

Dissociation of C-Reactive Protein Levels from Long-Chain Omega-3 Fatty Acid Status and Antidepressant Response in Adolescents with Major Depressive Disorder: An Open-Label Dose-Ranging Trial

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Abstract: Major depressive disorder (MDD) is associated with long-chain omega-3 (LCn-3) fatty acid deficits and indices of chronic sustained inflammation including elevated C-reactive protein (CRP) levels. The present study combined a case-control analysis and a prospective 10-week open-label fish oil (FO) supplementation trial to investigate the relationships among plasma phospholipid LCn-3 fatty acid levels, plasma CRP concentrations, and depressive symptoms in adolescent MDD patients. Compared with healthy controls (n=20), MDD patients (n=20) exhibited significantly lower EPA+DHA levels (-62%, p<0.0001) and a higher ratio of arachidonic acid (AA) to EPA+DHA (+78%, p=0.0002). CRP concentrations did not differ between controls and MDD patients (0.16 vs. 0.17 mg/dL, p=0.96), and were positively correlated with depression symptom severity scores in MDD patients (r = +0.55, p=0.01). CRP concentrations were positively correlated with BMI in MDD patients (r = +0.63, p=0.005) and controls (r = +0.69, p=0.002). Low-dose (2.4 g/d) and high-dose (15 g/d) FO supplementation significantly increased EPA+DHA levels in MDD patients, but did not significantly alter CRP concentrations. Baseline and baseline-endpoint change in CRP levels were not correlated with baseline-endpoint reductions in depression severity. Together, these data demonstrate that the lower plasma phospholipid LCn-3 fatty acid composition exhibited by adolescent MDD patients is not associated with higher CRP levels, and that increasing LCn-3 fatty acid status reduces depression symptom severity independent of changes in CRP concentrations. Collectively, these data suggest that CRP concentrations are dissociable from LCn-3 fatty acid status and antidepressant response in adolescent MDD patients.

Keywords: Major depressive disorder, C-Reactive Protein (CRP), Omega-3 Fatty Acids, Fish oil, Docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA).

1. INTRODUCTION

Major depressive disorder (MDD) significantly increases the risk for cardiovascular diseases [1], and is associated with excess premature mortality due in part to cardiovascular disease [2,3]. Converging evidence suggests that a deficiency in long-chain omega-3 (LCn-3) fatty acids, including eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), may represent a modifiable risk factor for MDD and cardiovascular-related mortality [4]. A body of translational data further suggests that pathophysiology of MDD [5-10] and cardiovascular morbidity and mortality [11-13] are associated with chronic low-grade inflammation, evidenced in part by elevated plasma concentrations of the acute phase protein C-reactive protein (CRP). Therefore, elevated CRP concentrations may represent a risk mechanism linking low LCn-3 fatty acid status, MDD, and cardiovascular disease.

Existing evidence suggests that LCn-3 fatty acids and their bioactive metabolites have anti-inflammatory properties, whereas the metabolites of the omega-6 fatty acid arachidonic acid (AA, 20:4n-6) are predominantly pro-inflammatory [14-17]. However, metabolites of the omega-6 fatty acid homo- γ -linolenic acid (HGLA, 20:3n-6) have anti-inflammatory properties. Population studies have observed an independent inverse correlation between blood LCn-3 fatty acid levels and CRP levels among healthy adults [18-23] and in patients with coronary artery disease [24]. We demonstrated that chronic dietary n-3 fatty acid insufficiency leading to systemic LCn-3 fatty acid deficits significantly increased CRP concentrations in rat plasma [25]. Although case-control studies have consistently observed lower LCn-3 fatty acid levels in erythrocytes (red blood cells) and/or plasma phospholipids from MDD patients [26-31], the relationships among LCn-3 fatty acid status, CRP concentrations, and depressive symptoms are poorly understood.

The present study combined a case-control analysis and prospective open-label dose-ranging fish oil (FO) supplementation trial to investigate the relationships

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among LC n -3 fatty acid status, CRP concentrations, and depression symptom severity in adolescent MDD patients. It was hypothesized that patients with MDD would exhibit LC n -3 fatty acid deficits and associated elevations in CRP compared with healthy controls, and that increasing patient LC n -3 fatty acid status through FO supplementation would dose-dependently decrease CRP concentrations and depressive symptoms.

