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ORIGINAL RESEARCH

APOE ε4 Allele Is Associated with Elevated Levels of CSF VILIP-1 in Preclinical Alzheimer's Disease

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Lijun Wang[1]
Miao Zhang[2]
Qian Wang[3]
Xianguo Jiang[4]
Kunyi Li[5]
Jun Liu[1]

On Behalf of the Alzheimer's Disease Neuroimaging Initiative

[1]Department of Neurology, Institute of Neurology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [2]Department of Nuclear Medicine, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [3]Department of Medicine, Mount Sinai St Luke's and West Hospital, New York, NY, USA; [4]Department of Neurology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, People's Republic of China; [5]Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Neurology, Chongqing, People's Republic of China

Correspondence: Jun Liu
Email jly0520@hotmail.com

Objectives: Cerebrospinal fluid (CSF) visinin-like protein 1 (VILIP-1) has been suggested as a biomarker for neuron injury, which has been shown to have a important diagnostic value in symptomatic Alzheimer's disease (AD). The study purpose is investigating potential effects of apolipoprotein E (APOE) ε4 on CSF VILIP-1 levels among the preclinical AD.
Methods: A total of 110 subjects (including 43 APOE ε4 carriers and 67 ε4 non-carriers) were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) in the present study.
Results: The results showed that VILIP-1 concentrations in the CSF were statistically significantly increased in APOE ε4 carriers in comparison with non-carriers. Increased CSF VILIP-1 level was positively associated with the concentrations of both CSF-tau and P-tau levels.
Conclusions: Our findings suggested that APOE ε4 might affect CSF VILIP-1 level in preclinical AD, indicating an important role of APOE ε4 in neuron injury leading to AD.
Keywords: APOE ε4, VILIP-1, Alzheimer's disease, cerebrospinal fluid

Introduction

As we have known, Alzheimer's Disease (AD) is the most globally popular neurodegenerative disease. The apolipoprotein E (APOE) ε4 allelic variant has a crucial dose-dependent association with AD risk,[1,2] which can accelerate the age of symptom onset.[3] Based on the type of pathophysiology of each measurement, a core "A/T/N" system for biomarkers has been proposed that classifies the seven most important AD biomarkers into three binary categories, "A" represents the value of Aβ biomarker (amyloid PET or CSF Aβ42), "T" refers to the value of tau biomarker (CSF p-tau or tau PET), and "N" is a biomarker for neurodegeneration or neuronal injury (^{18}F-fluorodeoxyglucose-PET, structural MRI, or CSF total tau).[4] However, the mechanism underlying the regulation of AD progression associated with APOE ε 4 remains unknown.

As a neuronal calcium-sensor protein,[5,6] visinin-like protein 1 (VILIP-1) has been suggested as a biomarker of neuron injury.[7] Previous studies have shown that cerebrospinal fluid (CSF) VILIP-1 was significantly associated with AD, indicating that VILIP-1 may be a potential biomarker for neurodegeneration.[8–10] Although it is unclear whether low levels of APOE actually contribute to the pathological changes of AD, it is hypothesized that APOE is critical for Aβ clearance and aggregation.[11–13] Increasing evidence suggested that APOE was a major carrier of cholesterol required for neuronal activity and injury repair in the brain.[14,15]

Therefore, the hypothesis that APOE ε4 deleteriously influences neuron injury, and contributes to elevated CSF VILIP-1 concentrations, which subsequently leads to cognitive degeneration in APOE ε4 carriers who are at risk of progressing from mild cognitive impairment (MCI) to AD.

So, the objective of the research is to explore the effects of APOE ε4 on CSF VILIP-1 concentrations among the elderly participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods

ADNI Study

ADNI database (adni.loni.usc.edu) provided detailed data for the research. During the experiment, data collectors have no access to participant information. The ADNI was founded in 2003 as a public–private partnership with the leading of Principal Investigator Michael W. Weiner, MD. The principle aim of ADNI is to examine if serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological evaluation could be used to assess the progression of MCI and early AD. For more details, please find www.adni-info.org. All participants or authorized representatives offered written informed consent. And each ADNI site received institutional review board (IRB) individually.

