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Original Research Article

The Relationship of Omega-3 Fatty Acids with Dementia and Cognitive Decline: Evidence from Prospective Cohort Studies of Supplementation, Dietary Intake, and Blood Markers☆

Bao-Zhen Wei [1,2,†], Lin Li [3,†], Cheng-Wen Dong [2], Chen-Chen Tan [1], for the Alzheimer's Disease Neuroimaging Initiative, Wei Xu [1,*]

[1] *Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China;* [2] *The Affiliated Hospital of Qingdao University, Qingdao, China;* [3] *Department of Neurology, Linyi People's Hospital, Qingdao University, Qingdao, China*

A B S T R A C T

Previous data have linked omega-3 fatty acids with risk of dementia. We aimed to assess the longitudinal relationships of omega-3 polyunsaturated fatty acid intake as well as blood biomarkers with risk of Alzheimer's disease (AD), dementia, or cognitive decline. Longitudinal data were derived from 1135 participants without dementia (mean age = 73 y) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort to evaluate the associations of omega-3 fatty acid supplementation and blood biomarkers with incident AD during the 6-y follow-up. A meta-analysis of published cohort studies was further conducted to test the longitudinal relationships of dietary intake of omega-3 and its peripheral markers with all-cause dementia or cognitive decline. Causal dose–response analyses were conducted using the robust error meta-regression model. In the ADNI cohort, long-term users of omega-3 fatty acid supplements exhibited a 64% reduced risk of AD (hazard ratio: 0.36, 95% confidence interval: 0.18, 0.72; $P = 0.004$). After incorporating 48 longitudinal studies involving 103,651 participants, a moderate-to-high level of evidence suggested that dietary intake of omega-3 fatty acids could lower risk of all-cause dementia or cognitive decline by ~20%, especially for docosahexaenoic acid (DHA) intake (relative risk [RR]: 0.82, $I^2 = 63.6\%$, $P = 0.001$) and for studies that were adjusted for apolipoprotein APOE ε4 status (RR: 0.83, $I^2 = 65\%$, $P = 0.006$). Each increment of 0.1 g/d of DHA or eicosapentaenoic acid (EPA) intake was associated with an 8% ~ 9.9% ($P_{linear} < 0.0005$) lower risk of cognitive decline. Moderate-to-high levels of evidence indicated that elevated levels of plasma EPA (RR: 0.88, $I^2 = 38.1\%$) and erythrocyte membrane DHA (RR: 0.94, $I^2 = 0.4\%$) were associated with a lower risk of cognitive decline. Dietary intake or long-term supplementation of omega-3 fatty acids may help reduce risk of AD or cognitive decline.

Keywords: omega-3 fatty acid, dementia, AD, cognitive decline, dietary, biomarker

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder with a high prevalence among aging populations [1]. Given the lack of effective therapeutic strategies and the high disease burden, it is imperative to identify modifiable risk factors to prevent or postpone the onset of AD. Interest has raised recently in the role of omega-3 fatty acid dietary intake and blood concentrations in the prevention of dementia. Omega-3 fatty acids are a heterogeneous group of fatty acids with a double bond at the ω−3 carbon atom, mainly including DHA (22:6n-3), EPA (20:5n-3), and ALA (18:3n-3). Omega-3 fatty acids are primarily obtained through dietary intake, and fish is the primary dietary source of EPA and DHA in humans [2]. Plant-derived ALA is the most abundant omega-3 fatty acid in the diets of people who do not regularly consume fish [3].

Omega-3 fatty acids are nootropic agents that are beneficial for brain development, anti-inflammation, and cognitive preservation [4]. DHA is an essential fatty acid that maintains brain function and integrity, and its derivatives can modulate glial cell activity and improve cognition in the early stages of AD [5]. However, evidence

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; MCI, mild cognitive impairment.

☆ The data used in preparation for 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 the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-ontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

* Corresponding author.
E-mail address: dr_xuwei@qdu.edu.cn (W. Xu).

† B-ZW and LL contributed to the present work equally.

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from observational studies and clinical trials has produced unclear conclusions regarding the efficacy of omega-3 fatty acid supplementation for prevention of cognitive decline, dementia, or AD. Prospective studies have suggested that individuals who consume higher amounts of omega-3 fatty acids are less likely to develop AD [6], and erythrocyte DHA levels are inversely associated with risk of AD and all-cause dementia [7]. Compared with cognitively healthy individuals, patients with AD have been found to have lower concentrations of omega-3 fatty acids, especially DHA, in the serum, plasma phospholipids, and erythrocyte membranes [8,9]. In contrast, randomized clinical trials have shown limited efficacy of omega-3 fatty acid supplementation in reducing cognitive decline and probable AD [10]. Further, apolipoprotein ε4 (*APOE* ε4) genotype might modify the association between omega-3 fatty acid supplementation and cognitive decline [11], dementia, or AD [12]. The *APOE ε4* allele, the major genetic risk factor for AD, could mediate AD-associated pathology, including inducing abnormal cholesterol metabolism [13]. It remains unclear how *APOE* ε4 interacts with omega-3 fatty acids to affect risk of dementia and cognitive decline. A study has found an association between a higher intake of omega-3 fatty acids and slower rates of cognitive decline among *APOE* ε4 carriers but not among *APOE* ε4 noncarriers [11]. Other studies have reported opposite results, showing that omega-3 fatty acids are only beneficial for *APOE* ε4 noncarriers [9, 14]. The underlying mechanism may involve the reduced delivery of DHA and EPA into the brain caused by *APOE* ε4 [15].

To assess the longitudinal relationships between the intake of omega-3 polyunsaturated fatty acids and blood biomarkers and risk of AD, dementia, or cognitive decline, we analyzed data from Alzheimer's Disease Neuroimaging Initiative (ADNI) and conducted a systematic review and meta-analysis of newly published studies.

Methods

ADNI cohort study

Participants

Data were derived from the ADNI cohort (http://adni.loni.usc.edu/). As a multicenter study, the ADNI is designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD. The studied population are nondemented adults aged 55 y to 90 y at baseline. Participants underwent standardized neuropsychological assessments, in-person interviews for detailed medical history, and cognitive evaluation at study entry and follow-up (Figure 1A). The ADNI was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all participants according to the Declaration of Helsinki.

Supplementation and blood measurement of omega-3 fatty acids

Dietary supplement use information was collected at the initial screening visit as a part of the medication-taking questionnaire. The question was open-ended, and participants provided the information about all prescribed and over-the-counter medications as well as any oral supplement they are taking, including the name and the time from initiation of use to discontinuation. Omega-3 fatty acid supplements are defined as fish oil, omega-3 fatty acid, PUFA, DHA, EPA, or ALA.

