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Sex Difference in the Association of APOE4 with Memory Decline in Mild Cognitive Impairment

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Abstract. Our aim was to examine whether the influence of apolipoprotein E4 (APOE4) genotype on cognitive decline differs in male and female across the Alzheimer's disease (AD) continuum. Among individuals with normal cognition (NC; $n = 415$), mild cognitive impairment (MCI; $n = 870$), and AD ($n = 334$), we investigated the longitudinal associations of APOE4 genotype and sex with cognitive decline over 13 years. Our cognitive outcomes were Rey Auditory Verbal Learning Test (RAVLT) total learning score and delayed recall and Mini-Mental State Examination (MMSE) score. There were significant effects of the APOE4 × sex interaction on change in verbal memory in the MCI group, but not the NC or AD group. Specifically, among individuals with MCI, female APOE4 carriers had a steeper decline in RAVLT total learning score, but not delayed recall or MMSE score compared to all other groups (APOE4 + /Male, APOE4-/Female, APOE4-/Male). In conclusion, female APOE4 carriers have faster rates of memory decline than their male counterparts among MCI individuals.

Keywords: Alzheimer's disease, APOE, memory decline, sex differences

INTRODUCTION

An increasing number of studies support that apolipoprotein E ε4 allele (APOE4) is associated with the risks of cognitive impairment and cognitive decline [1–3]. However, there have been inconsistent results with some studies showing no relationship or an inverse one between APOE4 and cognitive deficits [1, 4, 5]. These discrepancies may be attributed to the potentially important modulating role of sex in the relationship between APOE4 and cognitive deficits.

Epidemiological studies have suggested sex can alter the risk conferred by the APOE4 allele: the risk for Alzheimer's disease (AD) was found to be greater in female carriers than in male carriers [6, 7]. More recently, an analysis of more than 50,000 participants has refined these early findings [8]. Female APOE4 carriers have an increased incidence of AD in individuals aged 65 to 75 years, indicating a susceptibility of female carriers [8]. Nevertheless, few studies have investigated the interactive effects of APOE4 and sex

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

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on cognitive outcomes [9–12], especially episodic memory, even though episodic memory deficits are the earliest and most prominent symptoms in AD [13]. For example, among community-dwelling older people, female APOE4 carriers had greater global cognitive decline than male APOE4 carriers [10, 11]. In subjects with mild cognitive impairment (MCI), APOE4 had a greater detrimental impact on episodic memory performance in female than male [9]; however, this finding was not replicated in a recent study [12]. Although previous cross-sectional studies generally supported a potential interaction between sex and APOE4 status, these studies were less conclusive than prospective longitudinal studies, especially in diseases like AD with a long presymptomatic period [14]. It is unclear whether the association of APOE4 with change in verbal memory over time is modified by sex, or whether sex differences in the effect of APOE4 on memory decline is varied by disease stage. Clarifying sex-specific effects in regard to APOE4 is particularly important in the early stages of AD, given that an increasing number of drugs are now being tested in cognitively normal older adults at risk of AD and in individuals with MCI [15]. If APOE4 differentially affects memory decline in females and males along the AD continuum, this will have important implications for patient selection and time of intervention in clinical trials.

In the present analysis, we systematically investigated the potential moderating effect of sex on the relationship between APOE4 genotype and episodic memory decline among individuals with normal cognition (NC), MCI, and mild AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

MATERIALS AND METHODS

Alzheimer's disease neuroimaging initiative

Longitudinal data used in the preparation of this article were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database in August 2018. The ADNI study was launched to examine whether clinical variables, cognitive assessments, serial MRI, PET, and other blood and CSF biomarkers can be integrated to predict the progression of MCI and AD. ADNI was approved by the institutional review board at each ADNI center, and all subjects provided written informed consent.

Participants

Inclusion criteria have been previously described elsewhere [16], and could be found at the ADNI website (http://adni.loni.usc.edu). In the present analysis, we included subjects who met criteria for NC, MCI, and mild AD and had APOE4 genotype data and follow-up measurements of global cognitive function and verbal memory. At baseline, there was a total of 1,619 participants, including 415 participants with NC, 870 participants with MCI, and 334 patients with AD (Table 1).