Participants

Demographic data were extracted from ADNI. Selection standard was discussed with details at http://www.adni-info.org. The participants involved in our analysis were aged from 55 to 90 years, with more than 6 years of schooling, and Spanish or English speaking. In addition, we excluded individuals having any other neurological disease other than AD. Totally, 110 individuals (including 43 APOE ε4 carriers and 67 non-carriers) were enrolled in our analysis.

Clinical Assessments

A certified cognitive evaluation containing the following listed contents was used to evaluate different domains of cognition in all participants: Mini-Mental State Examination (MMSE),[16] Alzheimer's Disease Assessment Scale-cognitive subscale 13 (ADAS-13),[17] and Global Clinical Dementia Rating Scale (CDR-SB)[18] were used to measure general cognitive function; The Rey Auditory Verbal Learning Test (RAVLT), including 5-min delayed recall (RAVLT-immediate recall), 30-min delayed recall (RAVLT-delayed recall), and yes-no recognition (RAVLT-recognition) were applied to measure memory;[19] The Trail Making Test-A and B (TMT-A/B)[20] was adopted to assess attention/executive function; Animal fluency and 30-item Boston Naming Task (BNT-30)[21] was used to evaluate language; Clock Drawing Test (CDT) was applied to measure visuospatial;[22] Functional Assessment Questionnaire (FAQ)[23] and Neuropsychiatric Inventory (NPI)[24] were used to assess psychosocial function.

Genotyping Analysis

APOE genotypes (gene map locus 19q13.2) were achieved from the ADNI database for all participants (adni.loni.usc.edu). Individuals involved were stratified into two groups: the ε2/ε4, ε3/ε4, or ε4/ε4 genotypes were defined as APOE ε4 carriers; the ε2/ε2, ε2/ε3, or ε3/ε3 genotypes were defined as APOE ε4 non-carriers.

CSF Measurements

A sandwich ELISA (together with the Erenna® immunoassay platform) was used to test VILIP-1 level in CSF.[9] CSF Aβ42, total-tau, and P-tau levels were analyzed using a multiplex xMAP Luminex system (Luminex Corp, Austin, TX, USA) combining an INNOBIA AlzBio3 kit (Fujirebio, Ghent, Belgium), which has been described in previous publications.[25–27] The unit for VILIP-1, Aβ42, total-tau and P-tau was pg/mL. More details of methodologies for the acquisition of ADNI and measurements as well as quality control process are located at www.adni-info.org.

Neuroimaging

The description of detailed information about ADNI neuroimaging standardized procedure can be found in a previous paper.[28] ADNI MRI data were obtained from a 3-Tesla MRI scanner. FreeSurfer version 5.1 image analysis (http://surfer.nmr.mgh.harvard.edu/)[29] was used to reflect cortical reconstruction and volumetric segmentation, as described in previous studies.[30–33] In the current study, we also measured the hippocampus, entorhinal cortex (EC), fusiform and medial temporal-lobe atrophy (MTA) volumes. More description regarding the imaging protocol of ADNI is located at http://adni.loni.usc.edu/methods/documents/mri- protocols/.

Statistical Analysis

Student's *t*-test for normally distributed continuous variables or Mann–Whitney test for skewed distributed variables was applied to tell demographic profile differences between APOE ε4 carriers and non-carriers in the elderly subjects. Chi-square test analysis was done to check the distribution

of categorical parameters. Spearman's correlation test was conducted to explore whether CSF VILIP-1 concentrations were linked to other core CSF biomarkers. In addition, linear regression models were adopted to examine if CSF VILIP-1 level is correlated to APOE ε4 genotype. SPSS software (version 23.0; IBM SPSS) was used for statistical analyses. A value of two-sided $P < 0.05$ was treated as the standard to show statistical significance in the paper. GraphPad Prism 6 was used to produce figures.

