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Associations of Plasma Omega-3 Fatty Acid Levels and Reported Fish Oil Supplement Use with Depression and Anxiety: A Cross-Sectional Analysis from the United Kingdom Biobank

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A B S T R A C T

Background: The role that marine omega-3 (n–3) polyunsaturated fatty acids (PUFAs) may play in reducing the risk for developing depression and/or anxiety is unclear.

Objectives: The present study examined the relationships between plasma levels of total omega-3 PUFAs, docosahexaenoic acid (DHA), and the non-DHA ω-3 PUFAs with medical record-documented depression and/or anxiety (both historical and recent, within the last 12 mo) in the United Kingdom Biobank. The associations of these outcomes with the reported use of fish oil supplements (FOS) were also examined.

Methods: Information from 258,354 participants who had data on plasma ω-3 PUFA levels and all covariates were used for the biomarker-based analyses, and data from 468,145 people who reported FOS use at baseline were used in the latter analysis.

Results: We found that all 3 ω-3 PUFA metrics were inversely associated with a history of both depression and anxiety. Specifically, risk for the former outcome was between 15% and 33% lower in Q5 compared with Q1, and for the latter outcome, between 19% and 22% lower comparing Q5 with Q1. Risk for recent depression was 29% and 32% lower (Q5 compared with Q1) for total ω-3 PUFAs and for non-DHA, respectively. FOS use was associated with a 9%–10% lower risk for a history of depression and anxiety, respectively, and a 20% lower risk for recent anxiety.

Conclusions: We found evidence that higher levels of ω-3 PUFAs may play a protective role in depression and anxiety.

Keywords: mental health, biomarkers, epidemiology, observational cohort, omega-3 fatty acids

Introduction

Depression is a mental health condition that involves a prolonged period of sadness, loss of interest, and difficulty with daily life. Its estimated prevalence in 2020 in the United States was ∼18% [1]. Some cross-sectional and prospective cohort studies have suggested that a low level of omega-3 polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid (DHA), in the blood/tissues is associated with increased risk for depression [2]. Furthermore, a meta-analysis of randomized clinical trials (RCTs) also supports this conclusion [3]. However, others have suggested no relationship. For example, a substudy of vitamin D and ω-3 Trial (VITAL, an RCT testing the effects of 840 mg/d eicosapentaenoic acid (EPA) + DHA ethyl esters for ∼5 y in >25,000 adults free of cardiovascular disease and cancer at baseline) entitled VITAL-Depression Endpoint Progression [4] examined the effects of ω-3 PUFA on incident depression in >18,000 participants free of depression at

Abbreviations: aORs, adjusted odds ratios; eO3I, estimated omega-3 index; FA, fatty acid; FOS, fish oil supplements; LA, linoleic acid; RCTs, randomized clinical trials; UKBB, United Kingdom Biobank; VITAL, vitamin D and omega-3 trial.

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baseline. Compared with placebo, treatment with ω-3 supplements yielded mixed results, with a small but statistically significant increase in risk of depression or clinically relevant depressive symptoms but no difference in mood scores. The authors concluded that "These findings do not support the use of ω-3 supplements in adults to prevent depression." On the other hand, in another study, treatment of individuals with depression with 3.2 g of ω-3 PUFAs for 12 wk had favorable results, with the authors concluding, "These findings suggested that monotherapy of ω-3 PUFAs could improve depression and potentially serve as an alternative option for patients with major depressive disorder" [5]. Thus, the relationship between ω-3 and depression remains unclear.

The situation is similar for anxiety, which is defined as an emotion characterized by feelings of fear, dread, tension, and worried thoughts. Like depression, anxiety levels continue to increase in the United States and globally, with a marked rise during and after the global pandemic. Both biomarker-based case-control studies [6] as well as meta-analyses of RCTs [7] support a beneficial role of ω-3 PUFAs in anxiety, but there are notable exceptions [8]. Hence, like depression, the role that ω-3 PUFAs may play in either the prevention or treatment of anxiety disorders requires further examination, especially in very large cohorts in the general population.

To attempt to clarify these relationships, we examined the cross-sectional relationships between plasma levels of ω-3 PUFAs (and DHA specifically), as well as reported fish oil use and the frequency of oily fish intake, and depression and anxiety in the United Kingdom Biobank (UKBB).

