Published in final edited form as:
J Clin Psychiatry. 2013 July ; 74(7): 732–738. doi:10.4088/JCP.12m07970.

Omega-3 Polyunsaturated Fatty Acid Status in Major Depression with Comorbid Anxiety Disorders

Joanne J. Liu, M.S.[1], **Hanga C. Galfalvy, Ph.D.**[2,3], **Thomas B. Cooper, M.A.**[3,4], **Maria A. Oquendo, M.D.**[2,3], **Michael F. Grunebaum, M.D.**[2,3], **J. John Mann, M.D.**[2,3,5], and **M. Elizabeth Sublette, M.D., Ph.D.**[2,3,*]

[1]Institute of Human Nutrition, Columbia University, NY, NY

[2]Department of Psychiatry, Columbia University, NY, NY

[3]Department of Molecular Imaging & Neuropathology, New York State Psychiatric Institute, NY, NY

[4]Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY

[5]Department of Radiology, Columbia University, NY, NY

Abstract

Objective—Although lower levels of omega-3 polyunsaturated fatty acids (PUFAs) are found in major depression, less is known about PUFA status and anxiety disorders.

Method—Medication-free participants with DSM-IV-defined major depressive disorder (MDD), with (n=18) and without (n=41) comorbid anxiety disorders, and healthy volunteers (n=62) were recruited from October 2006 to May 2010 at the New York State Psychiatric Institute. Depression and anxiety severity were assessed using depression and anxiety subscales from the 17-item Hamilton Depression Rating Scale. Plasma PUFAs eicosapentaenoic acid (20:5n-3, EPA), docosahexaenoic acid (22:6n-3, DHA), and the ratio of arachidonic acid (22:4n-6, AA) to EPA (AA:EPA) were quantified. This secondary analysis employed ANOVA with *a priori* planned contrasts to test for diagnostic group differences in log-transformed PUFA levels (logDHA, logEPA, and logAA:EPA).

Results—Plasma levels of logDHA (F=4.92, df=2,118, p=0.009), logEPA (F=6.44, df=2,118, p=0.002), and logAA:EPA (F=3.81, df=2,118, p=0.025) differed across groups. MDD participants had lower logDHA (t=2.324, df=118, p=0.022) and logEPA (t=3.175, df=118, p=0.002) and

*To whom correspondence should be addressed: New York State Psychiatric Institute, 1051 Riverside Drive, Unit 42, NY, NY 10032, Tel: (212) 543 – 6241, Fax:(212) 543 – 6017, es2316@columbia.edu.

CONFLICT OF INTEREST

Dr. Oquendo received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript, and was the recipient of a grant from Eli Lilly to support a year of the salary for a Lilly Suicide Scholar. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuko, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb. Dr. Mann has received past unrelated grants from Novartis and GSK. Dr. Sublette has received a grant of nutritional supplements from Unicity International. The remaining authors have no conflicts of interest to report.

CONTRIBUTORS

Dr. Sublette designed the study.
Ms. Liu performed the literature searches, statistical analyses, and wrote the first draft of the manuscript.
Dr. Galfalvy supervised the statistical analysis.
Mr. Cooper performed the PUFA biochemical analyses.
Drs. Grunebaum, Oquendo, and Mann designed and directed mood disorders studies at NYSPI from which research participant data was obtained.
All authors contributed to and have approved the final manuscript.

higher logAA:EPA (t=–2.099, df=118, p=0.038) compared with healthy volunteers. Lower logDHA (t=2.692, df=118, p=0.008), logEPA (t=2.524, df=118, p=0.013), and higher logAA:EPA (t=–2.322, df=118, p=0.022) distinguished anxious from non-anxious MDD. Depression severity was not associated with PUFA plasma levels; however, anxiety severity across the entire sample correlated negatively with logDHA (r_p=–0.22, p=0.015) and logEPA (r_p=–0.25, p=0.005) and positively with logAA:EPA (r_p=0.18, p=0.043).

Conclusions—The presence and severity of comorbid anxiety were associated with the lowest EPA and DHA levels. Further studies are needed to elucidate whether omega-3 PUFA supplementation may preferentially alleviate MDD with more severe anxiety.

