



Discordance Between Plasma P-tau217 And PET Imaging As A Prognostic Marker In Alzheimer’s Disease:

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INTRODUCTION

- To investigate the impact of discordance between plasma biomarkers and PET imaging on longitudinal cognitive outcomes in Alzheimer’s disease.

METHODS

- A total of 232 participants were enrolled, all of whom underwent 18F-florbetaben (FBB), 18F-flortaucipir (FTP) PET, volumetric MRI, and neuropsychological assessments. Their plasma samples were tested for plasma p-tau217 at C2N Diagnostics. Plasma-PET discordance was defined using linear regression between plasma p-tau217 and FBB Centiloid values or FTP temporal meta-ROI SUVR. Standardized residuals were categorized into lower (L), middle (M), and upper (U) discordance groups based on ± 1 SD thresholds. Longitudinal cognitive change was analyzed using linear mixed-effects models with random intercepts and slopes, adjusting for demographic factors, APOE $\epsilon 4$ status, and baseline PET burden.

RESULTS

- Based on linear regression residuals using FBB amyloid PET Centiloid values, participants were classified into Amyloid-L (N = 27), Amyloid-M (N = 161), and Amyloid-U (N = 44) groups. Using FTP temporal meta-ROI tau PET SUVR, participants were similarly categorized into Tau-L (N = 21), Tau-M (N = 181), and Tau-U (N = 30) groups. In linear mixed-effects models, amyloid discordance was not associated with subsequent cognitive decline. In contrast, tau discordance was significantly associated with longitudinal cognitive deterioration, with individuals showing higher tau PET burden relative to plasma p-tau217 demonstrating accelerated decline over time (MMSE: $\beta = -2.077$, $p < 0.001$; CDR-SB: $\beta = 2.188$, $p < 0.001$).

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RESULTS

Table 1. Demographics of participants

	CU	MCI	DEM
n	57	97	78
Baseline age (years)	71.5 $\pm$ 7.1	72.0 $\pm$ 7.4	74.6 $\pm$ 8.1 ^a
Sex (M:F)	19:38	44:53	27:51
Education (years)	11.6 $\pm$ 4.2	12.3 $\pm$ 4.1	10.7 $\pm$ 4.9 ^b
ApoE $\epsilon 4$ genotype ($\epsilon 4$ +: $\epsilon 4$ -)	18:39	50:47 ^a	41:37 ^a
MMSE	27.7 $\pm$ 2.1	26.1 $\pm$ 2.7 ^a	19.5 $\pm$ 5.2 ^{ab}
CDR-SB	0.6 $\pm$ 0.3	1.4 $\pm$ 0.7	5.8 $\pm$ 3.7 ^{ab}
Neuropsychologic battery (SNSB-D)			
Attention	9.5 $\pm$ 2.5	9.9 $\pm$ 2.2	7.8 $\pm$ 2.2 ^{ab}
Language	23.4 $\pm$ 2.4	22.1 $\pm$ 3.1	16.7 $\pm$ 5.8 ^{ab}
Visuospatial	31.0 $\pm$ 3.3	29.5 $\pm$ 4.2	21.3 $\pm$ 10.2 ^{ab}
Memory	70.8 $\pm$ 17.8	47.5 $\pm$ 16.7 ^a	23.1 $\pm$ 14.1 ^{ab}
Frontal-executive	36.7 $\pm$ 12.7	33.3 $\pm$ 12.0	19.6 $\pm$ 11.6 ^{ab}
Total cognition score	171.4 $\pm$ 29.4	142.2 $\pm$ 26.1 ^a	88.5 $\pm$ 36.5 ^{ab}
¹⁸ F-Florbetaben Centiloid	29.0 $\pm$ 42.5	55.3 $\pm$ 49.0 ^a	89.0 $\pm$ 38.5 ^{ab}
¹⁸ F-Flortaucipir SUVR	1.24 $\pm$ 0.19	1.42 $\pm$ 0.34 ^a	1.84 $\pm$ 0.50 ^{ab}
Hippocampal volume (mm ³)	7.4 $\pm$ 0.9	7.1 $\pm$ 1.1	6.2 $\pm$ 1.1 ^{ab}
A β _{42/40} ratio	0.11 $\pm$ 0.02	0.11 $\pm$ 0.02	0.10 $\pm$ 0.03
p-tau 217	2.2 $\pm$ 2.3	4.5 $\pm$ 5.5 ^a	8.6 $\pm$ 5.5 ^{ab}
%p-tau217	4.5 $\pm$ 5.8	8.2 $\pm$ 7.1 ^a	13.4 $\pm$ 6.5 ^{ab}

Data are presented as mean $\pm$ SD. ^a $P < 0.05$ for the comparisons between the CU and each group. ^b $P < 0.05$ for the comparisons between the MCI and DEM groups. Abbreviations: CU = cognitively unimpaired; MCI = mild cognitive impairment; DEM = dementia; ApoE = apolipoprotein E; SUVR = standardized uptake value ratio; MMSE = Mini-Mental state examination; CDR-SB = clinical dementia rating sum-of-boxes; SNSB = Seoul neuropsychological screening battery; FBB = 18F-Florbetaben PET; FTP = 18F-Flortaucipir PET

