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RESEARCH ARTICLE

Cerebrospinal fluid levels of fatty acid–binding protein 3 are associated with likelihood of amyloidopathy in cognitively healthy individuals

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Abstract

Introduction: Fatty acid–binding protein 3 (FABP3) is a biomarker of neuronal membrane disruption, associated with lipid dyshomeostasis—a notable Alzheimer's disease (AD) pathophysiological change. We assessed the association of cerebrospinal fluid

(CSF) FABP3 levels with brain amyloidosis and the likelihood/risk of developing amyloidopathy in cognitively healthy individuals.

Methods: FABP3 levels were measured in CSF samples of cognitively healthy participants, > 60 years of age ($n = 142$), from the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL).

Results: FABP3 levels were positively associated with baseline brain amyloid beta (Aβ) load as measured by standardized uptake value ratio (SUVR, standardized $\beta = 0.22$, $P = .009$) and predicted the change in brain Aβ load (standardized $\beta = 0.32$, $P = .004$). Higher levels of CSF FABP3 (above median) were associated with a likelihood of amyloidopathy (odds ratio [OR] 2.28, 95% confidence interval [CI] 1.12 to 4.65, $P = .023$).

Discussion: These results support inclusion of CSF FABP3 as a biomarker in risk-prediction models of AD.

KEYWORDS
Alzheimer's disease, amyloid, early diagnosis, risk prediction, screening

1 | BACKGROUND

Evidence of high brain amyloid beta (Aβ) or amyloidopathy, ascertained via positron emission tomography (PET) or reduced levels of cerebrospinal fluid (CSF) Aβ42, is a key criterion for the identification of preclinical Alzheimer's disease (AD)—suggested by National Institute on Aging–Alzheimer's Association (NIA-AA) criteria 2011[1] and the International Working Group-2 (IWG-2) criteria 2014[2] and 2016.[3] This criterion has been used in several studies to identify cases of preclinical AD.[4–7] The recently proposed research framework by NIA-AA[8] recommends the use of biomarker guided ATN classification (A: Aβ , T: tau, N: neurodegeneration)[9] to identify cognitively healthy individuals who have preclinical AD or preclinical AD pathological change. Cognitively healthy individuals with a biomarker profile, A+T+/N± (preclinical AD) and A+T−N− (preclinical AD pathological change) fall within the AD spectrum.[8]

Given that neurodegenerative changes contribute to the development of AD, accompanied by amyloidopathy (increased Aβ PET),[3] it is worthwhile to identify the dynamics of brain amyloidopathy in cognitive healthy individuals via changes in pathophysiological biomarkers specific to different aspects of neurodegeneration, such as axonopathy, neuronal membrane disruption, and perturbed Ca^{2+} homeostasis.[10,11] Moreover, such biomarkers could quantify the effect of modifiable risk factors on the risk of developing preclinical AD. CSF fatty acid–binding protein 3 (FABP3) or heart type fatty acid–binding protein (H-FABP) is a biomarker of neuronal membrane disruption, associated with lipid dyshomeostasis—a notable AD pathophysiological change.[12] CSF levels of this protein are elevated in AD and predict disease progression in patients with mild cognitive impairment (MCI).[13–16] Evidence indicates the association of FABP3 with risk factors associated with AD—traumatic brain injury (TBI) and cardiovascular risk factors. In a recent study by Lagerstedt et al., blood levels of FABP3 have been shown to improve the predictive outcome in patients with TBI.[17] In addition, elevated blood levels of FAPB3 are associated with higher cardiovascular risk factors,[18] and can predict cardiovascular outcomes in patients with stable coronary heart disease.[19] Therefore, assessment of CSF or plasma levels of FABP3, and understanding their association with brain amyloidopathy (central AD pathological change) and its potential to indicate likelihood of amyloidopathy, can help determine the risk of AD among vulnerable individuals exposed to such risks—TBI and cardiovascular risk factors. Therefore, FABP3 could be used as one of the biomarkers in building biomarker-based risk-prediction models for dementia.

