ORIGINAL ARTICLE

Sex differences in the association of *APOE ε4* genotype with longitudinal hippocampal atrophy in cognitively normal older people

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Background and purpose: The aim of this study was to determine the effects of *apolipoprotein E ε4* (*APOE ε4*) genotype and sex together on longitudinal change in adjusted hippocampal volume [hippocampal volume:intracranial volume ratio (HpVR)] across the Alzheimer's disease (AD) continuum.
Methods: At baseline, we included 372 individuals with normal cognition (NC), 738 individuals with mild cognitive impairment (MCI) and 271 patients with mild AD from the Alzheimer's Disease Neuroimaging Initiative database. We examined the effects of the *APOE ε4* by sex interaction on longitudinal change in HpVR within the overall sample and within each diagnostic group.
Results: Female gender was found to be associated with longitudinal reduction of HpVR in the NC and MCI groups, but not in the AD group. Similarly, *APOE ε4* was associated with longitudinal reduction of HpVR in the NC and MCI groups, but not in the AD group. Further, female *APOE ε4* carriers showed a greater longitudinal reduction of HpVR than their male counterparts in the NC group, but not in the MCI or AD group. However, due to the relatively short duration of follow-up visits in patients with AD, further studies are needed to replicate these findings.
Conclusion: Female *APOE ε4* carriers show a greater longitudinal reduction of HpVR than their male counterparts in cognitively normal older adults.

Introduction

The *apolipoprotein E ε4* allele (*APOE ε4*) has been considered to be the strongest genetic risk factor for sporadic Alzheimer's disease (AD) [1]. Epidemiological studies suggested that *APOE ε4* was associated with a higher risk of AD in females than in males [1–4]. These findings were further supported by highly powered meta-analyses [5,6].

In addition to having a greater risk of AD, female *APOE ε4* carriers also showed reduced hippocampal volume compared with their male counterparts in individuals with mild cognitive impairment (MCI) [7] and AD [8]. In MCI, a recent longitudinal study reported no significant association of the *APOE ε4* by sex interaction with longitudinal hippocampal atrophy over a 2-year period [9]. To date, however, differences in longitudinal hippocampal atrophy between males and females and *APOE ε4* genotype have not been systematically studied across the AD continuum (healthy aging, MCI and AD dementia). Additionally, with the increase in interest in utilizing hippocampal volume as an outcome in clinical trials, it would be important to examine whether *APOE ε4* and sex interact to affect longitudinal hippocampal atrophy.

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Data used in the 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 the ADNI and/or provided data but did not participate in the 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

In the present study, the primary aim was to investigate whether the *APOE ε4* by sex interaction was associated with longitudinal hippocampal atrophy in individuals with normal cognition (NC), MCI and AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

Methods

Alzheimer's Disease Neuroimaging Initiative

Longitudinal data were obtained from the ADNI database (adni.loni.usc.edu) in October 2018. The primary aim of the ADNI study has been to investigate whether a variety of variables, such as neuropsychological assessments, blood and cerebrospinal fluid biomarkers, and serial magnetic resonance imaging and positron emission tomography, could be combined to predict the progression of MCI and AD. Further information can be found on the ADNI website (http://www.adni-info.org). Each ADNI site was approved by the local institutional review board and each participant provided written informed consent.

Participants

In this analysis, we included individuals who met the following criteria for mild AD, MCI and NC, and had baseline *APOE ε4* genotype data and follow-up measurements of hippocampal volume. At baseline, there was a total of 1381 individuals, including 372 individuals with NC, 738 individuals with MCI and 271 patients with mild AD. The numbers of individuals present at each follow-up visit are listed in Table 1.

Patients with mild AD had a Mini-Mental State Examination (MMSE) score ranging between 20 and 26, a Clinical Dementia Rating score of 0.5 or 1, and a diagnosis of probable AD dementia based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [10]. Individuals with MCI had an MMSE score ≥24, a Clinical Dementia Rating score of 0.5, objective memory impairment as demonstrated by the Wechsler Memory Scale Logical Memory II, relatively preserved activities of daily living and an absence of dementia. Individuals with NC had an MMSE score ≥24 and a Clinical Dementia Rating score of 0.