2. MATERIALS AND METHODS

2.1. Subjects

Written informed consent and assent were provided by a legal guardian and the subject, respectively, and all procedures were approved by the University of Cincinnati Institutional Review Board. Patients (ages 8-21 years) were diagnosed with MDD (DSM-IV-TR criteria), which was confirmed with the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [32]. Patients were required to have a baseline score of >28 (i.e., symptomatic) on the Children Depression Rating Scale-Revised (CDRS-R) [33] despite being administered a standard therapeutic dose of a selective serotonin reuptake inhibitor (SSRI) for a minimum of 6 weeks (i.e., treatment-resistant). Patients were maintained on their current SSRI and dose over the course of this supplementation trial. Healthy controls with no personal history of any DSM-IV-TR Axis I disorder were recruited from the greater Cincinnati area. Subjects were excluded if they tested positive for pregnancy or illicit substance use or were currently taking LC n -3 fatty acid supplements. Cigarette smoking status and body mass index (BMI, kg/m²) were also determined.

2.2. Treatment

Patients were randomized to open-label FO supplements (supplied by the Inflammation Research Foundation) at a fixed dose of either 2.4 g/day (Low-Dose: EPA 1.6 g + DHA 0.8 g; 4 capsules/d) or 15 g/day (High-Dose: EPA, 10.8 g + DHA 5.4 g; 2 tablespoons/day) for 10 weeks. Independent analysis of the fatty acid composition of the FO confirmed that it was composed of approximately 45% EPA (20:5 n -3) and 26% DHA (22:6 n -3) wt % total fatty acids. Compliance was evaluated by determining capsule counts (low-dose) or bottle volumes (high-dose).

2.3. Depression Symptom Ratings

At baseline and all weekly visits, depression symptom severity was determined with the Children's

Depression Rating Scale-Revised (CDRS-R), a 17-item observer-rated questionnaire [33,34], administered by experienced raters with established reliability (ICC > 0.8).

2.4. Fatty Acid Analysis

At baseline and study endpoint (Week 10), whole venous blood (10 ml) was collected into EDTA-coated BD Vacutainer tubes. Blood was centrifuged for 20 min (1,500 \times g, 4°C), and plasma collected and stored at -80°C. The gas chromatography procedure used to determine phospholipid fatty acid composition has been described in detail previously [35]. Briefly, fatty acid methyl esters (FAMES) were analyzed using an HP 6890/5973 gas chromatograph/mass selective detector (Agilent Technologies, Santa Clara, CA). The column used to separate FAME's was an Agilent J&W DB-FFAP 15 m \times 0.1 mm with 0.1 μ m of film thickness. Helium was used as carrier gas at a flow rate of 17.6 ml/min and a constant pressure of 53.8 psi. Fatty acid identification was based on retention times of authenticated fatty acid methyl ester standards (GLC 473B) and controls (GLC 462 and GLC 463) to ensure reproducibility (NuCheck Prep, Elysian, MN). Data are expressed as weight percent of total fatty acid pool (mg fatty acid/100 mg fatty acids). Primary measures of interest were EPA, DHA, homo- γ -linolenic acid (20:3 n -6, HGLA), AA, and the AA/DHA, AA/EPA, and AA/EPA+DHA ratios.

2.5. Plasma CRP Levels

Plasma CRP levels were determined using a high-sensitivity quantitative enzyme immunoassay according to manufacturers instructions (SYNCHRON[®] Systems Inc.). The lower limit of detection was 0.02 mg/dL, and the average intra-assay and inter-assay coefficients of variation were below 5% and 10%, respectively. Cardiovascular risk categories based on CRP concentrations were also evaluated (Low-to-mild risk: \leq 0.11 mg/dL; Moderate risk: 0.12-0.19 mg/dL, and High risk: \geq 0.2 mg/dL) [36].

2.6. Statistical Analyses

Case-control differences in primary outcome measures were evaluated using unpaired *t*-tests (2-tailed, $\alpha=0.05$) for continuous variables and Chi-squared tests (2-tailed, $\alpha=0.05$) for dichotomous variables. Analysis of gender effects was performed with a two-way ANOVA using gender (male, female) and group (control, MDD) as the main factors. Baseline-endpoint changes in primary outcome

measures were evaluated with a two-way ANOVA, with dose (low-dose, high-dose) and study time point (baseline, endpoint) as the main factors. For depressive symptom scores (CDRS) obtained at weekly visits, a repeated measures ANOVA was used on the intent-to-treat (ITT) population which included all patients who received at least one dose of study medication and also had at least one post-baseline assessment. Parametric linear regression analyses were performed to determine the interrelationship among selected fatty acids levels, CRP concentrations, and/or selected clinical variables (2-tailed, $\alpha=0.05$). Statistical analyses were performed using GB-STAT (V.10, Dynamic Microsystems, Inc., Silver Springs MD).

