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 debression; 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*

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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*

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

The PubMed MeSH database was searched using the following terms: ((''Psychiatry and Psychology Category'' [Mesh] OR ''Fatigue Syndrome, Chronic''[Mesh]) AND (''Fatty Acids, Essential''[Mesh] OR ''Fatty Acids, Omega-3''[Mesh] OR ''Fish Oils''[Mesh] OR ''Eicosapentaenoic Acid''[Mesh] OR ''Docosahexaenoic Acids''[Mesh])) AND ''Randomized Controlled Trial ''[Publication Type]

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

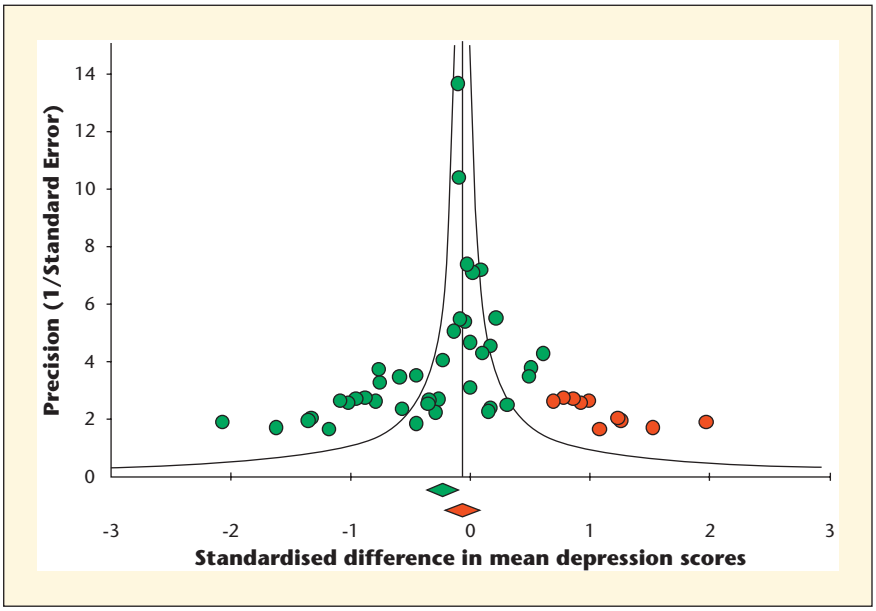

Figure 1. *Funnel plot for all 35 studies of precision (1/standard error) by standardized difference in mean depression scores. Observed studies are shown in green circles with the associated pooled estimate in a green diamond (–0.230; 95% CI –0.361, –0.100). Imputed studies (n = 10), using Duval and Tweedie's trim and fill method, are shown in red circles with the adjusted estimate in a red diamond (–0.062; 95% CI –0.205, 0.082).*

Table 1. *Characteristics of the 35 included studies, listed chronologically according to publication date.*

