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Polyunsaturated fatty acid composition and childhood adversity: independent correlates of depressive symptom persistence

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Abstract

Childhood experiences, personality, and polyunsaturated essential fatty acid (PUFA) composition have all been shown to affect the likelihood of depressive symptoms. Few studies have addressed relationships between these factors in their influence on the occurrence or course of depressive symptoms. The following analysis was designed to do so. Subjects, 15 to 20 years old, had either begun antidepressant treatment within the preceding month (n=88), or had never taken psychiatric medications (n=92). Baseline assessments included a structured diagnostic interview, the self-completed Multiphasic Personality Questionnaire, and a determination of plasma PUFA phospholipid composition. Depressive symptom levels were assessed at baseline and again at 4, 8 and 12 months. Omega-3 composition and general childhood trauma scores were unrelated to each other but both correlated, in predicted directions, with negative emotionality. Low omega-3 composition and history of childhood trauma were associated with persistence of depressive symptoms during follow-up, largely through their effects on negative emotionality. Negative

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Results were presented in a poster session. Summaries were not distributed nor were abstracts published in the program.

emotionality appears to comprise a final common pathway to depressive disorder through which the diverse risk factors of childhood adversity and low omega-3 composition are expressed.

Keywords

PUFA; omega-3; depressive disorder; negative emotional temperament

1.) Introduction

Many ecological and therapeutic studies have demonstrated the importance of polyunsaturated fatty acids (PUFA) to risks for¹⁻⁵, and recovery from^{6, 7}, depressive disorders. PUFAs are important components of neuronal membranes and particular PUFA deficits adversely affect both the serotonergic and dopaminergic systems^{8,9}. In addition, most PUFAs in the omega-3 series are anti-inflammatory, while those in the omega-6 series are pro-inflammatory¹⁰. A balance in the PUFAs favoring the omega-6 component is therefore associated with increases in pro-inflammatory cytokines and, as an apparent consequence, with increased risks for depressive symptoms¹¹.

PUFA measurements at one point reflect not only an individual's concurrent dietary habits, but also that person's activity of desaturases and elongases, enzymes responsible for the interconversion to effector omega-3 and omega-6 fatty acids¹². Therefore, a single PUFA measure is likely to predict, at least to some degree, future values and thus to have prognostic weight for the course of depressive illness. Most prospective studies that have examined relationships between baseline dietary omega-3 intake and incident depressive disorder have failed to find them, however¹³⁻¹⁶. Another reporter identified a group of adolescents with MDD who had failed to respond to a six-week trial of SSRI antidepressants and found clear deficits in docosahexaenoic acid (DHA) levels relative to those of a nested control group¹⁷. The majority went on to achieve remission of symptoms in a ten-week trial of DHA and eicosapentanoic acid (EPA). Several that did not exclude individuals with depressive disorders at baseline, and that could therefore be considered studies of prevalence rather than incidence, did find association between omega-3 dietary intake and depressive morbidity during follow-up^{5, 18, 19}. Only two prospective studies have employed direct measures of PUFA composition as potential predictors of depressive morbidity. One found no relationship between baseline serum phospholipid PUFA measures and the occurrence of depressive illness as revealed by records of antidepressant prescriptions²⁰. In contrast, a much smaller, case-control report found significantly higher ratios of omega-6 to omega-3 concentrations among women who developed post-partum depression in comparison to those who did not²¹.

Several additional prospective studies are germane if suicidal behavior is viewed as a proxy for depressive illness. Sublette²² found higher ratios of omega-6 to omega-3 composition in patients who attempted suicide during follow-up and Lewis²³ reported lower DHA composition in a large sample of active duty military service members who later committed suicide in comparison to demographically-matched control individuals.

Childhood adversity is a well-established antecedent of depressive illness^{24–26}. Moreover, among individuals with depressive disorder, those who have experienced such adversity have poorer outcomes^{27–30}. While variables such as socio-economic status (SES) may influence both the likelihood of childhood adversity and subsequent dietary habits³¹, it may be that PUFA composition and childhood adversity measures are orthogonal in their relationships to the risk for, and course of, depressive illness. If both measures are independently predictive of greater depressive morbidity over time, their combination would be more predictive in at least an additive fashion. Even so, these two factors may share a common pathway in the causal route to depressive illness. A candidate for such a shared intermediary is neuroticism or negative affectivity.

