Neuroscience Letters 722 (2020) 134824

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Sex difference in the association of APOE4 with cerebral glucose metabolism in older adults reporting significant memory concern

Lingxiang Jiang*, Hui Lin, Alzheimer's Disease Neuroimaging Initiative[1], Yide Chen*

Department of General Medicine, Taizhou First People's Hospital, Zhejiang, China

ARTICLE INFO

Keywords:
Sex differences
Significant memory concern
Cerebral glucose metabolism
Apolipoprotein E
FDG-PET

ABSTRACT

There is accumulating evidence that the association of apolipoprotein E4 (APOE4) with the risk of developing Alzheimer's disease (AD) is modified by sex. However, the associations of APOE4 status and sex with AD-related markers in older adults with significant memory concern (SMC) remain elusive. Among individuals with SMC (n = 106), we investigated the associations of APOE4 status and sex with multiple AD-related markers, including verbal memory, hippocampal volumes, cerebral glucose metabolism and cortical amyloid burden. In individuals with SMC, we found a significant APOE4*sex interaction for cerebral glucose metabolism, but not verbal memory, hippocampal volumes or cortical amyloid burden. Specifically, female APOE4 carriers showed significantly higher cerebral glucose metabolism compared to female APOE4 non-carriers whereas male APOE4 carriers had lower cerebral glucose metabolism than male APOE4-noncarriers. In conclusion, the effect of APOE4 on cerebral glucose metabolism is altered by sex in individuals with SMC.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder that has proven resistant to all attempts to prevent or slow its progression. It is reasonable to believe that effective treatments to prevent or slow cognitive decline may best be targeted at the early stage of AD, even before cognitive symptoms [1]. Therefore, it would be very important to identify individuals who have an increased risk for cognitive decline and AD. One group considered to be at risk is cognitively normal older people with significant memory concern (SMC) or subjective cognitive decline (SCD) [2,3]. Emerging evidence has suggested that individuals with SMC or SCD have an increased risk for future cognitive decline and dementia [4–6], and AD-like pathological changes in cerebrospinal fluid (CSF) and neuroimaging markers [7–9].

The 4 allele of the apolipoprotein E (APOE4) gene is the strongest genetic risk factor for sporadic late-onset AD [10]. Among individuals with normal cognition, a significant APOE4 by SMC status interaction was observed, with the APOE4 + /SMC + group demonstrating the lowest cerebral glucose metabolism and the highest levels of CSF p-tau and p-tau/Aβ42 as compared with all other groups (APOE4 + /SMC-, APOE4-/SMC +, APOE4-/SMC-) [11]. Interestingly, there is accumulating evidence that APOE4 carriers have an increased risk for AD in females than in males [12,13]. In addition, previous studies reported an association of the APOE4 × sex interaction with AD-related markers (e.g. cortical amyloid accumulation, cerebral glucose metabolism, hippocampal volumes and CSF tau levels) in cognitively normal older adults, individuals with mild cognitive impairment (MCI) and AD [14–18]. However, no previous studies have attempted to examine whether sex difference in the association of APOE4 status with AD-related markers exists in individuals with SMC.

In the present study, we examined the independent and interactive effects of sex and APOE4 status on AD-related markers (verbal memory, hippocampal volumes, cerebral glucose metabolism and cortical amyloid accumulation) in individuals with SMC. Our study may offer insight into potential mechanisms by which sex affects APOE4-related pathological changes in the earliest stage of AD.

2. Methods

2.1. Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were obtained from the

* Corresponding authors at: Department of General Medicine, Taizhou First People's Hospital, 218 Hengjie Road, Huangyan District, Taizhou City, Zhejiang Province, China.

E-mail addresses: 13291687813@163.com (L. Jiang), cyd.wl@163.com (Y. Chen).

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

https://doi.org/10.1016/j.neulet.2020.134824
Received 6 May 2019; Received in revised form 7 January 2020; Accepted 5 February 2020
Available online 07 February 2020

ADNI database (adni.loni.usc.edu). The primary aim of the ADNI study has been to investigate whether multiple variables, including demographics, cognitive assessments, neuroimaging markers, and fluid biomarkers, could be combined to predict the progression of MCI and mild AD. Further information on the ADNI study can be found at the ADNI website (adni.loni.usc.edu).