Study	Clinical group	Number, total (ω3 LC–PUFA/ placebo)	ω3 LC–PUFA preparation (source)	Daily dosage regime(s)	Treatment status	Duration (days)	Outcome measure(s)	Quality
Behan *et al.*, 1990	Chronic fatigue	63 (39/24)	Fish oil triglycerides (Efamol Marine)	0.136 g EPA + 0.088 g DHA	Therapeutic Monotherapy	90	Likert scale	6
Stoll *et al.*, 1999	Bipolar disorder	30 (14/16)	Fish oil triglycerides (Menhaden fish body oil concentrate)	6.2 g EPA + 3.4 g DHA	Preventative Adjunctive	112	HDRS-31	7
Warren *et al.*, 1999	Chronic fatigue	50 (24/26)	Fish oil triglycerides (Efamol Marine)	0.136 g EPA + 0.088 g DHA	Therapeutic Monotherapy	90	BDI	7
Fenton *et al.*, 2001	Schizophrenia	87 (43/44)	Ethyl ester (Laxdale Ltd)	3 g Ethyl-EPA	Therapeutic Adjunctive	112	MADRS	8
Nemets *et al.*, 2002	Major depression	20 (10/10)	Ethyl ester (Laxdale Ltd)	2 g Ethyl-EPA	Therapeutic Adjunctive	28	HDRS-24	9
Peet and Horrobin, 2002	Major depression	70 (17, 18, 17/18)	Ethyl ester (Laxdale Ltd)	1 g Ethyl-EPA *or* 2 g Ethyl-EPA *or* 4 g Ethyl-EPA	Therapeutic Adjunctive	84	BDI HDRS-17 MADRS	6
Zanarini and Frankenburg, 2003	Borderline personality disorder	30 (20/10)	Ethyl ester (Laxdale Ltd)	1 g Ethyl-EPA	Therapeutic Monotherapy	56	MADRS	4
Llorente *et al.*, 2003	Prevention of perinatal depression	99 (44/45)	Algal DHA (Martek Biosciences Corporation)	0.2 g DHA	Preventative Monotherapy	120	BDI EPDS SCID-IV	6
Marangell *et al.*, 2003	Major depression	36 (18/18)	Algal DHA (Martek Biosciences Corporation)	2 g DHA	Therapeutic Monotherapy	42	HDRS-28 MADRS	6
Su *et al.*, 2003	Major depression	28 (14/14)	Fish oil triglycerides (Menhaden fish body oil concentrate)	4.4 g EPA + 2.2 g DHA	Therapeutic Adjunctive	56	HDRS-21	5
Hirashima *et al.*, 2004	Bipolar disorder	21 (6, 6/9)	Fish oil triglycerides (not specified)	5.0–5.2 g EPA + 3.0–3.4 g DHA *or* 1.3 g EPA + 0.7 g DHA	Therapeutic Adjunctive	28	HDRS-23	2
Silvers *et al.*, 2005	Major depression	77 (40/37)	Fish oil triglycerides (DHA enriched tuna oil, Clover Corporation PLC)	2.4 g DHA + 0.6 g EPA	Therapeutic Adjunctive	84	BDI HDRS-SF	10
Fontani *et al.*, 2005	Non-clinical healthy participants	33 (33/33)[1]	Fish oil triglycerides (not specified)	1.6 g EPA + 0.8 g DHA	Preventative Monotherapy	70	POMS	5
Frangou *et al.*, 2006	Bipolar disorder	75 (24, 25/26)	Ethyl ester (Laxdale Ltd)	1 g EPA *or* 2 g EPA	Therapeutic Adjunctive	84	HDRS-17	9

Table 1. *(Continue)*

Study	Clinical group	Number, total (ω3 LC–PUFA/ placebo)	ω3 LC–PUFA preparation (source)	Daily dosage regime(s)	Treatment status	Duration (days)	Outcome measure(s)	Quality
Nemets *et al.*, 2006	Major depression in childhood	28 (13/15)	Fish oil triglycerides (Ocean Nutrition or Sears Laboratory)	0.4 g EPA + 0.2 g DHA	Therapeutic Monotherapy	112	CDI CDRS	6
Keck *et al.*, 2006	Bipolar disorder	116 (59/57)	Ethyl ester (Laxdale Ltd)	6 g EPA	Therapeutic Adjunctive	120	IDS-C	6
Hallahan *et al.*, 2007	Recurrent self-harm	49 (22/27)	Fish oil triglycerides (EPAX 5500)	1.22 g EPA + 0.908 g DHA	Therapeutic Adjunctive	84	BDI HDRS	8
Grenyer *et al.*, 2007	Major depression	83 (40/43)	Fish oil triglycerides (DHA enriched tuna oil, Clover Corporation PLC)	2.2 g DHA + 0.6 g EPA	Therapeutic Adjunctive	112	BDI HDRS	10
Frangou *et al.*, 2007	Bipolar disorder	14 (7/7)	Ethyl ester (Laxdale Ltd)	2 g EPA	Therapeutic Adjunctive	84	HDRS	6
Rogers *et al.*, 2008	Mild to moderate depression	218 (109/109)	Fish oil triglycerides (Minami Nutrition)	0.85 g DHA + 0.63 g EPA	Therapeutic Monotherapy	84	BDI DASS	11
Jazayeri *et al.*, 2008	Major depression	48 (32/16)	Ethyl ester (Minami Nutrition)	1 g EPA	Therapeutic Adjunctive	56	HDRS-17	6
Rees *et al.*, 2008	Treatment of perinatal depression	26 (13/13)	Fish oil triglycerides (DHA enriched tuna oil, Clover Corporation PLC)	1.638 g DHA + 0.414 g EPA	Therapeutic Monotherapy	42	EPDS HDRS-17 MADRS	11
Su *et al.*, 2008	Treatment of perinatal depression	33 (17/16)	Fish oil triglycerides (Menhaden fish body oil concentrate)	2.2g EPA + 1.2g DHA	Therapeutic Monotherapy	56	BDI EPDS HDRS-21	9
Freeman *et al.*, 2008	Treatment of perinatal depression	59 (31/28)	Fish oil triglycerides (Pronova/EPAX)	1.1 g EPA + 0.8 g DHA	Therapeutic Montherpay[2]	56	EPDS HDRS	5
van de Rest *et al.*, 2008	Non-clinical elderly participants	302 (100, 96/106)	Fish oil triglycerides (Lipid Nutrition)	0.226 g EPA + 0.176 g DHA *or* 1.093 g EPA + 0.847 g DHA	Preventative Monotherapy	182	CES-D GDS-15 MADRS	10
da Silva *et al.*, 2008	Major depression in patients with Parkinson's disease	29 (6, 8/7, 8)	Fish oil triglycerides (Herbarium Foundation for Health and Research)	0.720 g EPA + 0.480 g DHA as monotherapy *or* 0.720 g EPA + 0.480 g DHA + antidepressant	Therapeutic Monotherapy & Adjunctive	84	BDI MADRS	5
Lucas *et al.*, 2009	Mild to moderate depression	120 (59/61)	Fish oil ethyl esters (Isodis Natura)	1.05 g Ethyl-EPA + 0.15 g DHA	Therapeutic Monotherapy	56	HDRS HSCL-D-20	11

