A Meta-Analytic Review of Polyunsaturated Fatty Acid Compositions in Patients with Depression

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Background: On the basis of evidence from studies showing the antidepressant effects of omega-3 polyunsaturated fatty acids and the inverse relation between fish consumption and the prevalence of depression, the phospholipid hypothesis seems promising in ascertaining the etiology and treatment of depression. Although several studies have shown lower levels of omega-3 (n-3) polyunsaturated fatty acids in depressive patients, the results of individual polyunsaturated fatty acids, including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and the omega-6 (n-6) polyunsaturated fatty acid arachidonic acid (AA), were inconsistent.

Methods: We conducted the meta-analyses of 14 studies comparing the levels of polyunsaturated fatty acids between depressive patients and control subjects. The effect size of each study was synthesized by using a random effects model.

Results: Compared with control subjects, the levels of EPA, DHA, and total n-3 polyunsaturated fatty acids were significantly lower in depressive patients. There was no significant change in AA or total n-6 polyunsaturated fatty acids.

Conclusions: The results showed lower levels of EPA, DHA, and total n-3 polyunsaturated fatty acids in patients with depression, thus implying that n-3 polyunsaturated fatty acids play a role in the pathogenesis of depression. Our findings provide further support to the phospholipid hypothesis of depression and a rationale for using n-3 polyunsaturated fatty acids as an alternative treatment for depression. With these results, future studies examining specific roles of DHA and EPA in different clusters of depressive symptoms are warranted.

Major depressive disorder (MDD) is a serious affective illness with a high lifetime prevalence rate (1). The World Health Organization estimated that major depressive disorder will become the second leading cause of disability worldwide by 2020, second to ischemic heart disease, and will be the leading cause in developing regions (2). However, the unmet need of pharmacotherapy and high occurrence of somatic symptoms and physical illness in depression imply that the traditional monoamine hypothesis is not enough to approach the etiology of depression (3). Recently, the phospholipid polyunsaturated fatty acids (PUFAs) hypothesis of depression is providing a promising path to discover a new treatment for depression (4–6). For example, it has been observed that societies with high consumption of fish, which is a good source of omega-3 PUFAs, appear to have a lower prevalence of MDD (7–9). In addition, several clinical trials, if not all (10,11), have shown that omega-3 PUFAs were more effective than placebo (12–16), or as effective as conventional antidepressant medication fluoxetine (17), in treating patients with major depression. In terms of treating special populations with depressive disorders, such as pregnant women (18,19), children (16), patients with bipolar depression (15), and patients with Parkinson's disease (20), the usage of omega-3 PUFAs have been found to be beneficial as well.

The mechanism of the antidepressant effect of omega-3

PUFAs has yet to be elucidated. It has been suggested that the abnormal cell membrane fatty acid composition may be of etiologic significance in depression (4,21). The PUFAs are classified mainly into n-3 (or omega-3) and n-6 (or omega-6) groups. EPA and docosahexaenoic acid (DHA), the major bioactive components of n-3 PUFAs, are not synthesized in the human body and should be obtained directly from the diet, particularly in fatty fish (22). The main n-3 PUFAs in the brain is DHA, comprising up to 10% to 20% of total fatty acids composition in the brain, whereas the n-3 PUFAs α-linolenic acid (ALA), EPA, and docosapentaenoic acid (DPA) comprise only .1% of total brain fatty acid composition (23). DHA is associated with neuronal membrane stability and the functions of serotonin and dopamine transmission, which might connect to the etiology of mood and cognitive manifestations of depression (4,12,24). In contrast, EPA is important in the balance of the immune and neuronal functions by antagonizing membrane arachidonic acid (arachidonic acid [AA], an n-6 PUFA) and reducing prostaglandin E_2 (PGE_2) synthesis (25). For example, animals fed with a high EPA diet could attenuate the sickness behaviors induced by the high AA diets or the PGE_2 treatment (26,27). Interestingly, the sickness behaviors, including anorexia, low activity, and a change in sleep pattern and attention, are similar to somatic symptoms of depression (28).

