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RESEARCH ARTICLE

Omega-3 blood biomarkers relate to brain glucose uptake in individuals at risk of Alzheimer's disease dementia

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Abstract

INTRODUCTION: Brain glucose hypometabolism is a preclinical feature of Alzheimer's disease (AD). Dietary omega-3 fatty acids promote brain glucose metabolism, but clinical research is incipient. Circulating omega-3s objectively reflect their dietary intake.

METHODS: This was a cross-sectional study in 320 cognitively unimpaired participants at increased risk of AD dementia. Using lipidomics, we determined blood docosahexaenoic (DHA) and alpha-linolenic (ALA) acid levels (omega-3s from marine and plant origin, respectively). We assessed brain glucose metabolism using [18-F]-fluorodeoxyglucose (FDG) positron emission tomography (PET).

RESULTS: Blood ALA directly related to FDG uptake in brain areas known to be affected in AD. Stronger associations were observed in apolipoprotein E ε4 carriers and homozygotes. For DHA, significant direct associations were restricted to amyloid beta–positive tau-positive participants.

DISCUSSION: Blood omega-3 directly relate to preserved glucose metabolism in AD-vulnerable brain regions in individuals at increased risk of AD dementia. This adds to the benefits of omega-3 supplementation in the preclinical stage of AD dementia.

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KEYWORDS
biomarkers, diet, fatty fish, fish oil, n-3 fatty acids, nuts, polyunsaturated fatty acids, walnuts

Highlights

- Blood omega-3s were related to brain glucose uptake in participants at risk of Alzheimer's disease (AD) dementia.
- Complementary associations were observed for omega-3 from marine and plant sources.
- Foods rich in omega-3 might be useful in early features of AD.

1 | BACKGROUND

In sporadic Alzheimer's disease (AD), brain changes take place much before the onset of clinical symptomatology.[1] Brain glucose hypometabolism is a feature of AD forerunning clinical symptoms.[2] Positron emission tomography with fluorine-18 fluorodeoxyglucose ([18-F]-FDG PET) has been instrumental for better mapping patterns of altered brain glucose metabolism within the AD continuum. Reduced uptake of [18-F]-FDG in the so-called Landau signature (comprising right and left angular gyri, right and left inferior temporal gyri, and bilateral posterior cingulate) is widely regarded as a predictor of AD dementia.[3]

Preventive nutritional interventions during mid-life might contribute to prevent or ameliorate cerebral bioenergetic dysfunction associated to AD dementia.[2] Docosahexaenoic acid (C22:6n-3, DHA) is an omega-3 fatty acid naturally found in fatty fish, and highly enriched in the brain membranes.[4] DHA plays a key role in many brain functions.[5] There is a large body of experimental research on the role of DHA and other omega-3s in promoting brain glucose metabolism at the molecular, mitochondrial, cellular, and whole brain levels.[6] However, the gap between experimental and clinical research focused on AD on the topic persists, as the effect of dietary omega-3 on brain glucose has only been tested with FDG PET before and after 3 weeks of omega-3 supplementation in healthy young and elderly adults.[7]

In contrast to marine-derived omega-3 fatty acids, the plant-derived omega-3 alpha-linolenic acid (C18:3n-3, ALA) has been largely unexplored in relation to AD. Although ALA has been long believed to merely act indirectly via marginal conversion to DHA,[8] there is increasing evidence that ALA intake might promote brain health on its own.[9] Research on ALA and cognition is highly relevant because plant omega-3 sources are sustainable, widely available, and inexpensive, and because ALA may be particularly important to populations with poor access to seafood and to vegan and vegetarian individuals.

In the present observational study, we hypothesized that in a middle-aged cognitively unimpaired population at increased risk of AD dementia, dietary intake of omega-3 fatty acids from either marine (DHA) or plant (ALA) origin would relate to a preserved glucose uptake in AD-vulnerable brain regions. To test our hypothesis, we determined the proportions of DHA and ALA in red blood cells (RBCs) by gas chromatography (an objective and valid surrogate biomarker of omega-3 dietary intake, absorption, and metabolism, not affected by the inaccuracy of methods based on self-reported data[10]), and examined their association with [18-F]-FDG uptake in the Landau signature and, exploratorily, in the whole brain.

2 | METHODS

2.1 | Study participants

The present study was performed in the ALFA+ cohort, a nested longitudinal study to the ALFA (for Alzheimer's and Families) study.[11] The ALFA+ study (ALFA-FPM-0311) was approved by the Independent Ethics Committee "Parc de Salut Mar," Barcelona, and registered at ClinicalTrials.gov (identifier: NCT02485730). All participants signed the study's informed consent form that had also been approved by the same independent ethics committee. The ALFA+ study includes 419 middle-aged (45–65) individuals, who were invited to participate on the basis of their specific high AD risk profile, determined by an algorithm considering participants' AD parental history, apolipoprotein E (*APOE*) status, verbal episodic memory score, and CAIDE (cardiovascular risk factors, aging and dementia) score. ALFA+ exclusion criteria were (1) cognitive impairment (Clinical Dementia Rating score > 0, Mini-Mental State Examination score < 27, or semantic fluency < 12), (2) any significant systemic illness or unstable medical condition that could lead to difficulty complying with the protocol, (3) any contraindication to any test or procedure, and (4) family history of monogenic AD. At baseline, besides reporting sociodemographic, clinical, and lifestyle data,[11] ALFA+ participants underwent an extended cognitive testing and magnetic resonance imaging (MRI) protocol, a lumbar puncture to obtain cerebrospinal fluid (CSF), as well as [18-F]-FDG PET. We excluded *APOE* $\varepsilon 2$ carriers ($n = 28$) due to the low sample size and because this allele promotes brain glucose metabolism.[12] Therefore, in this substudy, we included 320 participants with available RBC omega-3 data and [18-F]-FDG PET scans. The time interval between blood sampling and [18-F]-FDG PET acquisition ranged from 31 to 1151 days (median = 154 days; interquartile range [IQR] = 106 and 276 days). A subset of participants ($n = 304$) also had available CSF biomarker data.