Table 1. *(Continue)*

Study	Clinical group	Number, total (ω3 LC–PUFA/ placebo)	ω3 LC–PUFA preparation (source)	Daily dosage regime(s)	Treatment status	Duration (days)	Outcome measure(s)	Quality
Doornbos *et al.*, 2009	Prevention of peri-natal depression	119[3] (42, 41/36)	Fish oil triglycerides (Marinol D40, Lipid Nutrition B.V.)	0.22 g DHA + 0.034 g EPA[4] *or* 0.22 g DHA + 0.034 g EPA + 0.22 g AA	Preventative Monotherapy	252	EPDS	4
Poppitt *et al.*, 2009	Prevention of depression after Stroke	102 (51/51)	Fish oil triglycerides (processed Hoki liver oil, Sea Dragon, NZ)	0.7 g DHA + 0.3 g EPA	Preventative Monotherapy	84	GHQ-28	8
Carney *et al.* (2009)	Major depression in patients with CHD	122 (62/60)	Ethyl esters (GlaxoSmithKline Inc)	0.93 g EPA + 0.75 g DHA	Therapeutic Adjunctive	70	BDI HDRS-17	8
Rondanelli *et al.* (2010)	Major depression in elderly women	46 (22/24)	Fish oil triglycerides	1.67 g EPA + 0.67 g DHA	Therapeutic Monotherapy	56	GDS	10
Bot *et al.* (2010)	Major depression in patients with diabetes	25 (13/12)	Ethyl ester (Minami Nutrition)	1.0 g EPA	Therapeutic Adjunctive	84	MADRS	6
Lespérance *et al.* (2010)	Major depression	432 (218/214)	Fish oil ethyl esters (Isodis Natura)	1.05 g EPA + 0.15 g DHA	Therapeutic Adjunctive or Monotherapy	56	IDS-SR MADRS	10
Mischoulon *et al.* (2009)	Major depression	35 (16/19)	Ethyl ester (Amarin Neuroscience Ltd [Laxdale])	1 g EPA	Preventative Monotherapy	56	HDRS	9
Makrides *et al.* (2010)	Prevention of peri-natal depression	2399 (1197/1202)	DHA enriched fish oil (Incromega 500 TG, Croda Chemicals)	0.8 g DHA + 0.1 g EPA	Preventative Monotherapy	180	EPDS	7

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.