Herein we aimed to assess the association of CSF FABP3 levels with brain amyloidopathy and its potential to indicate the likelihood or risk of amyloidopathy. We measured CSF FABP3 levels in CSF samples of cognitively healthy participants from the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL) and evaluated the association of FABP3 CSF levels with brain amyloidosis and likelihood of amyloidopathy using positron emission tomography PET Aβ imaging. The influence of apolipoprotein E (*APOE*) genotype, sex, and age in driving these associations was also assessed.

2 | METHODS

2.1 | Participants

This study included cognitively healthy participants ($n = 142$) from AIBL who gave consent for CSF collection (collected between 2009 and 2016 at either of the two study centers (Melbourne, VIC and Perth, WA) and underwent PET imaging at baseline corresponding to CSF collection. Participants were classified as cognitively healthy based on performance on neuropsychological and cognitive tests (e.g.,

RESEARCH IN CONTEXT

1. **Systematic Review**: Fatty acid–binding protein 3 (FABP3) is a biomarker of neuronal membrane disruption—a notable pathophysiological change in Alzheimer's disease (AD). Evidence indicates the association of FABP3 with AD risk factors. Therefore, assessment of CSF levels of FABP3, and understanding their association with brain amyloidosis could help in determining the likelihood of amyloidopathy in cognitively healthy individuals and making an early diagnosis.
2. **Interpretations**: Our findings indicate that CSF FABP3 levels are positively associated with baseline brain amyloid beta (Aβ) load, predict the change in brain Aβ load, and are associated with a likelihood of amyloidopathy.
3. **Future Directions**: Findings support the inclusion of FABP3 in diagnostic models to predict risk of AD/screen preclinical AD. Furthermore, we aim to assess the utility of CSF FABP3 to predict disease onset in cognitively healthy individuals and progression in individuals with mild cognitive impairment.

Mini Mental State Examination [MMSE], California Verbal Learning Test, Second edition [CVLT-II], and a CogState battery). Participants' MMSE scores ranged from 24 to 30 and had a Clinical Dementia Rating (CDR) of 0. [20] Exclusion criteria included heavy alcohol consumption (exceeding two standard drinks per day for women and four per day for men), past serious head injury, history of non-AD dementia, significant current depression (15-item Geriatric Depression Scale [GDS-15] score >5), schizophrenia, bipolar disorder, epilepsy, amnesia, Parkinson disease, cancer (other than basal cell skin carcinoma) within the last 2 years, history of stroke, uncontrolled diabetes, lack of fluency in the English language, and withdrawal of consent.[20] Poor performance on cognitive tests due to current medical illness, medical history (as above), or medication use was another criterion for exclusion.[20] The study was approved by the Human Research Ethics Committees of Edith Cowan University, Austin Health and St. Vincent's Health and Hollywood Private Hospital. Information on participants' baseline characteristics (sex, age, and presence of *APOE* ε4) was collected as part of cohort characterization. Aβ positivity (Aβ+) was determined using PET-derived standardized uptake value ratio (SUVR), commensurate with neocortical Aβ burden (described in the next section).

2.2 | Brain Aβ imaging

Neocortical Aβ burden (brain Aβ load) was assessed for all participants (n = 142) at baseline, and for 91 participants at follow-up, via PET using different Aβ tracers, ^{11}C-Pittsburgh compound B (^{11}C-PiB),^{18}F-florbetapir, and ^{18}F-flutemetamol as described previously.[21–23] The PET image were analyzed using the CapAIBL software.[24] The average SUVR, computed as the area-weighted mean SUVR of different cortical regions (frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions), was used as a quantitative measure of neocortical Aβ burden. The SUVR generated with F-18 tracers were linearly transformed into PiB-like SUVR units called the Before the Centiloid Kernel Transformation (BeCKeT), to place all SUVR on a continuous scale,[25] and Aβ positivity (Aβ+) was determined using a SUVR/BeCKeT cutoff value of 1.4.[26] The time interval between baseline (corresponding to CSF collection) and follow-up PET imaging ranged from 1.2 to 3.5 years (average 1.7 years).

