EPA but not DHA appears to be responsible for the efficacy of omega-3 LC-PUFA supplementation in depression: evidence from an updated meta-analysis of randomized controlled trials

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Abstract: Background: Epidemiological and case-control data suggest that increased dietary intake of omega-3 long-chain polyunsaturated fatty acids (ω3 LC-PUFA) may be of benefit in depression. However, the results of randomized controlled trials are mixed and controversy exists as to whether either eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) or both are responsible for the reported benefits. Objective: To update a recently published meta-analysis (Martins JG, J Am Coll Nutr, 2009; 28: 525-42) of double-blind, placebo-controlled, randomized controlled trials examining the effect of ω3 LC-PUFA supplementation where depressive symptoms were a reported outcome. The differential effectiveness of EPA versus DHA has been reassessed through meta-regression and subgroup analyses. Design: Studies were selected using the PubMed database on the basis of the following criteria: i) randomized design; ii) placebo controlled; iii) use of an ω3 LC-PUFA preparation containing DHA, EPA or both where the relative amounts of each fatty acid could be quantified; and iv) reporting sufficient statistics on scores of a recognizable measure of depressive symptoms. Results: 370 studies were identified (22/01/2011) of which 35 met the above inclusion criteria (7 additional to Martins JG, 2009) and were therefore included for analysis. Using a random effects model, overall standardized mean depression scores were reduced in response to ω3 LC-PUFA supplementation as compared with placebo (standardized mean difference = –0.230, 95% CI = –0.361 to –0.099, p = 0.001). However, significant heterogeneity and evidence of publication bias was present. Meta-regression studies showed a significant effect of EPA:DHA ratio on therapeutic efficacy. Subgroup analyses showed significant effects for: i) baseline depression; ii) diagnostic category (bipolar disorder and major depression showing significant improvement with ω3 LC-PUFA supplementation versus mild to moderate depression, perinatal depression, chronic fatigue and non-clinical populations not); iii) therapeutic as opposed to preventative intervention; iv) adjunctive treatment and to a lesser extent monotherapy; and v) supplement type. Symptoms of depression were not significantly reduced in 2 studies using pure DHA of algal origin (standardized mean difference = –0.111, 95% CI = –0.590 to 0.368, p = 0.649), in 3 studies using a mixture of DHA and EPA ethyl esters (standardized mean difference = –0.027, 95% CI = –0.200 to 0.147, p = 0.764), or in 7 studies using fish oil triglyceride supplements containing greater than 50% DHA (standardized mean difference = 0.027, 95% CI = –0.148 to 0.202, p = 0.763). In contrast, symptoms of depression were significantly reduced in 13 studies using fish oil triglyceride supplements containing greater than 50% EPA (standardized mean difference = –0.513, 95% CI = –0.840 to –0.185, p = 0.002) and in 10 studies using pure EPA ethyl ester (standardized mean difference = –0.360, 95% CI = –0.597 to –0.123, p = 0.003). However, further meta-regression studies showed significant...
Background
Epidemiological and case-control data suggest that increased dietary intake of omega-3 long-chain polyunsaturated fatty acids (ω3 LC–PUFA) may be of benefit in depression (Appleton et al., 2007; Appleton et al., 2007; Hibbeln, 1998; Hibbeln, 2002; Noaghiul and Hibbeln, 2003; Silvers and Scott, 2002; Tanskanen et al., 2001; Tanskanen et al., 2001; Timonen et al., 2004). However, the results of randomized controlled trials are mixed and controversy exists as to whether either eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) or both are responsible for the reported benefits (Ross et al., 2007). A recently published meta-analysis by the author of double-blind, placebo-controlled, randomized controlled trials examining the effect of ω3 LC–PUFA supplementation where depressive symptoms were a reported outcome identified that EPA rather than DHA appeared to be responsible for the therapeutic efficacy of ω3 LC–PUFA in depression (Martins, 2009). Because a number of new trials have recently been published, an update of this meta-analysis is presented below, with a reassessment of the differential effectiveness of EPA versus DHA conducted through meta-regression and subgroup analyses.

Methods

Studies were selected on the basis of the following criteria: i) randomized design; ii) placebo controlled; iii) use of an ω3 LC–PUFA preparation containing DHA, EPA or both where the relative amounts of each fatty acid could be quantified; and iv) reporting sufficient statistics on scores of a recognizable measure of depressive symptoms.

