

Longitudinal prognostic value of brain-derived and total plasma pTau biomarkers for amyloid and clinical progression in ADNI

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INTRODUCTION

Background

- Plasma phosphorylated tau biomarkers are increasingly used for Alzheimer's disease detection, treatment decision-making, and clinical trial enrichment.¹⁻³
- Brain-derived pTau217 assays selectively measure CNS-type tau species and may improve cross-sectional diagnostic performance compared with total pTau217.³⁻⁵
- Whether this improved diagnostic performance translates to better longitudinal prediction of future disease progression remains unclear.³⁻⁵
- Prognostic performance may differ by outcome, as amyloid PET progression more directly reflects biological AD progression, whereas clinical progression reflects downstream cognitive change influenced by multiple factors.^{6,7}

Study aims

- Compare the prognostic performance of baseline brain-derived and total plasma pTau biomarkers for predicting future amyloid PET progression.
- Evaluate time-dependent discrimination of plasma biomarkers for A- to A+ progression across follow-up intervals.
- Determine whether brain-derived pTau217 provides added prognostic value for clinical progression from CU to MCI/AD.

Figure 1. Study overview

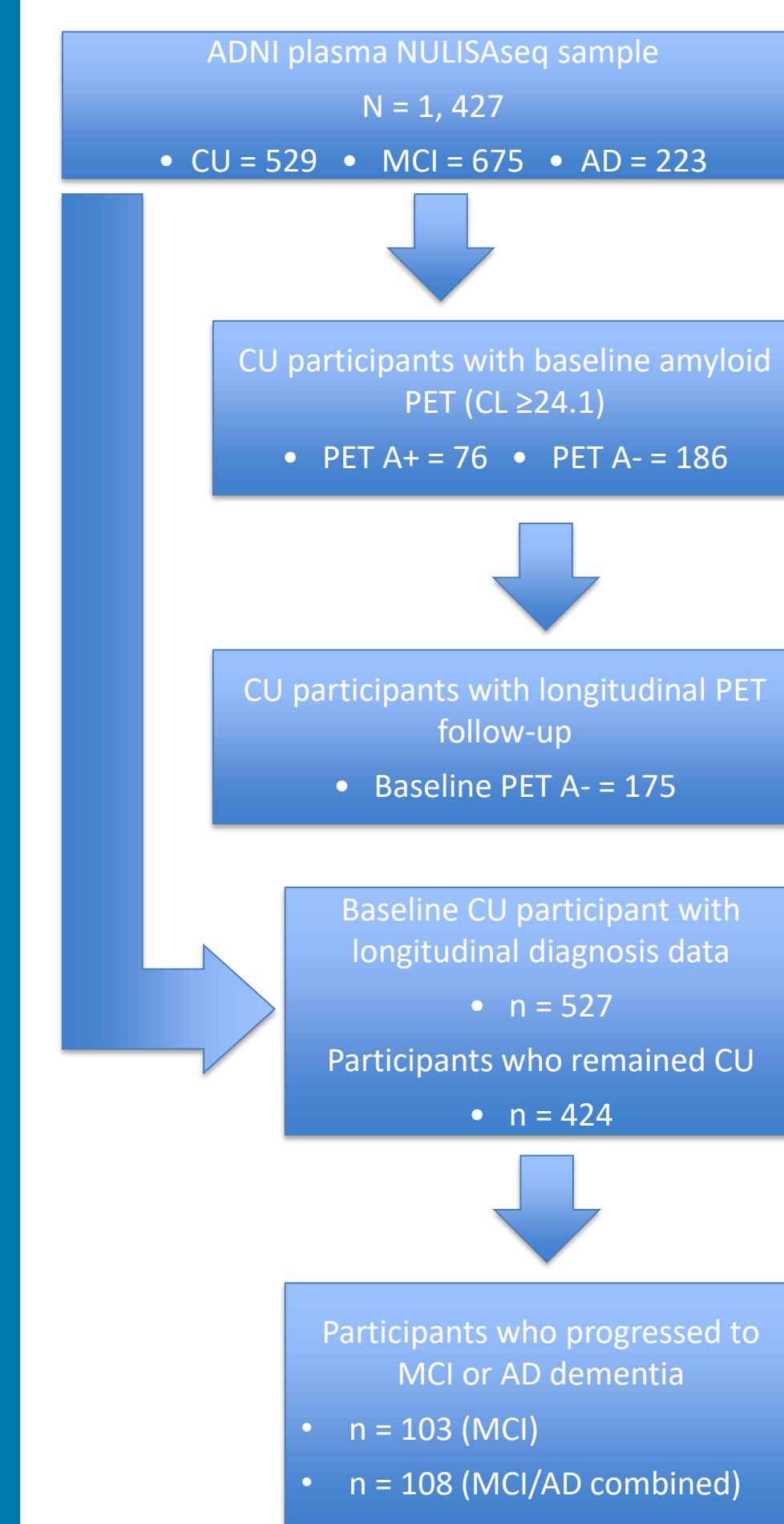


Figure 2. BD-pTau217 best predicts amyloid PET progression

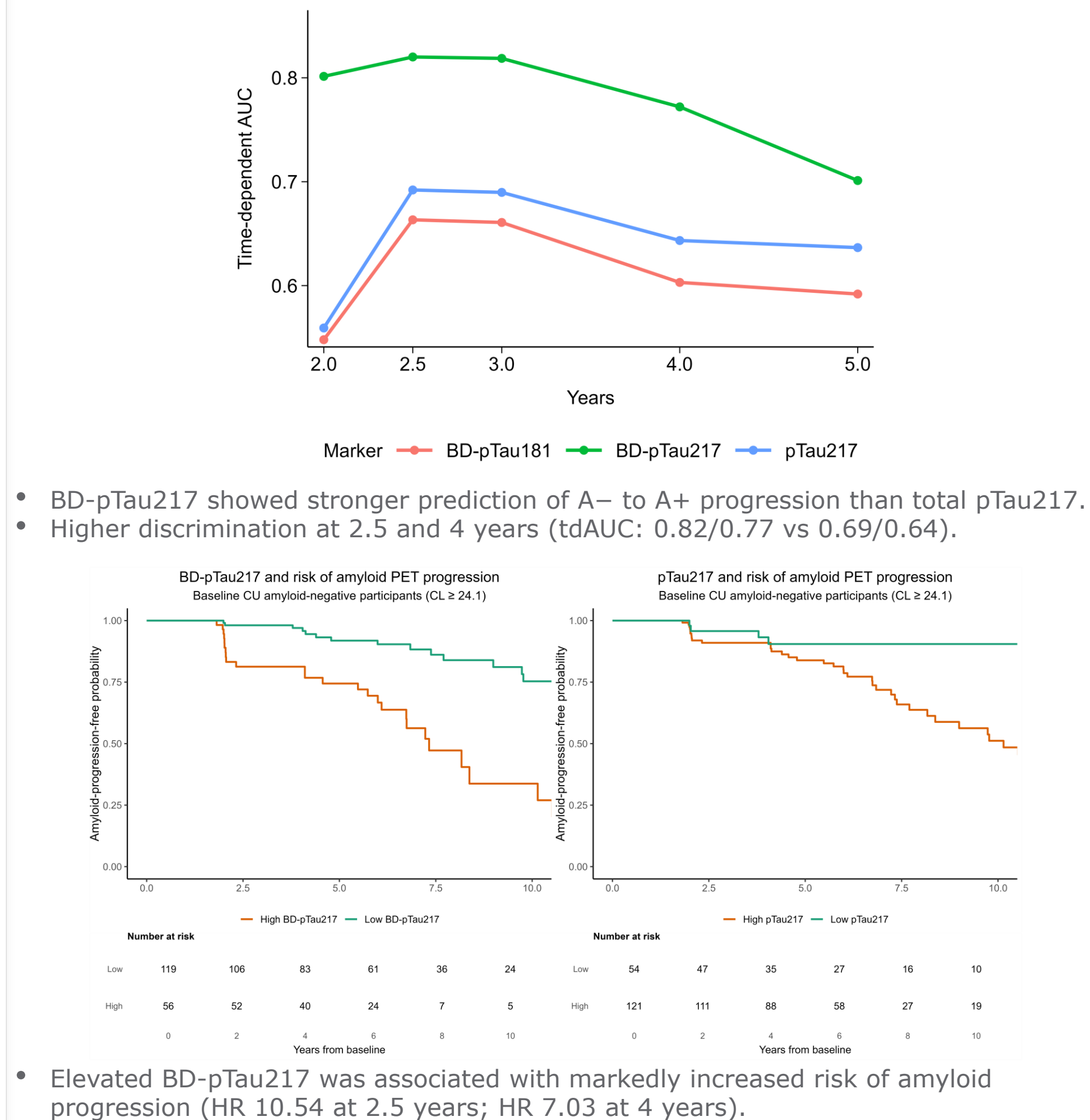
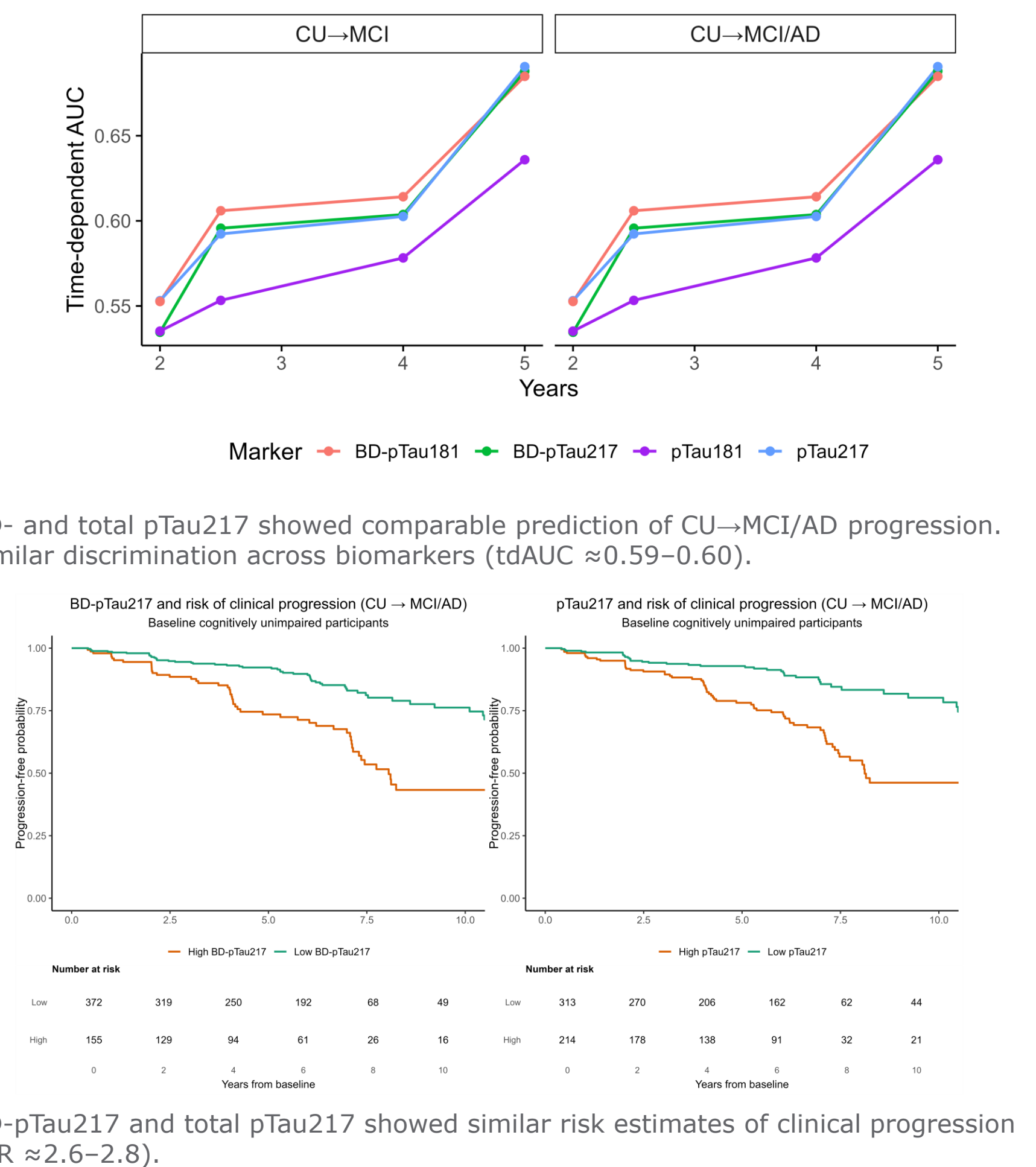


