Data supplement to Hallahan et al. Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. Br J Psychiatry doi: 10.1192/bjp.bp.114.160242

Online Supplement DS1

Table DS1 Systematic Review of randomised controlled trials of omega-3 highly unsaturated fatty acids (HUFAs) in mood disorders

Study group	*n* (Total; *n*-3 HUFA/placebo) and *n* of strata in meta-analysis	Study duration and time of assessments	Illness type and patient group	HUFA formulations (daily dose) *v.* placebo	Measurement used and outcome of trial	Clinical depression rating	Design issues and possible threats to validity	Jadad rating of study quality	Diagnosed *v.* non-diagnosed depression
1. Andreeva *et al*, 2012[1]	2000 – 1000 *n*-3 HUFA – 1000 placebo Both *n*-3 HUFA and placebo groups were split into those who attained B Vitamins and those who did not Split according to men and women Strata 2	5 years Assessment: 0, 3, 5 years	Post-myocardial infarction, stroke or unstable angina in 45–80 year olds	**EPA 0.4g** + DHA 0.2g	GDS (French Version; GDS > 10=depression) No difference between groups Men treated with *n*-3 HUFA had a trend (*P*=0.053) towards attaining depressive symptoms	3	Individuals were not depressed at baseline	3	EPA: non-Clinical
2. Appleton *et al*, 2011[81]	113 – 53 *n*-3 HUFA – 60 placebo Not receiving antidepressant treatment	12 weeks	Mild–moderate depression (measured on DASS)	EPA 0.63g + **DHA 0.85g**	DASS (10–24)	–	No statistical data relating to depression is presented	–	–
3. Bot *et al*, 2010[2]	25 – 13 *n*-3 HUFA – 12 placebo Strata 1	12 weeks Assessment: 0, 1, 3, 5, 7, 9, 12 weeks	Diabetes mellitus and comorbid MDD (CIDI)	**E-EPA 1g**	MADRS No difference between the groups	2	Small sample size Heterogonous sample, in relation to antidepressant usage and type of diabetes	5	EPA: clinical
4. Carney *et al*, 2009[3]	122 – 62 *n*-3 HUFA – 60 placebo Strata 1	10 weeks Assessment: 0, 4, 10 weeks	MDD in coronary heart disease (BDI-II ≥16 and PHQ ≥10) Adults	**EPA 0.930g** + DHA 0.75g	HDRS, BDI, PHQ No differences between the groups	2	Short trial duration	6	EPA: clinical
5. Chiu *et al*, 2005[50]	15 *n*-3 HUFA, placebo but unclear how many per group Not included in meta-analysis	4 weeks Assessment: 0, 1, 2, 3, 4 weeks	BPAD (Manic, YMRS >20)	**EPA 2.2g** + DHA 1.6g	YMRS, HDRS, PANSS, CGI No significant difference between groups for any measure	–	Small number of study participants Statistical data not available for inclusion in meta-analysis	–	–

6. da Silva *et al*, 2008[4]	29 – 6 *n*-3 HUFA – 8 *n*-3 HUFA and antidepressant – 7 placebo – 8 placebo and antidepressant Strata 2	12 weeks Assessment: 0, 12 weeks	MDD in individuals with Parkinson's disease Adults (45–78 years old)	**EPA** 0.72g + DHA 0.48g	MADRS, BDI, CGI *n*-3 HUFAs were superior to placebo for individuals both on and off antidepressants	2	Relatively small sample size	6	EPA: clinical
7. Doornbos et al, 2009[5]	119 – 42 DHA – 41 DHA+ arachidonic acid – 36 placebo Strata 1	24 weeks of pregnancy and 6 weeks post-partum Assessment: weeks 16, 36 of pregnancy and 6 weeks post-partum	Healthy pregnant women to investigate the emergence of perinatal depression Adults	**DHA 0.22g** / DHA 0.22g + arachidonic acid 0.22g	EPDS DHA or DHA+ arachidonic acid were not superior to placebo in preventing the emergence of depressive symptoms	4	Large drop-out rates during pregnancy	4	DHA: non-clinical
8. Frangou *et al*, 2006[6]	75 – 24 EPA 1g – 25 EPA 2g – 26 placebo Strata 2	12 weeks Assessment: 0, 4, 12 weeks	BPAD (depressed/ rapid cycling) HDRS >10) Adults	**EPA** 1g or 2g	HDRS, YMRS, CGI EPA at both doses was superior to placebo at study end (P=0.03)	1	Various psychotropic agents were used, with alterations in medication allowed during study	6	EPA: clinical
9. Freeman *et al*, 2008[7]	51 – 28 *n*-3 HUFA – 23 placebo Strata 1	8 weeks Assessment: 0, 8 weeks	Perinatal MDD (EPDS >9) Adults	**EPA** 1.1g + DHA 0.8g	HDRS, EPDS, CGI No significant difference between the groups	3	Short trial duration Study included pregnant and post-partum individuals	6	EPA: clinical
10. Freund-Levi *et al*, 2008[8]	178 – 91 *n*-3 HUFA – 87 placebo Strata 1	26 weeks Assessment: 0, 26 weeks	Mild–moderate Alzheimer's disease in elderly population	**DHA** 1.72g + EPA 0.6g	MADRS No difference between groups, but non-APOE4 Alzheimer's disease group treated with *n*-3 HUFA (n=27) had improved scores on MADRS compared with placebo (n=18)	4	Individuals were not depressed at baseline Presence of variable levels of Alzheimer's disease suggest cautious interpretation of mood scores Per-protocol rather than intention-to-treat analysis used	5	DHA: non-Clinical

