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

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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 dementia was not significantly different between
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; 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 AD13 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 amnestic 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://humanbds.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. 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 LMIIIA 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 A$\beta$ 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 A$\beta$ 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-$\beta$ 42 in CSF ($A\beta_{42} < 333\text{ pg/mL}$). In the NA-ADNI data set, positivity of A$\beta$ accumulation was defined as an SUVR > 1.5 in $^{11}$C-PiB PET, SUVR > 1.11 in AV45 (florbetapir)-PET, or CSF $A\beta_{42} < 192\text{ pg/mL}$. 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 A$\beta$-positive group.
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 ε4 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 variables (ie, MMSE, CDR, or ADAS-Cog) from baseline 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 ε4 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 ε4 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 ApoE positivity verified by CSF Aβ42 and/or 11C-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 ε4 carriers and 201 non-carriers in the early AD cohort are shown in Table 1A. The ε4 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 ε4 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 ε4 carriers showed slightly lower CSF Aβ42 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 ε4 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 ε4 carriers and non-carriers, suggesting that the carriage of ε4 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 ε4 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 ε4 carriers and non-carriers in J-ADNI or NA-ADNI (Table 2B), suggesting the lack of regional differences in the effect of the ε4 allele on the progression rate in early AD. Furthermore, we compared the speed of cognitive decline among the ε4 non-carriers (0), heterozygotes (1), or homozygotes (2) of ε4 alleles, to see if there is a gene dosage effect of ε4 alleles on the rate of progression. The progression rates of cognitive decline in heterozygotes and homozygotes were not significantly different from those in ε4 non-carriers, suggesting that the number of the ε4 alleles had little effect on the symptomatic progression in early AD (Table 2C). Taken together, the APOE ε4 carriage did not affect the rate of progression in cognitive deterioration in early AD, regardless of the regional difference or the gene dosage of ε4 alleles.

3.2 Differential effects of APOE ε4 carriage on the rate of disease progression in LMCI and mild AD

To examine the effects of the ε4 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 ε4 carriers and 116 non-ε4 carriers) and 301 mild AD (216 ε4 carriers and 85 non-ε4 carriers) are shown in Table 1B. In LMCI, ε4 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 ε4 non-carriers. CSF biomarkers at baseline showed higher total tau and p-tau levels in ε4 carriers than in ε4 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. ε4 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 ε4 affects the time to conversion to dementia, another indicator of cognitive decline of LMCI. Time to conversion of ε4 carriers and non-carriers were shown as the Kaplan-Meier plots (Figure 3), suggesting that carriage of APOE ε4 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 ε4 carriers and 85 non-carriers. The demographics of ε4 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 ε4-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 ε4 alleles decelerate the progression of cognitive decline in mild AD (Table 3B).
## TABLE 1  Baseline demographics of ε-4 carriers and non-carriers in early AD (A) and LMCI/AD (B)

### A  Early AD (649)

|                   | ε-4 carriers (448) | non-ε-4 carriers (201) | P (χ² or t test) |
|-------------------|--------------------|------------------------|-----------------|
| Sex (% male)      | 56.03              | 58.21                  | .6036           |
| Age at baseline   | 73.09 (6.839)      | 74.56 (8.150)          | .0172           |
| Education         | 15.15 (3.083)      | 15.31 (3.218)          | .5426           |
| AD family history–mother (%) | 22.77 | 9.95 | <.0001 |
| AD family history–father (%) | 9.15 | 2.99 | .0025 |
| MMSE at baseline  | 25.14 (2.700)      | 25.10 (2.793)          | .8365           |
| CDR-SB at baseline| 2.95 (1.836)       | 2.74 (1.806)           | .1953           |
| ADAS-Cog 13 at baseline | 24.72 (8.466) (n = 443, 5 missed values) | 23.94 (9.159) (n = 200, 1 missed value) | .2924 |
| CSF Aβ (n = 412)  | 152.48 (58.508)    | 161.75 (54.505)        | .0354           |
| CSF tau           | 126.21 (61.763)    | 116.87 (63.542)        | .0939           |
| SUVR of amyloid PET* | 1.606 (0.403) (n = 239) | 1.601 (0.473) (n = 107) | .906 |

