Received: 16 December 2019 | Accepted: 13 January 2020 | Published online: 20 March 2020

DOI: 10.1002/trc2.12007

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Effect of apolipoprotein E ε4 allele on the progression of cognitive decline in the early stage of Alzheimer's disease

Kazushi Suzuki[1] | **Akihiro Hirakawa**[2] | **Ryoko Ihara**[1] | **Atsushi Iwata**[3] | **Kenji Ishii**[4] | **Takeshi Ikeuchi**[5] | **Chung-Kai Sun**[6] | **Michael Donohue**[6] | **Takeshi Iwatsubo**[1,7] | **Alzheimer's Disease Neuroimaging Initiative, Japanese Alzheimer's Disease Neuroimaging Initiative**[†]

[1]Unit for Early and Exploratory Clinical Development, The University of Tokyo Hospital, Tokyo, Japan

[2]Department of Biostatistics and Bioinformatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[3]Department of Neurology, The University of Tokyo Hospital, Tokyo, Japan

[4]Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

[5]Niigata University, Niigata, Japan

[6]Alzheimer's Therapeutics Research Institute, University of Southern California, San Diego, California

[7]Department of Neuropathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Correspondence
Kazushi Suzuki, Unit for Early and Exploratory Clinical Development, The University of Tokyo Hospital, Tokyo, Japan.
Email: kazusuzuki-tky@umin.ac.jp
Takeshi Iwatsubo, Department of Neuropathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.
Email: iwatsubo@m.u-tokyo.ac.jp

Funding information
Alzheimer's Disease Neuroimaging Initiative; National Institutes of Health, Grant/Award Number: U01 AG024904; Department of Defense, Grant/Award Number: W81XWH-12-2-0012; National Institute on Aging; National Institute of Biomedical Imaging and Bioengineering; Japan Society for the Promotion of Science, Grant/Award Number: 17K09794; Japan Agency for Medical Research and Development, Grant/Award Numbers: JP17DK0207028, JP19DK0207048

[†]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

Abstract

Introduction: Possession of the apolipoprotein E (*APOE*) ε4 allele advances amyloid β (Aβ) deposition and symptomatic onset of Alzheimer's disease (AD), whereas its effect on the rate of cognitive decline remained controversial. We examined the effects of *APOE* ε4 allele on cognition in biomarker-confirmed late mild cognitive impairment (LMCI) and mild AD subjects in the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) and North American ADNI (NA-ADNI).

Methods: The "early AD" (ie, combined LMCI and mild AD) cohort of 649 subjects from J-ADNI and NA-ADNI were selected based on positivity of Aβ confirmed by amyloid positron emission tomography (PET) or cerebrospinal fluid testing. The rates of cognitive decline in the Mini Mental State Examination (MMSE), the Clinical Dementia Rating Sum of Boxes (CDR-SB), and the Alzheimer's Disease Assessment Scale-cognitive subscale 13 (ADAS-Cog) from baseline were examined using mixed-effects model. The effect of ε4 on time to conversion to dementia was also analyzed in LMCI using the Kaplan-Meier estimator and log-rank test.

Results: The rates of cognitive decline were not significantly different between ε4 carriers and ε4 non-carriers in the total early AD cohort, which were affected neither by region nor by the number of ε4 alleles. In LMCI, ε4 carriers showed almost the same progression rates as ε4 non-carriers, except for a significantly faster decline in MMSE ($P = .0282$). Time to conversion to demenita was not significantly different between

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.
‡The full membership of the Japanese ADNI investigators is listed at: https://humandbs.biosciencedbc.jp/en/hum0043-j-adni-authors.

ε4 carriers and ε4 non-carriers. In ε4-positive mild AD, the rates of decline in MMSE ($P = .003$) and CDR-SB ($P = .0071$) were slower than those in ε4 non-carriers.
DISCUSSION: The *APOE* ε4 allele had little effect on the rates of cognitive decline in the overall biomarker-confirmed early AD, regardless of region and number of ε4 alleles, with a slight variability in different clinical stages, the ε4 allele being slightly accelerative in LMCI, while decelerative in mild AD.

KEYWORDS
ADNI, amyloid PET, *APOE*, CSF biomarkers, early Alzheimer's disease, J-ADNI, mild cognitive impairment

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of neurodegenerative dementia, which is pathologically characterized by amyloid deposits composed of amyloid β (Aβ) peptides and neurofibrillary tangles rich in tau protein. Recent studies suggest that pathological changes in AD brains, especially Aβ accumulation, precede symptomatic manifestation by ~15 to 20 years, followed by tau-mediated neurodegeneration.[1,2] The ε4 allele of the apolipoprotein E (*APOE*) gene is a strong genetic risk factor for the development of AD. Among the three genetic polymorphisms of the human *APOE* gene causing variation in two amino acid residues, that is, ε2, ε3, and ε4,[3] possession of one or two ε4 alleles increases the risk of developing AD by ~3 to 4 and >10 times, respectively.[4-7] Furthermore, carriage of one ε4 allele is estimated to advance the symptomatic onset of AD by ~10 years.[8,9]

