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The blood lipidome fatty acid profile predicts the disease risk and clinical phenotypes of Alzheimer's disease: associations from two prospective cohort studies

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The relationship between fatty acids and Alzheimer's Disease (AD) risk has been an area of growing interest but remains insufficiently understood. This study aimed to develop and validate a fatty acid score (FAS) derived from blood fatty acid levels and explore its association with AD risk. We analyzed 148,308 UK Biobank participants (age 37–73; mean 55.96 years) with a mean follow-up of 12.3 years (maximum 16), and 1193 ADNI subjects (age 55–90; mean 73.50 years) with a mean follow-up of 4.2 years (maximum 8). Lasso regression was used to construct the FAS based on UKB, and Cox regression and linear regression was employed to assess the relationships of FAS with AD risk, cognition, hippocampal volume, and/or cerebrospinal fluid markers in both cohorts. Stratified effects by *APOE* ε4 status were examined. Causal mediation, proteomic, and bioinformatic analyses were performed to reveal potential mechanisms. Higher FAS was associated with increased AD risk in both cohorts (UKB: HR = 1.298, 95% CI 1.183–1.423, $P < 0.001$; ADNI: HR = 1.413, 95% CI 1.105–1.808, $P = 0.006$). In UKB, higher FAS was linked to reduced hippocampal volume ($P < 0.001$), and in ADNI, it was associated with faster hippocampal atrophy ($P = 0.002$) and cognitive decline ($P < 0.001$). These associations were stronger in *APOE* ε4 carriers. Hippocampal volume partly mediated the link between FAS and cognitive decline. Proteomic analyses demonstrated that the protein expression levels of Adhesion G protein-coupled receptor G1 (ADGRG1), Chitinase-3-like protein 1 (CHI3L1), RNA-binding FOX-1 homolog 3 (RBFOX3), and Growth differentiation factor 15 (GDF15) could mediate the effect of FAS on AD risk. The enriched pathways include cytokine activity, neurotrophic signaling, and pathways related to nervous system development. Blood levels of fatty acid could aid in AD prediction, but further research is needed to confirm causality.

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INTRODUCTION

Alzheimer's Disease (AD) is the leading cause of dementia globally and places significant burdens on societies [1]. It is crucial to prevent and postpone AD occurrence. Compared to the biomarker framework based on cerebrospinal fluid (CSF) or PET imaging, the blood-based biomarker exhibited multiple advantages including accessible reproducibility, non-invasiveness, ease of measurement, and cost-effectiveness [2]. Identifying reliable blood signals can facilitate risk stratification and personalized intervention in early stage of AD. Lines of studies have shown that multiple circulating proteins are associated with risk of dementia [3] and AD [4–8]. Moreover, peripheral blood proteins may drive AD onset by modulating neuroinflammation, metabolism, and the extracellular matrix [9–11].

Recently, some specific blood fatty acids were reported to modulate the levels of peripheral blood proteins associated with AD pathology [12, 13], making them potential biomarkers for predicting AD. We and other researchers have found that higher levels of omega-3 polyunsaturated fatty acids (PUFAs) were associated with a reduced risk of cognitive decline [14] and AD [15, 16], whereas higher levels of saturated fatty acids (SFAs) could increase the risk of AD [17]. However, the associations of blood fatty acids with cognitive function [18] or AD [19] remained inconclusive. These inconsistencies may be attributed to variations in sample size and confounding by *APOE* genotype [20–22]. In addition, the diverse types of blood fatty acids and their interactions will also complicate the associations [20]. Therefore, a strategy of weighting and incorporating different components of blood fatty acids could better estimate the contributions to AD.

On the other hand, the mechanisms by which blood fatty acids were associated with AD were still unclear. Previous evidence showed that disrupted fatty acid metabolism and imbalance in proportions were critically implicated in AD pathogenesis

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[20, 23, 24]. High-fat diet increased hippocampal SFAs and decreased PUFAs [25], while this intake triggered inflammation, endoplasmic reticulum stress, and apoptotic signaling in the murine hippocampus [26]. Additionally, the omega-6/omega-3 fatty acid ratio imbalance influenced amyloid pathology in the hippocampus and cortex of transgenic mice [27]. It was reasonably hypothesized that neurodegeneration and neuroinflammation could be the underlying mechanisms, but other mediating pathways could exist.

In the present study, we aimed to (1) develop a blood FAS associated with incident AD risk using a UK cohort and validate this association in an independent North America cohort, (2) explore the relationships of the FAS with cognition, hippocampus, and cerebrospinal fluid (CSF) AD biomarkers, (3) investigate the effect of hippocampus in mediating the relationship between FAS and cognition, and (4) examine the potential biological mechanisms by which FAS was associated with AD.

METHODS

Participants

The UK Biobank (UKB) is a prospective cohort study of around 500,000 individuals aged 37–73 years recruited between 2006 and 2010. UKB participants completed comprehensive assessments including questionnaires, interviews, biological sampling, and physical measurements at 22 centers across the UK [28]. Baseline data covered socio-demographics, lifestyle, diet, and medical history, with follow-up via electronic health records. Ethical approval was obtained (Ref. 11/NW/0382), and all participants provided informed consent.

Serving as the validation cohort, ADNI is an established multi-center cohort in North America (adni.loni.usc.edu). ADNI is launched to test clinical, imaging, genetic, and biochemical biomarkers of AD. The participants, aged 55–90 years, were enrolled after approval from the institutional review boards of all participating centers, with written informed consent obtained from all participants or their authorized representatives in accordance with the 1975 Declaration of Helsinki. Detailed information can be found at http://www.adniinfo.org.

For both cohorts, we excluded participants who were diagnosed with dementia or major neuropsychiatric disorders at baseline, or were lost to follow-up, or had incomplete covariate or fatty acid data. Any participant with a missing value for variables of interest was excluded.

Assessment of plasma fatty acids

In UKB, plasma fatty acids levels (absolute concentrations and percentages of specific component to total fatty acids) were measured by nuclear magnetic resonance (NMR) in blood samples [29]. In ADNI, serum fatty acids were analyzed using Nightingale Health's NMR metabolomics platform [17]. For both cohorts, 17 fatty acid indicators were included: total fatty acids (TFA), saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acid (PUFA), omega-3, omega-6, docosahexaenoic acid (DHA), and linoleic acid (LA), and various ratios including SFA to TFA ratio, MUFA to TFA ratio, PUFA to TFA ratio, omega-3 to TFA ratio, omega-6 to TFA ratio, DHA to TFA ratio, LA to TFA ratio, PUFA to MUFA ratio, omega-6 to omega-3 ratio.

Diagnosis of AD dementia

In UKB, dementia diagnoses were ascertained using the International Classification of Diseases (ICD) coding system from hospital records and death registers. The Alzheimer's disease codes included F00, F00.0, F00.1, F00.2, F00.9, G30, G30.0, G30.1, G30.8, and G30.9. The follow-up duration was calculated as the shorter interval between the initial evaluation and the diagnosis of dementia, death, last follow-up, or loss to follow-up [30, 31]. In ADNI, neuropsychological testing and diagnostic criteria details can be found on the ADNI website (http://adni.loni.usc.edu/methods). In brief, AD patients had an MMSE score of 20–26, a CDR-SB score of 0.5 or 1, and met the NINDS-ADRDA criteria for probable AD. Cognitive diagnoses were recorded annually, with progressors identified by changes from NC to AD dementia or MCI to AD dementia [22].