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

Variable	Parameter	Estimate	95% CI	*p* value
Study quality	Intercept	−0.5333	−1.0894 to −0.0228	0.0801
	Slope	0.0361	−0.0337 to 0.1059	0.3080
Study duration	Intercept	−0.5066	−0.8303 to −0.1829	0.0022
	Slope	0.0027	−0.0004 to 0.0057	0.0834
Sample size	Intercept	−0.2844	−0.4487 to −0.1201	0.0007
	Slope	0.0003	−0.0004 to 0.0009	0.4048

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 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 (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

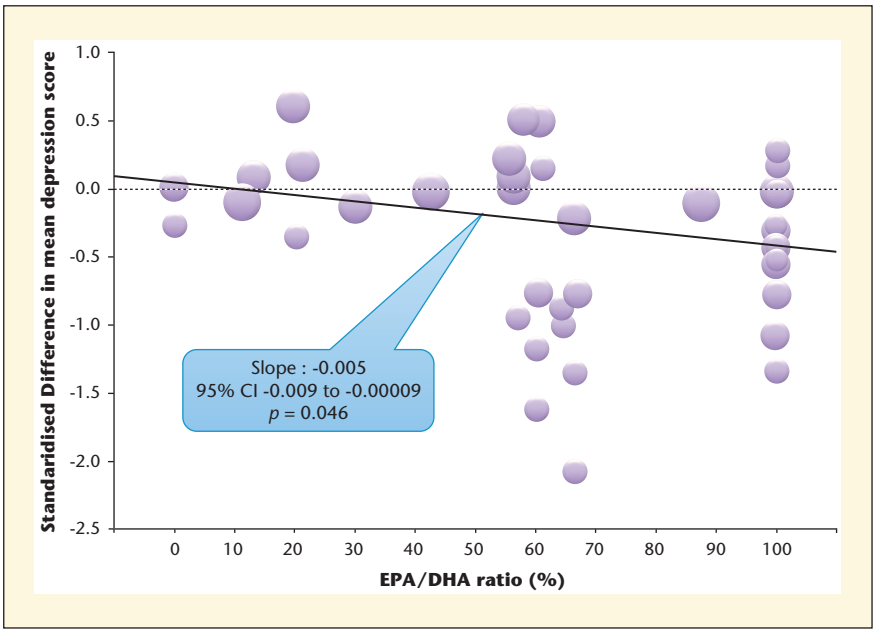

Figure 2. *Meta-regression analysis of EPA:DHA ratio. The size of the circles corresponds to the random-effects weighting attached to each study.*

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

Group	n	Estimate	95% CI	*p* value
Pure algal DHA	2	−0.111	−0.590 to 0.368	0.649
EPA + DHA ethyl esters	3	−0.027	−0.200 to 0.147	0.764
Pure EPA ethyl ester	10	−0.360	−0.597 to −0.123	0.003
Fish oil triglycerides >50% DHA	7	0.027	−0.148 to 0.202	0.763
Fish oil triglycerides >50% EPA	13	−0.513	−0.840 to −0.185	0.002

(figure 6). In contrast, the group of fish oil triglyceride studies were less affected by sample size and duration, with non-significant meta-regression line slopes for these indices *(table 4)*.

