

Stage-dependent Prognostic Utility of Amyloid and Tau PET Across Cognitive Trajectories In Alzheimer's Disease

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Background

- Amyloid- and tau-PET quantify Alzheimer's disease pathology in vivo and are increasingly used to stage disease and stratify clinical risk^{1,2}, but biomarker-positive cognitively unimpaired adults show highly variable cognitive and functional trajectories.
 - Amyloid positivity is common in cognitively unimpaired older adults, so biomarker positivity alone may be insufficient to identify near-term clinical risk; short-term amyloid associations are inconsistent, while tau and combined amyloid–tau positivity may be more closely linked to decline^{3,4}.
 - Prior PET prognostic studies⁵ often pooled all baseline cognitively unimpaired participants, which may obscure heterogeneity; observed PET–decline associations may be disproportionately driven by the minority who later convert to MCI or dementia.
- We use longitudinal ADNI amyloid- and tau-PET data to test whether baseline PET burden predicts cognitive and functional decline differently across clinical trajectories: stable cognitive unimpaired (CU), CU-to-MCI/dementia Converters, and cognitively impaired (CI) participants.
- We examine whether concomitant markers of neurodegeneration, vascular burden, and neuroinflammation, together with baseline clinical/demographic measures, can explain trajectory heterogeneity and improve enrichment strategies for preclinical AD prevention trials.

Methods

Cohort: Longitudinal ADNI participants with baseline amyloid-PET (n = 1,286) and/or tau-PET (n = 642) plus follow-up ADAS-13 and/or CDR-SB assessments.

Clinical trajectories: Participants were classified as stable CU, Converters (CU to MCI/dementia), or CI; Converter follow-up was restricted to visits before diagnosis conversion.

PET measures: Amyloid burden was harmonized as Centiloids; tau burden was quantified as meta-temporal SUVR; AT profiles used cutoffs of Centiloid ≥ 24 and SUVR ≥ 1.23 .

Primary models: Linear mixed-effects models tested PET $\times$ time associations with ADAS-13 and CDR-SB within each trajectory group, adjusting for age, sex, and APOE $\epsilon 4$ status.

Secondary analyses: Concomitant markers — hippocampal volume, FDG-PET, WMHI, plasma GFAP, and NfL — were compared across trajectory/amyloid-status groups; logistic regression tested baseline clinical predictors of conversion.

Discussion

- Amyloid/tau PET prognostic value was not uniform across baseline CU individuals; near-term PET–decline associations were largely absent in stable CU, modest in Converters, and strongest after clinical impairment.
- Significant associations in pooled CU analyses appear to be driven by the Converter minority, suggesting that biomarker-positive CU participants include many individuals unlikely to decline within typical trial windows.
- Concomitant markers, especially hippocampal volume and WMHI, may help explain why some biomarker-positive individuals progress while others remain clinically stable.
- Results should be interpreted as near-term prognostic findings; stable CU participants may still progress later.

