



Differential associations of *APOE-ε2* and *APOE-ε4* alleles with PET-measured amyloid-β and tau deposition in older individuals without dementia

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Abstract

Purpose To examine associations between the *APOE-ε2* and *APOE-ε4* alleles and core Alzheimer's disease (AD) pathological hallmarks as measured by amyloid-β (Aβ) and tau PET in older individuals without dementia.

Methods We analyzed data from 462 ADNI participants without dementia who underwent Aβ (¹⁸F]florbetapir or [¹⁸F]florbetaben) and tau (¹⁸F]flortaucipir) PET, structural MRI, and cognitive testing. Employing *APOE-ε3* homozygotes as the reference group, associations between *APOE-ε2* and *APOE-ε4* carriership with global Aβ PET and regional tau PET measures (entorhinal cortex (ERC), inferior temporal cortex, and Braak-V/VI neocortical composite regions) were investigated using linear regression models. In a subset of 156 participants, we also investigated associations between *APOE* genotype and regional tau accumulation over time using linear mixed models. Finally, we assessed whether Aβ mediated the cross-sectional and longitudinal associations between *APOE* genotype and tau.

Results Compared to *APOE-ε3* homozygotes, *APOE-ε2* carriers had lower global Aβ burden (β_{std} [95% confidence interval (CI)]: -0.31 [$-0.45, -0.16$], $p = 0.034$) but did not differ on regional tau burden or tau accumulation over time. *APOE-ε4* participants showed higher Aβ (β_{std} [95%CI]: 0.64 [$0.42, 0.82$], $p < 0.001$) and tau burden (β_{std} range: 0.27 - 0.51 , all $p < 0.006$).

Gemma Salvadó and Michel J. Grothe contributed equally to this work.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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In mediation analyses, *APOE-ε4* only retained an Aβ-independent effect on tau in the ERC. *APOE-ε4* showed a trend towards increased tau accumulation over time in Braak-V/VI compared to *APOE-ε3* homozygotes (β_{std} [95%CI]: 0.10 [− 0.02, 0.18], $p = 0.11$), and this association was fully mediated by baseline Aβ.

Conclusion Our data suggest that the established protective effect of the *APOE-ε2* allele against developing clinical AD is primarily linked to resistance against Aβ deposition rather than tau pathology.

Keywords Tau · Amyloid-β · Cross-sectional · Longitudinal · Sex interaction · Cognition · Hippocampal volumes · APOE · PET

Introduction

The apolipoprotein-E (*APOE*) $\epsilon 4$ allele is the major genetic risk factor for sporadic Alzheimer's disease (AD). *APOE-ε4* is associated with increased levels of amyloid-β (Aβ) [1–4] and tau aggregates [5–9], the two main pathological hallmarks of AD. However, the question whether *APOE-ε4* directly impacts tau pathology or increases tau in an Aβ-dependent fashion remains controversial [10–14].

Contrary to the detrimental effect of *APOE-ε4*, the *APOE-ε2* allele is protective against AD [2, 15, 16]. Studies focusing on *APOE-ε2* are scarce due to the low prevalence of this allele in the general population (~ 8%) and especially in AD populations (~ 5%) [17, 18]. Previous cerebrospinal fluid (CSF) and PET studies have reported robust associations between *APOE-ε2* and decreased levels of Aβ pathology [19–21]. Regarding tau pathology, nearly all biomarker studies on this topic reported no association with the *APOE-ε2* allele [19, 21, 22], with one exception reporting lower phosphorylated tau (p-tau) [23]. However, all these studies measured the amount of tau pathology in CSF, which provides information on global soluble p-tau burden but not on the regional distribution of neurofibrillary tau tangles as provided by tau-sensitive PET imaging techniques. Of note, multiple studies have assessed the concordance between CSF tau and tau PET reporting a moderate association [24–26]; however, this association may be dependent on disease stage, neurodegeneration, and the tau fragments measured in CSF [27, 28]. Furthermore, a recent study showed that dichotomization of PET and CSF-derived tau measures could lead to ~ 25% discordance, which does impact future cognitive decline [29]. Thus, potential associations between *APOE-ε2* and regional tau deposition on PET remain to be investigated, which is all the more important as a recent PET study has identified a clear regional predilection for *APOE-ε4*-related tau deposition confined to the medial temporal lobe [9]. Given that this association was found to be partly independent of amyloid-β aggregation, *APOE* was even proposed as a potential target for anti-tau disease-modifying therapies.

In the present study, we leveraged available *APOE* genotyping and multitracer PET imaging data from a large cohort of older individuals without dementia to study cross-sectional and longitudinal associations of the *APOE-ε2* and $\epsilon 4$ alleles with regional tau deposition and put these in the context

of *APOE* effects on Aβ pathology. At a cross-sectional level, we hypothesized that *APOE-ε4* participants would have higher levels of both Aβ and tau pathology as previously reported, and that the *APOE-ε2* allele would be associated with lower Aβ—but not tau—burden. We further hypothesized that Aβ would mediate the effect of *APOE-ε4* on tau differently depending on the brain region under investigation, as a previous PET study reported an Aβ-independent association with tau pathology in the medial temporal lobe, but not in the rest of the brain [9]. In the longitudinal analysis, we hypothesized to observe faster increase in tau accumulation in $\epsilon 4$ carriers, but no difference in accumulation rates in $\epsilon 2$ carriers compared to *APOE-ε3* homozygotes. Finally, as recent studies have indicated a possible interaction effect between the *APOE-ε4* allele and female sex on both Aβ and tau pathology [4, 8, 21, 30, 31], we also investigated this in the current PET study. Our study, assessing the impact of genetic variants on Aβ and tau imaging, will contribute evidence required for their diagnostic use, as outlined in the strategic biomarker roadmap for the validation of AD diagnostic biomarkers [32].

Material and methods

Participants

From the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, we selected all participants without dementia (i.e., cognitively unimpaired [CU] or diagnosed with mild cognitive impairment [MCI]) that underwent Aβ PET (^{18}F florbetapir or ^{18}F florbetaben), tau PET (^{18}F flortaucipir), and magnetic resonance imaging (MRI) ($n = 462$). Participants were grouped as *APOE-ε2* carriers (i.e., 1 or 2 *APOE-ε2* alleles; $n = 45$), *APOE-ε3* homozygotes ($n = 257$), or *APOE-ε4* carriers (i.e., 1 or 2 *APOE-ε4* alleles, $n = 160$). We excluded *APOE-ε2ε4* participants ($n = 7$) from further analyses. A subset of 156 individuals (10 *APOE-ε2*, 76 *APOE-ε3ε3*, 70 *APOE-ε4*) also underwent at least one follow-up ^{18}F flortaucipir tau PET scan on average 1.6 (0.7) years later.