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.*,

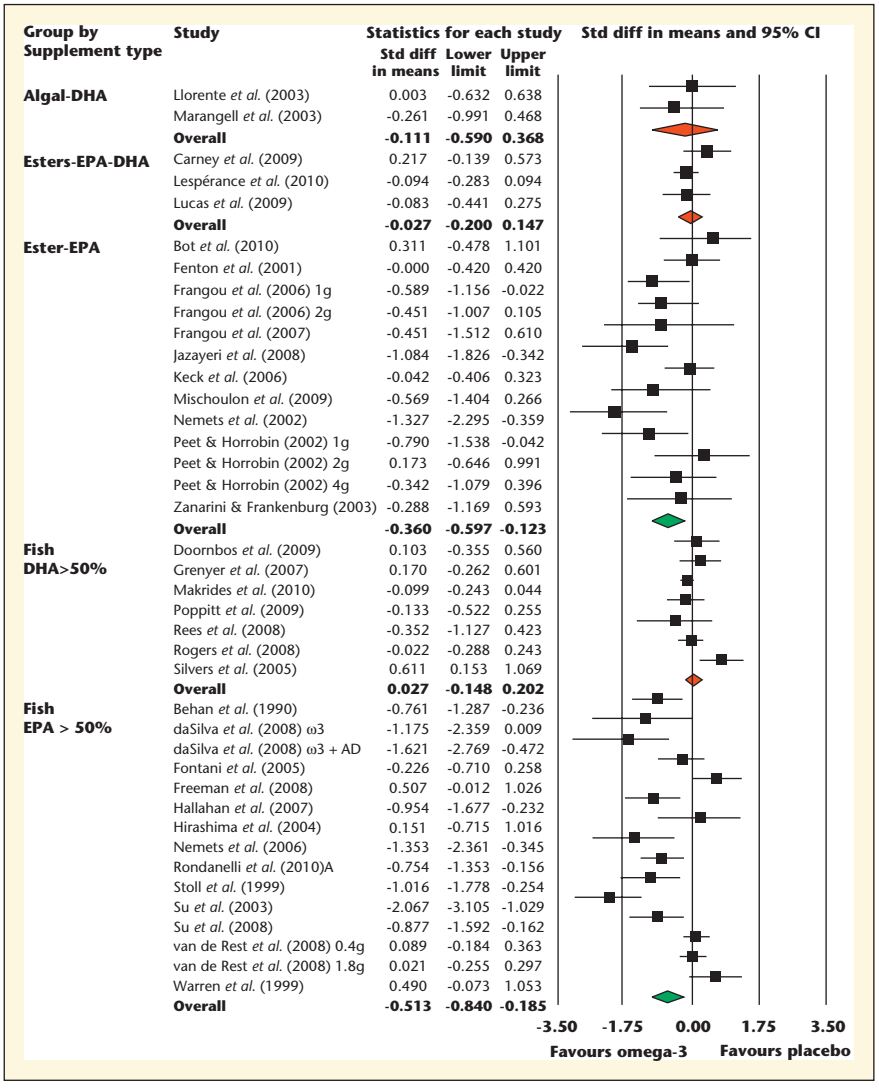

Figure 3. *Forest plot grouped by supplement type.*

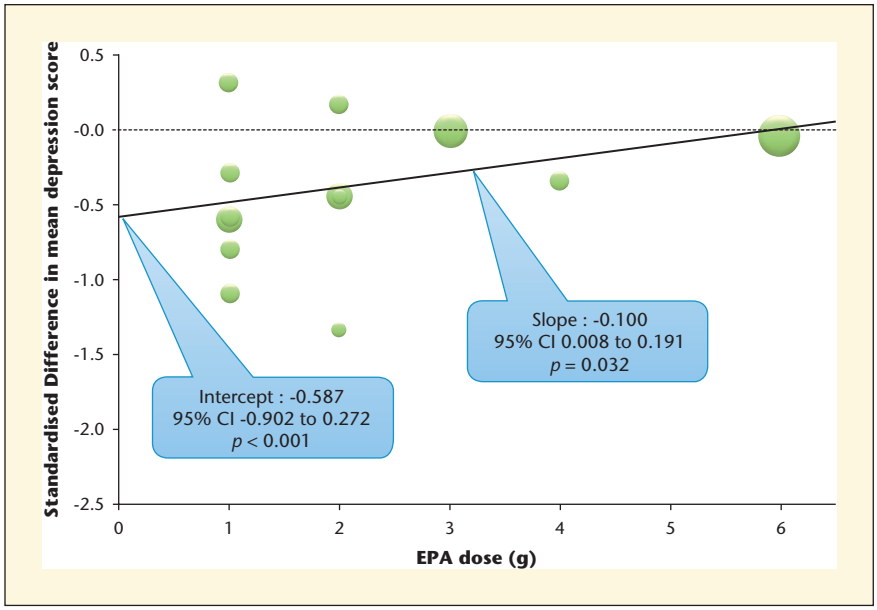

Figure 4. *Meta-regression analysis of EPA dose within the pure EPA ethyl ester subgroup. The size of the circles corresponds to the random-effects weighting attached to each study.*