The time interval between blood sampling and CSF sampling ranged from 0 to 815 days (median = 35 days; IQR = 20 and 72 days).

2.2 | Sample collection and biomarker measurements

Whole blood was drawn with a 20G or 21G needle gauge into a 10-mL ethylenediaminetetraacetic acid (EDTA) tube (BD Hemogard, 10 mL, K_2EDTA, catalog no. 367525). Tubes were gently inverted 5 to 10 times and stored at −80 °C until the fatty acid analysis, which was conducted at Hospital del Mar Research Institute (Barcelona, Spain). Forty microliters of EDTA-collected whole blood was spiked with 10 µg of the internal standard (ISTD) 1,2-dinonadecanoyl-sn-glycero-3-phosphocholine (Avanti, Merck) into a chloroform-resistant Eppendorf containing 700 µL of distilled water. Once cells were hemolyzed, they were spun for 5 minutes at 4°C at 2800 g in a microcentrifuge (Hermle Z 233 MK-2; Midwest Scientific). The supernatant (containing hemoglobin and serum lipids) was discarded, and the pellet (consisting of > 99.5% of RBC membranes) was extracted with chloroform–methanol (2:1, v/v) containing butylated hydroxytoluene (50 mg/mL) and evaporated to dryness under N_2, at 37°C. The lipid extract was redissolved in 1 mL boron trifluoride–methanol and transferred to a screw-cap test tube, which was heated for 10 minutes at 100°C to hydrolyze and methylate the membrane glycerophospholipid fatty acids. The extracts were cooled at 25°C, and fatty acid methyl esters (FAMEs) were isolated by adding 300 µL of n-hexane. After shaking for 1 minute, 1 mL of a saturated NaCl solution was added, and the tubes were centrifuged for 10 minutes at 2200 g at room temperature to separate the layers. The upper (hexane) layer was removed and a 50 µL aliquot was transferred into an automatic injector vial equipped with a volume adapter of 300 µL. FAMEs were analyzed by gas chromatography/electron ionization mass spectrometry (GC-MS), using an Agilent 6890N GC equipped with an Agilent 7683 autosampler, and an Agilent 5973N mass spectrometry detector. FAMEs were separated with a J&W DB-FastFAME capillary column (30 m × 0.2 mm × 0.25 µm film thickness; Agilent) and detected using the selected ion monitoring (SIM) mode. Based on the work of Thurnhofer and Vetter,[13] several m/z ions common to saturated, monounsaturated, and polyunsaturated FAMEs were monitored. Twelve mixtures of FAME external calibration standards, spiked with C19:0-methyl ester in an equivalent amount to that included in samples as phospholipid, were prepared by diluting FAME mix certified reference material (Supelco 37 Component FAME Mix, Merck) in hexane. The concentrations of FAMEs in the samples were calculated by linear regression of the peak area ratio relative to that of the internal standard. The amount of each omega-3 of interest is expressed as a percentage of the total amount of 24 determined fatty acids.

CSF sample collection and processing followed standard procedures[14] and have been described previously.[15] CSF levels of amyloid beta (Aβ)42[16] and Aβ40 were measured with the prototype NeuroToolKit (Roche Diagnostics International Ltd.) on a cobas e 411 instrument. Phosphorylated tau at threonine 181 (p-tau)[17] was measured using Elecsys electrochemiluminescence immunoassays on a fully automated cobas e 601 instrument (Roche Diagnostics International Ltd.). Individuals were classified into amyloid/tau (AT) groups[18] using cutoffs of CSF Aβ42/40 ratio (A+: < 0.071) and p-tau (T+: > 24 pg/mL), which have been previously validated for research purposes.[15] All CSF biomarker measurements were analyzed at the Clinical Neurochemistry Laboratory at the University of Gothenburg, Sweden.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed), preprinted (e.g., medRxiv), as well as presentations and posters from the annual Alzheimer's Association International Conference. Experimental research supports the view that dietary omega-3 fatty acids, in particular docosahexaenoic acid (DHA, the main marine omega-3) promotes brain glucose metabolism at a molecular, mitochondrial, cellular, and whole brain level.
2. **Interpretation**: Red blood cell proportion of alpha-linolenic acid (ALA, the main plant-derived omega-3), which objectively reflects its dietary intake, was associated with more preserved glucose uptake in brain areas vulnerable to hypometabolism in Alzheimer's disease (AD), in particular in individuals with higher apolipoprotein E ε4 allele load. Red blood cell proportion of DHA related to glucose uptake in amyloid beta–positive tau-positive participants, suggesting that DHA might increase brain resistance to AD pathology.
3. **Future directions**: This study encourages further clinical investigations on the potential effect of omega-3–rich foods in early features of AD.