Keywords

Anxiety Disorders; Omega-3; Polyunsaturated fatty acids; Major Depressive Disorder

INTRODUCTION

Recognition of the importance of essential dietary polyunsaturated fatty acids (PUFAs) in human health and disease has grown considerably in the last few decades. Omega-3 PUFAs, which include alpha-linolenic acid (ALA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3), are present in varying proportions in many tissues throughout the body. Omega-3 PUFAs and their metabolites serve important physiologic functions, including regulating gene expression during early development[1] and cell membrane responsiveness,[2] acting as second messengers,[3] and balancing pro- and anti-inflammatory processes.[4] Nevertheless, omega-3 PUFA deficiency is estimated to occur in nearly 70% of people in the United States,[5] and may impact public health by contributing to a diverse array of health problems, including cardiovascular,[6,7] inflammatory,[8] and neuropsychiatric[9] diseases.

Recent research suggests an etiological role for omega-3 PUFA intake in mood disorders, such as Major Depressive Disorder (MDD) and Bipolar Disorder (BD). Depressed patients have lower omega-3 PUFA levels in plasma[10–14] and serum[15–18] phospholipids, red blood cell membranes,[19–23] and adipose tissue,[24–28] results that have been supported by meta-analytic findings.[29] The hypothesis that omega-3 PUFA deficiency is causal in depression is supported by studies showing that omega-3 supplementation improves depression. Although randomized, placebo-controlled clinical trials of omega-3 PUFA supplementation in depression have reported mixed efficacy results[30–48], meta-analyses find that omega-3 PUFA supplements have efficacy when: 1) patients have a diagnosis of Major Depressive Episode (MDE), as opposed to depressive symptoms within another disorder;[49] and 2) there is a higher proportion of EPA than DHA in the omega-3 PUFA supplement.[49–51]

Anxiety disorders are frequently comorbid with major depression,[52] raising the possibility that omega-3 PUFA levels may contribute to their pathophysiology, and that supplementation may be an effective treatment of anxiety and anxiety disorders. Collectively, anxiety disorders, which include post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, and specific phobias, are among the most common mental disorders, affecting approximately 20% of the United States population.[53] With the average age-of-onset for anxiety disorders being 11 years of age,[54] and only one-third of people with anxiety disorders receiving adequate treatment for their symptoms,[55] there is an urgent need for the implementation of effective, well-tolerated treatments for anxiety disorders.

We performed an exploratory study to test our hypothesis that low omega-3 PUFA levels would be associated with anxiety disorders comorbid with major depression. We compared

plasma concentrations of the omega-3 PUFAs EPA and DHA as well as the ratio of plasma levels of the omega-6 PUFA arachidonic acid (22:4n-6, AA) to EPA (AA:EPA) in three groups of subjects: healthy volunteers and MDD patients with and without comorbid anxiety disorders (anxious MDD and non-anxious MDD, respectively). DHA and EPA are PUFA species shown to be relevant in depression,[29] and AA:EPA is an additional useful marker that conveys information about the balance between omega-3 and omega-6 PUFAs. Whereas AA levels have not been found to differentiate between depressed and healthy volunteers[29], AA:EPA is elevated in cholesterol esters and plasma phospholipids in major depression compared with healthy controls or minor depression[56], and its unesterified form correlates positively with manic symptoms[57]. Although other PUFA indices may be equally valid, we restricted the number of outcome measures to limit the number of comparisons employed. Improved understanding of the relationship between PUFAs and anxiety disorders comorbid with depression could have important implications for treatment.

METHOD

Sample

Participants were 121 adults, aged 18–73 yrs (mean age 35.8 ± 12.6 yrs), from the greater New York metropolitan area who provided written informed consent to participate in IRB-approved mood disorder studies at the New York State Psychiatric Institute (NYSPI) including measurement of PUFA plasma levels. The sample was recruited from October 2006 to May 2010 and consisted of healthy volunteers (n=62) and MDD patients with (n=18) and without (n=41) comorbid anxiety disorders. All patients had a DSM-IV (SCID)[58] diagnosis of acute MDE in the context of MDD. Co-morbid anxiety disorders included panic disorder, social anxiety disorder, simple phobia, OCD, GAD, somatization disorder, hypochondriasis, and PTSD. Individuals were excluded from participation if they had active medical or neurologic illness. Participants were not on psychotropic medications for at least two weeks prior to the collection of blood samples, with the exception of one healthy volunteer who was taking zolpidem; two non-anxious and one anxious MDD participant(s) who were taking sertraline; and one anxious MDD participant who was taking mirtazapine.

