



Temporal Associations of Alzheimer's Disease and Cerebrovascular Disease Biomarkers with Memory Decline

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BACKGROUND

Alzheimer's disease (AD) and cerebrovascular disease (CeVD) are common causes of cognitive decline and often co-evolve^{1,2}. The concurrent temporal evolution of these pathologies and contributions to cognitive decline are not well understood. The goal of this study is to evaluate the temporal association of AD and CeVD biomarkers with cognitive decline in a population-based sample.

METHODS

PARTICIPANTS The study included 630 Mayo Clinic Study of Aging (MCSA)³ participants, age 78 (±10) years, 46% female, 532 (84%) cognitively unimpaired, 81 (13%) MCI, and 17 (3%) AD dementia.

MULTI-OUTCOME NON-LINEAR MIXED EFFECTS (NLME) MODELS^{4,5} were fit with outcomes:

AD biomarkers

- Amyloid PET: PiB global meta-ROI
- Tau PET: flortaucipir temporal meta-ROI
- C2N plasma p-tau217

CeVD biomarkers

- White matter hyperintensity (WMH) percent of total intracranial volume
- ARTerioLoSclerosis (ARTS)
- Peak width of skeletonized mean diffusivity (PSMD), marker of early white-matter disease

Memory scores

- Auditory verbal learning test (AVLT) sum of trials as outcomes

Covariates: sex, APOE ε4 carriership, education, and cardiovascular metabolic conditions (CMC) score

Model output included a per-participant individual adjustment, correlation between adjustments for each pair of biomarkers, and covariate effects on each biomarker's timing. Applying cutpoints to model output, we generated curves of the percentage of individuals with abnormal biomarker values versus age to estimate the order the biomarkers become abnormal.

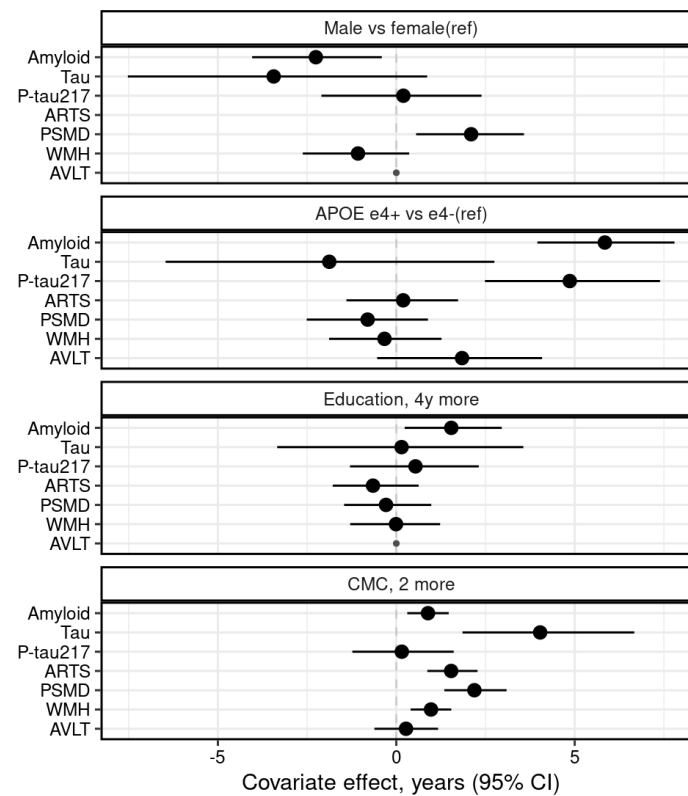


FIGURE 1. COVARIATE EFFECTS in years with 95% credible interval. A higher positive value indicates an earlier onset.

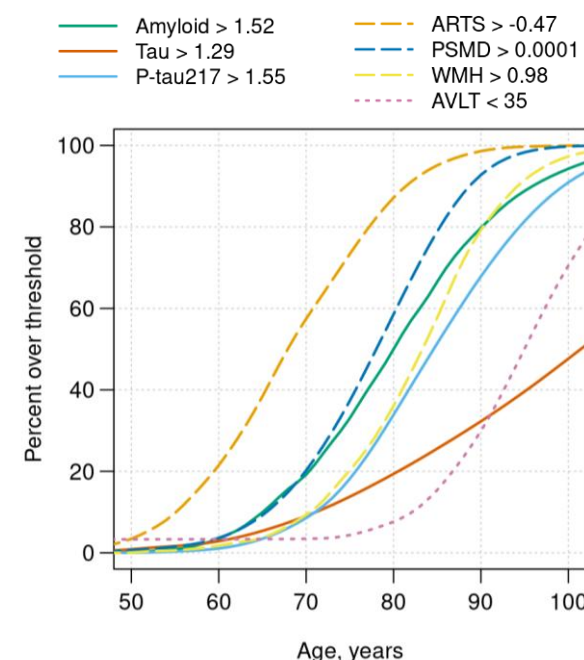


FIGURE 3. TIMING OF BIOMARKER AND COGNITIVE PROGRESSION. By age, predicted proportion of participants with abnormal biomarker levels using established cutpoints.