We included CU and MCI patients because we aimed to investigate how *APOE* modified the early development of Aβ and tau pathology, and *APOE* is a known AD-risk factor in these individuals [1]. On the other hand, it has previously been

reported that patients with AD dementia showed different associations between *APOE* and A β and tau biomarkers, compared to patients without dementia [33–35]. Thus, to avoid possible bias in our results, we excluded AD dementia patients from our analyses. Although *APOE* effects may be influenced by diagnosis status (i.e., CU or MCI), we pooled these two groups to increase the sample size (especially for $\epsilon 2$ carriers, the main *APOE* allele of interest in our study) while adjusting for clinical diagnosis in the statistical models (please see the “Statistical analyses” section).

ADNI is a multi-site open access dataset designed to accelerate the discovery of biomarkers to identify and track AD pathology (adni.loni.usc.edu). Data collection and sharing in ADNI were approved by the Institutional Review Board of each participating institution, and written informed consent was obtained from all participants.

***APOE* genotyping**

APOE genotype was determined by genotyping the two single-nucleotide polymorphisms that define the *APOE*- $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles (rs429358, rs7412) with DNA extracted by Cogenics from a 3-mL aliquot of EDTA blood (adni.loni.usc.edu/data-samples/genetic-data/).

Image acquisition

All image acquisition procedures are described in detail on the ADNI website (<http://adni.loni.usc.edu/methods/documents/>). Briefly, [^{18}F]flortaucipir tau PET images were acquired in six frames of 5 min each, 75–105-min post-injection (p.i.). A β PET images were acquired in four frames of 5 min each, 50–70 min p.i. for [^{18}F]florbetapir and 90–110 min p.i. for [^{18}F]florbetaben. Finally, structural MRI data were acquired on 3-T scanning platforms using T1-weighted sagittal 3-dimensional magnetization-prepared rapid-acquisition gradient echo sequences (MP-RAGE).

Image processing

Regional tau PET data were downloaded from the ADNI Laboratory of Neuroimaging (LONI) database (<https://ida.loni.usc.edu>). The full preprocessing pipeline is specified elsewhere [36]. In brief, first the T1-weighted MR image closest in time to the [^{18}F]flortaucipir PET scan was segmented in native space using Freesurfer (v5.3.0). Then, each [^{18}F]flortaucipir image was co-registered to the MRI. Finally, the MR-segmented regions were used to calculate mean volume-weighted uptake in the corresponding region on PET. Standardized uptake value ratios (SUVR) were computed using inferior cerebellar gray matter as reference region. For this study, we selected the following regions-of-interest (ROI): the entorhinal cortex (ERC), inferior temporal cortex

(ITC), and a neocortical Braak V/VI composite region [37], representing early, intermediate, and late regions of tau accumulation, respectively. The hippocampus was not merged with the ERC into an early Braak I/II region due to known [^{18}F]flortaucipir PET signal confounds in this region [38, 39].

For A β PET, we downloaded global neocortical composite SUVR values (using the whole cerebellum as reference) from the ADNI-LONI database (adni.loni.usc.edu/methods/pet-analysis). We converted these values to the common Centiloid scale using equations previously derived by the ADNI PET Core (<http://adni.loni.usc.edu/data-samples/access-data/>) in order to be able to combine data from [^{18}F]florbetapir and [^{18}F]florbetaben scans [40].

Preprocessed structural MR images were downloaded from the ADNI server to calculate hippocampal volumes. We extracted the hippocampal gray matter volume using an automated atlas-based volumetry approach based on a hippocampal standard space mask representing harmonized delineation criteria as described previously [41]. Total intracranial volumes, calculated as the total sum of segmented gray matter, white matter, and CSF volumes, were used to normalize the hippocampal volumes.

Neuropsychological assessment

We downloaded the widely used composite scores of episodic memory (ADNI-MEM) [42] and executive function (ADNI-EF) [43] from the ADNI-LONI website, as well as the recently validated composites of language (ADNI-LAN) and visuospatial functioning (ADNI-VS) [44].

Statistical analyses

We compared demographic information between *APOE* groups in the main sample and the longitudinal subsample using ANOVA for continuous variables and Chi-squared tests for categorical variables.

The primary cross-sectional analysis assessed the associations between *APOE* alleles and the two main hallmarks of AD (A β and tau) measured with PET. We performed this analysis using linear regression with *APOE* groups (i.e., $\epsilon 2$ carriers, $\epsilon 3$ homozygotes, and $\epsilon 4$ carriers) as independent variable, and Centiloids (global A β PET measure), ERC, ITC, and Braak V/VI [^{18}F]flortaucipir SUVR (regional tau PET measures) as dependent variables, while adjusting for age, sex, education, and diagnosis (CU or MCI), in independent models. Gene-dose effects were not investigated due to the complete lack of $\epsilon 2$ homozygotes in the sample. We also examined *APOE* by sex interaction effects on A β and tau PET variables. As a secondary analysis, we examined *APOE* by A β status interactions on tau PET burden. To that end, we dichotomized A β load using a previously validated threshold of > 12

Centiloids, which has been shown to sensitively detect early A β pathology in an independent neuropathologic validation study and a CSF study [45, 46]. Additionally, we investigated main *APOE* effects on normalized hippocampal volumes and cognitive composite scores using analog covariate-controlled linear regression models.

We performed *post hoc* mediation analyses to test whether the associations between *APOE* and regional tau PET burden were mediated by global A β burden. Age, sex, education, and diagnosis were included as covariates in these models and this analysis was only performed for associations that were significant in the primary analysis described above. We repeated this mediation analysis when stratifying by sex and A β status.

In a complementary longitudinal analysis on a subset of participants with serial tau PET acquisitions ($n = 156$), we assessed whether the *APOE* groups showed differential rates of tau accumulation over time. To this end, we applied linear mixed models with random slopes and intercepts. Regional tau burden (ERC, ITC, and Braak V/VI) served as dependent variables, and we included main effects for time and *APOE* groups as well as an interaction term for time**APOE*. These models were adjusted for age, sex, education, and diagnosis. Note that we performed this analysis only for tau PET and not A β PET, because longitudinal A β PET imaging was performed before tau PET and our primary focus was on *APOE* associations with tau PET.

