

A Plasma Biomarker–based Cognitive Reserve Predicts Progression in Alzheimer’s Disease

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A plasma pTau217-derived cognitive reserve index may help identify individuals with relatively preserved clinical trajectories within the amyloid-positive AD spectrum, particularly at the MCI stage.

INTRODUCTION

- **Cognitive Reserve (CR):** Brain's capacity to tolerate pathology without clinical decline.
- **Traditional CR Proxies:** Education, occupation, and cognitive activities (indirect).
- **Residual-Based CR:** Quantifies the mismatch between *observed cognition* and *predicted cognition* based on AD pathology.
- **New Approach:** Plasma pTau217 may enable a scalable biomarker-based CR index.
- **Objective:** Investigated if p-tau217-derived CR predicts functional decline and clinical progression in amyloid-positive AD-spectrum participants.

METHODS

- Cohort: 611 amyloid-positive K-ROAD participants (CU–MCI–DAT) with plasma biomarkers and longitudinal CDR-SB follow-up.
- CR index: residual from a model predicting MMSE from log-transformed pTau217, Aβ ratio, age, sex, and education.
- Outcomes: CDR-SB trajectories and progression from global CDR 0.5 to 1, with models adjusted for age, sex, education, APOE ε4, and baseline CDR-SB.

RESULTS

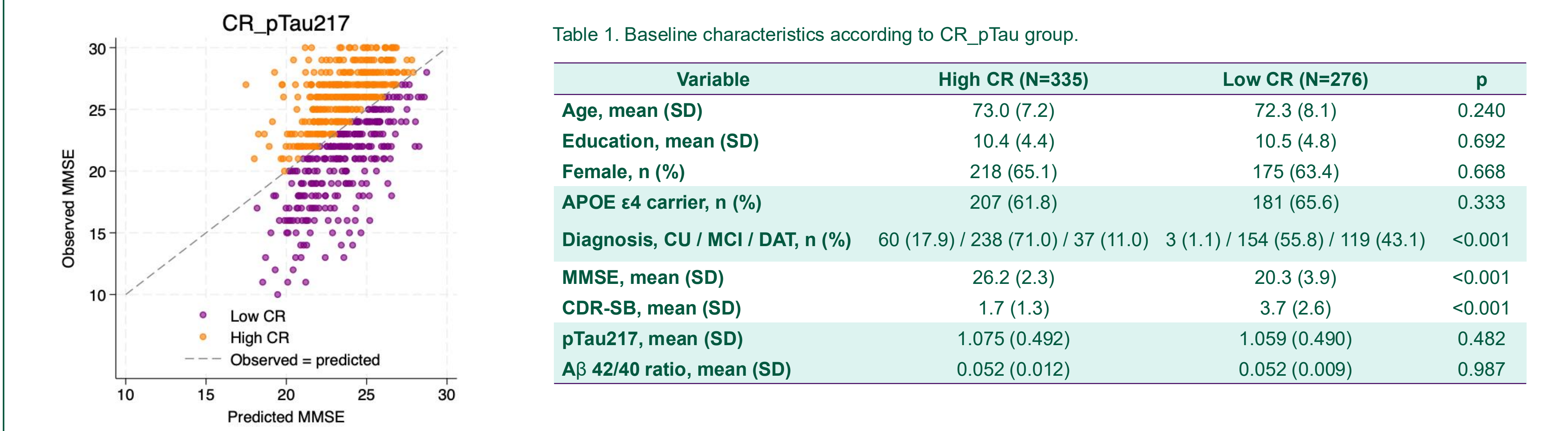


Table 1. Baseline characteristics according to CR_pTau group.

Variable	High CR (N=335)	Low CR (N=276)	p
Age, mean (SD)	73.0 (7.2)	72.3 (8.1)	0.240
Education, mean (SD)	10.4 (4.4)	10.5 (4.8)	0.692
Female, n (%)	218 (65.1)	175 (63.4)	0.668
APOE ε4 carrier, n (%)	207 (61.8)	181 (65.6)	0.333
Diagnosis, CU / MCI / DAT, n (%)	60 (17.9) / 238 (71.0) / 37 (11.0)	3 (1.1) / 154 (55.8) / 119 (43.1)	<0.001
MMSE, mean (SD)	26.2 (2.3)	20.3 (3.9)	<0.001
CDR-SB, mean (SD)	1.7 (1.3)	3.7 (2.6)	<0.001
pTau217, mean (SD)	1.075 (0.492)	1.059 (0.490)	0.482
Aβ 42/40 ratio, mean (SD)	0.052 (0.012)	0.052 (0.009)	0.987

- MCI: High CR was associated with slower CDR-SB worsening ($\beta = -0.352$, $p = 0.004$); not significant in AD dementia.
- Progression: High CR was associated with lower risk of CDR 0.5→1 progression (HR = 0.61, 95% CI 0.45–0.84, $p = 0.002$).

CONCLUSION

- pTau217-derived CR was associated with longitudinal CDR-SB change in MCI, but not significantly in AD dementia.
- Higher CR was also associated with lower risk of progression from global CDR 0.5 to 1.
- Further validation in independent cohorts is needed to clarify the utility of plasma biomarker–derived CR in early symptomatic AD.

KEY NUMBERS

611
amyloid-positive participants

54.8%
classified as High CR

HR 0.61
progression risk (CDR 0.5→1) in High CR group

$\beta -0.35$
CDR-SB slope in High CR group (MCI, $p=0.004$)

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