Hippocampal volume data

The hippocampal volume data were extracted from the ADNI file 'ADNIMERGE.csv' (accessed October 2018). The neuroimaging techniques utilized by ADNI have been previously described [11]. Further information on magnetic resonance imaging acquisition and measurement of hippocampal volume can be found on the ADNI website (www.adni-info.org/methods). In an effort to adjust sex differences in head size, the hippocampal volume:intracranial volume ratio

Table 1 Demographic and clinical data

Variable	NC (n = 372)	MCI (n = 738)	AD (n = 271)	P-value
Age (years)[a,b]	74.7 ± 5.55	72.6 ± 7.44	74.7 ± 7.99	<0.001
Education (years)[b,c]	16.2 ± 2.74	15.8 ± 2.88	15.2 ± 2.91	<0.001
Female	48.9%	42%	44.3%	0.09
APOE ε4[a,b,c]	26.1%	50.8%	68.6%	<0.001
MMSE score[a,b,c]	29.1 ± 1.1	27.6 ± 1.81	23.1 ± 2.06	<0.001
RAVLT immediate recall[a,b,c]	44.5 ± 9.75	34.6 ± 10.8	22.9 ± 7.28	<0.001
HpVR[a,b,c]	4.88 ± 0.628	4.44 ± 0.802	3.78 ± 0.647	<0.001
Follow-up visits (n)				
Baseline	372	738	271	
1 year	330	637	196	
2 years	288	524	108	
3 years	132	233	0	
4 years	124	179	0	
5 years	66	68	0	
6 years	70	54	0	
7 years	21	18	0	
8 years	17	14	0	
9 years	9	2	0	
10 years	1	0	0	

AD, Alzheimer's disease; *APOE ε4*, *apolipoprotein E ε4*; HpVR, hippocampal volume:intracranial volume ratio (hippocampal/intracranial volume × 10^3); MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NC, normal cognition; RAVLT, Rey Auditory Verbal Learning Test. *Post hoc* analysis provided significant differences across the groups: [a]NC vs. MCI, $P < 0.05$; [b]MCI vs. AD, $P < 0.05$; [c]NC vs. AD, $P < 0.05$. Continuous variables were demonstrated as mean ± sd.

(HpVR) (hippocampal volume/intracranial volume $\times 10^3$) rather than hippocampal volume was used as our dependent variable.

APOE ε4 allele genotyping

APOE ε4 genotype data of the study participants were extracted from the ADNI database (adni.loni.usc.edu, accessed October 2018). *APOE ε4* carriers (*APOE ε4+*) and *APOE ε4* non-carriers (*APOE ε4−*) were defined by the presence or absence of the *APOE ε4* allele, respectively.

Statistical analyses

In the three diagnostic groups, the *F*-test and Pearson x^2 test were utilized to investigate the differences in continuous variables [age, educational attainment, MMSE scores, Rey Auditory Verbal Learning Test [12] immediate recall and HpVR] and categorical variables (*APOE ε4*, sex), respectively. The Tukey HSD test was used for *post hoc* comparison of significant ANOVA analyses. In the cross-sectional analysis, we used the two-way ANOVA test to examine the effect of *APOE ε4* genotype and sex on demographic and clinical variables in the overall sample and in each diagnostic group. To examine the effect of the *APOE ε4* by sex interaction on longitudinal hippocampal atrophy, linear mixed models were fitted in the overall sample and in each diagnostic group, i.e. inclusion of interactions of *APOE ε4* with time and sex with time along with their joint interaction with time. All models were adjusted for baseline age, educational attainment, Rey Auditory Verbal Learning Test immediate recall and their interactions with time, as well as random effects consisting of a random intercept and a random slope for each subject. To examine interactions between *APOE ε4* and sex, longitudinal hippocampal atrophy across all pairwise group contrasts was conducted (*APOE ε4+*/male, *APOE ε4+*/female, *APOE ε4−*/male, *APOE ε4−*/female). Multiple comparisons correction was applied using the Tukey HSD test. Analyses were conducted using R v3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and clinical information

The demographic and clinical variables of the study participants are summarized in Table 1. Some groups differed significantly for age, educational attainment, proportion of subjects with the *APOE ε4* genotype, MMSE scores, Rey Auditory Verbal Learning Test immediate recall scores and HpVR (Table 1).