Measures of neuroticism correlate with both the likelihood and the persistence of depressive symptoms. Separate studies have shown significant associations between neuroticism and both low PUFA³² intake or composition³³, and childhood adversity^{34, 35}. Notably, at least one study has shown that neuroticism mediated the relationship between cumulative lifetime adversity, inclusive of childhood adversity, and current depressive symptoms³⁶. A demonstration that PUFA composition and childhood adversity have independent influences on neuroticism would have important implications for the mechanisms underlying depressive disorders.

2.) Methods

2.1 Participants

Participants, 15 to 20 years old, who were within one month of starting a selective serotonin reuptake inhibitor (SSRI) (n=88), or who were taking no psychotropic medication (n=92), were enrolled from outpatient and inpatient clinical settings, as well as by e-mail solicitation and word of mouth, into a longitudinal observational study designed to examine the effects of SSRIs on bone mass³⁷. Of those taking SSRIs, 25 (28.4%) were taking fluoxetine, 25 (28.4%) sertraline, 6 (6.8%) escitalopram and 2 (2.3%) paroxetine.

Those treated with other psychotropic medications over the preceding two years were excluded, though entry criteria permitted the use of benzodiazepines, antihistaminic agents, trazodone, α_2 -agonists, mirtazapine, or stable doses of a psychostimulant. Other grounds for exclusion were the presence of eating disorders, substance dependence, pregnancy, significant medical or surgical history, the chronic use of medications potentially affecting bone metabolism (e.g., extended corticosteroid use), and plans to move out of state in the following year. The University of Iowa Institutional Review Board approved the study and adult participants provided informed consent. The parent/guardian of minor participants provided written informed consent while the minors gave written assent to the study.

2.2 Procedures

Trained research coordinators collected demographic and clinical data in an intake assessment battery that included the researcher-administered Inventory for Depressive Symptomatology (IDS), the NIMH Diagnostic Interview Schedule for Children (DISC-IV)³⁸, and an unstructured interview by a child psychiatrist (CAC). Parents of minors were

also interviewed. Intake assessment included as well the Early Trauma Inventory – Self Report (ETISR)^{39,40}, a 19-item questionnaire covering general adverse life events that occurred before the age of 18. These included physical, sexual, and emotional abuse. Participants described their recent food intake with the Food Questionnaire (www.NutritionQuest.com), an instrument that required the subject to estimate their usual intake of a given food type over the preceding year.

Participants completed the Multidimensional Personality Questionnaire (MPQ)⁴¹ at their first follow-up visit. The MPQ is a factor-analytically derived, broadband inventory of normal personality. It has 11 primary scales that load on three higher order factors: Positive Emotionality (Well-Being, Social Potency, Social Closeness, and Achievement), Negative Emotionality (Stress Reaction, Alienation, and Aggression), and Constraint (Control, Harm Avoidance, and Traditionalism). Negative emotionality correlates strongly with the construct of neuroticism from the NEO Personality Inventory^{42, 43}. Because of the importance of neuroticism to the heritability⁴⁴ and course⁴⁵ of depressive disorders, this measure was selected as a focus in the following analysis.

Raters arranged for face-to-face visits 4, 8 and 12 months after study entry and completed an Inventory of Depressive Symptoms (IDS)⁴⁶ was administered at each in-person visit to assess depression symptom severity during the week prior to administration.