Methods

Sample

The UKBB is a prospective, population-based cohort of 502,411 individuals, aged 40–70 y, recruited in the United Kingdom between April 2007 and December 2010 [9]. UKBB has ethical approval (Ref. 11/NW/0382) from the Northwest Multi-centre Research Ethics Committee as a Research Tissue Bank, and the University of South Dakota Institutional Review Board approved the use of these deidentified, publicly available data for research purposes (IRB-21-147). Within the cohort, a random set of 258,354 participants had available plasma fatty acid (FA) data after exclusion of those missing covariates and those who withdrew from the UKBB project. In some analyses, we consider a sample of 468,145 people with answers to a question on fish oil use and complete covariate data.

Exposures

The primary exposures in this study were the two plasma n-3 PUFA metrics available from the nuclear magnetic resonance (NMR) analysis (Nightingale Health Plc) [10]: DHA (%) and total n3 PUFA (%). A third metric, the non-DHA n3 PUFA (%), defined as total n3 PUFA minus DHA, was used as a surrogate for the sum of EPA, docosapentaenoic acid (DPA), and alpha-linolenic acid (ALA), although the exact amounts of each of these are unknown. An estimated ω-3 Index [erythrocyte EPA + DHA (%), eO3I] was derived from an interlaboratory experiment as described by Schuchardt et al. [11]. Self-reported regular fish oil supplement (FOS) use was collected at baseline by touch screen answer to the question, "Do you regularly take any of the following?" with "fish oil (including cod liver oil)" being one of several optional answers. No further information regarding dose, product, or frequency of use was collected. Finally, we explored the associations with reported oily fish intake obtained from the food frequency questionnaire administered at baseline. Oily fish was described as "like sardines, salmon, mackerel, and herring," and the options for intake frequency ranged from "never" to "daily." Here, we collapsed them into four categories: never, $<$1/wk, 1/wk, and $\geq$2/wk.

Outcomes

Lifetime prevalence of depression or anxiety was assessed by any ICD10 code related to these diagnoses in the subjects' medical records at the time of FA. Depression codes were ICD9-296 or 311, and ICD10F3X; anxiety codes were ICD9-3XX and ICD10F4X. The recent prevalence of depression or anxiety was assessed by any ICD10 coded depression or anxiety diagnosis within 12 mo of the FA measurement.

Covariates

We adjusted for several demographic, behavioral, biomarker, and medical history variables: age, biological sex (male/female), self-reported race/ethnicity (Asian, Black, White, and other), marital status (married/not), BMI, smoking (pack years), self-reported alcohol consumption (rarely, monthly, 1–2x/wk, 3–4x/wk, and daily), Townsend Deprivation Index, education status (college, high school, or less), self-reported exercise (quartiles of moderate-to-vigorous exercise min/wk expressed as metabolic equivalents), self-reported multivitamin use (yes/no), linoleic acid (LA) levels, and non-LA ω-6 levels. Additional details on covariates, along with corresponding UKBB variable IDs, are provided in Supplemental Table 1.

Statistical analysis

Sample characteristics are summarized using standard statistical methods (e.g., means, SDs, %s). Logistic regression models were fit when predicting history of depression, history of anxiety, current depression, and current anxiety (yes/no) with separate models for each of three n3 PUFA exposures and each of the four outcomes in both partially adjusted (age, sex, and race/ethnicity; model 1) and fully adjusted (all variables shown in Table 1; model 2) models. A model 3 was also included in the analysis that focused on oily fish intake and FOS use. Here, these two exposures were mutually adjusted for the other when computing the adjusted odds ratios (aORs) for each study outcome. Each exposure was analyzed for its relationship for mental health diagnosis continuously [per interquintile range (IQ_5R), defined as the difference between the 90th and 10th percentiles] and per quintile (Q). Cubic splines were fit using the splines package in R with knots specified at each quintile, and were adjusted for all model 2 covariates. Tests of nonlinearity were conducted by comparing spline models compared with models with standard linear terms. For the associations of outcomes with FOS use, the same model covariates were used except for the plasma PUFA values. Statistical significance was set to 0.05 for all analyses, and 95% confidence intervals are provided where appropriate. R (www.r-project.org) was used for all analyses.