Consistent with the theoretical relevance and findings from epidemiologic data and clinical trials, the abnormal fatty acid compositions in cell membranes in patients with mood disorders have been reported extensively (29–45), and the findings of the differences in individual PUFAs between patients and control groups are inconsistent. In 1996, Maes and colleagues (30) reported that depression was associated with the significantly higher levels of AA in phospholipids, the AA:EPA ratio in both serum cholesteryl esters and phospholipids, and an n-6:n-3 ratio in cholesteryl esters, as well as lower levels of EPA in both serum cholesteryl esters and phospholipids and the total n-3 PUFAs in cholesteryl esters. However, Peet and colleagues (33) reported that the only abnormal erythrocyte PUFAs level was lower DHA, not EPA or AA. Contrary to Maes's previous report (30), the AA

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level was lower in the depressed patients in their 1999 report (34). In a study of elderly patients with depressive disorders, subjects had lower DHA and higher AA, n-6:n-3, AA:EPA, and AA:DHA ratios than healthy volunteers (36). In samples of patients with acute coronary syndromes, depressed patients had lower DHA, total DHA, and EPA and higher AA and n-6:n-3, AA:EPA, and AA:DHA ratios than those without depression (38). Interestingly, lower DHA levels before starting interferon (IFN)-α therapy predicted IFN-α-induced depression in patients with chronic hepatitis C viral infection (46). The deficit in PUFA levels and abnormal compositions have also been reported in other mood disorders, including lower DHA and total n-3 PUFAs in postpartum depression (35), lower DHA and EPA in social anxiety disorder (47), and lower DHA and AA in bipolar disorder (37).

To understand this discrepancy, we performed a meta-analysis to examine polyunsaturated fatty acid compositions in patients with depression. We pooled results from all case–control studies to analyze individual n-3 and n-6 PUFA compositions in patients with depression.

Methods and Materials

Literature Search

To identify eligible studies for this meta-analysis, a computerized search was performed for all publications available up to August 2009 through PubMed at the National Library of Medicine using the following key words: (depression OR depressive disorder) AND (omega-3 OR EPA or DHA OR polyunsaturated fatty acid), limited to literature in English and human studies. Reference lists from identified articles and relevant reviews were scrutinized for studies not indexed in the electronic databases.

Inclusion Criteria of Studies in the Meta-Analysis

Studies included in this meta-analysis had to meet the following criteria: 1) measured level of any of EPA, DHA, AA, total n-3, or total n-6; 2) used samples from red blood cell (RBC) membrane, blood phospholipids, or cholesteryl esters; 3) included subjects with depression and control subjects; 4) provided enough data to calculate an effect size; 5) were published in peer-reviewed journals; and 6) separate groups of subjects among studies. Studies that included and reanalyzed the same data set as previously published studies were not regarded as independent, and only the study with the highest number of participants was included. When the articles provided data from different sample tissues from the same subjects, we first used data from RBC membrane or blood phospholipids; if both were not available, we used data from blood cholesteryl esters. See Figure S1 in Supplement 1 for the flow chart showing the selection of included studies.

Meta-Analytic Methods

In our analysis, the primary outcomes were comparisons of levels of EPA, DHA, AA, total n-3 PUFA, and total n-6 PUFAs between depressed and control subjects for all included studies. The secondary outcomes were comparisons of the PUFA levels between patients with MDD based on DSM criteria (28) and healthy controls, without major systemic diseases or pregnancy.

For each identified study, the effect size (ES) expressing the difference in each of the PUFA indexes between depressive and control subjects was described as the standardized mean difference (SMD) on the basis of Hedges's adjusted *g*, in which a value greater than 0 indicated that the index was higher in depressive

subjects. The means and standard deviations of each PUFA index of both depressive and control groups were used to derive the ES from each study. When these data could not be retrieved from the publications, we contacted the authors to acquire the data or derived the ES from other measures of variability. The results of individual studies were synthesized by the random effects model (48), by which ESs were pooled and 95% confidence intervals (CIs) were calculated. The significance of the pooled ES was determined by the *z* test. Sensitivity analyses were performed to determine whether any individual study was responsible for the significant result. Each study was individually removed, and the significance was retested.