2.2. Participants

In the present study, we included individuals with SMC who had verbal memory assessment and neuroimaging measures of hippocampal volumes, cerebral glucose metabolism and cortical Aβ accumulation. All data points were taken from baseline visits. All participants provided written informed consent, and the ADNI study was approved by institutional review board at each ADNI site.

The diagnostic criteria for SMC can be found on the website (http://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI-2_Protocol.pdf). Briefly, individual with SMC had subjective memory complaints as evidenced by the Cognitive Change Index (CCI) [19], a score of 24 or higher on the mini-mental state examination (MMSE), a score of 0 on Clinical Dementia Rating (CDR) scale and normal performance on the Wechsler Logical Memory-delayed recall.

2.3. APOE allele genotyping

APOE genotypes of the study participants were extracted from the ADNI database. Individuals were categorized into APOE4 noncarriers and APOE4 carriers (no APOE4 allele = APOE4 negative; one or two APOE4 allele = APOE4 positive).

2.4. AD-related markers

The Rey Auditory Verbal Learning Test (RAVLT) was used to assess verbal memory in individuals with SMC [20]. RAVLT immediate recall score (ranging from 0 to 75) was the primary cognitive outcome. RAVLT immediate recall was chosen as the primary verbal memory outcome because it was not utilized in diagnostic criteria. Further, compared with retention deficits, learning deficits may be more sensitive to discriminate individuals with preclinical AD from cognitive normal older adults [21].

Hippocampal volumes were extracted from the ADNI file "ADNIMERGE.csv". The neuroimaging techniques used by the ADNI study have been previously described elsewhere [22]. In an effort to control for sex differences in head size, hippocampal volume ratio (HpVR) was used in the analyses (formula: HpVR = hippocampal/intracranial volume × 10^3).

Cerebral glucose metabolism was assessed using FDG-PET. Standardized uptake value ratios (SUVRs) were determined by averaging FDG uptake of five hypometabolic regions of interest (left angular gyrus, right angular gyrus, left inferior temporal gyrus, right inferior temporal gyrus, and bilateral posterior cingulate gyrus) and dividing by a reference region (pons and cerebellum) [23]. These five brain regions were selected due to the fact that these regions commonly show metabolic changes in AD [24]. The FDG data were obtained from the ADNI file "ADNIMERGE.csv".

Cortical Aβ burden was assessed using [^{18}F]florbetapir PET (AV45 PET), details of which can be found at the ADNI website (http://www.adni-info.org). SUVRs were determined by averaging AV45 uptake of four regions (frontal, anterior/posterior cingulate, lateral parietal and lateral temporal) and dividing by whole cerebellum. The AV45 data were extracted from the ADNI file "ADNIMERGE.csv".

2.5. Statistical analysis

Differences in demographics and clinical variables between sex and APOE4 status were assessed by Student's *t*-test for continuous variables and x^2 test for categorical variables. To examine the independent and interactive associations of sex and APOE4 status with AD-related markers (RAVLT immediate recall scores, HpVR, FDG SUVR and AV45 SUVR), several multiple linear regression models were applied. The first model investigated the independent effects of APOE4 and sex and did not include the APOE by sex interaction term. To examine the interactive effect of APOE4 and sex, the APOE4 by sex interaction term was included in the second model. All these models were adjusted for age and educational attainment. All statistical analyses were conducted using R statistical software (v. 3.5.1). The level of statistical significance was set at $p < 0.05$ (two-sided).

Table 1
Sample size by sex and APOE4 genotype for each AD-related marker.

	Total sample (n)	APOE4 carriers		APOE4 non-carriers	
		Female	Male	Female	Male
RAVLT immediate recall	106	22	13	40	31
HpVR	100	21	12	39	28
FDG SUVR	105	21	13	40	31
AV45 SUVR	102	20	11	40	31

Abbreviations: APOE4 apolipoprotein E4 allele; HpVR hippocampal volume ratio (hippocampal/intracranial volume × 10^3); RAVLT rey auditory verbal learning test; FDG fluorodeoxyglucose; SUVR standardized uptake value ratio; AV45 florbetapir positron emission tomography.