TABLE 1
Demographics of the sample ($N = 258{,}354$)

Characteristic	Mean (SD) or % (*n*)
Sex (female)	53.1% (137,237)
Age (y)	56.7 (8.1)
Ethnicity	
White	95.5% (246,789)
Asian	1.8% (4760)
Black	1.3% (3441)
Other	1.3% (3364)
Marital status (married/partnered)	72.8% (188,069)
Employment status	
Employed	59.1% (152,703)
Disabled	3.4% (8685)
Retired	34.5% (89,076)
Unemployed	1.6% (4115)
Other	1.5% (3775)
Educational status	
College	60.4% (156,123)
High school	22.1% (57,133)
Less than high school	17.5% (45,098)
Alcohol consumption[1]	
Daily	20.4% (52,801)
3–4×/wk	23.5% (60,692)
1–2×/wk	26.2% (67,775)
Rarely	29.8% (77,086)
BMI (mg/kg^2)	27.5 (4.8)
Smoking (pack years)	10.6 (15.5)
Townsend Deprivation Index	–1.4 (3.0)
Exercise -METS[1]	
Lowest quartile	22.5% (58,070)
Second quartile	23.0% (59,432)
Third quartile	23.1% (59,627)
Top quartile	23.2% (60,047)
Linoleic acid (%)	28.9 (3.4)
Nonlinoleic ω-6 fatty acids (%)	9.0 (1.9)
DHA (%)	2.0 (0.7)
Non-DHA ω-3 fatty acids (%)	2.4 (1.0)
Total ω-3 fatty acids (%)	4.4 (1.6)
Self-reported fish oil consumption	31.6% (80,912)

[1] Metabolic equivalents. Missing data of ~8.2% for this variable.

Results

The sample size for this cross-sectional study was 258,354 individuals with data on plasma FA levels, the covariates used in the model building, and the outcomes of interest. In the aggregate, they were mostly White individuals, over half were female, their mean age was 56 y, and the vast majority was either still working or retired. Over half had post-high school education. About 32% reported that they regularly used FOS (Table 1). The mean (SD) plasma total ω-3 level was 4.97% (1.64) in the FOS users and 4.12% (1.43) in the nonusers ($P < 0.0001$).

Associations between plasma ω-3 levels and outcomes

For the analysis comparing plasma ω-3 levels with the study outcomes, there were the following numbers of events out of 258,354 subjects: history of depression, 2699; history of anxiety, 1296; recent depression, 848; and recent anxiety, 470.

For a lifetime history of depression and anxiety, we found in model 2 that DHA, total ω-3, non-DHA ω-3, and FOS use were all significantly and inversely associated with history of depression, both linearly (per IQ_5R) and comparing Q5 with Q1. Briefly, relative risk was between 7% and 13% lower for these metrics in linear analyses, and between 15% and 33% lower in Q5 compared with Q1 (Table 2). For the eO3I, relative

TABLE 2
Association of ω-3 fatty acid levels with lifetime prevalence of depression and anxiety[1]

