

# The Role of Apolipoprotein E $\epsilon$ 4 in Early and Late Mild Cognitive Impairment

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## Keywords

Amyloid beta · Apolipoprotein E · Cognition · Late mild cognitive impairment · Early mild cognitive impairment

## Abstract

**Background:** Apolipoprotein E (*APOE*)  $\epsilon$ 4 is highly associated with mild cognitive impairment (MCI). However, the specific influence of *APOE*  $\epsilon$ 4 status on tau pathology and cognitive decline in early MCI (EMCI) and late MCI (LMCI) is poorly understood. Our goal was to evaluate the association of *APOE*  $\epsilon$ 4 with cerebrospinal fluid (CSF) tau levels and cognition in EMCI and LMCI patients in the Alzheimer's Disease Neuroimaging Initiative database, and whether this association was mediated by amyloid- $\beta$  ( $A\beta$ ). **Methods:** Participants were 269 cognitively normal (CN), 262 EMCI, and 344 LMCI patients. They underwent CSF  $A\beta$ 42 and tau detection, *APOE*  $\epsilon$ 4 genotyping, Mini-Mental State Examination, (MMSE), and Alzheimer's disease assessment scale (ADAS)-cog assessments. Linear regressions were used to examine the relation of *APOE*  $\epsilon$ 4 and CSF tau levels and cognitive scores in persons with and without  $A\beta$  deposition ( $A\beta+$  and  $A\beta-$ ). **Results:** The prevalence of *APOE*  $\epsilon$ 4 is higher in EMCI and LMCI than in CN ( $p < 0.001$  for both), and in LMCI than in EMCI ( $p = 0.001$ ). *APOE*  $\epsilon$ 4 allele was significantly higher in  $A\beta+$  subjects than in  $A\beta-$  subjects ( $p < 0.001$ ). Subjects who had a lower CSF  $A\beta$ 42 level and were *APOE*  $\epsilon$ 4-positive experienced higher

levels of CSF tau and cognitive scores in EMCI and/or LMCI. **Conclusions:** An *APOE*  $\epsilon$ 4 allele is associated with increased CSF tau and worse cognition in both EMCI and LMCI, and this association may be mediated by  $A\beta$ . We conclude that *APOE*  $\epsilon$ 4 may be an important mediator of tau pathology and cognition in the early stages of AD. © 2021 S. Karger AG, Basel

## Introduction

Mild cognitive impairment (MCI) reflects a degree of cognitive impairment that is greater than expected for a specific age, but is not sufficient to interfere with an individual's activities of daily living [1]. Patients with MCI have a high rate of progressing to Alzheimer's disease (AD) dementia, which is about 10–15% annually [2]. The subtypes of amnesic MCI (aMCI) based on neuropsychological profiles have been proposed previously, which

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/wpcontent/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

may indicate the initial form of different dementia [3]. Due to the increasing interest in early intervention and prediction, aMCI is further divided into early MCI (EMCI) and late MCI (LMCI) [4]. EMCI and LMCI subtypes are distinguished by the severity of amnesic impairment with EMCI requiring memory test scores to be lower than the standardized norm between 1.0 and 1.5 SD, and LMCI requiring memory test scores to be lower than the standardized norm by  $>1.5$  SD [4]. This classification has been used in Alzheimer's Disease Neuroimaging Initiative (ADNI) studies [5]. EMCI is characterized by patients displaying subtle memory impairments or other cognitive impairments in neuropsychological testing and not fully meeting the diagnostic criteria for aMCI. Furthermore, EMCI subjects show significant differences between intelligence and memory scores or tests compared to well-matched healthy controls [6]. However, LMCI patients show worse performance in most areas of testing, and LMCI may be associated with a higher degree of medial temporal lobe atrophy and has a greater risk of conversion to dementia than EMCI [6].

Apolipoprotein E (*APOE*) has been identified as a consistent genetic risk factor for late life cognitive decline, MCI, and AD [7–9]. *APOE* is located in a single locus on chromosome 19, which has 3 alleles ( $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ ) responsible for the 3 major *APOE* isoforms (*APOE*  $\epsilon 2$ , *APOE*  $\epsilon 3$ , and *APOE*  $\epsilon 4$ ) [10]. A large amount of evidence suggests that the main mechanism of *APOE* affecting AD is to affect amyloid- $\beta$  ( $A\beta$ ) deposition via *APOE* dose- and isoform-specific manner ( $\epsilon 4 > \epsilon 3 > \epsilon 2$ ) [11], thought to trigger a series of events that eventually leads to neurofibrillary tangles formation and cognitive dysfunction [12, 13]. Recent tau-positron emission tomography (PET) studies have provided evidence of an amyloid-independent association between *APOE*  $\epsilon 4$  and tau pathology in medial temporal cortices [14]. It is unclear whether the relationships between *APOE*  $\epsilon 4$ , tau, and cognitive function are different in EMCI and LMCI. In this study, we test the hypothesis that the associations of *APOE*  $\epsilon 4$  with the cerebrospinal fluid (CSF) tau and cognition are significant and may be mediated by  $A\beta$  in both EMCI and LMCI.