Methodological quality was assessed using the Jadad score (Jadad et al., 1996) plus six additional components: i) whether similarities in baseline characteristics between groups were adequately described; ii) whether attempts were made to conceal the fish taste of the active intervention; iii) whether the outcome assessors were adequately blinded; iv) whether data were analyzed according to intention-to-treat methods; v) whether compliance was assessed through measurement of red blood cell or plasma fatty acids; and vi) whether blinding success was evaluated. This gave a maximum possible quality score of 11.

The meta-analytic strategy employed was as follows: i) to compute standardized mean differences in depression scores using random effects rather than fixed effects models, as there was considerable variation in clinical populations studied, methodologies employed, and outcome measures used; ii) to examine overall effect sizes using forest plots; iii) to examine for possible publication bias using funnel plots with Duval and Tweedie’s trim and fill method; iv) to assess heterogeneity using Cohen’s Q; v) to conduct sensitivity analyses on subgroups of studies using random effects ANOVA, specifically to examine inverse associations between efficacy and study sample size and duration, thus limiting the confidence of these findings. Conclusions: This updated meta-analysis provides evidence that EPA may be more efficacious than DHA in treating depression. However, owing to the identified limitations of the included studies, larger, well-designed randomized controlled trials of sufficient duration are needed to confirm these findings.

Key words: depression, omega-3 long-chain polyunsaturated fatty acids, dietary supplementation, meta-analysis.
Table 1. Characteristics of the 35 included studies, listed chronologically according to publication date.