	History of depression		
	Lifetime prevalence (%)	Model 1[2]	Model 2[3]
DHA			
IQ_5R	1.04	0.49 (0.44, 0.55)***	0.86 (0.76, 0.96)**
Q1	1.53	1.00	1.00
Q2	1.18	0.74 (0.66, 0.83)***	1.00 (0.89, 1.12)
Q3	0.97	0.60 (0.53, 0.67)***	0.92 (0.81, 1.04)
Q4	0.77	0.47 (0.41, 0.53)***	0.82 (0.71, 0.94)**
Q5	0.77	0.46 (0.41, 0.53)***	0.85 (0.73, 0.98)*
Total ω-3			
IQ_5R	1.04	0.64 (0.58, 0.71) ***	0.77 (0.69, 0.86) ***
Q1	1.53	1.00	1.00
Q2	1.18	0.83 (0.74, 0.93)**	0.94 (0.83,1.05)
Q3	0.97	0.77 (0.68, 0.86) ***	0.88 (0.78, 0.99)*
Q4	0.77	0.68 (0.60, 0.76) ***	0.83 (0.73, 0.94)**
Q5	0.77	0.59 (0.52, 0.67) ***	0.74 (0.64, 0.85)***
Non-DHA ω-3			
IQ_5R	1.04	0.81 (0.73, 0.89)***	0.72 (0.64, 0.81)***
Q1	1.53	1.00	1.00
Q2	1.18	0.91 (0.81, 1.03)	0.90 (0.79, 1.01)
Q3	0.97	0.85 (0.75, 0.96)**	0.79 (0.69, 0.89)***
Q4	0.77	0.83 (0.73, 0.94)**	0.73 (0.64, 0.84)***
Q5	0.77	0.77 (0.68, 0.87)***	0.67 (0.58, 0.77)***
	History of anxiety		
DHA			
IQ_5R	0.50	0.64 (0.56, 0.75)***	0.87 (0.74, 1.02)
Q1	0.66	1.00	1.00
Q2	0.52	0.76 (0.64, 0.89) ***	0.92 (0.78, 1.1)
Q3	0.50	0.72 (0.61, 0.85) ***	0.96 (0.81, 1.15)
Q4	0.40	0.57 (0.47, 0.68) ***	0.82 (0.67, 1.00)*
Q5	0.43	0.60 (0.51, 0.72) ***	0.87 (0.71, 1.07)
Total ω-3			
IQ_5R	0.50	0.78 (0.68, 0.90) ***	0.84 (0.73, 0.98)*
Q1	0.61	1.00	1.00
Q2	0.48	0.78 (0.66, 0.92)	0.84 (0.71, 1)*
Q3	0.49	0.80 (0.67, 0.94)**	0.87 (0.73, 1.03)
Q4	0.46	0.74 (0.62, 0.88) ***	0.83 (0.69, 0.99)*
Q5	0.46	0.73 (0.61, 0.87) ***	0.81 (0.67, 0.98)*
Non-DHA ω-3			
IQ_5R	0.50	0.91(0.79, 1.05)	0.82 (0.70, 0.96)*
Q1	0.55	1.00	1.00
Q2	0.50	0.90 (0.76, 1.07)	0.89 (0.75, 1.06)
Q3	0.47	0.86 (0.72, 1.02)	0.81 (0.68, 0.98)*
Q4	0.49	0.89 (0.74, 1.06)	0.81 (0.67, 0.98)*
Q5	0.49	0.88 (0.74, 1.05)	0.78 (0.64, 0.95)*

Abbreviation: FOS, fish oil supplements, IQ_5R, interquintile range.
$*P < 0.05$, $** P < 0.01$, $*** P < 0.001$.
[1] N for IQ5R models was 258,354; for individual quintile models, N~51,500 each.
[2] Model 1 is adjusted for age, sex, and ethnicity.
[3] Model 2 is adjusted for model 1 variables plus BMI, marital status, smoking (pack-years), education, Townsend deprivation index, exercise (metabolic equivalents), employment status, and linoleic acid levels, nonlinoleic ω-6, and multivitamin use. No tests of nonlinearity for any of the 3 fatty acid metrics for both outcomes were statistically significant ($P > 0.05$ in all cases).

TABLE 3
Association of the estimated ω-3 index with historical and recent (within the previous 12 mo) depression and anxiety

	Prevalence (%)	Model1 OR (95% CI)	Model2 OR (95% CI)
		History of depression	
IQ5R	1.04	0.52 (0.47, 0.58)***	0.82 (0.74, 0.92)***
Q1	1.47	1.0	1.0
Q2	1.21	0.8 (0.72, 0.89)***	1.03 (0.92, 1.16)
Q3	0.97	0.63 (0.56, 0.71)***	0.93 (0.82, 1.05)
Q4	0.82	0.53 (0.47, 0.6)***	0.85 (0.75, 0.98)*
Q5	0.76	0.5 (0.44, 0.56)***	0.82 (0.71, 0.95)**
		History of anxiety	
IQ5R	0.50	0.68 (0.59, 0.79)***	0.86 (0.74, 1)*
Q1	0.65	1.0	1.0
Q2	0.50	0.75 (0.63, 0.88)***	0.88 (0.75, 1.05)
Q3	0.49	0.72 (0.61, 0.86)***	0.92 (0.78, 1.1)
Q4	0.44	0.63 (0.53, 0.75)***	0.85 (0.71, 1.03)
Q5	0.42	0.6 (0.5, 0.72)***	0.81 (0.66, 0.98)*
		Recent depression	
IQ5R	0.37	0.6 (0.5, 0.71)***	0.84 (0.7, 1.01)
Q1	0.49	1.0	1.0
Q2	0.39	0.76 (0.62, 0.91)**	0.92 (0.76, 1.12)
Q3	0.38	0.73 (0.6, 0.88)***	0.99 (0.81, 1.2)
Q4	0.30	0.57 (0.46, 0.7)***	0.82 (0.66, 1.03)
Q5	0.28	0.53 (0.43, 0.66)***	0.79 (0.62, 1)*
		Recent anxiety	
IQ5R	0.18	0.75 (0.59, 0.95)*	0.99 (0.78, 1.27)
Q1	0.20	1.0	1.0
Q2	0.20	0.96 (0.72, 1.27)	1.16 (0.87, 1.54)
Q3	0.18	0.83 (0.62, 1.11)	1.1 (0.81, 1.48)
Q4	0.17	0.78 (0.58, 1.05)	1.11 (0.81, 1.53)
Q5	0.17	0.77 (0.57, 1.04)	1.14 (0.81, 1.59)