To examine whether longitudinal tau accumulation was dependent on A β burden at baseline, we performed another mediation analysis using the rate of tau accumulation as dependent variable and baseline A β load as mediator. Rates of tau accumulation were calculated by extracting the subject-specific slopes from a linear mixed model including only time as predictor. Age, sex, education, and diagnosis at baseline were included as covariates in all paths of the mediation analysis. Mediation analyses were only performed on the associations that were significant or showed a trend towards significance in the previous analysis.

For all analyses, *APOE*- $\epsilon 3\epsilon 3$ participants were selected as the reference group. Statistical significance was set at $p < 0.05$. Following recommendations described in the statistical literature, we did not apply a correction for multiple comparisons in this hypothesis-driven study with a limited number of planned comparisons that are motivated by previous literature [47] as the main analysis. However, we included multiple comparisons-adjusted results of the main analyses as supplementary information. We used the *mvt* method of the *emmeans* package to perform these adjustments. All statistical analyses were performed with R (v3.6.2), except mediation analyses that were performed with the PROCESS (v3.4.1) toolbox from SPSS (www.processmacro.org) [48]. Statistics were derived using a bootstrapping approach with $n = 1000$ iterations as implemented in the R package *boot*.

Results

Sample characteristics

Participant demographics, imaging, and cognitive data of the study sample are presented in Table 1. Participants were mainly CU (67.9%), had a mean age of 74.3 years and evenly distributed sex (52.8% women). Across *APOE* groups, $\epsilon 4$ carriers were slightly younger than $\epsilon 2$ carriers and $\epsilon 3$ homozygotes ($F = 3.940$, $p = 0.020$). There were no other differences in demographic characteristics across *APOE* groups. Out of the 462 participants, 324 underwent [^{18}F]florbetapir A β PET (70.1%) and 138 [^{18}F]florbetaben A β PET (29.9%). *APOE*- $\epsilon 4$ carriers had a higher proportion of A β -positive subjects (74.4%, $p < 0.001$) and *APOE*- $\epsilon 2$ carriers a lower proportion (33.3%, $p = 0.054$) compared to the $\epsilon 3$ homozygotes (49.0%). Characteristics of the subsample with longitudinal tau PET did not differ significantly from the main sample on any of the variables (Table s1). Demographic information stratified by *APOE* and sex and by *APOE* and A β status are shown in Table s2 and Table s3, respectively.

Associations between *APOE* alleles and cross-sectional A β and tau PET

Compared to *APOE*- $\epsilon 3\epsilon 3$ participants, $\epsilon 2$ carriers showed lower global A β burden (β_{std} [95% confidence interval (CI)] = -0.31 [$-0.45, -0.16$], $p = 0.034$), but no differences in regional tau burden (Table 2 and Fig. 1). On the contrary, $\epsilon 4$ carriers exhibited higher A β load (β_{std} [95%CI]: 0.64 [$0.42, 0.82$], $p < 0.001$) as well as higher tau load in all regions assessed (ERC: β_{std} [95%CI] = 0.51 [$0.33, 0.70$], $p < 0.001$; ITC: β_{std} [95%CI] = 0.30 [$0.08, 0.49$], $p = 0.002$; Braak V/VI: β_{std} [95%CI] = 0.27 [$0.03, 0.49$], $p = 0.006$; Table 2 and Fig. 1). Results corrected for multiple comparisons can be found in Table s4.

There was also a sex**APOE*- $\epsilon 4$ interaction effect on ERC tau burden (β_{stand} [95%CI]: 0.39 [$0.03, 0.76$], $p = 0.038$; Table 3), with the deleterious effects of the $\epsilon 4$ allele on tau being higher in women. Detailed results of the sex-stratified analyses are provided in Table s5. The significant interaction between A β status and *APOE*- $\epsilon 4$ on ERC tau burden (β_{stand} [95%CI]: 0.62 [$0.28, 0.91$], $p = 0.002$; Table 3) indicates a stronger *APOE*- $\epsilon 4$ effect on tau burden in A β -positive participants. Detailed results of the analyses stratified by A β status are provided in Table s6 and Figure s1. Results of the sex and A β status interactions corrected for multiple comparisons can be found in Table s7.

Regarding non-PET measures, neither *APOE*- $\epsilon 2$ nor *APOE*- $\epsilon 4$ were significantly associated with hippocampal volumes. *APOE*- $\epsilon 4$ carriers showed lower memory scores (β_{stand} [95%CI]: -0.17 [$-0.33, 0.01$], $p = 0.048$), but no other associations were observed between *APOE* and non-amnesic cognitive domain scores ($p > 0.24$, Table 2).

Table 1 Demographics, imaging, and cognitive information of the study sample. Values reflect group means and standard deviations in parentheses, unless otherwise specified. A β status was positive (negative) if A β load was higher (lower) than 12 Centiloids [45, 46]. *p*-

values correspond to the overall group (i.e., *APOE* genotype) effects, while superscript letters indicate significance of the pair-wise group differences (a: *APOE*- ϵ 4 carriers vs. *APOE*- ϵ 3 ϵ 3; b: *APOE*- ϵ 2 carriers vs. *APOE*- ϵ 4 carriers)

