

BACKGROUND

- **Not all individuals age at the same rate.** DunedinPACE, a DNA-methylation clock, measures the pace of biological aging – linked to cognitive decline and Alzheimer's disease (AD) risk

THE GAP

- **Single-timepoint** clock measures conflate sustained acceleration with transient variation.
- Most cohorts focus on **older adults**, missing the midlife window when interventions may still alter trajectories.

AIM & HYPOTHESIS

Do 15-year DunedinPACE trajectories in midlife predict cognition and plasma AD biomarkers 15–20 years later?
faster aging will be associated with worse outcomes.

METHODS

- **Cohort** — 2,833 CARDIA adults (mean age 40; 59% female, 44% Black) with ≥ 3 DunedinPACE measures (baseline to 15 years later).
- **Aging trajectories** — Linear mixed-effects model (random intercept + slope) $\rightarrow$ individual rate of DunedinPACE change.
 - Grouped as mean $\pm$ 1SD Fast, Slow, Typical.
- **Outcomes** — 5 cognitive domains (assessed 15 -20 years later); plasma AD biomarkers NfL, p-tau217, A β 42/40 (measured 20 years later).
- **Models** — Linear regression vs. Typical Agers, adjusted for age, sex, race, education, physical activity, APOE* ϵ 4 (+ eGFR for biomarkers).