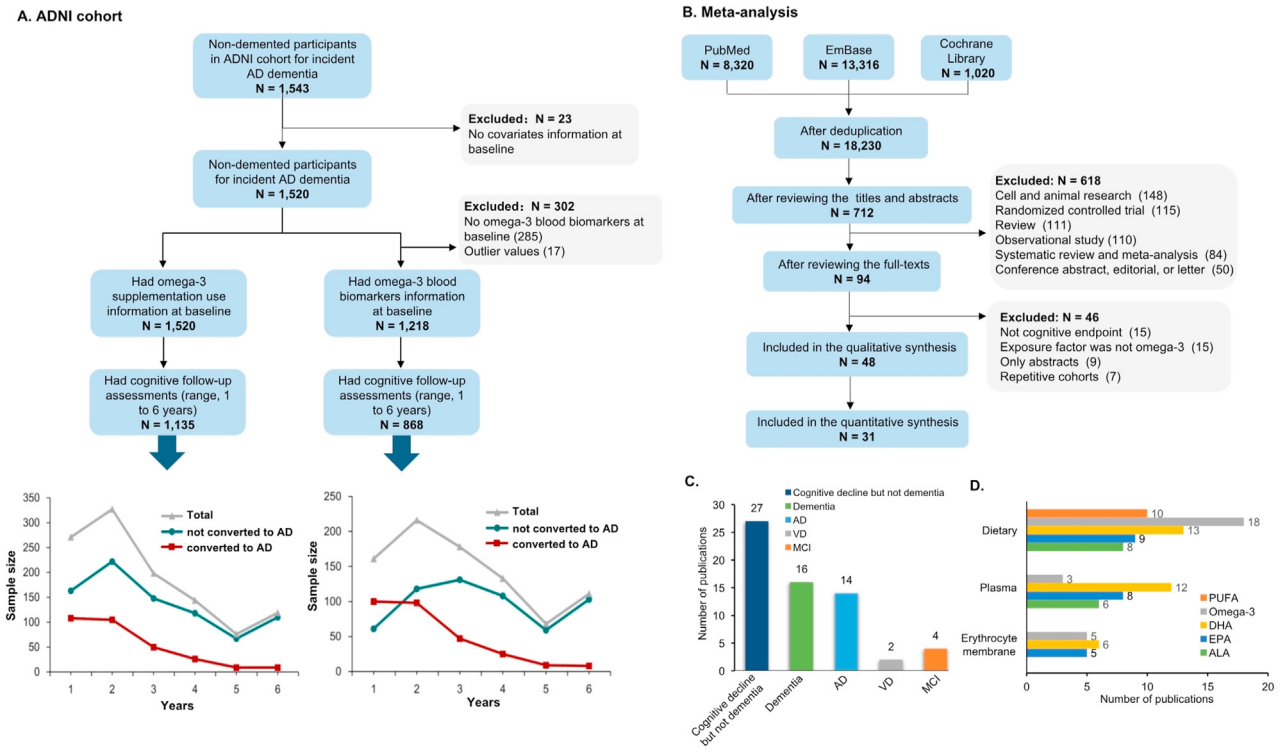

FIGURE 1. Flowchart for the overall selection process and summary characteristics of included studies. (A) Flowchart of the participants included in the ADNI cohort study. (B) Overall selection process in the meta-analysis of published longitudinal studies. (C) Most studies reported cognitive decline but not dementia ($n = 27$) followed by dementia ($n = 16$) or AD ($n = 14$), and only a few reported MCI ($n = 4$) or VD ($n = 2$). Of all 48 studies included in systematic review, most studies reported omega-3 fatty acid dietary intake ($n = 31$), followed by plasma ($n = 14$) and erythrocyte membrane ($n = 6$). (D) All 31 studies included in the meta-analysis; 18 reported dietary omega-3 including DHA ($n = 13$), EPA ($n = 9$), and ALA ($n = 8$). AD, Alzheimer's disease; MCI, mild cognitive impairment; VD, vascular dementia.

Self-reported omega-3 fatty acid supplementation information was recorded at the initial screening visit with participants and their partners. Duration of omega-3 fatty acid supplementation was calculated as the time from initiation of use to discontinuation. Participants who used omega-3 fatty acid supplements for over 1 y were defined as the "exposed group" and others as "nonexposed group." The "exposed" subjects were further divided into "medium-term users (1 ~ 9 y)" group and "long-term users (≥10 y)."

Plasma samples for each subject were obtained in the morning following an overnight fast. The time from collection to freezing was mostly within 2 h. Lab technicians were blinded to the clinical information of samples. Fatty acid composition was quantified using Nightingale Health's nuclear magnetic resonance (NMR) metabolomics platform. The samples were processed following the automated standard protocol provided by Nightingale's technology, and blood metabolites were quantified in absolute concentrations and percentages using NMR spectroscopy [16].

Ascertainment of AD

AD was diagnosed by neurologists according to brain structure scans, cognitive score, and independent living ability, based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) for definite, probable, or possible AD [17].

Covariate measurements

The covariates included age (continuous variable), sex (female =1, male = 0), education (continuous variable), cognitive status (mild cognitive impairment =1, normal cognition = 0), and *APOE* ε4 status ("44/34/24" = 1, "33/22/23" = 0). rs7412 and rs429358 were used to define the *APOE* ε2/ε3/ε4 isoforms [18]. Other potential covariates were obtained from baseline medical history, including dichotomous variables (hyperlipidemia, hypertension, diabetes, stroke history, insomnia, depression, anxiety, current smoking status, coronary artery disease, alcohol intake, multivitamin, vitamin B12, and folate supplementation, anti-hypertensive drugs, and anti-diabetic drugs) and continuous variable (BMI).

Evidence evaluation via meta-analysis

Search strategy and selection criteria

We registered the protocol on PROSPERO in advance (CRD42021238393). Meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines (PRISMA) statement [19]. PubMed, EMBASE, and Cochrane Library were searched using the strategy: ((fish) OR (fish oil) OR (omega-3) OR (omega) OR (polyunsaturated fatty acid) OR (PUFA) OR (docosahexaenoic acid) OR (DHA) OR (eicosapentaenoic acid) or (EPA) OR (Alpha linolenic acid) OR (ALA)) AND ((cognitive) OR (dementia) OR (Alzheimer)) until March 17, 2022. Reference lists of articles identified through database searches were manually screened to locate additional relevant studies. The inclusion criteria were as follows: *1*) the relationships of omega-3 fatty acid intake and its peripheral biomarkers with risk of AD, all-cause dementia, or cognitive decline were investigated; *2*) study designs were cohort studies or nested case-control studies; *3*) risk estimates or the raw data that can be used to calculate these numbers were available; *4*) publication type was original article. No restriction was imposed on language. Studies were excluded if they did not meet the inclusion criteria mentioned above.

Data extraction

A pre-designed template was used to extract the data (Supplementary Table 1). For data unavailable in the article, we attempted to obtain them by contacting the corresponding authors. Literature selection and data extraction were performed by 2 experienced investigators (B-ZW and C-WD), and a third reviewer (WX) occasionally participated in the negotiation to solve any discrepancies.

Identification of AD, dementia, and cognitive decline

Cognitive decline is a common outcome of aging and may lead to dementia, and AD is the primary kind of dementia. Participants underwent cognitive assessments at baseline and during follow-up, and a decline in scores on the Mini-Mental State Examination scale was considered as cognitive decline. AD and dementia were diagnosed by the consensus of physicians according to the NINCDS-ADRDA and the Diagnostic and Statistical Manual of Mental Disorders 4th/5th Edition (DSM-IV/DSM-V), respectively.

Assessment of study quality and credibility of meta-analyses

An evolving Newcastle- Ottawa Quality Assessment Scale for observational cohort studies [20] was employed to evaluate the quality of eligible studies (Supplementary Table 2). The evidence robustness of the meta-analysis was assessed by summing scores from 5 domains: risk of bias, heterogeneity, publication bias, effect size, and imprecision. Scores were ranked in descending order; the top third was categorized into high level (H), the middle third was moderate level (M), and the bottom third was low level (L) (Supplementary Table 3). To better utilize the whole body of evidence and avoid missing important research unsuitable for meta-analysis, we developed a semiquantitative index named "index S" [21] (Supplementary Table 4).