APOE allele genotyping

APOE (gene map locus 19q13.2) genotypes of the study participants were extracted from the ADNI database (http://adni.loni.usc.edu). The APOE genotype was classified into two groups: APOE4 carriers (APOE4+) and APOE4 noncarriers (APOE4-).

Neuropsychological outcomes

Subjects underwent clinical and neuropsychological measurements at each follow-up visit. The neuropsychological outcomes are as following: 1) Mini-Mental State Examination (MMSE) [17] to examine global cognitive function; and 2) Rey Auditory Verbal Learning Test (RAVLT) [18] to evaluate verbal episodic memory. The RAVLT is a list-learning and memory test that has two primary outcomes: total learning score (range: 0–75) and delayed recall score (range: 0–15).

Statistical analysis

The APOE genotype was divided into APOE4+ and APOE4- due to the low prevalence of homozygous carriers of APOE4 when stratifying by gender and diagnosis (for example, 4 women and 7 men in the NC group). Group differences were examined with F tests for continuous variables and χ^2 tests for categorical variables. The Tukey's HSD test was utilized for multiple comparisons of means. To examine contributions of APOE4 and sex to longitudinal change in MMSE and RAVLT scores, linear mixed models were fitted for each neuropsychological outcome: inclusion of interactions of APOE4 with time and sex with time along with their joint interaction with time. All models were adjusted for baseline age, educational attainment, and their interactions with time, as well as random effects consisting of a random intercept and

Table 1
Demographic and clinical data

Variables	NC ($n=415$)	MCI ($n=870$)	AD ($n=334$)
Age, y	74.8 ± 5.73	73 ± 7.57 [a]	74.9 ± 7.82 [c]
Education, y	16.3 ± 2.73	15.9 ± 2.84	15.1 ± 2.99 [b,c]
Female, *n* (%)	206 (49.6)	355 (40.8) [a]	149 (44.6)
White, *n* (%)	373 (90.1)	812 (93.3) [a]	310 (92.8)
APOE4, *n* (%)	114 (27.5)	438 (50.3) [a]	222(66.5) [b,c]
MMSE score	29.1 ± 1.12	27.6 ± 1.81 [a]	23.2 ± 2.06 [b,c]
RAVLT total learning score	44.3 ± 9.82	34.2 ± 10.7 [a]	22.9 ± 7.57 [b,c]
RAVLT delayed recall	5.8 ± 2.3	4.15 ± 2.49 [a]	2.08 ± 1.6 [b,c]
Follow-up visits, *n* subjects			
Baseline	415	870	334
1 y	386	794	263
2 y	361	680	166
3 y	219	575	10
4 y	233	406	2
5 y	134	261	2
6 y	183	204	1
7 y	110	124	0
8 y	70	70	0
9 y	57	42	0
10 y	46	28	0
11 y	38	16	0
12 y	20	7	0
13 y	3	0	0

NC, normal controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE4, apolipoprotein $\varepsilon 4$ allele; RAVLT, Rey auditory verbal learning test. Comparison between NC group and MCI group is marked behind "MCI group", [a]$p < 0.05$. Comparison between NC group and AD group is marked behind "AD group", [b]$p < 0.05$. Comparison between MCI group and AD group is marked behind "AD group", [c]$p < 0.05$.

a random slope for each subject. To evaluate whether clinical diagnosis had a moderating effect, all analyses were performed within each diagnostic group separately. In linear mixed models, any row of the long-format data frame that has a missing value was omitted. When missing values occurred for dependent variable, a subject was included in the linear mixed model as long as he or she has at least one non-missing time point. Analyses were conducted using R software (version 3.3.3) [19]. The level of statistical significance was set at $p < 0.05$.

RESULTS

Demographic and clinical information

At baseline, our sample included 1,619 individuals with MMSE scores, 1,613 individuals with RAVLT total learning score, and 1,484 individuals with RAVLT delayed recall score. Results of comparisons of demographic and clinical variables across three diagnostic groups are present in (Table 1). Further, the numbers of individuals present at each follow-up visit are listed in (Table 1).

Demographics by APOE4 genotype and sex

Participants were divided into four groups based on joint APOE4 genotype and sex (Table 2). Differences in age and educational levels across the four groups were examined using two-way ANOVA. The Tukey's HSD test was utilized for multiple comparisons of means (Table 2).