2.3 | Sample collection and biomarker analyses

Sample collection involved lumbar puncture (LP), as per the Alzheimer's Biomarkers Standardization Initiative protocol.[27] Samples were stored at −80°C, following centrifugation within 2 hours, at 2000 × g for 10 minutes and making aliquots into polypropylene tubes (0.5 mL). Samples went through one freeze-thaw cycle to aliquot the samples further.

Concentrations of CSF Aβ42, total tau (t-tau), and phosphorylated tau (p-tau) were measured using enzyme-linked immunosorbent assays (ELISAs): INNOTEST β-AMYLOID $_{(1–42)}$ (Aβ42), INNOTEST hTAU Ag (t-tau), and INNOTEST PHOSPHO-TAU $_{(181P)}$ (p-tau181P) (Fujirebio, Ghent, Belgium), at the National Dementia Diagnostics Laboratory (NDDL), Florey Institute, The University of Melbourne.

CSF FABP3 concentrations were quantified on the meso scale discovery (MSD) platform using electrochemiluminescence on the SECTOR Imager 2400A, with Human FABP3 Kits (Meso Scale Diagnostics, USA) according to the manufacturer's protocol, at the laboratory of School of Medical and Health Sciences, Edith Cowan University. The assay uses detection antibodies (goat polyclonal) conjugated with electrochemiluminescent label (MSD SULFO-TAG), and assay plates are pre-coated with capture antibodies (mouse mAb) on an electrode surface. The assay has an average lower limit of detection of 0.103 ng/mL. A pooled control CSF was run to check for interplate variation. The percentage coefficient of variance (CV) between duplicates was <10% (average 2%) and between plates was 10%.

2.4 | Statistical analyses

Statistical analyses were conducted using IBM SPSS version 27 (for Microsoft Windows). Cross-sectional differences in mean values of continuous variables were assessed using analysis of covariance (ANCOVA) and t-tests. Group comparisons for categorical variables were made using chi-square tests. Correlation of CSF FABP3 with age was evaluated through Pearson rho correlation coefficient. In addition, using the median age (73 years) as a cutoff, participants were dichotomized into two groups—(1) ≤73 years and (2) >73 years—to further assess influence of age on CSF FABP3 levels by comparing

TABLE 1 Influence of *APOE* ε4, sex, age on CSF FABP3 levels

	Groups		
	***APOE* ε4 carriers (*n* = 107, 75%)**	***APOE* ε4 non-carriers (*n* = 35, 25%)**	***P* value**
CSF FABP3	2.80 (1.19)	2.89 (1.00)	0.410
	Age group ≤73 (*n* = 69)	**Age group >73 (*n* = 73)**	
CSF FABP3	2.60 (1.15)	3.03 (1.11)	0.006
	Male (*n* = 64, 45%)	**Female (*n* = 78, 55%)**	
CSF FABP3	3.12 (1.21)	2.58 (1.04)	0.005

Note: The values in the table represent raw means (SDs) unless indicated. CSF FABP3 were transformed using the natural logarithm and differences were compared among the groups using independent-sample *t*-test.
Abbreviations: *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; FABP3, fatty acid–binding protein 3.

