Meta-analysis of erythrocyte polyunsaturated fatty acid biostatus in bipolar disorder

Robert K McNamara[a] and **Jeffrey A Welge**[b]

[a]Division of Bipolar Disorders Research, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[b]Division of Epidemiology and Biostatistics, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Abstract

Objectives—Dietary deficiency in polyunsaturated fatty acids (PUFA), including omega-3 fatty acids eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), and excesses in omega-6 fatty acids including linoleic acid (LA, 18:2n-6) and arachidonic acid (AA, 20:4n-6), may be associated with the pathophysiology of bipolar disorder. In an effort to provide clarification regarding the relationship between PUFA biostatus and bipolar disorder, this meta-analysis investigated studies comparing erythrocyte (red blood cell) membrane PUFA composition in patients with bipolar disorder and healthy controls.

Methods—A meta-analysis was performed on case–control studies comparing erythrocyte PUFA (EPA, DHA, LA, AA) levels in patients with bipolar I disorder. Standardized effect sizes were calculated and combined using a random effects model.

Results—Six eligible case–control studies comprising patients with bipolar I disorder (n = 118) and healthy controls (n = 147) were included in the analysis. Compared with healthy controls, patients with bipolar I disorder exhibit robust erythrocyte DHA deficits (p = 0.0008) and there was a trend for lower EPA (p = 0.086). There were no significant differences in LA (p = 0.42) or AA (p = 0.64).

Conclusions—Bipolar I disorder is associated with robust erythrocyte DHA deficits. These findings add to a growing body of evidence implicating omega-3 PUFA deficiency in the pathophysiology of bipolar disorder.

Keywords

arachidonic acid; bipolar disorder; omega-3 fatty acids; omega-6 fatty acids

Corresponding author: Robert K. McNamara, Ph.D., Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 260 Stetson Street, Cincinnati, OH 45219-0516, USA, Fax: 513-558-4805, ; Email: robert.mcnamara@uc.edu

A growing body of evidence suggests that lower habitual dietary intake of omega-3 polyunsaturated fatty acids (PUFA), including eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), is associated with the pathophysiology of bipolar disorder. Cross-national epidemiological surveys suggest that greater habitual dietary intake of fish/seafood, primary dietary sources of preformed EPA and DHA, are associated with reduced lifetime prevalence rates of bipolar disorder (1). A meta-analysis of controlled trials suggest that short-term fish oil supplementation is more effective than placebo for reducing depressive, but not manic, symptom severity in patients with bipolar disorder (2). Fish oil supplementation has also been shown to reduce manic and depression symptom severity in bipolar youth (3, 4). Emerging translational evidence additionally suggests that DHA is required for normal brain development (5). Additional evidence also suggest that patients with bipolar disorder exhibit abnormalities in the metabolism of the omega-6 PUFA linoleic acid (LA, 18:2n-6) (6). Moreover, arachidonic acid (AA, 20:4n-6), a derivative of LA, has pro-inflammatory effects which are blocked by mood-stabilizer medications (7).

Erythrocyte (red blood cell) membrane EPA and DHA composition is highly correlated with habitual intake of fish or fish oil (8, 9) and represents a valid and reliable biomarker of omega-3 PUFA biostatus (10). In contrast, plasma fatty acid levels are potentially confounded by prior meals and exhibit larger within-subject variability (11, 12). Moreover, erythrocyte DHA is correlated with cortical gray matter DHA composition (13, 14), and neuroimaging studies suggest that DHA intake and erythrocyte biostatus are correlated with corticolimbic structure and function (15–18). Low erythrocyte EPA+DHA levels are also associated with increased risk of cardiovascular mortality (19), and cardiovascular-related diseases are a primary cause of excess premature mortality in bipolar disorder (20, 21). These and other findings suggest that erythrocyte EPA and/or DHA levels may be relevant to the pathophysiology of bipolar disorder.