Figure 3. Similar prediction of clinical progression



METHODS

Study Design

- Longitudinal observational analysis of ADNI1/GO/2/3 participants with baseline plasma NULISaseq measurements.
- Baseline plasma biomarkers were evaluated as predictors of:
 - Amyloid PET progression from A- to A+.
 - Clinical progression from CU to MCI / AD dementia.

Participants / Samples

- ADNI1/GO/2/3 participants with plasma NULISaseq CNS panel data.
- Total sample: N = 1,427.
- Cognitively unimpaired subset: N = 529.
- Participants included CU, MCI, and AD dementia diagnostic groups.

Measurements

- Plasma biomarkers: BD-pTau217, total pTau217, BD-pTau181.
- Longitudinal amyloid PET and clinical follow-up.
- Amyloid PET positivity: Centiloid ≥ 24.1.^{6,7}

Statistical Analysis

- Cox regression, Kaplan-Meier analyses, and time-dependent AUCs.

CONCLUSION / DISCUSSION

Conclusions

- We report one of the first large-scale comparisons of brain-derived versus total plasma pTau217 for longitudinal disease progression in ADNI.
- Plasma pTau217 biomarkers provided prognostic information for both biological and clinical progression.
- BD-pTau217 showed stronger prediction of future amyloid PET progression than total pTau217, supporting greater specificity for early AD pathological change.
- In contrast, BD-pTau217 and total pTau217 showed similar performance for clinical progression from CU to MCI/AD.
- These findings suggest that BD-pTau217 may be particularly useful for identifying A- individuals at risk of near-term amyloid PET progression and for enriching early-stage AD clinical trials.

Take-home message

- BD-pTau217 improved prediction of future amyloid PET progression.
- BD-pTau217 and total pTau217 showed similar prediction of clinical progression.
- Brain-derived pTau217 may be most useful for early biological risk stratification.

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