CSF levels among the two groups. Linear regression analyses were conducted to assess the effect of baseline levels of biomarkers (CSF FABP3, t-tau, and p-tau), and other variables (age, sex, and presence of *APOE* ε4) on baseline brain Aβ load (measured via SUVR) and change in Aβ load at follow-up. Associations between CSF biomarkers and SUVR were assessed by adjusting for covariates, ages, sex, and *APOE* genotype. A natural log transformation was applied to SUVR to meet the assumptions of linear regression. Participants were dichotomized into groups using median value (50th percentile) of CSF FABP3 concentration as a cutoff (75 ng/mL), as well as the value corresponding to the best sensitivity and specificity (Aβ+ vs Aβ−) as a cutoff (2.85 ng/mL). Cutoff was determined using a receiver-operating characteristic (ROC) curve analysis by keeping sensitivity (61%) and specificity (62%) approximately equal. Participants were designated as having high CSF FAPB3 concentration (CSF FABP3+), if the concentration was more than the median or ROC cutoff; otherwise they were designated as CSF FABP3−. Logistic regression analyses were used to assess the effect of elevated levels of FABP3 (as a categorical variable) on the likelihood of preclinical AD (identified by Aβ positivity) as odds ratio (OD) with 95% confidence interval (CI). The effect of higher CSF FABP3 levels or CSF FAPB3 positivity on the likelihood of having preclinical AD was assessed (1) individually, (2) by adjusting for all covariates, (3) adjusting only for presence of *APOE* ε4, and (4) by interaction with the presence of *APOE* ε4 in the respective models. Before applying all parametric tests, assumptions of normality were met, and where required continuous variables were transformed into their natural logarithm. For all analyses $P < 0.05$ was considered significant.

3 | RESULTS

3.1 | Association of CSF FABP3 with age, sex, and *APOE* ε4 genotype

Participants' ages varied between 61 and 88 years. The potential association of CSF FABP3 with age was assessed via correlational analysis. Significant correlation was noted between CSF FABP3 levels and age ($r = 0.276$, $P < 0.001$). Participants were dichotomized based on the median value of age (73 years). CSF FABP3 levels (mean levels) were significantly higher in the group with age >73 years as compared to the group with age ≤ 73 years ($P = 0.006$; Table 1). These results reflect the age-dependent increase in CSF FAPB3 levels. A comparison of CSF FABP3 levels among *APOE* ε4 carriers versus non-carriers indicated no difference in CSF levels between the two groups ($P = 0.410$; Table 1). On the other hand, a comparison of CSF FABP3 levels between the male and female participants indicated higher CSF levels to be associated with the male sex ($P = 0.005$; Table 1).

3.2 | Association with brain amyloidosis—Baseline SUVR

The association of CSF FABP3 levels, demographic variables (age, sex, and *APOE* ε4), and core CSF biomarkers of tau pathology and neurodegeneration (CSF t-tau and t-tau) with brain Aβ load (measured by SUVR/BeCKeT, transformed to natural logarithm) was assessed via linear regression analyses. Results are summarized in Table 2. No association was noted for sex (male vs female) and age with SUVR ($P = 0.167$ for sex and $P = 0.068$ for age). The presence of *APOE* ε4 allele was positively associated with baseline SUVR/BeCKeT (standardized $\beta = 0.26$, $P = 0.002$). Associations between CSF biomarkers (FABP3, t-tau, and p-tau) and baseline SUVR/BeCKeT were assessed after controlling for covariates (age, sex, and *APOE* ε4 presence). CSF FABP3 levels were positively associated with baseline brain Aβ load as measured by SUVR/BeCKeT, transformed to natural logarithm (standardized $\beta = 0.22$, $P = 0.009$), and accounted for 16% variability in baseline Aβ load. CSF measures (t-tau and p-tau) were rescaled to the same measurement unit (ng/mL) as that of CSF FABP3. CSF t-tau accounted for the maximum variability in baseline SUVR/BeCKeT (23%) and was the stronger predictor of baseline brain Aβ load (standardized $\beta = 0.35$, $p < 0.001$).