To provide clarification regarding the relationship between PUFA biostatus and bipolar disorder, the present meta-analysis was conducted on studies that compared erythrocyte PUFA composition in patients with bipolar I disorder and healthy comparison subjects.

Methods

A computerized search was performed to identify eligible peer-reviewed studies published up to December 2015 using PubMed at the National Library of Medicine. The following search terms were used: (bipolar *or* bipolar disorder) *and* (erythrocyte *or* red blood cell) *and* (fatty acid *or* omega-3 fatty acid). We focused our analysis on the primary omega-3 PUFAs DHA and EPA and the primary omega-6 PUFAs LA and AA. Effect sizes were based on unadjusted comparisons of fatty acid levels between cases and controls. Standardized effect sizes (*d*) were calculated and random effects models estimated. In addition to point and 95% confidence intervals of each mean effect, we computed estimates of I^2 (the percentage of total variation attributable to heterogeneity) and p-values under the null hypothesis of homogeneous effect sizes. As the power of these tests is generally low, we did not accept the validity of a fixed effect (homogeneous) model when the heterogeneity test was not significant but instead report results under both fixed and random effect models for comparison. We assessed potential internal sensitivity by repeated analyses with one-out

cross-validation (i.e., each study omitted in turn). Models were estimated by restricted maximum likelihood using PROC MIXED in the SAS system, version 9.4.

Results

The literature search yielded six case–control studies that compared erythrocyte PUFA levels in patients with bipolar I disorder (n = 118) and healthy controls (n = 147) (22–27) and all of these studies were included in the present analysis. In one study (23), a subset of patients with bipolar II disorder (n = 3) and bipolar disorder not-otherwise-specified (n = 5) were included in the bipolar disorder group (23). The remaining studies included only patients meeting DSM-IV criteria for bipolar I disorder. The demographic characteristics of study participants are presented in Table 1. Based on reported depression and mania symptom severity scores, four studies employed patients experiencing a manic or mixed episode (22, 24, 25, 27). One study did not report mania or depression symptom severity (23), and one study reported patients were euthymic (26).

As the number of studies was small, methods based on the funnel plot were unlikely to be informative about potential publication bias and were not employed. For the same reason, we did not consider potential study-level covariates that might account for heterogeneity. Forest plots of standardized effect sizes are shown in Figure 1. Effect sizes for DHA were the least heterogeneous of the four fatty acids analyzed (I^2 = 0.0%, p = 0.4358). The mean standardized effect size was significantly different from zero, with bipolar cases exhibiting lower levels than controls [d = −0.98 (−1.33, −0.63), p = 0.0008] (Fig. 1A). The point estimate of among-study variance was zero, and the fixed effect results were identical. Effect sizes for EPA were significantly heterogeneous (I^2 = 57.4%, p = 0.0385). The mean standardized effect size was not significantly different from zero [d = −0.46 (−1.01, 0.09), p = 0.0857] (Fig. 1B). This was the only finding that was qualitatively altered by inclusion of a single study (22), which slightly lowered this trending p-value to below 0.05 [d = −0.58 (−1.13, −0.04 0, p = 0.0414]. However, since the average effect was only modestly increased, the results cannot be considered particularly sensitive. Two of the six identified studies did not report LA (23, 26). Effect sizes exhibited moderate, though not statistically significant, heterogeneity (I^2 = 44.9%, p = 0.1418). The mean standardized effect size was not significantly different from zero [d = −0.18 (−0.82, 0.45), p = 0.4240) (Fig. 1C). When a fixed effect model was adopted for these data, the results remained qualitatively similar [d = −0.21 (−0.67, 0.25), p = 0.249]. Effect sizes for AA were highly heterogeneous (I^2 = 83.5%, p < 0.0001). The mean standardized effect size was not significantly different from zero [d = −0.18 (−1.12, 0.76), p = 0.6447] (Fig. 1D).

