Omega-3 Polyunsaturated Fatty Acid (PUFA) Status in Major Depressive Disorder With Comorbid Anxiety Disorders

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ABSTRACT

Background: Although lower levels of omega-3 polyunsaturated fatty acids (PUFAs) are found in major depressive disorder, 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 *DSM-IV* anxiety disorders, and healthy volunteers (n = 62) were recruited from October 2006 to May 2010 for mood disorder studies at the New York State Psychiatric Institute. Participants were 18–73 years of age (mean age, 35.8 ± 12.6 years). Depression and anxiety severity was assessed using depression and anxiety subscales from the 17-item Hamilton Depression Rating Scale. Plasma PUFAs eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) and the ratio of arachidonic acid (AA; 22:4n-6) to EPA (AA:EPA) were quantified. This secondary analysis employed analysis of variance 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 ($F_{2,118} = 4.923$, $P = .009$), logEPA ($F_{2,118} = 6.442$, $P = .002$), and logAA:EPA ($F_{2,118} = 3.806$, $P = .025$) differed across groups. Participants with MDD had lower logDHA ($t_{118} = 2.324$, $P = .022$) and logEPA ($t_{118} = 3.175$, $P = .002$) levels and higher logAA:EPA levels ($t_{118} = -2.099$, $P = .038$) compared with healthy volunteers. Lower logDHA ($t_{118} = 2.692$, $P = .008$) and logEPA ($t_{118} = 2.524$, $P = .013$) levels and higher logAA:EPA levels ($t_{118} = -2.322$, $P = .022$) distinguished anxious from nonanxious MDD. Depression severity was not associated with PUFA plasma levels; however, anxiety severity across the entire sample correlated negatively with logDHA ($r_p = -0.22$, $P = .015$) and logEPA ($r_p = -0.25$, $P = .005$) levels and positively with logAA:EPA levels ($r_p = 0.18$, $P = .043$).

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.

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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 α-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] regulating cell membrane responsiveness,[2] acting as second messengers,[3] and balancing proinflammatory 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 it 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 etiologic role for omega-3 PUFA intake in mood disorders, such as major depressive disorder (MDD) and bipolar disorder. 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[30–48] of omega-3 PUFA supplementation in depression have reported mixed efficacy results, meta-analyses[49–51] have found that omega-3 PUFA supplements have efficacy when (1) patients have a diagnosis of major depressive episode 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 the pathophysiology of these disorders and that supplementation may be an effective treatment for anxiety and anxiety disorders. Collectively, anxiety disorders, which include posttraumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias, are among the most common mental disorders, affecting approximately 20% of the US population.[53] With the average age at onset for anxiety disorders being 11 years of age[54] and with 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 MDD. 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 (AA; 22:4n-6) to EPA (AA:EPA) in 3 groups of subjects: healthy volunteers and MDD patients with and without comorbid anxiety disorders (anxious MDD and nonanxious MDD, respectively). Omega-3 PUFAs DHA and EPA are species shown to be relevant in depression,[29] and AA:EPA is an additional useful marker that conveys information about the

Clinical Points

- The presence and severity of anxiety were associated with the lowest omega-3 fatty acid levels across major depressive disorder (MDD) samples 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.

balance between omega-6 and omega-3 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 patients with major depression compared with healthy controls or patients with 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 years (mean age, 35.8 ± 12.6 years), from the greater New York City metropolitan area who provided written informed consent to participate in institutional review board–approved mood disorder studies at the New York State Psychiatric Institute; these studies included 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* diagnosis of acute major depressive episode in the context of MDD (diagnosed using the Structured Clinical Interview for *DSM-IV* Axis I Disorders).[58] Comorbid *DSM-IV* anxiety disorders included panic disorder, social anxiety disorder, simple phobia, obsessive-compulsive disorder, generalized anxiety disorder, somatization disorder, hypochondriasis, and posttraumatic stress disorder. Individuals were excluded from participation if they had active medical or neurologic illness. Participants did not take psychotropic medications for at least 2 weeks prior to the collection of blood samples, with the exception of 1 healthy volunteer who was taking zolpidem, 1 anxious and 2 nonanxious MDD participants who were taking sertraline, and 1 anxious MDD participant who was taking mirtazapine.

