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Background and Objectives

Detecting and monitoring Alzheimer’s disease (AD) onset and progression using cost-saving digital and fluid tools is critical for patient management and disease intervention.

Methods

In this study, we evaluated the diagnostic performance of novel digital markers, including an artificial intelligence (AI)-assisted virtual reality (VR) cognitive test, and eye-tracking digital markers, by investigating their relations with AD-related biomarkers and cognitive decline among 704 Chinese older adults from Greater-Bay-Area Healthy Aging Brain Study (GHABS)¹ cohort. Furthermore, we assessed the diagnostic and prognostic validity of longitudinal plasma phosphorylated tau217 (p-tau217) in AD across 2,117 participants from both the East Asian (GHABS) and Western (ADNI and A4 studies) older populations. We established baseline plasma p-tau217 cutoffs to assess their longitudinal diagnostic performance and the associations between longitudinal changes in plasma p-tau217 and changes in β-amyloid (Aβ)-PET, tau-PET, hippocampal volume, and incident dementia.

Results

The AI-VR cognitive scores were significantly correlated with AD-related biomarkers, accurately distinguishing cognitively impaired (CI) patients from cognitively unimpaired (CU) individuals (area under the curve (AUC): 0.908-0.969) (Figure 1A)². The eye-tracking panel demonstrated superior performance in distinguishing CI individuals from CU individuals, outperforming plasma Aβ42/40, p-Tau217, p-Tau217/Aβ42, GFAP, and NfL (Figure 1B)². Across the ADNI, A4 placebo, and GHABS cohorts (Figure 2), baseline-established p-tau217 cutoffs achieved high and stable accuracy (86%–95%) over a follow-up period of up to 5 years. Most individuals initially classified as p-tau217-positive remained stable (93%–98%), whereas those in an intermediate zone were more likely to convert to p-tau217 positivity (44%–78%) than p-tau217-negative individuals (4%–21%). Participants who were persistently or progressively p-tau217-positive more frequently developed Aβ abnormalities and experienced accelerated tau accumulation, hippocampal atrophy, and dementia onset compared with those persistently negative (Figure 3).

Discussion

In conclusion, these findings demonstrate the validity of digital markers for screening CI patients and provide novel markers for detecting cognitive decline in older adults. Meanwhile, we determined the robust cross-sectional and longitudinal validity of plasma p-tau217 for AD diagnosis and tracking heterogeneity in disease progression across ethnically diverse populations, supporting its integration into routine clinical practice for detecting and monitoring AD. The combination of digital and fluid markers may be used to detect and monitor AD.

