

Background

The apolipoprotein E (APOE) ε2 allele is considered protective against Alzheimer's disease (AD), yet its relationship with prevalent tau and amyloid neuropathology in the community remains uncharacterized. We aimed to examine the associations between APOE ε2 and PET-derived tau and amyloid deposition in community-dwelling middle-aged adults.

Results

Mean [SD] age was 57.7 [9.6] years, and 254 [53.6%] participants were women (Table 1). No significant associations between APOE ε2 and tau or amyloid PET measures were observed in the total sample (Table 2). However, among individuals with the highest (top quartile) amyloid burden, APOE ε2 was associated with lower tau in the entorhinal cortex, rhinal cortex, fusiform gyrus, and medial temporal region, with estimates ranging from $\beta_{\text{fusiform gyrus}} = -0.070$ (SE = 0.031, $p = 0.03$) to $\beta_{\text{entorhinal}} = -0.136$ (SE = 0.045, $p = 0.003$) – Table 3. Among individuals with lower amyloid burden, APOE ε2 was not associated with tau. Associations between APOE ε2 and tau PET measures were not modified by age or sex.

Table 2: Associations of APOE ε2 carriership with tau and amyloid PET measures.

Tau PET measure	n = 376		
	β	SE	p
Tau entorhinal cortex, SUVR	-0.012	0.015	0.42
Tau rhinal cortex, SUVR	-0.012	0.016	0.44
Tau inferior temporal cortex, SUVR	0.002	0.012	0.88
Tau precuneus, SUVR	0.000	0.011	0.99
Tau fusiform gyrus, SUVR	-0.004	0.012	0.74
Tau middle temporal cortex, SUVR	0.004	0.011	0.69
Tau medial temporal cortex, SUVR	0.000	0.016	0.98
Tau global cortical measure, SUVR	0.002	0.010	0.85
Amyloid PET measure	n = 462		
	β	SE	p
Amyloid FLR, DVR	-0.025	0.014	0.07
Amyloid precuneus, DVR	-0.034	0.018	0.06
Amyloid inferior temporal cortex, DVR	-0.014	0.013	0.28
Amyloid occipital cortex, DVR	-0.007	0.009	0.48

Results from linear regression models with the respective PET measure as the outcome and APOE ε2 carriership as the main predictor.

Models are adjusted for age at PET acquisition, sex, and PET camera.

Values represent beta coefficients (β), and their corresponding standard errors (SE) and p values (p).

Statistically significant findings at $p < .05$ are indicated in bold.

Abbreviations: APOE, apolipoprotein E; PET, positron emission tomography; SUVR, standard uptake volume ratio; FLR, frontal, lateral, and retrosplenial regions; DVR, distribution volume ratio.

Conclusions

In this community-based sample, APOE ε2 was associated with lower tau deposition in regions susceptible to early tau accumulation, but only among individuals with the highest (>75th percentile) amyloid burden. APOE ε2 carriership might exhibit protective influences on early tau deposition that emerge as amyloid pathology accumulates.

Methods

A total of 474 participants from the community-based Framingham Heart Study who underwent tau and/or amyloid PET imaging from September 2015 to June 2022 were included in this cross-sectional analysis. Participants without APOE genotype data or those carrying the ε2/ε4 genotype were excluded. 18F-Flortaucipir PET indices included regional (entorhinal cortex, rhinal cortex, inferior temporal cortex, middle temporal cortex, precuneus, fusiform gyrus) and composite (medial temporal, global cortical) tau measures. 11C-Pittsburgh Compound-B PET indices included a global composite (frontal, lateral, and retrosplenial [FLR]) and regional (precuneus, inferior temporal cortex, occipital cortex) amyloid measures. Primary analyses examined associations between APOE ε2 and PET measures using linear regression models adjusted for age at PET, sex, and PET camera. Secondary analyses examined whether associations with tau PET measures were modified by amyloid burden, age, or sex.