In contrast to the well-established effects of the ε4 allele on the onset age of AD, it is controversial whether ε4 allele affects the speed of cognitive decline after the symptomatic onset. Some studies have suggested the accelerating effects of the ε4 allele on the progression rate of AD: The cognitive decline in ε4 homozygotes has been reported to progress faster compared with ε4 heterozygotes[10]; a meta-analysis study showed that the ε4 allele is one of the significant risk factors for rapid cognitive decline in AD.[11] Furthermore, the rates of decrease in the hippocampal volume of patients with AD were shown to be greater in ε4 carriers compared with those in non-ε4 carriers, suggesting that carriage of ε4 allele potentially accelerates the progression of neurodegeneration in AD.[7,12] In sharp contrast, other studies have suggested that the ε4 carriage does not affect the rate of symptomatic progression in AD,[13] or even may slow it down.[14,15] Of interest, some studies have documented a longer disease duration and less mortality of ε4-positive patients with AD,[16,17] which should, however, be carefully interpreted, because it might reflect the longer life expectancy of ε4-positive AD patients resulting from the younger onset.

In view of the needs for earlier intervention into the pathophysiology of AD using mechanism-based therapies, the earlier stages of AD are being highlighted. Clinically, mild cognitive impairment (MCI) is defined as a stage between the cognitively normal stage and dementia,[18] and amnesic MCI has been highlighted as a state that exhibits high likelihood of the prodromal stage of AD (MCI due to AD) with Aβ pathology.[19] Carriage of the ε4 allele also has been shown to increase the risk of development of MCI.[20,21] Although the effects of the ε4 allele on the progression rate of MCI have not been established yet, some studies have suggested that ε4-positive MCI individuals show faster cognitive deterioration, higher rate of conversion to dementia, and faster brain structural changes than the ε4-negative individuals.[22-24] Statistical simulation based on 19 clinical studies has suggested that possession of the ε4 allele could slightly accelerate the rate of progression of MCI and AD dementia, although the effect was small.[25] However, previous clinical studies on MCI and AD, in which the diagnosis was not necessarily based on amyloid biomarkers, have been inaccurate in the diagnosis of the early stages of AD. Amyloid positron emission tomography (PET) data in recent phase 3 trials of solanezumab showed that ~22% of subjects diagnosed as mild AD by clinical criteria did not show evidence of amyloid accumulation.[26] Furthermore, a number of recent clinical trials of disease-modifying therapies for AD target "early AD," combining MCI due to AD (prodromal AD) and mild AD as a single continuous entity. Especially, in the recent phase 2 trial of an anti-Aβ protofibril antibody BAN2401 on early AD participants, the restriction of enrollment of ε4 carriers in the highest-dose, active-drug arm but not in the placebo group, raised a question if the observed significant effects of the antibody treatment were due in part to the difference in the rates of progression in cognitive decline between ε4 carriers and non-carriers.[27] This prompted us to examine the effects of the ε4 allele on the progression rate of early AD population with biomarker confirmation of Aβ pathology.

In this present study, we aimed at elucidating the impacts of *APOE* ε4 carriage on the progression of cognitive decline in the early AD population, based on the data sets of the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) and the North American Alzheimer's Disease Neuroimaging Initiative (NA-ADNI) studies, which provide ideal information for the analysis of longitudinal effects of *APOE* ε4 allele on individuals with confirmed Aβ pathology. These two studies are one of the largest observational studies on early AD in Asians and Caucasians, and can be compared and integrated because they were conducted with nearly identical protocols.[28] We further analyzed the regional

difference, allele-number dependency, and disease-stage specificity of the effects of $\varepsilon 4$ alleles on the progression rate of early AD.