3. Results

3.1. The numbers of participants by sex and APOE4 status for AD-related markers

In the present study, we included 106 participants with RAVLT scores, 100 with HpVR, 105 with FDG SUVR and 102 with AV45 SUVR. Table 1 demonstrates the numbers of participants by sex and APOE4 genotype for each AD-associated marker.

3.2. Demographic and clinical variables as a function of sex and APOE4 genotype

Student' *t*-test was used to compare the means of continuous variables between groups without adjustment of covariates. In individuals with SMC, females had higher RAVLT immediate recall scores and AV45 SUVR than males (Table 2). There was no significant difference in other variables between males and females. In addition, the presence of APOE4 allele was found to be associated with higher AV45 SUVR, but not other variables. We further examined the effect of the APOE4*sex interaction on age and years of education. However, the interaction was not significant for age or years of education (all $p > 0.05$).

3.3. Multiple linear regression modelling the independent and interactive associations of sex and APOE4 status with AD-related markers in individuals with SMC

There was a significant sex*APOE4 interaction on FDG SUVR, but not other AD-related markers (Table 3 and Fig. 1). In females, APOE4 carriers had higher FDG SUVR than non-carriers (unstandardized β = 0.08, SE = 0.03, p = 0.02). However, in males, APOE4 carriers had lower FDG SUVR than non-carriers (unstandardized β = -0.08, SE = 0.03, p = 0.02). There was a main effect of sex and APOE4 status for RAVLT immediate recall scores and AV45 SUVR, but not HpVR (Table 3). Females had higher RAVLT immediate recall scores ($p < 0.01$) and AV45 SUVR ($p < 0.01$) than males, and the APOE4 allele was associated with lower RAVLT immediate recall scores ($p < 0.05$) and higher AV45 SUVR ($p < 0.01$). Each linear regression

Table 2
Demographic and clinical variables as a function of sex and APOE4 genotype.

	Sex			APOE4 status		
Variables	Female	Male	P value	APOE4 +	APOE4 -	P value
Age, y	71.9 ± 5.4	72.6 ± 5.9	0.50	70.8 ± 5.1	72.9 ± 5.7	0.05
Education, y	16.4 ± 2.8	17.3 ± 2.1	0.07	17.2 ± 2	16.5 ± 2.7	0.17
MMSE	29 ± 1.2	29 ± 1.2	0.90	29.1 ± 1.1	29 ± 1.2	0.40
RAVLT immediate recall	48 ± 9	43.2 ± 10	0.01	45 ± 10	46.5 ± 9.4	0.50
HpVR	5.2 ± 0.7	5 ± 0.6	0.30	5.23 ± 0.7	5.03 ± 0.58	0.10
FDG SUVR	1.34 ± 0.1	1.3 ± 0.1	0.10	1.34 ± 0.13	1.32 ± 0.1	0.50
AV45 SUVR	1.2 ± 0.2	1.1 ± 0.1	< 0.01	1.25 ± 0.2	1.08 ± 0.14	< 0.01

Abbreviations: APOE4: apolipoprotein E4 allele; MMSE: mini-mental state examination; HpVR: hippocampal volume ratio (hippocampal/intracranial volume × 103); RAVLT: rey auditory verbal learning test; FDG: fluorodeoxyglucose; SUVR: standardized uptake value ratio; AV45: florbetapir positron emission tomography.

model was adjusted for age and years of education.

4. Discussion

To the best of our knowledge, this is the first study to examine sex differences in the association of APOE4 genotype with multiple AD-related markers in individuals with SMC. We found that the sex by APOE4 interaction was associated with FDG SUVR in individuals with SMC. Specifically, in SMC females, APOE4 carriers demonstrated higher FDG SUVR than non-carriers. However, in SMC males, APOE4 carriers had lower FDG SUVR than non-carriers.