11. Gertsik *et al*, 2012[9]	40 – 18 *n*-3 HUFA – 22 placebo Strata 1	8 weeks Assessment: 0, 1, 2, 4, 6, 8 weeks	MDD (HDRS > 17) Adults	**EPA 0.9g** + DHA 0.2g and citalopram 20–40mg	HDRS, MDRS, BDI, CGI *n*-3 HUFA group had a significant reduction in symptoms compared with controls (*P*=0.008)	1	Short trial duration Small sample size	5	EPA: clinical
12. Giltay *et al*, 2011[10]	4,068 – 1007 EPA–DHA (36 on antidepressants) – 1009 EPA–DHA +ALA (35 on antidepressants) – 1022 ALA (29 on Antidepressants) – 1030 placebo (40 on antidepressants) Strata 6	40 months	Adults, post-myocardial infarction	ALA 2g & **EPA 0.24g** + DHA 0.16g or **EPA 0.24g** +DHA 0.16g Or ALA 2g	GDS No difference between groups in depressive symptoms Benefit for EPA-DHA in group already taking antidepressants (*P*=0.04)	3	A small percentage of individuals had depression at study entry ALA increased EPA but not DHA serum levels and thus included in analysis in 'selectively enriched' EPA group	6	EPA: non-Clinical
13. Gracious *et al*, 2010[53]	51 – 25 α-LNA – 26 placebo Not in meta-analysis	16 weeks Assessment: 0, 2, 4, 6, 8, 10, 12, 16 weeks	BPAD (manic, hypomanic, mixed or depressed) CGI-BP≥3, YMRS ≥4,or CDRS-R ≥22. Children (6–17 years)	**ALA 0.55-5.5g** **EPA** but not DHA increased in serum in α-LNA group	YMRS, CDRS, CGI-BP No significant benefit over placebo Symptom severity was negatively correlated with serum % α-LNA and % EPA, and positively correlated with % arachidonic acid	–	HUFA agent was ALA and not EPA or DHA and thus study was not included in meta-analysis as dose of EPA or DHA was not possible to elucidate	6	–
14. Greyner *et al*, 2007[11]	83 – 43 *n*-3 HUFA – 40 placebo Strata 1	16 weeks Assessment: baseline and at weekly intervals	MDD (HDRS ≥16) Adults	**DHA** 2.2g + EPA 0.6g	HDRS, BDI, GAF No significant difference between the groups	1	Making was insufficient (most patients correctly guessed the supplements)	6	DHA: clinical