## Methods

### *Database Description and Participants*

Data used in the preparation of this article were obtained from the ADNI database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). The ADNI was launched in 2003 as a public-private partnership led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been

to test whether serial magnetic resonance imaging, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

In this study, 875 participants with initial analysis of CSF A $\beta$ 42, CSF total tau (T-tau), CSF phosphorylated tau (P-tau), Mini-Mental State Examination (MMSE), Alzheimer's disease assessment scale (ADAS)-cog, and Clinical Dementia Rating (CDR) scale were included. Demographic information was extracted from the ADNI database. In our study, there were 269 participants with cognitively normal (CN), 262 participants with EMCI, and 344 participants with LMCI.

### *Classification Criteria*

In brief, the criteria for CN included a MMSE score ranging between 24 and 30 and a CDR score of 0 [15]. Patients with MCI were classified essentially in the manner described by Petersen [16], but were then further divided into an "early" and "late" group based on performance on the Wechsler Memory Scale-Revised Logical Memory II. The EMCI group was defined based on scores between the cutoff of normal and that of the LMCI group [17]. (Further information about the inclusion/exclusion criteria may be found at [www.adni-info.org](http://www.adni-info.org) [accessed November 2020]).

### *Standard Protocol Approvals and Patient Consent*

Institutional review board approval was obtained at each ADNI site, and informed consent was obtained from each participant or authorized representative. ADNI makes all its data publicly available. Our manuscript was approved and acceptable for submission by the ADNI Data and Publications Committee. For more information please see: <http://adni.loni.usc.edu/data-samples/access-data/>.

### *APOE Genotyping*

*APOE* (gene map locus 19q13.2) genotypes of the study participants were obtained from the ADNI database files "APOERES.csv" (accessed November 2020). Individuals with at least one  $\epsilon 4$  allele were considered as  $\epsilon 4$  carriers.

### *CSF Analyses*

CSF A $\beta$ 42, T-tau, and P-tau (threonine 181) were measured by using the xMAP Luminex platform and Innogenetics/Fujirebio Alz-Bio3 immunoassay kits as described previously [18]. Participants were classified as with  $A\beta$  deposition ( $A\beta$  positive or  $A\beta+$ ) or without  $A\beta$  deposition ( $A\beta$  negative or  $A\beta-$ ) using a previously established cutoff of CSF A $\beta$ 42 ( $<192$  pg/mL) [18]. All of the CSF data used in this study were obtained from the ADNI files "UPEN-NBIOMK5-8.csv" and "FAGANLAB\_07\_15\_2015.csv," (accessed November 2020). Further details of ADNI methods for CSF acquisition and measurements and quality control procedures can be found at [www.adni-info.org](http://www.adni-info.org).

### *Cognitive Assessment*

To assess cognitive function, MMSE and ADAS-cog scores were used at baseline. The data used in this study were obtained from the ADNI files "MMSE.csv" and "ADAS\_ADNI1.csv," (accessed November 2020).

### *Statistical Methods*

Differences between *APOE*  $\epsilon 4$  carriers and noncarriers were performed using the  $\chi^2$  test for gender and  $A\beta$  status ( $A\beta+$  or  $A\beta-$ ),

**Table 1.** Main demographic and clinical characteristics of *APOE*  $\epsilon 4$  carriers and noncarriers, stratified by diagnostic group

Characteristic	CN		EMCI		LMCI		All	
	$\epsilon 4-$	$\epsilon 4+$	$\epsilon 4-$	$\epsilon 4+$	$\epsilon 4-$	$\epsilon 4+$	$\epsilon 4-$	$\epsilon 4+$
<i>N</i> , <i>n</i> (%)	200 (74.3)	69 (25.7)	154 (58.8)	108 (41.2)	156 (45.3)	188 (54.7)	510 (58.3)	365 (41.7)
Age, years	74.6 (5.8)	73.7 (6.6)	72.3 (7.2)	69.9 (7.4)	74.4 (8.3)	72.5 (6.8)	73.9 (7.1)	72.0 (7.1)
Gender (F), <i>n</i> (%)	101 (50.5)	33 (47.8)	74 (48.1)	42 (38.9)	51 (32.7)	83 (44.1)	226 (44.3)	158 (43.3)
Education, years	16.3 (2.6)	16.0 (2.8)	16.1 (2.7)	15.8 (2.7)	16.3 (2.8)	16.0 (2.9)	16.2 (2.7)	16.0 (2.8)
A $\beta$ 42, pg/mL	211.0 (48.0)	166.8 (53.3)	201.7 (47.7)	162.5 (46.6)	187.9 (55.7)	140.4 (38.1)	201.1 (51.2)	151.9 (45.4)
A $\beta-$ , <i>n</i> (%)	134 (49.8)	22 (8.2)	99 (37.8)	26 (10.0)	71 (20.6)	16 (4.7)	304 (34.7)	64 (7.3)
A $\beta+$ , <i>n</i> (%)	66 (24.5)	47 (17.5)	55 (21.0)	82 (31.3)	84 (24.4)	173 (50.3)	205 (23.4)	302 (34.5)