Samples for plasma PUFA composition assays were drawn under non-fasting conditions and stored at -80°C . Storage times were up to two years but fatty acid composition in such samples have been shown to be stable across periods of 8 to 10 years⁴⁷. Plasma lipids were extracted into chloroform-methanol⁴⁸ containing 0.01% (wt%) butylated hydroxytoluene as antioxidant. The phospholipid fraction was isolated by chromatography over aminopropyl silica gel. Fatty acids were methylated using acetyl chloride⁴⁹. Fatty acid methyl esters were separated by Hewlett-Packard model 5890 II gas chromatograph equipped with a DB23 column (30m x 0.25mm id; Agilent, Santa Clara, CA) and a flame ionization detector. Chromatograms of fatty acid methyl ester standard mixtures were obtained with each group of samples and the retention times of the standards were used to identify the fatty acids present in each phospholipid sample. Values are reported in mole %.

2.3 Data Analysis

To minimize risks for type 2 errors, analyses were limited, a priori, to those PUFA values that figure most prominently in the relevant literature, eicosapentanoic acid (EPA), docosahexanoic acid (DHA), arachidonic acid (AA) and the ratio of AA to the sum of EPA and DHA (AA/EPA+DHA). Natural log values were used for all analyses.

Analyses used both SPSS (version 22) and SAS 9.3. Group comparisons employed t-tests or one-way ANOVA as appropriate. IDS and negative emotionality scores were markedly skewed toward higher values and were therefore square root transformed when used as outcomes. Because we had no casual hypothesis for the relationship between PUFA composition and childhood adversity we simply described this relationship via partial correlation. Relationships between other baseline measures were also described by partial correlations, equivalent to covariate-adjusted regression models. For IDS scores that

included baseline and up to 3 additional measures over the ensuing year of follow-up we fit mixed effect linear regression that included a subject-specific random effect to account for repeated measure correlations. Regression coefficients from these analyses are referred to as *beta* throughout the results. Analyses of our relationships controlled for age and sex. The path model presented in Figure 1 was constructed by a synthesis of results from the corresponding adjusted correlation and regression analyses. This can be shown to be equivalent to simultaneous estimation of the entire path model via a structural equation model.

3.) Results

One hundred eighty individuals had baseline PUFA composition data available and, of these, 156 had completed MPQ and ETISR scales and at least one fellowship visit. IDS values for all three follow-up visits over the course of one year were available for 103 and 149 had at least. Completers did not differ from the full sample by any of the intake measures used in the present analysis (Table 1).

Partial correlations, controlling for age and sex, revealed positive relationships between baseline IDS scores and both negative emotionality and degree of general childhood adversity (table 2). The ETISR measure of childhood adversity was also positively correlated with negative emotionality. Negative emotionality correlated positively with log (AA/EPA+DHA) and negatively with log (EPA+DHA) and log (DHA). Neither baseline IDS scores nor childhood adversity correlated with PUFA measures. Body mass index correlated with none of these dependent variables.

Because one half of the individuals described in these analyses were taking SSRI antidepressants at the beginning of follow up and one half were not taking psychiatric medications we tested for interactions between treatment status and the relationships described in Figure 1. No significant interactions were found between the log (EPA+DHA), ETISR or negative emotionality measures in repeated-measures IDS scores. Nor did interactions exist between log (EPA+DHA) or ETISR measures in the negative emotional temperament score, or between log (EPA+DHA) and ETISR score. All the partial correlations displayed in Figure 1 were in the same direction when the path analyses were done separately for individuals taking, and those not taking, SSRIs. The relationship between baseline log (EPA+DHA) was stronger for those taking SSRIs (-1.07 , $p=0.09$) than for those not taking antidepressants ($-.43$, $p=0.35$). Treatment status was strongly associated with depressive severity at study entry IDS scores for those taking SSRIs showed minimal overlap with the IDS scores of untreated individuals. This finding precluded efforts to separate treatment effects from symptom severity.