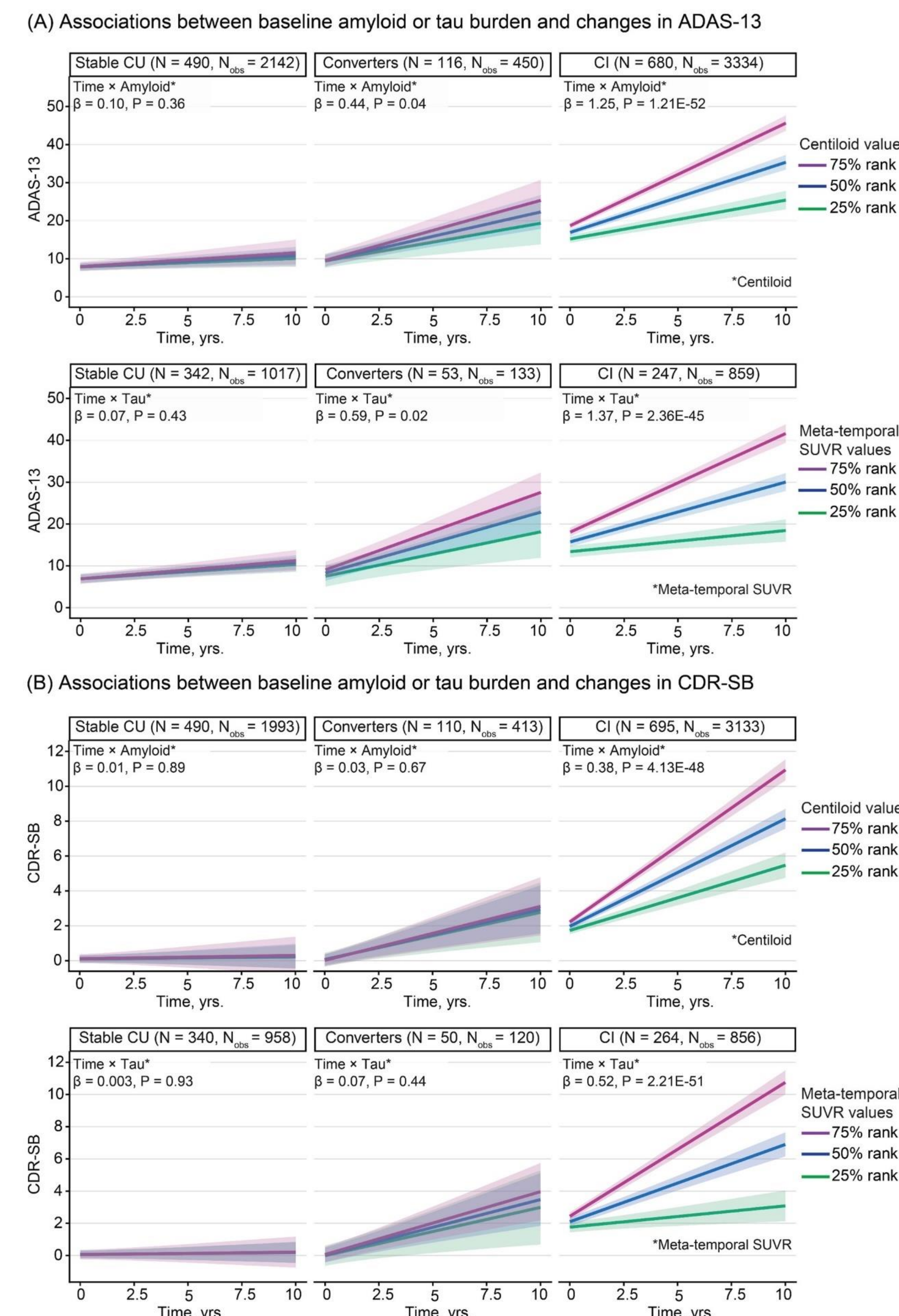


Figure 1. Stage-dependent PET associations with cognitive and functional decline. Predicted 10-year ADAS-13 and CDR-SB trajectories are shown across stable CU, Converters, and CI groups at low, median, and high amyloid or tau burden. Baseline amyloid and tau PET were not associated with decline in stable CU participants; in Converters, higher PET burden predicted modestly faster ADAS-13 worsening but not CDR-SB change; in CI, both amyloid and tau strongly predicted faster cognitive and functional decline.