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical group</th>
<th>Number, total (ω3 LC-PUFA/placebo)</th>
<th>ω3 LC-PUFA preparation (source)</th>
<th>Daily dosage regime(s)</th>
<th>Treatment status</th>
<th>Duration (days)</th>
<th>Outcome measure(s)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behan et al., 1990</td>
<td>Chronic fatigue</td>
<td>63 (39/24)</td>
<td>Fish oil triglycerides (Efamol Marine)</td>
<td>0.136 g EPA + 0.088 g DHA</td>
<td>Therapeutic</td>
<td>90</td>
<td>Likert scale</td>
<td>6</td>
</tr>
<tr>
<td>Stoll et al., 1999</td>
<td>Bipolar disorder</td>
<td>30 (14/16)</td>
<td>Fish oil triglycerides (Menhaden fish body oil concentrate)</td>
<td>6.2 g EPA + 3.4 g DHA</td>
<td>Preventative Adjunctive</td>
<td>112</td>
<td>HDRS-31</td>
<td>7</td>
</tr>
<tr>
<td>Warren et al., 1999</td>
<td>Chronic fatigue</td>
<td>50 (24/26)</td>
<td>Fish oil triglycerides (Efamol Marine)</td>
<td>0.136 g EPA + 0.088 g DHA</td>
<td>Therapeutic</td>
<td>90</td>
<td>BDI</td>
<td>7</td>
</tr>
<tr>
<td>Fenton et al., 2001</td>
<td>Schizophrenia</td>
<td>87 (43/44)</td>
<td>Ethyl ester (Laxdale Ltd)</td>
<td>3 g Ethyl-EPA</td>
<td>Therapeutic Adjunctive</td>
<td>112</td>
<td>MADRS</td>
<td>8</td>
</tr>
<tr>
<td>Nemets et al., 2002</td>
<td>Major depression</td>
<td>20 (10/10)</td>
<td>Ethyl ester (Laxdale Ltd)</td>
<td>2 g Ethyl-EPA</td>
<td>Therapeutic Adjunctive</td>
<td>28</td>
<td>HDRS-24</td>
<td>9</td>
</tr>
<tr>
<td>Peet and Horrobin, 2002</td>
<td>Major depression</td>
<td>70 (17, 18, 17/18)</td>
<td>Ethyl ester (Laxdale Ltd)</td>
<td>1 g Ethyl-EPA or 2 g Ethyl-EPA or 4 g Ethyl-EPA</td>
<td>Therapeutic Adjunctive</td>
<td>84</td>
<td>BDI HDRS-17 MADRS</td>
<td>6</td>
</tr>
<tr>
<td>Zanarini and Frankenburg, 2003</td>
<td>Borderline personality disorder</td>
<td>30 (20/10)</td>
<td>Ethyl ester (Laxdale Ltd)</td>
<td>1 g Ethyl-EPA</td>
<td>Therapeutic Monotherapy</td>
<td>56</td>
<td>MADRS</td>
<td>4</td>
</tr>
<tr>
<td>Llorente et al., 2003</td>
<td>Prevention of perinatal depression</td>
<td>99 (44/45)</td>
<td>Algal DHA (Martek Biosciences Corporation)</td>
<td>0.2 g DHA</td>
<td>Preventative Monotherapy</td>
<td>120</td>
<td>BDI EPDS SCID-IV</td>
<td>6</td>
</tr>
<tr>
<td>Marangell et al., 2003</td>
<td>Major depression</td>
<td>36 (18/18)</td>
<td>Algal DHA (Martek Biosciences Corporation)</td>
<td>2 g DHA</td>
<td>Therapeutic Monotherapy</td>
<td>42</td>
<td>HDRS-28 MADRS</td>
<td>6</td>
</tr>
<tr>
<td>Su et al., 2003</td>
<td>Major depression</td>
<td>28 (14/14)</td>
<td>Fish oil triglycerides (Menhaden fish body oil concentrate)</td>
<td>4.4 g EPA + 2.2 g DHA</td>
<td>Therapeutic Adjunctive</td>
<td>56</td>
<td>HDRS-21</td>
<td>5</td>
</tr>
<tr>
<td>Hirashima et al., 2004</td>
<td>Bipolar disorder</td>
<td>21 (6, 6/9)</td>
<td>Fish oil triglycerides (not specified)</td>
<td>5.0–5.2 g EPA + 3.0–3.4 g DHA or 1.3 g EPA + 0.7 g DHA</td>
<td>Therapeutic Adjunctive</td>
<td>28</td>
<td>HDRS-23</td>
<td>2</td>
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<tr>
<td>Silvers et al., 2005</td>
<td>Major depression</td>
<td>77 (40/37)</td>
<td>Fish oil triglycerides (DHA enriched tuna oil, Clover Corporation PLC)</td>
<td>2.4 g DHA + 0.6 g EPA</td>
<td>Therapeutic Adjunctive</td>
<td>84</td>
<td>BDI HDRS-SF</td>
<td>10</td>
</tr>
<tr>
<td>Fontani et al., 2005</td>
<td>Non-clinical healthy participants</td>
<td>33 (33/33)</td>
<td>Fish oil triglycerides (not specified)</td>
<td>1.6 g EPA + 0.8 g DHA</td>
<td>Preventative Monotherapy</td>
<td>70</td>
<td>POMS</td>
<td>5</td>
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<tr>
<td>Frangou et al., 2006</td>
<td>Bipolar disorder</td>
<td>75 (24, 25/26)</td>
<td>Ethyl ester (Laxdale Ltd)</td>
<td>1 g EPA or 2 g EPA</td>
<td>Therapeutic Adjunctive</td>
<td>84</td>
<td>HDRS-17</td>
<td>9</td>
</tr>
<tr>
<td>Study</td>
<td>Clinical group</td>
<td>Number, total (ω3 LC–PUFA/placebo)</td>
<td>ω3 LC–PUFA preparation (source)</td>
<td>Daily dosage regime(s)</td>
<td>Treatment status</td>
<td>Duration (days)</td>
<td>Outcome measure(s)</td>
<td>Quality</td>
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<tr>
<td>Nemets et al., 2006</td>
<td>Major depression in childhood</td>
<td>28 (13/15)</td>
<td>Fish oil triglycerides (Ocean Nutrition or Sears Laboratory)</td>
<td>0.4 g EPA + 0.2 g DHA</td>
<td>Therapeutic Monotherapy</td>
<td>112</td>
<td>CDI CDRS</td>
<td>6</td>
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<tr>
<td>Keck et al., 2006</td>
<td>Bipolar disorder</td>
<td>116 (59/57)</td>
<td>Ethyl ester (Laxdale Ltd)</td>
<td>6 g EPA</td>
<td>Therapeutic Adjunctive</td>
<td>120</td>
<td>IDS-C</td>
<td>6</td>
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<tr>
<td>Hallahan et al., 2007</td>
<td>Recurrent self-harm</td>
<td>49 (22/27)</td>
<td>Fish oil triglycerides (EPAX 5500)</td>
<td>1.22 g EPA + 0.908 g DHA</td>
<td>Therapeutic Adjunctive</td>
<td>84</td>
<td>BDI HDRS</td>
<td>8</td>
</tr>
<tr>
<td>Grenyer et al., 2007</td>
<td>Major depression</td>
<td>83 (40/43)</td>