To approximate an intent-to-treat SSRI response analysis we restricted the sample to individuals who began the study having recently begun treatment with SSRIs and who had returned for the first follow up visit at four months. Of these 84 individuals 53 (63.2%) were continuing to take SSRIs at the four-month follow up. The baseline IDS score was added to age and sex as a control variable. Relationships between predicted variables were like those for the larger sample. Log (EPA+DHA) was negatively, but not significantly, correlated with

the four-month IDS score ($r=0.15$, $p=0.232$) but was significantly predictive of negative emotional temperament ($r=-0.35$, $p=0.003$). In turn, negative emotional temperament was positively correlated with IDS score at four months ($r=0.423$, $p=0.003$). Childhood adversity was predictive of both four month IDS scores ($r=0.226$, $p=0.036$) and negative emotional temperament ($r=0.317$, $p=0.004$). When these analyses were repeated for those not taking SSRIs at intake, all correlations were in the same direction but none of the p values were less than 0.25.

Only three subjects were taking supplements that contained omega-3 components. After these were removed recent dietary intake of omega-3 foods did not correlate with log (AA/EPA +DHA) ($r=0.08$, $p=0.35$), log (EPA +DHA) ($r=-0.06$, $p=0.49$), log (DHA) ($r=-0.05$, $p=0.54$), log (EPA) ($r=0.09$, $p=0.42$) or log (AA) ($r=0.04$, $p=0.35$). The inclusion of dietary omega-3 intake with age and sex as control variables did not alter the significant correlation between PUFA plasma measures and negative emotionality. For log (EPA + DHA), log (AA/EPA+DHA) and log (DHA), correlations with negative emotionality were $r=-0.24$, $p=.005$, $r=0.26$, $p=0.003$ and $r=-0.23$, $p=0.009$, respectively.

Socioeconomic status during childhood, as estimated by parental yearly income, was correlated with the IDS score ($r=-0.17$, $p=0.018$) and the ETISR general score ($r=-0.18$, $p=0.011$), but not with negative emotionality ($r=-0.07$, $p=0.337$) or log (EPA+DHA) ($r=0.09$, $p=.281$). However, the inclusion with age and sex of parental income as a control variable had little effect on the partial correlations between ETISR and negative emotionality ($r=0.28$, $p<0.001$) or between ETISR and IDS score ($r=0.23$, $p=0.001$).

When baseline and follow-up IDS scores were combined and treated as repeated measures, correlations between symptom severity and both negative emotionality and childhood adversity remain robust (Table 3). Negative correlations emerged between repeated measure IDS scores and log values of both EPA and EPA+DHA. Because log (EPA+DHA) showed the strongest correlation with both mean IDS scores and negative emotionality, this PUFA value was used in subsequent analyses. Notably, partial correlations between log (EPA +DHA) showed no tendency to diminish across follow up interviews. Correlations and IDS scores (P) at 4, 8 and 12 were -0.02 (.036), -0.18 (.059) and -0.28 (.004), respectively.

In contrast to negative emotionality, neither positive emotionality ($r=-.04$, $p=0.629$) nor constraint ($r=0.01$, $p=0.895$) was significantly associated with childhood adversity. Similarly, neither positive emotionality ($r=0.08$, $p=0.298$) nor constraint ($r=.01$, $p=.870$) correlated significantly with log (EPA+DHA). Positive emotionality ($\beta=-.03$, $p<0.0001$), but not constraint ($\beta=0.006$, $p=0.365$) was, however, significantly associated with repeated measure IDS scores. When both positive and negative emotionality were included in a multivariate regression model, with age and sex as independent variables, both positive emotionality ($\beta=-0.02$, $p=0.0004$) and negative emotionality ($\beta=0.54$, $p<0.0001$) were significantly associated with repeated measure IDS scores.

With negative emotionality in a path model the relationship between log (EPA+DHA) ceased being significant (Figure 1). The presence of negative emotionality also substantially reduced the significance of the direct association between childhood trauma and IDS score.

4.) Discussion

This sample of high school and college students entered a prospective study with depressive symptoms that spanned chiefly the lower end of the severity spectrum. Those who finished one year of follow-up had a mean (SD) IDS score of only 11.5 (9.6), a value at the lower end of the range considered “mild”. Nevertheless, the hypothesized predictors of prospectively observed depressive symptoms performed as expected. Those with higher levels of negative emotionality and of childhood adversity experienced higher levels of depressive symptoms over the ensuing year. Those with lower omega-3 plasma composition also experienced higher mean depressive symptoms scores, as predicted. Notably omega-3 plasma composition was significantly associated with depressive symptoms when measured longitudinally rather than with a single measure in cross-section. Omega-3 composition and childhood adversity scores both predicted depressive symptom severity through their effects on negative emotionality.