*APOE*, apolipoprotein E; A $\beta$ , amyloid- $\beta$ ; A $\beta-$ , without A $\beta$  deposition; A $\beta+$ , with A $\beta$  deposition; CN, cognitively normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment.

and the Mann-Whitney U test for age, education, A $\beta$ 42, T-tau, P-tau, MMSE, and ADAS-cog. Linear regression models with an interaction term between *APOE*  $\epsilon 4$  status and A $\beta$  status were used to test differences in the association of *APOE*  $\epsilon 4$  with T-tau, P-tau, MMSE, and ADAS-cog in A $\beta+$  and A $\beta-$  subjects. Then stratified analyses regressing were used to examine *APOE*  $\epsilon 4$  status on T-tau, P-tau, MMSE, and ADAS-cog in A $\beta+$  and A $\beta-$  persons. Finally, we conducted stratified analyses regressing *APOE*  $\epsilon 4$  status on T-tau, P-tau, MMSE, and ADAS-cog for CN, EMCI, and LMCI groups, respectively. All models adjusted for age, sex, and education. In these models, all values are log-transformed. Statistical significance was defined as  $p < 0.05$ . All statistics were done using R (v. 3.4.2) and SPSS version 21.

## Results

### Demographic Results

*APOE*  $\epsilon 4$  carriers have more females than *APOE*  $\epsilon 4$  noncarriers in LMCI ( $p = 0.030$ ), but not in CN ( $p = 0.702$ ) and EMCI ( $p = 0.142$ ). There were no differences in age and education between *APOE*  $\epsilon 4$  carriers and noncarriers among the groups. *APOE*  $\epsilon 4$  carriership was more common in EMCI and LMCI than in CN ( $p < 0.001$  for both), and in LMCI than in EMCI ( $p = 0.001$ ). *APOE*  $\epsilon 4$  was present in 34.5% of persons with A $\beta+$  and only 7.3% of persons without A $\beta-$  in all participants ( $p < 0.001$ ). *APOE*  $\epsilon 4$  existed in 17.5, 31.3, and 50.3% of persons with A $\beta+$  and only 8.2, 10.0, and 4.7% of persons without A $\beta-$  in CN ( $p = 0.001$ ), EMCI ( $p < 0.001$ ), and LMCI ( $p < 0.001$ ). Demographic information of participants grouped according to *APOE*  $\epsilon 4$  status is shown in Table 1.