	Main sample				<i>p</i>
	All (<i>n</i> = 462)	<i>APOE</i> - ϵ 2 carriers (<i>n</i> = 45)	<i>APOE</i> - ϵ 3 ϵ 3 (<i>n</i> = 257)	<i>APOE</i> - ϵ 4 carriers (<i>n</i> = 160)	
Demographics					
Age, years	74.3 (7.6) [56-94]	74.7 (6.8) [61-92]	75.1 (7.8) [56-94]	72.9 (7.3) [57-94]	0.020 ^a
Women, <i>n</i> (%)	244 (52.8)	21 (46.7)	132 (51.4)	91 (56.9)	0.376
Education, years	16.6 (2.5)	16.3 (2.6)	16.8 (2.4)	16.4 (2.6)	0.282
Diagnosis, CU <i>n</i> (%)	315 (68.2)	29 (64.4)	184 (71.6)	102(63.8)	0.210
MMSE	28.4 (2.5)	28.6 (1.8)	28.4 (2.6)	28.2 (2.4)	0.443
Tau PET measurements (SUVR)					
ERC	1.19 (0.20)	1.16 (0.16)	1.15 (0.17)	1.26 (0.24)	< 0.001 ^{a,b}
ITC	1.26 (0.24)	1.22 (0.10)	1.24 (0.22)	1.32 (0.29)	0.002 ^{a,b}
Braak V/VI	1.09 (0.14)	1.06 (0.07)	1.08 (0.13)	1.12 (0.15)	0.005 ^{a,b}
Aβ PET measurement					
Centiloids	32.1 (37.1)	14.4 (14.8)	25.5 (33.6)	47.6 (41.4)	< 0.001 ^{a,b}
A β positive, <i>n</i> (%)	260 (56.3)	15 (33.3)	126 (49.0)	119 (74.4)	< 0.001 ^{a,b}
MRI measurement					
Hippocampal volumes	4.56 (0.52)	4.53 (0.51)	4.57 (0.51)	4.57 (0.54)	0.903
Cognitive composite measures (<i>z</i> scores)					
Episodic memory	0.78 (0.73)	0.73 (0.71)	0.83 (0.71)	0.71 (0.77)	0.262
Executive function	0.86 (0.93)	0.82 (0.71)	0.90 (0.97)	0.83 (0.91)	0.685
Language	0.68 (0.85)	0.64 (0.77)	0.67 (0.87)	0.69 (0.85)	0.943
Visuospatial functioning	0.12 (0.69)	0.22 (0.67)	0.12 (0.70)	0.10 (0.67)	0.596

Significant *p*-values (*p* < 0.05) are shown in bold.

CU cognitively unimpaired; MMSE Mini-Mental State Examination; SUVR standardized uptake value ratio; ERC entorhinal cortex; ITC inferior temporal cortex; A β amyloid- β ; MRI magnetic resonance imaging

Table 2 Linear regression parameters (standardized β) for the association of *APOE*- ϵ 2 and *APOE*- ϵ 4 genotypes with tau PET, A β PET, MRI, and cognition measurements. *APOE*- ϵ 3 ϵ 3 participants were selected as the reference group for all comparisons. Models included age, sex, education, and diagnosis as covariates

	<i>APOE</i> - ϵ 2		<i>APOE</i> - ϵ 4	
	β [95%CI]	<i>p</i>	β [95%CI]	<i>p</i>
Tau measurements				
ERC	0.03 [- 0.17, 0.39]	0.533	0.51 [0.33, 0.70]	< 0.001
ITC	- 0.10 [- 0.26, 0.10]	0.498	0.30 [0.08, 0.49]	0.002
Braak V-VI	- 0.12 [- 0.32, 0.08]	0.449	0.27 [0.03, 0.49]	0.006
Aβ measurement				
Centiloids	- 0.31 [- 0.45, - 0.16]	0.034	0.64 [0.42-0.82]	< 0.001
MRI measurement				
Hippocampal volumes	- 0.02 [- 0.35, 0.26]	0.461	- 0.08 [- 0.24, 0.10]	0.331
Cognitive composite measures				
Episodic memory	- 0.05 [- 0.30, 0.24]	0.475	- 0.17 [- 0.33, 0.01]	0.048
Executive function	- 0.04 [- 0.27, 0.23]	0.519	- 0.10 [- 0.27, 0.07]	0.241
Language	0.05 [- 0.25, 0.32]	0.451	0.03 [- 0.14, 0.22]	0.468
Visuospatial functioning	0.18 [- 0.12, 0.48]	0.246	- 0.03 [- 0.22, 0.18]	0.474

Statistically significant results (*p* < 0.05)

A β amyloid- β ; MRI magnetic resonance imaging; CU cognitively unimpaired; CI confidence interval

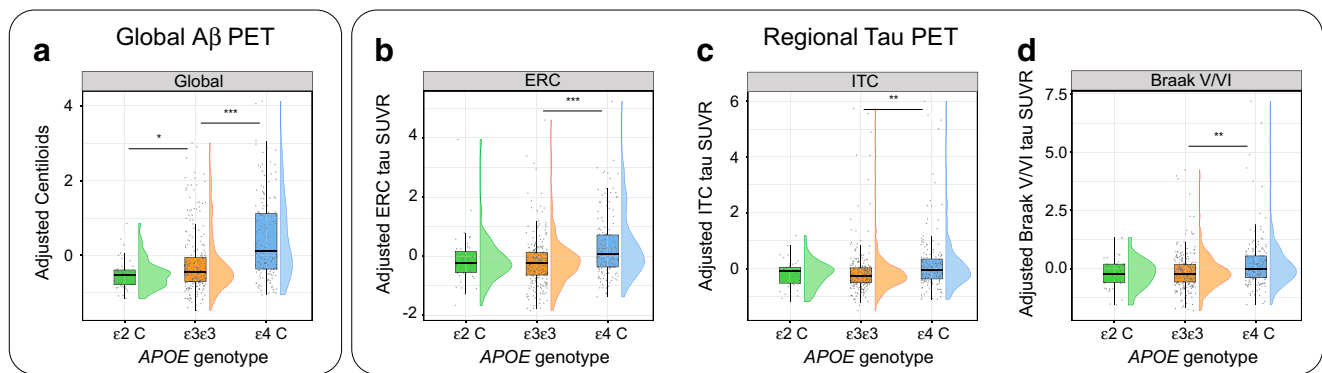


Fig. 1 Associations of *APOE-ε2* and *APOE-ε4* alleles with cross-sectional measures of Aβ (a) and tau burden (b–d). Tau regions studied were ERC (b), ITC (c), and Braak V–VI (d). PET measures are adjusted by age, sex, education, and diagnosis. Boxplots show median values (middle line) with lower and upper hinges corresponding to the first and

third quartiles. Dots represent individual adjusted PET measures, with violin plots showing their distribution. Aβ, amyloid-β; ERC, entorhinal cortex; ITC, inferior temporal cortex; SUVR, standardized uptake value ratio. * $p < 0.05$; *** $p < 0.001$

In the mediation analyses, we found that the association between *APOE-ε4* and tau burden was mediated by global Aβ burden (Fig. 2, Table 4), but this relationship was not homogeneous across brain regions. Specifically, in the ERC, Aβ only partially mediated the association between *APOE-ε4* and tau burden, leaving a significant Aβ-independent effect of *APOE-ε4* on tau burden that corresponded to 43% of the total effect (Table 4). On the other hand, Aβ fully mediated the association between *APOE-ε4* and tau in the ITC and Braak V/VI regions, indicating that there was no Aβ-independent effect of *ε4* on tau burden in these regions. Sex-stratified analyses revealed that the Aβ-independent *APOE-ε4* effect on tau burden in the ERC was only significant in women (Table s8). Restricting the mediation analyses to the Aβ-positive group revealed similar results as the main analyses. There was a significant Aβ-independent effect on ERC tau, whereas the *APOE-ε4* association with tau levels in the ITC was fully mediated by Aβ load (Table s9, Figure s2).