3.3 | Prediction of change in brain Aβ load

Regression analyses were carried out to test the utility of CSF FABP3 including the core CSF biomarkers to predict change in brain Aβ load (difference in baseline SUVR/BeCKeT and follow-up SUVR/BeCKeT, log transformed). Results are summarized in Table 2. Because the time interval between PET scans varied among individuals, analyses were

TABLE 2 Association of demographic variables and baseline CSF measures with baseline brain Aβ, and of CSF measures with change in brain Aβ as measured by SUVR

	Association with baseline SUVR/BeCKeT[a] ($n = 142$)			
Variable	**β (SE)**	**Standardized β**	**R^2**	***P* value**
Sex (male vs female)	0.06 (0.04)	0.13	0.01	.167
Age at LP in years	0.01 (0.00)	0.15	.026	.068
APOE ε4 allele (present vs not present)	0.14 (0.04)	0.26	0.07	.002
CSF t-tau ng/mL ($n = 141$)	0.70 (0.16)	0.35	0.23	<.001
CSF p-tau ng/mL ($n = 141$)	3.94 (1.01)	0.32	0.20	<.001
CSF FABP3 ng/mL ($n = 142$)	0.05 (0.02)	0.22	0.16	.009
	Prediction of change in SUVR/BeCKeT (ΔSUVR/BeCKeT; $n = 91$)			
CSF t-tau ng/mL	0.70 (0.23)	0.31	0.19	.003
CSF p-tau ng/mL	3.99 (1.35)	0.30	0.18	.004
CSF FABP3 ng/mL	0.07 (0.02)	0.32	0.18	.004

Note: Association of baseline CSF measures with baseline SUVR was assessed after controlling for covariates age, sex, and presence of *APOE* ε4. SUVR and ΔSUVR values were transformed to natural logarithm. CSF t-tau and p-tau were rescaled to ng/mL.
Abbreviations: *APOE*, apolipoprotein E; Aβ, amyloid beta; CSF, cerebrospinal fluid; FABP3, fatty acid–binding protein 3; LP, lumber puncture; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; t-tau, total tau.

TABLE 3 Likelihood of preclinical AD (Aβ positivity) as a function of higher levels of CSF FABP3 using (a) median value as cutoff and (b) using value corresponding to best sensitivity and specificity (Aβ+ vs Aβ−)

A) Median value as cutoff (2.75 ng/mL)				
Model	**Parameters**	**Odds ratio (OR)**	**95% CI**	***P* value**
Model 1	High CSF FABP3 (FABP3+)	2.28	1.12–4.65	.023
Model 2	High CSF FABP3 (FABP3+) controlled for age, sex, and presence of *APOE* ε4	2.29	1.03–5.11	.042
Model 3	High CSF FABP3 (FABP3+) controlled for presence of *APOE* ε4	2.58	1.20–5.51	.015
Model 4	Interaction of high CSF FABP3 (FABP3+) and presence of *APOE* ε4	3.15	1.12–8.89	.030
B) Value corresponding to best sensitivity and specificity (Aβ+ vs Aβ−) as cutoff (2.85 ng/mL)[a]				
Model 1	High CSF FABP3 (FABP3+)	2.62	1.28–5.33	.008
Model 2	High CSF FABP3 (FABP3+) controlled for age, sex, and presence of *APOE* ε4	2.86	1.28–6.42	.011
Model 3	High CSF FABP3 (FABP3+) controlled for presence of *APOE* ε4	3.11	1.44–6.73	.004
Model 4	Interaction of high CSF FABP3 (FABP3+) and presence of *APOE* ε4	3.26	1.09–9.79	.035

Note: aCutoff was determined by keeping sensitivity (61%) and specificity (62%) approximately equal.
Abbreviations: *APOE*, apolipoprotein E; Aβ, amyloid beta; CSF, cerebrospinal fluid; FABP3, fatty acid–binding protein 3.

controlled for the time interval between PET scans, in addition to age, sex, and *APOE* ε4 presence. CSF FABP3 levels predicted the change in brain Aβ load or the change in SUVR/BeCKeT (standardized $\beta = 0.32$, $P = 0.004$), and accounted for 18% variability in brain Aβ change, comparable to that noted for the core CSF biomarkers CSF t-tau (standardized $\beta = 0.31$, $R^2 = 0.19$, $P = .003$) and p-tau (standardized $\beta = 0.30$, $R^2 = 0.18$, $P = 0.004$).