### Levels of CSF T-Tau and P-Tau, MMSE, and ADAS-Cog in *APOE* $\epsilon 4$ Carriers and Noncarriers

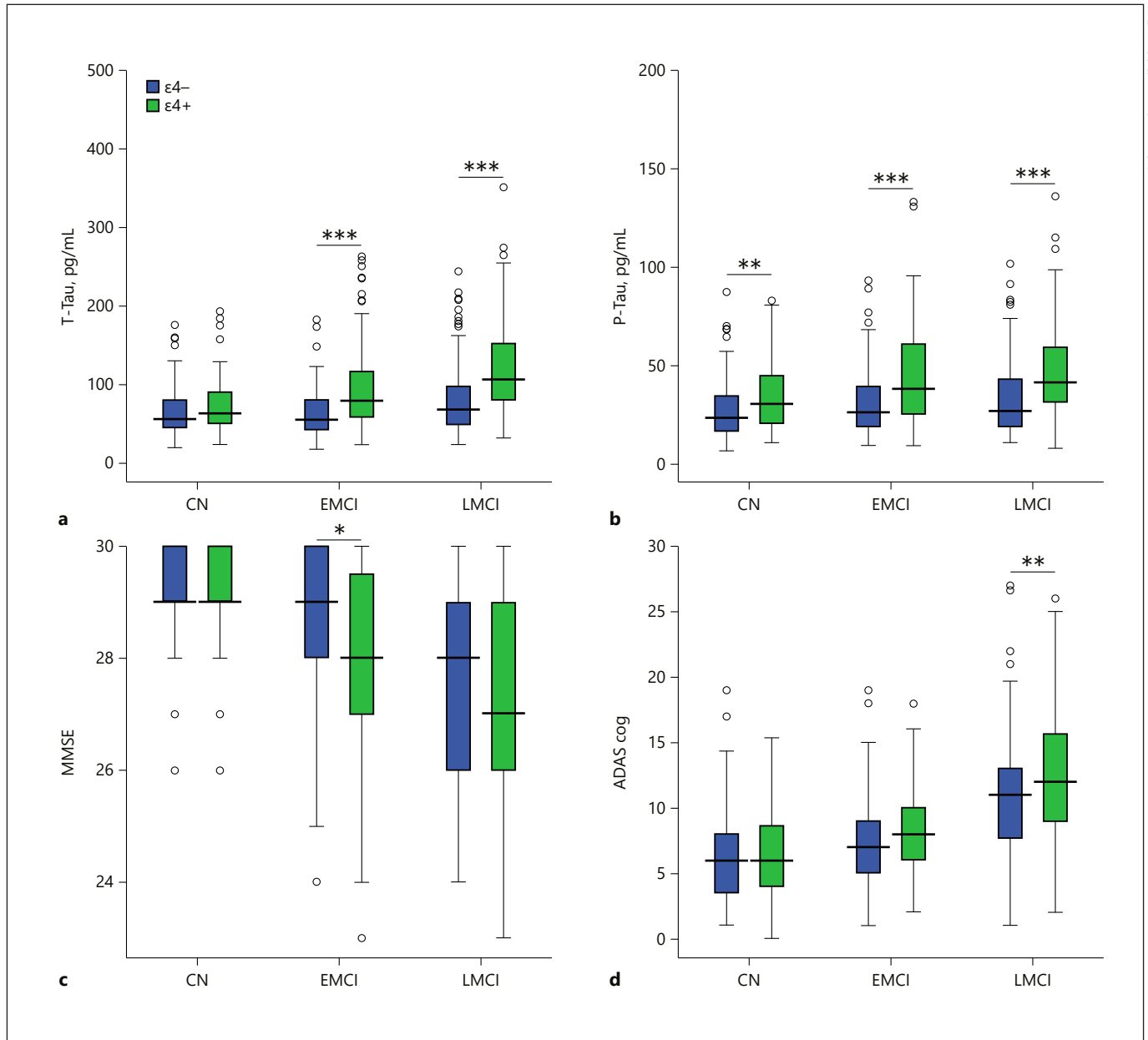
CSF T-tau levels were higher in *APOE*  $\epsilon 4$  carriers than *APOE*  $\epsilon 4$  noncarriers in EMCI and LMCI ( $p < 0.001$  for

both), but there was no difference in the CN group ( $p = 0.055$ ) (Fig. 1a). CSF P-tau levels were significantly higher in *APOE*  $\epsilon 4$  carriers than *APOE*  $\epsilon 4$  noncarriers in any group ( $p = 0.002$  for CN;  $p < 0.001$  for EMCI and LMCI) (Fig. 1b). MMSE scores were differences between *APOE*  $\epsilon 4$  carriers and noncarriers in the EMCI group ( $p = 0.042$ ) but not in CN ( $p = 0.415$ ) and LMCI groups ( $p = 0.278$ ) (Fig. 1c). ADAS-cog was higher in *APOE*  $\epsilon 4$  carriers than *APOE*  $\epsilon 4$  noncarriers in LMCI ( $p = 0.001$ ), but there were no significant differences between *APOE*  $\epsilon 4$  carriers and *APOE*  $\epsilon 4$  noncarriers in CN ( $p = 0.364$ ) and EMCI ( $p = 0.056$ ) (Fig. 1d).

### Associations of *APOE* $\epsilon 4$ with T-Tau, P-Tau, MMSE, and ADAS-Cog in All A $\beta+$ or A $\beta-$ Participants

The associations of *APOE*  $\epsilon 4$  with T-tau, P-tau, MMSE, and ADAS-cog were first tested in linear regression model with an interaction term between *APOE*  $\epsilon 4$  status and the presence of A $\beta$ , adjusting for age, sex, and education. The interaction was significant between *APOE*  $\epsilon 4$  status and the presence of A $\beta$  for T-tau ( $\beta = 0.19$ ,  $p = 0.013$ ), P-tau ( $\beta = 0.16$ ,  $p = 0.041$ ), and ADAS-cog ( $\beta = 0.23$ ,  $p = 0.009$ ) but not MMSE ( $\beta = 0$ ,  $p = 0.970$ ), suggesting that the association of the  $\epsilon 4$  genotype with T-tau, P-tau, and ADAS-cog was stronger among persons with A $\beta+$ , as shown in Table 2.