APOE associations with tau accumulation over time

In the subsample with longitudinal tau PET data, none of the regional tau accumulation rates was significantly different between *ε4* carriers and *ε3* homozygotes, although *ε4* carriers showed a trend towards a steeper increase in tau burden in Braak V/VI regions (β_{std} [95%CI]: 0.10 [−0.02, 0.18], $p = 0.111$) (Fig. 3, Table 5). *APOE-ε2* carriers did not show any differences in regional tau accumulation rates compared to *APOE-ε3ε3* participants (Fig. 3, Table 5). Multiple comparisons-corrected results are detailed in Table s10.

In mediation analyses, the association between *APOE-ε4* and increased rate of tau accumulation in Braak V/VI was fully mediated by baseline Aβ load (Table 4, Fig. 3). This effect remained significant when using baseline tau load as an additional covariate.

Table 3 Linear regression parameters (standardized β) for the interaction between *APOE* and sex, and *APOE* and Aβ status on tau and Aβ load. *APOE-ε3ε3* men and *APOE-ε3ε3* Aβ negative were selected as the reference group for sex and Aβ status comparisons,

respectively. Aβ status was positive (negative) if Aβ load was higher (lower) than 12 Centiloids [45, 46]. All models included age, education, and diagnosis as covariates

	<i>APOE-ε2</i> *sex		<i>APOE-ε4</i> *sex		<i>APOE-ε2</i> *Aβ status		<i>APOE-ε4</i> *Aβ status	
	β [95%CI]	p	β [95%CI]	p	β [95%CI]	p	β [95%CI]	p
Tau measurements								
ERC	− 0.18 [− 0.82, 0.24]	0.469	0.39 [0.03–0.76]	0.038	− 0.35 [− 0.88, 0.07]	0.256	0.62 [0.28, 0.91]	0.002
ITC	0.04 [− 0.33, 0.40]	0.679	0.12 [− 0.26, 0.56]	0.402	− 0.13 [− 0.55, 0.20]	0.629	0.38 [− 0.03, 0.67]	0.067
Braak V/VI	0.13 [− 0.27, 0.59]	0.609	0.12 [− 0.29, 0.54]	0.403	− 0.07 [− 0.50, 0.39]	0.645	0.30 [− 0.13, 0.62]	0.161
Aβ measurement								
Centiloids	0.08 [− 0.23, 0.39]	0.676	0.15 [− 0.27, 0.48]	0.342	-	-	-	-

Statistically significant results ($p < 0.05$) are shown in bold

Aβ amyloid-β; MRI magnetic resonance imaging; CU cognitively unimpaired; CI confidence interval

Table 4 Parameters of the mediation analyses. In the mediation analyses, the dependent variable (X) is the $APOE-\epsilon 4$ allele, the mediator (M) is the baseline $A\beta$ burden, measured as Centiloids, and the dependent variable (Y) is either the baseline tau PET SUVR (cross-sectional) or rate of tau PET SUVR change over time (longitudinal) in the different ROIs.

	Total effect (c)	Mediated effect ($a_1 \cdot b_1$)	Direct effect (c')	Percentage mediation ($a_1 \cdot b_1 / c$)	Percentage direct (c' / c)
Cross-sectional					
ERC	0.104 (0.019)	0.059 (0.014)	0.045 (0.018)	56.7%	43.3%
ITC	0.072 (0.025)	0.071 (0.017)	n.s.	98.6%	n.s.
Braak V/VI	0.036 (0.014)	0.035 (0.009)	n.s.	97.2%	n.s.
Longitudinal					
Δ Braak V/VI	0.033 (0.017)	0.020 (0.008)	n.s.	60.6%	n.s.

Only paths that were statistically significant ($p < 0.05$) or showed a trend to significance ($p < 0.1$, in italics) are shown

ERC entorhinal cortex; ITC inferior temporal cortex; n.s. not significant; $A\beta$ amyloid- β ; ROI region of interest; SE standard error

Discussion

In this PET study, we investigated the relationship of $APOE-\epsilon 2$ and $APOE-\epsilon 4$ alleles with $A\beta$ and tau load, the two main pathological hallmarks of AD in older individuals without dementia. We found an association of the $\epsilon 2$ allele with reduced $A\beta$ load but not with tau burden. Furthermore, we found that $\epsilon 4$ carriers showed higher load of both $A\beta$ and tau, and also a trend towards higher rate of longitudinal tau accumulation in neocortical regions representing advanced Braak tau stages V/VI. However, it

is important to note that all associations between the $\epsilon 4$ allele and baseline tau levels as well as rates of tau accumulation were at least partially mediated by $A\beta$. Furthermore, only the earliest tau deposition region (ERC) showed an $A\beta$ -independent association between the $\epsilon 4$ allele and tau load. Taken together, our data suggest that the protective effect of the $APOE-\epsilon 2$ allele for developing clinical AD appears to be primarily linked to resistance against $A\beta$ deposition [49] rather than tau pathology, and that the effect of the $APOE-\epsilon 4$ allele on tau burden is mostly secondary to the prominent effect on increased $A\beta$ load.