In agreement with previously published findings [25], we showed that cortical amyloid accumulation was higher in SMC females than SMC males irrespective of APOE4 status. In addition, we replicated the well-established notion that females show an advantage in verbal memory over males and suggested that this sex difference is regardless of APOE4 status [26]. This ostensibly paradoxical finding that SMC females have better verbal memory and higher AV45 SUVR indicates that these two criteria (better verbal memory and higher AV45 SUVR) may not contribute to mitigating adverse AD pathology and maintaining normal memory performance at the earliest stages of AD.

Our novel finding is that the effect of APOE4 genotype on brain glucose metabolism is modified by sex in the earliest stage of AD. Specifically, in SMC females, APOE4 carriers had higher brain glucose metabolism than non-carriers. However, in SMC males, APOE4 carriers had lower brain glucose metabolism than non-carriers. Inconsistent with our findings, previous epidemiological studies appeared to support the notion that APOE4 is associated with a higher risk for AD in females than in males [10,13]. Recently, Sundermann and colleagues examined the effect of the APOE4*sex on brain glucose metabolism across the AD continuum (healthy aging, MCI and mild AD) [18]. They found a significant APOE4* sex interaction for FDG SUVR in cognitively normal older adults, but not the MCI or AD group [18]. In cognitively normal older adults, female APOE4 carriers have a similar amount of FDG SUVR compared to female APOE4 non-carriers whereas male APOE4 carriers demonstrate lower FDG SUVR than male APOE4 non-carriers [18]. However, in the SMC stage of AD, we found that female APOE4 carriers show significantly higher FDG SUVR compared to female APOE4 non-carriers whereas male APOE4 carriers have lower FDG SUVR than male APOE4-noncarriers. Interestingly, as mentioned previously, we also found that females had higher better verbal memory (higher RAVLT immediate recall) but also higher cerebral amyloid burden (higher AV45 SUVR) than males. These finding may indicate that female APOE4 carriers may need to recruit more brain resources (higher cerebral glucose metabolism) to maintain normal verbal memory performance in the context of higher levels of AD pathologies in the earliest stages of AD. Although mechanisms underlying sex difference in glucose hypometabolism among APOE4 carriers with SMC are not clear, there are several potential possibilities, including hormonal changes that occur during and following menopause, lifestyle factors, risk factors and age of onset in men vs women [27–29]. These interactions of sex hormones, environmental factors and genetic factors may contribute to AD-related pathological changes. Taken together, these findings showed that sex difference in the association of APOE4 status with brain glucose metabolism may be modified by disease stage. Our data highlight an important role of sex differences in the effect of APOE4 on brain glucose metabolism in the earliest stages of AD.

A large meta-analysis found that males and females with one copy of APOE4 allele do not demonstrate a significant difference in risk of AD among individuals aged 55–85 years, but among those aged 55–75 years, females have a higher risk of AD than males [12], indicating an early vulnerability of female carriers. However, among those with two copies of APOE4 allele, no significant sex differences are observed [12]. In individuals with MCI, Altmann and colleagues reported no APOE4 by

Table 3
Multiple linear regression modelling the independent and interactive associations of sex and APOE4 status with AD-related markers in individuals with SMC.

	Linear regression models					
	Model 1: No interaction in model				Model 2: Interaction included in model	
	Male vs Female		APOE4+ vs APOE4-		Sex × APOE4 status	
Variables	β (SE)	P value	β (SE)	P value	β (SE)	P value
RAVLT immediate recall	−0.29 (0.09)	< 0.01	−0.18 (0.09)	< 0.05	−0.14 (0.13)	0.29
HpVR	−0.06 (0.1)	0.50	0.09 (0.1)	0.40	0.2 (0.14)	0.14
FDG SUVR	−0.15 (0.1)	0.10	0.01 (0.1)	0.90	−0.41 (0.13)	< 0.01
AV45 SUVR	−0.24 (0.08)	< 0.01	0.49 (0.09)	< 0.01	−0.17 (0.12)	0.16

There was a significant sex*APOE4 interaction on FDG SUVR, but not other AD-related markers. More specifically, in females, APOE4 carriers had higher FDG SUVR than non-carriers (unstandardized β = 0.08, SE = 0.03, p = 0.02). However, in males, APOE4 carriers had lower FDG SUVR than non-carriers (unstandardized β = -0.08, SE = 0.03, p = 0.02). Abbreviations: APOE4: apolipoprotein E4 allele; HpVR: hippocampal volume ratio (hippocampal/intracranial volume × 10^3); RAVLT: rey auditory verbal learning test; FDG: fluorodeoxyglucose; SUVR: standardized uptake value ratio; AV45: florbetapir positron emission tomography. β: standardized regression coefficient; SE: standard error.
Note: All models were adjusted for age and years of education.