Cognitive assessments

In UKB, the Numeric Memory Test (NMT) was selected as the primary cognitive outcome. The NMT collects comprehensive data, including the number and value of digits remembered, response accuracy, response times, and overall test completion status [32]. Higher scores in NMT indicated better cognitive performance. In ADNI, cognitive functions were evaluated using multiple scales, including global cognition by the cognitive section of the Alzheimer's Disease Assessment Scale (ADAS) and specific memory functions (MEM) by extracting relevant neuropsychological batteries to identify relevant items [33, 34].

Hippocampal volume measurement

The volume of hippocampus in both UKB and ADNI were obtained from magnetic resonance imaging (MRI). T1-weighted and T2-FLAIR structural images were acquired in a straight sagittal orientation and centrally processed to extract hippocampal volumes. Detailed descriptions of image processing for both UKB and ADNI cohorts are available in other publications [35, 36].

Measurements of CSF biomarkers

Data on CSF biomarkers were accessible only in ADNI cohort. The detailed protocols for CSF procedures have been documented in [37]. Briefly, concentrations of CSF $A\beta_{1-42}$, p-tau_{181}, and total tau proteins (pg/mL) were measured using electrochemiluminescence immunoassays (Elecsys; Roche Diagnostics) on a fully automated Elecsys cobas e 601 instruments, as detailed in the UPENNBIOMK9.csv file [38].

Blood proteomics

In UKB, blood samples were collected in EDTA tubes, centrifuged at 2500 g for 10 min at 4 °C, and the plasma was aliquoted and stored at −80 °C. Proteomic assays were conducted on approximately 55,000 plasma samples using dual-barcoded antibody technology on the Olink platform [39]. A total of 2923 types of proteins were retained for current analyses.

Covariate measurements

In UKB, the covariates included age, gender, educational attainment level, *APOE* ε4, Townsend deprivation index, depression, anxiety, hypertension, diabetes mellitus, hyperlipidemia, smoking, alcohol, stroke, obesity, and cancer. In ADNI, the covariates included age, gender, education, *APOE* ε4, diagnosis, depression, anxiety, hypertension, diabetes, smoking, stroke, obesity, and cancer. *APOE* ε4 carrier status was determined by genetic information (rs7412 and rs429358).

Statistical analyses

R software version 4.3.1 was used for statistical analyses. A two-sided $p < 0.05$ was considered as statistical significance. Baseline characteristics were summarized as mean (standard deviation [SD]) for normally distributed continuous variables, median (interquartile range [IQR]) for non-normally distributed continuous variables, and number (percentage) for categorical variables. The population was divided into high-risk and low-risk groups based on the highest quartile of blood fatty acid score (FAS). Comparisons between groups were performed using the Mann-Whitney U test for non-normally distributed continuous variables, the t-test for normally distributed continuous variables, and the chi-square test for categorical variables.

The research design and flowchart are shown in Fig. 1. Firstly, Lasso regression and Cox proportional hazards regression were employed to identify significant variables associated with risk of AD based on UKB cohort. The identified variables were then used to construct risk scores using Cox regression which met the proportional hazards assumption. The proportional hazards assumption for the Cox regression model was assessed using Schoenfeld residuals. If the assumption was violated, interaction terms with time were incorporated. Subsequently, the FAS for each participant was calculated based on the coefficients of the feature variables. Specifically, variable selection was performed using the Lasso regression model. Twenty-fold cross-validation was conducted to identify the optimal penalty parameter (lambda). Virtual vertical lines were drawn at lambda1.1SE and lambda.min, with the model at lambda.min set to 0.000 being selected as the best diagnostic model. Predictors with non-zero coefficients were considered relevant and included in further analysis to develop a more concise multi-factor Cox regression prediction model. A nomogram of the multi-factor Cox regression prediction model was then constructed using the R package 'rms' to visualize the AD risk related to FAS. The population was then stratified into high-risk and low-risk groups according to the highest quartile of FAS. The restricted cubic spline