<td>Fish oil triglycerides (DHA enriched tuna oil, Clover Corporation PLC)</td>
<td>2.2 g DHA + 0.6 g EPA</td>
<td>Therapeutic Adjunctive</td>
<td>112</td>
<td>BDI HDRS</td>
<td>10</td>
</tr>
<tr>
<td>Frangou et al., 2007</td>
<td>Bipolar disorder</td>
<td>14 (7/7)</td>
<td>Ethyl ester (Laxdale Ltd)</td>
<td>2 g EPA</td>
<td>Therapeutic Adjunctive</td>
<td>84</td>
<td>HDRS</td>
<td>6</td>
</tr>
<tr>
<td>Rogers et al., 2008</td>
<td>Mild to moderate depression</td>
<td>218 (109/109)</td>
<td>Fish oil triglycerides (Minami Nutrition)</td>
<td>0.85 g DHA + 0.63 g EPA</td>
<td>Therapeutic Monotherapy</td>
<td>84</td>
<td>BDI DASS</td>
<td>11</td>
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<tr>
<td>Jazayeri et al., 2008</td>
<td>Major depression</td>
<td>48 (32/16)</td>
<td>Ethyl ester (Minami Nutrition)</td>
<td>1 g EPA</td>
<td>Therapeutic Adjunctive</td>
<td>56</td>
<td>HDRS-17</td>
<td>6</td>
</tr>
<tr>
<td>Rees et al., 2008</td>
<td>Treatment of perinatal depression</td>
<td>26 (13/13)</td>
<td>Fish oil triglycerides (DHA enriched tuna oil, Clover Corporation PLC)</td>
<td>1.638 g DHA + 0.414 g EPA</td>
<td>Therapeutic Monotherapy</td>
<td>42</td>
<td>EPDS HDRS-17 MADRS</td>
<td>11</td>
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<tr>
<td>Su et al., 2008</td>
<td>Treatment of perinatal depression</td>
<td>33 (17/16)</td>
<td>Fish oil triglycerides (Menhaden fish body oil concentrate)</td>
<td>2.2g EPA + 1.2g DHA</td>
<td>Therapeutic Monotherapy</td>
<td>56</td>
<td>BDI EPDS HDRS-21</td>
<td>9</td>
</tr>
<tr>
<td>Freeman et al., 2008</td>
<td>Treatment of perinatal depression</td>
<td>59 (31/28)</td>
<td>Fish oil triglycerides (Pronova/EPAX)</td>
<td>1.1 g EPA + 0.8 g DHA</td>
<td>Therapeutic Monotherapy</td>
<td>56</td>
<td>EPDS HDRS</td>
<td>5</td>
</tr>
<tr>
<td>van de Rest et al., 2008</td>
<td>Non-clinical elderly participants</td>
<td>302 (100, 96/106)</td>
<td>Fish oil triglycerides (Lipid Nutrition)</td>
<td>0.226 g EPA + 0.176 g DHA or 1.093 g EPA + 0.847 g DHA</td>
<td>Preventative Monotherapy</td>
<td>182</td>
<td>CES-D GDS-15 MADRS</td>
<td>10</td>
</tr>
<tr>
<td>da Silva et al., 2008</td>
<td>Major depression in patients with Parkinson’s disease</td>
<td>29 (6, 8/7, 8)</td>
<td>Fish oil triglycerides (Herbarium Foundation for Health and Research)</td>
<td>0.720 g EPA + 0.480 g DHA or 0.720 g EPA + 0.480 g DHA + antidepressant</td>
<td>Therapeutic Monotherapy &amp; Adjunctive</td>
<td>84</td>
<td>BDI MADRS</td>
<td>5</td>
</tr>
<tr>
<td>Lucas et al., 2009</td>
<td>Mild to moderate depression</td>
<td>120 (59/61)</td>
<td>Fish oil ethyl esters (Isodis Natura)</td>
<td>1.05 g Ethyl-EPA + 0.15 g DHA</td>
<td>Therapeutic Monotherapy</td>
<td>56</td>
<td>HDRS HSCl-D-20</td>
<td>11</td>
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<tr>
<td>Study</td>
<td>Clinical group</td>
<td>Number, total (ω3 LC-PUFA/placebo)</td>
<td>ω3 LC-PUFA preparation (source)</td>
<td>Daily dosage regime(s)</td>
<td>Treatment status</td>
<td>Duration (days)</td>
<td>Outcome measure(s)</td>
<td>Quality</td>
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<tr>
<td>Doornbos et al., 2009</td>
<td>Prevention of perinatal depression</td>
<td>119^2 (42, 41/36)</td>
<td>Fish oil triglycerides (Marinol D40, Lipid Nutrition B.V.)</td>
<td>0.22 g DHA + 0.034 g EPA or 0.22 g DHA + 0.034 g EPA + 0.22 g AA</td>
<td>Preventative Monotherapy</td>
<td>252</td>
<td>EPDS</td>
<td>4</td>
</tr>
<tr>
<td>Poppitt et al., 2009</td>
<td>Prevention of depression after Stroke</td>
<td>102 (51/51)</td>
<td>Fish oil triglycerides (processed Hoki liver oil, Sea Dragon, NZ)</td>
<td>0.7 g DHA + 0.3 g EPA</td>
<td>Preventative Monotherapy</td>
<td>84</td>
<td>GHQ-28</td>
<td>8</td>
</tr>
<tr>
<td>Carney et al. (2009)</td>
<td>Major depression in patients with CHD</td>
<td>122 (62/60)</td>
<td>Ethyl esters (GlaxoSmithKline Inc)</td>
<td>0.93 g EPA + 0.75 g DHA</td>
<td>Therapeutic Adjunctive</td>
<td>70</td>
<td>BDI, HDRS</td>
<td>8</td>
</tr>
<tr>
<td>Bot et al. (2010)</td>
<td>Major depression in patients with diabetes</td>
<td>25 (13/12)</td>
<td>Ethyl ester (Minami Nutrition)</td>
<td>1.0 g EPA</td>
<td>Therapeutic Adjunctive</td>
<td>84</td>
<td>MADRS</td>
<td>6</td>
</tr>
<tr>
<td>Lepèreance et al. (2010)</td>
<td>Major depression</td>
<td>432 (218/214)</td>
<td>Fish oil ethyl esters (Isodis Natura)</td>
<td>1.05 g EPA + 0.15 g DHA</td>
<td>Therapeutic Adjunctive or Monotherapy</td>
<td>56</td>
<td>IDS-SR, MADRS</td>
<td>10</td>
</tr>
<tr>
<td>Mischoulon et al. (2009)</td>
<td>Major depression</td>
<td>35 (16/19)</td>
<td>Ethyl ester (Amarin Neuroscience Ltd [Laxdale])</td>
<td>1 g EPA</td>
<td>Preventative Monotherapy</td>
<td>56</td>
<td>HDRS</td>
<td>9</td>
</tr>
<tr>
<td>Makrides et al. (2010)</td>
<td>Prevention of perinatal depression</td>
<td>2399 (1197/1202)</td>
<td>DHA enriched fish oil (Incromega 500 TG, Croda Chemicals)</td>
<td>0.8 g DHA + 0.1 g EPA</td>
<td>Preventative Monotherapy</td>
<td>180</td>
<td>EPDS</td>
<td>7</td>
</tr>
</tbody>
</table>