Depressed participants were administered the 17-item Hamilton Depression Rating Scale (HDRS-17)[59] and Beck Depression Inventory (BDI)[60] to assess depression severity. We computed an anxiety severity sub-score from the total HDRS-17 using factor analysis and principal components analysis as described in detail elsewhere[61], comprised of four items: 9 (agitation), 10 (psychic anxiety), 11 (somatic anxiety), and 15 (hypochondriasis). The depression severity sub-score comprised the remaining 13 items (HDRS-13). This use of an Anxiety factor derived from the HDRS-17 has considerable precedent, and in a meta-analysis of studies of the factor structure of the HDRS-17, when a two-component factor solution was sought, the first component was Anxiety, with the remaining items as a general component.[62]

Clinical and demographic information was obtained, including the participant-estimated level of tobacco consumption: non-smoker (0 cigarettes/day), light (10), moderate (20), heavy (40).

Plasma PUFA Analysis

Blood samples were collected in EDTA-containing tubes and maintained in an ice-water bath prior to refrigerated centrifugation for 10 minutes. Blood samples were then transferred to cryotubes and stored at −80°C until analysis. Analytical procedures for separation and quantification of plasma PUFAs DHA and EPA fatty acid methyl esters (FAMEs) have been

described previously.[63] Briefly, the process required direct transesterification of all classes of lipids in a one-step procedure using 0.1 mL of plasma. FAMEs were then separated by gas chromatography/flame ionization detector with hydrogen carrier gas in a capillary column DB-FPAP- 30 m x 0.25 mm x 0.25 μm; both gas chromatograph (Model 6890) and column are from Agilent Technologies (formerly Hewlett-Packard; Wilmington, DE). A retention lock program allowed for the elution of an internal standard with a specific retention time. A known equal-weight mixture of 28 FAMEs commercially available as GLC462 from Nu-Chek Prep (Elysian, MN) was used to define methyl ester retention times and response factors. All blood samples were run in duplicate, and retention times were virtually constant between chromatographic runs. Plasma FAMEs were identified by retention time; data were automatically quantified. The intra-assay coefficients of variance, a measure of reproducibility, were <5% for EPA, DHA, and AA, with a corresponding inter-assay variance of <9%.

Dietary Omega-3 PUFA Intake

Dietary intake of DHA and EPA was assessed using our validated food-frequency questionnaire.[64]

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics (version 19 for Mac [Apple, Inc., Cupertino, CA]). Plasma levels of EPA and DHA as well as the AA to EPA ratio were skewed to the left due to a cluster of very low levels of omega-3 PUFAs, and there were significant outliers at the right-hand portion of the distribution. Therefore, parametric tests were executed using data normalized by log-transformation of EPA levels (logEPA), DHA levels (logDHA), and the ratio of AA to EPA (logAA:EPA). Similarly, as the dietary intake of both omega-3 PUFA species had a skewed distribution, data were log-transformed; zero intake values were avoided by adding a constant value of 0.0001 to all data points.

For the principal outcome measure, an analysis of variance (ANOVA) was performed with log-transformed PUFA status (logPUFA) as the dependent variable, and three predictor groups: anxious MDD, non-anxious MDD, and healthy volunteers. Two *a priori* planned contrasts were then performed: anxious MDD vs. non-anxious MDD, and all MDD participants vs. healthy volunteers. As a sensitivity analysis, these calculations were repeated leaving out participants who were on medications. Age, sex, race, and tobacco consumption were also tested separately as covariates in the model. Given the small sample size, we were only able to test two categories of race (white vs. non-white).

Additional exploratory analyses were performed in the MDD group and in the sample as a whole to investigate whether anxiety severity, as measured by the anxiety-specific items on the HDRS, correlated with logPUFA status. For all analyses, $p \leq 0.05$ was considered significant.