2.3 | Image data acquisition and preprocessing

A high-resolution 3D T1 weighted MRI sequence was acquired in a 3 T Philips Ingenia CX scanner (echo time/repetition time = 4.6/9.9 ms, flip angle = 8°; voxel size = 0.75 × 0.75 × 0.75 mm^3). [18-F]-FDG PET scans were acquired for 20 minutes (4 frames of 5 minutes each) 45 minutes (mean ± standard deviation [SD] 45.69 ± 4.67 minutes) after the administration of 185 MBq (range 181.3–222 MBq; mean ± SD, 200.83 ± 12.83 MBq) of [18-F]-FDG in a Siemens Biograph mCT scanner. PET images were reconstructed using the 3-dimensional ordered subset expectation maximization algorithm by incorporating time of flight and point spread function modeling. Quantification of FDG uptake in Landau's signature was performed by calculating the standardized uptake value ratio (SUVR) within a metaregion of interest (meta-ROI composite) including right and left angular gyri, right and

left middle/inferior temporal gyrus, and bilateral posterior cingulate gyrus.[3] To this end, [18-F]-FDG PET scans were first co-registered to the corresponding T1-weighted MRI scans at the MRI subject space, and then were normalized into standard Montreal Neurological Institute (MNI) space with SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).[19] SUVR values were calculated as the ratio between the average FDG uptake in the meta-ROI voxels and those of the cerebellar vermis, as the reference region. Unsmoothed images were used to calculate Landau's meta-ROI SUVR, whereas parametric SUVR images were calculated with the smoothed images (Gaussian kernel of 8 mm full-width half maximum) for voxel-wise analyses.

2.4 | Self-reported dietary intake

Participants were asked to provide dietary data by completing a web-based self-administered food frequency questionnaire. This validated questionnaire has a closed list of 166 items representing typical foods in northeastern Spain.[20] For each food item, participants were asked to indicate their usual consumption from nine frequency categories, ranging from never or less than once per month to ≥ 6 times/day. The questionnaire also contained an open section to admit additions to the food list for foods, beverages, and nutritional supplements not included in the closed list of food items. Intakes were converted to mean grams per day using standard reference portion sizes, defined by natural (e.g., 1 orange, 1 slice of bread) or household units (e.g., 1 spoon, 1 cup, 1 glass). We computed intakes of energy using Spanish food composition tables and the Medisystem 2000 software (Conaycite). After further excluding participants with incomplete dietary data ($n = 49$) and those who reported total energy intake outside predefined limits (> 4000 or < 800 kcal/d in men and > 3500 or < 500 kcal/d in women,[21] $n = 22$), 249 participants remained in the present analyses.

2.5 | Statistical analyses

We expressed categorical variables as frequencies and percentages, whereas quantitative variables following a normal distribution were expressed as mean (95% confidence interval [CI]). The normal distribution of continuous variables was assessed by the Kolmogorov–Smirnov test. Skewed variables, which are reported as medians and IQRs, were rank-transformed for further parametric analyses.

We constructed regression models to search for associations between RBC DHA (predictor 1) and RBC ALA (predictor 2) and Landau's meta-ROI [18-F]-FDG SUVR (outcome). For each predictor, Model 1 was adjusted for age, sex, years of education, days between blood sampling and [18-F]-FDG PET acquisition, and *APOE* ε4 carriership. We tested the distinct models of *APOE* ε4 penetrance, namely the dominant (ε4 carriers vs. non-carriers—Model 1A), additive (0 vs. 1 vs. 2 ε4 alleles—Model 1B), and recessive effects (non-carriers and ε4 heterozygotes vs. ε4 homozygotes—Model 1C). Model 2 further included variables related to cardiovascular risk, such as body mass index (BMI), ever smoker (yes vs. no), hypertension (self-reported diagnosis and/or current use of antihypertensive medication vs. none of them), dyslipidemia (self-reported diagnosis and/or use of cholesterol-lowering medications and/or fasting plasma total cholesterol ≥ 200 mg/dL, and/or fasting plasma triglycerides ≥ 150 mg/dL vs. none of them), and diabetes (self-reported diagnosis and/or use of antidiabetic medications and/or blood hemoglobin A1c ≥ 6.5% vs. none of them). Model 3 further included reciprocal adjustment for the two types of omega-3 examined.

We constructed additional models after stratifying for *APOE* ε4 (dominant, recessive, and additive; with age, sex, years of education, and days between blood sampling and [18-F]-FDG PET acquisition as covariates), for sex (with age, years of education, *APOE* ε4 carriership, and days between blood sampling and [18-F]-FDG PET acquisition as covariates), and for AT status (A−T− vs. A+T− vs. A+T+; with age, sex, years of education, *APOE* ε4 carriership, and days between blood sampling and [18-F]-FDG PET acquisition as covariates). We excluded A−T+ participants ($n = 12$) from the latter due to the low sample size and because this profile is suggestive of non-AD pathology.[18] In each case, we stratified and further searched for group-specific associations by determining the Pearson correlation coefficients between the omega-3 of interest and standardized residuals outputted from the general linear model including the covariates. For all regression analyses, standard diagnostic checks on the residuals from the fitted models showed no evidence of any failure of the assumptions of normality and homogeneity of the residual variance.

We also explored for the relationship between ALA blood status and self-reported consumption of walnuts and olive oil. To this end, we determined the Pearson correlation coefficients between RBC ALA and: (1) servings per week of walnuts; (2) tablespoons per day of olive oil, regardless of the type (extra-virgin olive oil, virgin olive oil, refined olive oil, pure olive oil, olive pomace oil). We also assessed differences in RBC ALA between categories of self-reported consumption of walnuts (less than once per month vs. 1 per month to less than 1 per day vs. daily) by one-factor analysis of variance.

Statistical significance was set at the $P < 0.05$ level in all cases. Analyses were performed using SPSS software, release 22.0 (SPSS Inc.). Figures were built using R software (R Foundation for Statistical Computing; http://www.r-project.org/).