Results

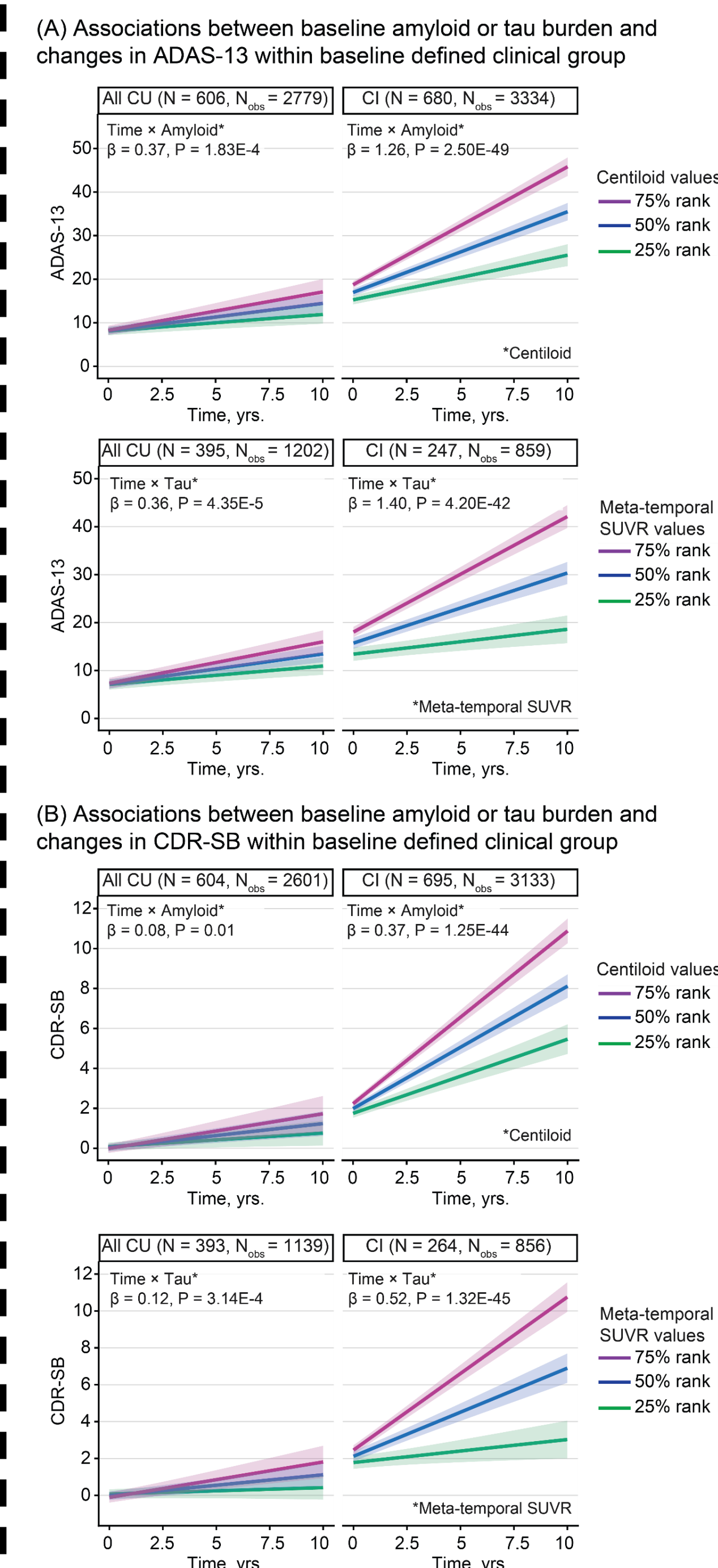


Figure 2. Pooled CU analyses amplify PET–decline associations. When stable CU and Converters were analyzed together as baseline CU, amyloid/tau PET appeared to predict decline, suggesting that pooled CU associations are largely driven by the progressing minority.

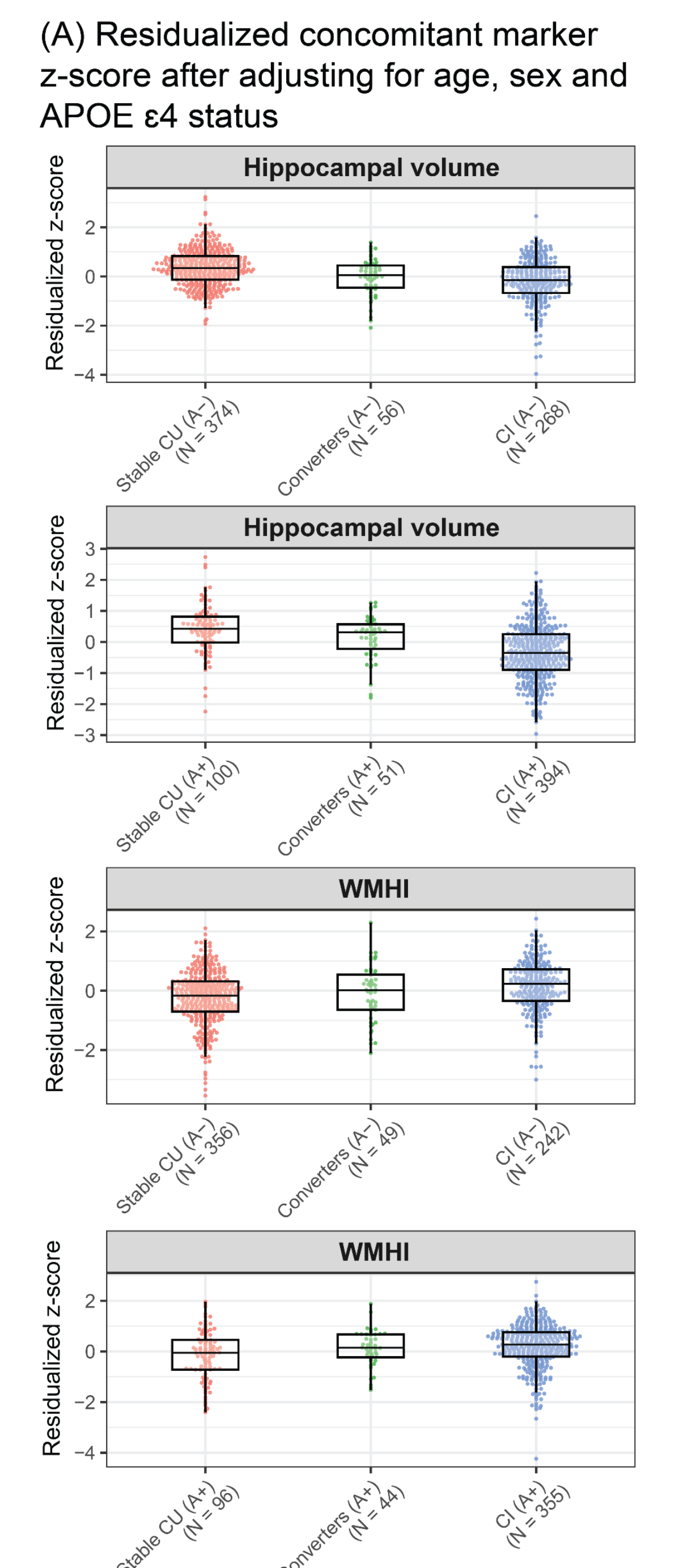


Figure 3. Concomitant markers differ by trajectory and amyloid status. Residualized hippocampal volume and WMHI z-scores show complementary neurodegenerative and vascular differences across stable CU, Converter, and CI groups, especially among amyloid-positive participants.