This study is a secondary analysis performed on a subset of data from mood disorders research protocols in which participants gave informed consent to obtain plasma biochemistry. Portions of this dataset have been utilized in other analyses with different objectives.[64,65]

RESULTS

Sample Characteristics

Demographic and clinical characteristics (Table 1) did not differ between the three groups, except for race and smoking status. Tobacco consumption differed among the diagnostic

groups (mean rank scores: anxious MDD 69.92 > non-anxious MDD = 63.23 > healthy volunteers = 55.09; Kruskal-Wallis $\chi^2 = 7.019$, df = 2, p=0.030). Our sample did not include any heavy smokers (40+ cigarettes/day).

Anxiety disorder diagnoses within the anxious MDD group included: GAD (3); hypochondriasis (1); OCD (3); panic disorder (2); PTSD (7); and social phobia (6). Four participants had more than one anxiety disorder.

Associations Between Plasma Omega-3 PUFA Levels and Anxiety Disorder Comorbidity in Depressed Patients

Levels of logPUFA differed across the three groups (see Table 1). MDD participants had lower levels of logDHA ($t = 2.324$, $df = 118$, $p = 0.022$) and logEPA ($t = 3.175$, $df = 118$, $p = 0.002$), and higher levels of logAA:EPA ($t = -2.099$, $df = 118$, $p = 0.038$) compared to healthy volunteers. The anxious group was distinguishable from the non-anxious group on the basis of lower logDHA ($t = 2.692$, $df = 118$, $p = 0.008$) and logEPA levels ($t = 2.524$, $df = 118$, $p = 0.013$), and higher logAA:EPA levels ($t = -2.322$, $df = 118$, $p = 0.022$). Sensitivity analyses conducted excluding the 5 participants who were taking medication remained significant (N=116 and df=2 for all tests: logDHA, F=4.615, p=0.012; logEPA, F=6.544, p=0.002; logAA:EPA, F=3.600, p=0.031).

Log-transformed dietary intakes of DHA and EPA did not differ between the three groups (DHA, F=1.64, df=2, p=0.199; EPA, F=1.97, df=2, p=0.145) but mean levels of omega-3 PUFA intake were numerically ordered consistent with plasma results: healthy volunteers > MDD without comorbid anxiety > MDD with comorbid anxiety.

Effects of Including Demographic and Clinical Characteristics in the Model

Of the characteristics included in the statistical model, only age and race had effects, on logEPA and logAA:EPA. EPA levels and EPA relative to AA increased with increasing age (for logEPA, B=0.006 per year [SE= 0.002], t=3.322, p=0.001; for logAA:EPA, B=−0.003 per year [SE 0.002] t=−2.125, p=0.036). For race, B represents the adjusted difference between whites and nonwhites with regard to logPUFA. Whites had higher logEPA levels (B=0.116 [SE=0.045], t=2.583, p=0.011) and lower logAA:EPA levels (B=−0.123 [SE=0.041], t=−2.961, p=0.004) than non-whites.

However, none of the characteristics explained the effects of diagnostic group on logPUFA; that is, with individual covariates included in the model, the effects of diagnostic group on logPUFA remained statistically significant (for EPA, DHA, and AA:EPA, respectively, including age as a covariate: P = .001, P = .014, and P = .049; including race as a covariate: P = .011, P = .006, and P = .003).

Effect of Depression Severity on Association Between PUFA and Comorbid Anxiety

The HDRS-17 contains 4 items concerning anxiety (24% of the total score), and the BDI has 1 anxiety item out of 21 (5%). Without the anxiety items of the HDRS-13, there was no depression severity difference between MDD patients with and without comorbid anxiety disorders, consistent with the BDI results. Thus, lower DHA and EPA levels observed in anxious MDD were not due to greater depression severity.

Correlation of Anxiety Severity and PUFA Levels

Anxiety severity measured with the HDRS anxiety subscore in the combined MDD sample (n=59) correlated negatively with logDHA levels ($r_p = -0.34$, $p = 0.009$) and exhibited a trend toward negative correlation with logEPA levels ($r_p = -0.24$, $p = 0.067$). No correlation was observed with logAA:EPA levels ($r_p = 0.11$, $p = 0.410$). When examined in the entire

sample (n=121), however, all logPUFAs correlated in the expected direction with severity of anxiety symptoms (logDHA, $r_p = -0.22$, $p = 0.015$; logEPA, $r_p = -0.25$, $p = 0.005$; logAA:EPA, $r_p = 0.18$, $p = 0.043$). An inspection of the scatterplots indicates that these relationships are comparable with respect to logDHA and logEPA in anxious depressed, non-anxious depressed, and healthy participants.