Statistical analyses

In the ADNI, the statistical differences on baseline variables (see "Covariate measurements") between participants who developed AD and those who were free of dementia during follow-up was compared by Pearson chi-squared test or independent samples t-test. Cox proportional hazards models with age as the time metric were used to assess the influence of omega-3 fatty acid at baseline on AD incidence. Risk estimate was expressed as hazard ratio (HR) and 95% CI. The proportional hazards assumption was checked using Schoenfeld's global test. No variable was statistically significant, suggesting that the proportional hazards assumption was not violated ($P > 0.05$). To examine the potential stratification or interaction effect, stratified analyses were performed according to sex, age, *APOE* ε4 status, and baseline cognitive diagnosis. Sensitivity analyses were conducted by excluding those who progressed to dementia within 1 y follow-up.

As for meta-analyses, data were analyzed using the 'metagen,' 'metabias,' and 'trimfill' packages in R V.3.4.3 software (https://www.r-project.org). All statistical tests were 2-sided and used a significance level of $P < 0.05$. The pooled risk estimates were first calculated based on the comparison of the highest versus the lowest category of exposure. For studies wherein the reference group was not the lowest category, we recalculated the effect size using the method of Orsini [22]. For studies reporting odd ratios (ORs), we transformed ORs to RRs using the following algorithm: $RR_{adjusted} = OR_{adjusted}/[(1 - P0) + (P0 \times OR_{adjusted})]$ where P0 indicates the incidence of the endpoint (AD, dementia, or cognitive decline) in the nonexposed group of the cohort. When P0 was not available, the incidence rate of total participants was used as a proxy [23]. The multivariable-adjusted risk estimates and 95% CIs were log-transformed and pooled using random

models (DerSimonian–Laird method) [24]. Heterogeneity was examined using the I^2 statistic, and the source of heterogeneity was explored via sensitivity analyses, meta-regression (if n ≥ 10), and subgroup analyses according to multiple variables, including study design, region, sex, sample size, cognitive status at baseline, age stage (late life [mean age ≥ 65 y] or midlife), follow-up duration, whether *APOE* ε4 status was adjusted, type of outcome, effect estimate, and quality score. Publication bias was assessed by determining the symmetry of the funnel plot by Egger's test and enhanced-contour funnel plots after the trim-and-fill method. Dose–response meta-analyses were conducted using the inverse variance weighted least squares regression with cluster robust error variances (random effects meta-regression model) [25,26]. The midpoint of the lower and upper bounds was regarded as the dose of each category if the study only reported the range. For studies with an open-ended boundary, we multiplied or divided the reported boundary by 1.25.

Results

ADNI cohort study

Baseline characteristics of the study population

In the ADNI cohort for incident AD, a total of 1135 participants (46.2% females, aged 73.36 ± 7.22 y) were included, with a mean follow-up time of 2.81 ± 1.60 y (range, 1–6 y) (Figure 1A). Compared with participants free of dementia, those who developed AD tended to be *APOE* ε4 carriers, have a lower BMI, were more likely to have a history of depression, and less likely to have a history of insomnia (Table 1).

TABLE 1
Population characteristics at baseline in ADNI cohort

Variable	Total	Participants free of AD	Participants who developed AD	*P*
n	1,135	828	307	
Age, y, mean ± SD	73.36 ± 7.22	73.11 ± 7.26	72.02 ± 7.05	0.057
Female, %	524 (46.2%)	400 (48.3%)	124 (40.4%)	0.017
Education, y	16.16 ± 2.69	16.24 ± 2.66	15.94 ± 2.78	0.101
MCI, %	711 (62.6%)	417 (50.4%)	294 (95.8%)	<0.001
APOE ε4 carriers, %	513 (45.2%)	314 (37.9%)	199 (64.8%)	<0.001
Omega-3 supplementation				
Exposure (yes or no)	272 (24.0%)	213 (25.7%)	59 (19.2%)	0.023
Medium-term exposure (1~9 y)	204 (18.0%)	153 (18.5%)	51 (16.6%)	0.397
long-term exposure (≥10 y)	68 (6.0%)	60 (7.2%)	8 (2.6%)	0.030
Blood markers (N-867)				
Omega-3	0.43 ± 0.12	0.43 ± 0.12	0.42 ± 0.12	0.420
DHA	0.13 ± 0.04	0.13 ± 0.04	0.13 ± 0.04	0.692
ALA	0.41 ± 0.06	0.41 ± 0.06	0.41 ± 0.06	0.786
Insomnia, %	82 (7.2%)	71 (8.6%)	11 (3.9%)	0.004
Depression, %	247 (21.8%)	163 (19.7%)	84 (27.4%)	0.005
Anxiety, %	76 (6.7%)	52 (6.3%)	24 (7.8%)	0.357
Hypertension, %	528 (46.5%)	383 (46.3%)	145 (47.2%)	0.770
BMI (kg/m^2)	27.04 ± 4.86	27.31 ± 4.95	26.33 ± 4.54	0.002
Diabetes, %	102 (9.0%)	75 (9.1%)	27 (8.8%)	0.891
Hyperlipidemia, %	225 (19.8%)	162 (19.6%)	63 (20.5%)	0.720
Stroke, %	41 (3.6%)	22 (2.7%)	19 (6.2%)	0.005
CAD, %	92 (8.1%)	65 (7.9%)	27 (8.8%)	0.605
Current smoker, %	166 (14.6%)	122 (14.7%)	44 (14.3%)	0.865

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; MCI, mild cognitive impairment.

Association of omega-3 fatty acid supplementation use with AD risk

In the unadjusted analysis (Model 1), omega-3 fatty acid supplementation was significantly associated with a lower risk of AD (HR: 0.73, 95% CI: 0.55, 0.97; $P = 0.029$) compared with that of omega-3 fatty acid nonusers. Moreover, long-term users had a 64% lower AD risk (HR: 0.36, 95% CI: 0.18, 0.72; $P = 0.004$) compared with nonusers. The results were similar in Models 2 and 3, which included more confounders (Table 2). Separate analyses by subgroup indicated that compared with no consumption, long-term use of omega-3 dietary supplements was significantly associated with risk of incident AD for males, those of advanced age, *APOE* ε4 carriers, and patients with mild cognitive impairment (MCI) (Table 3). Similar results were obtained in the sensitivity analyses after removing cases diagnosed in the first year (Supplementary Table 5).

Association of blood omega-3 fatty acid and its components with AD risk

Plasma omega-3 fatty acid and its components were not significantly associated with AD risk (Table 2). Similar results were obtained when performing sensitivity analyses after removing cases diagnosed in the first year. (Supplementary Table 5).

Meta-analysis

Searching results and characteristics of studies

We initially identified 18,230 articles after de-duplication. After scanning the titles and abstracts, 709 articles were considered potentially eligible. Following detailed assessments, 48 longitudinal studies met the inclusion criteria, of which 31 were included in the meta-analysis, with a total of 103,651 participants (Figure 1B). The detailed characteristics of the studies included in this meta-analysis are presented in Table 4. Most studies reported omega-3 fatty acid dietary intake ($n = 31$), followed by plasma ($n = 14$), and erythrocyte membrane ($n = 6$).