Baseline demographics by *APOE ε4* genotype and sex

Participants were classified into four groups based on joint *APOE ε4* genotype and sex: *APOE ε4+*/male, *APOE ε4+*/female, *APOE ε4−*/male and *APOE ε4−*/female (Table 2). In the cross-sectional analyses, some groups differed significantly for age and educational attainment in the overall sample and in diagnosis-

Table 2 Characteristics of each diagnostic group as a function of *apolipoprotein E ε4* (*APOE ε4*) genotype and sex

	APOE ε4+/male	*APOEε4+*/female	*APOE ε4−*/male	*APOE ε4−*/female
Variables (overall sample)				
n	367	291	402	321
Age (years)[b,c,d]	74.1 ± 7.03	71.4 ± 6.73	74.5 ± 7.01	73.9 ± 7.54
Education (years)[a,b,c,d]	16.2 ± 2.84	14.9 ± 2.74	16.5 ± 2.83	15.5 ± 2.78
Variables (NC)				
n	45	52	145	130
Age (years)	74 ± 6.72	73.5 ± 4.44	75.4 ± 5.63	74.6 ± 5.37
Education (years)[a,b,c,d]	16.8 ± 2.53	15.4 ± 2.7	17.1 ± 2.59	15.5 ± 2.69
Variables (MCI)				
n	216	159	212	151
Age (years)[b,d,e]	73.6 ± 6.83	70 ± 6.9	73.5 ± 7.42	72.8 ± 8.25
Education (years)[b,d]	16.2 ± 2.81	15 ± 2.89	16.2 ± 2.96	15.7 ± 2.68
Variables (AD)				
n	106	80	45	40
Age (years)	75.1 ± 7.5	72.8 ± 7.05	76.2 ± 8.42	76 ± 9.87
Education (years)[a,b,d]	15.7 ± 3	14.4 ± 2.4	16.3 ± 2.7	14.5 ± 3.25

AD, Alzheimer's disease; MCI, mild cognitive impairment; NC, normal cognition. *Post hoc* analysis provided significant differences across the groups: [a]*APOE ε4−*/male vs. *APOE ε4−*/female, $P < 0.05$; [b]*APOE ε4−*/male vs. *APOE ε4+*/female, $P < 0.05$; [c]*APOE ε4+*/male vs. *APOE ε4−*/female, $P < 0.05$; [d]*APOE ε4+*/male vs. *APOE ε4+*/female, $P < 0.05$; [e]*APOE ε4−*/female vs. *APOE ε4+*/female, $P < 0.05$. Continuous variables were demonstrated as mean ± sd.

stratified analyses (Table 2). Multiple comparison correction was performed using the Tukey HSD test.

Association of *APOE ε4* genotype with longitudinal hippocampal volume:intracranial volume ratio change

In the overall sample, *APOE ε4* carriers had a greater longitudinal reduction of HpVR than non-carriers (estimate: −0.0385, $P < 0.0001$; Table 3). Further, in diagnosis-stratified analyses, *APOE ε4* carriers had a greater longitudinal reduction of HpVR than non-carriers in the NC (estimate: −0.0220, $P = 0.0036$) and MCI (estimate: −0.0369, $P < 0.0001$) groups, but not in the AD (estimate: −0.0282, $P = 0.1713$) group.

Association of sex with longitudinal hippocampal volume:intracranial volume ratio change

In the overall sample, females had a greater longitudinal reduction of HpVR than males (estimate: −0.0359, $P < 0.0001$; Table 3). Further, in diagnosis-stratified analyses, females had a greater longitudinal reduction of HpVR than males in the NC (estimate: −0.0249, $P = 0.0007$) and MCI (estimate: −0.0378, $P < 0.0001$) groups, but not in the AD (estimate: −0.0369, $P = 0.0505$) group.

Association of the *APOE ε4* by sex interaction with longitudinal hippocampal volume:intracranial volume ratio change

Terms indicating associations with longitudinal HpVR change are presented in Table 4. In the overall sample, longitudinal analysis found that the three-way interaction between *APOE ε4*, sex and time was not significant for HpVR (estimate: −0.0108, $P = 0.2670$; Fig. 1a). In diagnosis-stratified analyses, this three-way interaction was found to be significant for HpVR in the NC group (estimate: −0.0321, $P = 0.0307$; Fig. 1b), but not in the MCI or AD group (all

Table 3 Summary of linear mixed models examining the independent effects of *apolipoprotein E ε4* (*APOE ε4*) and sex on longitudinal hippocampal volume:intracranial volume ratio (HpVR) (hippocampal/intracranial volume × 10^3) change