15. Hallahan *et al*, 2007[12]	49 – 22 *n*-3 HUFA – 27 placebo Strata 1	12 weeks Assessment: 0, 3, 4, 6, 8, 9, 12 weeks	Individuals with a history of repetitive self-harm MDD (BDI score >19 (mean 35) and 46 patients had HDRS score >14 (mean 24)) Adults	**EPA** 1.2g + DHA 0.9g	HDRS, BDI, PSS, OAS-M, DHUS *n*-3 HUFAs were superior to placebo on the HDRS from 6 weeks (P<0.05) and the BDI from 8 weeks (P=0.02)	1	Although all participants were depressed on the HDRS and BDI, not all had a pre-existing diagnosis of MDD A comorbid personality disorder was present in 80% of individuals	6	EPA: clinical
16. Jazayeri *et al*, 2008[13]	48 – 16 *n*-3 HUFA & placebo – 16 fluoxetine & placebo – 16 *n*-3 HUFA & fluoxetine (*n*=32 for meta-analysis) Strata 1	8 weeks Assessment: 2, 4, 6, 8 weeks	MDD (HDRS ≥15) Adults	**EPA** 1g or fluoxetine 20mg or EPA 1g + fluoxetine 20mg	HDRS The combination of EPA and fluoxetine demonstrated greater benefit than either fluoxetine/EPA alone EPA and fluoxetine showed similar efficacy	1	20% of individuals did not complete 4 weeks of the study and were not included in the analysis The dose of fluoxetine was quite low and a higher dose may have had greater clinical efficacy Short trial duration	6	EPA: clinical
17. Keck *et al*, 2006[55]	116 –59 *n*-3 HUFA –57 placebo	16 weeks Assessment: baseline and 9 further occasions	BPAD (depressed) Adults	**EPA** 6g	IDS–C, YMRS, CGI No significant difference between the groups	–	Various psychotropic agents were used High drop-out rate of 54% Sufficient statistical data not presented	–	–
18. Kiecolt-Glaser *et al* 2012[14]	138 – 46 *n*-3 HUFA 2.5g – 46 *n*-3 HUFA 1.25g – 46 placebo Strata 2	16 weeks Assessment: 0, 4, 8, 12, 16 weeks	Older adults (mean age 51 years), sedentary lifestyle, not depressed (CES-D median 5)	**EPA 2.085g**+ DHA 0.348g or **EPA 1.042g** + DHA 0.124g	CES-D No difference between groups	4	Individuals were not depressed at baseline	6	EPA: non-clinical

19. Krauss-Etschmann et al, 2007[54]	311 77 *n*-3 HUFA 77 folate 77 *n*-3 HUFA + folate 80 placebo Not in meta-analysis	18 weeks (22 weeks gestation delivery)	Healthy pregnant women	**DHA 0.5g** + 0.15g EPA	EPDS	–	Statistical data for EPDS not presented and only collected 2 months post-delivery	–	–
20. Lesperance *et al*, 2011[15]	432 – 218 n-3 HUFA (113 with comorbid anxiety disorder) – 214 placebo (115 with comorbid anxiety disorder) Strata 1	8 weeks Assessment: 0, 8 weeks	MDD (MINI 5.0.0 criteria) Adults	**EPA 1.05g** + DHA 0.15g	MADRS; IDS-SR (30) *n*-3 HUFA group had a trend towards reduced depressive symptoms that became significant when those without comorbid anxiety disorders were excluded	1	Short trial duration Approximately 40% of individuals were on antidepressants and no separate data was presented for this group (thus only one strata possible), however, the authors describe no evidence for interaction with *n*-3 HUFA effect by participants taking antidepressants	6	EPA: clinical
21. Llorente et al 2003[16]	89 – 44 DHA – 45 placebo Strata 1	16 weeks Assessment: 3, 8,16 weeks	Postnatal depression (BDI >10)	**DHA** 0.2g	BDI, EPDS There was no difference in the emergence of depression between the two groups	3	Only 6.7% of subjects had a moderate depressive illness	6	DHA: non-clinical
22. Lucas et al 2009[17]	120 – 59 *n*-3 HUFA (13 MDE) – 61 placebo (16 MDE) Strata 2	8 weeks Assessment: 0, 4, 8 weeks	MDD (PGWBS ≤72) Adults (women)	**EPA 1.05g** + DHA 0.15g	HDRS, HSCL-D-20, PGWBS No differences between groups	3	Short trial duration The study included non-depressed participants and pre- and post-menopausal women. A subgroup had MDD	6	EPA: non-clinical

23. Makrides *et al*, 2010[18]	2399 – 1197 *n*-3 HUFA –1202 placebo Strata 1	19 weeks (pregnant women <21 weeks gestation to birth of child) Assessment: 6, 26 weeks post delivery	Healthy pregnant women Depression diagnosed if EPDS >12 Adults	**DHA** 0.8g + EPA 0.1g	EPDS (children of mothers also examined for cognitive and language development) No difference in rates of depression between the groups	3	No formal diagnosis of depression was made on any individual *n*-3 HUFAs and placebo were not administered for a period post-gestation, which may have altered the findings	6	DHA: non-clinical
24. Marangell *et al*, 2003[19]	35 – 18 *n*-3HUFA –17 placebo Strata 1	6 weeks Assessment: 0, 2, 6 weeks	MDD (MADRS ≥ 12) and HDRS ≥ 17) Adults	**DHA** 2g	MADRS No significant difference between groups	1	Short trial duration Differences in baseline mood scores between groups	5	DHA: clinical
25. Marangell *et al*, 2006[51]	10 – 6 *n*-3 HUFA – 4 placebo Not included in meta-analysis	52 weeks Assessment: Several occasions (frequency not stated in paper)	BPAD (euthymic) Psychotropic agents tapered during study Women planning to conceive	**DHA 2g**	BDI No significant difference between the groups	–	Small sample size Insufficient data for analysis or interpretation of trial result and thus not included in meta-analysis	–	–
26. Mattes *et al*, 2009[20]	75 – 37 *n*-3 HUFA – 38 placebo Strata 1	20 weeks (20 weeks gestation to birth of child) Assessment: 0, 20 weeks	Healthy pregnant women Only 16 individuals had BDI >10 (8 in each group)	**DHA 2.24g** + EPA 1.12g	BDI	–	Most participants were not depressed, and a low BDI cut-off of 10 for depression may be associated with false positives for depression	–	–
27. Mischoulon *et al*, 2009[21]	35 – 16 *n*-3 HUFA – 19 placebo Strata 1	8 weeks Assessment:0, 2, 4, 6, 8 weeks	MDD (HDRS ≥ 18) Adults	**EPA 1g**	HDRS, CGI No difference between groups	1	Short trial duration Small sample size	6	EPA: clinical