Association of dietary intake of omega-3 fatty acid and its components with cognitive decline

A meta-analysis of 18 studies with 46,548 participants revealed a significant protective effect of dietary omega-3 fatty acid intake on lower risk of cognitive decline (RR: 0.91, 95% CI: 0.82, 1.00; $I^2 = 60.0\%$, Level M) (Figure 2). Meta-regression analysis revealed that no factor could explain the source of heterogeneity. The significantly protective effect was observed in the subgroup adjusting for *APOE* ε4 status ($n = 8$, RR: 0.83, 95% CI: 0.71, 0.97; $I^2 = 65.0\%$) (Supplementary Table 6). In addition, the dose–response analysis (27,161 participants and 3797 cases) revealed that risk of cognitive decline was reduced when the intake of omega-3 fatty acids exceeded 1.0 g/d. However, the decrease in risk was not significantly linear with the increase in dietary intake (Figure 3A).

Regarding its components, the pooled estimate for dietary DHA from 13 studies was 0.82 (95% CI: 0.72, 0.93; $I^2 = 63.6\%$, Level H) (Figure 2). Dietary intake of DHA was associated with a 27% decreased

TABLE 2
Cox proportional hazards regression analysis of omega-3 supplementation use and its blood biomarkers for AD risk in ADNI cohort

	AD cases/total	Model 1	*P*	Model 2	*P*	Model 3	*P*
		HR (95%CI)		HR (95%CI)		HR (95%CI)	
Omega-3 supplementation							
non-exposure	248/863	1 (reference)		1 (reference)		1 (reference)	
exposure	59/272	0.73 (0.55-0.97)	0.029	0.71 (0.53-0.94)	0.018	0.72 (0.54-0.97)	0.031
medium-term exposure	51/204	0.87 (0.64-1.18)	0.370	0.84 (0.62-1.14)	0.262	0.85 (0.62-1.16)	0.304
long-term exposure	8/68	0.36 (0.18-0.72)	0.004	0.35 (0.17-0.71)	0.004	0.37 (0.18-0.75)	0.006
Blood markers							
omega-3	287/867	0.91 (0.52-1.61)	0.752	1.15 (0.65-2.03)	0.640	1.28 (0.71-2.30)	0.407
DHA	287/867	0.86 (0.57-1.30)	0.485	1.05 (0.70-1.57)	0.832	1.13 (0.74-1.71)	0.571
ALA	287/867	1.08 (0.64-1.83)	0.781	1.23 (0.74-2.05)	0.428	1.27 (0.75-2.17)	0.374

Model 1: crude HR with no covariates adjusted;
Model 2: HR adjusted for age, sex, education, clinical diagnosis, and *APOE* ε4;
Model 3: HR adjusted for Model 2 plus insomnia, depression, anxiety, hypertension, diabetes mellitus, hyperlipidemia, smoking, BMI, stroke, and coronary artery disease, alcohol intake, multivitamins, vitamin B12, folate, anti-hypertensive drugs and antidiabetic drugs.

TABLE 3
Hazard ratios with corresponding 95% CIs of the association of omega-3 supplementation use and its blood biomarkers with risk of AD according to strata of age, sex, *APOE* ε4 status and cognitive status in the ADNI cohort

		Omega-3 supplementation				Blood markers		
		Non-exposure	Exposure	Medium-term exposure	Long-term exposure	Omega-3	DHA	ALA
Sex	Male	1 (reference)	0.80 (0.56-1.15)	0.10 (0.68-1.46)	0.33 (0.13-0.82)	1.04 (0.50-2.18)	1.02 (0.61-1.72)	1.11 (0.57-2.17)
	Female	1 (reference)	0.62 (0.38-1.02)	0.65 (0.38-1.11)	0.50 (0.16-1.61)	1.84 (0.67-5.04)	1.40 (0.67-2.92)	1.85 (0.75-4.61)
Age	Midlife <65 y	1 (reference)	0.87 (0.33-2.35)	0.94 (0.35-2.53)	0.78 (0.00-∞)	0.91 (0.12-6.70)	0.79 (0.18-3.44)	4.09(0.76-22.00)
	Late life ≥65 y	1 (reference)	0.69 (0.47-0.88)	0.75 (0.54-1.05)	0.35 (0.17-0.73)	1.29 (0.71-2.37)	1.15 (0.75-1.76)	1.18 (0.68-2.06)
APOE ε4	*APOE* ε4 (+)	1 (reference)	0.75 (0.52-1.08)	0.90 (0.61-1.32)	0.29 (0.11-0.83)	2.03 (0.98-4.23)	1.60 (0.94-2.71)	1.11 (0.58-2.14)
	APOE ε4 (-)	1 (reference)	0.71 (0.44-1.14)	0.81 (0.48-1.35)	0.45 (0.16-1.25)	0.49 (0.17-1.38)	0.57 (0.28-1.18)	1.72 (0.65-4.57)
Cognitive status	CN	1 (reference)	0.27 (0.03-2.36)	0.44 (0.05-3.84)	0.45 (0.00-∞)	0.10 (0.00-2.42)	0.20 (0.02-2.13)	0.44 (0.03-6.94)
	MCI	1 (reference)	0.75 (0.56-1.00)	0.87 (0.63-1.18)	0.40 (0.20-0.82)	1.36 (0.75-2.48)	1.17 (0.77-1.80)	1.41 (0.82-2.43)

A separate Cox regression model was conducted for each stratum of the covariate
Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment.

risk of dementia and a 24% decreased risk of AD, whereas dietary intake of ALA (Level H) and EPA (Level L) did not have a significant protective effect on cognitive decline (Supplementary Figures 1–3). The dose–response analysis revealed that an increment of 0.1 g/d of DHA or EPA intake was associated with an 8.0% ($P_{linear} = 0.0005$) or 9.9% ($P_{linear} = 0.0004$) lower risk of cognitive decline, respectively (Figure 3B, C). No publication bias was identified.

Association of plasma omega-3 fatty acid and its components with cognitive decline

No significant association was found between higher levels of plasma DHA and a lower risk of cognitive decline (RR: 0.88, 95% CI: 0.76, 1.03; $I^2 = 63.6\%$, Level L), with publication bias (Egger's $P = 0.007$, corrected RR: 0.99, 95% CI: 0.85, 1.14; $I^2 = 69\%$) (Figure 2). Meta-regression analysis indicated that the mean age could partly account for the heterogeneity ($P = 0.02$, $tau^2 = 0.002$). Risk of cognitive decline in older participants (with an average baseline age ≥ 65 y) was significantly reduced by 23%, whereas in younger participants, no significant association was indicated for plasma levels of DHA (Supplementary Table 6). Higher levels of plasma EPA were significantly associated with lower risk of cognitive decline (RR: 0.88, 95% CI: 0.78, 0.995; $I^2 = 38.1\%$, Level M), and dementia (RR: 0.84, 95% CI: 0.73, 0.96; $I^2 = 0.0\%$, Level M). Plasma levels of omega-3 fatty acid (Level L) and ALA (Level L) did not have a significant protective effect on cognitive decline (Figure 2 and Supplementary Figures 4 and 5).

Association of erythrocyte membrane omega-3 fatty acid and its components with cognitive decline

Five longitudinal studies involving 14,940 participants explored the association between omega-3 fatty acid levels in erythrocyte membranes and risk of cognitive decline. No significant protective effect was revealed (RR: 0.96, 95% CI: 0.90, 1.02; $I^2 = 34.5\%$, Level M). However, higher levels of erythrocyte membrane DHA (RR: 0.94, 95% CI: 0.89, 0.98; $I^2 = 0.4\%$, Level H) and EPA (RR: 0.95, 95% CI: 0.89, 1.00; $I^2 = 0\%$, Level H) were associated with a lower risk of cognitive decline (Figure 2 and Supplementary Figures 6 and 7).