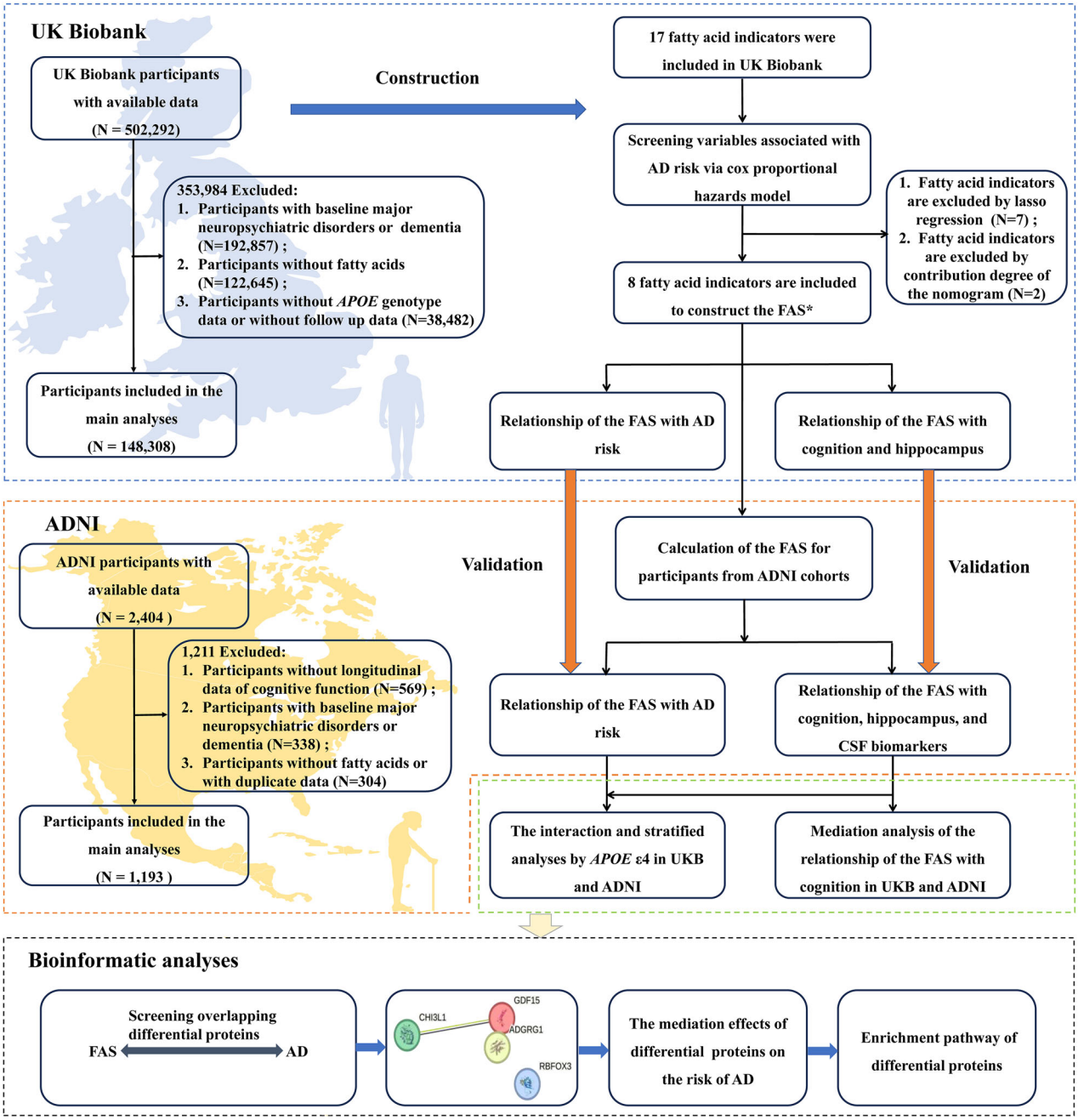

Fig. 1 Study design and workflow. Seventeen blood fatty acid indicators were initially considered. Cox proportional hazard models were used to identify indicators closely associated with the risk of Alzheimer's disease (AD). After Lasso regression ($n = 7$) and considering contribution degree in the nomogram ($n = 2$), a total of 8 indicators were finally included to construct the fatty acid risk score. The association of risk score with AD risk, cognition, hippocampus, and/or cerebrospinal fluid AD markers were tested in both UKB and ADNI cohorts. Mediation effects and interaction analyses by *APOE* ε4 were performed. Finally, proteomic analyses were conducted to elucidate the biological mechanisms of the interaction. "*" See e-Fig. 1 for details. FAS Fatty acid score.

analysis was used to explore the linear or nonlinear relationship between FAS and AD risk, validating the appropriateness of the group classifications. Next, multivariable Cox proportional hazard regression models were used to investigate the relationship of FAS with the risk of AD in UKB and ADNI. The "survival", "ggplot2", "pub", "gritty" and "survminer" packages were used for these analyses.

Next, multiple linear regression models were employed to explore the associations of FAS with cognition and hippocampal volume in UKB and ADNI. All dependent variables were checked for normal distribution. When dependent variables exhibited skewed distributions, Box-Cox transformation was applied to make the data meet or approximate normality (Kolmogorov-Smirnov test p-value > 0.01). Residuals were visually assessed for linearity, homoscedasticity, and normality. To further validate the cross-sectional findings, the linear mixed-effects (LME) models were used to depict the longitudinal relationship of FAS with cognitive decline, hippocampal atrophy, and changing rates of CSF biomarkers in ADNI. The LME models had random intercepts and slopes for time and an unstructured covariance matrix for the random effects, and included the interaction between time (continuous) and the dependent variable as predictors. Regression diagnostics were performed, and outliers were excluded to confirm that all models satisfied the required assumptions: residuals following a normal distribution and no signs of heteroscedasticity. In all the analyses mentioned above, covariate adjustments were made across three models: Model I (no variables were adjusted), Model II

(UKB: adjusted for age, gender, education, *APOE* ε4, and Townsend index; ADNI: adjusted for age, gender, education, *APOE* ε4, and baseline cognitive diagnosis [mild cognitive impairment vs. normal cognition]), and Model III (UKB: covariates from Model II plus depression, anxiety, hypertension, diabetes mellitus, hyperlipidemia, smoking, alcohol use, stroke, obesity, and cancer; ADNI: covariates from Model II plus depression, anxiety, hypertension, diabetes, smoking, stroke, obesity, and cancer). The "lm", "name", "ggplot2" and "car" packages were used to conduct the above analyses.

Mediation analyses were performed to investigate the mediating role of hippocampus in the relationship of FAS with cognitive function scores in UKB and ADNI. To strengthen the robustness of our findings, we calculated the longitudinal changing rates of hippocampal atrophy and cognitive decline based on LME models and performed mediation analysis on these rates in ADNI. Covariates were consistent with those used in Model II. Mediation analyses were executed using the "Mediation" package, employing nonparametric bootstrapping with 10,000 iterations to estimate direct effects (DE), indirect effects (IE), the proportion mediated, and associated *P*-values.

Moreover, interaction and stratified analyses by *APOE* ε4 status were performed to investigate whether the associations of FAS with AD risk, hippocampus, cognition, and CSF biomarkers was influenced by *APOE* ε4 status. As for the longitudinal interaction analyses, LME models were employed due to their suitability for managing unbalanced and censored data, as well as continuous time variables. Fixed effects included the primary effects of FAS, *APOE* ε4 status, and follow-up duration (time), in addition to interaction terms such as FAS × *APOE* ε4, time × FAS, time × *APOE* ε4, and the three-way interaction of time × FAS × *APOE* ε4. The overall significance of the three-way interaction was assessed using a likelihood ratio test by contrasting the full model with a nested model that excluded the three-way interaction term. Diagnostic evaluations of the regression models were conducted, with outliers removed to ensure that the assumptions of normality in residuals and homoscedasticity were met. Group differences were statistically examined by comparing model coefficients using the Wald test, executed via the 'aod' package.

Lastly, proteomic and bioinformatic analyses were conducted to explore the potential biological mechanisms through which FAS was associated with AD risk. Cox proportional hazards adjusting for covariates in Model II and logistic regression models adjusting for age and gender were used to identified differentially expressed proteins associated with AD risk and FAS, respectively. Bonferroni correction was applied to define statistical significance ($P < 1.71 \times 10^{-5}$, number of proteins tested = 2923). Mediation analyses were further used to assess the roles of the overlapped proteins in mediating the relationships of FAS with AD risk. Subsequently, functional enrichment analyses targeting these tagged proteins were performed using the STRING database (http://string-db.org). The Benjamini-Hochberg (BH) procedure was employed for multiple testing corrections. The False Discovery Rate (FDR) value indicates the significance of the enrichment. Finally, we selected the top 10 pathways with the lowest FDR values in each category for bubble mapping. In addition, we included the FDR correction as sensitivity analysis. These results are reported in the supplementary materials.

RESULTS

Construction and validation of fatty acid risk score

In UKB cohort ($N = 148{,}308$; median age 57 years; maximum follow-up = 16 years), participants with high FAS were older, were more likely to be female, had lower education levels, and had higher rates of obesity, hypertension, diabetes, smoking, and stroke ($P < 0.001$). In ADNI cohort ($N = 1193$; median age 74 years; maximum follow-up 8 years), participants with high FAS were more often female ($P = 0.004$). (Table 1).