A homogeneity test (*Q* statistic) was performed to determine whether the group of ESs came from a homogeneous source (48). A rejection of homogeneity suggests that there may have been systemic differences existing among the included studies. In addition, publication bias was assessed by linear regression analysis (49), in which the standard normal deviate of the ES was regressed on the precision of the ES (the inverse of the standard error of the ES). When there was no publication bias, the regression line should traverse the origin, and the expected value of the intercept would be zero. The slope (b) of the regression line indicated the size and direction of the association. An examination of publication bias was a test of the null hypothesis that intercept (a) was equal to zero, as determined by the *t* test. Meta-analyses were conducted by applying Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, New Jersey). Two-sided *p* values $< .05$ were considered statistically significant.

Results

On the basis of the aforementioned search strategy, our initial search identified 1007 studies, of which only 14 were included in current meta-analysis according to the inclusion criteria (29,30, 32–36,38,40–45) (Figure S1 in Supplement 1), which included 3318 subjects (648 depressive and 2670 control subjects). The characteristics of these articles are described in Table 1.

The primary outcomes were comparisons of PUFA levels between depressive (defined arbitrarily in individual studies) and control subjects. The results showed a significant but mild decrease in depressive subjects in the level of EPA (ES = −.18, *p* = .004; Figure 1) and DHA (ES = −.35, *p* = .0002; Figure 2) and moderately decreased level of total n-3 PUFA (ES = −.51, *p* < .0001; Figure 3). The levels of AA (*p* = .95; Figure 4) and total n-6 PUFAs (*p* = .94; Figure 5) were not significantly different. Sensitivity analyses showed that the significant changes in the levels of EPA, DHA, and total n-3 were not influenced by any single study. Linear regression analysis showed that there was no publication bias in each group of PUFA measurements.

To examine the abnormalities of PUFA levels between patients with DSM-defined MDD and healthy control subjects, we repeated the analyses in the secondary outcomes by excluding studies not using DSM criteria or using subjects with concomitant medical disorders. In these analyses, 318 subjects (191 depressive subjects, 127 healthy control subjects) from six studies (30,32–34, 43,45) were identified and analyzed for the secondary outcomes. Again, the levels were significantly lower in MDD subjects in EPA (ES = −.42, *p* = .0008; Figure 1), DHA (ES = −.54, *p* = .0008; Figure 2), and total n-3 (ES = −.85, *p* < .0001; Figure 3). The levels of AA (Figure 4) and total n-6 PUFAs (Figure 5) were not significantly higher in MDD patients. As in the primary outcomes, the significant difference in EPA, DHA, and total n-3 was not

Table 1. Characteristics of Studies Included in This Meta-Analysis

Studies	Patients, *n*	Controls, *n*	Patient Source	Inclusion Psychiatric Disorders	Use of DSM Criteria	Types of Control Subjects	Country	Sampling Tissue
Fehily (1981) (29)	26	26	Not stated	Bipolar and unipolar endogenous depression	No	Healthy controls	UK	Erythrocytes
Maes (1996) (30)	36	24	Psychiatric inpatients	MDD, mean HDRS = 22.2	Yes	Healthy controls	Belgium	Serum
Edwards (1998) (32)	10	14	Not stated	MDD, mean BDI = 26.9	Yes	Healthy controls, mean BDI = 4.9	UK or Canada	Erythrocytes
Peet (1998) (33)	15	15	Not stated	MDD, evaluated by MADRS	Yes	Healthy controls	UK or Canada	Erythrocytes
Maes (1999) (34)	34	14	Psychiatric inpatients	MDD, evaluated by HDRS	Yes	Healthy controls	Belgium	Plasma
De Vriese (2003) (35)	10	38	Healthy pregnant women	Postpartum women with depression	Yes	Postpartum women without depression	Belgium	Serum
Tiemeier 2003 (36)	106	461	Populated-based community subjects	MDD, dysthymia, and minor depression in elderly people	Yes	Elderly people without depression	The Netherlands	Plasma
Frasure-Smith (2004) (38)	54	54	Hospital-based subjects with high risk of ACS	MDD, in patients with recent ACS	Yes	Patients with recent ACS, without depression	Canada	Plasma
Amin (2008) (40)	118	641	Hospital-based subjects with ACS	ACS patients, PHQ ≥ 10	No	ACS patients, PHQ < 10	US	Erythrocytes
Aupperle (2008) (41)	10	28	Outpatient from MS Clinic	MS patients with depression, by CMDI	No	MS patients without depression	US	Erythrocytes
Feart 2008 (42)	117	1273	Populated-based community subjects	Elderly subjects (≥65 y) with depressive symptoms, CES-D ≥17 in men and ≥23 in women	No	Other elders	France	Plasma
Dinan (2009) (43)	20	24	Not stated	MDD, HADS ≥ 20	Yes	Healthy controls	Ireland	Plasma
Rees (2009) (44)	16	22	Women in the third trimester of pregnancy	pregnant women with MDD, EDS ≥13, HADS >14 or MADRS >25	Yes	Pregnant women without depression, EDS < 8	Australia	Plasma
Riemer (in press) (45)	76	36	Psychiatric inpatients	MDD	Yes	Healthy controls	Germany	Serum