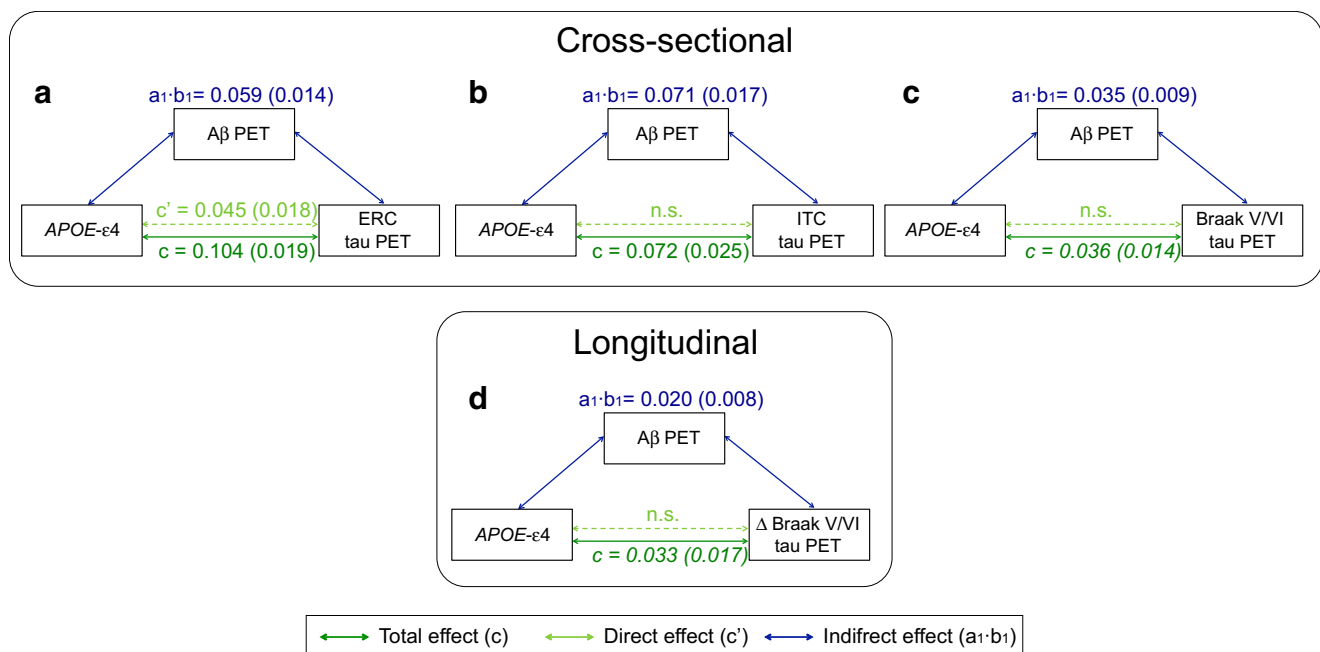


Fig. 2 Mediation effect of $A\beta$ on the association of $APOE-\epsilon 4$ with cross-sectional (top) and longitudinal (bottom) tau deposition in the ERC (**a**), ITC (**b**), and Braak V-VI (**c** and **d**). Dark green lines show the total effect of $APOE-\epsilon 4$ allele on tau burden, light green lines show the direct effect (i.e., without mediation), and blue lines depict the $A\beta$ mediation effect. Path weights are only shown for significant paths and are displayed as

(unstandardized) beta values with standard errors in brackets. Significance of the indirect effect was determined using bootstrapping with 5000 iterations. All models were adjusted by age, sex, education, and diagnosis. $A\beta$, amyloid- β ; ERC, entorhinal cortex; ITC, inferior temporal cortex

Table 5 Linear mixed model regression parameters (standardized β) for the association of *APOE- ϵ 2* and *APOE- ϵ 4* genotypes with longitudinal rates of regional tau SUVR change over time. *APOE- ϵ 3 ϵ 3* participants were selected as the reference group for all comparisons. The model included age at baseline, sex, education, and diagnosis as covariates

	<i>APOE-ϵ2</i> *time		<i>APOE-ϵ4</i> *time	
	β [95%CI]	<i>p</i>	β [95%CI]	<i>p</i>
ERC	-0.10 [-0.25, 0.07]	0.396	0.08 [-0.04, 0.15]	0.200
ITC	-0.07 [-0.17, 0.07]	0.505	0.08 [-0.01, 0.15]	0.147
Braak V/VI	-0.01 [-0.18, 0.18]	0.629	0.10 [-0.02 to 0.18]	0.111

A β amyloid- β ; *ERC* entorhinal cortex; *ITC* inferior temporal cortex; *CI* confidence intervals

The finding of an association between ϵ 2 carrier status and *A β* , but not with tau, is in accordance with previous studies assessing *A β* and p-tau levels in CSF [19, 21, 22]. The novelty of our study is the use of tau PET imaging, which allowed us to rule out the possibility of potential *APOE- ϵ 2* effects on regional neurofibrillary tau burden not captured by CSF-based tau biomarkers (i.e., providing a single value representing the entire brain). In addition, PET-based and CSF-based biomarkers appear to reflect different aspects of tau pathology that may also be differentially affected by *APOE* genotype. In this context, it has been recently shown that tau PET is more closely related to cognition and atrophy than tau levels in CSF [28]. On the other hand, tau abnormalities might be detected earlier in CSF than on PET [50]. However, in addition to the missing *APOE- ϵ 2* effect on regional tau burden in the cross-sectional PET data, here we also found that tau accumulation over time in serial PET acquisitions was not significantly

attenuated in *APOE- ϵ 2* carriers compared to *APOE- ϵ 3* homozygotes. Before the advent of tau PET tracers, only neuropathological studies could investigate *APOE* effects on regional tau pathology. However, the association between the *APOE- ϵ 2* allele and tau deposition in post-mortem studies has been controversial, as some studies showed no association [51, 52], while others reported lower levels of tau in *APOE- ϵ 2* carriers [6, 10, 53, 54]. Difference in methodology across studies is a likely explanation for this disparity. For example, some of the older studies only found differences when comparing ϵ 2 carriers to non-carrier groups that also included ϵ 4 carriers, or included very low numbers of ϵ 2 carriers ($n < 5$) [6, 54]. In another study, ϵ 2 allele associations with tau were only found in the hippocampus, whereas this association was not significant in the neocortex nor in the ERC [53]. Finally, *APOE* effects on regional tau burden may be affected by differences in disease stage across *APOE* groups, where ϵ 2 carriers are typically also less clinically advanced than ϵ 3 homozygotes, which may explain their lower levels of tau pathology [10]. In the current study, we only included participants with no or only mild cognitive impairment and controlled all analyses for cognitive status.