2 | METHODS

2.1 | Sample datasets

The data set of the J-ADNI (Research ID: hum0043.v1, 2016) was obtained from the National Bioscience Database Center (Tokyo, Japan) with approval from its data access committee (https://humandbs.biosciencedbc.jp/en/hum0043-v1). Entire data were downloaded on October 11, 2017. The inclusion/exclusion criteria of LMCI and AD in J-ADNI are described in a previous report.[28] Briefly, the age of participants must be between 60 and 85 years. LMCI and AD subjects must have memory complaints by subject or study partner that is verified by a study partner. The Mini-Mental State Examination (MMSE) score must be between 24 and 30 for LMCI and between 20 and 26 for AD. The global Clinical Dementia Rating (CDR) score must be 0.5 (and memory box must be 0.5) for LMCI, and 0.5 or 1 for AD. The cutoff score of Wechsler Memory Scale—Revised logical memory IIA (WMS-R LMIIA) is various depending on years of education: LMCI and AD subjects must be $\leq$8 for 16 or more years, $\leq$4 for 10 to 15 years, and $\leq$2 for 0 to 9 years. NA-ADNI data sets were obtained from The Image Data Archive at the Laboratory of Neuro Imaging (https://ida.loni.usc.edu) with their approval. Entire data were downloaded on July 11, 2017. The inclusion/exclusion criteria of LMCI and AD in NA-ADNI are generally comparable with those in J-ADNI, except for age (between 55 and 90) and range of years of education in WMS-R LMIIA criterion: LMCI and AD subjects must be $\leq$8 for 16 or more years of education, $\leq$4 for 8 to 15 years, and $\leq$2 for 0 to 7 years. Only LMCI subjects in NA-ADNI were used for analyses, and early MCI (EMCI) subjects in NA-ADNI were not included. The "early AD" cohort was defined as LMCI or mild AD with positivity of Aβ accumulation confirmed by cerebrospinal fluid (CSF) biomarker or amyloid PET.

2.2 | Assessments and variables analyzed

Progression rates of cognitive decline were evaluated by changes of the scores of MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale 13 (ADAS-Cog), and Clinical Dementia Rating Sum of Boxes (CDR-SB). In accordance with the study protocol of J-ADNI and NA-ADNI, longitudinal changes were evaluated by scores at baseline, 6 , 12, 18, 24, and 36 months for LMCI subjects and at 6, 12, and 24 months for mild AD subjects and early AD subjects. The data after those time points and one data point at 18 months in NA-ADNI were not used for analyses, in order to ensure comparability and consistency between NA-ADNI and J-ADNI. We analyzed age when subjects are diagnosed at baseline visit (age at diagnosis) instead of age at onset, because ADNI study does not collect age when symptoms start.

In the J-ADNI data set, positivity of Aβ accumulation was defined as the standardized uptake value ratio (SUVR) >1.5 in ^{11}C-Pittsburgh compound B (PiB) PET or low concentration of amyloid-β 42 in CSF (Aβ_{42}) <333 pg/mL.[28,29] In the NA-ADNI data set, positivity of Aβ accumulation was defined as an SUVR >1.5 in ^{11}C-PiB PET, SUVR >1.11 in AV45 (florbetapir)-PET, or CSF Aβ_{42} <192 pg/mL.[30,31] The amyloid status of subjects was determined to be positive when at least either of the PET or CSF results at baseline were positive. Subjects who showed contradictory results in PET and CSF tests were included in the Aβ-positive group.

HIGHLIGHTS

- It is controversial whether the apolipoprotein E (*APOE*) $\varepsilon 4$ allele affects the progression rate in early AD.
- The cognitive decline in the early Alzheimer's disease (AD) population from the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) and the North American ADNI (NA-ADNI) and North American ADNI (NA-ADNI)was analyzed.
- Possession of the *APOE* $\varepsilon 4$ allele did not significantly affect the progression rate in early AD.
- The region of the population and the number of $\varepsilon 4$ alleles did not affect the speed of cognitive decline.
- The $\varepsilon 4$ allele was slightly accelerative in mild cognitive impairment, while decelerative in mild AD.

RESEARCH IN CONTEXT

1. Systematic review: The authors thoroughly reviewed the literature using the PubMed database, and found that the effect of apolipoprotein E (*APOE*) $\varepsilon 4$ on the rate of progression in late mild cognitive impairment (LMCI) and mild Alzheimer's disease (AD) remained controversial. In most of the previous reports, AD and MCI were diagnosed by clinical criteria alone, without confirmation by biomarkers.
2. Interpretation: Our result clearly supported the hypothesis that the *APOE* $\varepsilon 4$ does not affect the progression rate of cognitive decline in early AD regardless of region and the number of $\varepsilon 4$ alleles. The effect of $\varepsilon 4$ was variable in different disease stages.
3. Future directions: Our results suggest that the frequency of $\varepsilon 4$ alleles has little effect on the natural course of cognitive decline of early AD patients in clinical trials. Longitudinal studies on a diverse population with biomarker-confirmed AD pathology will be needed to elucidate the long-term effects of the *APOE* $\varepsilon 4$ allele on the prognosis of AD.

2.3 | Statistical analyses

The distribution of categorical and continuous variables between groups was compared by using chi-square test and *t* test, respectively. The survival distributions of time to conversion to AD were estimated based on the Kaplan-Meier estimator, and the *APOE* $\varepsilon 4$ group difference was tested using the log-rank test. The changes of cognitive variables (ie, MMSE, CDR, or ADAS-Cog) from baseline were analyzed based on the mixed-effects model that includes the *APOE* $\varepsilon 4$ status (eg, presence/absence or number of alleles [0, 1, or 2] of *APOE* $\varepsilon 4$), time point (months), interaction between time point and *APOE* $\varepsilon 4$ status, baseline value of the cognitive variable, age (continuous), and data source (J-ADNI or NA-ADNI) as fixed effects and the time point as random effects. Using this model, we compared the slope of decline from baseline per month between the groups defined as *APOE* $\varepsilon 4$ status. *P*-value <.05 were considered statistically significant. All the statistical analyses were performed using the JMP pro 14.0.0 program and SAS version 9.4 (SAS Institute Inc, Cary, NC).