Summary of evidence credibility

The larger area of the pentagonal graph represents better evidence credibility, whereas Figures 4A–C represent omega-3 fatty acids in 3 states: dietary, plasma, and erythrocytes. The evidence credibility for dietary intake and erythrocytes was higher than that of plasma (Figure 4). A higher Index $S_{difference}$ indicates a stronger degree of consistency between the results of meta-analyses and the results of each individual cohort study included. Thus, the consistency of the results related to erythrocytes was greater than that of dietary intake and plasma. Overall, the evidence credibility, ranked from highest to

TABLE 4
Characteristics of 48 studies included in the systematic review and meta-analysis

N	First author, y	Design, Cohort name, Country	Follow-up duration (mean)	Age at baseline (mean)	Female (%)	Participants	Cases	Outcome	Categories	Exposure measurement	Study quality
1	Li 2021	RC; ADNI; Canada, Unites States	2.8y	73y	46%	1135[1]/867 [2]	307[1]/287[2]	AD	[1] omega-3 [2] omega-3, DHA, ALA	FFQ	6
2	Melo van Lent 2021 [27]	PC; AgeCoDe; Germany	7y	84y	64%	1264	233	AD	[2] omega-3; DHA; EPA; ALA	Blood sample	7
3	Koch 2021 [28]	PNCC; GEMS; Unites States	4.8y	78y	47%	1252	498/334	Dementia; AD	[2] omega-3; DHA; EPA; ALA	Blood sample	6.5
4	Nozaki 2021 [29]	PC; JPHC; Japan	15y	73y	69%	1127	380/54	Dementia; MCI	[1] PUFA; omega-3; EPA; DHA	FFQ	5.5
5	Thomas 2020 [30]	PC; 3C; France	17[4]y	74y	NA	1279	271	Dementia	[2] EPA; DHA	Blood sample	7.5
6	Jiang et al. [31] 2020	PC; SCHS; Singapore	20y	45-74y	NA	16736	2397	CD	[1] PUFA; omega-3; ALA	FFQ	8
7	Gustafson et al. [32] 2020	PC; WHICAP; Unites States	4.9y	76y	67%	2612	380	AD	[1] PUFA; omega-3; DHA; EPA	FFQ	7
8	Mao 2019 [33]	PC; CARDIA; Unites States	25y	25y	56%	3231	NA	CD	[1] omega-3; DHA; EPA	CARDI questionnaire	7.5
9	Bigornia 2018 [34]	PC; BPRHS; Unites States	2y	45-75y	73%	1032	151	CD	[1] and [3] ALA; EPA; DHA	FFQ and blood sample	6.5
10	Haution-bitker 2018 [35]	PNCC; GERIOX; France	11.5[5]m	80y	65%	140[2]/70[3]	44	CD	[2] and [3] omega-3; EPA; DHA; ALA	Blood sample	3
11	Nooyens 2018 [36]	PC; DS; Netherlands	5y	43-70y	51%	2612	NA	CD	[1] PUFA; omega-3; DHA; ALA; EPA	FFQ	7
12	Ammann 2017 [37]	PC; WHIMS-ECHO; Unites States	9.8[5]y	70y	100%	6706	587/671	Dementia; MCI	[3] omega-3; DHA; EPA	Blood sample	7.5
13	Yamagishi 2017 [38]	PNCC; CIRCS; Japan	12.5y	64y	66%	7586	315	Dementia	[2] DHA; EPA; ALA	Blood sample (serum)	7.5
14	Vanderest 2016 [39]	PC; MAP; Unites States	4.9y	81y	75%	915	NA	CD	[1] omega3; ALA	FFQ	7
15	Otsuka 2014 [40]	PC; NILS-LSA; Japan	10.2y	67y	46%	430	36	CD	[2] DHA; EPA	Blood sample	7
16	Bowman 2013 [41]	PC; OBAS; Unites States	3.9y	86y	62%	86	NA	CD	[2] omega-3	Blood sample	6.5
17	Titova 2013 [42]	PC; PIVUS; Sweden	5y	70y	48%	252	NA	CD	[1] omega-3	7-d food protocol	6.5
18	Ammann 2013 [43]	PC; WHISCA; Unites States	5.9[5]y	73y	100%	2157	NA	CD	[3] omega-3	Blood sample	6
19	Okereke 2012 [44]	PC; WHS; Unites States	4[4]y	66y	100%	6183	NA	CD	[1] PUFA	FFQ	5
20	Ronnemaa 2012 [45]	PC; ULSAM; Sweden	35[4]y	50y	0%	2009	213/91	Dementia; AD	[2] DHA; EPA; ALA	Blood sample	6.5
21	Lopez 2011 [46]	PC; RBS; Unites States	3y	80y	44%	242[1]/266[2]	42/30	Dementia; AD	[1] and [2] DHA	FFQ	6

(*continued on next page*)

TABLE 4 (*continued*)

N	First author, y	Design, Cohort name, Country	Follow-up duration (mean)	Age at baseline (mean)	Female (%)	Participants	Cases	Outcome	Categories	Exposure measurement	Study quality
22	Kesse-guyot 2011 [47]	PC; SUVIMAX 2; France	13y	51y	46%	3294	NA	CD	[1] omega-3; DHA; EPA	Repeated 24-h dietary records	6
23	Gao 2011 [48]	PC; SLAS; Singapore	1.5[5]y	66y	66%	1475	NA	CD	[1] omega-3	A self-reported single question	5.5
24	Samieri 2011 [49]	PC; 3C; France	7[4]y	74y	61%	1228	NA	CD	[2] DHA; EPA	Blood sample	7.5
25	Vercambre 2010 [50]	PC; WACS; Unites States	5.4[4]y	72y	100%	2551	NA	CD	[1] PUFA	Willett FFQ	5
26	Vercambre 2009 [51]	PC; E3N; France	13[4]y	78y	100%	4809	598	CD	[1] PUFA; omega-3; ALA	FFQ	5.5
27	Devore 2009 [52]	PC; RS; Netherlands	9.6y	68y	59%	5395	465	Dementia;	[1] omega-3; DHA; EPA	SFFQ	7.5
28	Devore 2009(2) [53]	PC; NHS; Unites States	4.2y	74y	100%	1486	NA	CD	[1] PUFA	Willett FFQ	6
29	Kroger 2009 [54]	PC; CSHA; Canada	4.9[5]y	81y	66%	663	149/105	Dementia; AD	[3] omega-3; DHA; EPA	Blood sample	7
30	Vanderest 2009 [55]	PC; NAS; Unites States	6y	68y	0%	1025	NA	CD	[1] omega-3;	Willett FFQ	4
31	Samieri 2008 [56]	PC; 3C; France	4y[4]	74y	62%	1214	65	Dementia	[2] PUFA; omega-3; DHA; EPA;ALA	Blood sample	6.5
32	Eskelinen 2008 [57]	PC; CAIDE; Finland	21y	50y	62%	1449	82	MCI	[1] PUFA	FFQ	6.5
33	Velho 2008 [58]	PC; NA; Portugal	8.5m	70y	71%	187	NA	CD	[1] omega-3	3- d food dietary record	5
34	Whalley 2008 [59]	PC; SCRE; Scotland, United Kingdom	4[4]y	64y	60%	120	NA	CD	[3] omega-3; DHA; EPA	Blood sample	5
35	Barberger-Gateau 2007 [60]	PC; 3C; France	3.5y	≥65y	NA	8085	281/183	Dementia; AD	[1] omega-3	FFQ	7
36	Beydoun et al. [14] 2007	PC; ARIC; Unites States	6y	50-65y	55%	7814[1]/2251[2]	486/140	CD	[1, 2] omega-3; ALA	Blood sample	5.5
37	Vangelder 2007 [61]	PC; ZES ;Netherlands	5y	70-89y	51%	210	NA	CD	[1] omega-3	Cross-check dietary history method	6
38	Dullemeijer 2007 [62]	PC;FACIT; Netherlands	3y	50-70y	0%	404	NA	CD	[2] PUFA; omega-3; DHA; EPA; ALA	Blood sample	6.5
39	Solfrizzi 2006(2) [63]	PC; ILSA; Italy	2.6[5]y	65-84y	28%	278	18	MCI	[1] PUFA	FFQ	5.5
40	Schaefer 2006 [64]	PC; FHS; Unites States	9.1y	76y	45%	488[1]/899[2]	79	AD	[1] and [2] DHA	FFQ	7
41	Laitinen 2006 [65]	PC; CAIDE; Finland	21y	50y	64%	1341	117/76	Dementia; AD	[1] PUFA	FFQ	8.5
42	Solfrizzi 2006 [66]	PC; ILSA; Italy	8.5[5]y	73y	62%	278	NA	CD	[1]PUFA	FFQ	7
43	Morris 2005 [67]	PC; CHAP; Unites States	6[4]y	74y	45%	3718	NA	CD	[1] omega-3; DHA; EPA; ALA	FFQ	6.5

