Cerebrospinal fluid heart fatty acid-binding protein as a predictive biomarker of neurodegeneration in Alzheimer’s disease

Lu Pan1, Ya-Nan Ou2, Lin Tan2, Lan Tan1(✉), Jin-Tai Yu3(✉), on behalf of Alzheimer’s Disease Neuroimaging Initiative

1 Department of Neurology, Qingdao Municipal Hospital, Dalian Medical University, Dalian 116044, Liaoning, China.
2 Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao 266071, Shandong, China.
3 Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China.

ARTICLE INFO
Received: 2 November, 2020
Revised: 22 February, 2021
Accepted: 28 February, 2021

© The authors 2021. This article is published with open access at journals.sagepub.com/home/BSA

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

KEYWORDS
Alzheimer’s disease, heart fatty acid-binding protein (HFABP), cerebrospinal fluid, biomarker, neurodegeneration

ABSTRACT
Objective: This study aims to investigate whether the heart fatty acid-binding protein (HFABP) in the cerebrospinal fluid (CSF) was a potential predictive biomarker for Alzheimer’s disease (AD).

Methods: We evaluated the associations of CSF HFABP levels with core biomarkers, cognition, and brain structure in a sample population (n = 302) from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database. Multiple linear regression and mixed-effects models were employed in the analyses. AD progression was assessed using the Kaplan-Meier survival analysis.

Results: CSF HFABP was higher in patients with mild cognitive impairment and AD than in the normal controls (p < 0.001) and was particularly higher in those with amyloid-β (Aβ) pathologic features. CSF HFABP was associated with higher baseline CSF t-tau (p < 0.001), CSF p-tau (p < 0.001), and CSF t-tau/Aβ42 and CSF p-tau/Aβ42 (p < 0.01). Moreover, CSF HFABP was found to play predictive roles in hippocampal atrophy (p < 0.01), cognitive decline (p < 0.05), and the risk of AD (p < 0.001).

Conclusion: Our findings suggest that CSF HFABP can be a predictive biomarker of AD.

1 Introduction
Alzheimer’s disease (AD) is the most common form of dementia characterized by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles in the brain. Despite many attempts to reveal the pathogenesis of AD, no definitive therapies have been established. Of note, more attention has been paid to how to identify or prevent the disease in the early stage. Recently, a growing number of epidemiological and experimental studies have provided evidence...
that dyslipidemia can increase the risk of cognitive impairments or AD [1, 2] and participate in AD-associated pathogenesis [3]. Molecular mechanism studies have revealed that membrane lipids could modulate Aβ metabolism by means of lipid rafts [4]. Besides, gene-related studies suggest that the apolipoprotein E (APOE) epsilon 4 allele, the strongest genetic risk factor associated with AD [5], has been involved with the metabolism and transport of lipid [6]. Some studies have found that abnormal expression of proteins associated with fatty acid transport can affect the normal growth of the brain, which can lead to cognitive impairment [7, 8]. All these findings support that lipid metabolism plays a vital role in the occurrence of AD and early detection of lipid metabolism abnormalities could be of great value in predicting the development of AD.

As one of the critical proteins in lipid metabolism, heart fatty acid-binding protein (HFABP) is widely distributed in tissues, including expression in the brain [9], which is mainly responsible for the intracellular transport of long-chain polyunsaturated fatty acids [10, 11]. Recent research suggests that the levels of cerebrospinal fluid (CSF) HFABP were increased in AD patients [12, 13] and CSF HFABP has a moderate diagnosis value for AD [14]. Furthermore, studies found that CSF HFABP was associated with brain atrophy among people with low CSF Aβ42 [15]. However, relevant studies using CSF HFABP as a predictive tool for neurodegeneration in sporadic AD are rare.

Therefore, we investigated whether CSF HFABP is elevated in AD and associated with CSF biomarkers of AD pathologic features, neuroimaging abnormalities, cognitive impairment, and risk of progression to AD.