Depressed participants were administered the 17-item Hamilton Depression Rating Scale (HDRS-17)[59] and the Beck Depression Inventory (BDI)[60] to assess depression severity. We computed an anxiety severity subscore from the total HDRS-17 using factor analysis and principal-components analysis, as described in detail elsewhere,[61] composed of 4 items: item 9 (agitation), item 10 (psychic anxiety), item 11 (somatic anxiety), and item 15 (hypochondriasis). The depression severity subscore 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[62] of studies of the factor structure of the HDRS-17, when a 2-component factor solution was sought, the first component was anxiety, with the remaining items as a general component.

Clinical and demographic information was obtained, including the participant-estimated level of tobacco consumption according to the following scale: nonsmoker (0 cigarettes per day), light (average of 10 per day), moderate (average of 20 per day), heavy (average of 40 per day or more).

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 cryo tubes and stored at −80°C until analysis. Analytic procedures for separation and quantification of plasma PUFAs DHA and EPA fatty acid methyl esters have been described previously.[63] Briefly, the process required direct transesterification of all classes of lipids in a 1-step procedure using 0.1 mL of plasma. Fatty acid methyl esters were then separated by gas chromatography/flame ionization detector with hydrogen carrier gas in a DB-FFAP capillary column (30 m × 0.25 mm × 0.25 μm); both the gas chromatograph (model 6890) and the column are from Agilent Technologies (formerly Hewlett-Packard), Wilmington, Delaware. A retention lock program allowed for the elution of an internal standard with a specific retention time. A known equal-weight mixture of 28 fatty acid methyl esters, commercially available as GLC-462 from Nu-Chek Prep (Elysian, Minnesota), 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 fatty acid methyl esters 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 interassay 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 19 for Mac (IBM SPSS Inc; Chicago, Illinois). Plasma levels of EPA and DHA, as well as AA:EPA, 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

Table 1. Comparison of Participants by Study Group With Respect to Demographic and Clinical Characteristics (N = 121)

	Healthy (n = 62)		MDD Without Comorbid Anxiety Disorder (n = 41)		MDD With Comorbid Anxiety Disorder (n = 18)				
Variable	N	n (%)	N	n (%)	N	n (%)	χ^2	*df*	*P*
Demographic characteristics									
Sex, male	62	25 (40.3)	41	19 (46.3)	18	8 (44.4)	0.383	2	.826
Race, white	60	28 (46.7)	41	22 (53.7)	18	15 (83.3)	7.534	2	.023*
Tobacco use, yes[a]	62	6 (9.7)	39	9 (23.1)	18	6 (33.3)	6.622	NA	.033*
		Median (IQR)		Median (IQR)		Median (IQR)			
Personal income level ($1,000/y)[b]	62	20.0 (32.5)	40	22.5 (38.7)	18	25.0 (48.2)	NA	NA	.715
		Mean (SD)		Mean (SD)		Mean (SD)	*F*		
Age, y	62	36.2 (13.3)	41	37.0 (12.6)	18	31.2 (9.4)	1.42	2,118	.245
Body mass index (kg/m^2)	61	25.0 (5.1)	41	25.5 (5.7)	18	24.3 (5.2)	0.36	2,117	.699
Education, y	62	15.5 (2.9)	40	15.0 (2.9)	18	14.3 (2.7)	1.15	2,117	.320
Clinical characteristics									
Mood measures							*t*		
HDRS-17[c]	62	2.1 (2.7)	41	17.2 (5.7)	18	20.3 (3.8)	2.172	57	.034*
Nonanxiety HDRS items (HDRS-13)[c]	62	1.3 (2.0)	41	12.9 (4.8)	18	15.3 (3.1)	1.959	57	.055
BDI[c]	62	0.8 (2.4)	40	23.7 (10.3)	18	27.6 (6.7)	1.459	56	.150
Plasma PUFA levels, mg/L[d]							*F*		
DHA	62	61.1 (26.0)	41	60.4 (31.6)	18	42.1 (15.2)	4.923	2,118	.009*
EPA	62	26.4 (18.5)	41	22.2 (16.4)	18	14.8 (8.6)	6.442	2,118	.002*
AA:EPA ratio	62	13.8 (7.2)	41	14.1 (5.88)	18	19.3 (9.2)	3.806	2,118	.025*
Dietary PUFA intake, mg/d[d]									
DHA	54	93.7 (18.5)	35	45.2 (7.8)	14	25.3 (3.5)	1.639	2,100	.199
EPA	54	64.2 (18.2)	35	24.6 (3.9)	14	13.1 (1.8)	1.966	2,100	.145