ACS, acute coronary syndrome; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Depression Scale; CMDI, Chicago Multiscale Depression Inventory; DSM, Diagnostic and Statistical Manual; EDS, Edinburgh Depression Scale; HADS, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder; MI, myocardial infarction; MS, multiple sclerosis; PHQ, Patient Health Questionnaire.
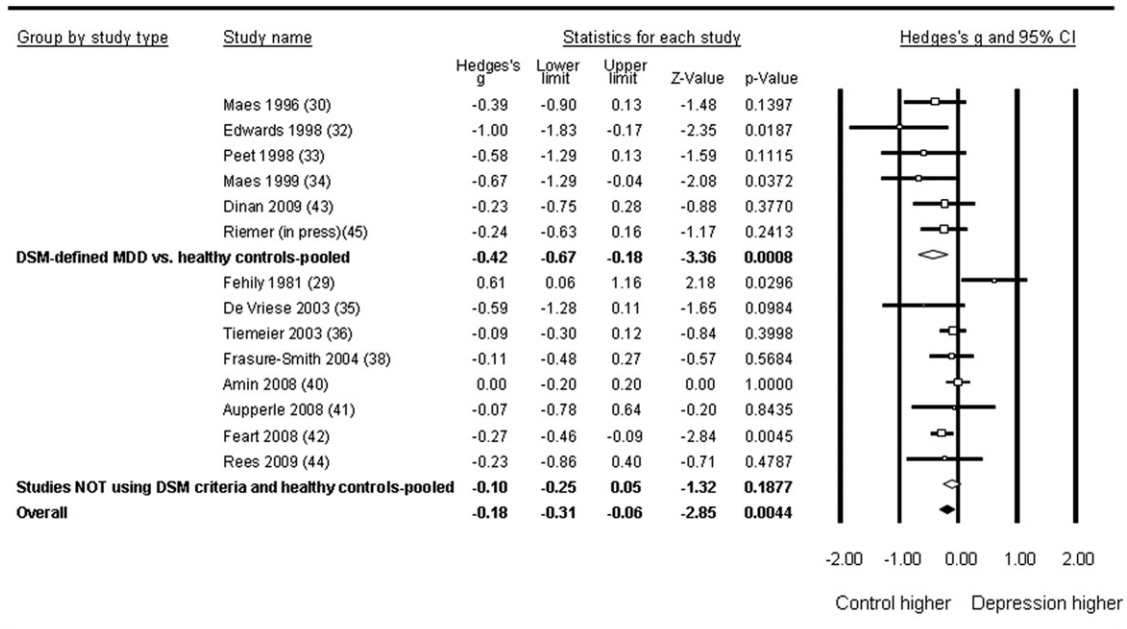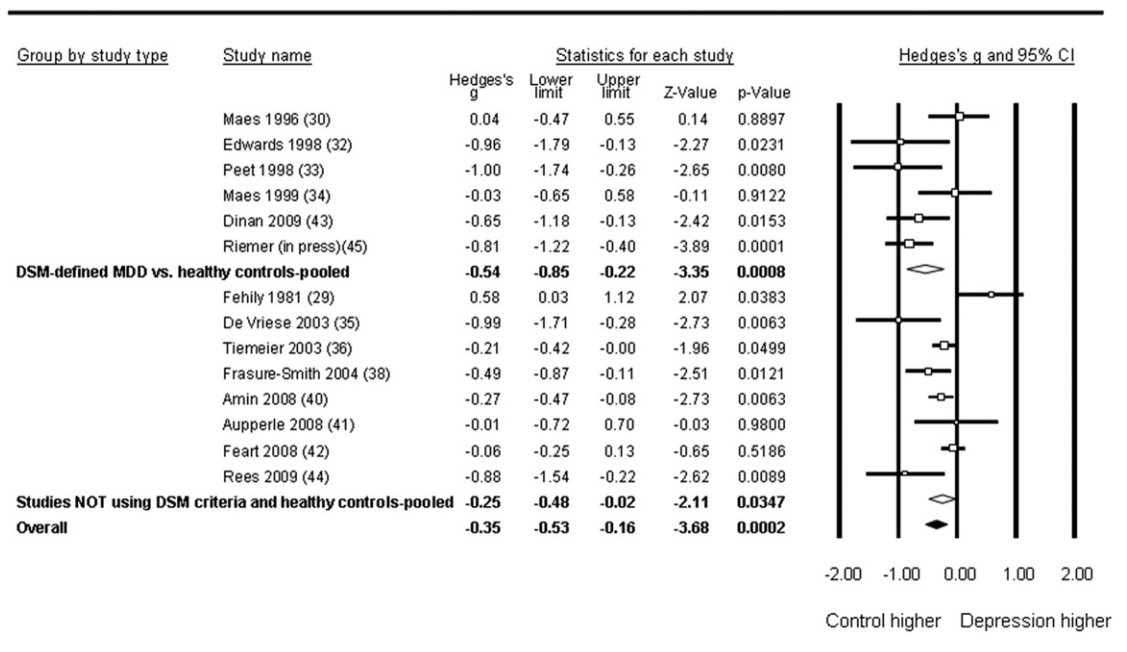
Figure 1. Forest plot showing effect sizes (Hedges's *g*) and 95% confidence intervals (CIs) from individual studies and pooled results comparing eicosapentaenoic acid level between depressed patients and control subjects. MDD, major depressive disorder.