(*continued on next page*)

TABLE 4 (*continued*)

N	First author, y	Design, Cohort name, Country	Follow-up duration (mean)	Age at baseline (mean)	Female (%)	Participants	Cases	Outcome	Categories	Exposure measurement	Study quality
44	Morris 2003 [68]	PC; CHAP; Unites States	3.9y	65-94y	62%	815	131	AD	[1] omega-3; DHA; EPA; ALA	FFQ	6
45	Heude 2003 [69]	PC; EVA; France	4y	63-74y	61%	246	27	CD	[3] PUFA; omega-3; DHA; EPA	Blood sample	5
46	Laurin 2003 [70]	PC; CSHA; Canada	5y	77y	58%	174	11	Dementia	[2] PUFA; omega-3; DHA; EPA	Blood sample	7.5
47	Engelhart 2002 [71]	PC; RS;Netherlands	6.0y	68y	66%	5395	197/146 /29	Dementia; AD; VD	[1] PUFA; omega-3	FFQ	6.5
48	Kalmijn 1997 [72]	PC; ZES; Netherlands	3y	69-89y	59%	342	51	CD	[1]PUFA; omega-3; DHA; EPA	Cross-check dietary history method	4.5

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; AgeCoDe, German Study on Aging, Cognition, and Dementia; BPRHS, Boston Puerto Rican Health Study; CAIDE, Cardiovascular risk factors, Aging and Dementia study; CARDIA, Coronary Artery Risk Development in Young Adults; CD, cognitive decline; CIRCS, Circulatory Risk in Communities Study; CHAP, Chicago Health and Aging Project; CHCS, Cardiovascular Health Cognition Study; CHNS, China Health and Nutrition Survey; CLHLS, Chinese Longitudinal Health Longevity Study; CSHA, Canadian Study of Health and Aging; DS, Doetinchem Study; EVA, Etude du Vieillissement Artériel Study; E3N, Etude Epideámiologique de Femmes de la Mutuelle Geáneárale de l'Education Nationale study; FACIT, Folic Acid and Carotid Intima-media Thickness Trial; FHS, Framingham Heart Study; GEMS, Ginkgo Evaluation of Memory Study; ILSA, Italian Longitudinal Study on Aging; JPHC, Japan Public Health Center-based Prospective Study; MAP, Rush Memory and Aging Project; MCI, mild cognitive impairment; NA, not available; NAS, Normative Aging Study; NILS-LSA, National Institute for Longevity Sciences-Longitudinal Study for Aging; NHS, Nurses' Health Study; OBAS, Oregon Brain Aging Study; Omega-3, omega-3 polyunsaturated fatty acid; PC, prospective cohort; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors Cohort; PNCC, Prospective nested case-control study; PUFA, polyunsaturated fatty acid; RBS, Rancho Bernardo Study; RC, retrospective cohort; RS, Rotterdam Study; SCHS, Singapore Chinese Health Study; SCRE, Scottish Council for Research in Education; SLAS, Singapore Longitudinal Aging Study; SUVIMAX, Supplementation with Antioxidant Vitamins and Minerals; ULSAM, Uppsala Longitudinal Study of Adult Men cohort; VD, vascular dementia; WACS, Women's Antioxidant Cardiovascular Study; WHICAP, Washington Heights-Hamilton Heights-Inwood Columbia Aging Project; WHISCA, Women's Health Initiative Study of Cognitive Aging; WHIMS-ECHO, Woman's Health Initiative Memory Study - Epidemiology of Cognitive Health Outcomes; WHS, Women's Health Study; ZES, Zutphen Elderly Study; 3C, Three-City Study.