	HpVR		
	Estimate	SE	*P*-value
Predictors (overall sample)			
Age × time	−0.0010	0.0004	0.0034
Education × time	−0.0004	0.0009	0.6375
Immediate recall × time	0.0023	0.0002	<0.0001
Female sex × time	−0.0359	0.0052	<0.0001
APOE ε4 × time	−0.0385	0.0050	<0.0001
Predictors (NC)			
Age × time	−0.0019	0.0006	0.0021
Education × time	−0.0001	0.0013	0.9091
Immediate recall × time	0.0005	0.0004	0.2123
Female sex × time	−0.0249	0.0073	0.0007
APOE ε4 × time	−0.0200	0.0076	0.0036
Predictors (MCI)			
Age × time	−0.0011	0.0005	0.0214
Education × time	−0.0011	0.0013	0.3850
Immediate recall × time	0.0025	0.0004	<0.0001
Female sex × time	−0.0378	0.0073	<0.0001
APOE ε4 × time	−0.0369	0.0069	<0.0001
Predictors (AD)			
Age × time	−0.0004	0.0012	0.7678
Education × time	0.0030	0.0033	0.3660
Immediate recall × time	−0.0013	0.0013	0.3251
Female sex × time	−0.0369	0.0189	0.0505
APOE ε4 × time	−0.0282	0.0206	0.1713

AD, Alzheimer's disease; MCI, mild cognitive impairment; NC, normal cognition; SE, standard error. Main effects of predictors are included in each linear mixed model (estimates not shown). Estimates are unstandardized values, indicating changes in HpVR per year.

Table 4 Summary of linear mixed models with inclusion of the *apolipoprotein E ε4* (*APOE ε4*) × sex × time interaction term

	HpVR		
	Estimate	SE	*P*-value
Predictors (overall sample)			
Age × time	−0.0011	0.0004	0.0026
Education × time	−0.0004	0.0009	0.6316
Immediate recall × time	0.0023	0.0002	<0.0001
Female sex × time	−0.0311	0.0067	<0.0001
APOE ε4 × time	−0.0339	0.0065	<0.0001
Female sex × *APOE ε4* × time	−0.0108	0.0098	0.2670
Predictors (NC)			
Age × time	−0.0019	0.0006	0.0021
Education × time	−0.0001	0.0013	0.9568
Immediate recall × time	0.0005	0.0004	0.1881
Female sex × time	−0.0168	0.0082	0.0415
APOE ε4 × time	−0.0064	0.0104	0.5425
Female sex × *APOE ε4* × time	−0.0321	0.0148	0.0307
Predictors (MCI)			
Age × time	−0.0011	0.0005	0.0214
Education × time	−0.0011	0.0013	0.3810
Immediate recall × time	0.0025	0.0004	<0.0001
Female sex × time	−0.0365	0.0101	0.0003
APOE ε4 × time	−0.0359	0.0088	<0.0001
Female sex × *APOE ε4* × time	−0.0024	0.0139	0.8605
Predictors (AD)			
Age × time	−0.0003	0.0012	0.7694
Education × time	0.0030	0.0033	0.3682
Immediate recall × time	−0.0013	0.0013	0.3249
Female sex × time	−0.0390	0.0350	0.2656
APOE ε4 × time	−0.0297	0.0295	0.3143
Female sex × *APOE ε4* × time	0.0029	0.0410	0.9435

AD, Alzheimer's disease; HpVR, hippocampal volume:intracranial volume ratio (hippocampal/intracranial volume × 10^3); MCI, mild cognitive impairment; NC, normal cognition; SE, standard error. Main effects of predictors are included in each linear mixed model (estimates not shown). Estimates are unstandardized values, indicating changes in HpVR per year.