In addition to the hypothesis-driven approach (association between selected RBC omega-3 and [18-F]-FDG uptake in the Landau signature), we also performed an unbiased voxel-wise approach. We used SPM12 to create a general linear model (GLM) for each predictor of interest, including age, sex, years of education, *APOE* ε4 carriership, and total intracranial volume as confounders in both sets of analyses. The statistical significance was set as $P < 0.001$ uncorrected for multiple comparisons with a cluster size of $k > 100$ voxels, further applying a correction for multiple testing using a family-wise error rate (FWE) and false discovery rate (FDR) approaches.

3 | RESULTS

Table 1 displays demographic and clinical data of the study population by *APOE* genotype.

TABLE 1 Characteristics of the study population by *APOE* genotype.

Variable	All ($n = 320$)	$\varepsilon3/\varepsilon3$ ($n = 134$)	$\varepsilon3/\varepsilon4$ ($n = 156$)	$\varepsilon4/\varepsilon4$ ($n = 30$)
Women—no. (%)	199 (62.2)	92 (68.7)	88 (56.4)	19 (62.2)
Age—y	61.0 (60.5; 61.5)	61.5 (60.6; 62.3)	61.6 (61.0; 62.2)	55.9 (54.5; 57.4)
Education—y	13.5 (13.1; 13.9)	13.6 (13.0; 14.2)	13.4 (12.9; 14.0)	13.7 (12.4; 15.0)
BMI—kg/m^2	26.9 (26.5; 27.4)	27.1 (26.4; 27.8)	27.0 (25.3; 28.6)	26.9 (26.5; 27.4)
Smoking—no. (%)				
Never smoker	135 (42.2)	58 (43.0)	65 (41.7)	12 (40.0)
Current smoker	44 (13.8)	14 (10.4)	19 (12.2)	11 (36.7)
Former smoker	141 (44.1)	62 (46.3)	72 (46.2)	7 (23.3)
Hypertension—no. (%)	93 (29.1)	43 (32.1)	41 (26.3)	9 (30.0)
Hypercholesterolemia—no. (%)	246 (76.9)	91 (67.9)	130 (83.3)	25 (83.3)
Diabetes—no. (%)	14 (4.4)	5 (3.7)	5 (3.2)	4 (13.3)
AT status—no. (%)				
A–T–	182 (62.3)	97 (79.5)	74 (51.7)	11 (40.7)
A+T–	86 (29.5)	15 (12.3)	56 (39.2)	15 (55.6)
A+T+	24 (8.2)	10 (8.2)	13 (9.1)	1 (3.7)
RBC omega-3–%				
DHA	3.98 (3.84; 4.12)	3.90 (3.66; 4.13)	4.07 (3.88; 4.26)	3.86 (3.33; 4.39)
ALA	0.14 (0.14; 0.15)	0.14 (0.13; 0.16)	0.15 (0.14; 0.16)	0.13 (0.10; 0.16)
[18-F]-FDG uptake–SUVR	1.30 (1.25, 1.37)	1.31 (1.24; 1.39)	1.29 (1.24; 1.36)	1.31 (1.26; 1.41)

Note: Data are mean (95% confidence interval), except for categorical variables (expressed as N and %) and [18-F]-FDG SUVR (expressed as median and interquartile range). For AT status, data from $n = 292$ participants (exclusion of $n = 12$ A–T+).
Abbreviations: [18-F]-FDG, positron emission tomography with fluorine-18 fluorodeoxyglucose; AD, Alzheimer's disease; ALA, alpha-linolenic acid; A+T–, amyloid beta–positive tau-negative; A–T–, amyloid beta–negative tau-negative; A+T+, amyloid beta–positive tau-positive; *APOE*, apolipoprotein E; BMI, body mass index; C18:3n-3; C22:6n-3; DHA, docosahexaenoic acid; RBC, red blood cell; SUVR, standardized uptake value ratio.

3.1 | Associations between selected RBC omega-3 and [18F]-FDG uptake in the Landau signature

As reported in Table 2, we observed a statistically significant direct association between DHA and glucose uptake (Model 1A to 1C, *P* from 0.035 to 0.042), which blunted after the inclusion of variables related to cardiovascular risk (Model 2, $P = 0.281$), and RBC ALA (Model 3, $P = 0.314$). Regarding ALA, we observed a direct association with [18-F]-FDG uptake in this metaROI of interest (Model 1, $P = 0.004$). Of note, such association survived in models that further included cardiovascular risk factors (Model 2, $P = 0.032$), and RBC DHA (Model 3, $P = 0.037$). For both exposures, adjustment for *APOE* ε4 allele load as either dominant (Model 1A), additive (Model 1B), or recessive (Model 1C) did not affect the sense or the magnitude of the associations.

3.2 | Effect modification by *APOE* ε4 status, sex, and AT grouping

For DHA, a stronger association was observed in *APOE* ε4 carriers compared to non-carriers ($P = 0.016$ and $P = 0.614$, respectively), although statistical significance blunted after the inclusion of cardiovascular risk factors ($P = 0.125$ and $P = 0.930$, respectively; Figure S1, panels A and B in supporting information). A similar pattern was observed for those carrying one *APOE* ε4 allele (Figure S1, panels C and D), and for *APOE* ε4 non-homozygotes (Figure S1, panels E and F). No relevant associations were observed for men and women when analyzed separately ($P = 0.766$ for women, $P = 0.206$ for men; Figure S2 in supporting information). Interestingly, AT status modified the association between RBC DHA and [18-F]-FDG uptake in the Landau signature, with a much stronger, direct association in the A+T+ group than in the other two groups, even after the inclusion of cardiovascular risk factors into the model ($P = 0.031$ for A+T+; $P > 0.6$ in the other two groups; Figure 1).

