Supplementary Information

Article: "*APOE*ε4 potentiates Aβ effects on longitudinal tangle accumulation via tau phosphorylation".

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Abbreviations: AD = Alzheimer's disease; *APOE*ε4 = apolipoprotein E ε4; Aβ = amyloid-β; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CI = confidence interval; CU = cognitively unimpaired; GM = grey matter; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PET = positron emission tomography; p-tau217^{+} = phosphorylated tau at threonine 217; ROI = region of interest; SD = standard deviation; SUVR = standardized uptake value ratio.

Supplementary Table 1. Demographic characteristics of the CU young population.

	CU young
No.	10
Age, years	22.1 (1.4)
Male, No. (%)	4 (40.0)
Education, years	15.8 (1.5)
APOEε4 carrier, No. (%)	1 (10.0)
MMSE score	29.8 (0.6)
Global Aβ-PET SUVR	1.21 (0.07)
Temporal meta-ROI tau-PET SUVR	0.68 (0.09)
Hippocampal volume, cm^3	4.22 (0.55)
Follow-up, years	2.5 (0.6)

Continuous variables are presented as mean (SD).

Supplementary Table 2. Coefficients and associated statistics from regression analysis testing the association of *APOE*ε4 and Aβ-PET with longitudinal tau-PET.

	β (95% CI)	*T*-value	*P*-value
Δ tau-PET SUVR ~ *APOE*ε4 status + Aβ-PET SUVR + age + sex + diagnosis + baseline tau-PET SUVR + *APOE*ε4 status x Aβ-PET SUVR			
*APOE*ε4 carriership	0.021 (-0.003 to 0.044)	1.737	0.086
Aβ-PET SUVR	-0.002 (-0.021 to 0.018)	-0.179	0.859
Age	-0.006 (-0.017 to 0.005)	-1.015	0.313
Male	-0.0001 (-0.023 to 0.023)	-0.005	0.996
Clinical diagnosis			
MCI	0.024 (-0.005 to 0.053)	1.623	0.108
AD	0.039 (-0.022 to 0.101)	1.267	0.209
Baseline tau-PET SUVR	0.007 (-0.010 to 0.024)	0.822	0.413
*APOE*ε4 carriership x Aβ-PET SUVR	0.040 (0.017 to 0.062)	3.450	< 0.001

Continuous predictors were standardized prior to model entry. Aβ-PET was assessed in the global neocortical composite, and tau-PET was assessed in the temporal meta-ROI. All predictors were assessed at the baseline visit.

Supplementary Table 3. Demographic comparison between the whole elderly population and the subsample with longitudinal plasma p-tau217$^+$.

	Whole elderly population	Subsample with longitudinal plasma p-tau217$^+$	*P*-value
No.	94	65	-
Age, years	70.9 (6.3)	70.9 (5.6)	0.952
Male, No. (%)	33 (35.1)	18 (27.7)	0.325
Education, years	15.6 (3.8)	15.8 (3.4)	0.781
APOEε4 carrier, No. (%)	34 (36.2)	22 (33.8)	0.763
Diagnosis, No. (%)			
CU	62 (66.0)	43 (66.2)	
MCI	25 (26.6)	20 (30.8)	0.465
AD	7 (7.4)	2 (3.1)	
MMSE score	28.4 (2.3)	28.6 (2.4)	0.659
Global Aβ-PET SUVR	1.65 (0.54)	1.65 (0.52)	0.952
Temporal meta-ROI tau-PET SUVR	0.92 (0.40)	0.91 (0.37)	0.830
Hippocampal volume, cm^3	3.42 (0.44)	3.47 (0.39)	0.500
Follow-up, years	2.3 (0.5)	2.4 (0.5)	0.610

Continuous variables are presented as mean (SD). Student's t test (continuous variables) and contingency $\chi 2$ test (categorical variables) tested demographic differences.

Supplementary Table 4. Coefficients and associated statistics from regression analysis testing the association of *APOE*ε4 and Aβ-PET with longitudinal plasma p-tau217^{+}.