AA = arachidonic acid; BDI = Beck depression Inventory; CDI = Children’s Depression Inventory; CDRS = Children’s Depression Rating Scale; CES-D = Center for Epidemiologic Studies of Depression Scale; CHD = coronary heart disease; DASS = Depression Anxiety and Stress Scales; EPDS = Edinburgh Postnatal Depression Scale; GDS-15 = Geriatric Depression Rating Scale; GHQ = General Health Questionnaire; HDRS = Hamilton Rating Scale for Depression (SF refers to short form); HSCL-D-20 = 20 item Hopkins Symptom Checklist Depression Scale; IDS = Inventory of Depressive Symptomatology; MADRS = Montgomery Åsberg Depression Rating Scale. POMS = Profile of Mood States; SCID-IV = Structured Clinical Interview for DSM-IV.

1 Cross-over design.
2 This study used ω3 LC-PUFA supplementation as monotherapy but adjunctive supportive psychotherapy was provided.
3 182 women were initially recruited, but 57 dropped out by the 36th week of pregnancy, data on the remaining 119 are presented.
4 Only data from the DHA + EPA group were entered into this meta-analysis.
supplements grouped by their EPA versus DHA content, and finally; vi) to conduct random effects meta-regression analyses on relevant moderator variables using the unrestricted maximum likelihoods (UREML) method.