2 Materials and methods

2.1 Participants

The data used in this study were downloaded from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database. The aim of ADNI has been to integrate clinical and neuropsychological examinations, neuroimaging evaluation, and biomarkers to study cognitive decline further. The demographic and clinical variables were obtained from the ADNI database. The details about inclusion and exclusion criteria were previously described [16]. In this study, we included 91 participants with normal cognition (or control, CN), 143 patients with mild cognitive impairment (MCI), and 68 patients with AD at baseline. We accessed publicly available data from the ADNI. The participants were enrolled in the ADNI based on the criteria outlined in the ADNI protocol. For the present analyses, we included all participants with CSF multiplex data that went through ADNI quality-control procedures (defined further on) and were measured for Aβ42, total tau (t-tau), and phosphorylated-tau (p-tau), and underwent neuroimaging or cognitive outcome tests of interest. The ADNI samples for the present study were limited to the individuals who had a blood draw for assessment of HFABP levels (n = 302) at the baseline. We selected the subjects who had completed the annual examinations of flurodeoxyglucose positron emission tomoraphy (FDG-PET; n = 148, follow-up = 5 years), hippocampus magnetic resonance imaging (MRI; 233, 5 years), and cognition (298, 5 years) in the longitudinal analysis to lower the influences of attrition bias. As for the AD risk cohort, 234 participants were included in the analysis.

2.2 Measurement of CSF biomarkers

All the CSF samples were obtained from the
participants in the morning, stored in a freezer at ~80 °C, and aliquoted and processed according to ADNI's standardized operating procedures. The concentrations of Aβ42, t-tau, and p-tau in the CSF were measured using the Elecsys (Roche) assays on the fully automated Elecsys cobas e601 analyzer. The Elecsys immunoassays are electrochemiluminescence immunoassays, based on the quantitative sandwich principle, with an 18-min duration. CSF HFABP was calculated as a part of a CSF multiplex proteomic processing stream using an xMAP multiplex panel (MyriadRBM) with better sensitivity and repeatability. Also, the rescaling process improved the precision performance across time and different batches of reagents to overcome the batch effect, as previously described [16]. Lastly, the participants were classified as Aβ-positive or Aβ-negative using a previously established cutoff CSF Aβ42 value of less than 1096 ng/L [17].

2.3 Cognition

The cognitive assessments for this study included MMSE, Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-Cog), episodic memory (ADNI-MEM), and executive function (ADNI-EF). The last two assessments are comprehensive evaluations of cognitive performance as previously reported [18, 19].

2.4 Neuroimaging

Structural brain images were acquired using a 1.5-T MRI system with T1-weighted MRI scans with a sagittal volumetric magnetization-prepared rapid acquisition gradient echo sequence. The images for hippocampal volume were processed with the FreeSurfer image analysis suite version 4.3 (http://surfer.nmr.mgh.harvard.edu/). The subjects were injected with a dose of 18F-FDG to study cerebral glucose metabolism using a PET scan. The cerebral brain metabolism was examined with the mean FDG-PET counts of the lateral and medial frontal regions, anterior and posterior cingulate regions, and lateral parietal and temporal regions.

2.5 Statistical analysis

The intergroup differences of demographic factors were analyzed using the Chi-square test and Kruskal–Wallis test for categorical and continuous variables, respectively. The Spearman rank correlation analysis was used to analyze the relationship between CSF levels of HFABP and age. Linear regression was used to explore the associations between CSF HFABP and other biomarkers, including CSF Aβ42, CSF t-tau, CSF p-tau, t-tau/Aβ42, p-tau/Aβ42 cognition measure, and hippocampal volume. We tested associations of CSF HFABP with longitudinal cognition, hippocampal volume, and brain metabolism using linear mixed-effects models. The time-by-exposure interaction terms were tested to examine whether CSF HFABP was associated with the changes in the given outcomes, such as MMSE, ADAS11, MEM, EF, hippocampal volume, and FDG. All the regression analyses were adjusted for age, gender, educational level, cognitive diagnosis, APOE ε4 genotype, type 2 diabetes mellitus, hypertension, hyperlipidemia, depression, cardiovascular disease, and body mass index. The analysis of brain atrophy was adjusted additionally for intracranial volume. The baseline levels of t-tau were adjusted in the longitudinal analysis. In addition, we excluded four of the Aβ-negative patients with AD in the baseline and longitudinal analysis. The diagnostic accuracy of the various biomarkers was assessed by the area under the curve of the receiver operating characteristic (ROC) curve. The Kaplan–Meier survival analysis was employed for the HFABP using the optimal
cutoff for dichotomizing HFABP values determined from the Youden index [20]. All data analyses were performed using the R software (R, Version 3.2.3; The R Foundation). The p-values less than 0.05 were considered significant for all the statistical analyses.