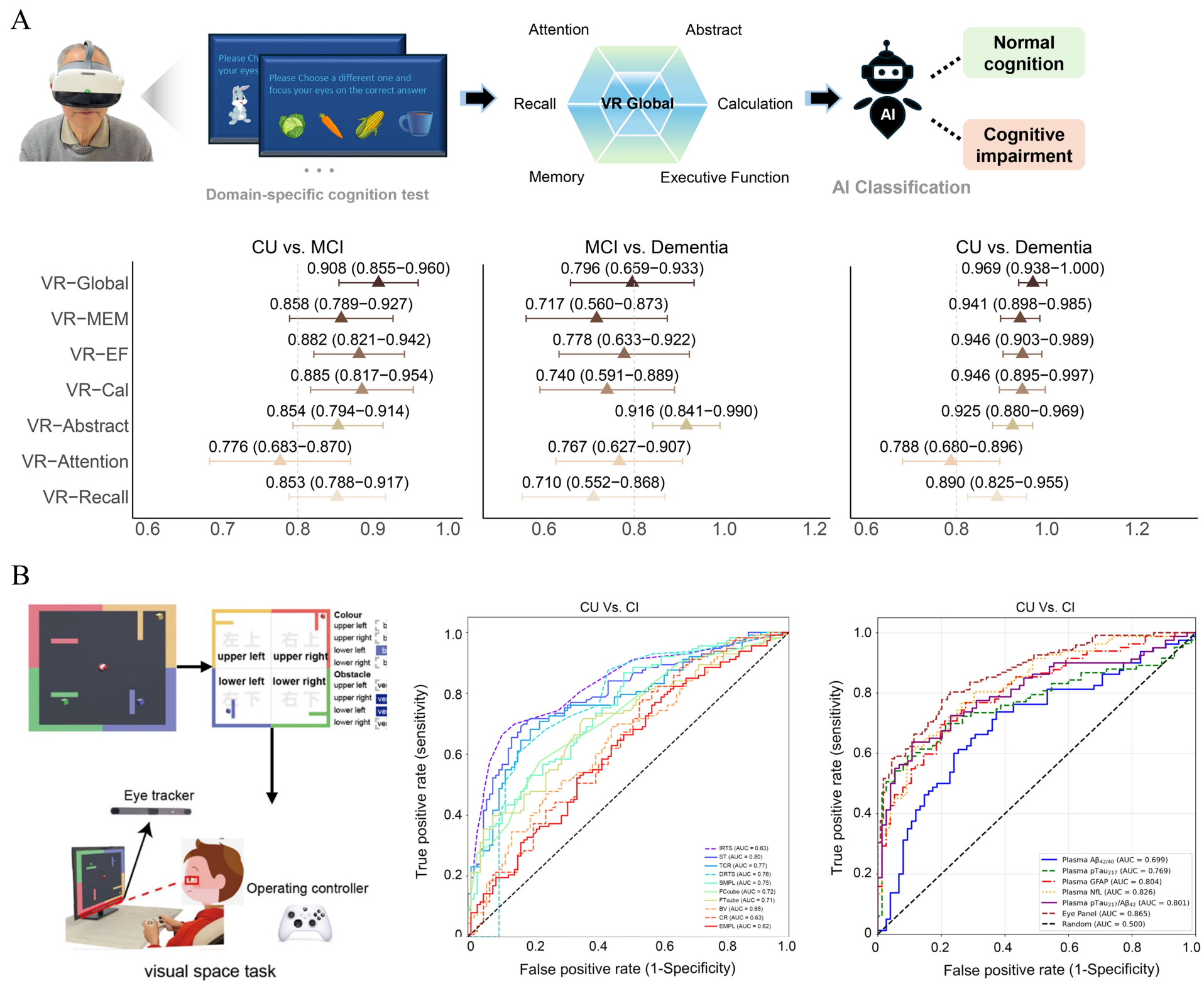
Acknowledgements

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