As secondary outcomes, we investigated associations of the ϵ 2 allele with hippocampal volumes and cognition, but we did not find any statistically significant associations. This is in agreement with a previous multimodal study examining differences between ϵ 2 carriers and ϵ 3 homozygotes, in which these groups only differed in terms of *A β* burden but not on hippocampal volumes or memory performance (tested cross-sectionally and longitudinally) [19]. We expand on these findings by also including executive function measures and the new ADNI composite measures for language and visuospatial functioning, which have been shown to predict diagnostic

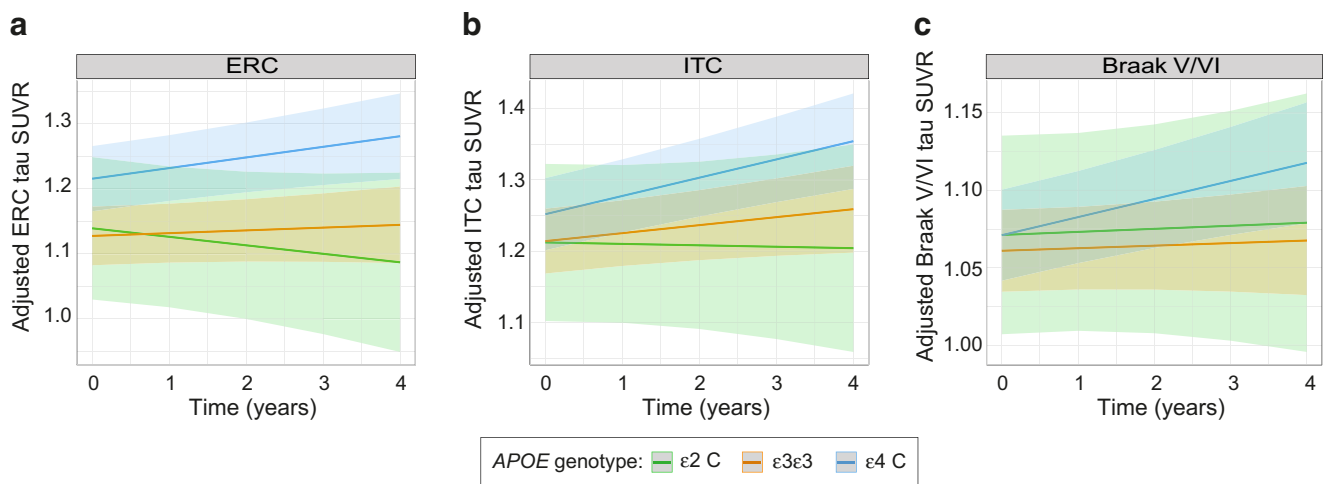


Fig. 3 Associations of *APOE- ϵ 2* and *APOE- ϵ 4* alleles with longitudinal measures of regional tau accumulation. Linear slopes of tau PET SUVR change over time and their 95% confidence intervals, as determined from linear mixed models, are depicted for the different *APOE* genotypes and

for the following regions: ERC (a), ITC (b), and Braak V-VI (c). PET measures are adjusted by age, sex, education, and diagnosis. ERC, entorhinal cortex; ITC, inferior temporal cortex. * $p < 0.05$

conversion from MCI to AD dementia and are associated with MRI and CSF measurements [44]. While a positive effect of *APOE-ε2* carriership on preserved cognitive function in advanced age would be expected based on its known protective effect for developing AD dementia, the sample size of our PET-based sample may not provide sufficient power to detect such an effect [55, 56].

In contrast to our findings in $\epsilon2$ carriers, $\epsilon4$ carriers showed higher levels of both $A\beta$ and tau in all the regions we investigated. Of note, we found that the effect size of the association between $\epsilon4$ and tau was higher in regions of early tau deposition (ERC > ITC > Braak V/VI). Results related to $A\beta$ are in agreement with many previous studies showing higher levels of this AD pathological hallmark in $\epsilon4$ carriers, both in CSF and PET [2–4]. Multiple neuropathological studies have also shown higher neurofibrillary tangles in $\epsilon4$ carriers [6, 12, 51, 53, 57–60]. However, biomarker studies of *APOE-ε4* carriership effects on tau in CSF or PET are rather scarce and presented disparate results. Thus, some studies showed an association between the $\epsilon4$ allele and higher tau levels [21, 61], but others presented opposite associations [35] or no associations at all [8, 62]. These disparities may be related to disease stage of participants, with $\epsilon4$ carriers having higher tau burden in early clinical stages (i.e., CU or MCI) but not in more advanced stages, as has also been shown for $A\beta$ burden [33, 63]. Together, our study is largely in line with established neuropathological results and adds more certainty to the inconclusive in vivo literature on the association of the *APOE-ε4* allele with tau pathology. Moreover, in the longitudinal analysis, we also found a trend-level association between the $\epsilon4$ allele and higher tau accumulation over time in neocortical Braak V/VI regions indicative of advanced tau pathology. The scarce previous studies examining *APOE-ε4* effects on longitudinal tau change also showed no or only limited associations between *APOE-ε4* carriership and tau accumulation. A previous study showed a higher rate of CSF tau accumulation over time in $\epsilon4$ carriers, but only in participants who were $A\beta$ positive [8]. On the other hand, a previous longitudinal tau PET study did not find any significant *APOE-ε4* effect on regional tau accumulation rates in CU individuals from the Berkeley aging cohort, although this negative finding could be related to the relatively low number of $\epsilon4$ carriers in that study [64]. Finally, a recent longitudinal tau PET study found no *APOE-ε4* effect on tau accumulation rates among CU individuals after controlling for baseline $A\beta$ load [65]. However, the study reported a marginally significant independent *APOE-ε4* effect on higher tau accumulation rates in a group of cognitively impaired individuals, but the interpretation of this finding is complicated by the mixed clinical composition of this group that included patients with MCI as well as typical and atypical AD dementia phenotypes.

Regarding non-PET measures, hippocampal volume and most of the cognitive measures were not associated with the $\epsilon4$

allele in our sample, although we observed a slightly lower memory performance in $\epsilon4$ carriers. Although in earlier stages, this is in line with the results found in a recent meta-analysis including only AD patients showing that $\epsilon4$ carriers present worse cognition than non-carriers only in the memory domain [66]. A review studying the effects of *APOE* on cognition also suggested that some of the cognitive deficits seen in $\epsilon4$ carriers might be related to AD pathology [67]. Therefore, the lack of an association between *APOE* and non-amnesic cognitive domain scores in our sample may stem from selecting only participants without dementia, as more robust *APOE* effects on neurodegeneration and cognition have been reported in participants with dementia [34, 68, 69].