Results

Demographic Features for Participants, Stratified by APOE Alleles

Baseline demographic details of the subjects are shown in Table 1. We included 43 APOE ε4 carriers together with 67 APOE ε4 non-carriers in the current study. In brief, APOE ε4 carriers were younger than APOE ε4 non-carriers ($P = 0.021$). Gender ($P = 0.796$) and education levels ($P = 0.284$) did not appear to be different between the two groups. Furthermore, the scores of RAVLT-immediate recall ($P = 0.003$), RAVLT-delayed recall ($P < 0.001$), and RAVLT-recognition ($P = 0.016$) were lower among APOE ε4 carriers when comparing to APOE ε4 non-carriers. APOE ε4 carriers performed worse on MMSE ($P = 0.003$), ADAS13 ($P < 0.001$), CDR-SB ($P < 0.001$), and FAQ ($P = 0.002$) than APOE ε4 non-carriers. However, no significantly statistical differences existed in TMT-A, TMT-B, Animals fluency, BNT-30, CDT, or NPI ($P = 0.693$; $P = 0.379$; $P = 0.437$; $P = 0.377$; $P = 0.534$; $P = 0.130$) between APOE ε4 carriers and non-ε4 carriers. Finally, the CSF Aβ42, total tau, and P-tau levels appeared to be significantly different between two groups ($P < 0.001$; $P < 0.001$; and $P < 0.001$; respectively). Significantly smaller volumes of hippocampus and entorhinal cortex were found in APOE ε4 carriers in comparison to APOE ε4 non-carriers ($P = 0.020$; $P < 0.001$; respectively).

Table 1 Demographic and Clinical Characteristics of Participants by APOE ε4 Zygosity

Characteristics	ε4 Carriers (n = 43)	ε4 Non-Carriers (n = 67)	P-value
Age, years	73.17 (6.09)	75.82 (5.58)	0.021
Gender (female), %	15 (34.88)	25 (37.31)	0.796
Education, years	16 (14–18)	16 (14–18)	0.284
MMSE	27 (26–29)	29 (27–30)	0.003
ADAS-13	17.65 (7.04)	12.10 (6.31)	<0.001
CDR-SB	1.5 (0.5–2.0)	0 (0–1)	<0.001
RAVLT-immediate recall	4.35 (3.91)	6.52 (3.52)	0.003
RAVLT-delayed recall	1 (0–5)	7 (3–9)	<0.001
RAVLT-recognition	10 (8–14)	13 (11–14)	0.016
TMT-A	34 (29–45)	36 (29–45)	0.693
TMT-B	92 (70–118)	85 (67–106)	0.379
Animals fluency	16.88 (4.38)	17.61 (5.01)	0.437
BNT-30	28 (26–29)	28 (25–30)	0.377
CDT	5 (4–5)	5 (4–5)	0.534
FAQ	1 (0–5)	0 (0–1)	0.002
NPI	0 (0–0)	0 (0–0)	0.130
CSF Aβ42 (pg/mL)	576.8 (498.6–723.1)	1148.0 (775.6–1643.0)	<0.001
CSF-tau (pg/mL)	333.29 (107.99)	248.92 (85.90)	<0.001
CSF P-tau (pg/mL)	33.71 (12.69)	23.15 (9.28)	<0.001
CSF VILIP-1 (pg/mL)	189.16 (58.90)	148.25 (50.55)	<0.001
Hippocampus (mm^3)	6385.54 (1051.64)	6872.28 (1052.59)	0.020
Entorhinal (mm^3)	3177.65 (717.05)	3762.28 (772.20)	<0.001
Fusiform (mm^3)	17,168.63 (2260.15)	16,819.05 (1932.13)	0.388
MTA (mm^3)	19,307.09 (2643.83)	19,345.96 (2769.64)	0.942

Notes: Data are presented as mean ± SD by using Student's *t* test for normally distributed continuous variables, median (M) and the interquartile range (IQR) by Mann–Whitney test for skewed distribution variables. For gender, values are presented as number (%) by using Chi-square test.

Abbreviations: ADAS-13, Alzheimer's disease assessment scale-cognitive subscale 13; BNT-30, boston naming task; CDR-SB, global clinical dementia rating scale; CDT, clock drawing Test; CSF, cerebrospinal fluid; FAQ, functional assessment questionnaire; MMSE, mini-mental state examination; MTA, mesial temporal atrophy; NPI, neuropsychiatric inventory; RAVLT, rey auditory verbal learning test; SD, standard deviation; TMT, the trail making test; VILIP-1, visinin-like protein-1.