Longitudinal change models

Terms reflecting associations with change in MMSE and RAVLT scores are listed in (Table 3). In the overall sample, the 3-way interaction between APOE4, sex and time was significant for total learning score, but not MMSE or delayed recall (Table 3 and Fig. 1). In diagnosis-stratified analyses, the APOE4 × sex × time interaction was significant in the MCI group, but not the NC or AD group. More specifically, in the MCI group, there was an APOE4 × sex × time interaction for total learning score, but not MMSE or delayed recall (Table 3 and Fig. 1). To further understand this interaction, we contrasted groups based on APOE4 genotype and sex

Table 2
Characteristics of each diagnostic group as a function of APOE4 genotype and sex

	APOE4+/Male	APOE4+/Female	APOE4–/Male	APOE4–/Female
Variables (Overall sample)				
N	438	336	471	374
Age[c,e,f]	74.2 ± 7.1	71.5 ± 6.7	74.9 ± 7.2	74.3 ± 7.55
Education[b,c,d,e]	16.2 ± 2.88	15 ± 2.75	16.5 ± 2.84	15.5 ± 2.76
Variables (NC)				
N	53	61	156	145
Age	74.8 ± 6.94	73.5 ± 4.88	75.5 ± 5.57	74.6 ± 5.68
Education[b,c,d]	16.7 ± 2.64	15.5 ± 2.6	17.1 ± 2.58	15.6 ± 2.68
Variables (MCI)				
N	260	178	255	177
Age[c,e,f]	73.7 ± 6.98	70.2 ± 6.89	74 ± 7.7	73.5 ± 8.25
Education[c,e]	16.3 ± 2.78	15.2 ± 2.88	16.2 ± 2.92	15.8 ± 2.62
Variables (AD)				
N	125	97	60	52
Age[c]	75.1 ± 7.37	72.8 ± 6.87	77.2 ± 8.14	76 ± 6.87
Education[b,c,d,e]	15.7 ± 3.11	14.3 ± 2.48	16.1 ± 2.84	14.3 ± 2.48

NC, normal controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE4, apolipoprotein ε4 allele. [a]APOE4–/Male versus APOE4+/Male, $p < 0.05$. [b]APOE4–/Male versus APOE4–/Female, $p < 0.05$.[c]APOE4–/Male versus APOE4+/Female, $p < 0.05$. [d]APOE4+/Male versus APOE4–/Female, $p < 0.05$. [e]APOE4+/Male versus APOE4+/Female, $p < 0.05$. [f]APOE4–/Female versus APOE4+/Female, $p < 0.05$

Table 3
Summary of linear mixed models

	MMSE			RAVLT total learning score			RAVLT delayed recall		
	Estimate	SE	*p*	Estimate	SE	*p*	Estimate	SE	*p*
Predictors (overall sample)									
Age × time	–0.0091	0.0055	0.0949	–0.0391	0.0084	0.0001	–0.0060	0.0019	0.0021
Education × time	0.0228	0.0139	0.1006	0.0295	0.0211	0.1613	0.0026	0.0047	0.5820
Female sex × time	0.0100	0.1051	0.9242	0.0101	0.1509	0.9464	–0.0051	0.0330	0.8767
APOE4 × time	–0.7329	0.1021	0.0001	–0.8518	0.1535	0.0001	–0.0133	0.0347	0.7012
Female sex × APOE4 × time	–0.1003	0.1548	0.5172	–0.4704	0.2339	0.0443	–0.0762	0.0531	0.1517
Predictors (NC)									
Age × time	–0.0115	0.0038	0.0023	–0.0352	0.0152	0.0204	–0.0049	0.0039	0.2089
Education × time	0.0042	0.0081	0.5998	0.0515	0.0316	0.1033	–0.0010	0.0076	0.9010
Female sex × time	0.0142	0.0497	0.7758	0.1292	0.1941	0.5056	–0.0376	0.0470	0.4241
APOE4 × time	–0.0514	0.0670	0.4427	–0.2300	0.2628	0.3815	0.0373	0.0645	0.5630
Female sex × APOE4 × time	–0.1202	0.0929	0.1957	–0.6527	0.3658	0.0744	–0.1451	0.0903	0.1081
Predictors (MCI)									
Age × time	–0.0187	0.0062	0.0024	–0.0597	0.0107	0.0001	–0.0081	0.0024	0.0008
Education × time	0.0008	0.0163	0.9594	–0.0086	0.0284	0.7623	0.0037	0.0063	0.5549
Female sex × time	–0.0654	0.1275	0.6080	–0.0852	0.2187	0.6967	0.0008	0.0485	0.9861
APOE4 × time	–0.6102	0.1157	0.0001	–0.7591	0.2000	0.0001	–0.0460	0.0443	0.2993
Female sex × APOE4 × time	–0.1691	0.1835	0.3567	–0.6358	0.3201	0.0470	–0.0776	0.0720	0.2808
Predictors (AD)									
Age × time	0.0816	0.0221	0.0002	0.1620	0.0301	0.0001	0.0226	0.0092	0.0147
Education × time	–0.1092	0.0579	0.0591	0.0294	0.0759	0.6983	0.0034	0.0227	0.8824
Female sex × time	0.6777	0.6162	0.2714	0.4452	0.8343	0.5936	0.1737	0.2605	0.5049
APOE4 × time	0.9765	0.5120	0.0565	0.8395	0.7041	0.2331	0.3389	0.2199	0.1232
Female sex × APOE4 × time	–0.9644	0.7287	0.1857	–0.2606	0.9798	0.7903	–0.1206	0.3008	0.4434