**Results**

371 studies were identified as of 22/01/2011, of which 35 met the above inclusion criteria, representing 7 additional studies to those analysed in the author’s recently published meta-analysis [11]. The characteristics of the selected studies are shown in table 1.

Using a random effects model, overall standardized mean depression scores were reduced in response to \( \alpha_3 \) LC-PUFA supplementation as compared with placebo (standardized mean difference = \(-0.230\), 95% CI = \(-0.361\) to \(-0.099\), \(p = 0.001\)). However, significant heterogeneity (Q = 108.4, \(p < 0.001\) and evidence of publication bias (figure 1) was present, with studies of small sample size showing lack of efficacy being underrepresented in the published literature. Duval and Tweedie’s trim and fill method demonstrated that 10 imputed studies were necessary to balance the funnel plot, and that had these been available the overall pooled estimate of effect would have been non-significant (figure 1). Furthermore, meta-regression analysis showed that studies of short duration and of small sample size were more likely to demonstrate efficacy (table 2).

Meta-regression analysis showed a significant relationship between the ratio of supplement EPA to DHA and efficacy; the higher the proportion of EPA within the supplement the greater the efficacy (figure 2).

A subgroup ANOVA by supplement type showed significant differences between supplements and accounted for a substantial proportion of the observed heterogeneity between studies (Q = 13.3, \(p = 0.010\), although residual heterogeneity was still present (table 3 and figure 3). Symptoms of depression were not significantly reduced in 2 studies using pure DHA of algal origin (standardized mean difference = \(-0.111\), 95% CI = \(-0.590\) to 0.368, \(p = 0.649\)), in 3 studies using a mixture of DHA and EPA ethyl esters (standardized mean difference = \(-0.027\), 95% CI = \(-0.200\) to 0.147, \(p = 0.764\)), or in 7 studies using fish oil triglyceride supplements containing greater than 50% DHA (standardized mean difference = 0.027, 95% CI = \(-0.148\) to 0.202, \(p = 0.763\)). In contrast, symptoms of depression were significantly reduced in 13 studies using fish oil triglyceride supplements containing greater than 50% EPA (standardized mean difference = \(-0.513\), 95% CI = \(-0.840\) to \(-0.185\), \(p = 0.002\)) and in 10 studies using pure EPA ethyl ester (standardized mean difference = \(-0.360\), 95% CI = \(-0.597\) to \(-0.123\), \(p = 0.003\)).

Within the pure EPA ethyl ester subgroup, meta-regression analyses showed paradoxical inverse relationships between efficacy and EPA dose (figure 4), sample size (figure 5) and study duration.

### Table 2. Meta-regression analysis of study quality, study duration and sample size in all studies (n = 35).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study quality</td>
<td>Intercept</td>
<td>(-0.5333)</td>
<td>(-1.0894) to (-0.0228)</td>
<td>0.0801</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>0.0361</td>
<td>(-0.0337) to (0.1059)</td>
<td>0.3080</td>
</tr>
<tr>
<td>Study duration</td>
<td>Intercept</td>
<td>(-0.5066)</td>
<td>(-0.8303) to (-0.1829)</td>
<td>0.0022</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>0.0027</td>
<td>(-0.0004) to (0.0057)</td>
<td>0.0834</td>
</tr>
<tr>
<td>Sample size</td>
<td>Intercept</td>
<td>(-0.2844)</td>
<td>(-0.4487) to (-0.1201)</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>0.0003</td>
<td>(-0.0004) to (0.0009)</td>
<td>0.4048</td>
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</tbody>
</table>