Levels of CSF VILIP-1 in the Two Groups

To further look into the association between APOE ε4 genotype and concentration of CSF VILIP-1, the concentrations of CSF VILIP-1 between APOE ε4 carriers and non-carriers were compared. We saw an obvious increased VILIP-1 level among the APOE ε4 carriers than the APOE ε4 non-carriers (mean, 189.16 vs. 148.25 pg/mL, $P < 0.001$, Table 1, Figure 1A). Furthermore, to evaluate the gene dose-effect of APOE ε4 on the level of CSF VILIP-1, the concentrations of CSF VILIP-1 among APOE ε4 (+/+), APOE ε4 (+/-) and APOE ε4 (-/-) subjects (APOE ε4 +/+, n = 8; APOE ε4 +/-, n =35; APOE ε4 -/-, n = 67) were compared. The results showed that CSF VILIP-1 concentrations were higher in APOE ε4 (+/+) compared to APOE ε4 (-/-) ($P = 0.001$), and CSF VILIP-1 levels were elevated in APOE ε4 (+/-) compared to APOE ε4 (-/-) subjects ($P = 0.003$) (Figure 1B).

Correlations Between Aβ42, Tau, P-Tau and CSF VILIP-1

In order to evaluate if changes in CSF concentrations of VILIP-1 are associated with Aβ42, Tau and P-tau in the elderly, the associations between CSF VILIP-1 and other core CSF biomarkers in the whole sample (Table 2) were examined by conducting Spearman's correlation analyses. The results demonstrated that CSF VILIP-1 concentration was positively related to Tau and P-tau (R = 0.857, $P < 0.001$; R = 0.815, $P < 0.001$). Nevertheless, no significant association between the levels of CSF VILIP-1 and Aβ42 (R = 0.000, $P = 0.997$) was found.

Relation Between CSF VILIP-1 Concentrations and APOE ε4 Levels

The linear regression analysis revealed the possible correlation of the presence of APOE ε4 allele and CSF VILIP-1 levels between the elderly subjects (Table 3). In the unadjusted model (Model 1), the CSF VILIP-1 concentration was statistically related with APOE ε4 (standardized β = 0.350, $P < 0.001$). In model 2 on the basis of fixed age, sex and education level, a significant association between concentrations of CSF VILIP-1 and APOE ε4 (standardized β = 0.344, $P < 0.001$) was witnessed. In the adjusted model 3 (which is model 2 plus MMSE, CDR-SB, RAVLT-immediate recall and RAVLT-delayed recall), the VILIP-1 level was still linked to APOE ε4 (standardized β = 0.298, $P = 0.003$). In model 4 (which is model 3 plus CSF Aβ42 and P-tau), the association between CSF VILIP-1 level and APOE ε4 (standardized β = 0.137, $P = 0.050$) continued to exist. In model 5 (model 4 plus volumes of hippocampus and entorhinal cortex), the concentration of CSF VILIP-1 was still linked with APOE ε4 (standardized β = 0.144, $P = 0.049$).

Discussion

As a neuronal calcium-sensor protein,[5,6] VILIP-1 has been suggested as a marker for neuron injury in brain injury models.[7,34,35] Previous studies indicated that the level of CSF VILIP-1 was associated with the concentrations of CSF-tau and P-tau,[6,8,9] supporting its utilization as a neurodegeneration marker. In addition, some studies revealed that CSF VILIP-1 could diagnostically discriminate AD from other dementias.[36,37] Therefore, these numerous studies implied that CSF VILIP-1 might be a useful biomarker for AD pathophysiology.[9,10,38-44] Although only one study found no significant difference in the longitudinal changes of CSF VILIP-1 levels in cognitively normal subjects and AD patients.[45] Importantly, researchers also showed elevated levels of plasma VILIP-1 in AD patients compared to non-demented controls.[9] Generally, the current VILIP-1 data suggest a possible role in the selection and prognosis of