### B  LMCI (348)

|                   | ε-4 carriers (232) | non-ε-4 carriers (116) | P (χ² or t test) |
|-------------------|--------------------|------------------------|-----------------|
| Sex (% male)      | 55.17              | 63.79                  | .1229           |
| Age at baseline   | 72.56 (6.479)      | 74.15 (7.681)          | .0441           |
| Education         | 15.53 (3.007)      | 15.59 (3.151)          | .8525           |
| AD family history–mother (%) | 25 | 10.34 | <.0008 |
| AD family history–father (%) | 11.64 | 1.72 | .0004 |
| MMSE at baseline  | 27.00 (0.121)      | 26.82 (1.903)          | .4107           |
| CDR-SB at baseline| 1.71 (0.898)       | 1.65 (0.961)           | .5232           |
| ADAS-Cog 13 at baseline | 20.42 (6.396) (n = 231, 1 missed values) | 18.92 (6.639) (n = 116) | .0427 |
| CSF Aβ (n = 218)  | 154.06 (59.332)    | 167.56 (57.312)        | .05             |
| CSF tau           | 123.02 (59.307)    | 105.03 (56.946)        | .0809           |
| SUVR of amyloid PET* | 1.609 (0.418) (n = 120) | 1.507 (0.425) (n = 50) | .1529 |

### AD (301)

|                   | ε-4 carriers (216) | non-ε-4 carriers (85) | P (χ² or t test) |
|-------------------|--------------------|-----------------------|-----------------|
| Sex (% male)      | 56.94              | 50.59                 | .3189           |
| Age at baseline   | 73.66 (7.177)      | 75.14 (8.763)         | .1337           |
| Education         | 14.74 (3.118)      | 14.92 (3.287)         | .6502           |
| AD family history–mother (%) | 20.37 | 9.41 | .0174 |
| AD family history–father (%) | 6.48 | 4.71 | .5497 |
| MMSE at baseline  | 23.15 (1.989)      | 22.74 (1.965)         | .1021           |
| CDR-SB at baseline| 4.27 (1.656)       | 4.24 (1.601)          | .9013           |
| ADAS-Cog 13 at baseline | 29.41 (7.949) (n = 212, 4 missed values) | 30.88 (7.488) (n = 84 1 missed value) | .1465 |
| CSF Aβ (n = 194)  | 150.71 (57.669)    | 152.61 (48.780)       | .8053           |
| CSF tau           | 129.78 (74.377)    | 135.47 (69.399)       | .5357           |
| CSF p-tau         | 56.10 (29.961)     | 56.01 (29.588)        | .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  |

(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, the frequency of ε4 carriers within the treatment group becomes often...
problematic. Furthermore, amyloid-related imaging abnormalities (ARIAs), an important adverse event in amyloid-removing antibody trials, are more frequent in ε4 carriers. 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, 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. It has also been shown that the accelerating effect of ε4 on cognitive decline was observed in Aβ-positive cognitively normal individuals, but not in Aβ negatives. 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. 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. Although at least one study suggested the effects of ApoE ε4 on tau-mediated neurodegeneration, 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, 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, further analysis on the domain-specific effects will resolve the problem.

**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.
TABLE 3  Difference of decline of MMSE, CDR-SB, and ADAS-Cog per month between different ε4 carriages in LMCI (A) and mild AD (B) 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          |                                                                                                                                  |                         |         |
| LMCI       | MMSE                                                               | −0.033                  | (−0.063, −0.004) | 0.0282  |
|            | CDR-SB                                                              | 0.016                   | (−0.004, 0.036) | 0.582   |
|            | ADAS-Cog                                                            | 0.027                   | (−0.04, 0.094)  | 0.4368  |
| B          |                                                                                                                                  |                         |         |
| Mild AD    | MMSE                                                               | 0.114                   | (0.039, 0.189)  | 0.003   |
|            | CDR-SB                                                              | −0.06                   | (−0.104, −0.016) | 0.0071  |
|            | ADAS-Cog                                                            | −0.041                  | (−0.187, 0.105) | 0.5823  |

FIGURE 3  Comparison of time to AD conversion between the ε4 carriers and non-carriers in LMCI. The probability of remaining LMCI over 3 years were shown in the Kaplan-Meier plots. ε4 carriers and non-ε4 carriers shown in solid line and broken line, respectively.

In sum, our present study showed that the APOE ε4 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 ε4 alleles on the pathophysiological and symptomatic progression of AD at its early stages.

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