3.4 | Association with likelihood or risk of amyloidopathy

Significantly higher levels of CSF FABP3 (mean [SD]) were noted in the individuals who were Aβ+ ($n = 49$, 3.27 [1.19] ng/ml) compared to Aβ− ($n = 93$; 2.58 [1.05] ng/mL, $P = .001$). Logistic regression analyses were used to assess the effect of elevated levels of FABP3 (as a categorical variable) on the likelihood or risk of amyloidopathy or Aβ positivity, OD, 95% CI (Table 3). Participants were classified as FABP3+ and FABP3− based on median measure as a cutoff (2.75 ng/mL), as well as the value corresponding to the best sensitivity and specificity (Aβ+ vs Aβ−) as a cutoff (2.85 ng/mL), determined using the ROC curve analysis. For median as a cutoff, FABP3 positivity (higher levels of CSF FABP3) was associated with the likelihood or risk of amyloidopathy (model 1; OR 2.28, 95% CI 1.12–4.65, $P = .023$). Associations were also assessed with inclusion of age, sex, and *APOE* ε4 presence (model 2; OR 2.29, 95% CI 1.03–5.11, $P = .042$), as well as with only *APOE* ε4 presence (model 3; OR 2.58, 95% CI 1.20–5.51, $P = .015$). The interaction of FABP3+ and *APOE* ε4 presence was associated with a higher likelihood or risk of amyloidopathy (model 4; OR 3.15, 95% CI 1.12–8.89, $P = .030$).

For ROC cutoff (Aβ+ vs Aβ−), FABP3 positivity (higher levels of CSF FABP3) was also associated with a likelihood or risk of amyloidopathy (model 1; OR 2.62, 95% CI 1.28–5.33, $P = .008$). Again, associations were also assessed with inclusion of age, sex, and *APOE* ε4 presence (model 2; OR 2.86, 95% CI 1.28–6.42, $P = .011$), as well as with only *APOE* ε4 presence (model 3; OR 3.11, 95% CI 1.44–6.73, $P = .004$). The interaction of FABP3+ and *APOE* ε4 presence was associated with a higher likelihood or risk of amyloidopathy (model 4; OR 3.26, 95% CI 1.09–9.79, $P = .035$).

4 | DISCUSSION

The inextricable association between lipid dyshomeostasis and AD neuropathology has been extensively studied and validated.[28] FABP3 is a biomarker of neuronal membrane disruption, associated with lipid dyshomeostasis,[12] whose potential for diagnosis of AD has been verified by several studies.[13,16,29,30] Given the lack of evidence concerning the utility of CSF FABP3 for early diagnosis of AD, and given its association with AD risk factors, we tested the utility of CSF FABP3 to identify the likelihood of amyloidopathy. A positive association of elevated CSF FABP3 levels with brain Aβ load at baseline and change in Aβ load, found in this study, support the utility of this biomarker in identifying individuals who are likely in the preclinical phase of the AD continuum. Furthermore, we noted elevated levels of CSF FABP3 in individuals with Aβ pathology (Aβ+), highlighting the potential of this biomarker for identifying AD-associated central pathophysiological changes in cognitively healthy individuals. Vidal-Pinerio et al. indicated that CSF levels of FAPB3 predict brain atrophy among older cognitively healthy individuals, independent of biomarkers of amyloidopathy and tauopathy.[31] Hoglund et al. noted higher levels of CSF FABP3 in cognitively healthy individuals at risk of developing AD—those who were CSF Aβ+ (CSF Aβ below the threshold).[32] Desikan et al. indicated that elevation in CSF FABP3 levels reflect on Aβ-associated neurodegeneration in a cohort of demented and non-demented older individuals. They noted that elevated CSF FABP3 levels were associated with longitudinal brain atrophy only in individuals with Aβ pathology (low CSF Aβ42, Aβ+).[29] Collectively, findings from these studies and the present data emphasize the likely association of elevated CSF FABP3 levels with Aβ pathology, which can be leveraged for making an early diagnosis of AD. Although our study focused on CSF FABP3, it would be worthwhile for future studies to evaluate our hypothesis by measuring blood FABP3 levels in cognitively healthy participants. Previously our team has reported elevated levels of FABP3 in plasma samples of AIBL participants (healthy controls vs AD and MCI).[33] Moreover, given the association of blood FABP3 levels with AD risk factors—cardiovascular diseases[18,19] and TBI[17,34]—blood levels of FABP3 could help to build sensitive biomarker-based risk-prediction models along with additional biomarkers associated with other risk factors or neuropathological changes. Future studies are needed to build and test such models for the early diagnosis of dementia. Such diagnostic models will involve a feasible and non-invasive approach of sample collection, enabling a population wide screening in a routine clinical setting. Such biomarker-based risk-prediction models can ascertain an "individual specific" magnitude of risk associated with developing AD/cognitive impairment and could improve diagnostic sensitivity.