3. RESULTS

3.1. Case-Control Analysis

Patient and control demographic, fatty acid, and CRP data are presented in Table 1. The LCn-3 fatty acids EPA and DHA, were both significantly lower in MDD patients, and the omega-6 fatty acids AA and HGLA were not different (Table 1). The ratios of AA to EPA and/or DHA were significantly greater in MDD patients. CRP concentrations did not differ significantly between groups, and the relative distribution of CRP values in low ($n=12$ vs. $n=12$, $p=1.0$), moderate ($n=4$ vs. $n=4$, $p=1.0$), and high ($n=4$ vs. $n=4$, $p=1.0$) risk categories did not differ between patients and controls.

Table 1: Case-Control Comparisons

Variable ¹	Controls (n=20)	MDD (n=20)	P-value ²
Age (yrs)	17.3 ± 0.9	16.1 ± 0.7	0.14
Gender (n)			
Male	8	6	0.74
Female	12	14	
Race (n)			
Caucasian	14	19	0.10
African American	2	1	
Hispanic	4	0	
Height (cm)	168.1 ± 2.4	163.2 ± 3.1	0.17
Weight (kg)	68.0 ± 3.9	64.4 ± 4.4	0.56
BMI (kg/m ²)	24.0 ± 1.3	24.2 ± 1.6	0.91
Smoking status (current) (n)	2	2	1.0
Age at Onset (yrs)	-	13.1 ± 0.7	-
CDRS-R Total Score	-	34.7 ± 1.0	-
SSRI (n)			
Prozac	-	9	-
Celexa	-	3	-
Lexapro	-	2	-
Zoloft	-	6	-
Fatty Acids (wt % TTL)			
Homo- γ -linolenic acid (20:3 n-6)	1.6 ± 0.1	1.5 ± 0.1	0.61
Arachidonic acid (AA, 20:4 n-6)	9.6 ± 0.4	9.7 ± 0.6	0.99
Eicosapentaenoic acid (EPA, 20:5 n-3)	0.42 ± 0.0	0.09 ± 0.0	0.0001
Docosahexaenoic acid (DHA, 22:6 n-3)	0.49 ± 0.3	0.28 ± 0.1	0.01
EPA+DHA	0.89 ± 0.1	0.34 ± 0.1	0.0001
AA:DHA	24.6 ± 3.2	63.3 ± 10.8	0.001
AA:EPA	27.7 ± 3.5	192.8 ± 17.6	0.0001
AA:EPA+DHA	12.9 ± 1.6	57.4 ± 10.8	0.0002
CRP (mg/dL)	0.16 ± 0.2	0.17 ± 0.2	0.96
Low risk (≤ 0.11 mg/dL)(n)	12	12	1.0
Moderate risk (0.12-0.19 mg/dL)(n)	4	4	1.0
High risk (≥ 0.2 mg/dL)(n)	4	4	1.0

¹Values are group mean ± S.E.M.

²2-tailed t-test or Chi-squared test.

Among MDD patients ($n=20$), CRP was positively correlated with depression symptom severity scores ($r = +0.55$, $p=0.01$) and BMI ($r = +0.63$, $p=0.005$), and there was a trend for a positive correlation between EPA+DHA and CRP ($r = +0.41$, $p=0.09$) but not other fatty acid measures. Among controls ($n=20$), CRP was positively correlated with BMI ($r = +0.69$, $p=0.002$) but not EPA+DHA ($r = +0.16$, $p=0.52$). Among all subjects ($n=40$), CRP concentrations were positively correlated with EPA ($r = +0.41$, $p=0.03$) and there was a trend for positive correlation with EPA+DHA ($r = +0.28$, $p=0.09$) but not other fatty acid measures including HGLA ($r = +0.17$, $p=0.30$) and the AA/EPA ratio ($r = +0.02$, $p=0.89$).