3 Results

3.1 Participant demographics

The demographic and clinical variables of the participants (Table 1) revealed no significant differences in age and educational level among the three diagnostic groups, CN, MCI, and AD. However, small differences were found in the gender among these groups. In addition, there were significant differences in CSF levels of Aβ42 (p < 0.001), t-tau (p < 0.001), p-tau (p < 0.001), HFABP (p < 0.001), and depression (p < 0.01) among the groups. In the entire cohort, there was a positive correlation between the CSF levels of HFABP and age (Spearman r = 0.11, p < 0.05) (Supplementary Fig. 1). CSF HFABP was also correlated with gender (mean, 3.4 ng/mL for women compared to 4.1 for men; p < 0.01) (Supplementary Fig. 2).

3.2 CSF HFABP in different subgroups

The CSF HFABP concentrations were found to be higher in the AD (p < 0.001) and MCI group (p < 0.001) compared to the controls [Fig. 1(A)]. CSF HFABP successfully discriminated between AD patients and the controls at the best cutoff of 3.55, with the area under the receiver operating characteristic curve (AUC) of 0.70 [Fig. 2(A)]. By comparison, CSF Aβ42 discriminated between AD and the controls with the AUC of 0.85, CSF t-tau discriminated between AD and the controls

Table 1 The demographics of the study population.

| Variables                  | CN (n = 91) | MCI (n = 143) | AD (n = 68) | p-value |
|----------------------------|-------------|---------------|-------------|---------|
| Age, y                     | 75.7 ± 5.4  | 74.8 ± 7.2    | 75.0 ± 7.6  | 0.769   |
| Female, n (%)              | 46 (50.5)   | 45 (31.5)     | 29 (42.6)   | 0.013   |
| Educational level, y       | 15.6 ± 2.9  | 16.0 ± 2.9    | 15.1 ± 3.0  | 0.083   |
| APOE ε4 genotype carriers, n (%) | 22 (24.2) | 77 (53.8)     | 48 (70.6)   | <0.001  |
| DM2, yes/no                | 4/87        | 8/135         | 2/86        | 0.667   |
| Hypertension, yes/no       | 45/46       | 70/73         | 34/34       | 0.989   |
| Hyperlipidemia, yes/no     | 39/52       | 66/77         | 33/33       | 0.558   |
| CVD, yes/no                | 6/85        | 4/39          | 4/84        | 0.346   |
| BMI, kg/m²                 | 25.6 ± 4.7  | 25.6 ± 3.8    | 25.3 ± 3.6  | 0.233   |
| Depression, yes/no         | 8/83        | 29/114        | 22/46       | 0.001   |
| CSF HFABP, ng/mL           | 2.9 ± 2.1   | 4.1 ± 2.2     | 4.5 ± 2.5   | <0.001  |
| CSF Aβ42, pg/mL            | 1260 ± 654  | 804 ± 441     | 625 ± 337   | <0.001  |
| CSF t-tau, pg/mL           | 239 ± 76    | 320 ± 119     | 360 ± 128   | <0.001  |
| CSF p-tau, pg/mL           | 22 ± 8      | 32 ± 14       | 36 ± 15     | <0.001  |
| MMSE                       | 29.1 ± 1.0  | 26.9 ± 1.8    | 23.5 ± 1.8  | <0.001  |
| ADASCI                     | 6.2 ± 2.9   | 11.8 ± 4.5    | 18.4 ± 6.7  | <0.001  |
| MIM                        | 1.0 ± 0.5   | -0.2 ± 0.6    | -0.9 ± 0.6  | <0.001  |
| EF                         | 0.7 ± 0.6   | -0.1 ± 0.7    | -1.0 ± 0.8  | <0.001  |

Note: Some variables are given as mean ± standard deviation (SD).

Abbreviations: Aβ42, β-amyloid 42; AD, Alzheimer’s disease; ADASCI, Alzheimer Disease Assessment Scale-cognitive subscale; BMI, body mass index; CN, controls; CSF, cerebrospinal fluid; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; EF, executive function composite score; HFABP, heart fatty acid-binding protein; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; p-values are from the Kruskal-Wallis test or Chi-square test; t-tau, total tau.
The levels of CSF HFABP in different subgroups. (A) The CSF levels of HFABP in the CN, MCI, and AD patients. (B) The CSF levels of HFABP in the CN, MCI, and AD patients were stratified by Aβ positivity with the CSF Aβ42 cutoff value of less than 1098 ng/L. The differences between the groups were analyzed using a Kruskal–Wallis test. AD, Alzheimer's disease; CN, control; MCI, mild cognitive impairment.