Next, we conducted separate regression analysis for persons with ( $n = 507$ ) and without A $\beta-$  ( $n = 368$ ). In persons with A $\beta+$ , *APOE*  $\epsilon 4$  was strongly associated with higher levels of T-tau ( $\beta = 0.29$ ,  $p < 0.001$ ), P-tau ( $\beta = 0.24$ ,  $p < 0.001$ ), MMSE ( $\beta = -0.02$ ,  $p = 0.008$ ), and ADAS-cog ( $\beta = 0.25$ ,  $p < 0.001$ ), as shown in Table 3. We did not find an association among persons without A $\beta-$ , as shown in Table 3.



**Fig. 1.** Levels of CSF T-tau and P-tau, MMSE, and ADAS-cog by *APOE*  $\epsilon 4$  in CN, EMCI, and LMCI groups. The levels of T-tau by *APOE*  $\epsilon 4$  status (**a**); the levels of P-tau by *APOE*  $\epsilon 4$  status (**b**); the MMSE scores by *APOE*  $\epsilon 4$  status (**c**); and the ADAS-cog scores by *APOE*  $\epsilon 4$  status (**d**). \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ . *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's disease assessment scale-cog; CSF, cerebrospinal fluid; CN, cognitively normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment.

#### Associations of *APOE* $\epsilon 4$ with T-Tau, P-Tau, MMSE, and ADAS-Cog in CN, EMCI, and LMCI Individuals $A\beta^+$ and $A\beta^-$

Finally, we performed stratified analyses regressing *APOE*  $\epsilon 4$  status on levels of T-tau, P-tau, MMSE, and ADAS-cog in CN, EMCI, and LMCI individuals  $A\beta^+$  and

$A\beta^-$ . We found that *APOE*  $\epsilon 4$  was strongly associated with higher levels of T-tau in EMCI ( $\beta = 0.39$ ,  $p < 0.001$ ) and LMCI ( $\beta = 0.20$ ,  $p = 0.002$ ) individuals with  $A\beta^+$  (Fig. 2a), higher levels of P-tau in CN ( $\beta = 0.22$ ,  $p = 0.033$ ), EMCI ( $\beta = 0.29$ ,  $p = 0.001$ ), and LMCI ( $\beta = 0.18$ ,  $p = 0.005$ ) individuals with  $A\beta^+$  (Fig. 2b), lower MMSE scores in

**Table 2.** Linear results of *APOE*  $\epsilon 4$  status and the presence of  $A\beta$ 

Parameter	Models	$A\beta$ $\beta$ (SE), <i>p</i> value	<i>APOE</i> $\epsilon 4$ $\beta$ (SE), <i>p</i> value	$A\beta$ + <i>APOE</i> $\epsilon 4$ (interaction) $\beta$ (SE), <i>p</i> value
T-tau	Model 1	0.47 (0.03), <0.001	–	–
	Model 2	–	0.4 (0.03), <0.001	–
	Model 3	0.31 (0.04), <0.001	0.1 (0.06), 0.099	0.19 (0.08), 0.013
P-tau	Model 1	0.53 (0.03), <0.001	–	–
	Model 2	–	0.39 (0.04), <0.001	–
	Model 3	0.4 (0.04), <0.001	0.08 (0.07), 0.210	0.16 (0.08), 0.041
MMSE	Model 1	–0.03 (0), <0.001	–	–
	Model 2	–	–0.03 (0), <0.001	–
	Model 3	–0.02 (0.01), <0.001	–0.02 (0.01), 0.046	0 (0.01), 0.970
ADAS-cog	Model 1	0.3 (0.04), <0.001	–	–
	Model 2	–	0.29 (0.04), <0.001	–
	Model 3	0.14 (0.05), 0.003	0.04 (0.07), 0.600	0.23 (0.09), 0.009

Table 2 indicated  $\beta$  coefficient, SE, and *p* value from the models without and with interaction term between  $\epsilon 4$  status and the presence of  $A\beta$ . All the models were adjusted for age, sex, and education. *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's disease assessment scale-cog;  $A\beta$ , amyloid- $\beta$ ; SE, standard error.

EMCI ( $\beta = -0.03$ , *p* = 0.01) individuals with  $A\beta+$  (Fig. 2c), and higher ADAS-cog scores in EMCI ( $\beta = 0.17$ , *p* = 0.015) and LMCI ( $\beta = 0.13$ , *p* = 0.025) individuals with  $A\beta+$  (Fig. 2d). However, we did not observe the same associations among persons without  $A\beta-$ , as shown in Figure 2a–d.

