



APOE Genotype-dependent Association Between Plasma P-tau217 and Amyloid Pathology in Alzheimer’s Disease

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INTRODUCTION

- This study aimed to investigate the differential association between plasma p-tau217 and amyloid burden across Apolipoprotein E (APOE) genotypes.

METHODS

- A total of 234 participants were included in the study, undergoing 18F-florbetaben (FBB), 18F-flortaucipir (FTP) PET, and plasma biomarker assessments, including %p-tau217, p-tau217, and APS2. Participants were categorized based on their APOE genotype: E2+ (E2/E2, E2/E3), E3/E3, and E4+ (E3/E4, E4/E4). The relationship between FBB centiloid values, FTP temporal meta-region-of-interest (ROI) SUVR values, and plasma biomarkers was analyzed across these genotypes, and differences in correlations were assessed using Fisher’s Z test. Longitudinal cognitive trajectories were analyzed using linear mixed-effects models, and mediation analyses assessed indirect pathways linking APOE genotype to cognitive decline.

RESULTS

- The association between plasma p-tau217 and amyloid burden varied significantly across APOE genotypes. Correlations between amyloid Centiloid and plasma biomarkers were strongest in E2+ carriers (APS2 $r=0.923$; %p-tau217 $r=0.868$; p-tau217 $r=0.826$), intermediate in E3/E3 homozygotes, and significantly attenuated in E4+ carriers (p-tau217 $r=0.538$; all $p<0.05$ vs. E2+ and E3/E3). In contrast, correlations between plasma p-tau217 and tau PET SUVRs did not differ significantly across genotypes. Longitudinally, both E3/E3 and E4+ groups exhibited faster cognitive decline than E2+ carriers after adjustment for baseline p-tau217, with E4+ carriers showing the steepest decline in MMSE and increase in CDR-SB. Mediation analysis demonstrated that the effect of E4 on cognitive decline was almost entirely indirect, operating through amyloid-driven tau accumulation, while plasma p-tau217 showed no independent mediating effect on cognitive decline.

STUDY FUNDING

This research was supported by a faculty research grant of Yonsei University College of Medicine for (6-2022-0073), a grant from the 2020 Research Grant of Gangnam Severance Hospital Research Committee, Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF2020R1F1A1076154, NRF2018R1D1A1B07049386, RS-2023-00247986), and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (Grant number : H118C1159, HU20C0164).

RESULTS

Table 1. Demographics of participants

	E2+	E3/E3	E4+
<i>n</i>	21	104	109
Baseline age (years)	71.50 ± 7.87	72.62 ± 8.08	73.22 ± 7.28
Sex (F:M)	15:6	59:45	65:44
Education (years)	11.50 ± 4.45	11.78 ± 4.40	11.65 ± 4.53
MMSE	26.81 ± 2.66	24.36 ± 4.96	23.83 ± 5.27 ^a
CDR-SB	1.12 ± 0.96	2.65 ± 3.20	2.95 ± 3.22 ^a
¹⁸ F-Florbetaben Centiloid	18.8 ± 45.0	52.9 ± 51.9 ^a	72.9 ± 42.1 ^{ab}
¹⁸ F-Flortaucipir SUVR	1.18 ± 0.23	1.50 ± 0.44 ^a	1.58 ± 0.45 ^a
p-tau 217	1.50 ± 1.32	4.79 ± 5.07 ^a	6.31 ± 5.96 ^a

Data are presented as mean ± SD. ^a $P < 0.05$ for the comparisons between the E2+ and each group. ^b $P < 0.05$ for the comparisons between the E3/E3 and E4+ groups.

Table 2. Longitudinal cognition changes across APOE genotype performed by linear mixed effect model adjusted for age, sex, education years, and baseline p-tau217