3.2. FO Supplementation Trial

Of the 20 patients randomized to treatment, a total of 14 patients completed the 10-week trial (low-dose, $n=7$; high-dose, $n=7$). Three patients were lost to follow-up post-randomization, and 3 patients terminated study participation early (2 patients in the low-dose group experienced a worsening of depressive symptoms and 1 patient declined to continue participation). The last available post-baseline CDRS score was used for patients with early termination. Based on capsule counts (low-dose) or bottle volumes (high-dose) at weekly visits, there was a compliance rate of 92% for the low-dose group and 97% for the high-dose group.

Primary outcome measures at baseline and endpoint (10 week) in patients treated with low-dose or high-dose FO are presented in Table 2. Both low-dose and high-dose FO supplementation significantly increased EPA+DHA composition, and reduced the ratio of AA to EPA and/or DHA. Baseline CDRS-R total scores in low-dose and high-dose groups did not differ significantly ($p=0.94$). For CDRS-R total scores, there was a significant main effect of time ($p=0.0001$), and the main effect of dose ($p=0.83$) and the Time x Dose interaction ($p=0.65$) were not significant. In the ITT analysis, baseline CDRS-R total scores declined significantly in the high-dose group (-40% , $p=0.0001$) and there was a trend for a decrease in the low-dose group (-20% , $p=0.06$) at endpoint. After removal of the $n=3$ patients in the low-dose group that did not complete the 10 week treatment trial, baseline CDRS-R total scores decreased significantly at endpoint (-27% , $p=0.002$).

Neither low-dose nor high-dose FO supplementation significantly altered CRP concentrations, and the main effect of dose and the dose by time interaction

were not significant. CRP concentrations exhibited non-significant increases in both low-dose ($+36\%$, $p=0.51$) and high-dose ($+25\%$, $p=0.62$) groups. Baseline CRP levels were not correlated with baseline-endpoint change in CDRS total scores ($r = +0.12$, $p=0.71$). At study endpoint, CRP concentrations were positively correlated with BMI ($r = +0.54$, $p=0.04$) but not CDRS total scores ($r = +0.01$, $p=0.96$), and there was a trend for a negative correlation between endpoint CRP and EPA+DHA ($r = -0.52$, $p=0.06$). There was a trend for a negative correlation between baseline-endpoint change in CRP and baseline-endpoint change in HGLA ($r = -0.52$, $p=0.12$). There were trends for a positive correlation between baseline-endpoint change in CDRS total scores and baseline-endpoint change in HGLA ($r = +0.52$, $p=0.06$), but not for EPA+DHA ($r = -0.04$, $p=0.88$) and the AA/EPA+DHA ($r = -0.13$, $p=0.66$) and AA/EPA ($r = -0.03$, $p=0.90$) ratios.

4. DISCUSSION

To our knowledge, this is the first study to investigate the relationships among LC $n-3$ fatty acid status, CRP levels, and depressive symptoms in MDD patients. Consistent with prior case-control studies, the present study found that patients with MDD exhibited significant EPA+DHA deficits compared with healthy controls. This deficit could not be attributed to group differences in age, gender, BMI, or cigarette smoking. Contrary to our hypothesis, however, plasma CRP concentrations were not elevated in MDD patients compared with healthy controls, and were not significantly correlated with EPA+DHA levels. We did find that CRP concentrations were positively correlated with depression symptom severity scores in patients, and consistent with prior reports [37,38], were positively correlated with BMI in both patients and controls. Following 10-week FO supplementation, plasma phospholipid EPA+DHA levels increased significantly in MDD patients receiving low-dose or high-dose FO to levels ~ 3.5 -fold greater than observed in healthy controls. Contrary to our hypothesis, however, we did not observe significant baseline-endpoint decreases in CRP levels despite elevations in EPA+DHA and reductions in depressive symptoms. Collectively, these data demonstrate that lower LC $n-3$ fatty acid status observed in adolescent MDD patients is not associated with greater CRP levels, and that increasing LC $n-3$ fatty acid status reduces depression symptom severity but not CRP concentrations.

