

APOE and Amyloid-Tau Pathology in Cognitively Unimpaired Older Adults

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MAIN FINDINGS

1

APOE $\epsilon 4$ showed **strong** dose-dependent associations with **amyloid burden** and age-related amyloid differences

2

APOE-related **global tau** associations were **modest**, only in $\epsilon 44$ carriers, with **larger medial temporal** effects among $\epsilon 4$ carriers

3

Higher tau burden was associated with **lower memory and language performance**, regardless APOE status

BACKGROUND

APOE genotype shows well-established dose-dependent associations with amyloid accumulation in cognitively unimpaired (CU) adults. In contrast, associations with tau burden and cognition are less well characterized

OBJECTIVE

To investigate associations among APOE genotype, amyloid burden, tau pathology, and cognition in CU older adults

METHODS

Participants: 4,380 CU older adults from the harmonized ADSP-PHC multicohort dataset were included in this cross-sectional study at baseline visit, with available APOE genotype, amyloid PET, and cognitive data. A subset of 758 participants also had tau PET imaging available

Outcomes of interest: associations between APOE, amyloid, tau, and cognitive performance (memory, language, executive function, visuospatial abilities)

Statistical analysis: linear and logistic regression models were used to evaluate these associations. Models were adjusted for age, sex, education, and study cohort. Regional tau analyses included medial temporal and neocortical regions

Table 1. Participant characteristics by APOE genotype

	Overall	$\epsilon 22$	$\epsilon 23$	$\epsilon 33$	$\epsilon 24$	$\epsilon 34$	$\epsilon 44$	p-value
N (%)	4,380	14 (0.3)	447 (10.2)	2,390 (54.6)	107 (2.4)	1,282 (29.3)	140 (3.2)	
Age, mean (SD), y	71.3 (5.6)	69.63 (4.12)	72.06 (5.71)	71.66 (5.74)	71.53 (5.65)	70.48 (5.36)	69.92 (5.36)	< 0.001
Women, N (%)	2,631 (60.1)	8 (57.1)	257 (57.5)	1,450 (60.7)	66 (61.7)	771 (60.1)	79 (56.4)	0.771
Education, mean (SD), y	16.7 (2.8)	16.86 (2.14)	16.60 (3.01)	16.60 (2.72)	16.60 (2.99)	16.80 (2.69)	16.77 (2.55)	0.699
Memory, mean (SD)	0.74 (0.44)	0.64 (0.32)	0.73 (0.42)	0.75 (0.45)	0.71 (0.44)	0.72 (0.43)	0.72 (0.46)	0.502
Executive, mean (SD)	0.86 (0.60)	—	0.89 (0.56)	0.87 (0.60)	0.74 (0.53)	0.86 (0.63)	0.73 (0.50)	0.562
Language, mean (SD)	0.85 (0.56)	—	0.79 (0.49)	0.85 (0.57)	0.82 (0.48)	0.87 (0.57)	0.87 (0.50)	0.822
Visuospatial, mean (SD)	0.49 (0.49)	—	0.49 (0.46)	0.48 (0.51)	0.43 (0.51)	0.52 (0.47)	0.57 (0.39)	0.804
A β positive, N (%)	1,300 (29.7)	2 (14.3)	76 (17.0)	454 (19.0)	52 (48.6)	614 (47.9)	102 (72.9)	< 0.001
A β SUVR (Centiloids), mean (95% CI)	17.91 (16.89–18.93)	4.64 (–2.92–12.20)	6.78 (4.46–9.09)	9.73 (8.59–10.87)	28.15 (21.70–34.60)	32.47 (30.32–34.63)	53.20 (46.40–60.00)	< 0.001
Tau SUVR, mean (95% CI)	1.24 (1.23–1.25)	1.18	1.21 (1.19–1.23)	1.23 (1.22–1.25)	1.23 (1.17–1.28)	1.26 (1.24–1.27)	1.31 (1.23–1.39)	< 0.001

Abbreviations: APOE, apolipoprotein E; SD, standard deviation; CI, confidence interval; A β , amyloid- β ; SUVR, standardized uptake value ratio; —, missing data.