Outcome	Model 1			Model 2		
	β	SE	p-value	β	SE	p-value
MMSE						
Intercept	26.60	1.03	<0.001	25.23	2.95	<0.001
Time (months)	-0.036	0.038	0.35	-0.035	0.040	0.372
E3/E3 vs E2+	-1.32	1.14	0.25	-1.38	1.07	0.199
E4+ vs E2+	-1.22	1.15	0.29	-1.26	1.08	0.244
Baseline p-tau217	-0.286	0.057	<0.001	-0.25	0.053	<0.001
Baseline age	-	-	-	-0.043	0.037	0.247
Education (years)	-	-	-	+0.35	0.066	<0.001
Sex	-	-	-	+0.56	0.60	0.352
Time × E3/E3 vs. E2+	-0.084	0.042	0.047	-0.084	0.044	0.057
Time × E4+ vs. E2+	-0.087	0.042	0.039	-0.090	0.043	0.039
CDR-SB						
Intercept	1.01	0.73	0.17	-3.00	2.15	0.164
Time (months)	+0.048	0.030	0.11	+0.051	0.030	0.096
E3/E3 vs E2+	+1.37	0.82	0.095	+1.33	0.78	0.090
E4+ vs E2+	+1.03	0.82	0.21	+1.06	0.78	0.178
Baseline p-tau217	+0.198	0.040	<0.001	+0.18	0.039	<0.001
Baseline age	-	-	-	+0.069	0.027	0.011
Education (years)	-	-	-	-0.057	0.048	0.241
Sex	-	-	-	-0.73	0.44	0.097
Time × E3/E3 vs. E2+	+0.053	0.033	0.105	+0.049	0.034	0.145
Time × E4+ vs. E2+	+0.067	0.032	0.040	+0.068	0.033	0.043