2.4 | Ethics

The study protocol was approved by the University of Tokyo ethics committee (11628).

3 | RESULTS

3.1 | *APOE* $\varepsilon 4$ carriage does not influence the rate of cognitive decline in early AD

We selected 74 LMCI and 70 mild AD subjects from the J-ADNI cohort, and 274 LMCI and 231 AD subjects from the NA-ADNI cohort, based on the Aβ positivity verified by CSF $A\beta_{42}$ and/or ^{11}C-PiB PET and the availability of *APOE* genotype. The "early AD" cohort of 649 subjects represented the total of the LMCI and AD subjects from J-ADNI and NA-ADNI. The demographics of the 448 $\varepsilon 4$ carriers and 201 non-carriers in the early AD cohort are shown in Table 1A. The $\varepsilon 4$ carriers presented a significantly lower age at baseline ($P = .0172$) and higher positivity of family history of AD (mother: $P < .0001$, father: $P = .0025$) compared with the non-carriers. No significant differences were found between the $\varepsilon 4$ carriers and non-carriers in sex, education, baseline scores of cognitive tests, CSF total tau, CSF phosphorylated tau (p-tau), and SUVR of amyloid PET, except that $\varepsilon 4$ carriers showed slightly lower CSF $A\beta_{42}$ compared with the non-carriers.

The 2-year longitudinal changes of MMSE, CDR-SB, and ADAS-Cog from baseline in early AD are shown in Figure 1. We compared the slopes of decline in MMSE, CDR, and ADAS-Cog between $\varepsilon 4$ carriers and non-carriers using a mixed-effects model, and found that the rates of decline in the above three cognitive scales were not significantly different between $\varepsilon 4$ carriers and non-carriers, suggesting that the carriage of $\varepsilon 4$ alleles does not affect the rate of progression after the symptomatic onset in early AD (Table 2A). To see the effects of regional difference, we compared the slopes of decline in $\varepsilon 4$ carriers and non-carriers separately in the J-ADNI and NA-ADNI data sets. No significant differences were observed in the slope of decline between $\varepsilon 4$ carriers and non-carriers in J-ADNI or NA-ADNI (Table 2B), suggesting the lack of regional differences in the effect of the $\varepsilon 4$ alleles on the progression rate in early AD. Furthermore, we compared the speed of cognitive decline among the $\varepsilon 4$ non-carriers (0), heterozygotes (1), or homozygotes (2) of $\varepsilon 4$ alleles, to see if there is a gene dosage effect of $\varepsilon 4$ alleles on the rate of progression. The progression rates of cognitive decline in heterozygotes and homozygotes were not significantly different from those in $\varepsilon 4$ non-carriers, suggesting that the number of the $\varepsilon 4$ alleles had little effect on the symptomatic progression in early AD (Table 2C). Taken together, the *APOE* $\varepsilon 4$ carriage did not affect the rate of progression in cognitive deterioration in early AD, regardless of the regional difference or the gene dosage of $\varepsilon 4$ alleles.

3.2 | Differential effects of *APOE* $\varepsilon 4$ carriage on the rate of disease progression in LMCI and mild AD

To examine the effects of the $\varepsilon 4$ allele on the rate of disease progression in different disease stages, we separately analyzed the data in LMCI and mild AD. The demographics of 348 LMCI (232 $\varepsilon 4$ carriers and 116 non-$\varepsilon 4$ carriers) and 301 mild AD (216 $\varepsilon 4$ carriers and 85 non-$\varepsilon 4$ carriers) are shown in Table 1B. In LMCI, $\varepsilon 4$ carriers showed significantly younger age at baseline ($P = .0441$), higher frequency of family history (mother: $P = .0008$, father: $P = .0004$), and higher score of ADAS-Cog at baseline ($P = .0427$) than $\varepsilon 4$ non-carriers. CSF biomarkers at baseline showed higher total tau and p-tau levels in $\varepsilon 4$ carriers than in $\varepsilon 4$ non-carriers. We analyzed the 3-year longitudinal changes of MMSE, CDR-SB, and ADAS-Cog in 348 LMCI subjects (74 from J-ADNI and 274 from NA-ADNI) using a mixed-effects model. $\varepsilon 4$ Carriers showed almost the same progression rates as non-carriers, except for a small but significantly faster cognitive decline in MMSE ($P = .0282$) (Figure 2A and Table 3A). We then asked whether carriage of $\varepsilon 4$ affects the time to conversion to dementia, another indicator of cognitive decline of LMCI. Time to conversion of $\varepsilon 4$ carriers and non-carriers were shown as the Kaplan-Meier plots (Figure 3), suggesting that carriage of *APOE* $\varepsilon 4$ may slightly accelerate the progression of LMCI, but the association was not statistically significant (log-rank test $P = .1623$).