In relation to ALA, a stronger association was observed in *APOE* ε4 carriers compared to non-carriers, and in *APOE* ε4 homozygotes compared to non-homozygotes, even after the inclusion of cardiovascular risk factors ($P = 0.025$ for *APOE* ε4 carriership; $P = 0.031$ for *APOE* ε4 homozygosis; Figure 2). We observed a statistically significant association in women ($P = 0.010$), but not in men, although it weakened after the inclusion of cardiovascular risk factors into the model ($P = 0.085$; Figure S3 in supporting information). When exploring the effect of the AT group, statistically significant direct associations were limited to A–T– participants ($P = 0.046$; Figure S4 in supporting information).

TABLE 2 Associations between selected RBC omega-3 and [18-F]-FDG uptake in the Landau signature ($n = 320$).

Omega-3	Model	*APOE ε4* in the model	Estimate (95 % CI)	*P*	R^2
DHA	1A	Carrier/non-carrier	0.009 (0.001; 0.017)	0.035	0.041
	1B	Number of alleles	0.009 (0.001; 0.017)	0.037	0.040
	1C	Homozygote/non-homozygote	0.009 (0.000; 0.017)	0.042	0.039
	2	Carrier/non-carrier	0.005 (−0.004; 0.013)	0.281	0.119
	3	Carrier/non-carrier	0.004 (−0.004; 0.013)	0.314	0.129
ALA	1A	Carrier/non-carrier	0.182 (0.058; 0.306)	0.004	0.051
	1B	Number of alleles	0.181 (0.057; 0.305)	0.004	0.050
	1C	Homozygote/non-homozygote	0.184 (0.059; 0.308)	0.004	0.049
	2	Carrier/non-carrier	0.134 (0.011; 0.254)	0.032	0.126
	3	Carrier/non-carrier	0.131 (0.008; 0.254)	0.037	0.129

Note: Data are presented for 1% of RBC omega-3, obtained by multiple linear regression analyses, being [18-F]-FDG SUVR rank-transformed. Model 1 was adjusted for age, sex, years of education, days between blood sampling and [18-F]-FDG PET acquisition, and *APOE ε4* carriership. Model 2 further included BMI, ever smoker, hypertension, dyslipidemia, and diabetes. Model 3 further included reciprocal adjustment for the two types of omega-3 examined.
Abbreviations: [18-F]-FDG, positron emission tomography with fluorine-18 fluorodeoxyglucose; ALA, alpha-linolenic acid; *APOE*, apolipoprotein E; BMI, body mass index; CI, confidence interval; DHA, docosahexaenoic acid; PET, positron emission tomography; RBC, red blood cell; SUVR, standardized uptake value ratio.

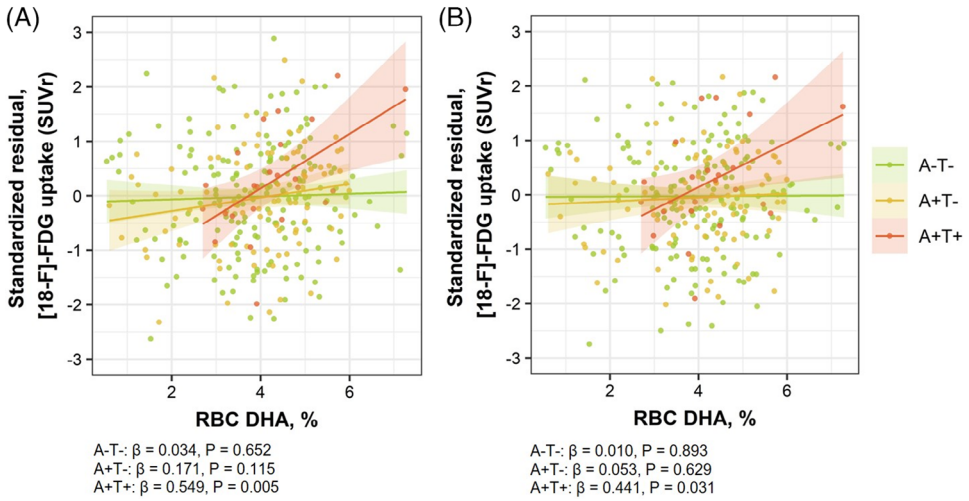

FIGURE 1 Association of DHA with [18-F]-FDG uptake by AT status. Scatterplots of the association between RBC DHA and standardized residuals of FDG uptake (SUVR), outputted from a general linear model including age, sex, years of education, days between blood sampling and [18-F]-FDG PET acquisition, and *APOE ε4* carriership (A), and further inclusion of BMI, ever smoking, hypertension, dyslipidemia, and diabetes (B). Each point depicts the value of an individual, and the solid lines indicate the regression line for each of the groups. Data include Pearson correlation coefficients and *P* values for each subgroup of interest. *APOE*, apolipoprotein E; AT, amyloid/tau; BMI, body mass index; DHA, docosahexaenoic acid; FDG, fluorodeoxyglucose; PET, positron emission tomography; RBC, red blood cell; SUVR, standardized uptake value ratio.

3.3 | Voxel-wise analyses

We used a hypothesis-free voxel-wise approach to identify which specific cerebral regions showed increased [18-F]-FDG uptake with exposures of interest. FWE-corrected statistical parametric maps showed that increasing ALA correlated with preserved [18-F]-FDG uptake predominantly in areas of the frontal and parietal regions (Figure 3; Table S1 in supporting information). No other significant associations were observed.

