

Longitudinal clinical and pathological progression across amyloid and tau PET–based Alzheimer’s disease biological stages

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STUDY OVERVIEW

Overall aim:

Characterize longitudinal progression of PET-based AD biological stages and determine their prognostic value for future clinical decline.

Aim 1. Characterize longitudinal progression of PET-defined biological stages.

Aim 2. Determine whether baseline biological stage predicts future clinical progression.

Study sample:

N = 2,040 ADSP-PHC participants from ADNI, HABS-HD, KBASE, Knight ADRC, NACC, and WRAP who underwent amyloid and tau PET and longitudinal clinical assessments (≥ 2 visits and ≥ 1 year of follow-up).

Participant Characteristics

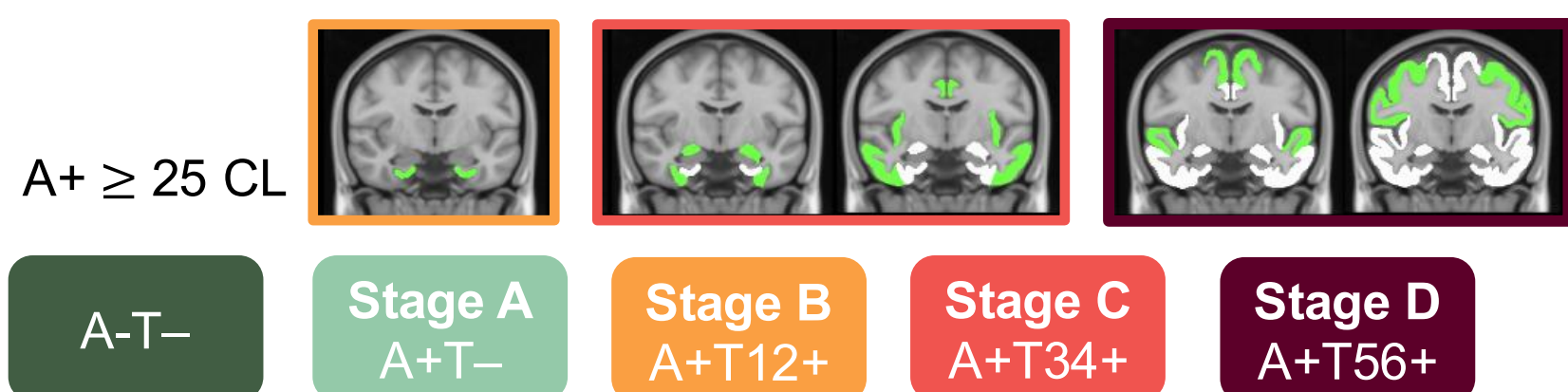
Baseline PET Age, yrs	70.2 (8.4)
Female	1,188 (58%)
APOE $\epsilon 4$ carrier ^a	709 (38%)
White race	1,664 (82%)
Education	16 (3)
PET follow-up, yrs	1.4 (2.1)
Dx follow-up, yrs	3.4 (1.8)

Values shown as M(SD) or n (%); ^aN=179 missing genetic data

PET imaging:

Amyloid (FBP, FBB, NAV, and PiB) and tau PET (FTP, MK6240, PI2620) data corresponding to ligand-specific post-injection windows were processed and standardized using an MRI-free pipeline. Regional T+/- was derived within ligand using gaussian mixture modeling and used to classify AD biological stages:

AD biological stages:



Statistical analyses:

- Aim 1A:** Longitudinal PET stage transitions were summarized at standardized follow-up intervals (~2 years, N = 528; ~4 years, N = 317).
- Aim 1B:** Logistic regression models evaluated risk of biological progression, adjusting for baseline age, sex, and cohort in the ~2-year and ~4-year follow-up samples.
- Aim 2A:** Clinical progression was summarized across baseline biological stages among participants with >1 year of clinical follow-up (N = 2,040).
- Aim 2B:** Kaplan–Meier analyses and Cox proportional hazards models assessed associations between baseline biological stage and risk of clinical progression (CU → MCI or Dementia; MCI → Dementia), adjusting for baseline diagnosis, age, sex, and cohort (N=1,329; 185 events).

ACKNOWLEDGEMENTS

The ADSP (NIH U24-AG074855) involves more than 350 investigators from institutions across the globe and is funded under several cooperative agreements and research grant awards. We thank the study participants and staff for their contributions to this research. This research was also supported by SCAN (NIH U24-AG074855). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

AIC-141 AAIC-Sun-0547 | Karly Cody | karly.cody@ucsf.edu

How do PET-based AD biological stages change over time?