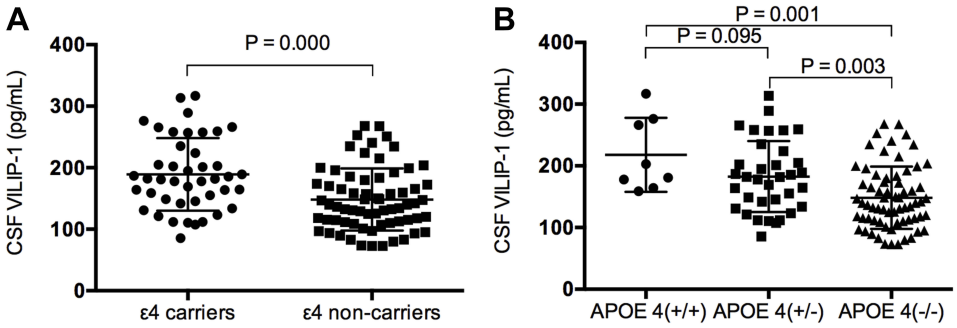

Figure 1 Comparison of CSF VILIP-1 concentrations in APOE ε4 carriers and APOE ε4 non-carriers in the elderly subjects. (**A**) CSF VILIP-1 levels were significantly elevated in APOE ε4 carriers compared with APOE ε4 non-carriers (P = 0.000). (**B**) The CSF VILIP-1 concentrations are elevated in a gene dose-dependent manner of APOE ε4. All data are shown as mean ± SD. P values tested by Student's *t*-test.
Abbreviations: CSF, cerebrospinal fluid; SD, standard deviation; VILIP-1, visinin-like protein-1.

Table 2 Correlations of CSF VILIP-1 Level with Aβ42, Tau and P-Tau

	Aβ42	Tau	P-Tau
CSF VILIP-1			
R	0.000	0.857**	0.815**
P	0.997	<0.001	<0.001

Notes: Associations were measured by Spearman's correlation analyses. **P < 0.01.
Abbreviations: CSF, cerebrospinal fluid; VILIP-1: visinin-like protein-1.

subjects (Table 4), but the results are different and require further investigation.

In our current study, we investigated the concentration of CSF VILIP-1 between APOE ε4 carriers and non-carriers in the elderly subjects. It was observed that CSF VILIP-1 level was statistically significantly elevated in APOE ε4 carriers than non-carriers. The concentration of CSF VILIP-1 was linked to CSF-tau and P-tau concentrations. What is more, CSF VILIP-1 level was substantially related to APOE ε4 genotype, regardless of age, gender, education, MMSE, CDR-SB, RAVLT-immediate recall, RAVLT-delayed recall, CSF Aβ42 and P-tau, volumes of hippocampus and entorhinal cortex. Notably, these findings are consistent with the previous follow-up study that in healthy individuals CSF VILIP-1 still has predictive value for future cognitive decline.[9,46]

APOE ε4 ranks top of genetic risk factors in the progression of sporadic AD.[2] However, the precise underlying pathophysiologic mechanisms of APOE ε4 in the development of AD remain debated. The hypothesis that APOE ε4 carriers may play a role in neuron injury and has values in predicting rates of cognitive decline was supported by our findings. That CSF VILIP-1 level was elevated among the APOE ε4 allele carriers suggesting that APOE may influence VILIP-1 level. In this study, we found a notable association between CSF VILIP-1 and CSF-tau protein. As the cross-sectional design does not indicate causality, future prospective studies were warranted.

There were a few limitations to our study. Firstly, the evaluation of the prospective changes of VILIP-1 levels over time was not conducted due to the cross-sectional design applied in our study. Further longitudinal researches are in needed to confirm the conclusions. Secondly, when interpreting our results, the restricted sample inclusion in ADNI database should be considered. The relationship between APOE ε4 and CSF VILIP-1 will warrant further investigations in prospective study. In summary, APOE ε4 carriers had elevated CSF VILIP-1 levels in comparison with APOE ε4 non-carriers in preclinical AD.

Conclusion

Our findings suggested that APOE ε4 might affect CSF VILIP-1 level in preclinical AD, indicating an important role of APOE ε4 in neuron injury leading to AD.

Data Sharing Statement

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

Table 3 Linear Regression to Evaluate the Potential Association Between CSF VILIP-1 and APOE ε4 Status in the Elderly (Unadjusted and Adjusted)