3.4 | Associations with self-reported dietary data

We observed no significant associations between self-reported daily tablespoons of olive oil (regardless of type) and RBC ALA (Figure S5, panel A in supporting information). However, statistical significance ($P = 0.001$) was observed for weekly servings of walnuts (Figure S5, panel B). In addition, RBC ALA increased across categories of walnut consumption (Figure S5, panel C).

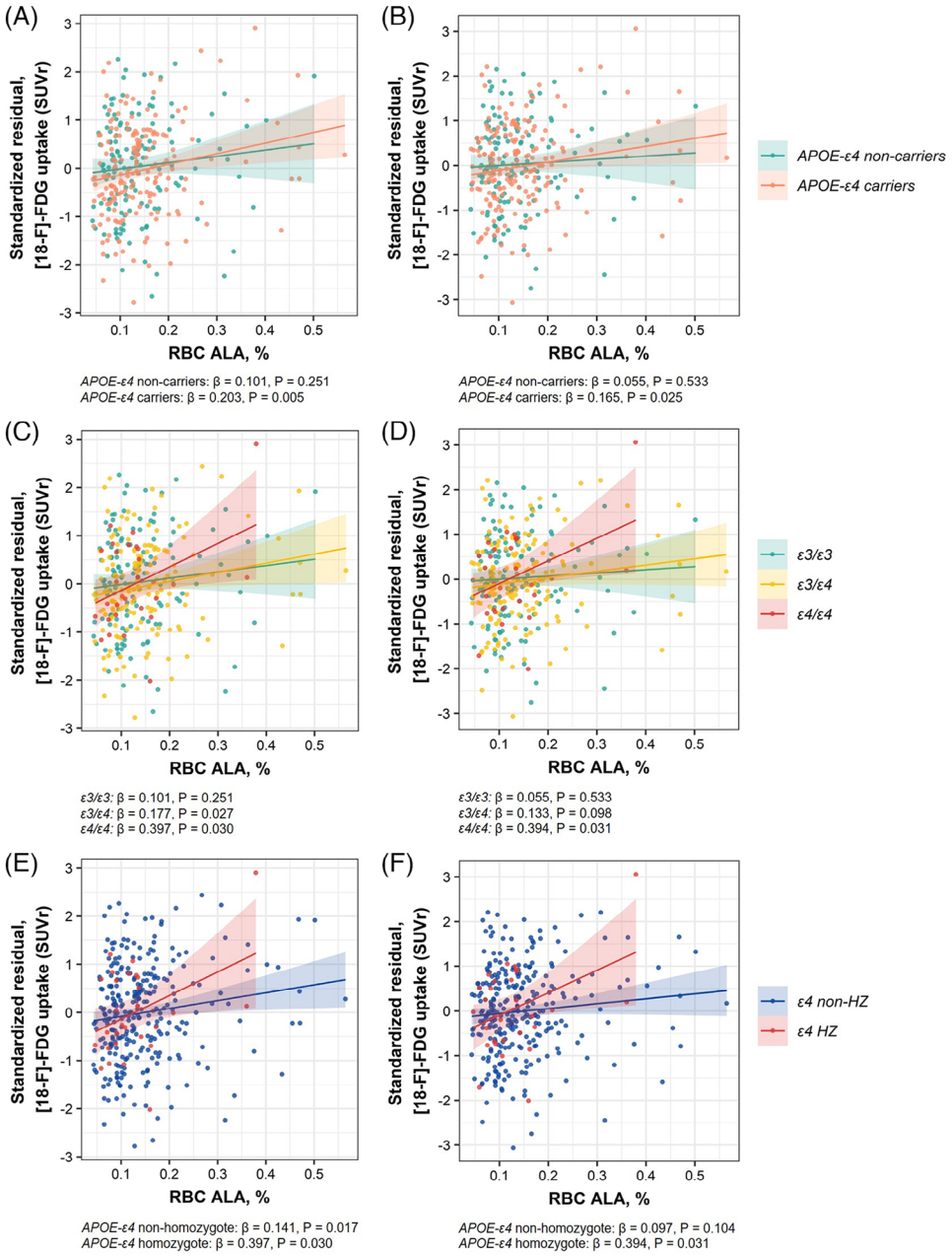

FIGURE 2 Association of ALA with [18-F]-FDG uptake by *APOE* ε4 status. Scatterplots of the association between RBC ALA and standardized residuals of FDG uptake (SUVR), outputted from a general linear model including age, sex, years of education, and days between blood sampling and [18-F]-FDG PET acquisition (A, C, and E), and further inclusion of BMI, ever smoking, hypertension, dyslipidemia, and diabetes (B, D, and F). Each point depicts the value of an individual, and the solid lines indicate the regression line for each of the groups. Data include Pearson correlation coefficients and *P* values for each subgroup of interest. ALA, alpha-linolenic acid; *APOE*, apolipoprotein E; BMI, body mass index; FDG, fluorodeoxyglucose; PET, positron emission tomography; RBC, red blood cell; SUVR, standardized uptake value ratio.