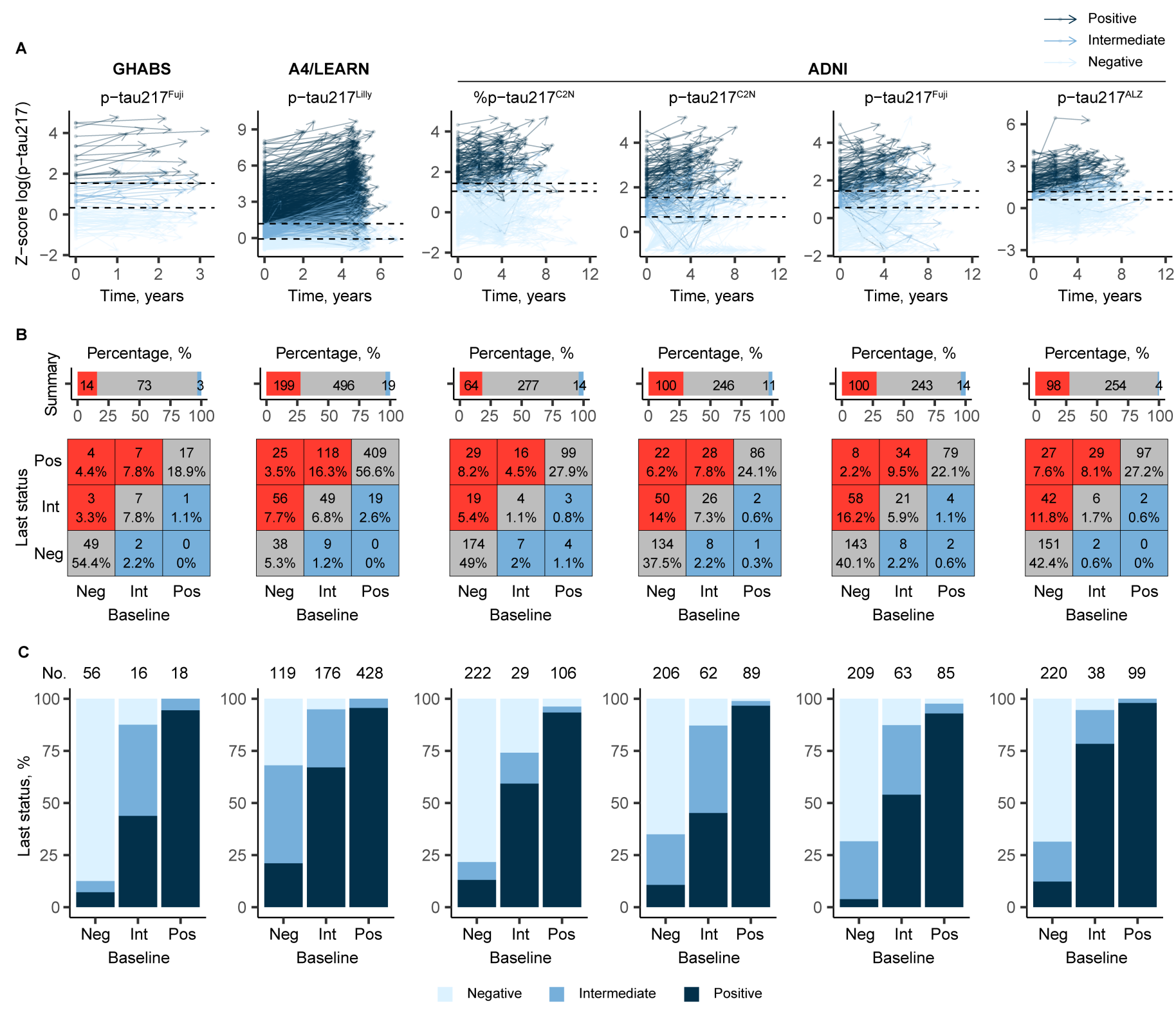
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Figure 1. Diagnostic performance of digital markers.