![Figure 2](image_url)  
**Figure 2.** Meta-regression analysis of EPA:DHA ratio. The size of the circles corresponds to the random-effects weighting attached to each study.
Within the group of fish oil triglyceride studies, meta-regression analyses showed that DHA dose did not show a significant relationship with efficacy (figure 7), whereas EPA dose showed a significant relationship; the higher the dose of EPA (up to 6.2 g/day) the greater the efficacy (figure 8). The highest efficacy was shown in 3 studies employing Menhaden body fish oil concentrate [Stoll et al.,

*Table 3. Subgroup ANOVA by supplement type. Cohen’s Q = 13.3, p = 0.010*

<table>
<thead>
<tr>
<th>Group by Supplement type</th>
<th>n</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure algal DHA</td>
<td>2</td>
<td>-0.111</td>
<td>-0.590 to 0.368</td>
<td>0.649</td>
</tr>
<tr>
<td>EPA + DHA ethyl esters</td>
<td>3</td>
<td>-0.027</td>
<td>-0.200 to 0.147</td>
<td>0.764</td>
</tr>
<tr>
<td>Pure EPA ethyl ester</td>
<td>10</td>
<td>-0.360</td>
<td>-0.597 to -0.123</td>
<td>0.003</td>
</tr>
<tr>
<td>Fish oil triglycerides &gt;50% DHA</td>
<td>7</td>
<td>0.027</td>
<td>-0.148 to 0.202</td>
<td>0.763</td>
</tr>
<tr>
<td>Fish oil triglycerides &gt;50% EPA</td>
<td>13</td>
<td>-0.513</td>
<td>-0.840 to -0.185</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Figure 3. Forest plot grouped by supplement type.*
1999; Su et al., 2003; Su et al., 2008), with a standardized mean depression score of –1.228 (95% CI –1.873 to –0.584; p < 0.001).

In addition to supplement type, other moderators of treatment effect were explored (table 5). Baseline depression was strongly associated with efficacy; individuals with moderate-to-severe baseline depression showed a standardized mean depression score of –0.547 vs –0.036 in individuals with none-to-mild baseline depression. Efficacy was greater in individuals receiving ω3 LC–PUFA supplementation as a therapeutic rather than a preventative intervention, but similar whether they were receiving supplementation as monotherapy or as an adjunct to antidepressant treatment. Finally, efficacy varied substantially by clinical diagnosis; ω3 LC–PUFA supplementation appeared to be effective in bipolar disorder and major depression, but not in mild-to-moderate depression, non-clinical populations or in chronic fatigue syndrome, although the number of studies examining these latter 3 diagnoses were limited (table 5).

**Discussion**

The results of the current updated meta-analysis appear to confirm the original observation made by Ross et al. (Ross et al., 2007) that EPA and not DHA may be the responsible agent conferring benefit for the treatment of depressive symptoms with ω3 LC–PUFA supplementation. Supplement type, use of the supplement as a therapeutic versus a preventative intervention, use of the supplement as an adjunctive treatment to antidepressants versus monotherapy, moderate-to-severe baseline depression versus none-to-mild baseline depression, and diagnosis type appeared to account for the observed heterogeneity between studies. However, evidence of severe publication bias was identified, limiting the confidence of the findings.

The inverse relationship between efficacy and pure EPA ethyl ester dose might at first sight appear to support the findings from Peet and Horrobin’s dose-ranging study (Peet and Horrobin, 2002) that stated 1 g/day as the optimal dose of EPA for treating depressive symptoms. However, in the current analysis the inverse relationships between efficacy and study duration and sample size for the pure EPA ethyl ester group of studies (n = 10), whilst possibly indicating that EPA has a temporary effect, are more likely to indicate that this inverse relationship is a spurious finding. This interpretation is supported by the established efficacy of 1.8 g/day of EPA ethyl ester for the prevention of cardiovascular disease as reported in the JELIS trials (Yokoyama et al., 2007), and the known association of cardiovascular disease with depression (Puri, 2008).