Nearly all the published efforts to test the importance of baseline PUFA status to subsequent depressive morbidity have been community studies that relied on dietary intake measures. Most found no clear relationship^{13–16}. Two studies that did report the predicted relationships between baseline dietary intake measures and depressive symptoms during follow-up found that they held only for women^{5, 19}. Two differences between these studies and the one described here may be relevant to the contrasting results. First, half of the group described here had begun treatment with a SSRI antidepressant shortly before follow-up commenced. It may be that a higher level depressive symptom severity is necessary to demonstrate the importance of PUFA status to subsequent depressive morbidity. Indeed, though the relationships between PUFA status and both follow-up depression scores and negative emotionality were in similar directions for untreated individuals, none were statistically significant.

Second, the link between dietary intake of PUFA's and the amounts available to tissues is mediated by enzymes that modulate the production of those PUFA's that are most important to depressive illness, EPA and DHA, from precursors available in the diet. Inter-individual variations in the polymorphisms of these genes may account for considerable differences between persons with equivalent PUFA intake⁵⁰. It is conceivable that alleles associated with slower production of EPA and DHA would comprise risk factors for depressive disorders. The finding here that recent dietary intake of omega-3 did not influence the relationship between PUFA plasma measures and negative emotionality supports this possibility though with the caveat that estimates of the intake of specific food types over the preceding year may be less meaningful than estimates of more recent intake.

The association of childhood adversity to later depressive morbidity replicates many earlier reports. However, few have explored negative emotionality or neuroticism as a mediator of this relationship. Evidence that negative emotionality mediates the effects of childhood trauma on depressive morbidity may help to focus efforts to identify mechanisms underlying depressive illness.

The apparent influence of omega-3 composition on negative emotionality was more surprising and has several implications. First, because measures of personality are designed to be more enduring characteristics of an individual than are levels of depressive symptoms measured in cross-section, it may be that mediator omega-3 fatty acid composition are likewise more stable than the variability of dietary intake would predict. Though previous research has focused on PUFA composition, the present findings suggest that genotypes pertaining to the conversion from precursors to the omega-3 PUFAs, EPA and DHA may play a role in the development of personality characteristics that are potent risk factors for depressive illness.

Pro-inflammatory cytokines are likely to mediate several of the relationships depicted in Figure The role of pro-inflammatory cytokines in the genesis of depressive symptoms has been demonstrated in a variety of ways and is now widely accepted⁵¹. Evidence that pro-inflammatory cytokines are also associated with high neuroticism scores⁵² suggests that the latter may explain some of the connection between pro-inflammatory states and stable depression-prone personality traits. Similarly, childhood trauma has also been linked to high pro-inflammatory cytokine levels in adults with MDD^{53, 54}. Studies have shown that depressive symptoms following inflammatory cytokine-inducing treatment with interferon are predicted by the baseline by PUFA status⁵⁵ and can be prevented by pretreatment with combinations of EPA and DHA⁵⁶. In this context it is notable that a large transcultural study found relationships between elevated interleukin-6 and negative emotions in the US but not in Japan where the average diet is much richer in high omega-3 foods⁵⁷.

Notable parallels exist in the reported relationships between PUFA status, neuroticism and risks for post-traumatic stress disorder (PTSD) following trauma. Neuroticism not only increases risks for depressive disorder but also substantially affects the likelihood that PTSD will develop following trauma⁵⁸. In adolescents in particular, studies have revealed robust interactions between measures of neuroticism obtained before trauma and the number of subsequent symptoms of PTSD⁵⁹. Moreover, at least two studies have shown that plasma concentrations of EPA, but not DHA, were protective against PTSD following discrete traumas^{60 61}. In further support for the importance of PUFA status to liability to PTSD, one group assigned victims of a natural disaster to psychoeducation plus fish oil supplements or to psychoeducation alone. Women in the latter group manifested significantly fewer PTSD symptoms 12 weeks later⁶². Though a subsequent trial failed to show efficacy of a predominantly DHA supplement in trauma victims⁶³ a post-hoc analysis showed that changes in EPA concentrations, but not in DHA concentrations, were negatively correlated with PTSD symptom levels⁶³. The retroconversion of DHA to EPA was thought to explain this finding and the authors concluded that a trial of EPA rather than DHA for prevention of PTSD was indicated.