Based on LASSO regression and cross-validation, a total of ten components were chosen, including MUFA, omega-6, omega-3, DHA, LA, the SFA to TFA ratio, the MUFA to TFA ratio, the omega-3 to TFA ratio, the LA to TFA ratio, and the omega-6 to omega-3 ratio. After excluding MUFA to TFA ratio and omega-3 which had negligible contributions in the nomogram, eight components were finally retained to construct the FAS (e-Fig. 1). When FAS was treated as continuous variable, higher FAS was significantly associated with an increased risk of AD (hazard ratio [HR] = 1.089, 95% confidence interval [CI] = 1.055–1.125, $P < 0.001$) in UKB cohort (Model II). The association still reached borderline significance in Model III (HR = 1.033, 95% CI: 0.998–1.070, $P = 0.064$). In ADNI, higher FAS was significantly associated with an increased risk of AD in both Model II (HR = 1.051, 95% CI: 1.018–1.085, $P = 0.002$) and Model III (HR = 1.047, 95% CI: 1.014–1.081, $P = 0.005$) (e-Table 1). Restricted cubic spline analysis supported the validity of the FAS high- and low-risk group stratification (e-Fig. 2). When FAS was treated as categorical variable, higher FAS was associated with higher risk of AD in Model II (HR = 1.298, 95% CI: 1.183–1.423, $P < 0.001$, Fig. 2A) and Model III. The associations were validated in ADNI (HR = 1.413, 95% CI 1.105–1.808, $P = 0.006$, Fig. 2B). The proportional hazards assumption for the Cox regression models in the UKB and ADNI cohort is presented in e-Fig. 3 and detailed in e-Table 2. No significant interaction by *APOE* ε4 status was found in both cohorts (e-Table 1). The stratified analysis by *APOE* ε4 status in two cohorts revealed that the association between FAS and AD risk remained significant in the *APOE* ε4 carrier group, but not in the non-carrier group (e-Table 3).

Higher FAS was associated with lower levels and faster decline of memory function

The characteristics of participants ($N = 13{,}035$ for UKB and $N = 1193$ for ADNI) included for analyses were given in the e-Table 4. The cross-sectional analyses showed that higher FAS was associated with worse numeric memory test performance (Model I, $\beta = -0.084$, $P < 0.001$) in UKB. The association reached borderline significance in Model II ($\beta = -0.036$, $P = 0.083$, Fig. 3A). In ADNI, individuals with higher FAS exhibited worse cognition, as indicated by a higher level of ADAS (Model II, $\beta = 0.122$, $P = 0.026$, Fig. 3B) and lower scores of MEM (Model II, $\beta = -0.101$, $P = 0.012$, Fig. 3C). The associations remained significant after controlling for more covariates (e-Table 5). Longitudinal analyses showed that higher FAS was associated with faster cognitive decline in memory (Model II, $\beta = -0.034$, $P < 0.001$, Fig. 3D). The association remained significant in Model III. Stratified analyses by *APOE* ε4 status showed that the association was significant only in the *APOE* ε4 carrier group ($\beta = -0.058$, $P < 0.001$, e-Table 6). No association was found for changing rates of general function (Model II, $\beta = 0.003$, $P = 0.812$, e-Table 7). No significant was found for interaction by *APOE* ε4 status (e-Table 8).

Higher FAS was associated with lower volume and faster atrophy of hippocampus

The characteristics of participants ($N = 22{,}626$ for UKB and $N = 977$ for ADNI) for analyses were given in the e-Table 9. Higher FAS was associated with lower volume of hippocampus at baseline (Model II, UKB: $\beta = -0.075$, $P = 5.83 \times 10^{-7}$, Fig. 3E; ADNI: $\beta = -0.119$, $P = 0.048$, Fig. 3F). Longitudinal analyses of ADNI data showed that individuals with higher FAS exhibited faster rates of hippocampal atrophy (Model II, $\beta = -0.024$, $P = 0.002$, Fig. 3G). The associations remained significant in Model III (e-Table 7). No significant interaction by *APOE* ε4 status was found in the longitudinal analysis (e-Table 8). However, subgroup analyses in ADNI showed that FAS was associated with hippocampus atrophy only in *APOE* ε4 carrier group ($\beta = -0.038$, $P = 0.003$, e-Table 6).

Higher FAS was associated with higher levels of CSF tau proteins

The characteristics of ADNI participants for CSF biomarker analyses were given in the e-Table 10. Individuals with higher FAS were older ($P = 0.021$), more often female ($P = 0.007$), and had a higher prevalence of *APOE* ε4 ($P = 0.035$). Among 870 participants with baseline data of CSF biomarker, 65.4% completed at least two follow-up evaluations over a maximum of 6 years. Higher FAS was linked to higher levels of CSF t-tau (Model II, $\beta = 0.183$, $P = 0.015$, Fig. 3I) and p-tau (Model II, $\beta = 0.197$, $P = 0.008$, Fig. 3J). The associations remained unchanged after controlling for more covariates (e-Table 5). No significant correlation was found

Table 1. Characteristics of participants.

Characteristics	UKB				ADNI			
	Total (*N* = 148,308)	**High-risk group (*N* = 37,077)**	**Low-risk group (*N* = 111,231)**	***p*-value**	**Total (*N* = 1193)**	**High-risk group (*N* = 298)**	**Low-risk group (*N* = 895)**	***p*-value**
Age, Years, (median [IQR])	57.00 [50.00, 62.00]	60.00 [53.00, 64.00]	56.00 [49.00, 62.00]	<0.001	74.00 [69.00, 78.00]	74.00 [69.25, 79.00]	73.00 [69.00, 78.00]	0.081
Female (%)	66,742 (45.00)	19,460 (52.49)	47,282 (42.51)	<0.001	528 (44.26)	154 (51.68)	374 (41.79)	0.004
APOE4 (%)	42,279 (28.51)	10,184 (27.47)	32,095 (28.85)	<0.001	512 (42.92)	141 (47.32)	371 (41.45)	0.088
MCI (%)	–	–	–	–	737 (61.78)	192 (64.43)	545 (60.89)	0.308
TDI (median [IQR])	−2.49 [−3.83, −0.24]	−2.43 [−3.80, −0.11]	−2.50 [−3.84, −0.29]	<0.001	–	–	–	–
Education, Years, (median [IQR])	13.00 [11.00, 22.00]	12.00 [11.00, 22.00]	14.00 [11.00, 22.00]	<0.001	16.00 [14.00, 18.00]	15.00 [13.00, 18.00]	16.00 [14.00, 18.00]	<0.001
Alcohol (%)	112 (0.08)	30 (0.08)	82 (0.07)	0.737	–	–	–	–
Anxiety (%)	1950 (1.32)	448 (1.22)	1502 (1.36)	0.043	68 (5.70)	13 (4.36)	55 (6.15)	0.315
Obesity (%)	51,305 (34.84)	19,050 (51.82)	32,255 (29.19)	<0.001	420 (35.21)	93 (31.21)	327 (36.54)	0.11
Cancer (%)	1631 (1.11)	435 (1.18)	1196 (1.08)	0.116	194 (16.26)	47 (15.77)	147 (16.42)	0.862
Depression (%)	7703 (5.23)	2048 (5.57)	5655 (5.12)	0.001	250 (20.96)	52 (17.45)	198 (22.12)	0.102
Diabetes (%)	5430 (3.69)	3576 (9.73)	1854 (1.68)	<0.001	97 (8.13)	24 (8.05)	73 (8.16)	0.99
Hyperlipidemia (%)	15,871 (10.78)	9544 (25.96)	6327 (5.73)	<0.001	–	–	–	–
Hypertension (%)	34,269 (23.27)	14,348 (39.03)	19,921 (18.03)	<0.001	554 (46.44)	144 (48.32)	410 (45.81)	0.493
Smoke (%)	90,173 (61.24)	24,255 (65.98)	65,918 (59.66)	<0.001	209 (17.52)	37 (12.42)	172 (19.22)	0.01
Stroke (%)	1313 (0.89)	733 (1.99)	580 (0.52)	<0.001	51 (4.27)	13 (4.36)	38 (4.25)	0.95

Mann-Whitney U test (for continuous variables with a non-normal distribution), student t test (for continuous variables with a normal distribution) and χ^2 tests (for categorical variables) were used to test the difference of baseline characteristics.