Abbreviations: CI, confidence interval; OR, odds ratio; IQ$_5$R, interquintile range.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
N for IQ5R models is 258,354, and for individual quintile models is ~51,500.
Model 1 is adjusted for age, sex, and ethnicity.
Model 2 is adjusted for model 1 variables plus BMI, marital status, smoking (pack-years), education, Townsend Deprivation index, exercise (metabolic equivalents), employment status, linoleic acid, non-linoleic ω-6, and multivitamin use.

risk was 18% lower in each analysis (Table 3). For anxiety (which was less prevalent than depression, ~0.5% compared with 1%), in linear analyses, total ω-3 levels were associated with a 5% lower risk per IQ$_5$R. For total ω-3 and non-DHA, risk for a history of anxiety was 19%–22% lower comparing Q5 with Q1. For the eO3I, the relative risk was 19% lower in Q5 compared with Q1. (The quintile cutoff values for each of the 3 exposures are shown in Supplemental Table 2.)

For recent depression and anxiety, the associations with ω-3 measures were less clear than those seen for a history of these conditions (Table 4). For recent depression, the only statistically significant findings were a 7% lower risk for total ω-3 levels and a 13% lower risk for non-DHA in the linear analysis, and a 29% and 32% lower risk in Q5 compared with Q1 for these 2 exposures, respectively. Comparing Q5 with Q1 for the eO3I, there was a 21% lower risk. Plasma ω-3 levels were not significantly linked with risk for recent anxiety. Finally, no tests of nonlinearity for any of the 3 ω-3 FA metrics by any of the outcomes were statistically significant.

TABLE 4
Association of ω-3 fatty acid levels with recent (within the previous 12 mo) depression and anxiety[1]