Finally, we analyzed the rate of progression in 301 AD subjects, including 216 $\varepsilon 4$ carriers and 85 non-carriers. The demographics of $\varepsilon 4$ carriers and non-carriers in the AD cohort were not significantly different in most variables analyzed, except for a higher frequency of having family history of the mother ($P = .0174$) (Table 1B). The 2-year longitudinal changes in MMSE, CDR, and ADAS-Cog in mild AD (Figure 2B) showed that $\varepsilon 4$-positive mild AD patients showed a significantly slower cognitive decline in MMSE and CDR ($P = .003$ in MMSE and $P = .0071$ in CDR) in contrast to LMCI, suggesting that the $\varepsilon 4$ alleles decelerate the progression of cognitive decline in mild AD (Table 3B).

TABLE 1 Baseline demographics of $\varepsilon 4$ carriers and non-carriers in early AD (A) and LMCI/AD (B)

A			
Early AD (649)			
	$\varepsilon 4$ carriers (448)	**non-$\varepsilon 4$ carriers (201)**	***P*** **(χ^2 or *t* test)**
Sex (% male)	56.03	58.21	.6036
Age at baseline	73.094 (6.839)	74.568 (8.150)	**.0172**
Education	15.152 (3.083)	15.313 (3.218)	.5426
AD family history–mother (%)	22.77	9.95	**<.0001**
AD family history–father (%)	9.15	2.99	**.0025**
MMSE at baseline	25.147 (2.700)	25.100 (2.793)	.8365
CDR-SB at baseline	2.950 (1.836)	2.749 (1.806)	.1953
ADAS-Cog 13 at baseline	24.724 (8.466) (n = 443, 5 missed values)	23.944 (9.159) (n = 200, 1 missed value)	.2924
CSF Aβ	152.485 (58.508) (n = 412)	161.752 (54.505) (n = 180)	**.0354**
CSF tau	126. 211 (61.763) (n = 412)	116. 870 (63.542) (n = 180)	.0939
CSF p-tau	54.616 (27.531) (n = 412)	50.569 (26.946) (n = 180)	.0983
SUVR of amyloid PET*	1.606 (0.403) (n = 239)	1.601 (0.473) (n = 107)	.906
B			
LMCI (348)			
	$\varepsilon 4$ carriers (232)	**non-$\varepsilon 4$ carriers (116)**	***P*** **(χ^2 or *t* test)**
Sex (% male)	55.17	63.79	.1229
Age at baseline	72.564 (6.479)	74.15 (7.681)	**.0441**
Education	15.530 (3.007)	15.595 (3.151)	.8525
AD family history–mother (%)	25	10.34	**.0008**
AD family history–father (%)	11.64	1.72	**.0004**
MMSE at baseline	27.000 (0.121)	26.828 (1.903)	.4107
CDR-SB at baseline	1.718 (0.898)	1.651 (0.961)	.5232
ADAS-Cog 13 at baseline	20.421 (6.396) (n = 231, 1 missed values)	18.921 (6.639) (n = 116)	**.0427**
CSF Aβ	154.064 (59.332) (n = 218)	167.564 (57.312) (n = 110)	.05
CSF tau	123.028 (59.307) (n = 218)	105.0328 (n = 110)	**.0089**
CSF p-tau	53.293 (25.168) (n = 218)	47.103 (24.639) (n = 110)	**.035**
SUVR of amyloid PET*	1.609 (0.418) (n = 120)	1.507 (0.425) (n = 50)	.1529
AD (301)			
	$\varepsilon 4$ carriers (216)	**non-$\varepsilon 4$ carriers (85)**	***P*** **(χ^2 or *t* test)**
Sex (% male)	56.94	50.59	.3189
Age at baseline	73.663 (7.177)	75.138 (8.763)	.1337
Education	14.745 (3.118)	14.929 (3.287)	.6502
AD family history–mother (%)	20.37	9.41	**.0174**
AD family history–father (%)	6.48	4.71	.5497
MMSE at baseline	23.157 (1.989)	22.741 (1.965)	.1021
CDR-SB at baseline	4.273 (1.656)	4.247 (1.601)	.9013
ADAS-Cog 13 at baseline	29.414 (7.949) (n = 212, 4 missed values)	30.882 (7.488) (n = 84 1 missed value)	.1465
CSF Aβ	150.710 (57.669) (n = 194)	152.619 (48.780) (n = 70)	.8053
CSF tau	129.788 (74.377) (n = 194)	135.471 (69.399) (n = 70)	.5357
CSF p-tau	56.102 (29.961) (n = 194)	56.014 (29.588) (n = 70)	.9834
SUVR of amyloid PET*	1.604 (0.390) (n = 119)	1.683 (0.500) (n = 57)	.2578

P-values were calculated by chi-square analysis for categorical data or *t* test for numerical data. Subjects included in the analysis have evidence of increased brain amyloid confirmed by biomarkers.