This study has several important limitations. First, patients were being treated with an SSRI prior to and

Table 2: Effects of Fish Oil Supplementation

Variable ¹	Baseline	Endpoint	P-value ²
Low-Dose			
Homo- γ -linolenic acid (20:3 <i>n</i> -6)	1.6 \pm 0.2	0.8 \pm 0.1	0.006
Arachidonic acid (AA, 20:4 <i>n</i> -6)	10.3 \pm 0.7	7.6 \pm 0.9	0.03
Eicosapentaenoic acid (EPA, 20:5 <i>n</i> -3)	0.1 \pm 0.0	1.2 \pm 0.4	0.0098
Docosahexaenoic acid (DHA, 22:6 <i>n</i> -3)	0.3 \pm 0.1	1.3 \pm 0.2	0.0004
EPA+DHA	0.4 \pm 0.1	2.5 \pm 0.5	0.001
AA:DHA	56.9 \pm 13.1	6.9 \pm 1.5	0.004
AA:EPA	94.8 \pm 26.8	24.4 \pm 13.9	0.0001
AA:EPA+DHA	45.8 \pm 11.0	4.8 \pm 1.6	0.004
CRP (mg/dL)	0.09 \pm 0.0	0.1 \pm 0.1	0.51
BMI (kg/m ²)	20.2 \pm 0.8	20.8 \pm 1.0	0.68
CDRS-R Total Score	34.4 \pm 1.2	28.1 \pm 3.2	0.06
High-Dose			
Homo- γ -linolenic acid (20:3 <i>n</i> -6)	1.3 \pm 0.1	0.8 \pm 0.3	0.13
Arachidonic acid (AA, 20:4 <i>n</i> -6)	8.0 \pm 1.3	5.8 \pm 0.6	0.19
Eicosapentaenoic acid (EPA, 20:5 <i>n</i> -3)	0.0 \pm 0.0	1.8 \pm 1.1	0.005
Docosahexaenoic acid (DHA, 22:6 <i>n</i> -3)	0.2 \pm 0.0	1.7 \pm 0.4	0.004
EPA+DHA	0.2 \pm 0.1	3.9 \pm 1.7	0.0002
AA:DHA	46.3 \pm 2.7	4.7 \pm 1.4	0.0001
AA:EPA	197.0 \pm 11.0	5.9 \pm 1.4	0.0001
AA:EPA+DHA	42.6 \pm 4.7	2.6 \pm 0.7	0.0001
CRP (mg/dL)	0.09 \pm 0.0	0.1 \pm 0.0	0.62
BMI (kg/m ²)	24.8 \pm 1.9	25.9 \pm 2.5	0.79
CDRS-R Total Score	34.9 \pm 1.3	20.3 \pm 1.2	0.0001
Low+High-Dose			
Homo- γ -linolenic acid (20:3 <i>n</i> -6)	1.5 \pm 0.1	0.8 \pm 0.1	0.001
Arachidonic acid (AA, 20:4 <i>n</i> -6)	9.4 \pm 0.7	7.0 \pm 0.6	0.02
Eicosapentaenoic acid (EPA, 20:5 <i>n</i> -3)	0.0 \pm 0.0	1.6 \pm 0.6	0.0088
Docosahexaenoic acid (DHA, 22:6 <i>n</i> -3)	0.2 \pm 0.1	1.5 \pm 0.2	0.0001
EPA+DHA	0.3 \pm 0.1	3.1 \pm 0.7	0.0011
AA:DHA	53.4 \pm 8.7	6.0 \pm 1.1	0.0001
AA:EPA	195.4 \pm 19.8	16.7 \pm 8.3	0.0001
AA:EPA+DHA	44.8 \pm 7.3	3.9 \pm 1.0	0.0001
CRP (mg/dL)	0.09 \pm 0.0	0.13 \pm 0.0	0.40
BMI (kg/m ²)	22.6 \pm 1.8	23.5 \pm 1.8	0.73
CDRS-R Total Score	34.6 \pm 0.9	24.2 \pm 2.3	0.0003

¹Values are group mean \pm S.E.M.²2-tailed *t*-tests.

during study participation. Therefore, it is possible that SSRI effects on primary outcome measures precluded observation of more robust group differences. For example, a prospective study found that SSRI

treatment reduced CRP levels in MDD patients [39], though other studies found that SSRI treatment increased [40] or did not alter [41] CRP levels. Second, this study enrolled predominantly adolescent MDD

patients (age range: 8-21 years), and prior population studies observing associations between CRP concentrations and depression were conducted in adults subjects [5-8]. Third, the relatively small number of subjects randomized to each treatment group may have been underpowered to detect statistically significant baseline-endpoint changes in CRP concentrations. However, we did not observe baseline-endpoint changes in CRP after combining both dose groups, and detected trends for increased CRP levels. Fourth, the intervention trial design was open-label, and the observed baseline-endpoint changes in primary outcome measures should be viewed as preliminary. Fifth, the duration of FO supplementation was relatively short (10 weeks), and greater changes in CRP concentrations may require a longer supplementation period. Therefore, larger and longer controlled studies employing older medication-free MDD patients with high CRP concentrations are warranted to extend and confirm the present findings.