Figure 1. Association between APOE and amyloid

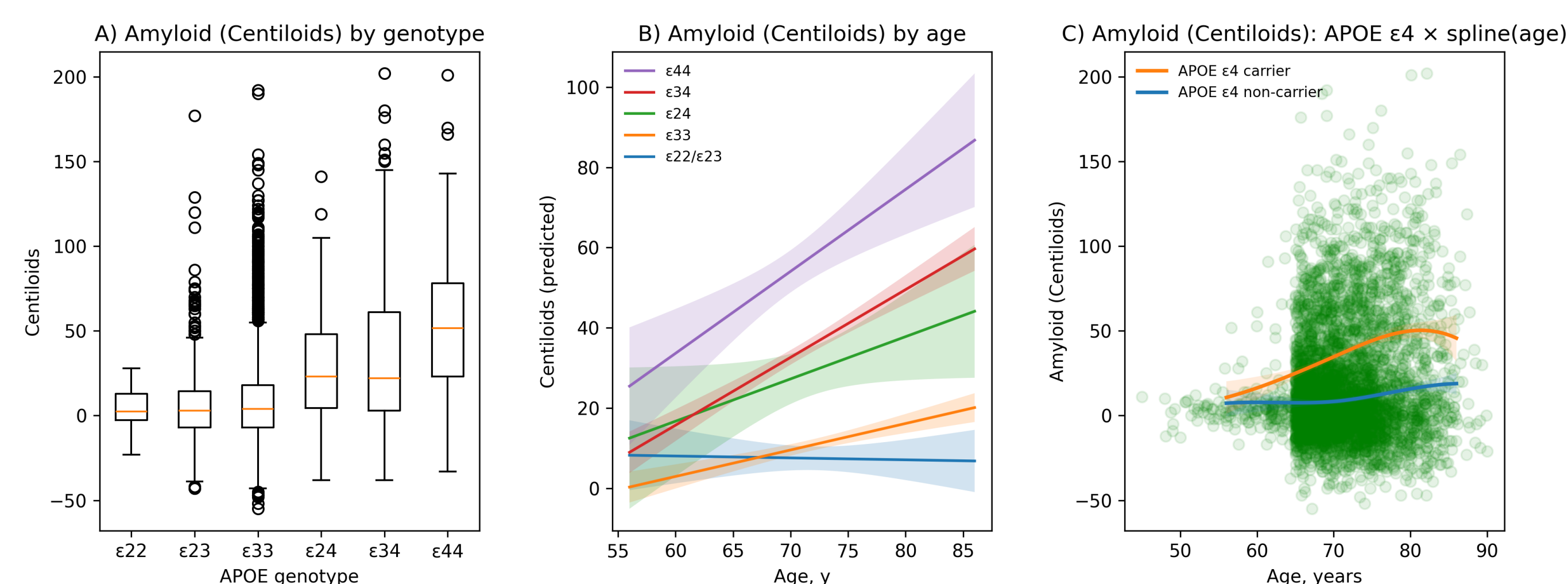
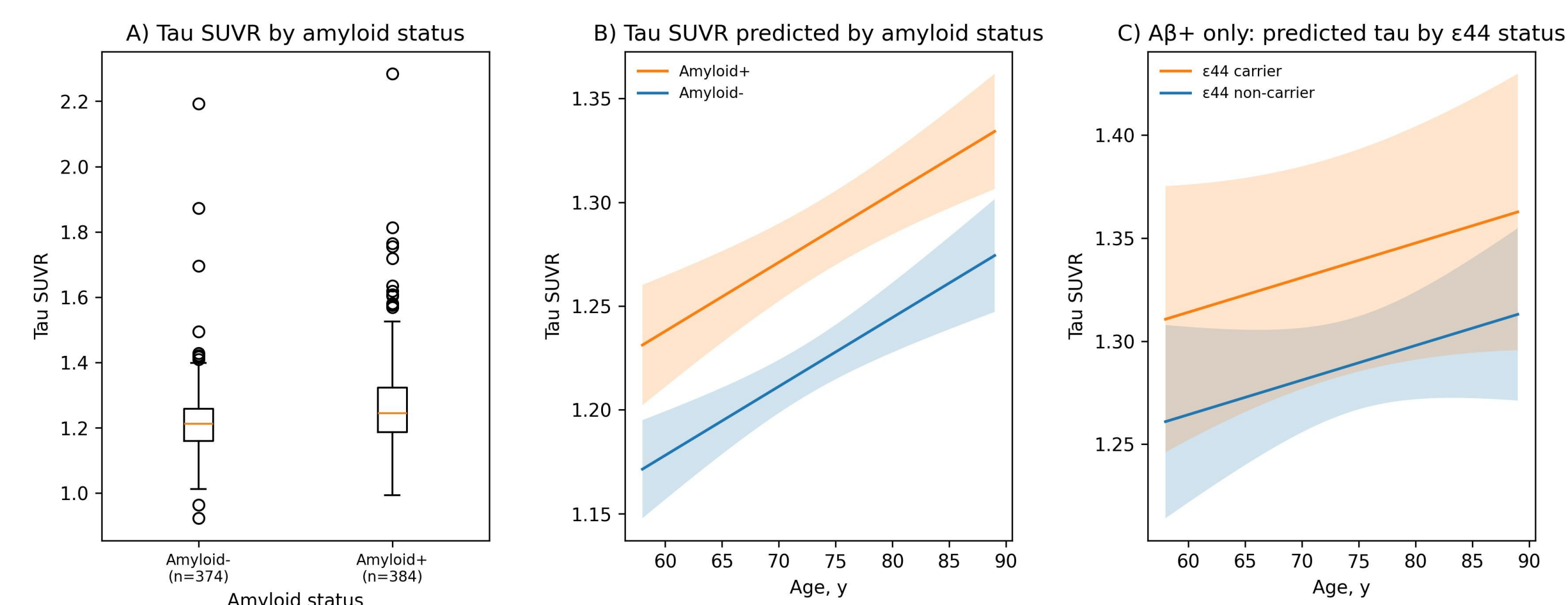