Table 1: Participant characteristics (N = 474).	
Age at PET acquisition, years, mean (SD)	57.7 (9.6)
Sex, n (%)	
Women	254 (53.6)
Men	220 (46.4)
APOE genotype, n (%)	
[ε2/ε2, ε2/ε3]	68 (14.3)
[ε3/ε3]	306 (64.6)
[ε3/ε4, ε4/ε4]	100 (21.1)
Tau-PET camera, n (%)	
GE Discovery MI	92 (24.3)
Siemens ECAT HR+	286 (76.7)
Amyloid-PET camera, n (%)	
GE Discovery MI	145 (31.1)
Siemens ECAT HR+	322 (69.0)
Tau PET measures (n = 376)	
Tau entorhinal cortex, SUVR, median (IQR)	1.05 (1.00, 1.10)
Tau rhinal cortex, SUVR, median (IQR)	1.09 (1.04, 1.15)
Tau inferior temporal cortex, SUVR, median (IQR)	1.14 (1.1, 1.19)
Tau precuneus, SUVR, median (IQR)	1.08 (1.04, 1.12)
Tau fusiform gyrus, SUVR, median (IQR)	1.14 (1.11, 1.18)
Tau middle temporal cortex, SUVR, median (IQR)	1.09 (1.04, 1.15)
Tau medial temporal cortex, SUVR, median (IQR)	1.10 (1.05, 1.16)
Tau global cortical measure, SUVR, median (IQR)	1.06 (1.02, 1.10)
Amyloid PET measures (n = 462)	
Amyloid FLR, DVR, median (IQR)	1.06 (1.03, 1.09)
Amyloid precuneus, DVR, median (IQR)	1.13 (1.09, 1.18)
Amyloid inferior temporal cortex, DVR, median (IQR)	1.01 (0.96, 1.08)
Amyloid occipital cortex, DVR, median (IQR)	1.07 (1.04, 1.11)
Centiloids	4.32 (-0.34, 9.5)

Abbreviations: PET, positron emission tomography; SD, standard deviation; APOE, apolipoprotein E; SUVR, standard uptake volume ratio; IQR, interquartile range; FLR, frontal, lateral, and retrosplenial regions; DVR, distribution volume ratio.

Table 3: Associations of APOE ε2 carriership with tau and amyloid PET measures by amyloid burden.

PET tau measure	Lower amyloid burden (Q1, Q2, Q3, n = 285) ^a				Highest amyloid burden (Q4, n = 79) ^b		
	p for interaction ^a	β	SE	p	β	SE	p
Tau entorhinal cortex, SUVR	0.0003	0.013	0.015	0.40	-0.136	0.045	0.003
Tau rhinal cortex, SUVR	0.006	0.009	0.017	0.60	-0.113	0.044	0.01
Tau inferior temporal cortex, SUVR	0.01	0.018	0.013	0.16	-0.063	0.032	0.05
Tau precuneus, SUVR	0.14						
Tau fusiform gyrus, SUVR	0.01	0.013	0.013	0.32	-0.070	0.031	0.03
Tau middle temporal cortex, SUVR	0.02	0.018	0.012	0.12	-0.053	0.030	0.08
Tau medial temporal cortex, SUVR	0.005	0.021	0.017	0.21	-0.103	0.046	0.03
Tau global cortical measure, SUVR	0.03	0.015	0.011	0.18	-0.046	0.028	0.10

^a Linear regression models with the respective PET measure as the outcome, and APOE ε2 carriership, amyloid subgroup, as well as their product term as the main predictors. Values represent the p value of the respective product term (p for interaction).

^b Linear regression models with the respective PET measure as the outcome and APOE ε2 carriership as the main predictor conducted in low and high amyloid burden subgroups.

All models are adjusted for age at PET acquisition, sex, and PET camera.

Values represent beta coefficients (β), and their corresponding standard errors (SE) and p values (p).

Statistically significant findings at $p < .05$ are indicated in bold.

Abbreviations: APOE, apolipoprotein E; PET, positron emission tomography; SUVR, standard uptake volume ratio; FLR, frontal, lateral, and retrosplenial regions; DVR, distribution volume ratio.