[1] dietary
[2] plasma/serum
[3] erythrocyte
[4] max age
[5] median age

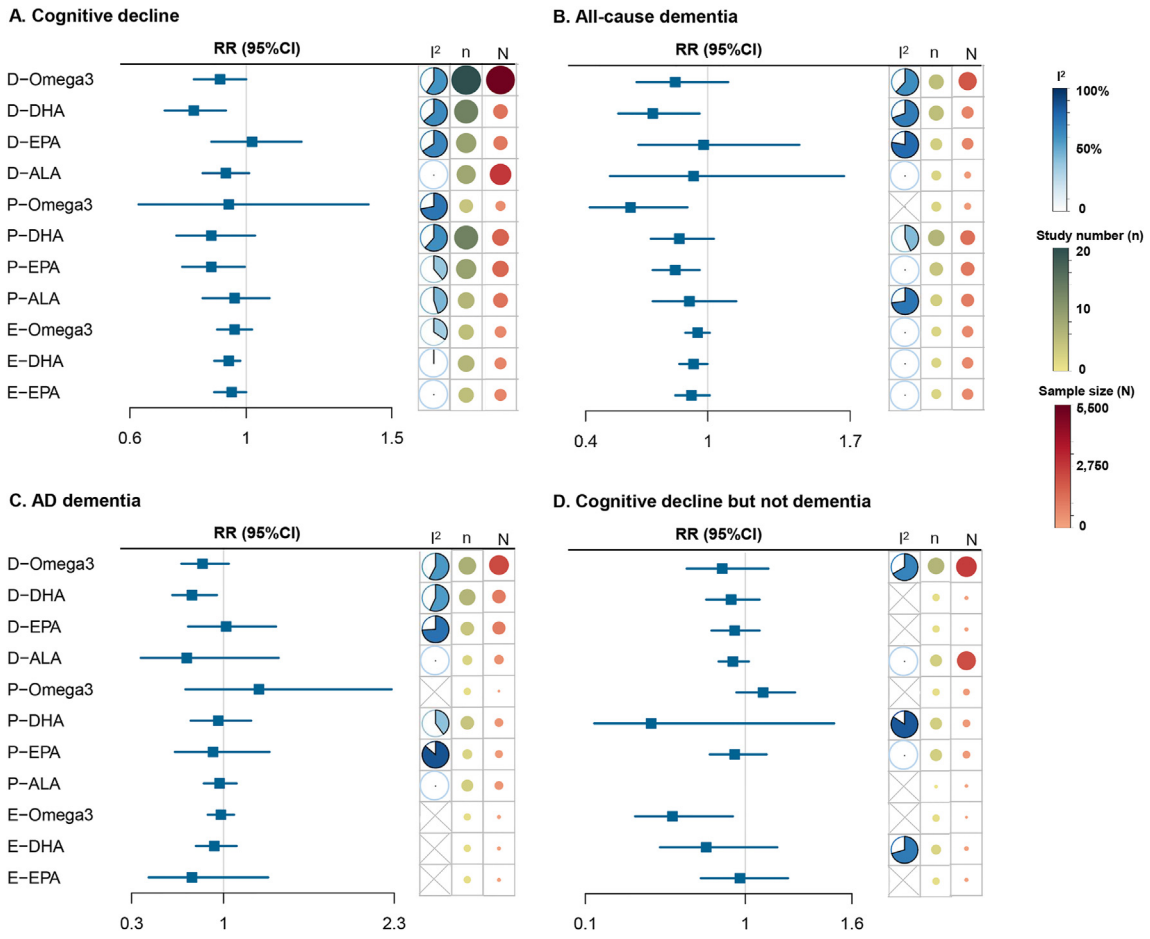

FIGURE 2. Association of omega-3 and its peripheral biomarkers with risk of cognitive decline. Squares represent overall estimate effects and solid lines represent 95% CIs (Supplementary Table 6). The blue fan represents proportion of heterogeneity among studies. Green/red dots represent the number of studies/participants included, respectively. D-omega-3, dietary intake of omega-3 fatty acid; E-omega-3, erythrocyte omega-3 fatty acid; P-omega-3, plasma omega-3 fatty acid.

lowest, was as follows: erythrocytes, diet, and plasma (Supplementary Table 4).

Discussion

In the present study, we found that supplemental omega-3 fatty acid use was significantly associated with a lower risk of AD, with a potential moderating effect by *APOE* ε4. Our meta-analysis findings strengthened the possible association between dietary omega-3 fatty acid intake and its peripheral biomarkers with AD, dementia, or cognitive decline. Compared with previous studies [73–75] (Supplementary Table 7), we included 27 new cohorts and provided the most comprehensive evidence of the relationship of omega-3 fatty acids and dementia.

APOE ε4 status may influence the association between omega-3 fatty acids and AD. *APOE* ε4 is the strongest genetic risk factor for AD [76]. The ADNI cohort revealed an inverse association between omega-3 fatty acid dietary supplements and AD only among *APOE* ε4 carriers, which is consistent with our previous finding [12]. Consistently, several studies concluded that omega-3 fatty acid supplementation could attenuate the effect of *APOE* ε4 on AD pathologic changes and that such protective effects existed in *APOE* ε4 carriers only [11, 77]. However, plasma DHA levels showed few changes after omega-3 fatty acid supplementation among *APOE* ε4 carriers [78,79]. It has also been proposed that *APOE* ε4 carriers are more likely to exhibit blood–brain barrier dysfunction, which can impair DHA delivery to the brain. Thus, it is questionable whether *APOE* ε4 carriers can gain benefits from supplementing with omega-3 fatty acids. A compensatory mechanism hypothesis might help explain the dispute, such that DHA utilization and metabolic demands are increased in *APOE* ε4 carriers. Consistent with the hypothesis, a positron emission tomography imaging study discovered a higher increase in DHA incorporation in several brain regions in *APOE* ε4 carriers as compared to noncarriers [80]. Future studies should focus on populations with high genetic susceptibility (e.g., *APOE* ε4 genotype) to test the efficacy of omega-3 fatty acid supplementation.

Our findings support the hypothesis that the efficacy of omega-3 fatty acid supplementation is dose-dependent. We found that omega-3 fatty acid supplementation was significantly associated with a decreased risk of AD, particularly among long-term users. Regular intake of omega-3 fatty acids may help maintain stable blood concentrations, which can benefit the prevention of dementia. Although we did not observe a significant linear relationship between dietary omega-3 fatty acid intake and risk of cognitive decline, risk of cognitive decline decreased when the intake of omega-3 fatty acids exceeded 1.0 g/d. For this reason, we propose that 1.0 g/d may be the threshold

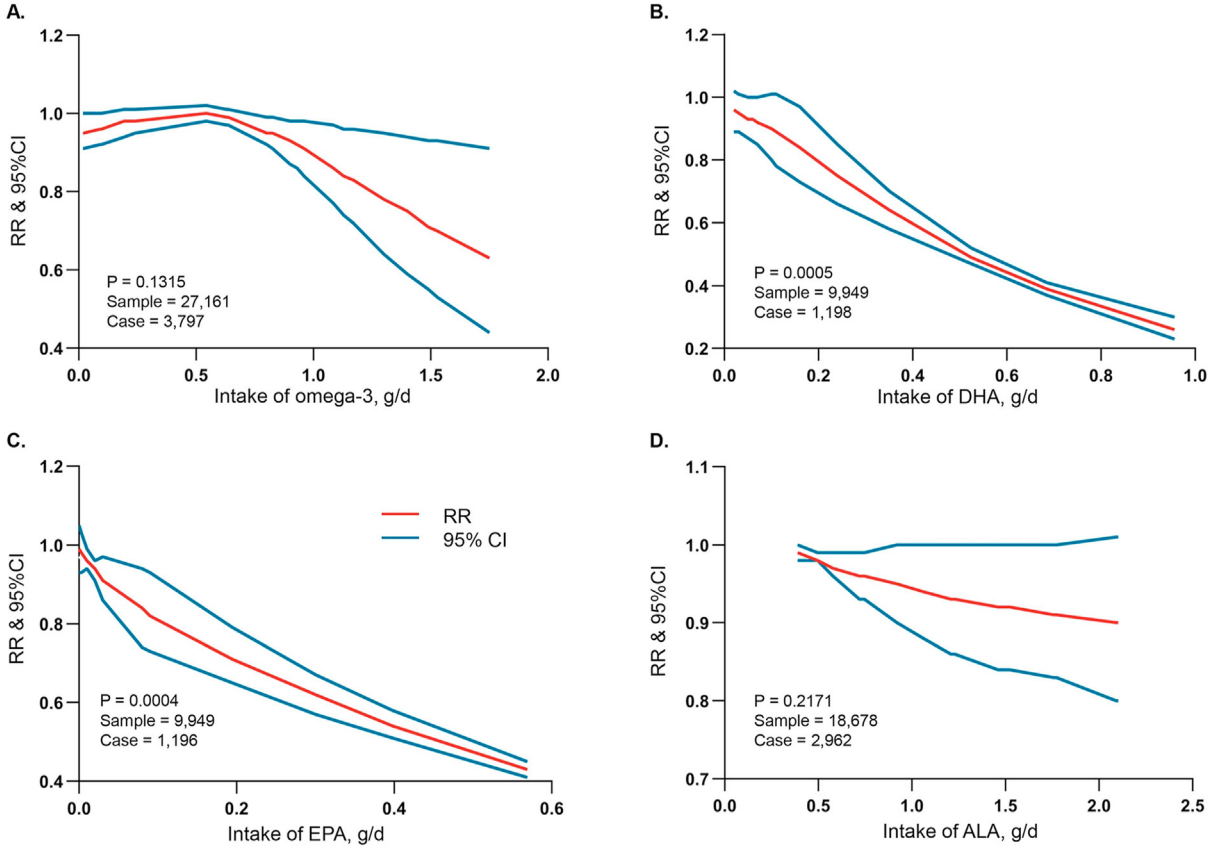

FIGURE 3. Dose–response relationships between dietary omega-3 and cognitive decline. The dose–response analyses revealed significantly linear associations between dietary intake of DHA (B) or EPA (C) and risk of cognitive decline. An increment of 0.1 g/d of DHA or EPA intake was associated with an 8.0% (P_{linear} = 0.0005) or 9.9% (P_{linear} = 0.0004) lower risk of cognitive decline, respectively. The dose–response analyses revealed a nonsignificant relationship between dietary intake of omega-3 (A), ALA (D) and risk of cognitive decline. AD, Alzheimer's disease; RR, relative risk.