Figure 2. Association between APOE $\epsilon 44$, amyloid and tau



RESULTS

Table 2. Associations between APOE $\epsilon 4$ carrier and regional tau

Region	APOE $\epsilon 4$ β (95% CI)	Unadjusted p	FDR-adjusted p
Entorhinal cortex	0.026 (0.005–0.047)	.016	.041
Amygdala	0.040 (0.018–0.062)	< .001	.003
Inferior temporal cortex	0.005 (–0.016–0.026)	.625	.637
Inferior parietal cortex	0.004 (–0.013–0.022)	.637	.637
Precuneus	0.004 (–0.011–0.020)	.596	.637

Abbreviations: APOE, apolipoprotein E; FDR = false discovery rate; CI, confidence interval

➤ APOE $\epsilon 4$ carriers showed the **highest amyloid burden and amyloid positivity** (Table 1), and APOE genotype remained **strongly associated** with amyloid burden **after adjustment** (LRT $\chi^2(4) = 666.40$; $p < .001$) (Figure 1)

➤ Only APOE $\epsilon 44$ carriers showed significantly **higher global tau burden** ($\beta = 0.0472$; $p = .03$) (Figure 2), while regional analyses showed significantly **APOE $\epsilon 4$ -related tau effects in medial temporal regions** (Table 2)

➤ APOE genotype was **not associated with cognition**. Independently, **higher tau burden** was associated with **worse memory** ($\beta = -0.439$, FDR $p = .012$) and **language** ($\beta = -0.61$, FDR $p = .020$)