DISCUSSION

To our knowledge, this is the first study of omega-3 PUFA levels in major depression stratified by presence of a comorbid anxiety disorder. Consistent with previous reports in major depression,[29] lower omega-3 PUFA plasma levels and a higher plasma AA to EPA ratio were seen in MDD compared to healthy volunteers. Notably, anxious MDD also was distinguished from non-anxious MDD by lower plasma DHA and EPA levels and higher AA:EPA. The ranking of both plasma levels and dietary intake of omega-3 PUFA (EPA and DHA) was anxious MDD < non-anxious MDD < healthy volunteers. Because the group differences remained robust after adjustment for non-anxiety depression severity, and because scores on the anxiety items of the HDRS-17 correlated negatively with plasma levels of logDHA, we conclude that the lower omega-3 PUFAs in anxious MDD were not simply a function of greater depression severity, but rather were related to the presence and severity of anxiety. Our results are consistent with a previous study that found inverse correlations between erythrocyte omega-3 PUFA concentrations and severity of social anxiety disorder.[66] Therefore, deficiencies in omega-3 PUFAs within a depressed sample may serve as a biomarker for the severity of anxiety symptoms.

Although age and race were associated with logEPA and logAA:EPA levels, and MDD patients had higher tobacco consumption than controls, none of these variables explained the associations between logPUFA and the presence of comorbid anxiety disorders. It is unclear why age and race affected logEPA but not logDHA levels. These results require confirmation in a larger sample.

Omega-3 PUFA Intake and Anxiety

Due to the frequent comorbidity of depression and anxiety disorders, it has been proposed that omega-3 PUFA supplementation may possess anxiolytic, in addition to antidepressant, properties.[67] However, to date, only a limited number of studies on omega-3 PUFA status in patients with anxiety have been performed. One epidemiological study of fish and seafood consumption[68] found greater intake of omega-3 PUFAs to be associated with a lower prevalence of anxiety, although this does not prove causality.

A few randomized, placebo-controlled clinical trials have examined the effects of omega-3 PUFA supplementation on symptoms of anxiety in otherwise healthy individuals. Benefits of omega-3 PUFAs on anxiety in healthy volunteers have been found in younger (mean age = 24.3 years),[69–72] but not in older populations (mean age = 70 years).[73] As in depression treatment,[49–51] the ratio of EPA to DHA in omega-3 PUFA supplements may also play a role in the effectiveness of the intervention. Healthy medical students given omega-3 PUFA supplements that contained 83.5% EPA[69] as well as substance abusers given 75% EPA omega-3 PUFA supplements[70,71] displayed reductions in anxiety symptoms. Such reductions were not seen when omega-3 PUFA supplements containing 57% EPA were administered to independently living older individuals.[73] Although preliminary, these results are consistent with our previous meta-analysis in depression, which found that an EPA proportion in supplements of at least 60% positively affected depression outcome.[51] Empirically observed greater therapeutic effects of EPA than DHA in depression[49–51] are counter-intuitive, given that DHA is far more abundant than EPA in brain. As we discuss elsewhere in detail[51], possible explanations include rapid brain EPA turnover or peripheral

EPA actions, and there are a number of physiological functions that differentiate EPA from DHA.

Only two randomized, placebo-controlled trials evaluating the efficacy of omega-3 PUFA supplementation as a therapeutic intervention for anxiety disorder have been published. A placebo-controlled cross-over trial in 11 patients with OCD who were given omega-3 PUFA supplementation (2000 mg EPA) adjunctive to SSRIs yielded no improvement in OCD or depression.[74] Another trial in patients with PTSD,[75] using a similar dose of omega-3 PUFA supplementation (2000 mg EPA) had to be terminated prematurely after 6 patients had enrolled, due to lack of improvement and a trend toward worsening symptoms.