4 | DISCUSSION

In the present study conducted in a cohort of middle-aged cognitively unimpaired individuals at increased risk of AD dementia, we determined cross-sectional associations between blood biomarkers of omega-3 (from either marine or plant origin) and brain glucose metabolism, as assessed by [18-F]-FDG PET imaging. Average values for both fatty acids were lower than those described in many populations from around the world, in which fatty acids were measured in RBCs by a shared reference method.[22] We found that blood status of ALA (the main plant-derived omega-3) directly related to preserved glucose uptake in brain regions vulnerable to AD-related hypometabolism (Landau's signature), in particular in those at increased genetic risk (i.e., *APOE* ε4 load). An unbiased voxel-wise approach also uncovered significant direct bilateral associations for ALA. Regarding DHA, an omega-3 that is readily incorporated in our

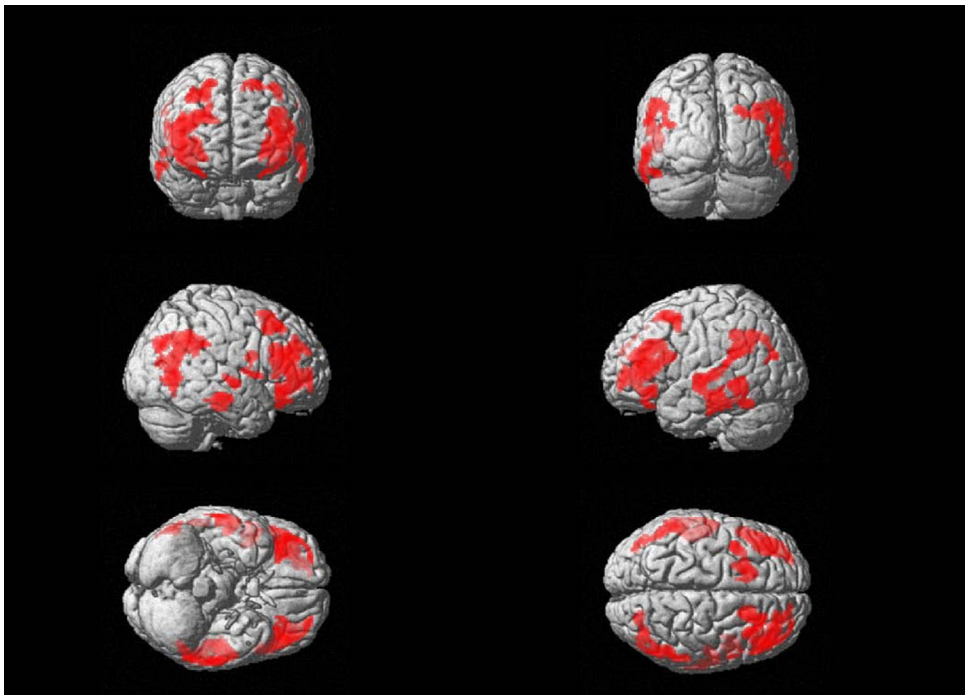

FIGURE 3 Three-dimensional brain statistical parametric maps highlighting in red areas the positive associations between red blood cell ALA and preserved [18-F]-FDG uptake.

brain membranes even before birth, statistically significant direct associations were limited to those in the preclinical stage of AD pathology (A+T+).

Methodologically, the importance of our study relies on three aspects. The first one is the use of blood biomarkers of dietary intake, the use of which is encouraged by the Nutrition for Dementia Prevention Working Group.[23] While many epidemiologic studies have strengthened the association of dietary omega-3 with AD dementia,[24] most studies rely on assessments of omega-3 intake by methods that require participants to record or recall their food and beverage consumption over a fixed period of time based (i.e., 24-hour recalls or food frequency questionnaires). However, these techniques have several limitations that affect both the accuracy and precision of the measurement. Given the marginal *de novo* synthesis of omega-3 (absent for ALA), direct chemical measurement of circulating omega-3 has emerged as an objective and valid surrogate of their dietary intake and metabolism.[10] The use of an objective biomarker of dietary intake might be particularly relevant in aging populations or those at increased risk of dementia who may be more prone to memory bias due to incipient memory deficits. Although blood omega-3 status is mostly driven by dietary omega-3 fatty acid intake, it also reflects other aspects related to metabolism, including rates of omega-3 absorption, which might be affected by concomitant use of lipid-lowering drugs.[25] The second one relates to the exposures: we also examined associations for the plant-derived ALA, which has been largely overlooked in relation to cognition, but may be particularly important to populations not consuming seafood. Finally, the third one relates to the outcome: most clinical research focused on circulating omega-3 and cognitive performance or brain structure, in particular on alterations related to vascular damage (including white matter hyperintensities, microbleedings, and enlargement of perivascular spaces) and cortical volume.[26,27] In contrast, research on omega-3 and other relevant key aspects of AD (e.g., brain glucose uptake) has received little attention to date. Brain glucose hypometabolism is widely regarded as a marker of neurodegeneration in AD[28] with strong diagnostic power.[29] Albeit decreases of [18-F]-FDG can be observed in other neurodegenerative disorders, the regional pattern of hypometabolism in the temporal-parietal region is highly specific for AD.[30] The most well-established way to quantitatively measure hypometabolism in specific AD regions is the so-called "Landau signature."[3]

In terms of clinical relevance, the main finding is the complementary associations observed for the two analyzed omega-3 fatty acids. On the one hand, we first examined associations for DHA, an omega-3 fatty acid abundant in fatty fish and fish oil that has been largely explored in relation to AD and its features, including brain glucose metabolism.[6] While a statistically significant association was observed in a model including age, sex, years of education, and *APOE* ε4 carriership, it weakened after further inclusion of classical cardiovascular risk factors. Given that cardiovascular risk factors (and subclinical carotid atherosclerosis) in asymptomatic middle-aged people are associated with impaired cerebral metabolism in key brain areas,[31] is it plausible that the neuroprotective role of DHA could be mediated through modification of these risk factors, as already suggested a while ago.[32] Of note, stratified analyses uncovered a direct, robust association in participants with preclinical AD (i.e., with altered core AD biomarkers [Aβ and tau], yet cognitively unimpaired). Besides adding to the notion that early DHA supplementation may be beneficial during the preclinical or early symptomatic stages of AD as previously suggested,[33] such

finding argues for the need of AD biomarkers in better selecting participants for preclinical studies on omega-3 and AD, in alignment with the "precision medicine" era.[23]