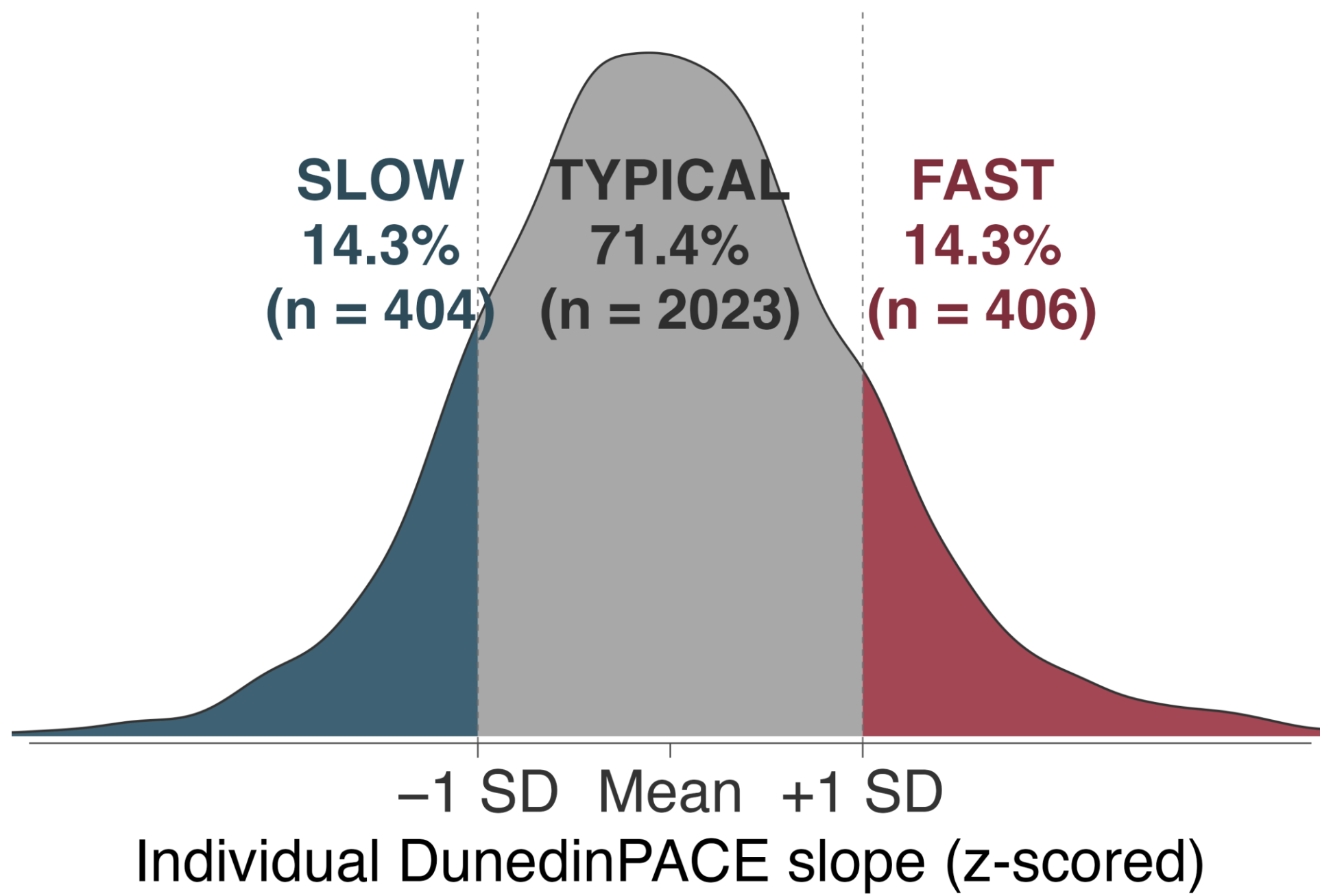
SAMPLE CHARACTERISTICS

	Slow Agers (n = 404)	Typical Agers (n = 2,033)	Fast Agers (n = 406)	<i>p</i>
N = 2,833				
Age, y	40.8 $\pm$ 3.4	40.3 $\pm$ 3.6	39.8 $\pm$ 3.8	0.004
Female	304 (75.2%)	1,169 (57.8%)	185 (45.6%)	<0.001
Black	118 (29.2%)	888 (43.9%)	240 (59.1%)	<0.001
Education, y	15.7 $\pm$ 2.5	15.0 $\pm$ 2.5	14.6 $\pm$ 2.5	<0.001

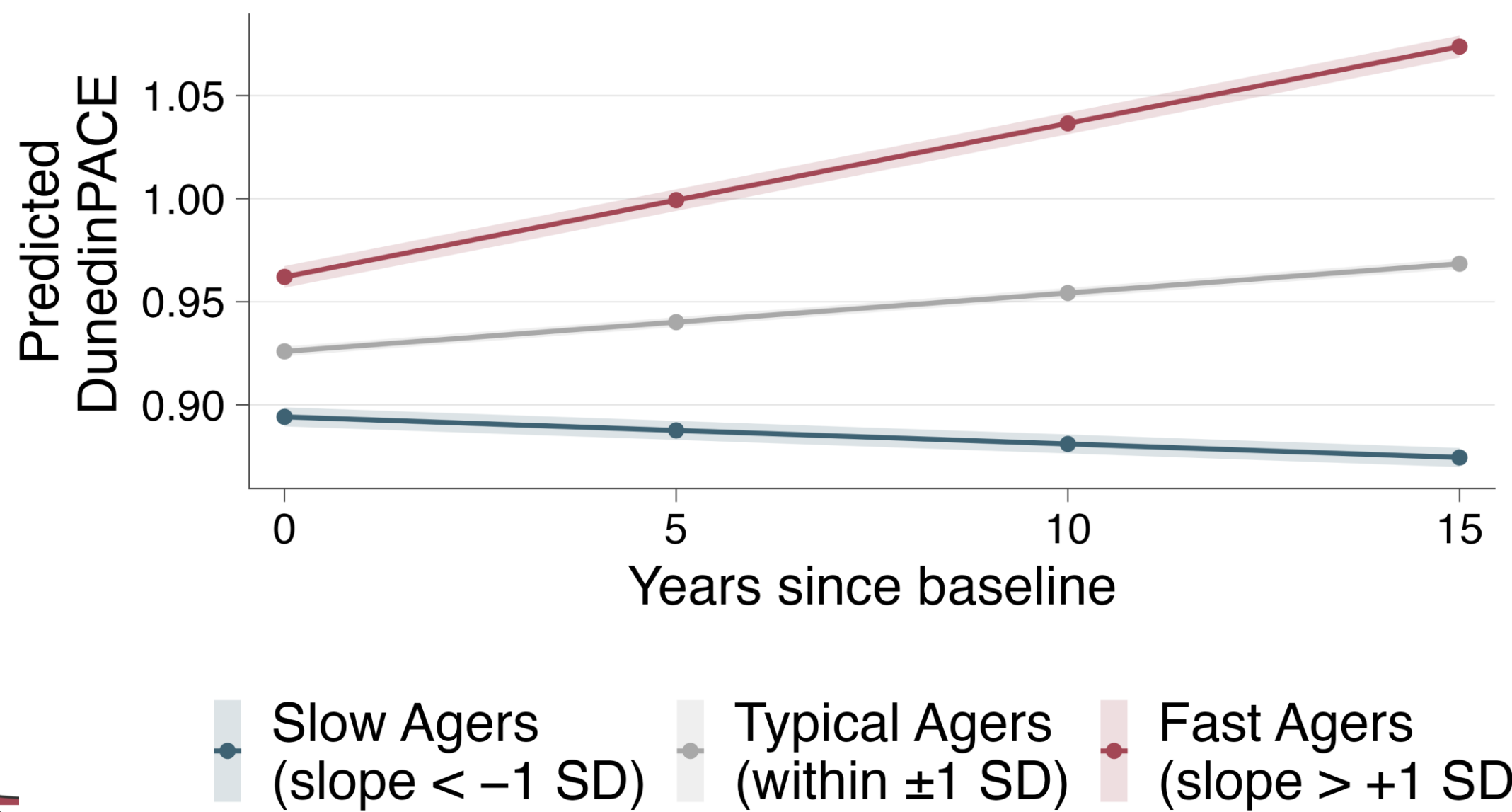
Continuous: mean $\pm$ SD; categorical: n (%). p from one-way ANOVA (continuous) and Pearson χ^2 (categorical).