## Discussion

This study provides an evaluation of the relationship between of *APOE*  $\epsilon 4$  status with CSF T-tau, P-tau, and cognition in CN, EMCI, and LMCI participants, and whether these effects are regulated by  $A\beta$ . We observed *APOE*  $\epsilon 4$  carriership was most common in LMCI, followed by EMCI, then in CN. *APOE*  $\epsilon 4$  carriers were significantly more likely to have elevated  $A\beta$  deposition. Then, CSF tau levels and cognitive performance were significantly associated with  $\epsilon 4$  status, with  $\epsilon 4+$  participants showing higher CSF tau levels and poorer ADAS-cog scores in EMCI and LMC. Furthermore, the associations of *APOE*  $\epsilon 4$  with T-tau, P-tau, and cognition were much stronger in persons with  $A\beta+$ . Finally, *APOE*  $\epsilon 4$  was strongly associated with higher levels of T-tau and P-tau in EMCI and LMCI individuals with  $A\beta+$ , lower MMSE scores in EMCI individuals with  $A\beta+$ , and higher ADAS-cog scores in EMCI and LMCI individuals with  $A\beta+$ .

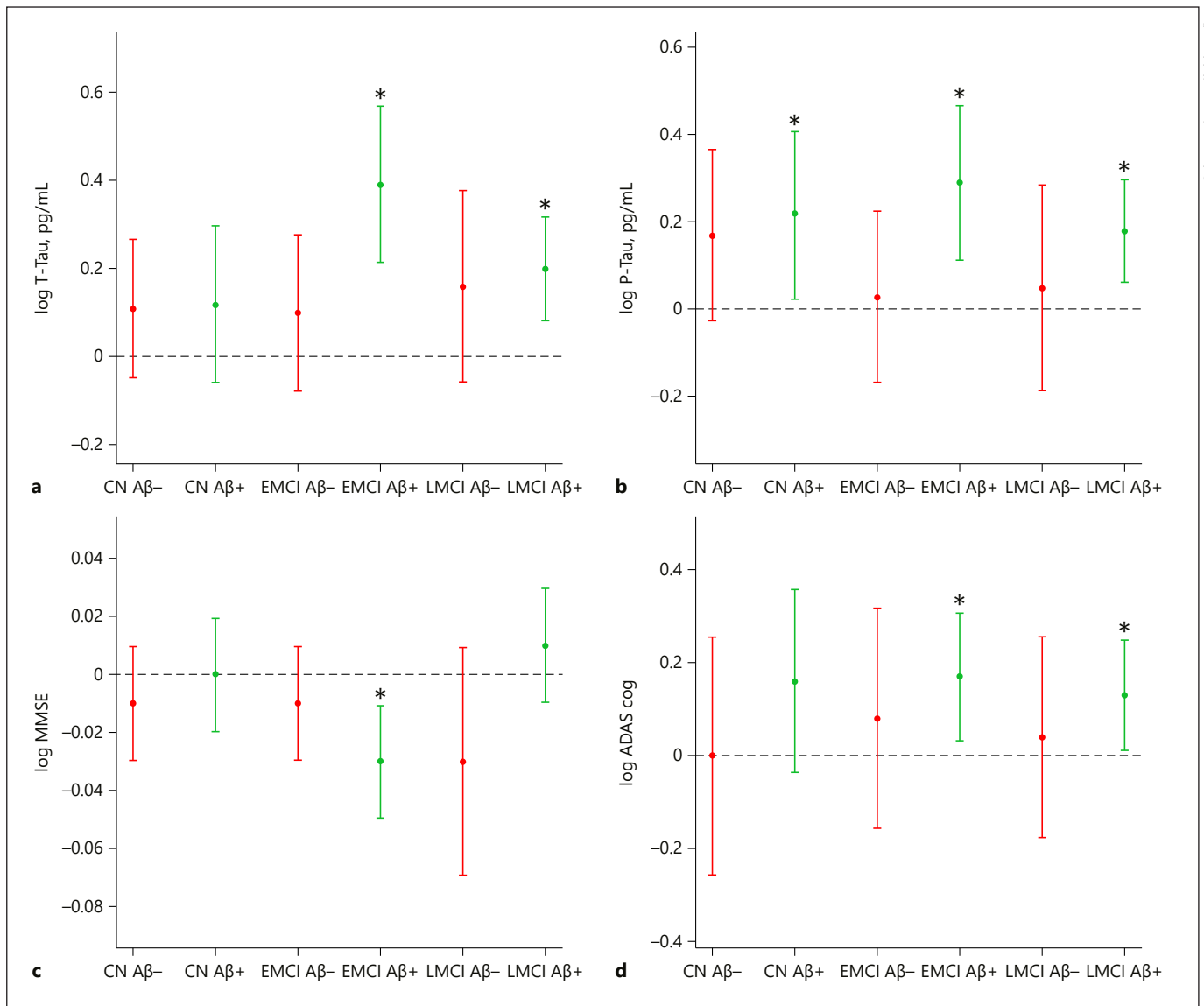
**Table 3.** Association of *APOE*  $\epsilon 4$  status with T-tau, P-tau, MMSE, and ADAS-cog