contributed by any single study, nor was there publication bias in any of these measurements of PUFAs.

Discussion

The main finding of this meta-analysis confirms that depression is associated with lower levels of total n-3 PUFAs and both types of n-3 PUFAs, EPA and DHA. Previous observational studies have indicated that clinical depression can be accompanied by low levels of n-3 PUFAs in RBC, plasma and,

as more found recently, brain tissue (50). Our findings extend the results from several studies, but not all, that n-3 PUFAs play an important role in depression. It has been reported that the deficit of n-3 PUFAs in rat brain is associated with impaired serotonergic and dopaminergic neurotransmission and in turn leads to an increase in 5-HT$_2$ receptors and a decrease in D$_2$ receptors in the frontal cortex (51–53). This upregulation of 5-HT$_2$ receptors is thought to play a role in the pathophysiology of depression (54).

Figure 2. Forest plot showing effect sizes (Hedges's *g*) and 95% confidence intervals (CIs) from individual studies and pooled results comparing docosahexaenoic acid levels between depressed patients and control subjects. MDD, major depressive disorder.
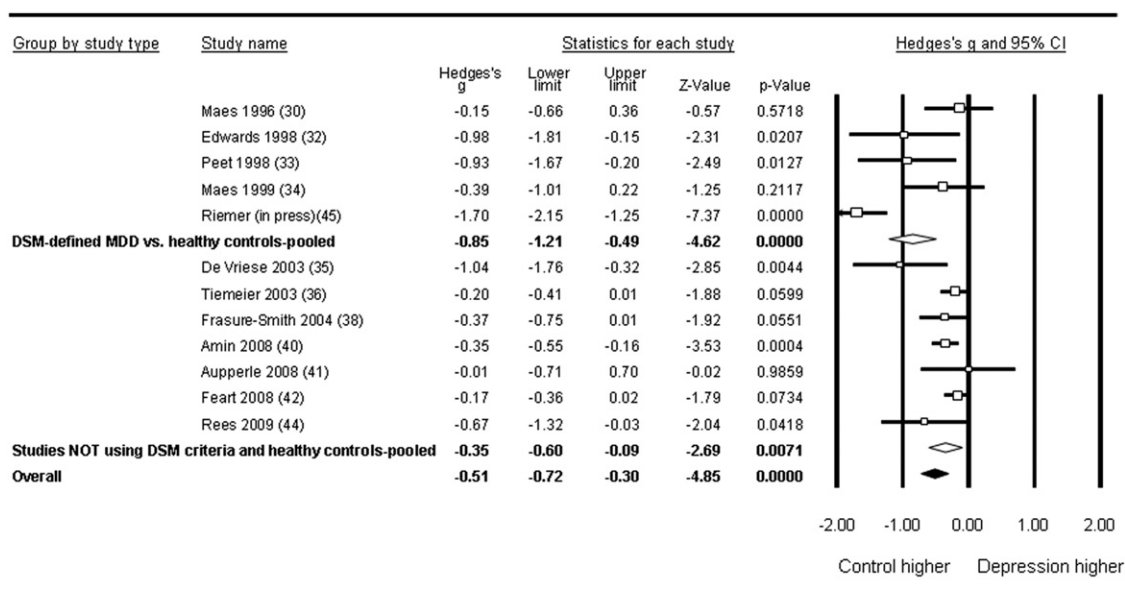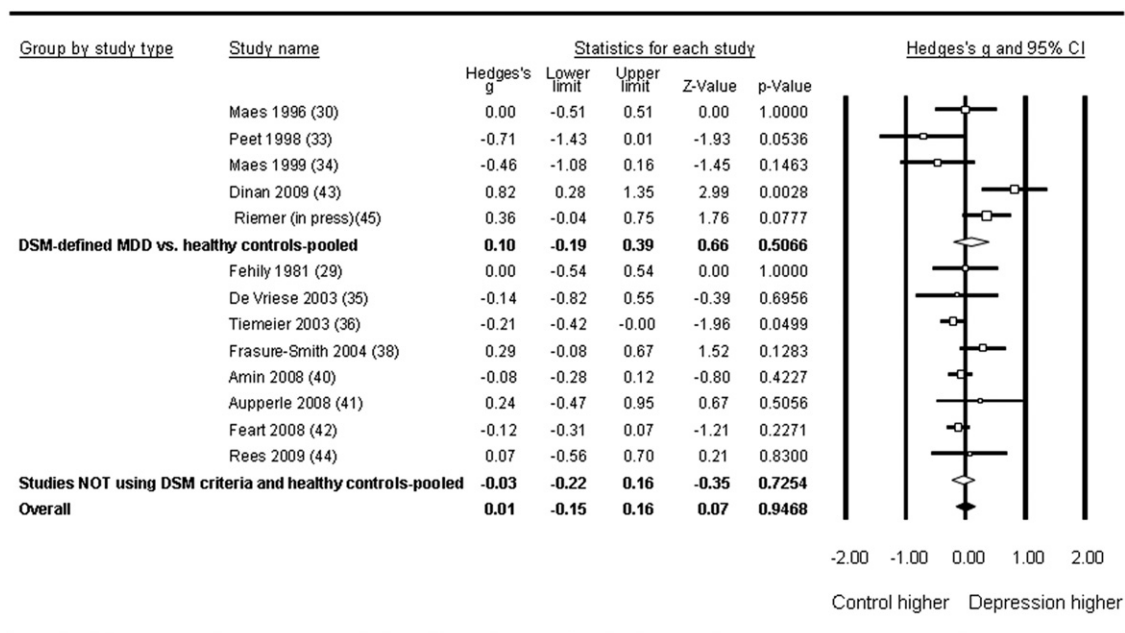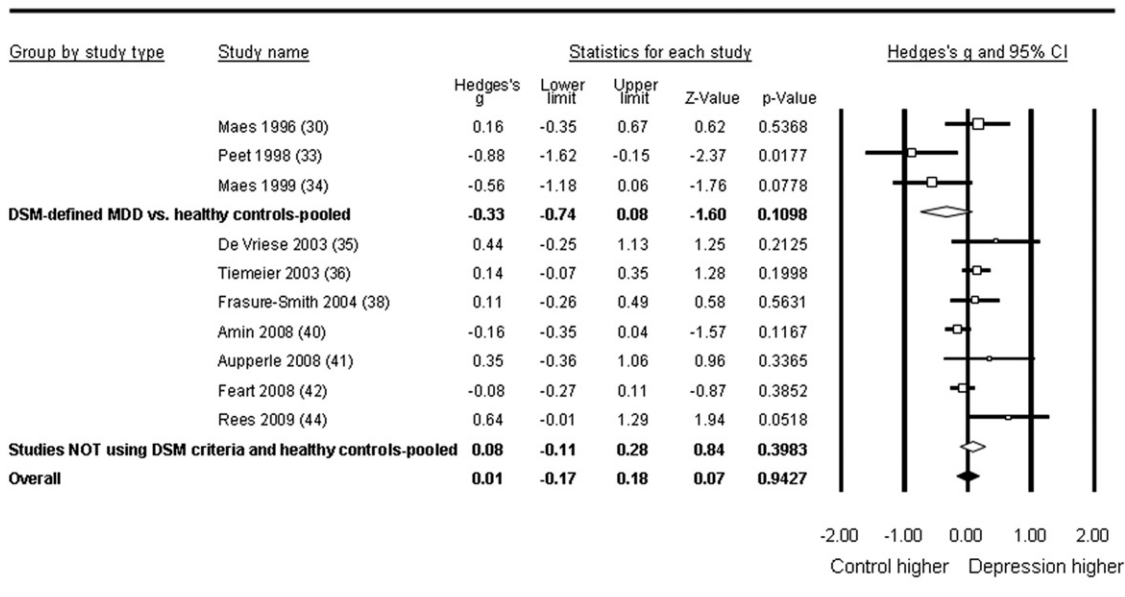
Figure 3. Forest plot showing effect sizes (Hedges's *g*) and 95% confidence intervals (CIs) from individual studies and pooled results comparing total omega-3 polyunsaturated fatty acid levels between depressed patients and control subjects. MDD, major depressive disorder.