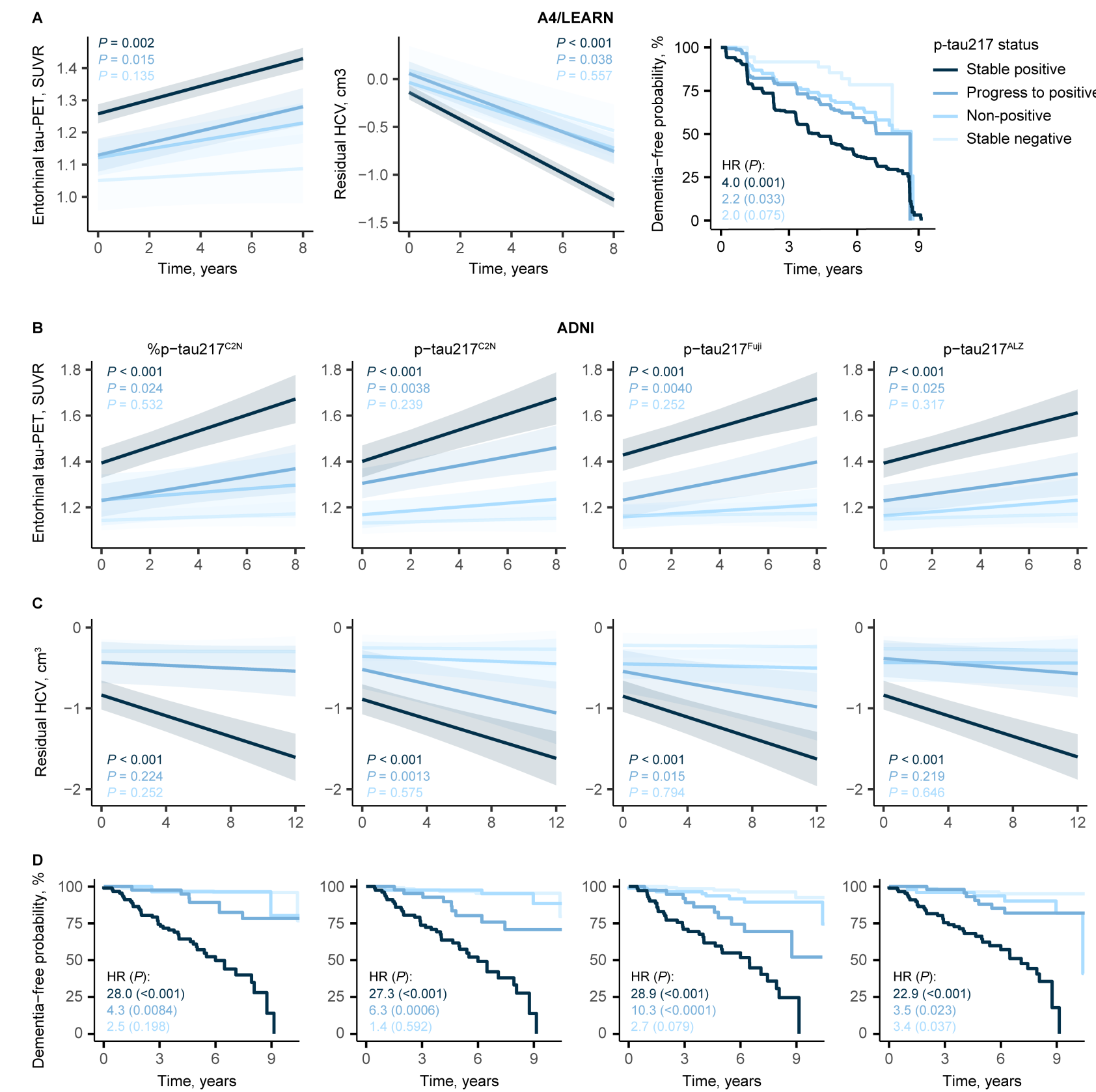
(A) ROC analysis of the AI-VR digital cognitive test in classifying different stages of AD. MEM: memory; EF: executive function; Cal: calculation; (B) ROC and AUC between cognitively unimpaired (CU) and cognitively impaired (CI) individuals for eye-tracking markers and plasma biomarkers. TCR: time-consuming rate; SMPL: sphere motion path length; CR: correlation rate; ST: saccades times; FCCube: fixation count of cubes; FTcube: fixation time of cubes; EMPL: eye movement path length; EMV: eye movement velocity; BV: ball velocity; IRTS: instantaneous recall task scores; DRTS: delayed recall task scores.

Figure 2. Longitudinal changes of plasma p-tau217 status



(A) Trajectory of plasma p-tau217 over time, stratified by baseline p-tau217 positivity. The horizontal dashed lines represented the assay-specific cutoffs established at baseline. (B) Distribution of participants according to their p-tau217 status at baseline and the last visit. The numbers and percentages reported are based on the total number of participants. The bar graph depicts the overall proportion in the three longitudinal categories according to changes in p-tau217 status: progressive (red), stable (grey), and reverted (blue). (C) The proportion of the last p-tau217 status across different initial p-tau217 statuses. Neg, p-tau217-negative; Int, intermediate zone; Pos, p-tau217-positive.

Figure 3. Longitudinal changes in AD-related measures and incident dementia across longitudinal plasma p-tau217 status



Longitudinal changes in entorhinal tau PET, residual HCV, and survival from dementia in A4/LEARN (A) and ADNI (B-D) participants, stratified by changes in plasma p-tau217 status. Two-sided P-values were computed using linear mixed-effects models that included the interaction between time and changes in p-tau217 status, while adjusting for age, sex, and APOE status, and incorporating random slopes and intercepts. The shaded area represents regression lines with 95% confidence intervals for each group. The Benjamini-Hochberg approach was used for multiple comparisons. For Kaplan-Meier curves, hazard ratios (HRs) and two-sided p-values were obtained from Cox proportional hazards models, adjusting for age, sex, APOE status, and education. In all analyses, participants with stable normal p-tau217 (stable negative) values were used as the reference.