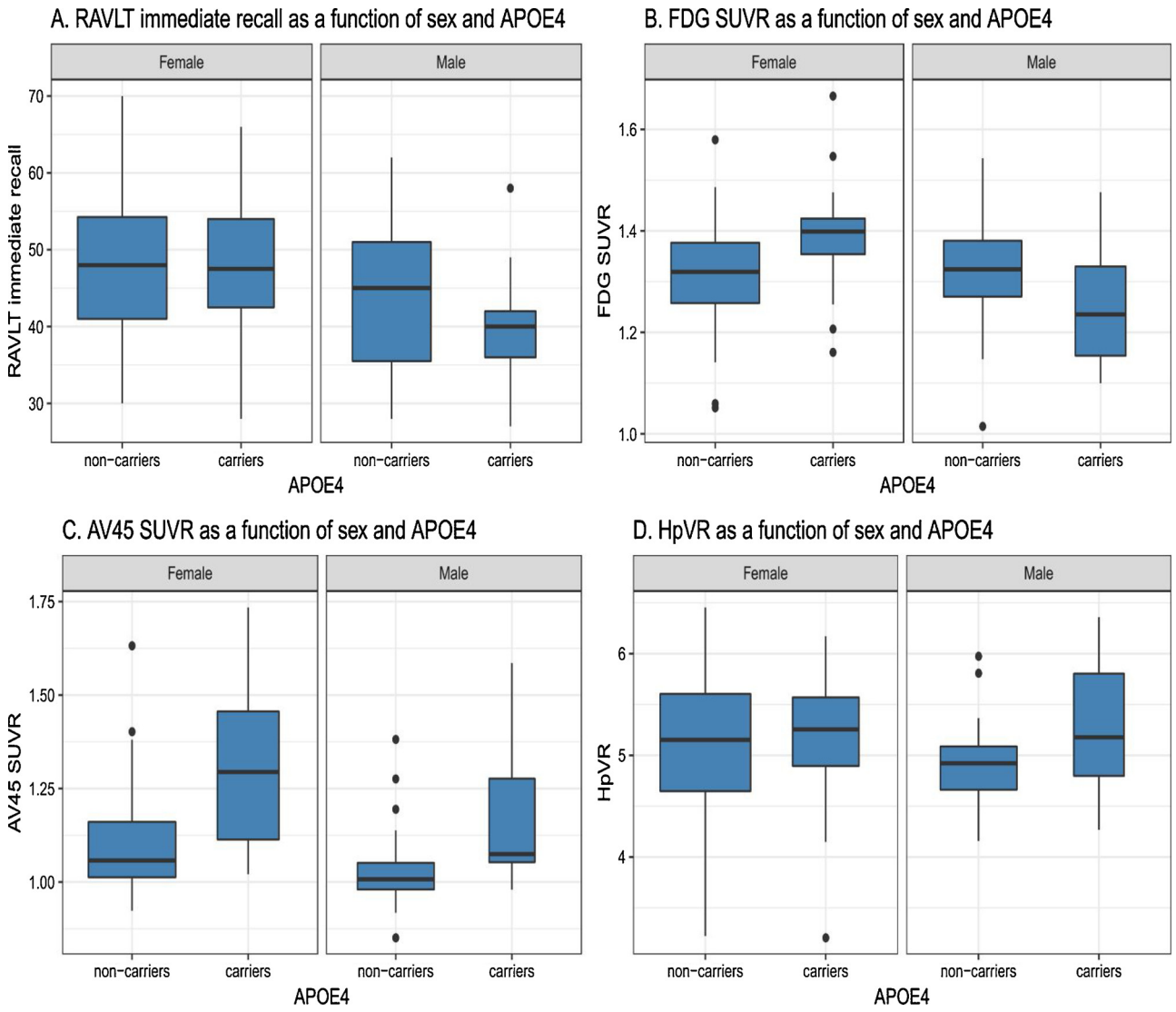

Fig. 1. AD-related markers as a function of sex and APOE4 status in individuals with SMC. There was a significant sex*APOE4 interaction on FDG SUVR, but not other AD-related markers. More specifically, in females, APOE4 carriers had higher FDG SUVR than non-carriers (unstandardized β = 0.08, SE = 0.03, p = 0.02). However, in males, APOE4 carriers had lower FDG SUVR than non-carriers (unstandardized β = -0.08, SE = 0.03, p = 0.02). Abbreviations: APOE4: apolipoprotein E4 allele; HpVR: hippocampal volume ratio (hippocampal/intracranial volume × 103); RAVLT: rey auditory verbal learning test; FDG: fluorodeoxyglucose; SUVR: standardized uptake value ratio; AV45: florbetapir positron emission tomography.

sex interaction in progression to AD [30]. Taken together, these studies indicate that the effect of the APOE4 by sex interaction on AD may be modified by age and the copies of APOE4 allele.

Several limitations should be noted. First, our cross-sectional design limits our ability to examine the associations of the APOE4*sex interaction with change in brain cerebral glucose metabolism over time. Further longitudinal studies will be needed to compare changes in cerebral glucose metabolism by sex and APOE4 genotype in the earliest stage of AD. Second, the ADNI cohort represents a convenience sample of volunteers who are generally well-educated. Thus, our findings need to be replicated in population-based studies. Third, indeed, we cannot rule out the possibility that a "survivor effect" may cloud the interpretation of our findings. As mentioned previously, however, our cross-sectional design precluded us from comparing rates of biomarker progression and memory decline by APOE4 and sex among individuals with SMC. Further, ADNI subjects represent a convenience sample of volunteers, which may help explain the fact that the percentage of