Our results indicate that baseline levels of CSF FABP3 predict change in brain Aβ load, corroborating the utility of this biomarker as an indicator of future change in brain amyloidopathy. Therefore, higher levels of CSF FABP3, along with other biomarkers, will accurately predict risk of AD development in the vulnerable population (middle-aged and older individuals). Furthermore, our analyses indicate that higher levels of CSF FABP3 associate with a higher likelihood or odds of preclinical AD (defined by Aβ positivity). Results from a longitudinal study by Bjerke et al. have also revealed the predictive utility of CSF FABP3 for AD. They reported that elevated levels of FABP3 at baseline predicted the development of AD (OR 1.38, $P= 0.019$) in older women over 8 years of follow-up.[35] Nonetheless, although in our study age and sex were found to influence CSF FABP3 levels, these covariates had minimal or negligible influence in mediating the effect of FABP3 on likelihood of preclinical AD as seen from the OR obtained upon controlling for all covariates. Th presence of the ε4 allele of *APOE* was found to have a positive effect on brain Aβ load—congruent with findings from other studies[36,37]—but had no influence in modulating CSF FABP3 levels. This indicates that elevation in CSF FABP3 (evidence of neurodegeneration/comorbid risk factors) and presence of *APOE* ε4 (evidence of genetic risk) independently influence brain Aβ amyloidopathy. FABP3 positivity (higher levels) and *APOE* ε4 presence together accounted for a higher likelihood of preclinical AD. Apparently, diagnostic models involving a combination of modifiable risk factors (accounted by biomarkers such as FABP3) and non-modifiable risk (accounted by genetic variants associated with the disease) could give an absolute prediction of likelihood of AD, help screen cases of preclinical AD with high accuracy, and predict cognitive decline among cognitively healthy individuals. Idland et al. noted that a combination of biomarkers including CSF FABP3 can help in improving prediction of cognitive decline among cognitively healthy individuals.[38]

The observed results in the current study, such as the estimated likelihood of amyloidopathy among cognitively healthy participants (high CSF FABP3 group vs low CSF FABP3) could have been overestimated and influenced by the small number of cognitively healthy participants. Future studies with larger sample numbers should be conducted to test the association.

In conclusion, findings from our study support that CSF FABP3 is a biomarker of early neurodegenerative changes. It can likely form an important component of sensitive risk-prediction models meant for early diagnosis of AD with Aβ asymptomatic amyloidosis, as well as predict change in brain Aβ load.

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CONFLICT OF INTEREST

K.B. has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). V.V. is and has been a consultant or paid speaker at sponsored conference sessions for Eli Lilly, Life Molecular Imaging, ACE Barcelona, GE Healthcare, IXICO, Hospicom, Abbvie, Lundbeck, Shanghai Green Valley Pharmaceutical Co Ltd, and Hoffmann La Roche. S.C. is currently a contracted adviser to Biogen. Other authors have no conflict of interests to disclose. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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