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

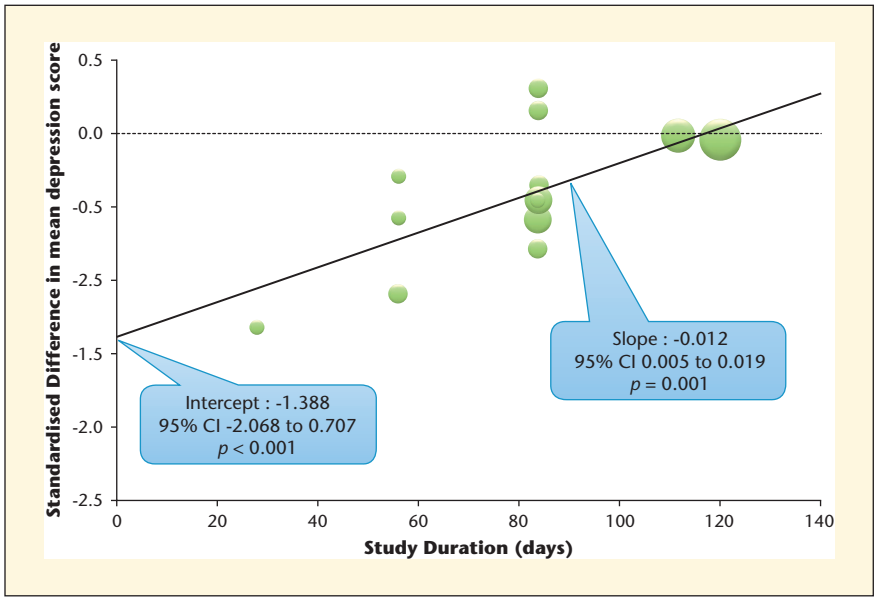

Figure 5. *Meta-regression analysis of study duration within the pure EPA ethyl ester subgroup. The size of the circles corresponds to the random-effects weighting attached to each study.*

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

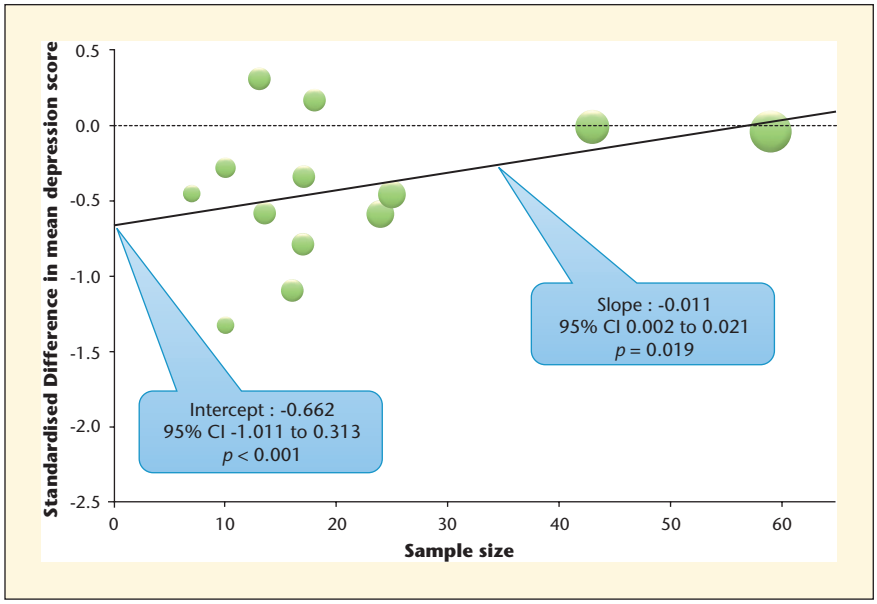

Figure 6. *Meta-regression analysis of sample size within the pure EPA ethyl ester subgroup. The size of the circles corresponds to the random-effects weighting attached to each study.*