APOE4+ males is low compared to population demographic. Further population-based studies are needed to replicate our findings. Finally, our finding that the APOE4*sex interaction was associated with FDG-PET among individuals with SMC may be due to selection bias. Therefore, further community-based studies should be conducted to address this issue.

In conclusion, the effect of APOE4 on brain glucose metabolism is altered by sex in individual with SMC.

Author credit statement

J.L.X and C.Y.D conceived, designed and performed the study. J.L.X and L.H analyzed the data, visualized figures, and did statistical work. J.L.X wrote the paper. All authors approved the final version of this work.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgements

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.

References

[1] R.A. Sperling, P.S. Aisen, L.A. Beckett, D.A. Bennett, S. Craft, A.M. Fagan, T. Iwatsubo, C.R. Jack Jr., J. Kaye, T.J. Montine, D.C. Park, E.M. Reiman, C.C. Rowe, E. Siemers, Y. Stern, K. Yaffe, M.C. Carrillo, B. Thies, M. Morrison-Bogorad, M.V. Wagster, C.H. Phelps, Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7 (2011) 280–292.

[2] L.A. Rabin, C.M. Smart, R.E. Amariglio, Subjective cognitive decline in preclinical Alzheimer's disease, Annu. Rev. Clin. Psychol. 13 (2017) 369–396.

[3] F. Jessen, R.E. Amariglio, M. van Boxtel, M. Breteler, M. Ceccaldi, G. Chetelat, B. Dubois, C. Dufouil, K.A. Ellis, W.M. van der Flier, L. Glodzik, A.C. van Harten, M.J. de Leon, P. McHugh, M.M. Mielke, J.L. Molinuevo, L. Mosconi, R.S. Osorio, A. Perrotin, R.C. Petersen, L.A. Rabin, L. Rami, B. Reisberg, D.M. Rentz, P.S. Sachdev, V. de la Sayette, A.J. Saykin, P. Scheltens, M.B. Shulman, M.J. Slavin, R.A. Sperling, R. Stewart, O. Uspenskaya, B. Vellas, P.J. Visser, M. Wagner, A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease, Alzheimers Dement. 10 (2014) 844–852.

