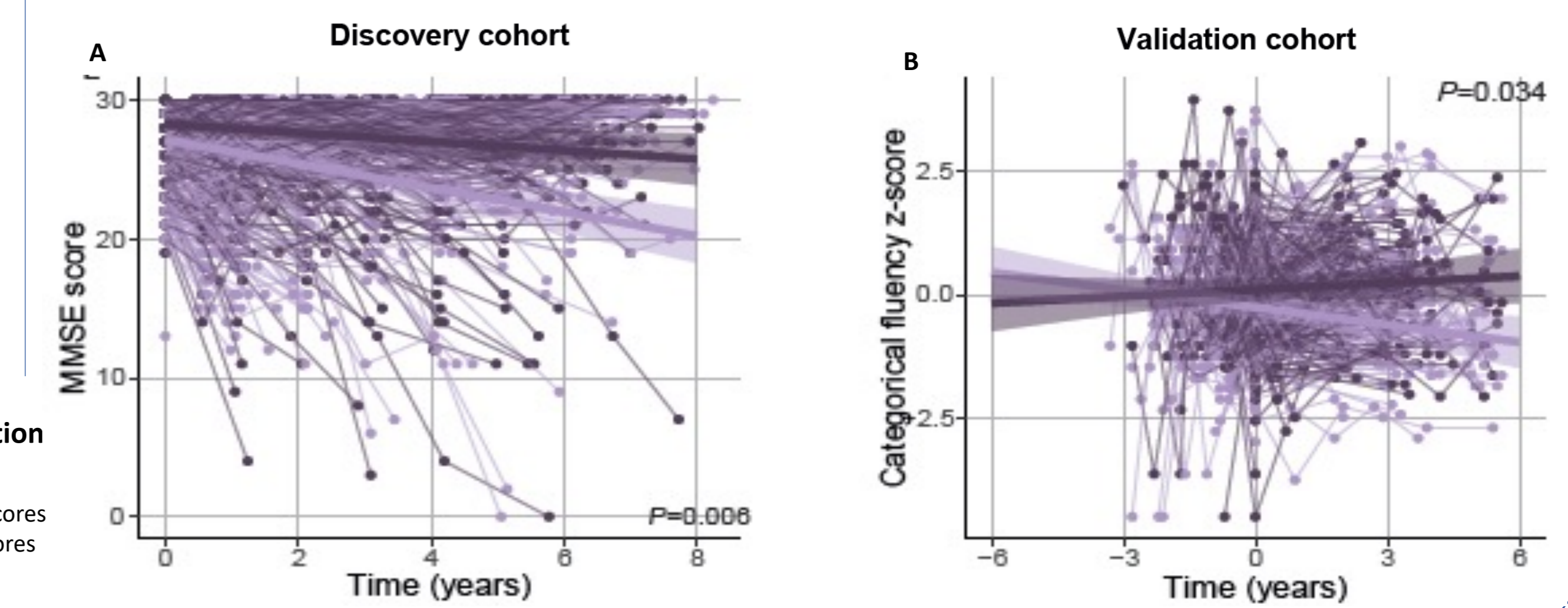
Conclusion

A continuous measure of soluble/aggregated Aβ biomarker imbalance was consistently associated with genetic risk, AD-associated CSF biomarkers, and cognition, possibly reflecting disease heterogeneity.

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