In contrast, fish oil triglyceride studies (n = 20), which were less affected by
study duration and sample size, showed a dose response relationship with EPA up to a maximum reported dose of 6.2 g/day (Stoll et al., 1999). These findings, together with the findings from the JELIS trials, would suggest little evidence exists for’s recommendation of 1 g/day of EPA for the treatment of depression (Peet and Horrobin, 2002). Unfortunately, the Peet and Horrobin study has been very influential concerning the dosages of \( \omega_3 \) LC-PUFA supplements chosen for many recent trials and may have contributed to the negative findings of some of these trials (Lespérance et al., 2010). Indeed, in the current meta-analysis, the strongest effects were observed in studies employing Menhaden body fish oil concentrate containing > 50% EPA at dosages of EPA ranging from 2.2-6.2 g/day (Stoll et al., 1999; Su et al., 2003; Su et al., 2008). However, it should be noted that in 2 of these studies (Su et al., 2003; Su et al., 2008), placebo-responders were excluded after a one-week single-blind placebo lead-in period and the expected changes in red blood cell EPA levels in response to supplementation were not observed.

**Conclusions**

This updated meta-analysis provides further evidence that EPA may be more efficacious than DHA in treating depression. However, owing to severe publication bias, the suboptimal dosages of EPA investigated in many recent studies, and the design limitations of the included studies, further trials are required that: i) compare pure EPA ethyl ester with fish oil triglycerides containing > 50% EPA at total EPA dosages of \( \geq 2 \) g/day; and ii) are of sufficient sample size, duration and methodological quality to robustly confirm EPA as a useful therapeutic agent in depression.

**Table 4. Meta-regression analysis of study quality, study duration and sample size in the fish oil triglyceride group of studies (n = 20).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study quality</td>
<td>Intercept</td>
<td>-0.747</td>
<td>-1.576 to 0.082</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>0.059</td>
<td>-0.045 to 0.162</td>
<td>0.266</td>
</tr>
<tr>
<td>Study duration</td>
<td>Intercept</td>
<td>-0.575</td>
<td>-1.096 to -0.055</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>0.003</td>
<td>-0.002 to 0.007</td>
<td>0.233</td>
</tr>
<tr>
<td>Sample size</td>
<td>Intercept</td>
<td>-0.335</td>
<td>-0.606 to -0.063</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>0.000</td>
<td>-0.001 to 0.001</td>
<td>0.519</td>
</tr>
</tbody>
</table>
4 studies were missing baseline depression scores.

Figure 8. Meta-regression analysis of EPA dose in fish oil triglyceride studies. The size of the circles corresponds to the random-effects weighting attached to each study.

Table 5. Subgroup ANOVA of other moderators of treatment effect.

<table>
<thead>
<tr>
<th>Moderator</th>
<th>n</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p value</th>
<th>Q</th>
<th>p of Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline depression*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.834</td>
<td>0.004</td>
</tr>
<tr>
<td>None to mild</td>
<td>14</td>
<td>-0.036</td>
<td>-0.179 to 0.107</td>
<td>0.620</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>17</td>
<td>-0.547</td>
<td>-0.821 to -0.274</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention type as</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.6</td>
<td>0.033</td>
</tr>
<tr>
<td>Preventative</td>
<td>7</td>
<td>-0.066</td>
<td>-0.199 to 0.066</td>
<td>0.327</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>28</td>
<td>-0.308</td>
<td>-0.486 to -0.130</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ω3 LC–PUFA use as</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.9</td>
<td>0.231</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>19</td>
<td>-0.152</td>
<td>-0.300 to 0.004</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapy</td>
<td>15</td>
<td>-0.384</td>
<td>-0.663 to -0.105</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.4</td>
<td>0.081</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>5</td>
<td>-0.364</td>
<td>-0.682 to -0.045</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>14</td>
<td>-0.453</td>
<td>-0.754 to -0.152</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate depression</td>
<td>2</td>
<td>-0.044</td>
<td>-0.257 to 0.170</td>
<td>0.687</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal depression</td>
<td>6</td>
<td>-0.061</td>
<td>-0.347 to 0.225</td>
<td>0.677</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>2</td>
<td>-0.140</td>
<td>-1.266 to 1.086</td>
<td>0.823</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-clinical</td>
<td>2</td>
<td>0.016</td>
<td>-0.164 to 0.197</td>
<td>0.859</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References:


Hibbelen JR. Fish consumption and major depression. Lancet 1998; 351: 1213.


Hirashima F, Parow AM, Stoll AL, et al. Omega-3 fatty acid treatment and T2


Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr 2009; 28: 525-42.


Ross BM, Seguin J, Siesswerda LE. Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? Lipids Health Dis 2007; 6: 21.