UKB UK biobank, *ADNI* Alzheimer's disease neuroimaging initiative, *TDI* townsend deprivation index, *MCI* mild cognitive impairment.

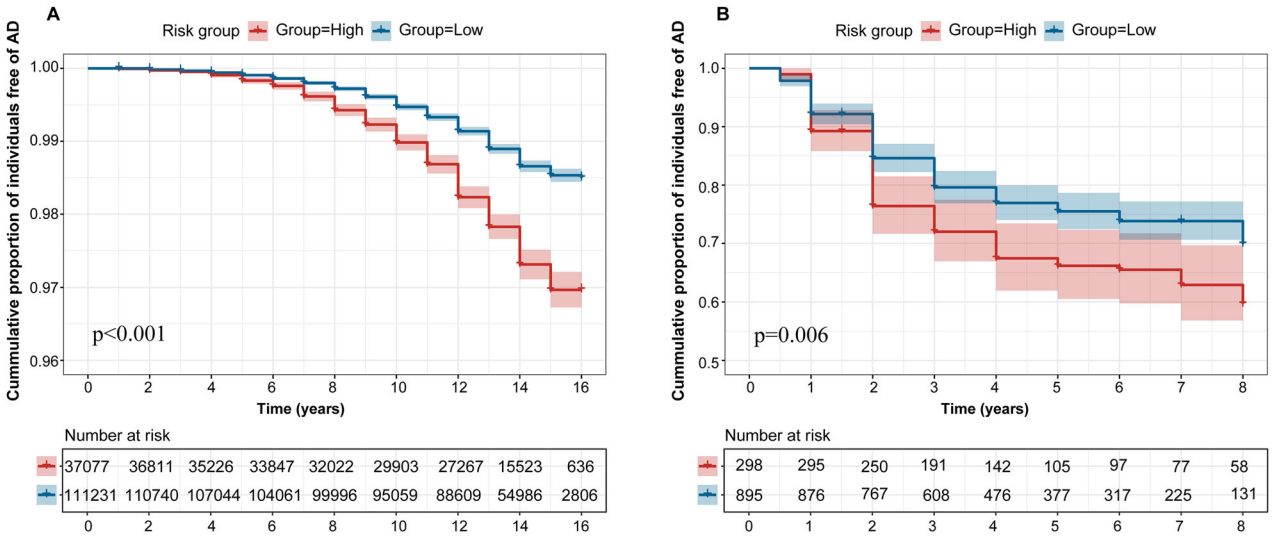

Fig. 2 Relationship between fatty acid score and incident risk of AD. Higher fatty acid score was associated with elevated risk of AD in UKB **A** and ADNI **B**.

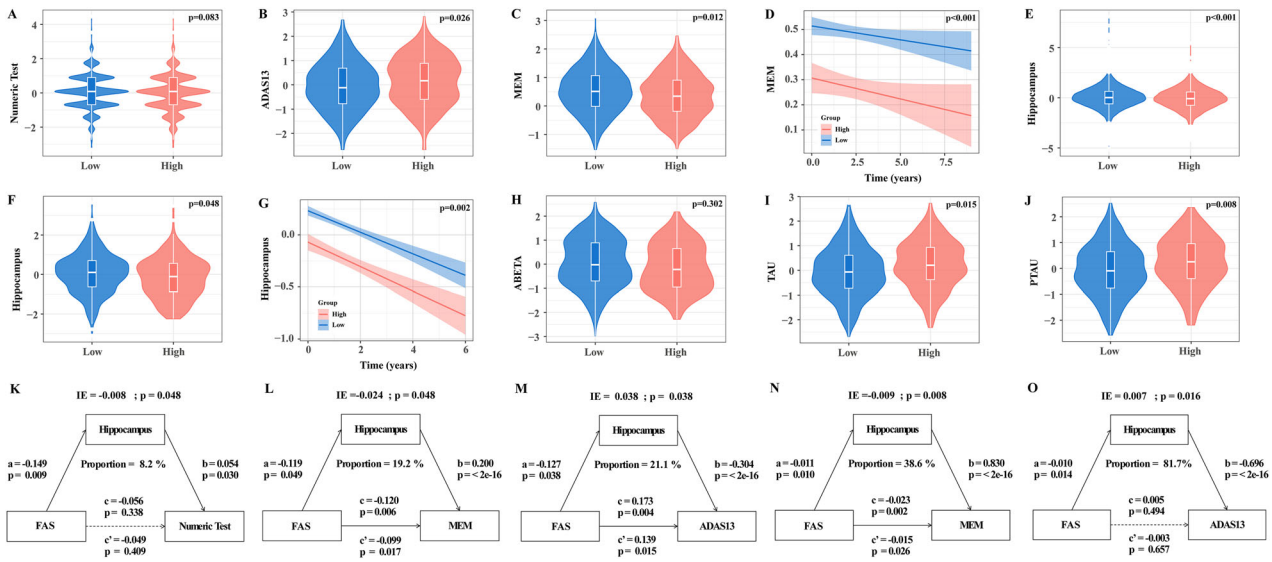

Fig. 3 Hippocampal volume mediated the relationship of fatty acid score with memory function. In UKB, numeric memory test scores were lower in the high-risk group, with marginal statistical significance **A**. In ADNI, ADAS **B** was higher and MEM **C** was lower in the high-risk group, with a faster rate of MEM decline **D**. Hippocampal volume was lower in the high-risk group in both UKB **E** and ADNI **F**, with a faster rate of decline in ADNI **G**. In ADNI, Aβ levels showed no difference **H**, while tau **I** and p-tau **J** were higher in the high-risk group. In mediation analyses, no significant mediation was found in UKB **K**, but in ADNI, hippocampal volume mediated effects on MEM **L** and ADAS **M**. Longitudinal analysis in ADNI showed hippocampal changes mediated MEM decline **N**, but not ADAS **O**. AD Alzheimer's disease, ADAS Alzheimer's Disease Assessment Scale, MEM memory function, Numeric Test numeric memory test, IE indirect effect.

between FAS and CSF $A\beta_{1-42}$ at baseline ($P = 0.302$, Fig. 3H). Though no longitudinal relationships were uncovered of FAS with CSF AD markers (e-Table 7), the likelihood ratio test indicated that the three-way interaction of FAS × *APOE* ε4 × time accounted for a significant amount of variance in CSF $A\beta_{1-42}$ (Model II, $P = 0.017$, e-Fig. 4A), t-tau protein (Model II, $P = 0.013$, e-Fig. 4B), and p-tau protein (Model II, $P = 0.032$, e-Fig. 4C). Specifically, compared to other groups, a greater rate of CSF t-tau or p-tau increase ($\beta = 0.04$, $P = 0.032$) was observed in the *APOE* ε4 carriers with higher FAS group (e-Table 6).