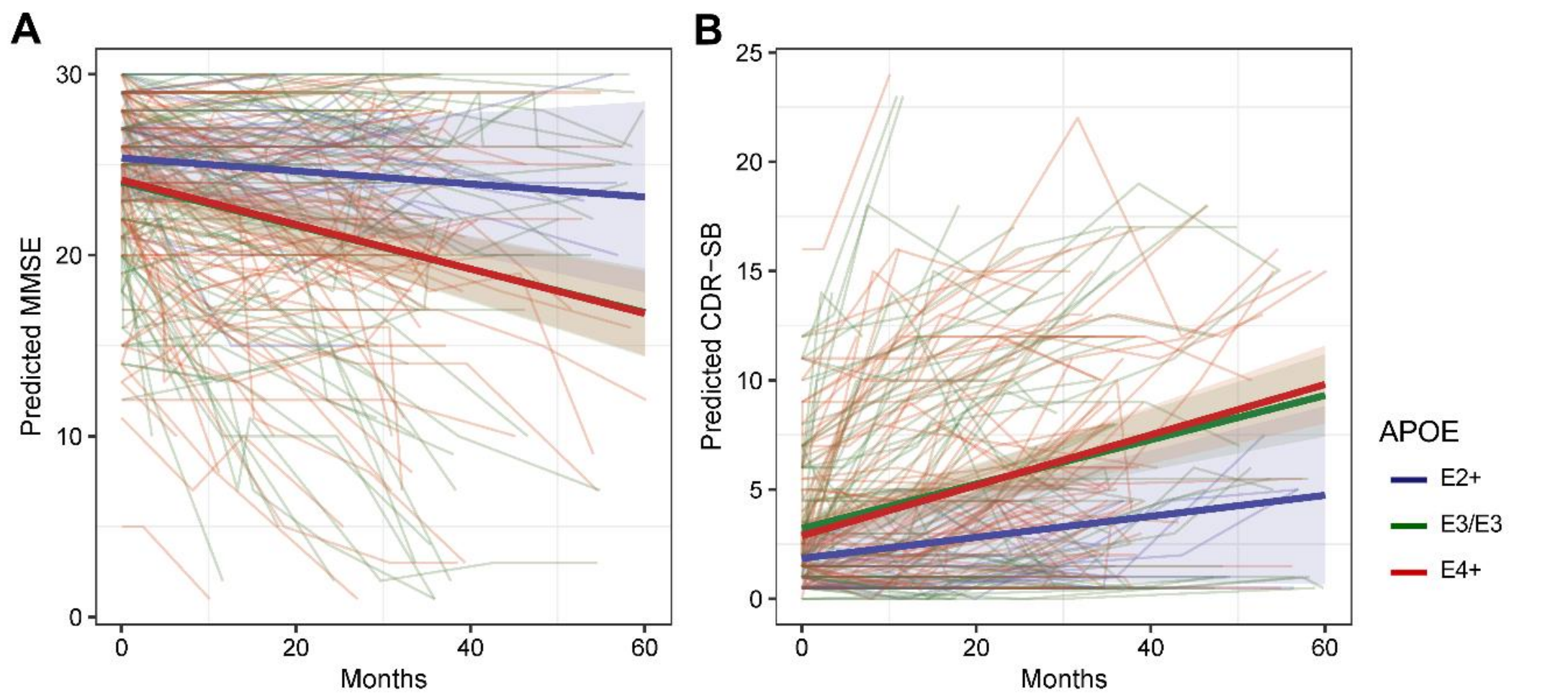


Figure 2. Longitudinal differences across APOE genotypes

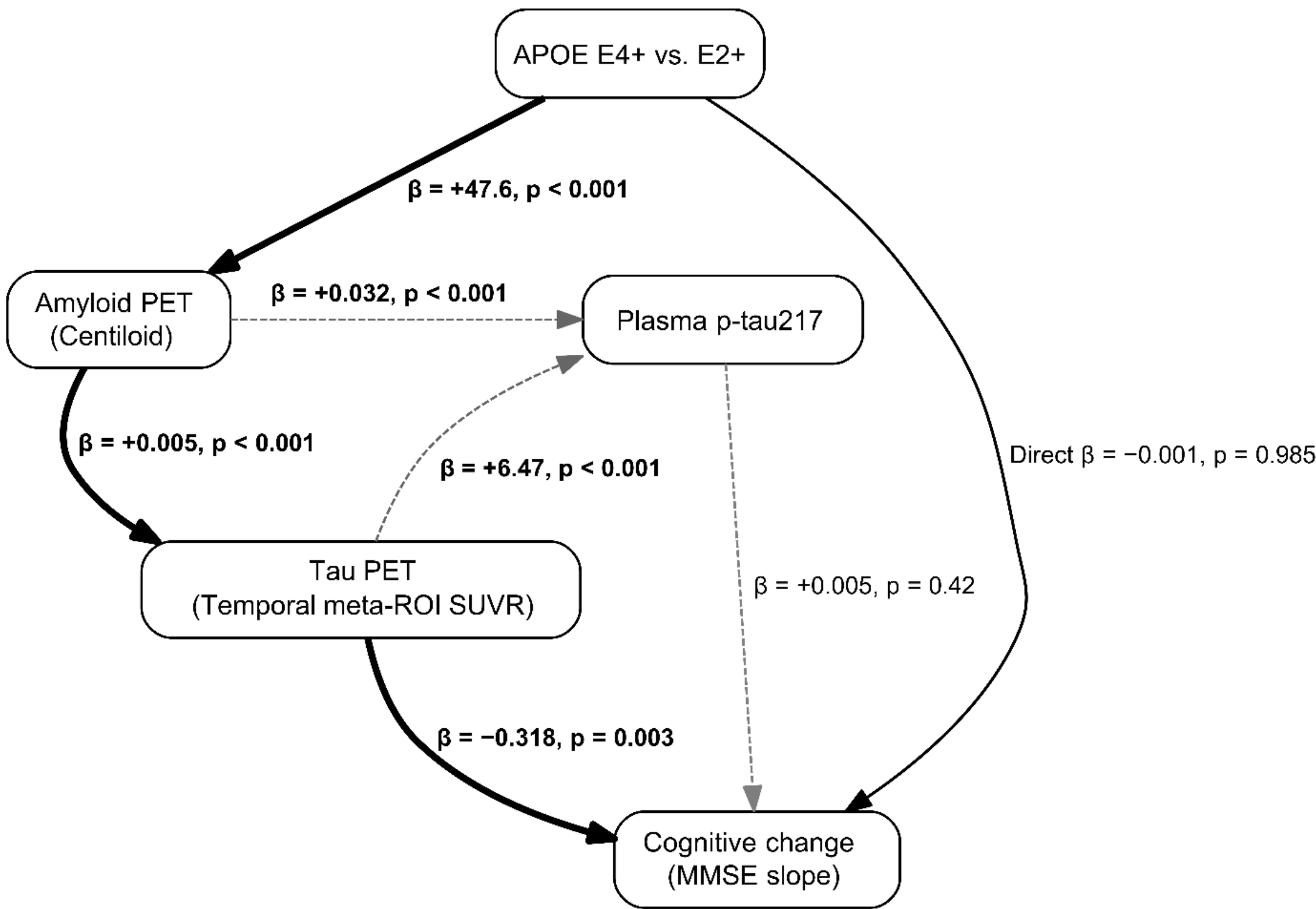


Figure 3. Mediation model
APOE E4+ compared to E2+ exerted its effect on cognitive decline predominantly through sequential amyloid and tau accumulation (indirect $\beta = -0.078$, $p = 0.027$), whereas the direct pathway was not significant ($\beta = -0.001$, $p = 0.985$). These findings support an amyloid-tau-mediated mechanism underlying E4-related cognitive deterioration.