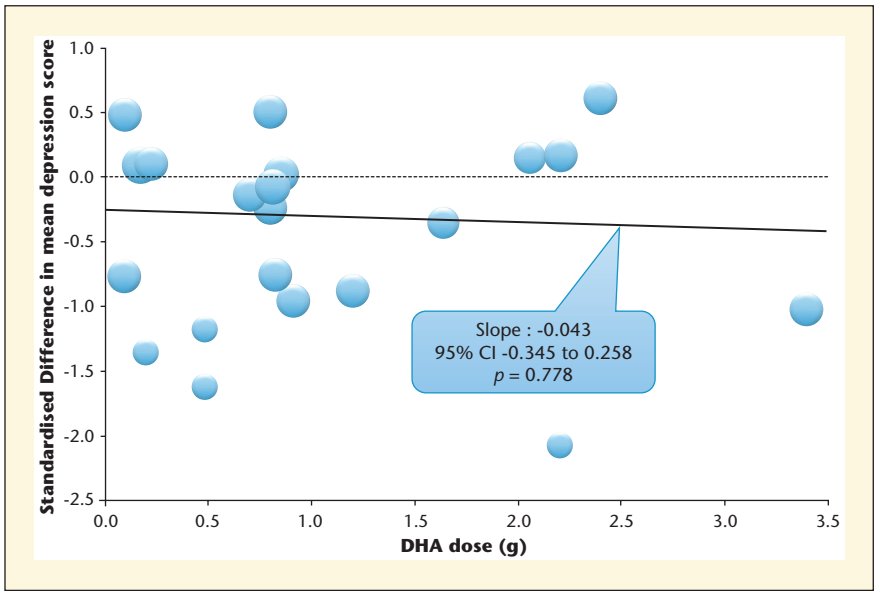

Figure 7. *Meta-regression analysis of DHA dose in fish oil triglyceride studies. The size of the circles corresponds to the random-effects weighting attached to each study.*

study duration and sample size, showed a dose response relationship with EPA up to a maximum reported doe of 6.2 g/day (Stoll *et al.*, 1999). These findings, together with the findings from the JELIS trials, would suggests 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 ω3 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 ≥ 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).*

Variable	Parameter	Estimate	95% CI	*p* value
Study quality	Intercept	−0.747	−1.576 to 0.082	0.077
	Slope	0.059	−0.045 to 0.162	0.266
Study duration	Intercept	−0.575	−1.096 to −0.055	0.030
	Slope	0.003	−0.002 to 0.007	0.233
Sample size	Intercept	−0.335	−0.606 to −0.063	0.016
	Slope	0.000	−0.001 to 0.001	0.519

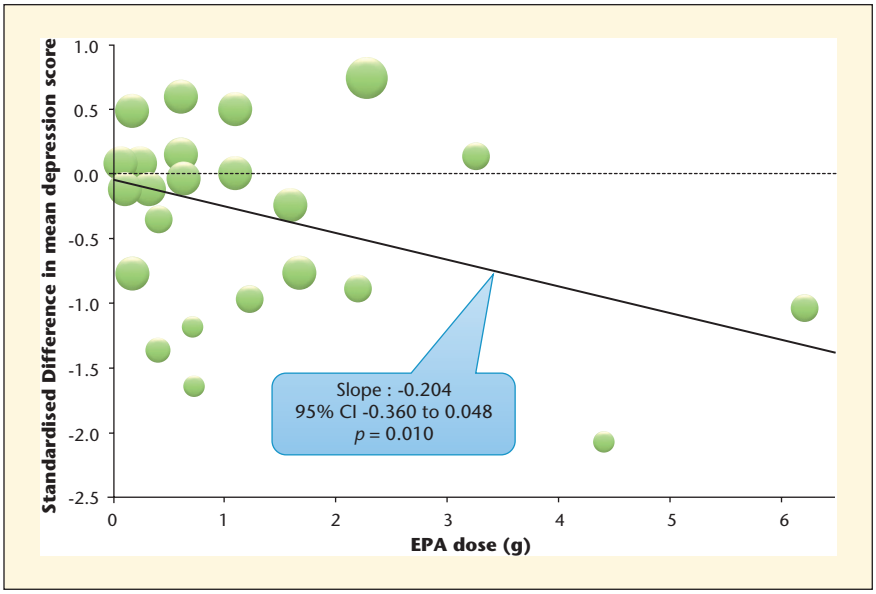

Figure 8. *Meta-regression analysis of EPA dose in fish oil triglyceride studies. The size of the circles corresponds to the random-effects weighting attached to each study.*

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

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

*4 studies were missing baseline depression scores. † In one study (Lespérance et al., 2010), patients could be treated with ω3 LC–PUFA either as monotherapy or as adjunctive treatment. ‡Diagnoses with only one representative study are not shown.

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