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale, CDR-SB, clinical dementia rating sum of boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, the mini-mental state examination; PET, positron emission tomography; SUVR, standardized uptake value ratio.

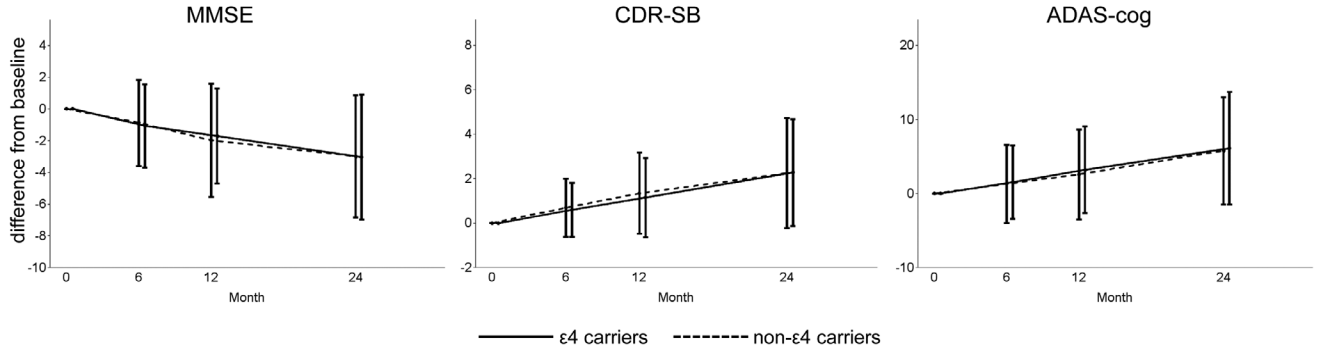

FIGURE 1 Two-year longitudinal changes of MMSE, CDR-SB, and ADAS-Cog from baseline in early AD cohort. ε4 carriers and non-carriers shown in solid line and broken line, respectively. Data were shown in average ± SD. ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; CDR-SB, Clinical dementia rating sum of boxes; MMSE, the mini-mental state examination; SD, standard deviation

TABLE 2 Difference of decline of MMSE, CDR-SB, and ADAS-Cog per month between different ε4 carriages in early AD cohort with their *P*-value and 95% CI

			Interaction of time and presence/absence of *APOE* ε4 allele (difference of decline between ε4 presence and absence groups per month)	95% CI	*P*-value
A					
All early AD		MMSE	0.009	(−0.028, 0.046)	.647
		CDR-SB	−0.006	(−0.029, 0.016)	.582
		ADAS-cog	0.018	(−0.051, 0.087)	.6063
B					
J-ADNI early AD		MMSE	0.021	(−0.031, 0.072)	.4303
		CDR-SB	−0.039	(−0.083, 0.005)	.0802
		ADAS-cog	−0.053	(−0.145, 0.038)	.2526
NA-ADNI early AD		MMSE	0.005	(−0.041, 0.052)	.8206
		CDR-SB	0.004	(−0.022, 0.03)	.7687
		ADAS-cog	0.04	(−0.047, 0.126)	.3698
		Number of *APOE* ε4 allele	Interaction of time and number of *APOE* ε4 allele (difference of decline between one (or two) alleles relative to zero allele per month	95% CI	*P*-value
C					
All early AD	MMSE	1	0.005	(−0.034, 0.044)	.8144
		2	0.019	(−0.027, 0.066)	.4135
	CDR-SB	1	−0.008	(−0.032, 0.016)	.5215
		2	−0.002	(−0.032, 0.028)	.874
	ADAS-cog	1	0.011	(−0.062, 0.083)	.7756
		2	0.038	(−0.056, 0.132)	.4273

(A) All early AD. (B) Analysis divided by data source, J-ADNI and NA-ADNI. (C) Analysis divided by the number of ε4 allele. Difference of decline of heterozygotes (1) and homozygotes (2) relative to non-ε4 carriers (0).