28. Mozaffari-Khosravi *et al*, 2013[22]	62 –21 EPA 1g –20 DHA 1g –21 placebo Strata 2	12 weeks Assessment: 0, 6, 12 weeks	MDD, on antidepressants	**EPA** 1g or **DHA** 1g	HDRS, EPA demonstrated improved mood compared with placebo and DHA (P=0.001)	2	Modest sample size Mean baseline mood scores in mild depression range. BDI scores not presented at follow-up	5	EPA clinical DHA clinical
29. Murphy *et al*, 2012[52]	45 – 15 cytidine (2g) and *n*-3 HUFA – 15 *n*-3 HUFA – 15 placebo Not included in meta-analysis	16 weeks Assessmentessment:0, 1, 2, 4, 6, 8, 10, 12, 14, 16 weeks	BPAD (clinically stable)	**EPA 3g** + DHA 2g	YMRS, MADRS, GAF Study retention rates poorer for *n*-3 HUFA and *n*-3 HUFA and cytidine groups compared with placebo	–	Small sample size Insufficient data presented at baseline or follow-up for analysis (data not separately presented for those who relapsed or those who did not attend a follow-up appointment) and thus not included in meta-analysis	–	–
30. Nemets *et al*, 2002[23]	20 – 10 *n*-3 HUFA – 10 placebo Strata 1	4 weeks Assessment: 0, 1, 2, 3, 4 weeks	MDD (HDRS ≥18) Adults	**EPA** 2g	HDRS EPA was superior to placebo after 2 weeks (P<0.001)	1	Small number of study participants. Short trial duration	4	EPA: clinical
31. Nemets *et al*, 2006[24]	20 – 10 *n*-3 HUFA – 10 placebo Strata 1	16 weeks Assessment: 0, 2, 4 8, 12, 16 weeks	MDD Children	**EPA** 0.4g + DHA 0.2g	CDRS, CDI, CGI *n*-3 HUFAs were superior to placebo from 8 weeks (P<0.04).	1	Eight individuals who initially enrolled in trial, did not complete first month of study and were not included in analysis Small sample size	6	EPA: clinical
32. Peet & Horrobin 2002[25]	70 – 17 EPA 1g – 18 EPA 2g – 17 EPA 4g – 18 placebo Strata 3	12 weeks Assessment: 0, 4,8,12 weeks	MDD (HDRS ≥16), Adults	**EPA** 1g, 2g or 4g	HDRS , BDI, MADRS EPA was superior to placebo at a dose of 1g only for all measures	1	Diagnosis was not attained using DSM-IV or ICD-10 criteria.	6	EPA: clinical
33. Poppitt et al, 2009[26]	102 – 51 DHA – 51 placebo Strata 1	12 weeks Assessment: 0, 12	Post stroke Adults >45 years	**DHA 0**.7g EPA 0.3g	GHQ (Depression Index) No difference between the groups	3	Individuals were not depressed at baseline	6	DHA: Non-clinical