	Recent depression		
	Prevalence (%)	Model 1[2] OR (95% CI)	Model 2[3] OR (95% CI)
DHA			
IQ$_5$R	0.37	0.58 (0.48, 0.69)***	0.88 (0.73, 1.06)
Q1	0.49	1.00	1.00
Q2	0.40	0.79 (0.65, 0.95)*	1.00 (0.82, 1.22)
Q3	0.37	0.72 (0.59, 0.87) ***	1.02 (0.83, 1.26)
Q4	0.28	0.53 (0.43, 0.66) ***	0.84 (0.66, 1.06)
Q5	0.29	0.55 (0.44, 0.68) ***	0.89 (0.70, 1.14)
Total ω-3			
IQ$_5$R	0.37	0.67 (0.57, 0.80) ***	0.78 (0.65, 0.93)**
Q1	0.45	1.00	1.00
Q2	0.40	0.88 (0.73, 1.07)	0.98 (0.81, 1.19)
Q3	0.38	0.84(0.69, 1.02)	0.94 (0.77, 1.15)
Q4	0.33	0.72 (0.58, 0.88)**	0.84 (0.68, 1.04)
Q5	0.27	0.60 (0.48, 0.74) ***	0.71 (0.56, 0.9)**
Non-DHA ω-3			
IQ$_5$R	0.37	0.79 (0.66, 0.93)**	0.72 (0.60, 0.87)***
Q1	0.42	1.00	1.00
Q2	0.40	0.97 (0.8, 1.18)	0.96 (0.79, 1.17)
Q3	0.38	0.95 (0.78, 1.15)	0.90 (0.73, 1.11)
Q4	0.33	0.81 (0.66, 1.00)*	0.74 (0.59, 0.93)**
Q5	0.30	0.75 (0.61, 0.94)**	0.68 (0.54, 0.87)**
	Recent anxiety		
DHA			
IQ$_5$R	0.18	0.73 (0.57, 0.92)**	1.03 (0.80, 1.33)
Q1	0.20	1.00	1.00
Q2	0.18	0.85 (0.64, 1.13)	1.07 (0.8, 1.44)
Q3	0.20	0.89 (0.67, 1.18)	1.25 (0.93, 1.69)
Q4	0.17	0.73 (0.55, 0.99)*	1.13 (0.82, 1.57)
Q5	0.16	0.71 (0.52, 0.96)*	1.14 (0.81, 1.62)
Total ω-3			
IQ$_5$R	0.18	0.95 (0.89, 1.01)	0.98 (0.92, 1.05)
Q1	0.20	1.00	1.00
Q2	0.17	0.79 (0.59, 1.06)	0.87 (0.65, 1.17)
Q3	0.17	0.80 (0.6, 1.07)	0.90 (0.67, 1.21)
Q4	0.18	0.81 (0.61, 1.09)	0.96 (0.71, 1.3)
Q5	0.19	0.86 (0.64, 1.15)	1.05 (0.77, 1.43)
Non-DHA ω-3			
IQ$_5$R	0.18	0.91 (0.72, 1.15)	0.87 (0.67, 1.13)
Q1	0.18	1.00	1.00
Q2	0.19	1.08 (0.8, 1.44)	1.09 (0.81, 1.46)
Q3	0.16	0.87 (0.64, 1.19)	0.87 (0.64, 1.2)
Q4	0.19	1.03 (0.77, 1.39)	1.01 (0.74, 1.39)
Q5	0.20	1.06 (0.79, 1.43)	1.05 (0.76, 1.46)

Abbreviations: CI, confidence interval; OR, odds ratio; IQ$_5$R, interquintile range.
*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$
[1] N for IQ5R models is 258,354, for individual quintile models N~51,500.
[2] Model 1 is adjusted for age, sex, and ethnicity.
[3] Model 2 is adjusted for model 1 variables plus BMI, marital status, smoking (pack-years), education, Townsend Deprivation Index, exercise (metabolic equivalents), employment status, linoleic acid, non-linoleic ω-6, and multivitamin use.

Associations between FOS use, oily fish consumption, and outcomes

For the analysis comparing FOS use and the consumption of oily fish with the study outcomes, there were the following numbers of events out of 468,145 subjects: history of

TABLE 5
Adjusted odds ratios (aOR) for the association between the reported use of fish oil supplements (yes vs. no) and self-reported oily fish intake on mental health outcomes

	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)
History of depression			
Oily fish			
Never	1.00	1.00	1.00
<1/wk	0.60 (0.55, 0.66)***	0.86 (0.78, 0.94)***	0.86 (0.79, 0.94)**
1×/wk	0.56 (0.51, 0.61)***	0.85 (0.77, 0.93)***	0.85 (0.78, 0.94)***
2+/wk	0.61 (0.55, 0.68)***	0.84 (0.76, 0.93)***	0.85 (0.77, 0.94)**
Fish oil			
Yes	0.82 (0.75, 0.88)***	0.91 (0.85, 0.98)*	0.92 (0.86, 0.99)*
History of anxiety			
Oily fish			
Never	1	1	
<1/wk	0.62 (0.55, 0.71)***	0.83(0.73, 0.95)**	0.84 (0.73, 0.95)**
1×/wk	0.57 (0.5, 0.65)***	0.8(0.7, 0.91)***	0.80 (0.70, 0.92)***
2+/wk	0.77 (0.67, 0.88)***	1.01(0.88, 1.17)	1.03 (0.89, 1.19)
Fish oil			
Yes	0.86 (0.78, 0.95)**	0.90 (0.81, 1.00)*	0.90 (0.81, 1.00)*
Recent depression			
Oily fish			
Never			
<1/wk	0.56 (0.48, 0.65)***	0.75 (0.65, 0.88)	0.76 (0.65, 0.88)***
1×/wk	0.57 (0.5, 0.66)***	0.82 (0.71, 0.95)**	0.82 (0.71, 0.96)**
2+/wk	0.62 (0.52, 0.73)***	0.82 (0.69, 0.97)*	0.82 (0.69, 0.98)*
Fish oil			
Yes	0.87 (0.78, 0.97)*	0.95 (0.85, 1.07)	0.97 (0.86, 1.09)
Recent anxiety			
Oily fish			
Never			
<1/wk	0.65 (0.52, 0.81)***	0.85 (0.68, 1.07)***	0.86 (0.69, 1.08)
1×/wk	0.65 (0.52, 0.80)***	0.89(0.72, 1.11)	0.91 (0.73, 1.14)
2+/wk	0.78 (0.61, 1.00)*	1.02(0.8, 1.3)	1.05 (0.82, 1.34)
Fish oil			
Yes	0.78 (0.66, 0.92)*	0.80 (0.68, 0.95)*	0.80 (0.67, 0.95)**