On the other hand, we report a direct, significant, and independent association for ALA and preserved brain glucose uptake, being stronger in those with higher *APOE* ε4 allele load. Such findings support the benefits of the sustained consumption of foods rich in this fatty acid, in particular in those at increased genetic risk of AD dementia. The figure concurs with a longitudinal study conducted in 915 older individuals, wherein association between ALA intake (as assessed by self-reported data) and 5-year decline in cognitive performance was weaker in *APOE* ε4 carriers than in non-carriers.[34] After stratifying, in contrast to DHA, slightly stronger significant associations were observed in A−T− participants than in those of other AT groups. Overall, significant associations for ALA were not observed for DHA, and vice versa. Models including reciprocal adjustment for the two types of omega-3 (Table 2, Model 3) showed no changes in sense or magnitude of associations. This supports the view that marine and plant omega-3 fatty acids might display complementary benefits, acting as partners in promoting brain glucose uptake across the AD continuum.

There are three possible mechanisms to explain the putative effect of ALA in promoting brain glucose uptake. First, there is the possibility that ALA was marginally converted to DHA. Given that blood DHA was unrelated to brain glucose uptake in our study, this mechanism can be discounted. Second, ALA might display an effect on its own. This is a likely possibility, which is consistent with the increasing body of experimental evidence on the benefits of ALA in AD pathophysiology.[35–37] Third, another conceivable event is that blood enrichment with ALA is a mere marker of intake of bioactive compounds in healthy foods containing the fatty acid. In Mediterranean areas, the main sources of ALA in the diet are walnuts (the nuts most consumed in Spain[38]) and, to a lesser extent, olive oil,[39] because other ALA-rich vegetables, such as soy and flaxseed-derived products, are as yet uncommon staples. We observed significant associations between RBC ALA and self-reported walnut consumption in our population. Therefore, bioactive molecules other than ALA present in walnuts cannot be ruled out as being the active agents, ALA then being just a contributor rather than the main driver in promoting brain glucose uptake. Further research is warranted to disentangle the exact contribution of ALA in itself in brain glucose metabolism.

Our study is not free of limitations. First, its cross-sectional nature precluded us from exploring whether selected blood omega-3 related to longitudinal changes in brain glucose uptake. Second, our cohort showed a low prevalence of common comorbidities and is enriched by family history of sporadic AD and *APOE* ε4 carriership,[11] which may limit the generalizability of the findings to other age groups or populations. In contrast, the strengths of the present study include the precise clinical characterization of the participants, the use of blood biomarkers of dietary omega-3, the large number of *APOE* ε4 homozygotes, and adjustment for a wide array of potential confounders in multivariable analyses.

In conclusion, in a cohort of cognitively unimpaired participants at higher risk of AD dementia, blood enrichment in omega-3 fatty acids, objectively reflecting their dietary intake, related to preserved glucose intake in AD-vulnerable brain regions. Of note, we report complementary associations for omega-3 from plant origin (ALA: in whole studied population; in *APOE* ε4 carriers; in *APOE* ε4 homozygotes; in A−T− participants) and from marine origin (DHA: in A+T+ participants). Results add to the increasing evidence that sustained consumption of foods rich in ALA and DHA might provide benefits in the AD continuum.

AUTHOR CONTRIBUTIONS

Collaborators of the ALFA Study are: Annabella Beteta, Anna Brugulat-Serrat, Raffaele Cacciaglia, Lidia Canals, Alba Cañas, Irene Cumplido-Mayoral, Marta del Campo, Carme Deulofeu, Ruth Dominguez, Maria Emilio, Ana Fernández-Arcos, Sherezade Fuentes, Patricia Genius, Laura Hernandez, Núria Tort-Colet, Paula Marne, Tania Menchón, Wiesje Pelkmans, Albina Polo, Sandra Pradas, Blanca Rodríguez-Fernández, Anna Soteras, Laura Stankeviciute, Marc Vilanova, and Natalia Vilor-Tejedor.

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The funding agencies had no input in the study design, data collection, analyses, or writing and submission of the manuscript.

CONFLICT OF INTEREST STATEMENT

MSC has given lectures in symposia sponsored by Roche Diagnostics, S.L.U. Roche Farma, S.A., and Amirall;and he has served as a consultant and at advisory boards for Roche Diagnostics International Ltd and Grifols S.L. He was granted with a project funded by Roche Diagnostics International Ltd; payments were made to the institution (BBRC). He received in-kind support for research (to the institution) from Roche Diagnostics International Ltd, Avid Radiopharmaceuticals, Inc., Eli Lilly, and Janssen Research & Development. JLM is currently a full-time employee of H. Lundbeck A/S and previously served as a consultant or on advisory boards for the following for-profit companies or has given lectures in symposia sponsored by the following for-profit companies: Roche Diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Janssen, Green Valley, MSD, Eisai, Alector, BioCross, GE Healthcare, and ProMIS Neurosciences. JDG receives research funding from Roche Diagnostics and GE Healthcare and has given lectures at symposia sponsored by Biogen and Philips. AS-V has received research grant funding through his institution and support to attend professional meetings from the California Walnut Commission. Other authors report no conflicts of interest. Disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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