34. Rees *et al*, 2008[27]	26 – 13 *n*-3 HUFA – 13 placebo Strata 1	6 weeks Assessment: Baseline and at weekly intervals	Perinatal MDD (EPDS >13 + HDRS >14 + MDRS >25) Adults	**DHA** 1.64g + EPA 0.41g	HDRS, EPDS, MDRS No significant difference between the groups	1	Short trial duration Study included pregnant and post-partum individuals	6	DHA: clinical
35. Rogers *et al*, 2008[47]	218 – 109 *n*-3 HUFA – 109 placebo Strata 1	12 weeks Assessment: 0, 12 weeks	MDD (DASS ≥10-28) Adults	**DHA** 2.5g + EPA 1.9g	BDI, DASS, GHQ, STAXI No difference between groups	2	No DSM-IV or ICD-10 criteria were utilised	6	DHA: clinical
36. Rondanelli *et al*, 2010[28]	46 –22 *n*-3 HUFA –24 placebo Strata 1	8 weeks Assessment:0, 8 weeks	MDD/dysthymia in elderly nursing home female patients using DSM-IV-TR criteria	**EPA 1.67g** + DHA 0.83g	GDS, SF-36 *n*-3 HUFA group had reduced depressive symptoms and improved quality of life	1	Short trial duration Only females included Some individuals had a diagnosis of dysthymia	6	EPA: clinical
37. Silvers *et al*, 2005[29]	77 – 40 *n*-3 HUFA – 37 placebo Strata 1	12 weeks Assessment: 0, 2, 4, 8, 12 weeks	MDD Adults	**DHA** 2.4g + EPA 0.6g	HDRS, BDI No significant difference between the groups	1	Participants were attending general practitioners only and perhaps did not have a severe depressive illness	6	DHA : clinical
38. Sinn *et al*, 2012[30]	50 – 17 EPA 1.67g – 18 DHA 1.55g – 15 placebo Strata 2	26 weeks	Elderly individuals with cognitive impairment	**EPA 1.67g** + DHA0.16g or **DHA 1.55g** + EPA 0.40g	GDS Both DHA (P=0.01) and EPA (P=0.04) demonstrated improved mood compared with placebo	3	Only 36% of individuals had a GDS score >4 indicating possible depression, and no statistical data available for meta-analysis for this subgroup Modest numbers	5	EPA: non-clinical and DHA: non-clinical
39. Stoll *et al*, 1999[31]	30 – 16 *n*-3 HUFA – 14 placebo Strata 1	16 weeks Assessment: 0, 2, 4, 6, 8, 12, 16 weeks	BPAD (euthymic/depressed) Adults	**EPA** 6.2g + DHA 3.4g	HDRS *n*-3 HUFA group had a significantly longer period of remission (P= 0.002)	1	Participants had to remain in the study for 30 days to be included in the analysis Varying concomitant medications were used	5	EPA: clinical

40. Su *et al*, 2003[32]	28 – 14 *n*-3 HUFA – 14 placebo Strata 1	8 weeks Assessment: 0, 1, 2, 4, 6, 8 weeks	MDD (HDRS >18) Adults	**EPA**4.4g + DHA 2.2g	HDRS *n*-3 HUFA was superior to placebo from week 4 (P=0.004)	1	Short duration of study Only individuals completing study (n=22) were included in analysis	6	EPA: clinical
41. Su *et al*, 2008[33]	33 – 17 *n*-3 HUFA – 16 placebo Strata 1	8 weeks Assessment: 0, 2, 4, 6, 8 weeks	Perinatal MDD (16–32 weeks gestation) (DSM-IV criteria; HDRS ≥18)	**EPA** 2.2g + DHA 1.2g	HDRS, EPDS, BDI *n*-3 HUFA group had lower HDRS scores (P=0.023)	1	Large drop-out rate Small sample size Short trial duration	6	EPA: clinical
42. Tajalizadekhoob *et al*, 2011[34]	66 – 33 *n*-3 HUFA (4 on antidepressants) – 33 placebo (7 on antidepressants) Strata 2	26 weeks Assessment: 0, 13, 26 weeks	GDS (5–11) to satisfy criteria for mild-moderate depression Elderly (MMSE ≥22)	**EPA 0.18g** + DHA 0.12g	GDS *n*-3 HUFA group had a reduction in depressive symptoms compared with controls (P=0.02)	3	Patients were selected with mild to moderate depression for treatment Although severe dementia was out-ruled, some cognitive impairment may have been present	6	EPA: non-clinical
43. Van de Rest *et al*, 2008[35]	302 – 96 EPA 1.09g (n=27 with CES-D ≥8) – 100 EPA 0.23g (n=33 with CES-D ≥8) – 106 placebo (n=44 with CES-D ≥8) Strata 4	26 weeks Assessment: 0,13, 26 weeks	Mental well-being (CES-D mean 5.9–6.8) Adults (≥65)	**EPA** 1.09g + DHA 0.85 or **EPA** 0.23g + DHA 0.18g	MADRS; CES-D, GDS, HADS-A No differences between groups	3	Included individuals who were predominantly free of depression	6	EPA: non-clinical