Table 2. Linear mixed effect model for longitudinal cognitive change by plasma-PET discordance

Term	β	SE	df	t value	p-value
MMSE					
FBB PET – plasma p-tau217					
Time $\times$ Amyloid-M	0.11	0.62	169.14	0.18	0.856
Time $\times$ Amyloid-U	-0.28	0.69	164.91	-0.41	0.684
FTP PET – plasma p-tau217					
Time $\times$ Tau-M	-0.60	0.47	123.42	-1.29	0.199
Time $\times$ Tau-U	-2.08	0.57	123.79	-3.62	<0.001
CDR-SB					
FBB PET – plasma p-tau217					
Time $\times$ Amyloid-M	-0.71	0.56	195.38	-1.26	0.209
Time $\times$ Amyloid-U	0.22	0.62	185.43	0.35	0.728
FTP PET – plasma p-tau217					
Time $\times$ Tau-M	0.71	0.42	134.1	1.72	0.088
Time $\times$ Tau-U	2.19	0.51	132.76	4.30	<0.001

CONCLUSION

- Individuals with disproportionately higher tau tangle burden relative to plasma p-tau217 exhibited more severe cognitive decline, indicating that plasm-PET tau discordance may serve as a prognostic biomarker for future cognitive deterioration.

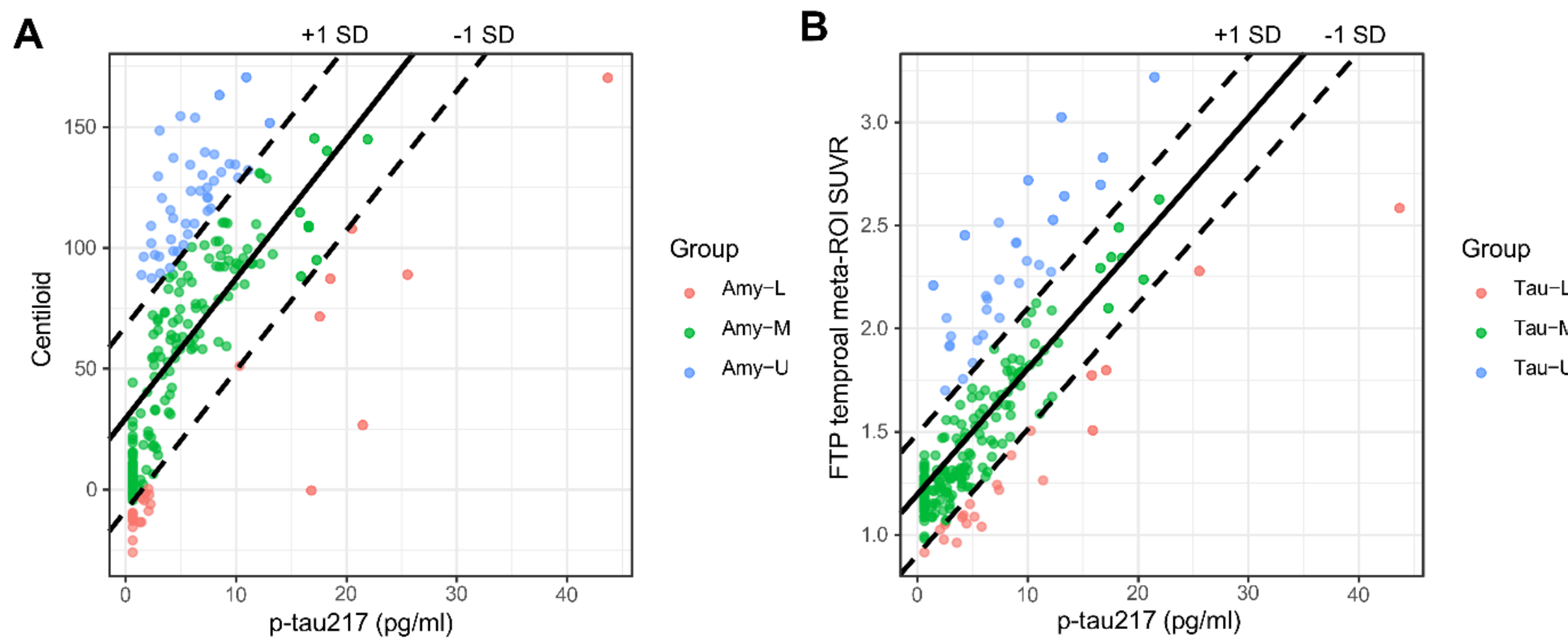


Figure 1. Definition of plasma-PET discordance using linear regression-based residual stratification. (A) Scatter plot illustrating the relationship between plasma p-tau217 and amyloid PET burden expressed in Centiloid. (B) Scatter plot illustrating the relationship between plasma p-tau217 levels and tau PET burden measured as FTP temporal meta-ROI SUVR. In each panel, a linear regression model was fitted to characterize the overall plasma-PET association (solid line). Dashed lines represent ± 1 standard deviation (SD) of the residuals from the regression line. Participants were classified into three discordance groups based on residual distribution: L (below -1 SD), M (within ± 1 SD), and U (above +1 SD). These groups represent individuals with relatively lower-than-expected PET burden, concordant plasma-PET levels, and higher-than-expected PET burden relative to plasma p-tau217, respectively.