Abbreviation: CI, confidence interval.
Model 1 is adjusted for age, sex, and ethnicity.
Model 2 is adjusted for model 1 variables plus BMI, marital status, smoking (pack-years), education, Townsend Deprivation index, exercise (metabolic equivalents), employment status, and multivitamin use.
Model 3 is adjusted for all model 2 variables, plus includes oily fish and fish oil consumption in the model simultaneously.

depression, 4794; history of anxiety, 2312; recent depression 1702; and recent anxiety, 829.

For FOS use, there were significant inverse relationships with risk for a history of depression and anxiety, and with risk for recent anxiety. Hazard ratios from model 2 were 9%, 10%, and 20% lower in FOS users, respectively (Table 5). In model 3, we adjusted for oily fish intake (see below). The associations seen in model 2 were not affected by this adjustment.

Oily fish consumption was separated into 4 categories, from never (reference) to ≥2/wk. Adjusted odds ratios (aORs) for the associations with the four outcomes are shown in Table 5. Model 2 adjusted for all variables in Table 1. Here, there was sporadic evidence of lower risk with higher intakes, but the reductions in risk above the reference category were similar regardless of the intake level. The situation was similar for recent depression. However, for recent anxiety, the aOR was statistically significant only for 1category (<1 time/wk) but not the two higher categories. When FOS use was included (model 3), these relationships were generally unchanged (i.e., they were independent of reported FOS use) (model 3).

Discussion

The purpose of this study was to examine the associations of plasma levels of ω-3 PUFAs, FOS use, and reported oily fish intake with depression and anxiety, both historically and concurrently. Inverse associations were generally found for the historical relationships in both of these disorders, but weaker (or nonexistent links) were seen with recent prevalence, although in some cases risk estimates were similar to historical disease but not statistically significant. This is in part owing to the lower prevalence (hence low power) of the recent conditions compared with a lifetime history (~0.37% compared with 1% for depression, and 0.18% compared with 0.5% for anxiety). The somewhat stronger associations between disease outcomes and the non-DHA metric compared with DHA suggest that some component of the former measure (likely EPA, see below) may influence susceptibility to these two conditions. The relationships between the eO3I and these outcome measures are reported to continue to build the evidence base for the relationship between disease outcomes and this common and well-validated measure of ω-3 status [12]. FOS use was significantly and inversely associated with both disorders and reporting periods, except for recent depression. Finally, reported oily fish consumption was generally associated with lower risk for depression and anxiety, irrespective of FOS use, and vice versa. The lack of an apparent dose–response relationship for reported oily fish intake, which was evident from the plasma analysis, perhaps reflects the lack of precision in the dietary intake estimates compared with the objectively measured biomarker.

Other recent studies have generally supported our findings. For example, Zhang et al. [13] reported that EPA intake was associated with a lower risk for depressive symptoms in ~31, 000 United States adults based on data from the NHANES 2005–2018.