[4] R.J. Caselli, K. Chen, D.E. Locke, W. Lee, A. Roontiva, D. Bandy, A.S. Fleisher, E.M. Reiman, Subjective cognitive decline: self and informant comparisons, Alzheimers Dement. 10 (2014) 93–98.

[5] K.A. Gifford, D. Liu, Z. Lu, Y. Tripodis, N.G. Cantwell, J. Palmisano, N. Kowall, A.L. Jefferson, The source of cognitive complaints predicts diagnostic conversion differentially among nondemented older adults, Alzheimers Dement. 10 (2014) 319–327.

[6] T.J. Hohman, L.L. Beason-Held, M. Lamar, S.M. Resnick, Subjective cognitive complaints and longitudinal changes in memory and brain function, Neuropsychology 25 (2011) 125–130.

[7] A.J. Saykin, H.A. Wishart, L.A. Rabin, R.B. Santulli, L.A. Flashman, J.D. West, T.L. McHugh, A.C. Mamourian, Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI, Neurology 67 (2006) 834–842.

[8] L.L. Chao, S.G. Mueller, S.T. Buckley, K. Peek, S. Raptentsetseng, J. Elman, K. Yaffe, B.L. Miller, J.H. Kramer, C. Madison, D. Mungas, N. Schuff, M.W. Weiner, Evidence of neurodegeneration in brains of older adults who do not yet fulfill MCI criteria, Neurobiol. Aging 31 (2010) 368–377.

[9] L.L. Barnes, J.A. Schneider, P.A. Boyle, J.L. Bienias, D.A. Bennett, Memory complaints are related to Alzheimer disease pathology in older persons, Neurology 67 (2006) 1581–1585.

[10] J. Poirier, J. Davignon, D. Bouthillier, S. Kogan, P. Bertrand, S. Gauthier, Apolipoprotein e polymorphism and Alzheimer's disease, Lancet (London, England) 342 (1993) 697–699.

[11] L. Mosconi, S. De Santi, M. Brys, W.H. Tsui, E. Pirraglia, L. Glodzik-Sobanska, K.E. Rich, R. Switalski, P.D. Mehta, D. Pratico, R. Zinkowski, K. Blennow, M.J. de Leon, Hypometabolism and altered cerebrospinal fluid markers in normal apolipoprotein E E4 carriers with subjective memory complaints, Biol. Psychiatry 63 (2008) 609–618.

[12] S.C. Neu, J. Pa, W. Kukull, D. Beekly, A. Kuzma, P. Gangadharan, L.S. Wang, K. Romero, S.P. Arneric, A. Redolfi, D. Orlandi, G.B. Frisoni, R. Au, S. Devine, S. Auerbach, A. Espinosa, M. Boada, A. Ruiz, S.C. Johnson, R. Koscik, J.J. Wang, W.C. Hsu, Y.L. Chen, A.W. Toga, Apolipoprotein e genotype and sex risk factors for Alzheimer disease: a meta-analysis, JAMA Neurol. 74 (2017) 1178–1189.

[13] H. Payami, K.R. Montee, J.A. Kaye, T.D. Bird, C.E. Yu, E.M. Wijsman, G.D. Schellenberg, Alzheimer's disease, apolipoprotein E4, and gender, Jama 271 (1994) 1316–1317.

[14] F. Sampedro, E. Vilaplana, M.J. de Leon, D. Alcolea, J. Pegueroles, V. Montal, M. Carmona-Iragui, I. Sala, M.B. Sanchez-Saudinos, S. Anton-Aguirre, E. Morenas-Rodriguez, V. Camacho, C. Falcon, J. Pavia, D. Ros, J. Clarimon, R. Blesa, A. Lleo, J. Fortea, APOE-by-sex interactions on brain structure and metabolism in healthy elderly controls, Oncotarget 6 (2015) 26663–26674.

[15] J.S. Damoiseaux, W.W. Seeley, J. Zhou, W.R. Shirer, G. Coppola, A. Karydas, H.J. Rosen, B.L. Miller, J.H. Kramer, M.D. Greicius, Gender modulates the APOE epsilon4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels, J. Neurosci. 32 (2012) 8254–8262.