RESULTS

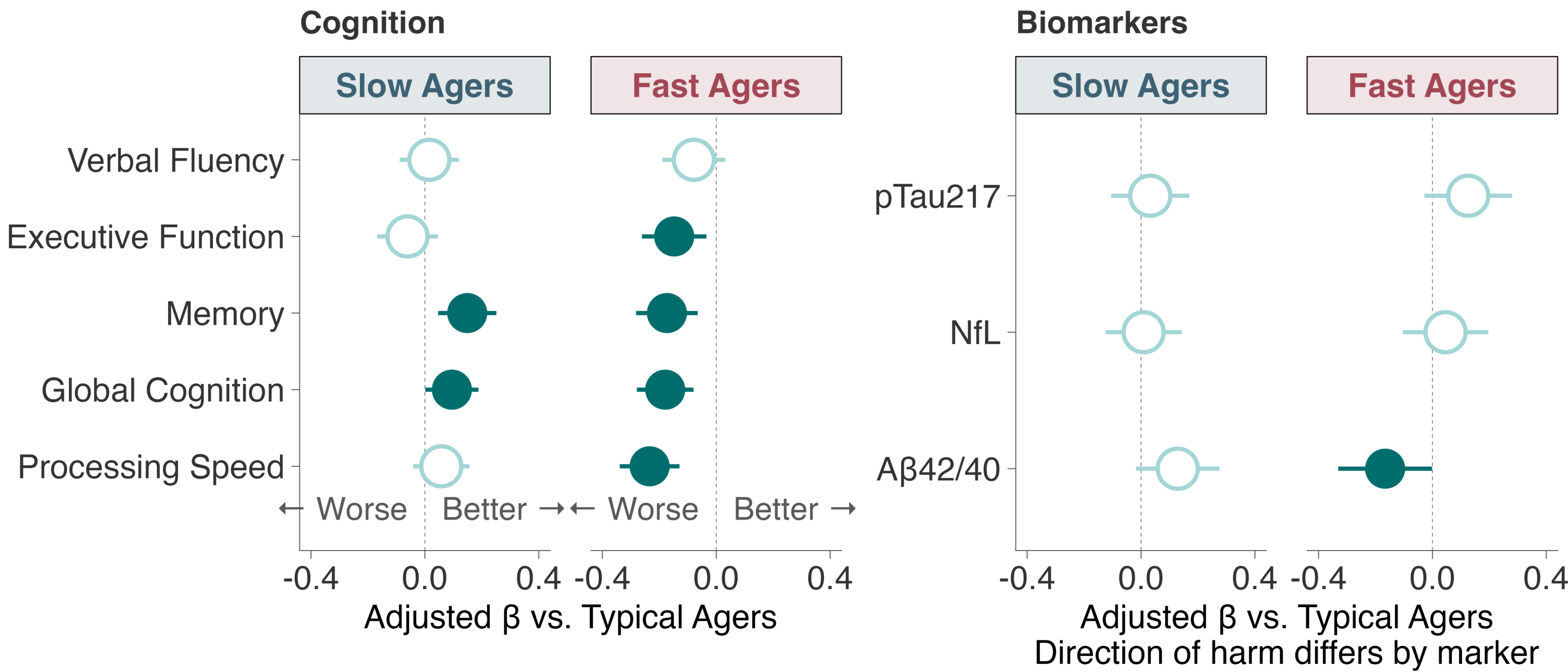
- **Random-slope distributions classified participants into slow, typical, and fast aging trajectory groups**



- **Three trajectory groups remained distinct across 15 years of midlife.**



- **Faster epigenetic aging was associated with worse cognition and lower A β 42/40 levels; slower aging was associated with cognitive resilience.**



INTERPRETATION & CONCLUSION

- Amyloid (A β 42/40) may be the earliest detectable marker of differential biological aging in midlife, preceding tau and neurodegeneration.
- Faster epigenetic aging tracks worse brain health well before the typical age of cognitive impairment.

Funding: The Coronary Artery Risk Development in Young Adults Study (CARDIA) is supported by contracts 75N92023D00002, 75N92023D00003, 75N92023D00004, 75N92023D00005, and 75N92023D00006 from the National Heart, Lung, and Blood Institute (NHLBI). Additional support was provided by the National Institute on Aging (NIA) through grants R01AG091431 and R35AG071916 (PI: Yaffe).