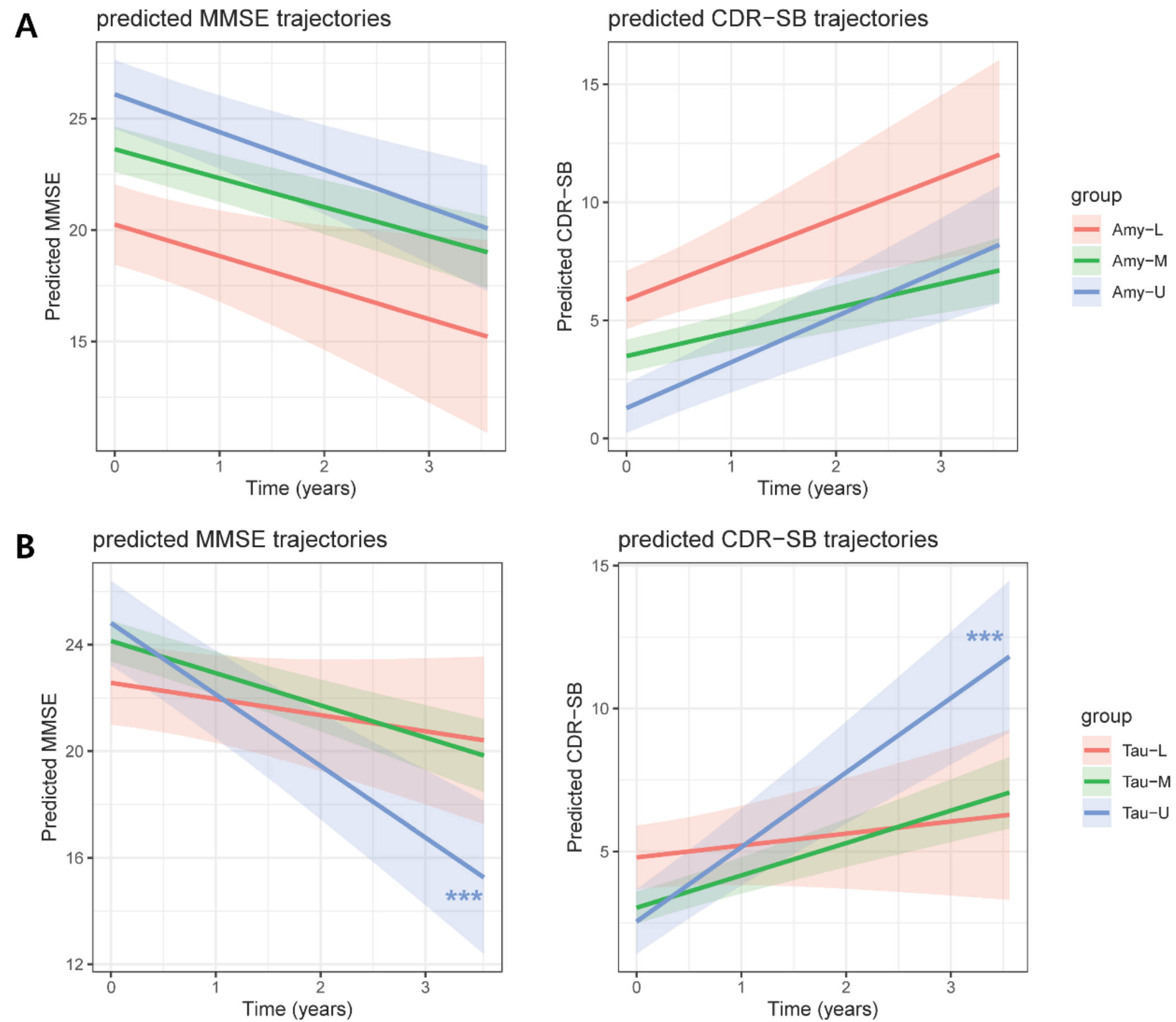


Figure 2. . Longitudinal cognitive trajectories according to plasma-PET discordance groups. (A) Comparison of longitudinal cognitive outcomes across amyloid PET-plasma p-tau217 discordance groups. No significant differences in longitudinal cognitive decline were observed between amyloid discordance groups in linear mixed-effects models. (B) Comparison of longitudinal cognitive outcomes across tau PET-plasma p-tau217 discordance groups. In linear mixed-effects models adjusted for age, sex, education, ApoE $\epsilon 4$ status, and baseline tau PET burden, individuals in the upper tau discordance group exhibited significantly greater longitudinal worsening in MMSE and CDR-SB compared with the other groups. Abbreviations: L = lower discordance groups; M = middle discordance groups (concordance groups); U = upper discordance groups; ***= $P < 0.001$