The observation that adolescent MDD patients exhibited robust LCn-3 fatty acid deficits compared with healthy adolescent controls is consistent with prior adult case-control studies [26-31]. However, plasma CRP concentrations did not differ significantly between MDD patients and healthy controls and were not inversely correlated with EPA+DHA levels. These data suggest that low LCn-3 fatty acid status is not associated with elevated CRP concentrations. This finding is consistent with two prior studies findings that lower EPA+DHA levels were not associated with group differences in CRP levels in depressed versus non-depressed cardiac patients [42] or among elderly subjects [43]. Together, these data do not support the observation of an inverse correlation between blood LCn-3 fatty acids and CRP levels in healthy adult populations [18-23]. Furthermore, the present data suggest that the inverse relationship between CRP concentrations and depression symptom severity in MDD patients at baseline is not mediated by lower LCn-3 fatty acid levels.

The observation that 10-week FO supplementation, and associated increases in LCn-3 fatty acid status, did not significantly reduce CRP levels in MDD patients is consistent with prior FO trials in healthy adult subjects [44-46] and patients with cardiovascular disease [47]. Indeed, we observed non-significant increases in CRP concentrations in low-dose (+36%, $p=0.51$) and high-dose (+25%, $p=0.62$) FO groups. It is of interest, therefore, that a prior FO intervention trial (5.2 g/d for 12 weeks) also observed a non-significant trend for

increased CRP concentrations (+9%) in patients with a prior myocardial infarction [47]. These data suggest that acute FO supplementation is not efficacious for reducing CRP concentrations in different populations including MDD patients. One potential mechanism that may account for increasing versus decreasing CRP concentrations following FO supplementation is an elevation in lipid peroxidation [48,49]. Additionally or alternatively, FO supplementation was associated with decreases in the omega-6 fatty acid homo- γ -linolenic acid (HGLA, 20:3n-6), which has anti-inflammatory properties, and we observed a trend for an inverse correlation between baseline-endpoint changes in CRP and HGLA. Additional studies will be required to investigate these and other potential mechanisms.

High-dose FO supplementation significantly reduced depression symptom severity scores (-40%, $p<0.0001$), and there was a trend in the low-dose FO group (-20%, $p=0.06$). This observation is consistent with prior studies finding that FO supplementation reduces depression symptom severity in adolescent [50,51] and adult [52-55] patients with mood disorders. Although baseline CDRS scores were positively correlated with CRP concentrations, the baseline-endpoint reduction in CDRS scores was not associated with changes in CRP levels and endpoint CDRS scores were not correlated with endpoint CRP levels. These data suggest that the antidepressant effects of FO supplementation are not mediated by reducing CRP levels. This observation is in general agreement with prior studies finding that serum CRP concentrations are poorly correlated SSRI treatment response in MDD patients [39,40,56] and in depressed patients with coronary heart disease [57]. Furthermore, a prospective surveillance study found that CRP concentrations were not associated with treatment-emergent increases in depressive symptoms in hepatitis C patients following interferon-alpha administration [35]. Together, these findings suggest that plasma CRP concentrations are not a suitable biomarker of vulnerability to inflammation-induced depression or antidepressant treatment response.

In conclusion, the present findings in adolescent MDD patients support previous case-control studies finding that adult MDD patients exhibit LCn-3 fatty acid deficits and demonstrate that low LCn-3 fatty acid status is not associated with greater CRP concentrations. The present findings further demonstrate that adjunctive FO supplementation significantly increases LCn-3 fatty acid status and decreases depression symptom severity but does not

alter CRP concentrations. Although additional research is needed to elucidate the pathogenic mechanisms linking low LCn-3 fatty acid status and mood dysregulation, the present data suggest that elevated CRP concentrations is not a mediating mechanism.

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