Similarly, one study of omega-3 PUFA supplementation in the treatment of MDE with and without comorbid anxiety[76] in adult patients with MDE (n=432) found that omega-3 PUFA supplementation (1,050 mg/d EPA and 150 mg/d DHA) was ineffective in the population as a whole, but after *post hoc* stratification by the presence of comorbid anxiety disorders, the supplementation was effective only in the subset of MDE patients *without* comorbid anxiety disorders.

It is unclear how to reconcile findings of inverse correlations between erythrocyte omega-3 PUFA concentrations with respect to severity of social anxiety disorder[66] and our current findings that MDD patients with comorbid anxiety disorders have the lowest omega-3 levels, with treatment studies which thus far have found no efficacy of omega-3 supplementation with regard to anxiety disorders[74–76]. One explanation could be that inverse relationships between omega-3 PUFA levels and anxiety severity are an epiphenomenon due to anxiety effects on appetite resulting in lower omega-3 PUFA intake, but that omega-3 intake does not have a specific causal role in the etiology of anxiety. However, none of the studies of PUFA supplementation for anxiety assessed plasma PUFA levels, so it is not known whether anxious patients in those studies also had lower plasma levels of omega-3 PUFAs or whether the levels increased with supplementation. Nor to our knowledge has any study reported whether effectiveness of omega-3 supplementation relates directly to magnitude of omega-3 deficiency. Thus, the existing literature is too limited to determine whether omega-3 PUFA supplementation may have therapeutic benefit for patients with diagnosed anxiety disorders. It is also possible that there is a differential involvement of PUFAs in different subtypes of anxiety disorders.

Anxiogenic Effects of Stress in the Context of Omega-3 PUFA Status

Some preclinical studies find that omega-3 PUFA supplementation is positively associated with decreases in anxiety-like behaviors in rodents[77,78] and non-human primates.[79] However, other studies of omega-3 PUFA deficiency from birth,[80] from conception,[81] and over multiple generations[82,83] have detected no differences in performance on tests measuring anxiety-like behaviors across control and omega-3 PUFA deficient diets. An additional relevant factor may be allostatic load, since omega-3 PUFA deficient rodents subjected to isolation stress,[84] inhibition of phosphoinositide-3-kinase to impair insulin signaling,[85] or early maternal separation,[83] display greater increases in anxiety-like behaviors than non-deficient animals.

These studies suggest that a pathologic synergism may occur when additional stressors are superimposed on omega-3 PUFA deficiency, resulting in the development and progression of anxiety disorders. Conversely, adequacy of omega-3 PUFA consumption may serve as a resilience factor and be beneficial in reducing anxiety symptoms in stressed populations. Consistent with this premise, one human study in a population (n=24) of omega-3 PUFA deficient substance abusers given omega-3 PUFA supplements of 450 mg/d of EPA, 100 mg/d of DHA, and 50 mg/d of other omega-3 PUFAs revealed declines in anxiety scores

compared to patients receiving vegetable oil placebos.[70,71] One neurobiological mechanism that could explain an anxiogenic response to omega-3 PUFA deficiency when coupled with additional stressors is PUFA regulation of immune responses to stress. For example, omega-3 supplementation reduces oxidative stress[86] and promotes production of anti-inflammatory cytokines, and reduction of pro-inflammatory cytokines[4] that are elevated in anxiety[87] and depression.[88,89]

Limitations

This secondary analysis had a cross-sectional design. The subsample of depressed participants with comorbid anxiety disorders was small and contained a variety of subtypes of anxiety disorders. Outcome measures were limited to DHA, EPA, and the AA to EPA ratio to reduce the magnitude of multiple comparisons. Plasma levels were selected from a number of valid measures of PUFA functioning, as they have been shown to be as good a biomarker of total long-chain omega-3 PUFA intake as erythrocyte levels.[90] However, in future studies, determination of PUFAs in phospholipid and unesterified fractions might yield additional information. The relatively young age of this sample may limit generalizability of these results for older populations.

CONCLUSIONS

Consistent with preclinical studies, our results suggest that omega-3 PUFA deficiency may be one, among other stressors that collectively contribute to anxiety. Although the findings of this study hold promise, larger studies are needed to more comprehensively elucidate potential relationships between omega-3 PUFA status and anxiety.

Acknowledgments

Sources of Support: This study was supported in part by the following grants: MH048514; NARSAD; MH076049; MH062185; MH048514; MH079033.