Lower levels in both DHA and EPA may have different physiologic meanings regarding the biological mechanisms of depression. DHA is a major structural component of phospholipids in neuronal cell membranes, whereas EPA is present in neuronal cell membranes in a very small amount. Therefore, it has been proposed that DHA is more important in brain functioning than EPA (55). However, EPA, rather than DHA, appears to be the effective component when treating clinical depression in published studies (56,57). The contradiction between theoretical mechanisms and clinical studies raises questions about different modes of action of DHA and EPA. For example, EPA,

but not DHA, has other important physiologic functions, including a role as a precursor for eicosanoids and a modulator of cytokines (58). It has been proposed that depression is accompanied by increased secretion of eicosanoids, such as prostaglandins, and by an excessive secretion of proinflammatory cytokines (59). EPA can act as the inhibitor of phospholipase A2 to reduce the secretion of eicosanoids and proinflammatory cytokines (26), which might have been associated with the improvement of somatic symptoms in patients with depression (3). In addition, because the designs of previous clinical trials have focused on the augmentation effects of n-3 PUFAs by enrolling only de-

Figure 4. Forest plot showing effect sizes (Hedges's *g*) and 95% confidence intervals (CIs) from individual studies and pooled results comparing arachidonic acid levels between depressed patients and controls. MDD, major depressive disorder.

Figure 5. Forest plot showing effect sizes (Hedges's *g*) and 95% confidence intervals (CIs) from individual studies and pooled results comparing total omega-6 polyunsaturated fatty acid levels between depressed patients and control subjects. MDD, major depressive disorder.

pressed patients receiving antidepressant medications simultaneously (56,57), the antidepressant effect of DHA might be hidden if the effects of DHA and the antidepressant medications overlap. According to the results of lower DHA levels in depression in this meta-analytic review, it is too early to exclude DHA's role in depression and its antidepressant effect.