The association of FAS with cognition was mediated by hippocampus volume

In UKB, potential mediating effects of hippocampus were found on the relationship of FAS with numeric test scores ($P = 0.048$, Fig. 3K). In ADNI, hippocampus volume mediated the relationship of FAS with MEM ($P = 0.048$, proportion = 19.2%, Fig. 3L) and ADAS ($P = 0.038$, proportion = 21.1%, Fig. 3M) scores. Furthermore, the relationship of FAS with changing rates of MEM ($P = 0.008$, proportion = 38.6%, Fig. 3N) but not ADAS ($P = 0.016$, proportion = 81.7%, Fig. 3O) was mediated by the atrophy rate of hippocampus.

Proteomic and bioinformatics analyses to reveal biological pathways

After Bonferroni correction ($P < 1.71 \times 10^{-5}$), we uncovered 16 proteins associated with AD risk (Fig. 4A) and 968 proteins associated with higher FAS (Fig. 4B). The Venn diagram illustrated four overlapping proteins that were positively correlated with both AD risk and higher FAS, including ADGRG1, CHI3L1, GDF15,

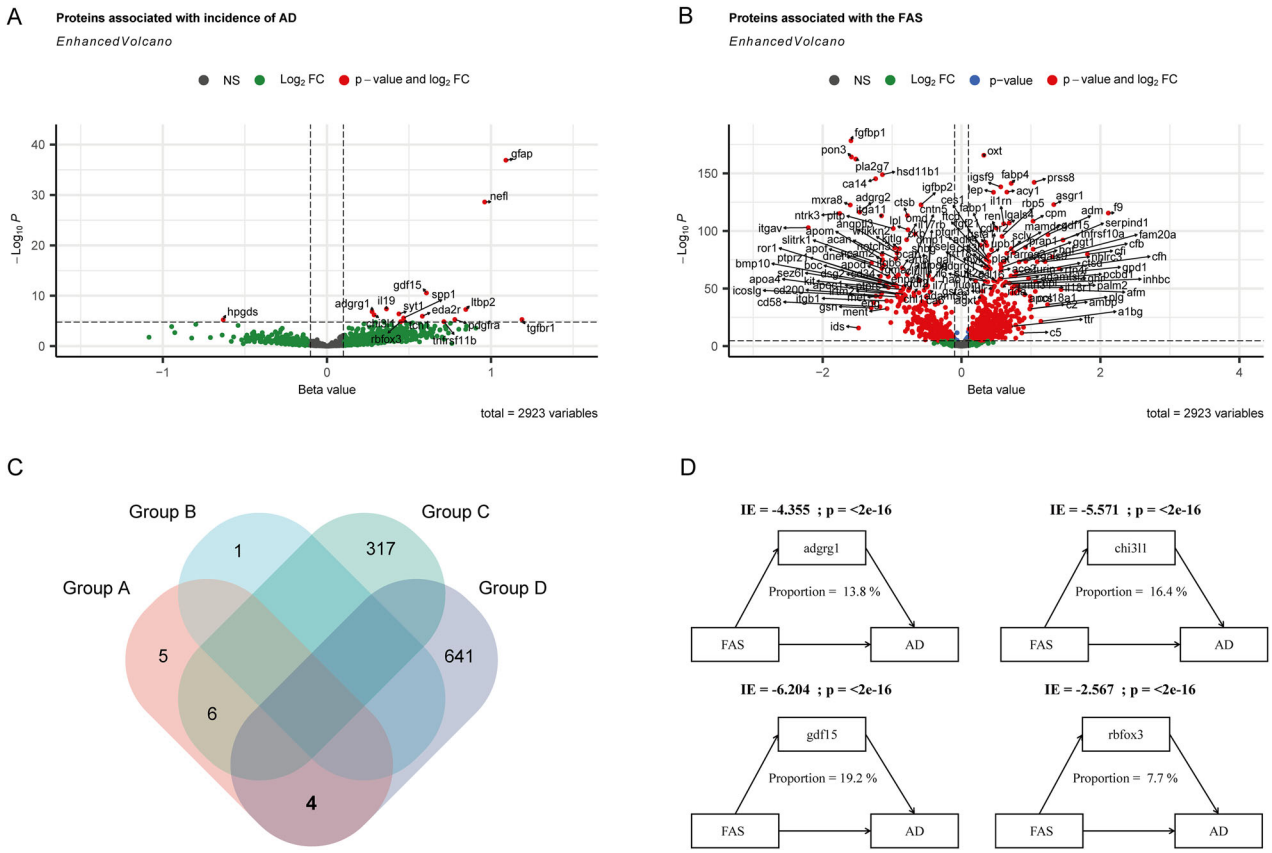

Fig. 4 Screening of overlapping differential proteins and their mediating effects on AD risk. Volcano plots of proteins associated with AD incidence **A** and FAS **B**. The Venn diagram illustrated the differential proteins among the four groups. Group A: proteins positively associated with AD incidence; Group B: proteins negatively associated with AD incidence; Group C: proteins negatively associated with higher FAS; Group D: proteins positively associated with higher FAS. Four overlapping proteins (adgrg1, chi3l1, gdf15, and rbfox3) were shared between Groups A and D, indicating significant relevance to both AD incidence and higher FAS. **C**. Mediation analyses indicated that the relationship between FAS and AD risk was mediated by screening differential proteins **D**. FAS Fatty acid score, IE indirect effect.

and RBFOX3 (Fig. 4C). We found that the relationships of FAS with AD risk were mediated by these four proteins (proportion ranging from 7.7–19.2%, $P < 2 \times 10^{-16}$, Fig. 4D). Because no significant protein-protein interaction (PPI) enrichment was found ($P = 0.053$), we separately explored the underpinning pathways for each protein. RBFOX3 is markedly involved in nervous system development, with significant emphasis on brain regions like the dentate gyrus, subventricular zone, and hippocampus (Fig. 5A). ADGRG1 is enriched in key pathways, including dopamine receptor signaling and G protein-coupled receptor (GPCR) signaling pathways (Fig. 5B). GDF15 is primarily involved in pathways like the glial cell-derived neurotrophic factor receptor signaling pathway and transforming growth factor beta receptor signaling pathway (Fig. 5C). The CHI3L1 bubble chart highlights its pivotal role in immune response, cytokine signaling, and inflammatory pathways, including cytokine and inflammatory responses, cytokine-cytokine receptor interactions, and regulation of leukocyte activation (Fig. 5D). FDR-corrected proteomics and bioinformatics results are presented in e-Fig. 5 and e-Table 11.