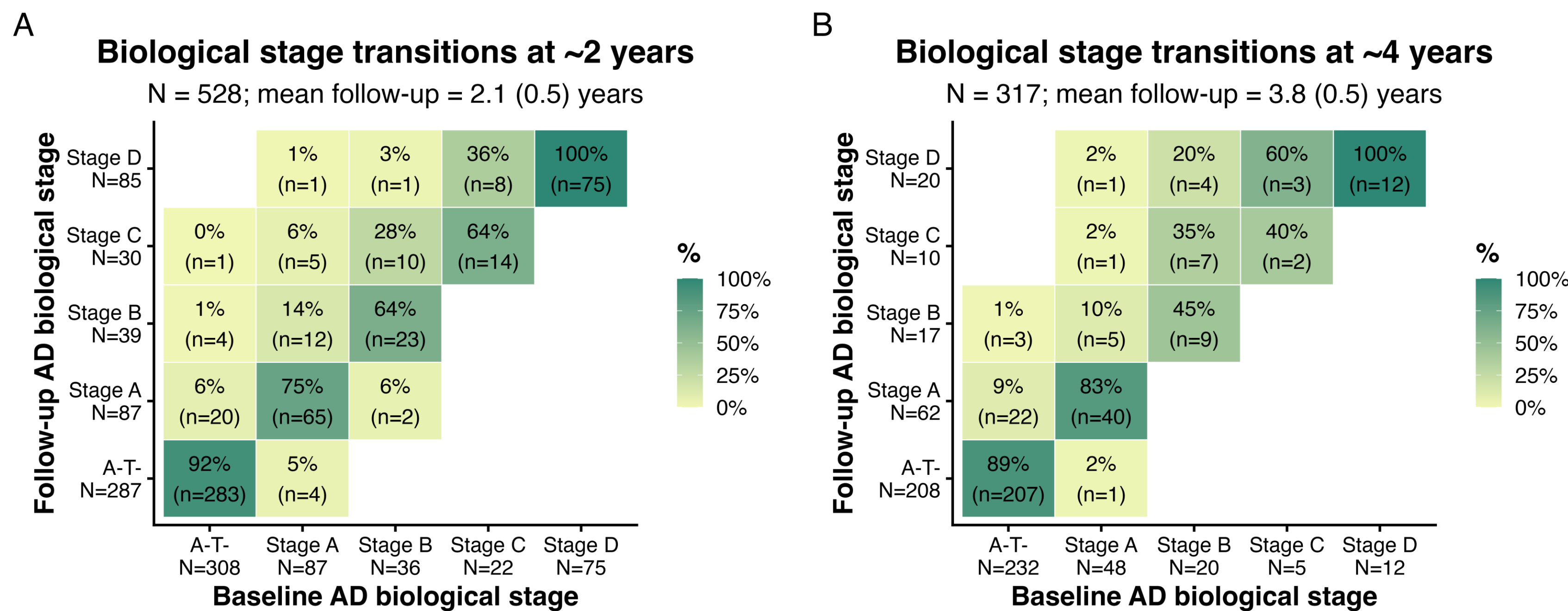


Figure 1. Heatmaps depict transitions in PET-based biological stages at ~2 years (**Panel A**; 1–3 year window; N = 528) and ~4 years (**Panel B**; 3–5 year window; N = 317). Cell values indicate the percentage and number of participants transitioning from baseline to the corresponding follow-up stage. Stable individuals are represented along the diagonal, whereas off-diagonal values indicate biological progression (above diagonal) or backward transition (likely misclassification/ below diagonal).

KEY FINDING: Longitudinal PET data supported the validity of the biological staging framework, demonstrating high stage stability, ordered progression, and infrequent backward transitions.

- Rates of progression largely increased with greater baseline stage severity and with longer follow-up:**
 - Stage A: 21% progressed by ~2 yrs; 15% by ~4 yrs.
 - Stage B: 31% progressed by ~2 yrs; 55% by ~4 yrs.
 - Stage C: 36% progressed by ~2 yrs; 60% by ~4 yrs.
- After adjustment for age, sex, and cohort, **each one-stage increase in baseline biological stage was associated with significantly greater odds of pathological progression** at both ~2 years (OR = 1.90, 95% CI: 1.42–2.55) and ~4 years (OR = 2.81, 95% CI: 1.86–4.35; both $p < 0.001$).