Model	$A\beta+$ [ $\beta$ (SE), <i>p</i> value]	$A\beta-$ [ $\beta$ (SE), <i>p</i> value]
T-tau	0.29 (0.05), <0.001	0.10 (0.05), 0.087
P-tau	0.24 (0.05), <0.001	0.08 (0.06), 0.170
MMSE	–0.02 (0.01), 0.008	–0.05 (0.01), 0.210
ADAS-cog	0.25 (0.05), <0.001	0.06 (0.08), 0.470

Table 3 presents  $\beta$  coefficient, SE, and *p* value from the models considering all subjects as a whole. All the models were adjusted for age, sex, and education. *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's disease assessment scale-cog;  $A\beta$ , amyloid- $\beta$ ;  $A\beta-$ , without  $A\beta$  deposition;  $A\beta+$ , with  $A\beta$  deposition; SE, standard error.

Overall, the results suggest that *APOE*  $\epsilon 4$  status impacts tau pathology and cognitive performance in EMCI and LMCI, and the mechanism of this impact may involve  $A\beta$ .

Possession of  $\epsilon 4$  allele increases the risk of developing AD by 2–3 times and occurs in approximately 60% of AD patients [19, 20]. It has also been demonstrated that the *APOE*  $\epsilon 4$  allele is highly associated with MCI [21–24]. In this study, the  $\epsilon 4$  allele carrier rate of patients with LMCI is significantly higher than that of patients with EMCI. This may be one of the reasons why LMCI is more likely to be converted to AD than EMCI. Compared to non- $\epsilon 4$



**Fig. 2.** *APOE*  $\epsilon 4$  status on levels of CSF T-tau and P-tau, MMSE, and ADAS-cog in CN, EMCI, and LMCI groups A $\beta$ + or A $\beta$ -. **a–d** The data are estimates ( $\beta$ -coefficients) from stratified analyses regressing with a confidence interval of 95%. All values are log transformed. Effects were significant (\*), for T-tau: in EMCI and LMCI with A $\beta$ + ( $\beta = 0.39$ ,  $p < 0.001$ ;  $\beta = 0.20$ ,  $p = 0.002$ , respectively) (**a**); for P-tau: in CN, EMCI, and LMCI with A $\beta$ + ( $\beta = 0.22$ ,  $p = 0.033$ ;  $\beta = 0.29$ ,  $p = 0.001$ ;  $\beta = 0.18$ ,  $p = 0.005$ , respectively) (**b**); for MMSE:

in EMCI with A $\beta$ + ( $\beta = -0.03$ ,  $p = 0.01$ ) (**c**); and for ADAS-cog: in EMCI and LMCI with A $\beta$ + ( $\beta = 0.17$ ,  $p = 0.015$ ;  $\beta = 0.13$ ,  $p = 0.025$ , respectively) (**d**). *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's disease assessment scale-cog; CSF, cerebrospinal fluid; A $\beta$ , amyloid- $\beta$ ; CN, cognitively normal; A $\beta$ +, with A $\beta$  deposition; A $\beta$ -, without A $\beta$  deposition; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment.

individuals,  $\epsilon 4$  carriers show brain A $\beta$  pathology at earlier ages [25, 26]. Studies using animal models of AD suggest that  $\epsilon 4$  allele carriers could increase the aggregation and deposition of A $\beta$  in brain compared to other polymorphisms [11, 27, 28]. A low CSF A $\beta$ 42 level is considered a marker of A $\beta$  plaque deposition in the brain of

patients with AD. In the present study, the  $\epsilon 4$  allele carrier rate is significantly higher in individuals with a lower CSF A $\beta$ 42 level than in individuals with a higher CSF A $\beta$ 42 level in any group. This also indicates that *APOE*  $\epsilon 4$  is significantly associated with A $\beta$  plaque deposition in MCI individuals.

It has been reported that *APOE*  $\epsilon 4$  binds to tau directly in vitro [29], and neuronal expression of human *APOE*  $\epsilon 4$  results in tau hyperphosphorylation in vivo [30]. In a mouse model of tauopathy, it suggests that *APOE*  $\epsilon 4$  affects tau pathogenesis and tau-mediated neurodegeneration [31]. A genome-wide association study shows a strong and significant correlation between *APOE* and CSF tau after adjusting for the effect of *APOE*  $\epsilon 4$  on  $A\beta$  levels [32]. In our study, *APOE*  $\epsilon 4+$  participants show higher CSF T-tau and P-tau levels in both EMCI and LMCI individuals. It shows that *APOE*  $\epsilon 4$  may impact tau pathogenesis in MCI individuals.