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CLINICAL POINTS

- The presence and severity of anxiety were associated with the lowest omega-3 fatty acid levels across MDD and healthy control samples.
- The association between low omega-3 fatty acid levels and the presence of comorbid anxiety disorders was not explained by depression severity, tobacco consumption, or demographic factors.
- At this time, it is not known whether omega-3 supplementation could have anxiolytic effects in MDD.

Table 1

Comparison of Participants With Respect to Demographic and Clinical Characteristics

	Participant Status								
	Healthy		MDD without Comorbid Anxiety Disorder		MDD with Comorbid Anxiety Disorder				
	n = 62		n = 41		n = 18				
Demographic Characteristics	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*F-score*	*df*	*p*
Age (yrs)	62	36.2 (13.3)	41	37.0 (12.6)	18	31.2 (9.4)	1.42	2, 118	0.245
BMI ($kg^{*}m^{-2}$)	61	25.0 (5.1)	41	25.5 (5.7)	18	24.3 (5.2)	0.36	2, 117	0.699
Education (yrs)	62	15.5 (2.9)	40	15.0 (2.9)	18	14.3 (2.7)	1.15	2, 117	0.320
	N	*Median (IQR)*	*N*	*Median (IQR)*	*N*	*Median (IQR)*			*p*
Personal Income [a] Level (US$1000/yr)	62	20.0 (32.5)	40	22.5 (38.7)	18	25.0 (48.2)	N/A	N/A	0.715
	N	*N with characteristic (%)*	*N*	*N with characteristic (%)*	*N*	*N with characteristic (%)*	χ^2	*df*	*p*
Sex (male)	62	25 (40.3)	41	19 (46.3)	18	8 (44.4)	0.383	2	0.826
Race (white)	60	28 (46.7)	41	22 (53.7)	18	15 (83.3)	7.534	2	0.023*
Tobacco use (yes)[b]	62	6 (9.7)	39	9 (23.1)	18	6 (33.3)	6.622	N/A	0.033*
Clinical Characteristics	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*t-score*	*df*	*p*
HDRS-17 [c]	62	2.1 (2.7)	41	17.2 (5.7)	18	20.3 (3.8)	2.172	57	0.034*
Non-anxiety HDRS Items (HDRS-13)[c]	62	1.3 (2.0)	41	12.9 (4.8)	18	15.3 (3.1)	1.959	57	0.055
BDI[c]	62	0.8 (2.4)	40	23.7 (10.3)	18	27.6 (6.7)	1.459	56	0.150
Plasma PUFA levels (mg/L)[d]	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*F-score*[d]	*df*	*p*
DHA	62	61.1 (26.0)	41	60.4 (31.6)	18	42.1 (15.2)	4.923	2, 118	0.009
EPA	62	26.4 (18.5)	41	22.2 (16.4)	18	14.8 (8.6)	6.442	2, 118	0.002

	Participant Status								
	Healthy		MDD without Comorbid Anxiety Disorder		MDD with Comorbid Anxiety Disorder				
	n = 62		n = 41		n = 18				
AA:EPA ratio	62	13.8 (7.2)	41	14.1 (5.88)	18	19.3 (9.2)	3.806	2, 118	0.025
Dietary PUFA intake (mg/d)[d]	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*F-score*[d]	*df*	*p*
DHA	54	93.7 (18.5)	35	45.2 (7.8)	14	25.3 (3.5)	1.639	2, 100	0.199
EPA	54	64.2 (18.2)	35	24.6 (3.9)	14	13.1 (1.8)	1.966	2, 100	0.145

[a] Kruskal-Wallis test of medians was performed.

[b] Fisher's exact test was performed.

[c] Student's t-test compared MDD with and without comorbid anxiety disorder (healthy volunteers not included in analysis).

[d] Non-log-transformed values are reported as more relevant to readers; however, statistical results reflect analyses performed with log-transformed values.

[*] $p < 0.05$.

Abbreviations: BDI = Beck Depression Inventory; BMI = Body-Mass Index; HDRS-17 = 17-item Hamilton Depression Rating Scale; MDD = Major Depressive Disorder; N/A = not applicable; IQR = Inter-Quartile Range; PUFA = Polyunsaturated Fatty Acids; SD = Standard Deviation.