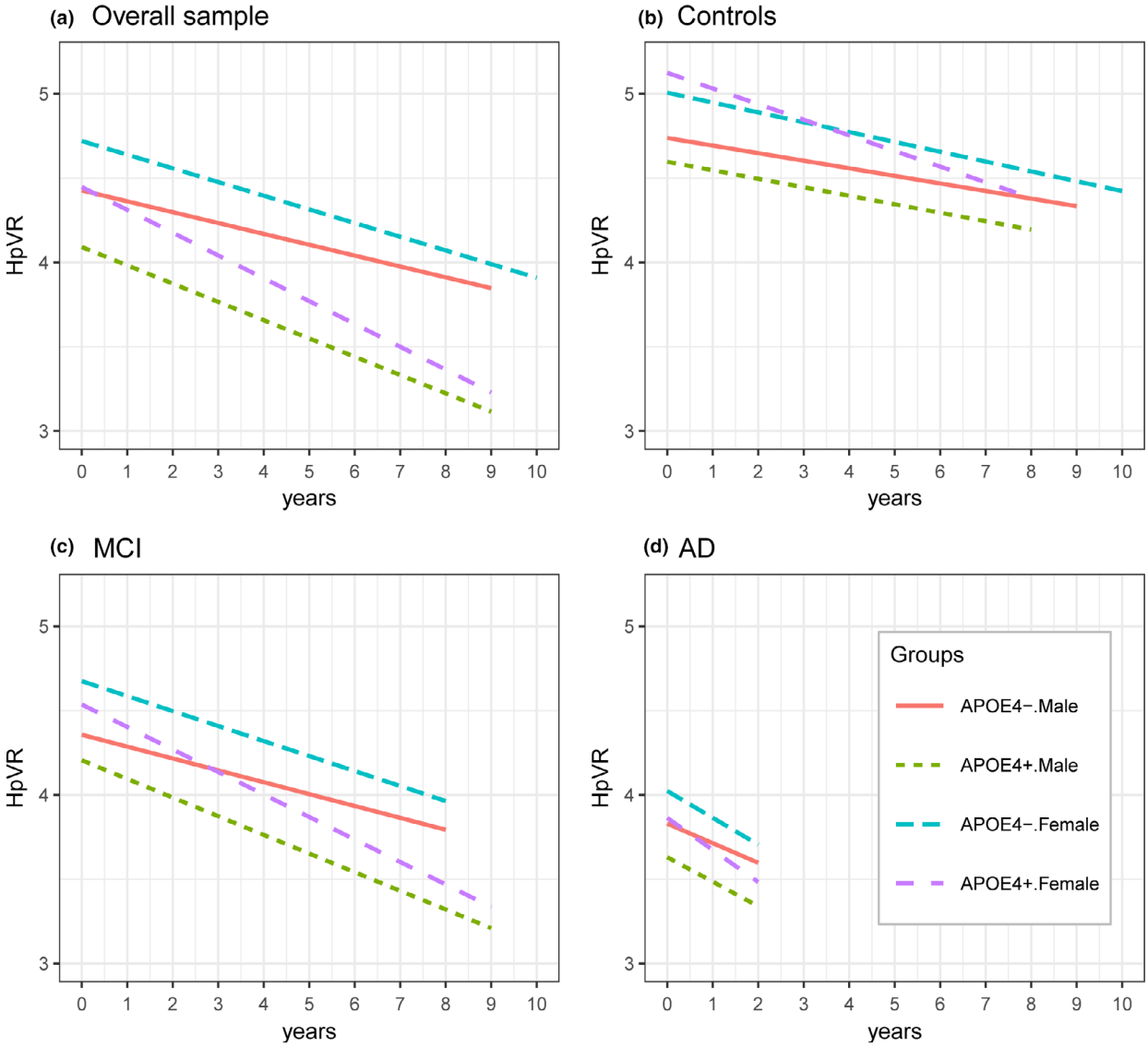

Figure 1 Longitudinal change in hippocampal volume:intracranial volume ratio (HpVR) stratified by *APOE ε4* genotype and sex. AD, Alzheimer's disease; MCI, mild cognitive impairment. [Colour figure can be viewed at wileyonlinelibrary.com]

$P > 0.05$; Fig. 1c and d). To further understand this significant interaction in the NC group, we contrasted groups according to *APOE ε4* genotype and sex (*APOE ε4*+/male, *APOE ε4*+/female, *APOE ε4*−/male, *APOE ε4*−/female; Fig. 1b and Table 5). The *APOE ε4*+/female group showed significantly faster longitudinal reduction of HpVR than all other groups (all $P < 0.01$, Table 5). No other significant pairwise difference was observed (all $P > 0.05$).

Discussion

This study has three major findings: (i) females had a greater longitudinal reduction of HpVR than males in the NC and MCI groups, but not in the AD group; (ii) the presence of the *APOE ε4* allele was associated with greater longitudinal reduction of HpVR in the NC and MCI groups, but not in the AD group; (iii) female *APOE ε4* carriers had a greater longitudinal reduction of HpVR than their male counterparts in the NC group, but not in the MCI or AD group.