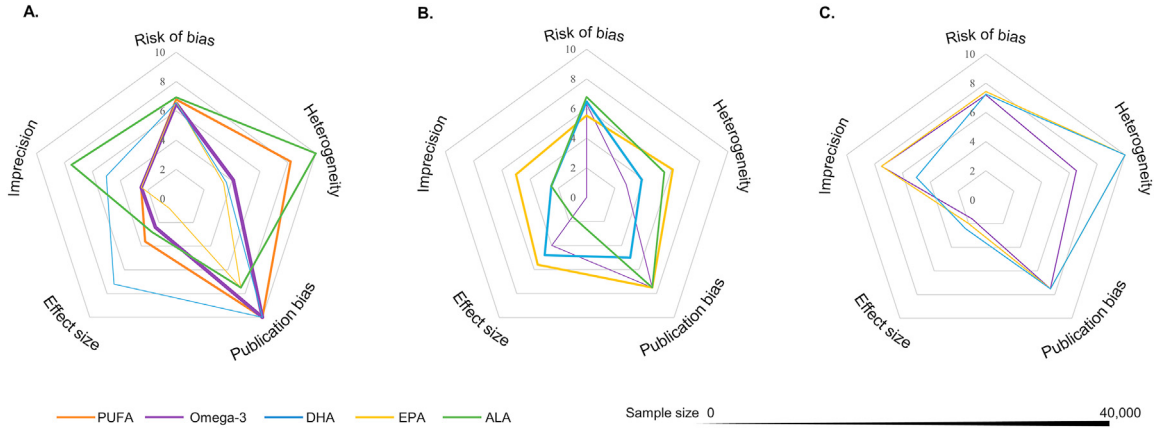

FIGURE 4. Evidence rating results. The credibility of each meta-analysis result was categorized into 3 levels: 'High (H)', 'Moderate (M)', and 'Low (L)' by summing the scores of 5 domains: risk of bias, heterogeneity, publication bias, effect size, and imprecision. Scores in each domain ranged from 0 to 10, and a score of 50 represents the highest level of evidence. (A) dietary; (B) plasma; (C) erythrocyte.

dosage of omega-3 fatty acids for the prevention of cognitive decline. Appropriate dosing of omega-3 fatty acids is beneficial not only for preventative purposes in individuals with healthy cognition but also for the treatment of patients with cognitive impairment. Previous randomized controlled trials discussed the appropriate dosage of omega-3 fatty acids and found that high doses (0.9–1.8 g/d) of DHA/EPA intake improved cognitive function [81–83], whereas low doses (0.3–0.7 g/d) failed to exert benefits [84,85]. Since the optimal doses for the prevention and treatment are not well established, future studies should explore the efficacious dose range. Furthermore, the recommended dose may differ for specific populations, such as *APOE* ε4 carriers.

This evidence-based summary revealed the significant role of erythrocyte DHA in predicting risk of cognitive decline and a suggestive role of plasma and erythrocyte EPA (high-level evidence). Several mechanisms may explain the importance of omega-3 fatty acid biomarkers in predicting dementia. First, DHA is commonly

considered beneficial for maintaining the integrity of brain neurons and expressing neuroprotection by inhibiting tau phosphorylation. Second, DHA could target AD-specific pathology pathways adversely affected in *APOE ε4* carriers, including microglia and inflammatory pathways, astrocytes and lipid metabolism, and pericytes and blood–brain barrier integrity [86]. Third, although EPA is rarely found in the brain, it is important to balance inflammation and immune function associated with AD pathogenesis. Based on our moderate-to-high evidence levels, it is reasonable to conclude that blood tests for EPA and DHA concentration may be useful for AD risk evaluation. Specifically, erythrocyte membrane concentration is a relatively more stable indicator for clinical research. Erythrocyte concentrations may reflect with higher precision dietary intake over a longer term (estimated range of the past 60 to 90 d) than plasma concentrations (estimated range of the past 7 to 14 d). Future studies should further investigate the different biological effects of EPA and DHA so that the assessment of their concentrations via regular blood tests in high-risk populations may be useful for early risk detection and reduction of AD.

Future cohort studies should be refined as follows: *1*) baseline measures for omega-3 fatty acids should include the dosage of daily intake and more detailed supplement information, *2*) baseline evaluation of population characteristics should include certain genetic factors (e.g., *APOE* ε4 genotype), and cognitive level (e.g., cognitively intact/nondemented/MCI and preclinical dementia) should be thoroughly screened using objective rating scales rather than self-reported questionnaire; *3*) special attention should be paid to the interaction of omega-3 fatty acids with other kinds of fatty acids because balanced blood levels of omega-3 fatty acids and other fatty acids are necessary for favorable cognitive outcomes. Some implications for practical use also apply as follows: *1*) maintaining an adequate intake of omega-3 fatty acids provides a tool for the potential prevention of dementia, especially in *APOE* ε4 carriers; *2*) particular attention should be paid to the regular examination of erythrocyte DHA in populations who are at increased risk of dementia, either based on the *APOE* ε4 genotype or other risk factors.

However, potential limitations of this study must be considered. First, although we adjusted for several relevant potential confounders, residual confounding from unmeasured confounders (such as dietary intake and physical activity) remains an issue. Second, the total duration of supplementation but not the accurate dose was used in the ADNI analyses, which might introduce certain risk of measurement bias. According to previous publications, the omega-3 supplement dose varied slightly from 0.6 to 1.3 g/d for the general population [31,32]. Third, all cohorts assessed omega-3 fatty acid exposure only at baseline, which may have resulted in misclassifications as the actual intake amount may change over time. Fourth, most cohort studies included in the meta-analysis assessed omega-3 fatty acid intake using FFQ, which are designed to measure the frequency of intake rather than exposure time, which was not verified in the meta-analysis. Fifth, due to too little data in the included studies, the associations between dementia subtypes and the role of omega-3 fatty acids in different *APOE* ε4 groups have not been thoroughly explored.

In conclusion, our findings suggest that *1*) long-term omega-3 fatty acid supplementation may reduce risk of AD; *2*) dietary omega-3 fatty acid intake, especially DHA, may lower risk of dementia or cognitive decline; and *3*) peripheral biomarkers of omega-3 fatty acids may serve as predictors of cognitive decline. However, further investigation is needed to understand the gene–environment interactions involved in the intake of omega-3 fatty acids.

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Author disclosures

The authors report no conflicts of interest.

Data availability

All data are available upon reasonable request or can be obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.04.001.

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