[16] A. Fleisher, M. Grundman, C.R. Jack Jr., R.C. Petersen, C. Taylor, H.T. Kim, D.H. Schiller, V. Bagwell, D. Sencakova, M.F. Weiner, C. DeCarli, S.T. DeKosky, C.H. van Dyck, L.J. Thal, Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment, Arch. Neurol. 62 (2005) 953–957.

[17] D. Tosun, P.S. Insel, M.W. Weiner, ApoE-ε4 genotype by gender interactions in regional amyloid accumulation in the Alzheimer's disease continuum, Alzheimer's Dementia 11 (2015) P195.

[18] E.E. Sundermann, M. Tran, P.M. Maki, M.W. Bondi, Sex differences in the association between apolipoprotein E epsilon4 allele and Alzheimer's disease markers, Alzheimers Dement. (Amsterdam, Netherlands) 10 (2018) 438–447.

[19] C. Rattanabannakit, S.L. Risacher, S. Gao, K.A. Lane, S.A. Brown, B.C. McDonald, F.W. Unverzagt, L.G. Apostolova, A.J. Saykin, M.R. Farlow, The cognitive change index as a measure of self and informant perception of cognitive decline: relation to neuropsychological tests, J. Alzheimers Dis. 51 (2016) 1145–1155.

[20] M. Schmidt, Rey Auditory Verbal Learning Test: A Handbook, Western Psychological Services, Los Angeles, CA, 1996.

[21] E. Grober, C. Kawas, Learning and retention in preclinical and early Alzheimer's disease, Psychol. Aging 12 (1997) 183–188.

[22] C.R. Jack Jr., M.A. Bernstein, B.J. Borowski, J.L. Gunter, N.C. Fox, P.M. Thompson, N. Schuff, G. Krueger, R.J. Killiany, C.S. Decarli, A.M. Dale, O.W. Carmichael, D. Tosun, M.W. Weiner, Update on the magnetic resonance imaging core of the Alzheimer's disease neuroimaging initiative, Alzheimers Dement. 6 (2010) 212–220.

[23] W.J. Jagust, D. Bandy, K. Chen, N.L. Foster, S.M. Landau, C.A. Mathis, J.C. Price, E.M. Reiman, D. Skovronsky, R.A. Koeppe, The Alzheimer's disease neuroimaging initiative positron emission tomography core, Alzheimers Dement. 6 (2010) 221–229.

[24] S.M. Landau, D. Harvey, C.M. Madison, R.A. Koeppe, E.M. Reiman, N.L. Foster, M.W. Weiner, W.J. Jagust, Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI, Neurobiol. Aging 32 (2011) 1207–1218.

[25] L. Wang, T. Tian, Gender differences in elderly with subjective cognitive decline, Front. Aging Neurosci. 10 (2018) 166.

[26] E.E. Sundermann, A. Biegon, L.H. Rubin, R.B. Lipton, W. Mowrey, S. Landau, P.M. Maki, Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy, Neurology 86 (2016) 1368–1376.

[27] M.T. Ferretti, M.F. Iulita, E. Cavedo, P.A. Chiesa, A. Schumacher Dimech, A. Santuccione Chadha, F. Baracchi, H. Girouard, S. Misoch, E. Giacobini, H. Depypere, H. Hampel, Sex differences in Alzheimer disease - the gateway to precision medicine, Nature reviews, Neurology 14 (2018) 457–469.

[28] B.C. Riedel, P.M. Thompson, R.D. Brinton, Age, APOE and sex: triad of risk of Alzheimer's disease, J. Steroid Biochem. Mol. Biol. 160 (2016) 134–147.

[29] K.R. Laws, K. Irvine, T.M. Gale, Sex differences in Alzheimer's disease, Curr. Opin. Psychiatry 31 (2018) 133–139.

[30] A. Altmann, L. Tian, V.W. Henderson, M.D. Greicius, Sex modifies the APOE-related risk of developing Alzheimer disease, Ann. Neurol. 75 (2014) 563–573.