[a]Fisher exact test was performed.
[b]Kruskal-Wallis test of medians was performed.
[c]Student *t* test compared MDD with and without comorbid anxiety disorder (healthy volunteers were not included in the analysis).
[d]Non–log-transformed values are reported as more relevant to readers; however, statistical results reflect analyses performed with log-transformed values.
*$P < .05$.
Abbreviations: AA = arachidonic acid, BDI = Beck Depression Inventory, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HDRS = Hamilton Depression Rating Scale, IQR = interquartile range, MDD = major depressive disorder, NA = not applicable, PUFA = polyunsaturated fatty acid, SD = standard deviation.

a constant value of 0.0001 to all datapoints. Tobacco consumption was compared among diagnostic groups using the Kruskal-Wallis test.

For the principal outcome measure, an analysis of variance was performed with log-transformed PUFA status (logPUFA) as the dependent variable, with 3 predictor groups: anxious MDD, nonanxious MDD, and healthy volunteers. Two a priori planned contrasts were then performed: anxious MDD versus nonanxious MDD, and all MDD participants versus healthy volunteers. As a sensitivity analysis, these calculations were repeated leaving out participants who were taking medications. Age, sex, race, and tobacco consumption were also tested separately as covariates in the model. Given the small sample size, we were able to test only 2 categories of race (white vs nonwhite).

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, $P \leq .05$ 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 characteristics (Table 1) did not differ between the 3 groups, except for race and smoking status. Tobacco consumption differed among the diagnostic groups (mean rank scores: anxious MDD, 69.92 > nonanxious MDD, 63.23 > healthy volunteers, 55.09; Kruskal-Wallis $\chi^2_2 = 7.019$, $P = .030$). Our sample did not include any heavy smokers (40+ cigarettes per day).

Anxiety disorder diagnoses within the anxious MDD group included generalized anxiety disorder (3), hypochondriasis (1), obsessive-compulsive disorder (3), panic disorder (2), posttraumatic stress disorder (7), and social phobia (6). Four participants had more than 1 anxiety disorder.

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

Levels of logPUFA differed across the 3 groups (see Table 1). Participants with MDD had lower levels of logDHA ($t_{118} = 2.324$, $P = .022$) and logEPA ($t_{118} = 3.175$, $P = .002$) and higher levels of logAA:EPA ($t_{118} = -2.099$, $P = .038$) compared to healthy volunteers. The anxious group was distinguishable from the nonanxious group on the basis of lower logDHA

($t_{118} = 2.692$, $P = .008$) and logEPA ($t_{118} = 2.524$, $P = .013$) levels and higher logAA:EPA levels ($t_{118} = -2.322$, $P = .022$). Sensitivity analyses conducted excluding the 5 participants who were taking medication remained significant (n = 116 for all tests) (logDHA: $F_2 = 4.615$, $P = .012$; logEPA: $F_2 = 6.544$, $P = .002$; logAA:EPA: $F_2 = 3.600$, $P = .031$).

Log-transformed dietary intakes of DHA and EPA did not differ between the 3 groups (DHA: $F_2 = 1.639$, $P = .199$; EPA: $F_2 = 1.966$, $P = .145$), but numerical ordering of mean levels of omega-3 PUFA intake was consistent with plasma results: healthy volunteers > MDD patients without comorbid anxiety > MDD patients 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 logPUFA as follows. Levels of EPA and levels of EPA relative to AA (both shown in log[mg/L] per year) increased with increasing age (for logEPA: $B = 0.006$ [standard error (SE) = 0.002], $t = 3.322$, $P = .001$; for logAA:EPA: $B = -0.003$ [SE = 0.002], $t = -2.125$, $P = .036$). For race, B represents the adjusted difference between whites and nonwhites with regard to logPUFA (levels shown in log[mg/L]). Whites had higher logEPA levels ($B = 0.116$ [SE = 0.045], $t = 2.583$, $P = .011$) and lower logAA:EPA levels ($B = -0.123$ [SE = 0.041], $t = -2.961$, $P = .004$) than nonwhites.