The first finding that females had a greater longitudinal reduction of HpVR than males is in line with previously published studies, which shows a longitudinal association between female sex and hippocampal atrophy [13,14]. Consistent with with our findings, epidemiological studies have shown that females have a greater risk of AD than males [15,16]. Although

Table 5 Comparisons of longitudinal hippocampal volume:intracranial volume ratio (HpVR) (hippocampal/intracranial volume × 10^3) change across *apolipoprotein E ε4* (*APOE ε4*)/sex groups in normal controls

	HpVR		
Contrast	Estimate	SE	*P*-value
APOE ε4−/male × years vs. *APOE ε4*+/male × years	0.0064	0.0104	0.9292
APOE ε4−/male × years vs. *APOE ε4*−/female × years	0.0168	0.0082	0.1737
APOE ε4−/male × years vs. *APOE ε4*+/female × years	0.0552	0.0112	<0.0001
APOE ε4+/male × years vs. *APOE ε4*−/female × years	0.0104	0.0108	0.7703
APOE ε4+/male × years vs. *APOE ε4*+/female × years	0.0488	0.0131	0.0012
APOE ε4−/female × years vs. *APOE ε4*+/female × years	0.0384	0.0106	0.0017

SE, standard error. Estimates are unstandardized values, indicating changes in HpVR per year.

some of this difference may be due to the greater longevity in females [15], a faster progression of neurodegeneration in females as indicated by our findings may partly explain the sex differences in the prevalence of AD. It should be noted that the lack of a significant effect of sex on longitudinal HpVR change in patients with AD may be due to a relatively short duration of follow-up visits. Further studies are needed to replicate these findings.

The second finding that *APOE ε4* carriers had a greater longitudinal reduction of HpVR than non-carriers in the NC and MCI groups is also consistent with previous studies. Mounting evidence has suggested that *APOE ε4* confers risk of AD through neurodegeneration [7,9,13]. However, in the AD group, we did not observe a significant effect of *APOE ε4* on longitudinal HpVR change. The lack of an association between *APOE ε4* and hippocampal atrophy has been reported previously [17,18] and may be due to a shorter follow-up time in patients with AD compared with the NC or MCI group, or because of the presence of the floor effect in neurodegeneration in patients with AD.

The third finding that female *APOE ε4* carriers showed a greater longitudinal reduction of HpVR than all other groups in cognitively normal older adults is novel. This finding is consistent with a recent meta-analysis, showing that *APOE ε4* carriers have a higher risk of AD in females than in males [5]. One potential explanation for this finding is that female *APOE ε4* carriers have greater amounts of underlying pathologies. For instance, numerous studies have suggested that female *APOE ε4* carriers demonstrate greater levels of AD-related pathological changes, including amyloid plaques [19], tau pathologies [19,20] and brain glucose hypometabolism [21]. Further longitudinal studies including multiple AD biomarkers will be important to examine the mechanisms underlying the effect of the *APOE ε4* by sex interaction.

Another explanation is that the deleterious effect of *APOE ε4* on neuronal and synaptic function can be amplified in females. Previous studies have suggested that *APOE ε4* can reduce spine density and dendritic complexity [22,23] and cause oxidative damage [24] and mitochondrial dysfunction [25,26] in AD mice and in living humans. For instance, in APOE transgenic mice, Shi and colleagues found that the detrimental effect of *APOE ε4* on synaptic terminals was stronger in female than in male mice [27]. In line with this, the susceptibility to *APOE ε4*-induced cognitive impairment was stronger in female than in male mice [28].

It is possible that these sex differences in the association of *APOE ε4* with longitudinal reduction of HpVR may be sex-hormone mediated. For instance, it has been reported that alterations in levels of estrogen in females could trigger more dramatic downstream responses to amyloid [29–31], an effect that can be amplified in *APOE ε4* carriers due to the fact that estradiol administration can trigger the release of APOE from microglia [32]. Further pre-clinical studies are needed to determine the mechanisms underlying the effect of this *APOE ε4* by sex interaction.

Several study limitations should be noted. First, the possibility that the lack of a significant effect of the *APOE ε4* by sex interaction on longitudinal HpVR change in patients with AD may be due to a relatively short follow-up time cannot be ruled out. Therefore, in patients with AD, further longitudinal studies with a long follow-up time are needed. Secondly, in the present study, changes in HpVR are used as an index of the degree of neurodegeneration. To investigate more effects of the *APOE ε4* by sex interaction, it would be interesting in future studies to include other AD-related neurodegenerative biomarkers, such as cerebral glucose metabolism, cerebrospinal fluid total tau levels or whole brain markers. Finally, it would be important to validate our findings in a population-based study as the ADNI cohort is a convenience sample of volunteers, which may limit the generalizability of our findings.

In conclusion, female *APOE ε4* carriers show a greater longitudinal reduction of HpVR than their male counterparts in cognitively normal older adults.

Acknowledgements

Acknowledgements are given in Appendix S1.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Acknowledgements

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