In an RCT of 71 adolescents with depression, Li et al. [14] found that adding ω-3 supplements to Paxil treatment significantly improved depressive symptoms over 12 wk. In older adults, a meta-analysis of five trials on depression in patients with mild cognitive impairment and/or dementia found that DHA but not EPA significantly reduced depressive symptoms in patients with dementia; however, EPA reduced depression in patients with mild cognitive impairment [15]. A study from the Cooper Center Longitudinal Study [16] found similar cross-sectional associations with depression and ω-3 PUFA levels (DHA, not EPA) and with FOS use as observed here.

As noted earlier, a meta-analysis of RCTs by Su et al. [7] found a beneficial effect of ω-3 PUFA supplementation, consistent with the observations made here. Yang et al. [17] studied the effects of ω-3 PUFA supplementation on anxiety in first-diagnosed patients with depression being treated with venlafaxine (Effexor). Although anxiety was reduced significantly compared with placebo (based on scores from the Hamilton Anxiety Scale), the reduction in scores did not correlate with changes in erythrocyte ω-3 PUFA levels [18].

Mechanistic considerations

Our first major finding—the observed inverse associations between ω-3 fatty acid status and mental health outcomes—is biologically plausible and consistent with proposed mechanistic pathways. ω-3 fatty acids, particularly EPA (a component of the non-DHA metric) is known to exert anti-inflammatory effects by reducing the production of proinflammatory cytokines and promoting the resolution of inflammation, which has increasingly been recognized as a key contributor to the pathophysiology of depression and anxiety [19–24]. Moreover, DHA, the most abundant ω-3 fatty acid in the brain, plays a critical role in maintaining neuronal membrane fluidity, enhancing receptor function, and facilitating neurotransmitter signaling, all of which are essential for mood regulation [20,25–29]. Previous studies have also suggested that ω-3 fatty acids may modulate the synthesis and availability of key neurotransmitters such as serotonin and dopamine, further supporting their potential antidepressant and anxiolytic effects [21,30–32]. EPA, in particular, has been shown to play a dominant role in reducing neuroinflammation, attenuating hyperactivity of the hypothalamic-pituitary-adrenal axis, and enhancing serotonergic and dopaminergic neurotransmission, mechanisms that are critically involved in the pathophysiology of depression and anxiety [21,27,33–38]. These mechanistic pathways may explain why stronger and more consistent associations were observed for non-DHA ω-3 PUFA and total ω-3 PUFA exposures compared with DHA alone. Collectively, our findings provide compelling biological support for the protective role of ω-3 fatty acids, especially EPA, in the maintenance of mental health and the prevention of mood disorders.

Strengths and limitations

A strength of this study was the reliance on electronic medical record data instead of self-report. Although our prevalence rates were lower than they would have been had we included self-reported data, our confidence that these conditions were real (and probably more serious) was greater using physician-diagnosed disorders. Obviously, the size of the UKBB cohort was a strength, as was relying on biomarkers (primarily) instead of dietary intake questionnaires; reported FOS use, although an imprecise exposure metric, has been commonly used in UKBB studies [39–43] linking FOS use with disease outcomes. Weaknesses included the cross-sectional and historical nature of the study, in which reverse causation cannot be ruled out.

In conclusion, this cross-sectional analysis of plasma ω-3 status and historical and recent depression and anxiety provides additional evidence for a favorable effect of these unique marine FAs in the etiology of these common mental disorders. Future studies should explore the prospective relationships between ω-3 PUFA biomarkers and incident depression and anxiety.

Author contributions

The authors' responsibilities were as follows – WSH, NLT, PPD, RWG, SHM: conception and design; NLT, JW: data access and statistical analysis; K-PS, W-CL, NLT, WSH: initial draft of manuscript; PDP, RWG, SHM: substantive revisions; and all authors: read and approved the final version.

Conflict of interest

WSH reports that financial support was provided by Pharmavite, LLC. PPD reports a relationship with Pharmavite LLC that includes: employment. RWG reports a relationship with Pharmavite LLC that includes: employment. SHM reports a relationship with Pharmavite LLC that includes: employment. WSH reports a relationship with OmegaQuant Analytics, LLC that includes: equity or stocks. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data used in this study were obtained by application from the UKBB and cannot be shared directly with others who have not been approved by the UKBB for data access.

Declaration of generative AI in scientific writing

The authors declare that they made no use of generative artificial intelligence (AI) and AI-assisted technologies in the process of writing this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2025.10.032.

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