Previous studies reported relationships between *APOE*  $\epsilon 4$  and  $A\beta$  deposition and tau pathogenesis [33, 34]. Post-mortem studies also demonstrated that cerebral  $A\beta$  and tau levels vary according to *APOE* genotype, with *APOE*  $\epsilon 4$  having the strongest effect [35, 36]. These studies suggest a concurrent and symmetrical association of *APOE*  $\epsilon 4$  with  $A\beta$  and tau pathogenesis, indicating that the interaction between *APOE*  $\epsilon 4$  and tau pathogenesis may be mediated by  $A\beta$  [37]. In this study, subjects who had a lower CSF  $A\beta 42$  level and were *APOE*  $\epsilon 4$  positive experienced higher CSF T-tau and P-tau levels in EMCI and LMCI. This indicates that  $A\beta$  deposition and *APOE*  $\epsilon 4$  positivity have a synergistic relationship with regards to tau pathogenesis in both EMCI and LMCI individuals. This study supports that the relationship between *APOE*  $\epsilon 4$  and tau may be mediated by  $A\beta$  in EMCI and LMCI.

*APOE*  $\epsilon 4$  has been found to be related to worse memory scores [38] and rates of cognitive and functional decline [39, 40] in MCI. This association with worsened early cognitive status and decline is accompanied by evidence of increased AD pathology associated with *APOE*  $\epsilon 4$  in MCI [41]. In the present study, MMSE scores were different between *APOE*  $\epsilon 4$  carrier and noncarrier in the EMCI group but not in the LMCI group. On the other hand, ADAS-cog was higher in *APOE*  $\epsilon 4$  carrier than noncarrier in LMCI but not in EMCI. In a meta-analysis, the authors found that MMSE was not reliable in early diagnosis, and it was not suitable to distinguish healthy people from MCI patients [42]. A systematic review showed that the sensitivity and specificity of MMSE were 0.81 and 0.89, respectively [43]. However, ADAS-cog is considered to be an effective measurement instrument for pre-dementia syndromes [44], and the sensitivity and specificity of ADAS-cog are 96.97 and 91.49%, respectively [45]. The difference of specificity and sensitivity to MCI may be one of the reasons for the difference between the 2 results. In addition, we observed that the interaction was significant between *APOE*  $\epsilon 4$  status and the presence

of  $A\beta$  for ADAS-cog, suggesting that the association of the  $\epsilon 4$  genotype with ADAS-cog was stronger among individuals with  $A\beta+$ . In addition, in stratified analysis, we found that *APOE*  $\epsilon 4$  was strongly associated with lower MMSE scores in EMCI individuals with  $A\beta+$  and higher ADAS-cog scores in EMCI and LMCI individuals with  $A\beta+$ . However, we did not observe the same associations among persons without  $A\beta-$ . These findings support the hypothesis that  $A\beta$  positive EMCI and LMCI *APOE*  $\epsilon 4$  carriers are at elevated risk of cognitive decline.

There are a few limitations in the investigation. First, we did not assess all known biomarkers of AD, including PET; thus, future studies evaluating these measures would augment the findings of the present report. Second, our present study evaluates only cross-sectional measures. Future studies using longitudinal data will allow assessment of the role of *APOE*  $\epsilon 4$  in progression of CN, EMCI, and LMCI. Finally, the ADNI database was volunteered by highly educated individuals for research focused on AD research. This may give rise to bias in choice because the study population is a self-selected individual who may have concerns about their cognition.

In summary, we assessed the role of *APOE*  $\epsilon 4$  status on CSF tau and cognitive measures in CN, EMCI, and LMCI participants from the ADNI cohort. We determined that the prevalence of *APOE*  $\epsilon 4$  is higher in EMCI and LMCI than in CN, and in LMCI than in EMCI. We also demonstrated that *APOE*  $\epsilon 4$  status is associated with increased CSF tau in both EMCI and LMCI, although this association may be mediated by  $A\beta$ . Therefore, we conclude that *APOE*  $\epsilon 4$  may be an important mediator of tau pathology and cognition in the earliest stages of AD-associated clinical decline.

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## Statement of Ethics

Institutional review board approval was obtained at each ADNI site, and informed consent was obtained from each participant or authorized representative. ADNI makes all its data publicly available. Our manuscript was approved and acceptable for submission by the ADNI Data and Publications Committee (ADNI DPC). (For more information, visit <http://adni.loni.usc.edu/data-samples/access-data/>)

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## Conflict of Interest Statement

The authors declare that they have no competing interests.

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## Author Contributions

Y.L. contributed to analysis and interpretation of data, composition of figures, and manuscript drafting. L.T. contributed to analysis and interpretation of data. J.T. contributed to manuscript drafting. H.Z. contributed toward composition of figures and manuscript drafting. Y.G. contributed to study concept, study supervision, and critical review of the manuscript for intellectual content. All the authors read and approved the final manuscript.



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