RESULTS

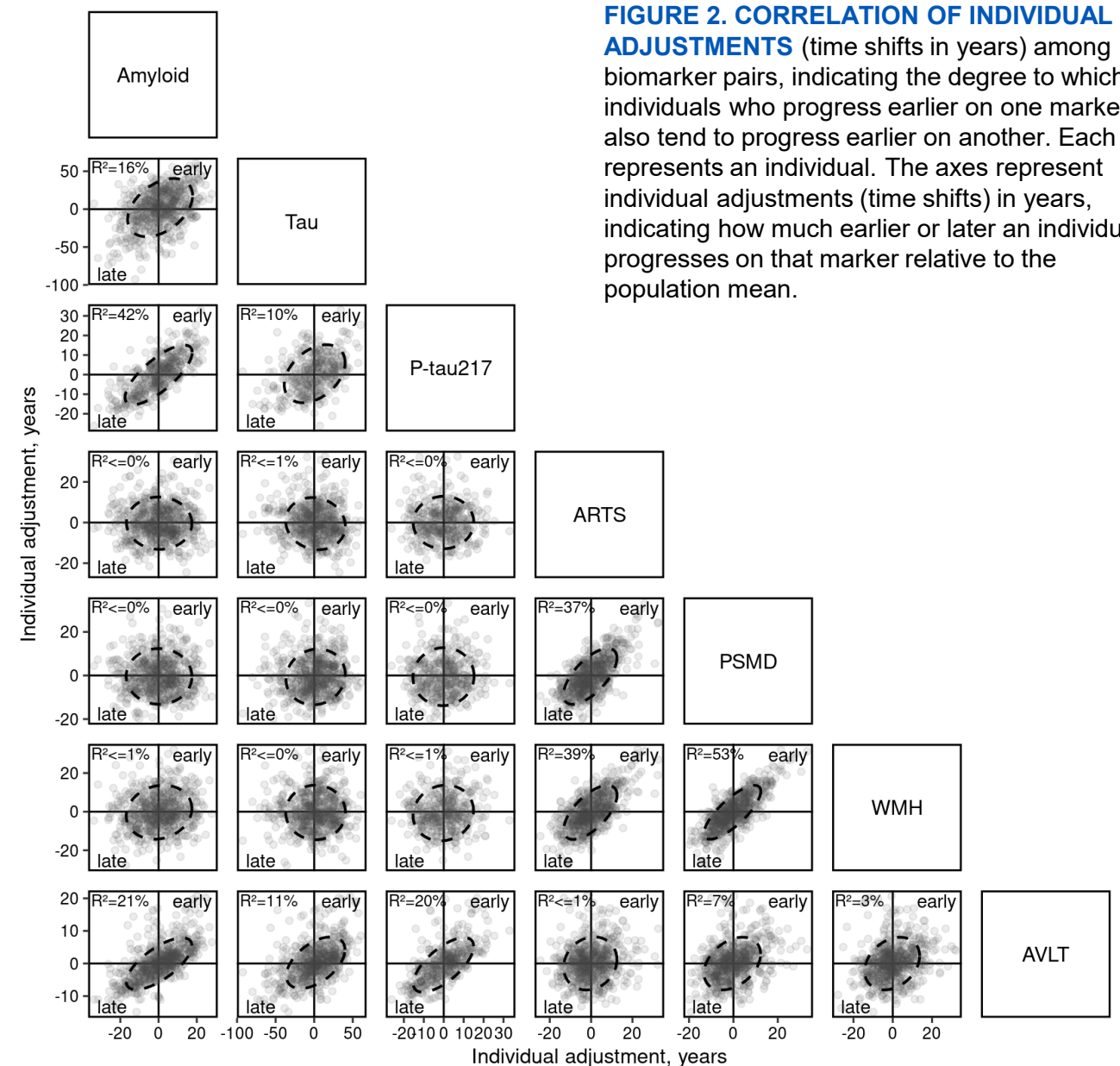


FIGURE 2. CORRELATION OF INDIVIDUAL ADJUSTMENTS (time shifts in years) among biomarker pairs, indicating the degree to which individuals who progress earlier on one marker also tend to progress earlier on another. Each dot represents an individual. The axes represent individual adjustments (time shifts) in years, indicating how much earlier or later an individual progresses on that marker relative to the population mean.

CONCLUSIONS

- Progression of AD biomarkers more closely tracked with memory decline than progression of CeVD biomarkers.
- The CMC score was associated with earlier progression on tau and amyloid PET, in addition to CeVD biomarkers.
- Future work will investigate temporal associations of these biomarkers with other cognitive domains.

REFERENCES

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