NC, normal controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE4, apolipoprotein ε4 allele; MMSE, Mini-Mental State Examination; RAVLT, Rey auditory verbal learning test. Estimates are unstandardized values, reflecting the amount of change in each cognitive outcome per year. Main effects of independent parameters are included in each linear mixed model (estimates not shown).

in MCI subjects (APOE4+/Male, APOE4+/Female, APOE4-/Male, APOE4-/Female groups; Fig. 1G and Table 4). APOE4+/Female MCIs showed significantly steeper decline than all other groups for RAVLT total learning score (Fig. 1G and Table 4). As expected, APOE4+/Male MCIs showed greater decline than APOE4-/Male and APOE4-/Female groups for RAVLT total learning score (Table 4).

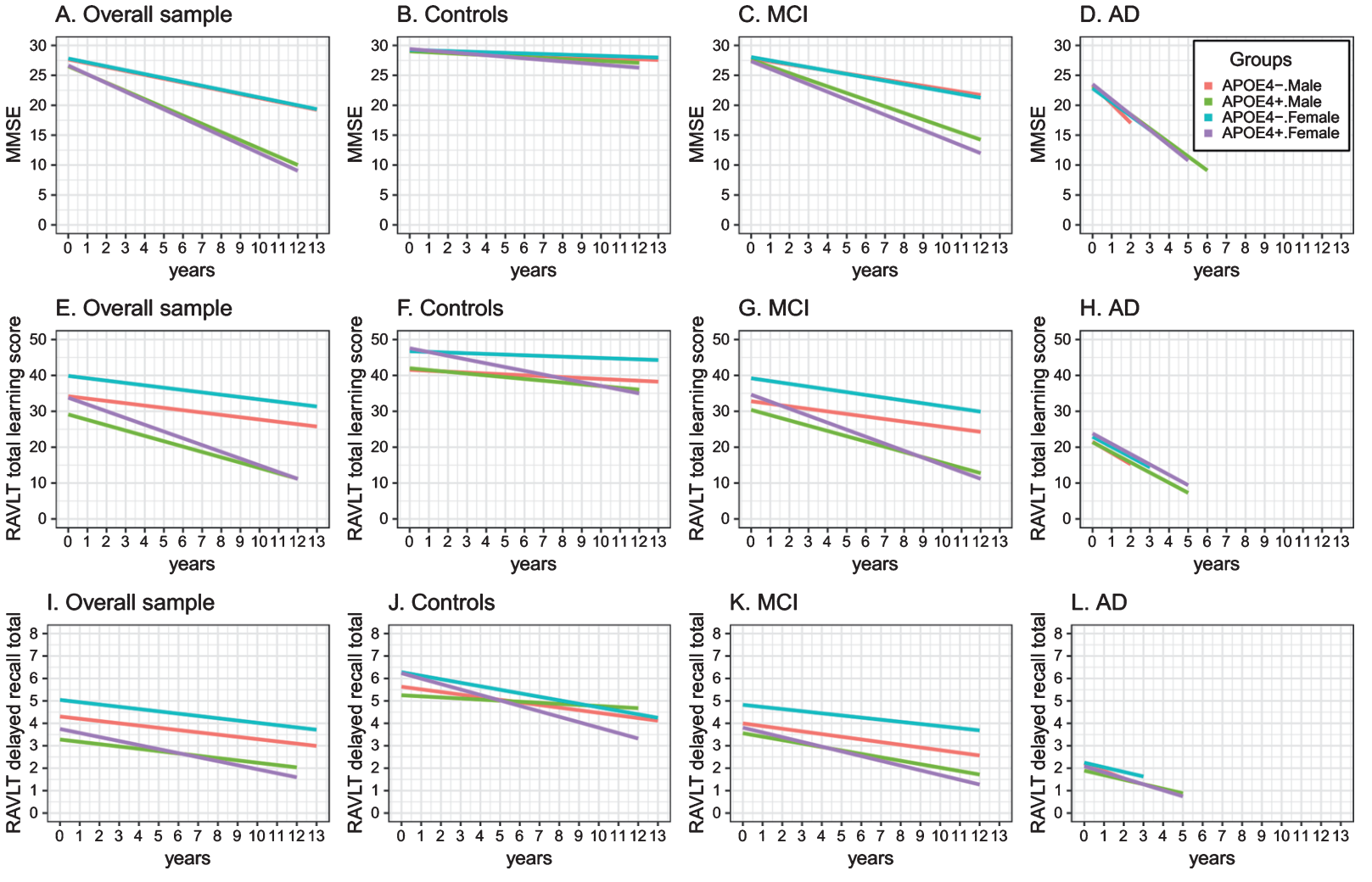

Fig. 1. Change in cognitive function by joint APOE4 and sex. NC, normal controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE4, apolipoprotein ε4 allele; MMSE, Mini-Mental State Examination; RAVLT, Rey auditory verbal learning test.

Table 4
Comparisons of RAVLT total learning score across APOE4/sex groups in MCI subjects

Contrast	RAVLT total learning score		
	Estimate	SE	*p*
APOE4-/Male × years versus APOE4+/Male × years	0.7591	0.2014	0.0008
APOE4-/Male × years versus APOE4-/Female × years	0.0852	0.2204	0.9799
APOE4-/Male × years versus APOE4+/Female × years	1.4801	0.2363	<0.0001
APOE4+/Male × years versus APOE4-/Female × years	–0.6739	0.2226	0.0124
APOE4+/Male × years versus APOE4+/Female × years	0.7210	0.2387	0.0126
APOE4-/Female × years versus APOE4+/Female × years	1.3949	0.2515	<0.0001

RAVLT, Rey auditory verbal learning test; APOE4, apolipoprotein ε4 allele. Estimates are unstandardized values, indicating the amount of change in memory per year.