4 | DISCUSSION

Our present study showed that the *APOE* ε4 allele does not affect the speed of cognitive decline in early AD, regardless of region and gene dosage of the ε4 alleles. This result may enable the precise interpretation of the rate of changes in MMSE, CDR-SB, and ADAS-Cog used as primary end points in clinical trials of disease-modifying therapies targeting Aβ on early AD. Because of the variability in drug responsiveness depending on the *APOE* genotype in the past clinical trials,[32,33] the frequency of ε4 carriers within the treatment group becomes often

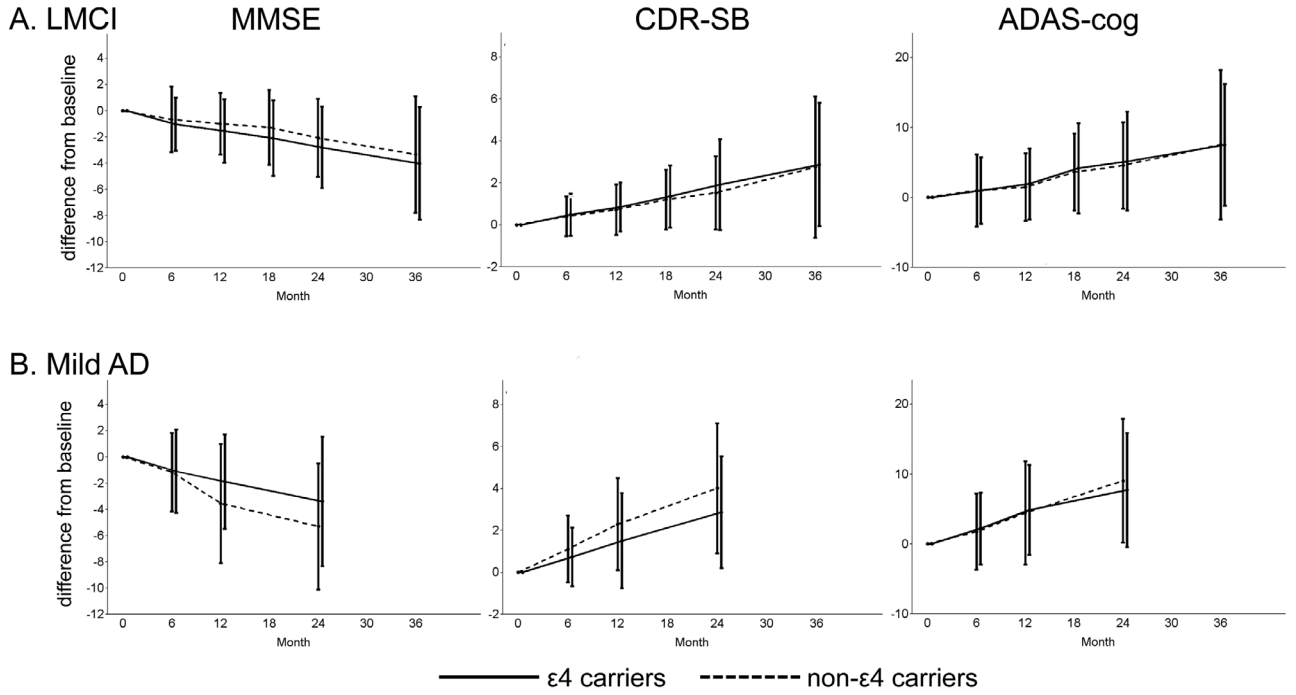

FIGURE 2 Longitudinal changes of MMSE, CDR-SB, and ADAS-Cog from baseline in LMCI (A) and mild AD (B). ε4 carriers and non-carriers shown in solid line and broken line, respectively. Data were shown in average ± SD

problematic. Furthermore, amyloid-related imaging abnormalities (ARIAs), an important adverse event in amyloid-removing antibody trials, are more frequent in ε4 carriers.[34] Notably, it has recently become controversial if the imbalanced allocation of ε4 carriers to the highest dose group in the trial of an anti-Aβ protofibril antibody BAN2401, in which enrollment of ε4 carriers in the active drug arm was avoided due to concerns of ARIAs, might have biased the effects in the active-drug group, if the natural course of progression of the ε4 carriers were faster. Our present results suggest that the effect of the frequency of ε4 carriers on the speed of progression in the early AD population might be negligibly small, validating the signal of efficacy observed in the trials.

The effects of the ε4 alleles on the progression rate were different between LMCI and mild AD; the decline was slightly faster in ε4 carriers than in non-carriers in LMCI, whereas slower in ε4 carriers than in non-carriers. The levels of CSF p-tau and total tau, markers of tau-related neurodegeneration,[35] were significantly higher in the ε4 carriers than non-carriers in LMCI subjects, raising the possibility that ε4-positive LMCI subjects had more advanced pathology compared with the non-carriers; in contrast, CSF levels of p-tau and total tau were similar between ε4 carriers and non-carriers in mild AD. These findings may suggest that the ε4 allele accelerates tau-mediated neurodegeneration in the LMCI stage, but no longer in the mild dementia stage. Previous studies on the effects of ApoE ε4 alleles in cognitively normal individuals suggested that ε4 contributes to lower cognitive performance and faster progression of cognitive decline.[36,37] It has also been shown that the accelerating effect of ε4 on cognitive decline was observed in Aβ-positive cognitive normal individuals, but not in Aβ negatives.[38] Taken together, our results suggest that the ε4 allele may contribute to neurodegeneration and associated cognitive decline in relatively earlier stages of AD pathophysiology, ranging from cognitively normal to amyloid-positive MCI stages.