Some previous neuropathological studies have raised the question whether *APOE-ε4* directly impacts tau pathology or only acts on tau through its effect on $A\beta$ [10, 11]. There are two results in our study that would support the latter hypothesis. First, we observed a significant interaction between the $\epsilon4$ allele and $A\beta$ status, where significant *APOE-ε4* effects on tau levels were only observed in the $A\beta$ -positive group. Second, we found that $A\beta$ levels significantly mediated the association between the $\epsilon4$ allele and tau pathology in all assessed brain regions. This reinforces the notion that the association between $\epsilon4$ carriership and tau burden is mainly driven by the pronounced $\epsilon4$ effect on increased $A\beta$ pathology. However, another interesting outcome of our cross-sectional mediation analysis was that the mediating effect of $A\beta$ was not complete for ERC tau levels, where the $\epsilon4$ allele also retained a significant $A\beta$ -independent association with increased tau burden. This effect was also observed when limiting the analyses to $A\beta$ -positive subjects only. These results are in agreement with a recent PET study, in which $A\beta$ -independent associations of the $\epsilon4$ allele with tau levels were only found in the medial temporal lobe [9]. In the analog analysis of longitudinal tau PET data, we only found a trend towards higher tau accumulation in Braak V/VI regions in $\epsilon4$ carriers, but this effect was also fully mediated by baseline $A\beta$ load. This mediation effect also remained significant when additionally adjusting the model for baseline tau load. Taken together, our results are in line with the hypothesis that the *APOE-ε4* allele might have an $A\beta$ -independent effect on tau accumulation in the medial temporal cortex that occurs with aging [11], but that $A\beta$ pathology is needed to accelerate tau pathology and facilitate its spread into the neocortex [11, 70–72]. However, it remains to be clarified whether this $A\beta$ -independent *APOE-ε4* effect on ERC tau burden may also be associated with detrimental effects on cognition, as suggested by a recent study [73].

Previous studies examining $\text{sex} \times \text{APOE-}\epsilon4$ interactions on tau burden have led to some contradictory results, especially when comparing CSF biomarker and neuropathological studies. Thus, the large majority of studies measuring tau in CSF have provided evidence in favor of this interaction [21, 30, 31,

74], although not all [75]. One recent study could also replicate this finding using tau PET in MCI patients [74]. Neuropathological studies, on the other hand, did not find significant sex**APOE-ε4* interactions on tau pathology [30, 76]. A recent large-scale CSF study proposed that this interaction may only be present in the early phases of the disease (i.e., subjective cognitive decline and MCI) but decreases in later stages (Alzheimer's dementia), which may explain the lack of results in neuropathological data [77]. Our present results would be in line with this notion as we only found a significant interaction in regions of early tau accumulation (i.e., the ERC), and sex-related differences in the *APOE-ε4* effect on tau burden were much lower for later regions (Table s2). Of note, in our Aβ mediation analysis stratified by sex, we found that only women presented the Aβ-independent effect of the *APOE-ε4* allele on tau levels in the ERC (Table s3). This suggests that the female-specific elevations in tau levels may stem from Aβ-independent pathways (e.g., sex hormones [78]). However, further investigation is needed to better understand these differences. Unfortunately, we were not able to perform meaningful longitudinal analysis stratified by sex due to the limited number of subjects in this subsample.

Among the main strengths of this study is that we investigated associations of the $\epsilon 2$ allele with tau levels measured using PET, which allowed us to assess cross-sectional and longitudinal differences in regional tau deposition as opposed to the global results of CSF and cross-sectional results in neuropathological studies. There are also several limitations. First, although the sample size was large for a multitracers Aβ and tau PET imaging study, the final number of $\epsilon 2$ carriers in this study was still limited, especially in the longitudinal analysis, which may have reduced the statistical power to detect more subtle associations with tau accumulation. However, at least in the cross-sectional analysis the effect size estimates were not indicative of even subtle differences in regional tau burden between $\epsilon 2$ carriers and $\epsilon 3$ homozygotes (Table 2). In this context, it is also important to note that statistical power was sufficient to fully replicate the previously reported *APOE-ε2* effect on reduced Aβ levels in this largely non-overlapping ADNI sample [19]. Another limitation is the use of linear models. We cannot discard that there might be some level of non-linearities in these associations, particularly in the cross-sectional analysis that covers a wide span of the clinical disease spectrum (CN to MCI). However, larger sample sizes would be needed to more comprehensively test these types of associations. A recent large-scale Aβ PET imaging study found that the Aβ load in *APOE-ε2ε4* participants was intermediate between that of $\epsilon 2$ and $\epsilon 4$ carriers, suggesting that the $\epsilon 2$ allele may counteract some of the detrimental effects of the $\epsilon 4$ allele [79]. Unfortunately, due to the low sample size of subjects with the *APOE-ε2ε4* genotype in our study ($n = 7$), we were not able to study these subjects as an

independent group. The effects of this allele combination on tau PET imaging markers remain to be determined in larger samples with available tau PET acquisitions. Finally, in addition to structural MRI scans, the NIA-AA revised research criteria [80] also include [^{18}F]fluorodeoxyglucose (FDG) PET as a neuroimaging marker of neurodegeneration. In the present study, we focused on MRI-derived hippocampal volumes instead of FDG PET measures due to the more limited availability of FDG PET and larger time lapse between this measure and Aβ and tau PET in the analyzed ADNI cohort. However, a previous study on multimodal neuroimaging correlates of the *APOE-ε2* allele indicated no significant differences in *APOE* effects on structural MRI and FDG PET-derived neurodegeneration measures [19].

In the context of this special issue on the Geneva roadmap for early diagnosis of AD based on biomarkers [32], our study contributes to phases 2 and 3 for both Aβ and tau PET imaging assessing the impact of genetics as covariate on biomarker results in healthy controls and in the early phases of disease. We would like to note that although at the time that the roadmap guidelines were formulated tau PET was still considered an emerging technology, this imaging biomarker has evolved enormously in recent years and is now shaping up to be considered a primary biomarker for diagnosis of AD [81].

Conclusions

The *APOE-ε2* allele is associated with lower Aβ—but not tau—load, suggesting that lower Aβ deposition represents the main pathologic correlate of the decreased AD risk of $\epsilon 2$ carriers. On the other hand, the elevated AD risk of $\epsilon 4$ carriers may be related with higher tau load, although this also appears to be primarily mediated by the strong *APOE-ε4* effect on increased Aβ pathology, except in the ERC where Aβ-independent effects were significant.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00259-021-05192-8>.

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Data availability Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed written consent was obtained from all participants at each site.

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