Fig. 2 The association between CSF HFABP and AD risk. (A) The AUC analyses for CSF HFABP and other biomarkers in the AD and control groups. (B) The Kaplan–Meier curves of progression from cognitively normal (CN) and MCI to AD for CSF HFABP.

with the AUC of 0.80, and CSF p-tau discriminated between AD and the controls with the AUC of 0.80. With regard to the amyloid status, CSF HFABP discriminated between the Aβ-positive AD patients and the Aβ-negative controls, with an AUC of 0.68 (Supplementary Fig. 3).

According to a combination of clinical diagnosis and Aβ pathologic features, we divided the entire population into the Aβ-negative control (CN−), Aβ-positive control (CN+), Aβ-negative MCI (MCI−), Aβ-positive MCI (MCI+), and Aβ-positive AD (AD+) patients and compared the level of CSF HFABP among these groups [Fig. 1(B)]. The AD+ group, at the mean of 4.4 ng/L, had higher CSF HFABP than the CN− group at 2.9 (p < 0.001) and the CN+ group 2.7 (p < 0.01). Moreover, the MCI+ group, at the mean of 4.1 ng/L, had higher CSF HFABP than the CN− group (p < 0.01) and the CN+ group (p < 0.05). The MCI− group, at the mean of 4.0 ng/L, also had higher CSF HFABP than the CN− group (p < 0.05) and the CN+ group (p < 0.05).
3.3 CSF HFABP and CSF AD biomarkers

At the baseline, CSF HFABP was found to be correlated with a high level of CSF t-tau (p < 0.001), CSF p-tau (p < 0.001), and CSF t-tau/Aβ42 (p < 0.001) and high p-tau/Aβ42 (p < 0.001).

However, CSF HFABP was not correlated with a lower level of CSF Aβ42 (p > 0.05) in the entire cohort. All these associations remained significant in all diagnostic subgroups of CN, MCI, and AD (p < 0.01) (Table 2).

| Biomarker | Total | CN | MCI | AD |
|-----------|-------|----|-----|----|
|           | β     | p-value | β     | p-value | β     | p-value | β     | p-value |
| CSF/Aβ42 | -0.001 | 0.320 | 0.013 | 0.980 | -0.009 | 0.230 | 0.006 | 0.208 |
| CSF t-tau | 0.104 | < 0.001 | 0.075 | < 0.001 | 0.109 | < 0.001 | 0.113 | < 0.001 |
| CSF p-tau | 0.115 | < 0.001 | 0.078 | < 0.001 | 0.121 | < 0.001 | 0.125 | < 0.001 |
| CSF t-tau/Aβ42 | 0.077 | < 0.001 | 0.022 | < 0.001 | 0.098 | < 0.001 | 0.065 | 0.004 |
| CSF p-tau/Aβ42 | 0.087 | < 0.001 | 0.023 | < 0.010 | 0.109 | < 0.001 | 0.078 | 0.002 |

Note: The data were β (with p-values) from linear regression models for correlations between CSF HFABP and other biomarkers (all standardized to z scores), adjusted for age, gender, educational level, APOE ε4 genotype, diagnosis, type 2 diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, body mass index, and depression. The models were tested on the entire cohort and individual diagnostic subgroups.

Abbreviations: AD, Alzheimer’s disease; CN, controls; CSF, cerebrospinal fluid; HFABP, heart fatty acid-binding protein; MCI, mild cognitive impairment; p-tau, phosphorylated tau; t-tau, total tau.
3.4 CSF HFABP and cognitive performance and neuroimaging measurements

The associations of CSF HFABP with longitudinal cognitive and imaging measurements were examined (Fig. 3), and the related coefficients and p-values were calculated (Supplementary Table 1). At the baseline, the level of CSF HFABP was not significantly associated with cognitive performance and imaging measurements. In the longitudinal analysis, higher CSF HFABP was associated with an accelerated decline for MMSE, ADAS11, MEM, and EF. Among all the cognitive measurements, the strongest influence was found in MMSE (β = −0.03, p < 0.001). As for the imaging measurements, higher CSF HFABP was associated with faster hippocampus atrophy (β = −0.01, p < 0.01), but not with FDG (p > 0.05) (Supplementary Table 1). Considering the strong correlation between tau and CSF HFABP, we repeated the longitudinal analysis after adjusting for baseline levels of t-tau and obtained the same results. We then explored whether the significant associations were driven by amyloid status and conducted subgroup analyses stratified by CSF Aβ42. We found the above associations to remain significant in Aβ-positive participants (Supplementary Table 2).