Previous clinical studies, including ADNIs, have shown a strong association between carriage of ε4 alleles and positive amyloid biomarkers in cognitive normal, MCI, and dementia.[28,39,40] Experimental studies in mice models of AD also have suggested that the *APOE* ε4 alleles affect the biological process of Aβ accumulation to increase its deposition.[41] Although at least one study suggested the effects of *APOE* ε4 on tau-mediated neurodegeneration,[42] our results may be consistent with the view that the *APOE* ε4 alleles do not directly affect the process of neurodegeneration including the tau pathology, the latter being more directly linked to the cognitive decline.

There are a couple of limitations in our study. First, the observation period of our analyses was limited to 2 to 3 years, which might have characterized a limited duration of the early stages of AD, although we believe that our data might have implications in the interpretation of results in clinical trials at the early AD stage, which usually have a maximum follow-up of 2 years. Second, the combined analysis of the J-ADNI and NA-ADNI data, which exhibited a couple of minor differences,[28] might have caused some inconsistencies; however, the impact of merging these two cohorts should be minor, because (1) we included data source as a fixed effect in the mixed-effects models and (2) the analyses separately performed in J-ADNI and NA-ADNI drew almost the same conclusions. Finally, our study focusing on the composite cognitive battery may have missed the differential effects of ε4 on specific cognitive domains; considering the previous report suggesting that ε4 might specifically affect the episodic memory,[43] further analysis on the domain-specific effects will resolve the problem.

TABLE 3 Difference of decline of MMSE, CDR-SB, and ADAS-Cog per month between different $\varepsilon 4$ carriages in LMCI (A) and mild AD (B) cohort with their *P*-value and 95% CI

		Interaction of time and presence/absence of *APOE* $\varepsilon 4$ allele (difference of decline between $\varepsilon 4$ presence and absence groups per month)	95% CI	*P*-value
A				
LMCI	MMSE	−0.033	(−0.063, −0.004)	**.0282**
	CDR-SB	0.016	(−0.004, 0.036)	.582
	ADAS-Cog	0.027	(−0.04, 0.094)	.4368
B				
Mild AD	MMSE	0.114	(0.039, 0.189)	**.003**
	CDR-SB	−0.06	(−0.104, −0.016)	**.0071**
	ADAS-Cog	−0.041	(−0.187, 0.105)	.5823

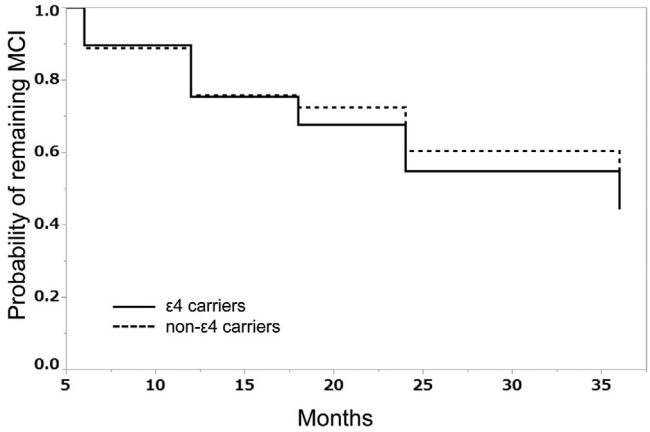

FIGURE 3 Comparison of time to AD conversion between the $\varepsilon 4$ carriers and non-carriers in LMCI. The probability of remaining LMCI over 3 years were shown in the Kaplan-Meier plots. $\varepsilon 4$ carriers and non-$\varepsilon 4$ carriers shown in solid line and broken line, respectively

In sum, our present study showed that the *APOE* $\varepsilon 4$ alleles do not significantly affect the speed of cognitive decline in the amyloid-positive early AD (ie, combined LMCI and mild AD) population. Further detailed analysis of data, especially those from the placebo group of large-scale clinical trials for disease-modifying therapies of AD with imaging and biomarker data, will elucidate the effects of *APOE* $\varepsilon 4$ alleles on the pathophysiological and symptomatic progression of AD at its early stages.

ACKNOWLEDGMENT

The authors would like to thank Drs. Michio Senda, Kengo Ito, Ryozo Kuwano, and Hiroshi Matsuda for useful discussions. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This work was supported by Japan Society for the Promotion of Science grant 17K09794 and by Japan Agency for Medical Research and Development grants JP17DK0207028 and JP19DK0207048.

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How to cite this article: Suzuki K, Hirakawa A, Ihara R, et al. Effect of apolipoprotein E ε4 allele on the progression of cognitive decline in the early stage of Alzheimer's disease. *Alzheimer's Dement*. 2020;6:e12007.
https://doi.org/10.1002/trc2.12007