Do baseline PET-based AD biological stages predict future clinical progression?

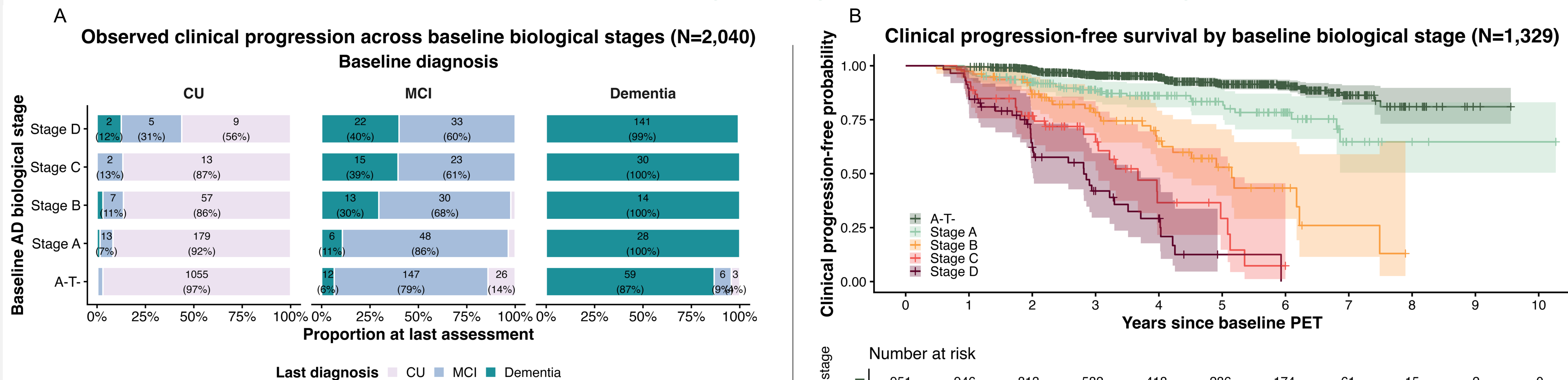


Figure 2. **Panel A (left)** shows the distribution of clinical diagnoses at last assessment stratified by baseline AD biological stage and baseline clinical diagnosis. Bars represent the proportion of participants classified as cognitively unimpaired (CU, $n = 1380$; 3.6 (1.8 years follow-up), mild cognitive impairment (MCI, $n = 378$; 3.3 (1.9 years follow-up), or dementia ($n = 282$; 2.5 (1.4 years follow-up) at follow-up. **Panel B (right)** shows Kaplan–Meier curves depicting time to any forward clinical progression (CU → MCI or Dementia; MCI → Dementia) among 1,329 non-demented participants stratified by baseline PET-based biological stage. Higher baseline biological stage was associated with a greater risk of clinical progression over follow-up (log-rank $p < 0.0001$). Shaded regions represent 95% confidence intervals, and numbers at risk are shown below the plot.

KEY FINDING: Clinical progression increased progressively with advancing baseline biological stage severity.

- Among baseline CU, progression to MCI or dementia was uncommon in A-T- and Stage A but increased with the presence of tau pathology (Stages B–D).
- Among baseline MCI, progression to dementia was common and increased with advancing biological stage (11% in Stage A, 30% in Stage B, and 39–40% in Stages C–D).

KEY FINDING: Higher baseline biological stage predicted greater risk of clinical progression and shorter progression-free survival.

- In Cox proportional hazards models adjusted for baseline diagnosis, age, sex, and cohort, **higher baseline PET biological stage was associated with progressively greater risk of clinical progression:**
 - Stage A vs A–T–:** HR = 2.3 (95% CI: 1.5–3.6), $p < 0.001$
 - Stage B vs A–T–:** HR = 6.4 (95% CI: 4.0–10.0), $p < 0.001$
 - Stage C vs A–T–:** HR = 10.3 (95% CI: 6.3–17.1), $p < 0.001$
 - Stage D vs A–T–:** HR = 17.7 (95% CI: 11.3–27.9), $p < 0.001$

OVERALL TAKEHOME

PET-based AD biological stages capture disease severity, demonstrating high longitudinal stability while strongly predicting future pathological and clinical progression across the Alzheimer’s disease continuum.