3.5 CSF HFABP and risk of AD

Next, we further studied the correlation between CSF HFABP and the risk of AD. The 234 non-demented participants (CN = 91, MCI = 143) included in this analysis were further categorized into low (n = 133, < 3.55 ng/mL) and high (n = 101, ≥ 3.55 ng/mL) CSF HFABP groups according to the same cutoff values of 3.55 ng/mL obtained from the two ROC analyses. Of the 234 participants, 80 of the 101 (79.2%) participants with high CSF HFABP and 82 of the 133 (61.7%) participants with low CSF HFABP progressed to AD during the follow-up period. The Kaplan–Meier curves for the baseline HFABP groups [Fig. 2(B)] indicated that the participants with high levels of CSF HFABP had an increased risk of developing AD (p < 0.001).

4 Discussion

In this study, we explored the relationship between HFABP and AD from various aspects and made some significant observations. First, we found that CSF HFABP was increased in the AD dementia group and the MCI+ groups, according to pathological and clinical diagnoses. Also, a higher CSF HFABP was significantly associated with higher levels of CSF t-tau, CSF p-tau, t-tau/Aβ42, and p-tau/Aβ42 regardless of the cognitive diagnosis. In addition, the higher CSF HFABP was associated with faster cognitive decline and hippocampal atrophy during the follow-up period. Lastly, the participants with a higher CSF HFABP were found to have an increased risk of AD progression. In summary, our study provides a comprehensive analysis and compelling evidence in support of CSF HFABP as a promising predictive biomarker for progression to AD. The use of CSF HFABP may enable the early identification of individuals at risk of AD and guide early intervention.

We observed that the CSF levels of HFABP were elevated in the MCI and AD groups and that CSF HFABP had a negative association with cognitive decline; the results were consistent with the previous studies [21, 22]. In addition, in the brains of patients with AD, HFABP was significantly decreased in the frontal, temporal, occipital, and parietal cortices [23]. These findings further supported the hypothesis of HFABP leaking into the interstitial fluid and further into the CSF.

In recent years, studies have demonstrated
that Aβ deposition is a crucial feature of AD. In the study, we included Aβ pathology into the subgroup analysis. Notably, the CSF level of HFABP was primarily increased in the MCI− and MCI+ groups. These results suggest that HFABP can be used in drug development, which mainly focuses on the early stage of AD [24], and in clinical practice because more patients with MCI are seeking comprehensive medical evaluation.

In our cohort, there was no significant difference in the CSF level of HFABP between the CN+ (preclinical AD) and CN− groups, consistent with the theory that substantial neuronal injury was absent in preclinical AD [25, 26]. Moreover, we found no significant difference in CSF HFABP between the MCI+ and AD groups. This result might be caused by the ceiling effect, which is based on the theory that the change rates of Aβ markers slowed down as AD progressed [27]. In addition, CSF HFABP has a comparable diagnostic value to three traditional CSF biomarkers (Aβ42, t-tau, and p-tau). AD likely involves multiple mechanisms and factors; therefore, CSF HFABP may facilitate the diagnosis and prediction of AD.

CSF HFABP was found to be significantly associated with CSF t-tau and CSF p-tau, but not with Aβ42, in line with a previous finding [13]. The association of CSF HFABP with t-tau, a reliable marker of neuronal injury, suggested that CSF HFABP might reflect the same pathological process, such as axonal damage, with t-tau. These data further verified the roles of HFABP in the formation of neurite and synapse and the activity of cholinergic and glutamatergic neurons [28, 29]. Previous research also found that a high CSF level of HFABP was associated with blood–brain barrier dysfunction [30]. These findings further suggested that HFABP might influence tau pathology indirectly through the blood–brain barrier. Our results demonstrated that CSF HFABP was involved in the early pathological changes of tau during the development of AD. At the same time, we found that high CSF HFABP was associated with faster hippocampus atrophy, further suggesting that intracranial lipid biology may influence the neurodegeneration of AD [31]. In addition, our results showed that CSF HFABP could predict future changes of hippocampal atrophy and changes in cognition, especially for the Aβ+ participants, consistent with the hypothesis about the disease characteristics and process of AD [26].