ALA, α-linolenic acid; BDI Beck Depression Inventory; BPAD, bipolar affective disorder; CDI, Childhood Depression Inventory; CDRS, Childhood Depression Rating Scale; CES-D, Center for Epidemiologic Studies Depression Scale; CGI, Clinical Global Impression; CGI-BP, Clinical Global Impression – Bipolar Version; CIDI, Composite International Diagnostic Interview; DASS, Depression and Anxiety Stress Scale; DHA, docosahexaenoic acid; DHUS, Daily Hassles and Uplifts Scale; EPA, eicosapentaenoic acid; EPDS, Edinburgh Post-Natal Depression Scale; GAF, Global Assessment of Functioning; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; HADS-A, Hospital Anxiety and Depression Scale; HDRS, Hamilton Depression Rating Scale; HSCL-D-20, Hopkins Symptom Checklist Depression Scale; IDS-C, Inventory of Depressive Symptomatology; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; MMSE, Mini-Mental State Examination; MINI, Mini-International Neuropsychiatric Interview; OAS-M, Overt Aggression Scale – Modified; PANSS, Positive and Negative Syndrome Scale; PGWBS, Psychological General Well-Being Schedule; PHQ, Public Health

Questionnaire; PSS, Perceived Stress Scale; SF-36, Short Form 36-Item Health Survey; STAXI, State Trait Anger Expression Inventory; YMRS, Young Mania Rating Scale.

Data Sources

We carried out a systematic bibliographic search using several databases and yielded 1,255 separate studies, 107 of which were reviewed in detail. We describe below the MEDLINE search strategy (Table DS2).

Table DS2 MEDLINE Search

Diagnosis	HUFA	Studies	Studies examined	Included studies
Depression	Omega-3 fatty acids	614	68	36
Depressive Disorder	Omega-3 fatty acids	254	2	36
Depression	Omega-3 PUFA(s) or Polyunsaturated fatty acids	551	4	38
Depressive Disorder	Omega-3 PUFA(s)	237	2	38
Depression	n-3 PUFA(s)	214	0	39
Depressive Disorder	n-3 PUFA(s)	59	1	39
Depression	Omega-3 HUFA(s)	15	0	39
Depressive Disorder	Omega-3 HUFA(s)	8	0	39
Depression	Omega-3 EFA(s) or Essential Fatty Acids	131	1	39
Depressive Disorder	Omega-3 EFA(s)	34	0	39
Depression	n-3 EFA(s)	56	0	40
Depressive Disorder	n-3 EFA(s)	15	0	40
Depression	HUFA(s) or Highly unsaturated fatty acids	62	1	40
Depressive Disorder	HUFA(s)	10	0	40
Depression	EPA or Eicosapentaenoic Acid	232	3	40
Depressive Disorder	EPA	70	0	40
Depression	DHA or Docosahexaenoic Acid	206	4	41
Depressive Disorder	DHA	73	0	41
Bipolar Disorder	Omega-3 fatty acids	127	1	41
Bipolar Disorder	Omega-3 PUFA(s)	117	0	41
Bipolar Disorder	n-3 PUFA	24	0	41
Bipolar Disorder	Omega-3 HUFA	117	0	41
Bipolar Disorder	Omega-3 EFA	4	0	41
Bipolar Disorder	n-3 EFA	0	0	41
Bipolar Disorder	HUFA	5	0	41

Bipolar Disorder	EPA	38	1	41
Bipolar Disorder	DHA	46	0	41
Bipolar Depression	Omega-3 fatty acids	131	1	41
Bipolar Depression	Omega-3 PUFA(s)	131	0	41
Bipolar Depression	n-3 PUFA	25	1	41
Bipolar Depression	Omega-3 HUFA	4	0	41
Bipolar Depression	Omega-3 EFA	30	0	41
Bipolar Depression	HUFA	5	0	41
Bipolar Depression	EPA	50	0	41
Bipolar Depression	DHA	2	0	41
Mood Disorder	Omega-3 fatty acids	359	1	41
Mood Disorder	Omega-3 PUFA(s)	461	3	41
Mood Disorder	n-3 PUFA	84	1	41
Mood Disorder	Omega-3 HUFA	12	0	41
Mood Disorder	Omega-3 EFA	57	0	41
Mood Disorder	n-3 EFA	23	0	41
Mood Disorder	HUFA	15	0	41
Mood Disorder	EPA	116	0	41
Mood Disorder	DHA	89	0	41
	-	-	95	41
Searching other articles			1*	42
Searching author names	-	-	1**	43
Total		1,255		43

*Poppitt S et al., (2009) paper ascertained by searching references of other articles (Giltay et al., 2012).

**Appleton et al., (2011) paper ascertained by searching specific authors working in this field. Multiple meta-analysis, systematic review and other review articles also accessed (n = 20).

No additional articles were attained from the other search strategies as outlined in the paper.