DISCUSSION

In this study, we 1) developed and validated a blood fatty acid score associated with AD risk, 2) confirmed the relationships of the scores with cognitive decline, hippocampus, and CSF AD markers, especially among *APOE* ε4 carriers, 3) found that hippocampal neurodegeneration could mediate the effects of FAS on cognition, and 4) uncovered several pathways, such as inflammatory pathways and neurogenesis, that were potentially responsible for bridging the relationship between blood fatty acids and AD occurrence. Overall, these findings underscored critical roles of blood fatty acid metabolic homeostasis in contributing to AD development.

Several fatty acid components included for the FAS calculation were also previously related to AD risk, such as omega-3 fatty acids family and SFAs [16, 40]. Elevated omega-3 levels were considered to mitigate the risk of dementia [15, 41], whereas SFAs were associated with cognitive decline and an increased risk of AD [40, 42]. While these results underscored the roles of omega-3 fatty acids and SFAs in AD risk, integrating these key fatty acids into a comprehensive risk score offered a more holistic approach. By integrating these key fatty acids into a comprehensive risk score, we for the first time offered a practical tool for clinicians to assist in risk assessment. In future trials, this scoring system might be used to evaluate the efficacy of dietary interventions or fatty acid supplementation in AD prevention.

As indicated by the proteomic analyses, the mechanisms by which blood fatty acids were involved in AD occurrence included multiple processes, such as modulation of neuroinflammatory pathways, promotion of synaptic plasticity, and neurogenesis [24, 43, 44]. CHI3L1 was found as a critical differential protein linking fatty acids to AD. CHI3L1 was primarily expressed in reactive astrocytes and microglia, acting as a key driver of neuroinflammation in AD pathogenesis [45]. In genetically modified mice models, high-fat diet feeding markedly increased CHI3L1 mRNA and protein expression in white adipose tissue and lung [46]. Mechanistically, SFAs might activate the TLR4–MyD88–IKK axis, leading to NF-κB [47–49] induction and

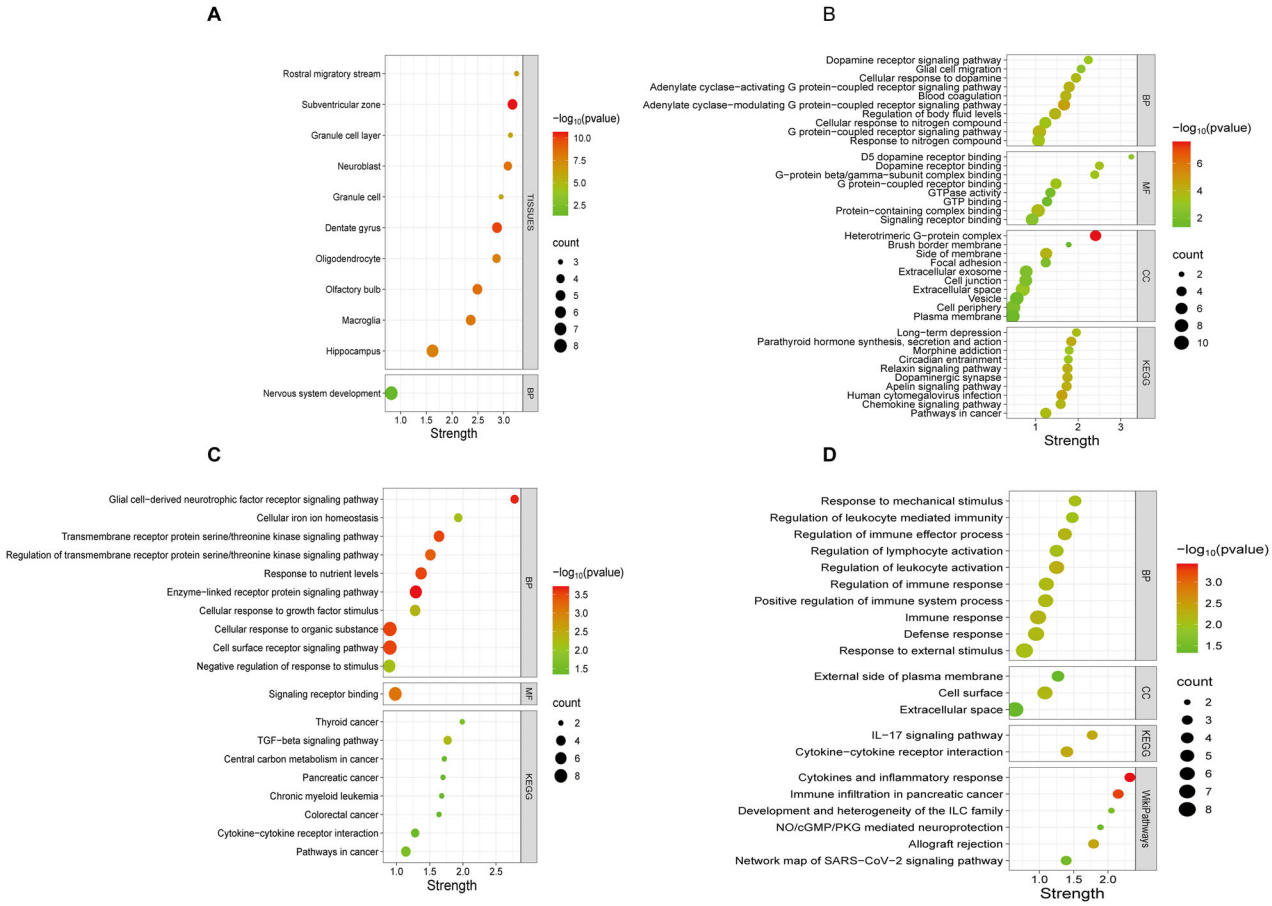

Fig. 5 Enrichment pathways for differential proteins. The enrichment bubble diagram showed functional and pathway analysis of four proteins, displaying the top 10 terms with the lowest *p*-values. The y-axis represented enriched pathways, the x-axis showed the gene ratio, the bubble color indicated the *p*-value, and the size reflected the number of enriched genes. KEGG, other pathways, and GO enrichment analyses were shown for enriched pathways associated with RBFOX3 **A**, ADGRG1 **B**, GDF15 **C**, and CHI3L1 **D**.

subsequent upregulation of CHI3L1 [50]. CHI3L1 then engages IL-13Rα2 and RAGE, triggering MAPK/ERK and PI3K–Akt signaling cascades [45] that exacerbate neuroinflammation and amyloid-β–associated inflammatory responses, thereby aggravating AD pathology. In contrast, unsaturated fatty acids (UFAs) activate PPARγ [51] and Nrf2 [52] pathways, suppress NF-κB signaling, and downregulate CHI3L1 expression [53]. Therefore, we hypothesize that modulation of CHI3L1 by distinct fatty acid species could regulate neuroinflammatory processes and thus influence AD progression. The disruption of SFA/UFA balance could amplify CHI3L1-mediated inflammation through NF-κB pathways, immune activation, and cytokine release. Future animal studies are needed to validate these hypotheses. Similarly, GDF15 is induced in response to cellular stress, mitochondrial dysfunction, and inflammation to maintain cellular and tissue homeostasis [54]. Saturated fatty acids promote GDF15 expression and secretion in human macrophages through inducing ER stress and activating the PERK/eIF2/CHOP signaling pathway [55]. Subsequently, GDF15 alleviates neuroinflammation and energy metabolism by inhibiting the TAK1/IKK/NF-κB cascade [56] and modulating GFRAL-mediated central metabolic routes [57], thereby indirectly mitigating amyloid-β and tau pathologies. It could be reasonably postulated that neuroinflammation could at least partially underpin the association of blood fatty acid with AD.