	Model 1		Model 2		Model 3		Model 4		Model 5	
	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P
APOE ε4 (+) vs. (-)	0.350	<0.001	0.344	<0.001	0.298	0.003	0.137	0.050	0.144	0.049
Age			−0.080	0.390	−0.061	0.526	−0.038	0.515	−0.044	0.484
Gender			0.208	0.033	0.211	0.035	0.027	0.659	0.032	0.633
Education			0.064	0.507	0.050	0.605	−0.042	0.48	−0.039	0.528
MMSE					0.069	0.537	0.042	0.539	0.045	0.518
CDR-SB					−0.010	0.929	0.010	0.889	0.006	0.936
RAVLT-immediate recall					0.020	0.907	0.054	0.607	0.062	0.574
RAVLT-delayed recall					−0.215	0.218	−0.101	0.346	−0.107	0.325
CSF Aβ42							0.314	<0.001	0.306	<0.001
CSF P-tau							0.776	<0.001	0.772	<0.001
Hippocampus									−0.033	0.691
Entorhinal									0.042	0.584

Notes: Model 1: unadjusted; Model 2: adjusted by age, gender, education; Model 3: adjusted by age, gender, education, MMSE, CDR-SB, RAVLT-immediate recall and RAVLT-delayed recall; Model 4: adjusted by age, gender, education, MMSE, CDR-SB, RAVLT-immediate recall, RAVLT-delayed recall, CSF Aβ42 and P-tau; Model 5: adjusted by age, gender, education, MMSE, CDR-SB, RAVLT-immediate recall, RAVLT-delayed recall, CSF Aβ42, P-tau, volumes of hippocampus and entorhinal cortex. Beta is standardized beta.
Abbreviations: CDR-SB, global clinical dementia rating scale; MMSE, mini-mental state examination; RAVLT, rey auditory verbal learning test.

Table 4 Studies to Assess the Role of CSF VILIP-1 as a Potential Biomarker

Study	AD	MCI	Controls	Analysis Method	Results
Lee et al (2008)[8]	33	/	24	ELISA	Significantly increased in AD compared to control subjects
Tarawneh et al (2011)[9]	98	/	211	Microparticle based immunoassay (Erenna, Singulex, CA)	Significantly higher in AD compared to controls
Tarawneh et al (2012)[10]	60	/	211	Microparticle based immunoassay (Erenna, Singulex, CA)	Significantly elevated in AD compared to controls
Luo et al (2013)[37]	61	/	40	ELISA	Significantly higher in AD patients than control subjects
Kester et al (2015)[45]	65	61	37	Microparticle based immunoassay (Erenna, Singulex, CA)	Baseline levels elevated in AD and MCI than controls but not significantly (P = 0.88); Baseline levels significantly increased in MCI progressed to AD than stable MCI; Longitudinal increased in MCI, but not in AD or cognitively normal individuals
Mroczko et al (2015)[39]	33	15	18	ELISA	Significantly higher in AD patients compared with MCI and control individuals
Sutphen et al (2015)[46]			169	Microparticle based immunoassay (Erenna, Singulex, CA)	Significantly increased in late middle-aged individuals compared with early and mid in APOE ε4 non-carriers
Tarawneh et al (2015)[38]	23	/	64	Microparticle based immunoassay (Erenna, Singulex, CA)	Significantly elevated in AD compared with controls
Babic´ Leko et al (2016)[36]	109	43	9	ELISA	Significantly higher in AD compared to MCI and control subjects
Tarawneh et al (2016)[41]	95	/	207	Microparticle based immunoassay (Erenna, Singulex, CA)	Significantly elevated in AD compared with controls
Höglund et al (2017)[47]	/	/	129	ELISA	No difference between high CSF Aβ and low CSF Aβ groups
Muszyn´ski et al (2017)[48]	45	18	23	ELISA	Significantly elevated only in AD group in comparison to control subjects
Sutphen et al (2018)[42]	16	76	56	Microparticle based immunoassay (Erenna, Singulex, CA)	Baseline levels elevated in the MCI Aβ+ and AD Aβ+ groups compared with MCI Aβ- and controls Aβ- groups; Longitudinally decreased in AD Aβ+ groups
Zhang et al (2018)[44]	18	24 sMCI, 47 pMCI	32	Microparticle based immunoassay (Erenna, Singulex, CA)	Significantly elevated in AD and pMCI groups compared with control and sMCI groups

Abbreviations: AD, Alzheimer's disease; sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment.

within the ADNI contributed to the design and implementation of 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.

Ethical Approval

This study was carried out in accordance with the recommendations of each ADNI site. The protocol was approved by the ADNI. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

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Disclosure

All authors claim that there are no conflicts of interest in this work.

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