Notably, compared with the primary outcomes of all the 14 studies, the magnitude of ES of differences in the levels of EPA (Figure 1), DHA (Figure 2), and total n-3 (Figure 3) became larger when the analyses were restricted to studies that used DSM criteria for MDD diagnosis, implying that the n-3 PUFA abnormalities were more significant in the more homogeneous groups of major depression. Interestingly, the significance of lower EPA levels in depressed subjects disappeared when we looked only at the studies with depressed subjects other than DSM-defined MDD (ES = −.10, 95% CI = −.25–.05, *p* = .19; Figure 1), implying that the lower EPA levels were presented only in patients with clinical major depression, but not in subjects with less strictly defined depressive symptoms. This negative finding in these subjects might be an explanation to the previous studies revealing negative findings of n-3 PUFAs' mood-improving effects in nonclinical symptomatic subjects (60,61). Specifically, two meta-analyses (from different groups) using only trials that enrolled patients with diagnosed MDD showed the beneficial effects of n-3 PUFAs, especially EPA, supplementation on depressed mood (56,57). However, the other meta-analyses (from the same group) involving individuals without diagnosis of major depression found no evidence of a beneficial effect of n-3 PUFAs on depressed mood (60,61). Further studies are warranted to investigate the relationship between pretreatment deficits and posttreatment effects of n-3 PUFAs.

The major limitation of this study is that PUFA levels from the clinical studies we analyzed were not directly from the tissues of the central nervous system; hence, the results cannot be applied to brain PUFA levels. Nonetheless, previous studies have revealed that the n-3 PUFA levels from peripheral blood tissues of RBC and plasma might reflect brain levels of n-3 PUFAs in mammals (62–65). For example, in a study measuring PUFAs

from tissues of blood plasma, erythrocytes, liver, muscle, adipose tissue, retina, and brain samples in piglets consuming assigned diets, the levels of EPA and DHA in both plasma and erythrocytes highly correlated to those levels in brain tissue (62). Specifically, the coefficients (*r*s) of EPA and DHA in plasma in correlation with brain tissue were .78 ($p < .001$) and .80 ($p < .001$), respectively. Meanwhile, the *r*s of EPA and DHA in erythrocyte in correlation with brain were .78 ($p < .001$) and .80 ($p < .001$), respectively. Although data from human subjects are not yet available, similar findings of this high brain plasma–erythrocyte correlation of EPA and DHA have been reported in rhesus monkeys (64) and in rats (65). Unlike the consistency among erythrocytes, plasma, and brain tissue in EPA and DHA levels, AA levels in the plasma or erythrocyte might not be as apparent in the brain (62,64). Therefore, caution is warranted in interpreting the finding of nonsignificant differences of AA levels between patients and controls in our study.

There are other methodologic limitations. Although the levels of n-3 and n-6 PUFAs are highly consistent in peripheral blood plasma and erythrocytes (62,65–68), the reliability of combining PUFA levels from plasma and erythrocytes for data analyses is uncertain. In this study, we expect the use of the "percentage" (individual PUFA from the obtained tissues) as the unit of measure might have offered better reliability in combining PUFAs levels for data analyses. Second, although gas chromatography has been used universally as the standard measurement of PUFA levels, the bias from the methodology across laboratories could not be eliminated. Again, we believe the use of percentage as the unit of measure would have better reliability than the use of the "absolute value" in this case. Finally, in our analyses, we excluded Mamalakis's studies (69–73), which measured PUFA levels from human adipose tissues. Although in two of the five studies, the authors also measured PUFA levels from serum phospholipids (71,73), they did not group patients according to clinical diagnosis or rating scales of depression to perform the difference analyses. Therefore, we could not use the data for meta-analyses.

In conclusion, the levels of total n-3 PUFAs, DHA, and EPA

are lower in patients with depression, implying that n-3 PUFAs play a role in the etiology of depression. This provides further support of phospholipid hypothesis of depression and a rationale for using n-3 PUFAs as an alternative treatment for patients with depression. Because individual PUFAs may have different biological functions, this study might provide essential background to examine specific roles of DHA and EPA in the classification of depressive disorders in future studies.

Supplementary material cited in this article is available online.

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