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 the Association Between PUFA Levels and Comorbid Anxiety

The HDRS-17 contains 4 items concerning anxiety (24% of the total score), and the BDI has 1 anxiety item of 21 total items (5%). Without the anxiety items of the HDRS-17 (ie, using 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 as measured with the HDRS anxiety subscore in the combined MDD sample (n = 59) correlated negatively with logDHA levels using the Pearson r ($r_p = -0.34$, $P = .009$) and exhibited a trend toward negative correlation with logEPA levels ($r_p = -0.24$, $P = .067$). No correlation was observed between anxiety severity and logAA:EPA levels ($r_p = 0.11$, $P = .410$). When examined in the entire sample (N = 121), however, all logPUFAs correlated in the expected direction with severity of anxiety symptoms (logDHA: $r_p = -0.22$, $P = .015$; logEPA: $r_p = -0.25$, $P = .005$; logAA:EPA: $r_p = 0.18$, $P = .043$). An inspection of the scatter plots indicates that these relationships are comparable with respect to logDHA and logEPA in anxious depressed, nonanxious depressed, and healthy participants.

DISCUSSION

To our knowledge, this study is the first to investigate omega-3 PUFA levels in MDD 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 patients compared to healthy volunteers. Notably, anxious MDD also was distinguished from nonanxious MDD by lower plasma DHA and EPA levels and higher AA:EPA ratio. The ranking of both plasma levels and dietary intake of omega-3 PUFAs (EPA and DHA) was anxious MDD patients < nonanxious MDD patients < healthy volunteers. Because the group differences remained robust after adjustment for nonanxious 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[66] that found inverse correlations between erythrocyte omega-3 PUFA concentrations and severity of social anxiety disorder. 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 although tobacco consumption differed among diagnostic groups, none of these variables explained the associations between logPUFA levels and the presence of comorbid anxiety disorders. It is unclear why age and race affected logEPA levels 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 epidemiologic study[68] of fish and seafood consumption found greater intake of omega-3 PUFAs to be associated with a lower prevalence of anxiety, although this finding 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. Beneficial effects 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 (mean age = 70 years)[73] populations. 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,[51] which found that an EPA proportion in supplements of at least 60% positively affected depression outcome. Empirically observed greater therapeutic effects of EPA than DHA in depression[49–51] are counterintuitive, given that DHA is far more abundant than EPA in the 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 physiologic functions that differentiate EPA from DHA.

Only 2 randomized, placebo-controlled trials[74–75] evaluating the efficacy of omega-3 PUFA supplementation as a therapeutic intervention for anxiety disorder have been published. A placebo-controlled crossover trial[74] in 11 patients with obsessive-compulsive disorder who were given omega-3 PUFA supplementation (2,000 mg/d EPA) adjunctive to selective serotonin reuptake inhibitors yielded no improvement in obsessive-compulsive disorder or depression. Another trial[75] in patients with posttraumatic stress disorder, which used a similar dose of omega-3 PUFA supplementation (2,000 mg/d EPA), had to be terminated prematurely, after 6 patients had enrolled, due to lack of improvement and a trend toward worsening symptoms.

Similarly, 1 study[76] of omega-3 PUFA supplementation in the treatment of major depressive episode with and without comorbid anxiety in adult patients with major depressive episode (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 patients with major depressive episode *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 that 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. Furthermore, to our knowledge, no study has 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 have found that omega-3 PUFA supplementation is positively associated with decreases in anxiety-like behaviors in rodents[77,78] and nonhuman primates.[79] However, other rodent 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 nondeficient animals.

These animal studies suggest that a pathological 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, 1 human study[70,71] in a population (N = 24) of omega-3 PUFA–deficient substance abusers who were given omega-3 PUFA daily supplements of 450 mg of EPA, 100 mg of DHA, and 50 mg of other omega-3 PUFAs revealed declines in anxiety scores for the patients receiving PUFA supplementation 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 proinflammatory 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: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 1 stressor 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.

Drug names: mirtazapine (Remeron and others), sertraline (Zoloft and others), zolpidem (Ambien, Edluar, and others).

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Author contributions: Dr Sublette designed the study. Ms Liu performed the literature searches and statistical analyses and wrote the first draft of the manuscript. Dr Galfalvy supervised the statistical analysis. Mr Cooper performed the polyunsaturated fatty acid biochemical analyses. Drs Grunebaum, Oquendo, and Mann designed and directed mood disorder studies at New York State Psychiatric Institute, from which research participant data were obtained. All authors contributed to and have approved the final manuscript.

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Additional information: The data for this study are part of a larger dataset maintained at the New York State Psychiatric Institute, in the Division of Molecular Imaging and Neuropathology, under the direction of J. John Mann, MD, Division Director. The data are not available for outside researchers to access, but requests for clarification concerning the data analysis in this article may be addressed to the corresponding author.

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