Discussion

The primary finding of this meta-analysis is that patients with bipolar I disorder exhibit robust erythrocyte DHA deficits compared with demographically similar healthy controls. While there was a trend for lower erythrocyte EPA in patients versus controls, differences in erythrocyte EPA levels were more variable across studies and did not reach significance. Moreover, there were no significant differences in the erythrocyte omega-6 PUFAs LA or AA. Similar erythrocyte DHA deficits were observed across studies conducted in five

different countries, including both Western and Eastern countries. Moreover, similar erythrocyte DHA deficits were observed in studies employing adolescent or adult patients, studies employing medicated or unmedicated patients. Although plasma fatty acid levels are more variable, it is also worth noting that a prior case-control study (28), but not others (6, 29, 30), similarly observed DHA deficits in plasma from patients with bipolar disorder. These present results suggest that bipolar I disorder is associated with robust and selective erythrocyte DHA deficits, and add to a growing body of evidence implicating omega-3 PUFA deficiency in the pathophysiology of bipolar I disorder.

A limitation of this meta-analysis is the relatively small number of studies included in the analysis, and the data obtained may not be representative of all individuals with bipolar disorder. However, the effect sizes for DHA were homogeneous and pooled analysis had a large sample size. Second, the cross-sectional design of the studies preclude evaluation of causality, and prospective longitudinal studies will be required to clarify the role of low erythrocyte DHA biostatus in bipolar risk progression. Third, several studies did not include data regarding potential confounders, including cigarette smoking and body mass index (BMI), to evaluate their contribution to the present findings. Nevertheless, studies that specifically investigated the contribution of cigarette smoking did not observe an association with erythrocyte PUFA status (22, 25), and two studies that reported BMI did not observe a difference between cases and controls (22, 25). While gender differences in blood DHA levels have been observed (31), the majority of studies employed both male and female subjects, and two studies that specifically investigated the contribution of gender did not observe an association with erythrocyte DHA status (24, 25).

The etiology of the erythrocyte DHA deficit observed in patients with bipolar disorder across studies may be multifactorial. Selective erythrocyte DHA deficits in the absence of EPA and AA deficits are consistent with impaired peroxisome function which is required for the final biosynthesis of DHA and associated with erythrocyte DHA deficits (32–34). However, peroxisomal-mediated DHA biosynthesis from fatty acid precursors is negligible even in healthy human subjects (35), and first-episode manic patients do not exhibit other lipid abnormalities characteristic of peroxisomal disorders (36). Alternatively, elevations in lipid peroxidation/oxidation may contribute to erythrocyte membrane DHA deficits (37). However, extant evidence suggests that erythrocyte DHA deficits in bipolar disorder are dissociable from indices of lipid peroxidation (27, 38). Medication effects are unlikely since erythrocyte DHA deficits are observed in chronically medicated, medication-withdrawn, and medication-naïve patients with bipolar disorder. Moreover, one study found that erythrocyte DHA deficits in medication-naïve patients with bipolar disorder were not significantly altered following 52-week treatment with either lithium or quetiapine (25). The low erythrocyte DHA levels observed in patients may reflect dietary DHA insufficiency. This is supported by the observations that (i) dietary intake of preformed DHA from fish or fish oil supplements increases erythrocyte DHA levels in a linear dose-dependent manner (8, 9), (ii) patients with bipolar disorder consume less DHA in their diet (6, 23), and (iii) fish oil supplementation significantly increases erythrocyte DHA levels in patients with bipolar disorder (3, 4). While to role of EPA and/or DHA supplementation in the treatment of manic or depressive symptoms is requires additional investigation, extant evidence suggests that DHA and EPA deficiency can be corrected with fish oil supplementation.