Excluded Studies

We excluded a number of double-blind, randomised placebo-controlled trials from the meta-analysis, largely due to the limited statistical data available. These studies are outlined here (Table DS3, see also Table DS1).

Table DS3

Study Group	N (Total: n-3 HUFA/Placebo)	Study Duration	Illness type of patient group	HUFA formulation (daily dose)	Reason(s) for exclusion from meta-analysis
Chiu et al., 2005	15 (unsure how many in each group)	4 weeks	BPAD - mania (YMRS >20)	EPA 2.2g + DHA 1.6g	We did not examine bipolar mania in meta-analysis. Statistical data not presented.
Marangell et al., 2006	6 = n-3 HUFA 4 = Placebo	52 weeks	BPAD - euthymic	2g DHA	Statistical data not presented
Keck et al., 2006	59 = n-3 HUFA 57 = Placebo	16 weeks	BPAD - depressed	6g EPA	Statistical data not presented.
Krauss-Etschmann et al., 2007	77 = n-3 HUFA 77 = Folate 77 = N-3 HUFA + Folate 80 = Placebo	18 weeks (22 weeks gestation to delivery)	Healthy Pregnant women	0.5g DHA + 0.15g EPA	Statistical data for EPDS (collected only 2 months after delivery) was not presented
Mattes et al., 2009	37 = n-3 HUFA 38 = Placebo	20 weeks (20 weeks gestation to delivery)	Healthy Pregnant Women =65, 16 = BDI>10 (8 in both groups)	2.24g DHA + 1.12g EPA	Statistical data not presented.
Gracious et al.,	25 = n-3 HUFA 26 = Placebo	16 weeks	BPAD Children	ALA 0.55-5.5g	n-3 HUFA in study formulation was not EPA or DHA and thus dose of either was not possible to elucidate
Appleton et al., 2011	53 = n-3 HUFA 60 = Placebo	16 weeks	Mild-Moderate Depression DASS 10-24	EPA 0.64g + 0.44g DHA	Statistical analysis for effect on mood not presented
Murphy et al., 2012[57]	15 = n-3 HUFA 15 = n-3 HUFA + 2g Cytidine 15 = Placebo	16 weeks	BPAD - euthymic	EPA 3g + DHA 2g	Statistical data not presented (data not separately presented for those who relapsed and those who failed to attend an appointment). Initial baseline data for 3 groups not presented

BDI = Beck Depression Inventory; BPAD = Bipolar Affective Disorder; DASS = Depression and Anxiety Symptom Scale; EPDS = Edinburgh Post-natal Depression Scale; YMRS = Young Mania Rating Scale

Publication Bias: Further Details

We ran Duval and Tweedie's trim and fill model initially using the random effects version as there was a great deal of variation between studies. The only mathematical difference between random and fixed models is that the random effects model adds a term "γ" to account for the between-study variance (Riebler, 2008) which the fixed effect model sets to 0. As it is very unlikely that between study variance is negligible in the group of studies presented, we feel that the random effects model is the more accurate model to assess publication bias in this study. The Cochrane Handbook for Systematic Reviews of Interventions specifically mentions the trim and fill model and states that it "is known to perform poorly in the presence of between-study heterogeneity" and suggests that the funnel plot might be, "inappropriate for heterogeneous meta-analyses, drawing attention to the premise that the studies come from a single underlying population given by the originators of the funnel plot" (Terrin et al., 2005). We noted that (without the imputed studies) all but one study made what seems a close approximation of a normal distribution:

Meta-Regression

We evaluated the association between omega-3 HUFAs and depression severity utilising a 4 point scale.

- "1" denoted studies of individuals as being moderately or severely clinically depressed if they were being treated for an episode of diagnosed (DSM/ICD) major

depressive episode, the depressed pole of a bipolar disorder, or multiple episodes of deliberate self-harm.

- "2" denoted studies of individuals with a depressive episode co-morbid with a medical disease such as Parkinson disease or diabetes mellitus.
- "3" denoted studies of individuals in healthy populations at risk for depression that included a sub-group of individuals with depression as determined by screening instruments, rating scales or clinical diagnosis.
- "4" denoted by presence of depressive symptoms in healthy populations at risk for depression such as elderly individuals, those in ante-natal or post-natal periods, and individuals with serious medical illnesses.

Ratings were undertaken blindly by BH and JD with a rank correlation of 0.9 attained between the raters. Sensitivity analyses carried out on using this alternative conceptualization of severity.