CONCLUSION

- The association between plasma p-tau217 and amyloid burden varies by APOE genotype, being strongest in E2 and E3 carriers and significantly attenuated in E4 carriers. Although APOE E4 carriers showed more rapid cognitive decline, mediation analyses indicate that this effect is primarily driven by downstream amyloid-related tau pathology rather than plasma p-tau217 levels, supporting a role for p-tau217 as an upstream pathological correlate rather than a direct mediator of neurodegeneration.

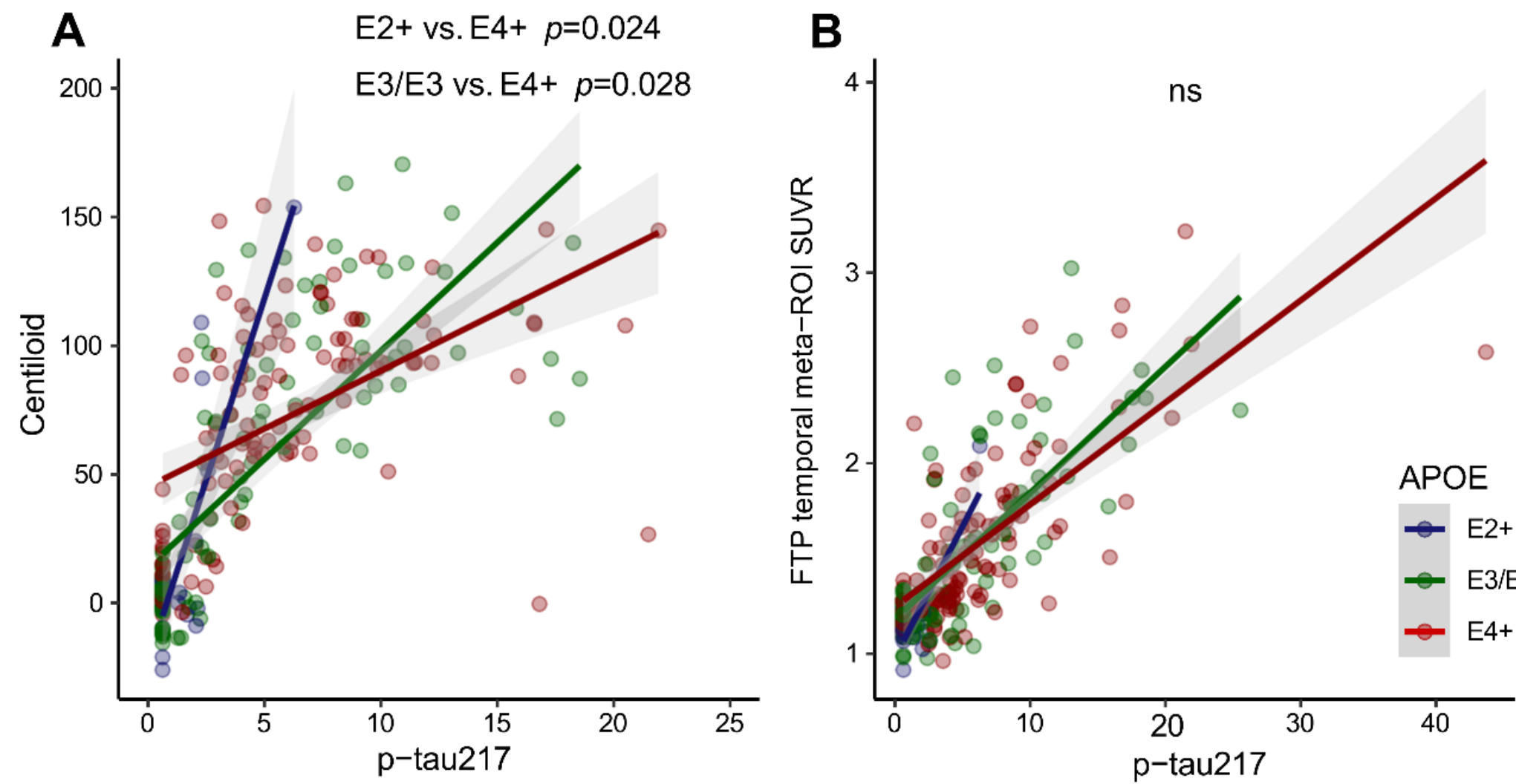


Figure 1. Correlation Between Centiloid and Tau Biomarkers Across APOE Genotypes