Because bipolar disorder is associated with recurrent episodes of depression, it is notable that a meta-analysis of case-control studies of patients with major depressive disorder (MDD) observed significant EPA and DHA deficits, and no difference in AA, compared with controls (39). It is also notable that a large percentage of patients with bipolar disorder have a history of psychotic symptoms (40) and a meta-analysis of case–control studies observed significant erythrocyte DHA as well as AA deficits in first-episode psychosis patients (41). Furthermore, there is a high rate of attention-deficit hyperactivity disorder (ADHD) comorbidity in youth with bipolar disorder (42), and a meta-analysis found that youth with ADHD also exhibit robust DHA deficits (43). Taken collectively, these and the present results suggest that erythrocyte DHA deficits are not unique to bipolar disorder, and are also associated with different psychiatric symptoms that are frequently comorbid with bipolar disorder.

The present findings may take on additional significance in view of evidence that DHA is the primary omega-3 fatty acid found in mammalian gray matter and erythrocyte DHA is correlated with cortical gray matter DHA composition (13, 14). Moreover, emerging neuroimaging evidence suggests that DHA intake and erythrocyte biostatus is correlated with corticolimbic structure and function (15–18). Additionally, erythrocyte EPA and DHA biostatus is positively correlated with immune cell (i.e., monocyte) EPA and DHA composition (44) and inversely correlated with pro-inflammatory cytokine levels (45). It is notable therefore that elevated pro-inflammatory cytokine levels have been observed in patients with bipolar disorder (46). Moreover, prospective studies have found that lower baseline DHA levels, or a higher AA/EPA + DHA ratio, are associated with increased risk for developing a major depressive episode (47, 48), as well as manic-like symptoms including anger and irritability increase (49), during treatment with the pro-inflammatory cytokine IFN-γ. Additional studies are therefore warranted to investigate the links between DHA deficiency, pro-inflammatory signaling, and alterations in cortical structural and functional maturation in bipolar disorder.

Conclusions

In summary, the results of this meta-analysis demonstrate that bipolar I disorder is associated with robust erythrocyte DHA deficits compared with demographically similar healthy subjects. This result was obtained from studies conducted in five different countries, and adds to a growing body of cross-national and cross-sectional findings implicating dietary omega-3 PUFA deficiency in the pathophysiology and potentially pathoetiology of bipolar disorder. These and other data further suggest that erythrocyte DHA deficits may represent a candidate prodromal risk biomarker warranting additional investigation in prospective studies. Additionally, prospective supplementation studies are warranted to determine whether correcting low erythrocyte DHA biostatus by increasing fish or fish oil intake can mitigate risk progression in youth at high-risk for developing bipolar disorder. This approach is supported by the observation that fish oil supplementation prevented or delayed the onset of psychosis in ultra-high risk youth (50).