DISCUSSION

In a large dataset of participants with NC, MCI, and mild AD, we found that the effects of the interaction between APOE4 and sex on memory decline are significant in the MCI group, but not the NC or AD group. More specifically, among MCI individuals, the association between APOE4 and accelerated episodic memory decline, as examined by RAVLT total learning score, was stronger in female than male. Finally, in the MCI sample, the APOE4+/Female group showed significantly steeper episodic memory decline than all other groups (APOE4+/Male, APOE4-/Male, and APOE4-/Female groups).

We extend previous studies in three aspects. First, in the present study, we examined the association of the APOE4 × sex interaction with change in verbal memory over time. Other studies investigated the cross-sectional relationship between this interaction and memory performance [9, 12]. Second, our study examined the association between this interaction and memory decline across disease stages (NC, MCI, and AD). To our knowledge, only one prospective longitudinal study has investigated the effect of this interaction on cognitive decline, as assessed by the Preclinical Alzheimer Cognitive Composite-5 [20]. However, they only included cognitively normal older adults in their analyses. Third, we examined the effect of this interaction on change in verbal memory over time across the AD continuum, and found that female APOE4 carriers had steeper memory decline than their male counterparts in individuals with MCI, but not the NC or AD group. Our findings may have important implications for patient selection and time of intervention in clinical trials.