	β (95% CI)	*T*-value	*P*-value
Δ plasma p-tau217^{+} ~ *APOE*ε4 status + Aβ-PET SUVR + age + sex + diagnosis + baseline plasma p-tau217^{+} + *APOE*ε4 status x Aβ-PET SUVR			
*APOE*ε4 carriership	0.010 (-0.001 to 0.021)	1.839	0.071
Aβ-PET SUVR	0.001 (-0.007 to 0.010)	0.318	0.751
Age	0.004 (-0.002 to 0.009)	1.321	0.192
Male	0.003 (-0.007 to 0.014)	0.630	0.531
Clinical diagnosis			
MCI	0.002 (-0.011 to 0.016)	0.331	0.742
AD	0.013 (-0.029 to 0.056)	0.637	0.527
Baseline plasma p-tau217^{+}	-0.007 (-0.016 to 0.002)	-1.653	0.104
*APOE*ε4 carriership x Aβ-PET SUVR	0.020 (0.009 to 0.032)	3.690	< 0.001

Continuous predictors were standardized prior to model entry. Aβ-PET was assessed in the global neocortical composite. All predictors were assessed at the baseline visit. Analysis involving plasma p-tau217^{+} was conducted in a subset of 65 individuals with longitudinal plasma p-tau217+ measurements (**Supplementary Table 3**).

Supplementary Table 5. Coefficients and associated statistics from regression analysis testing the longitudinal association of plasma p-tau217$^+$ with tau-PET.

	β (95% CI)	*T*-value	*P*-value
Δ tau-PET SUVR ~ Δ plasma p-tau217$^+$ + age + sex + diagnosis + baseline tau-PET SUVR			
Δ plasma p-tau217$^+$	0.048 (0.032 to 0.064)	5.999	< 0.001
Age	-0.010 (-0.026 to 0.006)	-1.238	0.221
Male	-0.022 (-0.054 to 0.010)	-1.386	0.171
Clinical diagnosis			
MCI	0.023 (-0.010 to 0.057)	1.389	0.170
AD	-0.092 (-0.222 to 0.037)	-1.425	0.160
Baseline tau-PET SUVR	0.022 (-0.003 to 0.046)	1.770	0.082

Continuous predictors were standardized prior to model entry. Aβ-PET was assessed in the global neocortical composite, and tau-PET was assessed in the regions showing *APOE*ε4 and Aβ interaction effects on longitudinal tau tangle accumulation as measured by PET.

Supplementary Table 6. Coefficients and associated statistics from linear regression models testing the longitudinal association of tau-PET SUVR with cortical GM density.

	β (95% CI)	*T*-value	*P*-value
Δ Cortical GM density ~ Δ tau-PET SUVR + age + sex + diagnosis + education + baseline cortical GM density			
Δ tau-PET SUVR	-0.0010 (-0.0017 to -0.0003)	-2.715	0.008
Age	-0.0009 (-0.0016 to -0.0002)	-2.437	0.017
Male	0.0010 (-0.0007 to 0.0026)	1.164	0.248
Diagnosis			
MCI	-0.0004 (-0.0020 to 0.0011)	-0.562	0.576
AD	-0.0031 (-0.0060 to -0.0002)	-2.157	0.034
Education	-0.0002 (-0.0009 to 0.0005)	-0.566	0.573
Baseline cortical GM density	-0.0014 (-0.0022 to -0.0005)	-3.226	0.002

Continuous predictors were standardized prior to model entry. Tau-PET SUVR values were extracted from the regions showing *APOE*ε4 and Aβ interaction effects on longitudinal tau tangle accumulation as measured by PET. Brain atrophy was indexed with global cortical GM density using voxel-based morphometry.

Supplementary Table 7. Coefficients and associated statistics from linear regression models testing the longitudinal association of tau-PET SUVR with CDR-SB score.

	β (95% CI)	*T*-value	*P*-value
Δ CDR-SB score ~ Δ tau-PET SUVR + age + sex + diagnosis + education + baseline CDR-SB score			
Δ tau-PET SUVR	0.212 (0.108 to 0.315)	4.075	< 0.001
Age	0.042 (-0.058 to 0.143)	0.841	0.403
Male	0.039 (-0.174 to 0.252)	0.364	0.716
Diagnosis			
MCI	0.295 (0.029 to 0.562)	2.208	0.030
AD	2.389 (1.750 to 3.027)	7.448	< 0.001
Education	-0.047 (-0.150 to 0.055)	-0.917	0.362
Baseline CDR-SB score	-0.403 (-0.566 to -0.240)	-4.929	< 0.001

Continuous predictors were standardized prior to model entry. Tau-PET SUVR values were extracted from the regions showing *APOE*ε4 and Aβ interaction effects on longitudinal tau tangle accumulation as measured by PET. Analysis assessing clinical decline was conducted in a subset of 84 individuals with longitudinal CDR-SB data.