Acknowledgments

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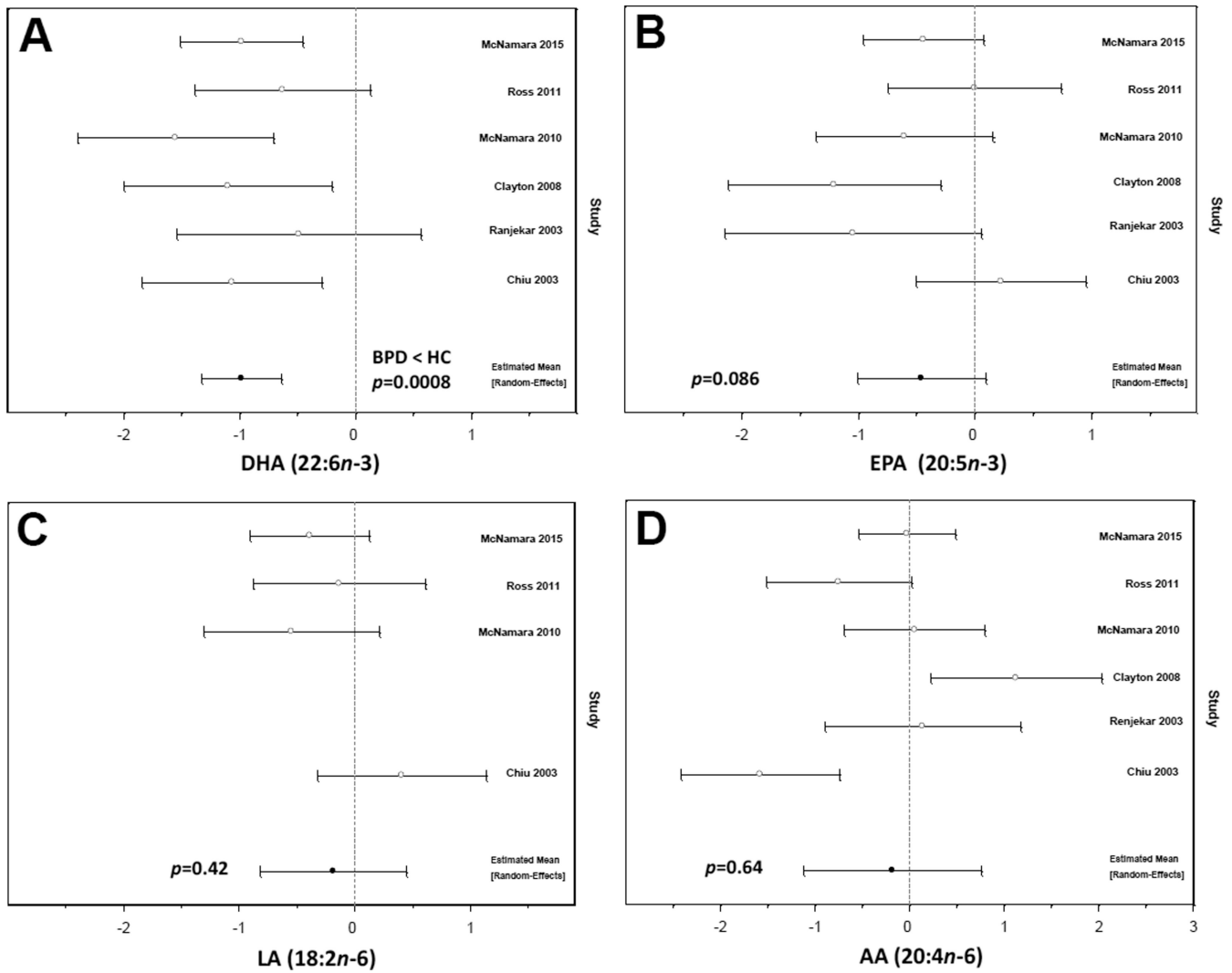
Fig. 1.
Forest plot illustrating standardized effect sizes (*d*) and 95% confidence intervals for individual studies comparing erythrocyte docosahexaenoic acid (DHA, 22:6*n*-3) (**A**), eicosapentaenoic acid (EPA, 20:5*n*-3) (**B**), linolenic acid (LA, 18:2*n*-6) (**C**), and arachidonic acid (AA, 20:4*n*-6) (**D**) levels in patient with bipolar I disorder (BPD) and healthy controls (HC). Pooled results and associated p-values are presented.

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Table 1

Demographic characteristics of participants

Study	Number, n		Mean age, years		% female		% medicated	Diagnostic instrument	Country
	Control	Case	Control	Case	Control	Case			
McNamara et al. 2015 (25)	40	40	18.5	17.8	50	50	0	DSM-IV	USA
Ross et al. 2011 (27)	25	15	36.0	42.0	46	47	100	DSM-IV	Scotland
McNamara et al. 2010 (24)	20	18	36.2	30.7	50	33	0	DSM-IV	USA
Clayton et al. 2008 (23)	15	15	14.7	13.6	60	60	100	DSM-IV	Australia
Ranjekar et al. 2003 (26)	27	10	39.7	40.9	0	0	100	DSM-IV	India
Chiu et al. 2003 (22)	20	20	38.7	39.0	55	50	75	DSM-IV	Taiwan

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