In summary, our results demonstrated the predictive power of CSF HFABP for AD in a more comprehensive and detailed manner including cross-sectional and longitudinal analyses. However, our study had some limitations. First, our sample size was relatively modest. Also, the patients with other neurodegenerative diseases than AD were not included in our study; therefore, it was difficult to determine the disease specificity of CSF HFABP. In addition, we did not test for changes in CSF HFABP over time and could not assess the impact of its dynamic changes on the results.

5 Conclusion

CSF HFABP may be a valuable tool for evaluating neurodegeneration, identifying individuals at risk for cognitive decline and brain structure atrophy, and predicting disease progression. However, more longitudinal studies are warranted to confirm the associations in the future.

Ethical approval

The ADNI study was approved at each study site across the United States and Canada, and all
study participants provided written informed consent.

**Conflict of interests**

The authors declared no potential conflict of interests with respect to the research, authorship, and/or publication of this article.

**Financial support**

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; CereSp, Inc.; Cogstate; Eisai Inc; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech; 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.

**Authors’ contributions**

JTY and LT conceptualized the study. LP and YNO analyzed and interpreted the data, drafted and revised the manuscript, did the statistical analysis, and prepared all the figures. All authors interpretation of the data and revision of the manuscript. All authors contributed to the writing and revisions of the paper and approved the final version.

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.

**References**

[1] Moon JH. Endocrine risk factors for cognitive impairment. Endocrinol Metab (Seoul) 2016, 31(2): 185–192.
[2] Reitz C. Dyslipidemia and the risk of Alzheimer’s disease. Curr Atheroscler Rep 2013, 15(3): 307.
[3] Oliveira BCL, Bellozi PMQ, Reis HJ, et al. Inflammation as a possible link between dyslipidemia and Alzheimer’s disease. Neuroscience 2018, 376: 127–141.
[4] Walter J, van Echten-Deckert G Cross-talk of membrane lipids and Alzheimer-related proteins. Mol Neurodegener 2013, 8: 34.

https://mc03.manuscriptcentral.com/brainsa | Brain Science Advances
Veerkamp JH, Zimmerman AW. Fatty acid-binding protein's role in Alzheimer's disease. *J Genet Genomics* 2014, 41(5): 261–274.

Bourre JM. Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing. *J Nutr Health Aging* 2004, 8(3): 163–174.

Abumrad NA, Ajmal M, Pothakos K, et al. CD36 expression and brain function: does CD36 deficiency impact learning ability? *Prostaglandins Other Lipid Mediat.* 2005, 77(1-4): 77–83.

Veerkamp JH, Zimmerman AW. Fatty acid-binding proteins of nervous tissue. *J Mol Neurosci* 2001, 16(2/3): 133–42; discussion 151–7.

Glatz JF, Schaap FG, Binas B, et al. Cytoplasmic fatty acid-binding protein facilitates fatty acid utilization by skeletal muscle. *Acta Physiol Scand* 2003, 178(4): 367–371.

Zimmerman AW, Veerkamp JH. New insights into the structure and function of fatty acid-binding proteins. *Cell Mol Life Sci* 2002, 59(7): 1096–1116.

Olsson B, Hertz J, Ohlsson M, et al. Cerebrospinal fluid levels of heart fatty acid binding protein are elevated prodromally in Alzheimer's disease and vascular dementia. *J Alzheimers Dis* 2013, 34(3): 673–679.

Chiasserini D, Parnetti L, Andreasson U, et al. CSF levels of heart fatty acid binding protein are altered during early phases of Alzheimer's disease. *J Alzheimers Dis* 2010, 22(4): 1281–1288.

Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol* 2016, 15(7): 673–684.

Desikan RS, Thompson WK, Holland D, et al. Heart fatty acid binding protein and Aβ-associated Alzheimer's neurodegeneration. *Mol Neurodegener* 2013, 8: 39.

Shaw LM, Vanderstichelen H, Knapik-Czaja M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 2009, 65(4): 403–413.

Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimers Dement* 2018, 14(4): 1460–1469.

Crane PK, Carle A, Gibbons LE, et al. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav* 2012, 6(4): 502–516.

Gibbons LE, Carle AC, Mackin RS, et al. A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behav* 2012, 6(4): 517–527.

Youden WJ. Index for rating diagnostic tests. *Cancer* 1950, 3(1): 32–35.

Mollenhauer B, Steinacker P, Bahn E, et al. Serum heart-type fatty acid-binding protein and cerebrospinal fluid tau: marker candidates for dementia with Lewy bodies. *Neurodegener Dis* 2007, 4(5): 366–375.

Steinacker P, Mollenhauer B, Bibl M, et al. Heart fatty acid binding protein as a potential diagnostic marker for neurodegenerative diseases. *Neurosci Lett* 2008, 379(1–3): 36–39.

Cheon MS, Kim SH, Fountoulakis M, et al. Heart type fatty acid binding protein (H-FABP) is decreased in brains of patients with Down syndrome and Alzheimer's disease. *J Neural Transm Suppl* 2003, 67: 225–234.

Mattsson N, Carrillo MC, Dean RA, et al. Revolutionizing Alzheimer's disease and clinical trials through biomarkers. *Alzheimers Dement (Amst)* 2015, 1(4): 412–419.

Vis JI, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol* 2013, 12(10): 957–965.

Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010, 9(1): 119–128.

Wunderlich MT, Hanhoff T, Goertler M, et al.
Release of brain-type and heart-type fatty acid-binding proteins in serum after acute ischaemic stroke. *J Neurol* 2005, **252**(6): 718–724.

[29] Shioda N, Yamamoto Y, Watanabe M, et al. Heart-type fatty acid binding protein regulates dopamine D2 receptor function in mouse brain. *J Neurosci* 2010, **30**(8): 3146–3155.

[30] Bjerke M, Zetterberg H, Edman A, et al. Cerebrospinal fluid matrix metalloproteinases and tissue inhibitor of metalloproteinases in combination with subcortical and cortical biomarkers in vascular dementia and Alzheimer's disease. *J Alzheimers Dis* 2011, **27**(3): 665–676.

[31] di Paolo G, Kim TW. Linking lipids to Alzheimer's disease: cholesterol and beyond. *Nat Rev Neurosci* 2011, **12**(5): 284–296.

Lu Pan received her Bachelor's degree from Bengbu Medical College, China, in July 2018. Since October 2018, she is majoring in neurology in Dalian Medical University, China, for her Master's degree. E-mail: 1791897835@qq.com

Ya-Nan Ou received her Master's degree from Qingdao University, China, in July 2020. Since October 2020, she has been majoring in neurology in Qingdao University for her Ph.D. degree. She has published several high-quality articles on journals, including *Journal of Hypertension, Alzheimer's Research & Therapy*, and *Journal of Alzheimer's Disease*. E-mail: ouyanan0522@163.com

Lin Tan received her Ph.D. degree from Ocean University of China (2017). Her research focuses on the epigenetics, diagnostic markers, and pathogenesis of AD. She has published many impact papers on journals including *Molecular Neurobiology*, and *Journal of Alzheimer's Disease*. E-mail: tanlinq4@163.com
Lan Tan received her Ph.D. degree from College of Medicine and Pharmaceutics, Ocean University of China (2009). She is the director of Brain Center in Qingdao Municipal Hospital. She is focusing on basic and clinical research for AD and related dementia. She has published many high impact papers as the corresponding author or first author, on journals including New England Journal of Medicine, Annual Review of Neuroscience, Alzheimer's & Dementia, Trends in Molecular Medicine, Progress in Neurobiology, and Neurobiology of Aging. E-mail: dr.tanlan@163.com

Jin-Tai Yu received his Ph.D. degree from Ocean University of China (2014). He then worked as an associate specialist of neurology at the University of California, San Francisco (UCSF) Medical Center, USA (2015). He is a full professor of Neurology and the Vice Director of the Institute of Neurology, WHO Collaborating Center for Research and Training in Neurosciences, Fudan University, Shanghai, China. Currently, he is focusing on basic and clinical research for AD and related dementia. He has published more than 100 research papers that have been cited more than 8000 times in the field. E-mail: yu-jintai@163.com