An important limitation to this study is that it was not originally designed to test the hypotheses being addressed here. A study so designed might have been powered more specifically and might have included a wider age-range so that the importance of age on the identified relationships could be explored. Likewise, a broader range of symptom severity would have shown whether the relationship held across this spectrum.

In comparison to PUFA composition measured in erythrocyte membranes, those taken from plasma phospholipids are more sensitive to recent changes in dietary intake of PUFAs. To the degree that this is so, the use of plasma phospholipids would lessen the likelihood that significant relationships would exist with measures of personality with depressive symptoms enduring over a year of follow-up.

The above caveats notwithstanding, the results described here underscore the potential value of including multiple unrelated predictors of depressive morbidity each analysis and of identifying mediating variables. The linkage of disparate risk factors to depressive illness through a common pathway may serve to productively focus research on underlying mechanisms.

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Relationships between IDS¹ Scores and
Three Risk Factors: Controlled for Age and Sex, path coefficients (p)

¹ Inventory for Depressive Symptoms

² Log EPA+DHA

³ ETISR- General

⁴ Multidimensional Personality Questionnaire

⁵ Baseline+4+8+12 month scores/4

⁶ Controlled for negative emotional temperament

Fig.1.

1 Inventory for Depressive Symptoms 2 Log EPA+DHA 3 ETISR- General 4

Multidimensional Personality Questionnaire 5 Baseline+4+8+12 month scores/4 6

Controlled for negative emotional temperament

Table 1.

Sample Description

	Baseline Assessment	Completed 1 year Follow-up
n	180	122
n (%) female	128 (71.1)	85 (69.7)
n (%) taking SSRI	88 (48.9)	50 (41.0)
mean (SD)		
- age	19.1 (1.5)	19.1 (1.4)
- IDS	14.0 (10.6)	12.3 (10.1)
- BDI	12.0 (10.6)	10.2 (9.8)
- ETISR - general	1.8 (1.8)	1.7 (1.8)
- Negative emotionality	35.9 (16.3)	34.3 (15.2)
- Positive Emotionality	72.5 (14.6)	72.9 (14.9)
- EPA, % (SD)	0.46 (.34)	0.43 (.20)
- DHA, % (SD)	2.2 (7.4)	2.24 (.71)
- AA, % (SD)	10.2 (1.9)	10.2 (1.8)
- EPA + DHA, % (SD)	2.7 (.92)	2.7 (.76)
- AA/EPA + DHA, % (SD)	4.0 (1.0)	4.0 (1.1)

Table 2.

Baseline Correlations between Negative Emotionality, Childhood Adversity and IDS Score with Control for Age and Sex, N=156

	IDS Score	Negative Emotionality	ETISR General
negative Emotionality	.53 ***		
ETISR, General	.28 ***	.31 ***	
log EPA	-.16	-.07	-.01
log EPA+DHA	-.07	-.23 **	-.09
log AA	.07	-.01	-.10
log AA/EPA+DHA	.12	.22 **	.014
log DHA	-.04	-.23 **	-.10

*
p < 0.05

**
p < 0.01

p < .001

Table 3

Relationships between Negative Emotionality, Childhood Adversity and Repeated Measure IDS Scores with Control for Age and Sex, n=156

	beta	p
negative emotionality	.58	<.0001
childhood trauma	.23	<.0001
log EPA	-.48	.031
log EPA + DHA	-.77	.028
log AA	-.25	.622
log AA/EPA+DHA	.66	.062
log DHA	-.59	.071