Our finding of steeper decline in APOE4+/Female MCIs is consistent with previous epidemiological studies reporting sex differences in the association of APOE4 with the risk of AD [8, 21, 22]. For instance, a recent meta-analysis of more than 50,000 participants found that the risk of AD is 4 times higher in female than that in male among adults aged between 65 and 75 years with one copy of the APOE4 allele [8]. Similarly, females with the APOE 3/4 genotype had AD dementia diagnosed 5 years earlier than their male counterparts [7]. In addition, several longitudinal studies have suggested that female APOE4 carriers had a faster rate of cognitive decline than male APOE4 carriers [10, 11, 20, 23, 24]. In community-dwelling older people, the association of APOE4 with global cognitive and verbal memory decline was stronger in female than in male [10, 11–23]. Among cognitively normal older adults, Buckley and colleagues did not observe a APOE4 × sex interaction effect on cognitive decline [20], which is consistent with our finding in the NC group. However, the authors found a mild three-way sex × APOE4 × Aβ interaction, suggesting that females who are APOE4 and Aβ positive show steeper cognitive decline than their male counterparts [20]. In participants with MCI, one cross-sectional study found that APOE4 has a greater detrimental impact on memory performance in female than male [9]. Another longitudinal study showed that the association of APOE4 with cognitive and functional decline, as examined by Alzheimer's Disease Assessment Scale-cognitive subscale and Clinical Dementia Rating-sum of boxes, was stronger in female versus male [24]. In the present study, the lack of an association of the APOE4 by sex interaction with cognitive decline in AD patients may be due to a relatively short follow up time or because of the floor effect of cognitive deficits in AD patients. Although increasing evidence demonstrates a sex difference in the association between APOE4 and cognitive decline, the data regarding the APOE4 by sex interaction effect on cognitive decline, particularly memory decline, across the AD continuum (normal aging, MCI, and AD) are scarce. Our data provide evidence that the APOE4 by sex interaction may differentially

affect memory decline dependent on the stages of AD.

There are several possible mechanisms that may accelerate memory decline in APOE4+/Female MCIs. First, it is possible that APOE4+/Female MCIs may have more advanced AD-related neuropathological changes, including amyloid plaque [25], tau pathologies [22, 25–27], hippocampal atrophy [9], cerebral glucose hypometabolism [28], and reduced functional connectivity in the default mode network [27]. Future studies that include these AD-related biomarkers will be important to clarify the mechanisms underlying memory decline in the APOE4+/Female group. Second, it is possible that the association of APOE4 with synaptic dysfunction may be stronger in female than male. For instance, a previous animal study using transgenic APOE4 mice suggested a neuropathological relevance of the APOE4 × sex interaction, showing that female but not male APOE4 mice have reduced presynaptic density in the hippocampus [29]. Finally, it is possible that the effect of this interaction on cognitive decline may be sex-hormone mediated. For instance, a genetic study reported that estrogen receptor α and APOE4 polymorphisms interact to increase risk for late-onset AD in female but not in male [30]. It has been reported that estradiol can elevate long term potentiation in hippocampus among female APOE4 mice [31]. Further, epidemiological observations showed decreased risk of AD in users of hormone replacement therapy [32], but clinical trials failed to support this notion [33].

Our study has several limitations. First, we investigated the influence of the APOE4 by sex interaction on global cognitive function (MMSE) and verbal episodic memory (RAVLT total learning score and delayed recall). It would be intriguing to investigate a more comprehensive neuropsychological profile, such as executive and visuospatial domains, to further understand the temporal relationship between this interaction and other measures. Second, the mechanisms underlying the effect of this interaction on memory decline remain unclear. To examine whether AD biomarkers are involved, further studies that investigate the three-way Aβ × APOE4 × sex interactions on cognitive decline across the AD continuum are needed. Third, the ADNI cohort is a convenience sample of volunteers, which may limit our ability to generalize our findings to other populations. Finally, it is also possible that the lack of an association of the APOE4 by sex interaction with cognitive decline in the NC and AD groups is actually due to the relatively small sample size. Further studies with larger sample size are needed to clarify this notion.

In conclusion, we found that female APOE4 carriers have faster rates of memory decline than their male counterparts among MCI individuals.

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