ADGRG1 is an adhesion G protein-coupled receptor closely associated with developmental processes [58]. Although no studies have directly examined the relationship between fatty acids and ADGRG1. Other adhesion GPCRs such as GPR116 and GPR97 have been implicated in lipid homeostasis and high-fat diet–induced metabolic changes [59, 60], suggesting potential roles for ADGRG1 in fatty acid regulation. We hypothesize that ADGRG1 may act as a novel lipid-regulatory receptor. Its intracellular G protein–coupled domains activate downstream cAMP and RhoA signaling networks [61], influencing metabolic homeostasis. Notably, beyond its potential role in lipid metabolism, ADGRG1 has also been implicated in immune regulation. ADGRG1 has been shown to regulate the cytotoxicity of natural killer (NK) cells [58]. As sentinels of the immune system, NK cells are pivotal in the early coordination of local inflammatory responses and have profound implications for the onset and progression of neuroinflammation in aging and AD-related neurodegenerative disease [62]. Fatty acids may engage ADGRG1 through ligand binding or co-regulatory mechanisms, thereby modulating NK cell–mediated inflammatory responses to drive Alzheimer's disease pathogenesis. Elucidating this axis could inform novel therapeutic strategies targeting both lipid metabolism and immune regulation in AD.

In addition, our mediation analyses revealed that hippocampal volume mediated the relationship between fatty acids and cognition, especially memory function. This aligned with previous research linking fatty acids to hippocampus. High-fat diets were reported to trigger neuroinflammation in the hippocampus, promoting its atrophy and cognitive decline [25, 63]. Elevated blood levels of omega-3 were instead associated with less hippocampal atrophy, better cognitive performance, and reduced risk of cognitive decline in the elderly [64]. These results

emphasized the modulation effects of fatty acid profile on neurodegeneration in hippocampus. The possible mechanisms included neuroinflammation, synaptic activity, and neurogenesis [65]. Interestingly, our bioinformatics analyses identified RBFOX3 as a key bridging protein, which was enriched in pathways critical for hippocampal neurogenesis and synaptic plasticity in subventricular zone and dentate gyrus. These regions are vital for neuronal differentiation, synaptic remodeling, and cognition [66]. RBFOX3 is crucial for neurogenesis and synaptogenesis, with knockout models showing deficits in synaptic plasticity and cognition [67]. RBFOX proteins also supported neuronal maturation and axon assembly, which were critical for neuron integration into circuits [68]. We thus inferred that one key pathway by which blood fatty acids influenced cognition was by regulating RBFOX3 and enhancing synaptic plasticity. Regrettably, there have been no studies confirming that fatty acids or their metabolites can regulate the expression of RBFOX3. Future studies should investigate the impact of fatty acids on RBFOX3 expression. Gene knockout techniques could be employed to investigate whether the effects of fatty acids on synaptic function are mediated through RBFOX3, in both in vivo and in vitro models.

The interaction of fatty acids such as omega-3 with *APOE* ε4 gene has been a controversial topic in the field. We previously reported the cognitive and pathological benefits of omega-3 supplementation were depending on presence of *APOE* ε4 [22], while others reported greater benefits in individuals with lower genetic risk [69, 70]. In the present study, we found that the associations of FAS with AD were more pronounced among *APOE* ε4 carriers, reinforcing the idea that *APOE* ε4 may amplify the effects of fatty acids on AD [14, 22]. Two mechanisms could help explain the interaction effect. Firstly, *APOE* ε4 is associated with reduced delivery of DHA to the brain [21], which may limit the protective effects of beneficial fatty acids. Secondly, dietary fatty acids have been shown to modulate microglial states, thereby influencing neuroinflammation and contributing to AD-related neuropathology [71]. Similarly, *APOE* ε4 may cause overactivation of microglia and the release of pro-inflammatory cytokines, leading to neuronal damage and tau hyperphosphorylation [72]. The combined effects of imbalanced fatty acid ratios and *APOE* ε4 may amplify neuroinflammation, thereby exacerbating the progression of AD. However, this *APOE* ε4 × FAS interaction should be interpreted cautiously, considering several important limitations: First, as an observational study, causal inference is difficult; the interaction may reflect shared upstream determinants rather than a true biological synergism. Second, residual confounding by unmeasured factors—such as dietary patterns, or other genetic variants—could influence both fatty acid profiles and AD risk. Finally, statistical interaction does not necessarily imply mechanistic interaction, and replication in independent cohorts with more detailed phenotyping will be necessary to confirm these findings.

Our study demonstrated several strengths. First, we constructed a risk score by rigorously screening blood fatty acids profile associated with AD risk. This comprehensive approach allows for a thorough evaluation of the interactions among various fatty acids. Second, the association of FAS with AD was validated across independent cohorts from two different continents, enhancing the generalizability and reliability of our findings. Third, multiple methods were further used to explore the potential mechanisms. There were several limitations. First, plasma fatty acids can fluctuate with dietary intake, which may not accurately represent the accumulating levels of fatty acid during the follow-up. Second, the associations or the pathways were based on the observational study but not equal to the causal relationship. Future experiments were warranted to test the hypothesis in the future. Third, the absence of CSF data and ATN-based AD confirmation in UKB remains a key limitation of our study. Future studies should leverage multicenter cohorts with multimodal data (CSF, PET, and plasma biomarkers) to confirm these findings. Fourth, differences in ethnicity between ADNI and UKB may limit generalizability. Future studies should include multi-ethnic cohorts and adjust for ancestry to minimize confounding.

CONCLUSION

Overall, our study developed and validated a blood fatty acid score associated with incident AD risk in two dependent cohorts. The potential underpinning mechanisms could be hippocampal neurodegeneration, neuroinflammation, neurogenesis, and synaptic plasticity. Future researches are needed to further validate this risk score in more community-based populations as well as in the clinic settings.

DATA AVAILABILITY

All data are available upon reasonable request or can be obtained from the UKB (https://biobank.ctsu.ox.ac.uk/) and Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

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AUTHOR CONTRIBUTIONS

Dr. Wen-Zheng Liu and Dr. Liang-Yu Huang: analysis of the data, drafting and revision of the manuscript, and prepared all the figures. Prof. Lan Tan, Prof. Chen-Chen Tan, Prof. Song Chi, and Dr Ya-Hui Ma: revision of the manuscript. Prof. Wei Xu: conceptualization and design of the study, analysis of the data, drafting and revision of the manuscript. Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The UKB and ADNI were approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants or authorized representatives according to the 1975 Declaration of Helsinki. All methods in this study were performed in accordance with the relevant guidelines and regulations, and the UK Biobank has approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank (RTB) approval. Researchers with approved access operate under the RTB approval and do not require separate ethical approval. The ADNI was approved by the Institutional Review Boards (IRB) all participating centers.

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