Data and Results

Statistical Indices:

The Q statistic of heterogeneity describes the proportion of total variation in study estimates due to heterogeneity, where $p<0.05$ indicates that statistically significant heterogeneity is present. I^2 is an estimation of the proportion of overall variation attributable to between-study heterogeneity, and Tau square is an estimation of standard deviation of variance across studies, (complete data tables are available in the web supplement). Q, I^2, and Tau square reflect a particular branch of the hypothesis testing meta-analysis and cannot be used to compare different branches (see Fig. 2).

Implications for further research

Diagnosed Depression in Clinical Population versus Depressive symptoms non-clinical population:

Our primary distinction to separate episodes of diagnosed depressive illness from milder depressed symptoms among non-clinical populations at risk for depression was a dichotomous classification and is supported by this meta-regression.

The meta-regression may more fully capture the complex distinction, in explaining the contradictory findings. We found the EPA versus placebo difference to be considerably smaller in monotherapy. These require a long duration of treatment (1-2 years), to have a reasonable likelihood of detecting a difference in time to relapse (using survival statistics) or number of relapses. Our meta-analysis is exploratory and results should be interpreted with cautions. Augmentation studies must be done on participants sufficiently depressed to need antidepressant treatment, and with the standard methodology of clinical trials of treatments of depression. Maintenance studies need a criterion of number of past episodes per unit time, as this is an important aspect of severity in secondary preventive studies to prevent relapse. These studies require a long duration of treatment (1-2 years), to have a reasonable likelihood of detecting a difference in time to relapse (using survival statistics) or number of relapses. There has been only one prophylactic study of recurrent depression, of one month duration. It is too short a time to expect that many will relapse, and so is vastly underpowered. These patients had a severity rating in the middle of the normal range, so there was little likelihood that omega-3 HUFAs would have much of an effect to the floor effects.

This is a much more difficult problem in studies of primary prevention studies or mixed primary secondary prevention studies. In studies of primary prevention, such as administration during pregnancy to prevent antenatal and or post-natal depression, depending on the criteria, most patients will not have had a prior depression. Even for severe depression, most patients are not depressed most of their lives, even before treatment were available. Severe depression is a recurrent disease with often long periods of normal function between episodes of depression. It is much harder to detect that they will be depressed on a given day, and might be easier to detect that participants had an episode of depression sometime during the time on omega-3 HUFA administration. Weekly diaries might be better than a one-time

intensive questionnaire. Studies of primary prevention often require very large sample to detect a preventive effects of a treatment proven to the efficacious in secondary prevention. It is possible that there would be enough studies of EPA to efficacy to warrant larger studies, but by that time much more might be known how to design such studies.

There are all also studies to determine the health benefits of omega-3 HUFAs. Sometimes a measure of mood is included as a secondary measure in studies of other health benefits. There are considerable day to day, week to week fluctuation in mood. It is not at all clear that normal mood variation from happy to sad, is the same phenomena as manic or depression. Mood is a normal affect. We think studies of mood is a conceptually different study outcome from clinical depression. More studies are needed of this as well, but positive or negative results of mood may not necessarily translate into positive or negative outcome of clinical depression.

Additional references

Riebler A. *Publication Bias in Meta-analysis. The Trim and Fill Method*. Biostatistics Unit, Institute of Social and Preventative Medicine, University of Zurich, Switzerland, PhD Seminar, 25 May, 2008.

Terrin N, Schmid CH, Lau J. IN a empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol* 2005; **58**; 894-90.

Table DS4 High v. low n-3 dose

		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau^2	Tau^2	Tau^2	Tau^2
Group	**Studies n**	**Point estimate**	**s.e**	**Variance**	**Lower limit**	**Upper limit**	**Z**	**P**	**Q**	**df (Q)**	**P**	**I^2**	**Tau^2**	**s.e.**	**Variance**	**Tau**
Fixed effect analysis																
< 1.5g n-3	13	0.44	0.09	0.01	0.26	0.62	4.8	0.00000	32.3	12	0.00122	63	0.21	0.17	0.03	0.46
> 1.5g n-3	10	0.51	0.10	0.01	0.32	0.70	5.3	0.00000	23.1	9	0.00603	61	0.16	0.13	0.02	0.40
Total within									55.4	21	0.00006					
Total between									0.3	1	0.58898					
Overall	23	0.47	0.07	0.00	0.34	0.60	7.1	0.00000	55.7	22	0.00009	61	0.16	0.10	0.01	0.41
Mixed effects analysis																
< 1.5g n-3	13	0.58	0.17	0.03	0.24	0.92	3.3	0.00087								
> 1.5g n-3	10	0.65	0.17	0.03	0.33	0.98	3.9	0.00009								
Total within																
Total between									0.1	1	0.75906					
Overall	23	0.62	0.12	0.01	0.38	0.85	5.1	0.00000								

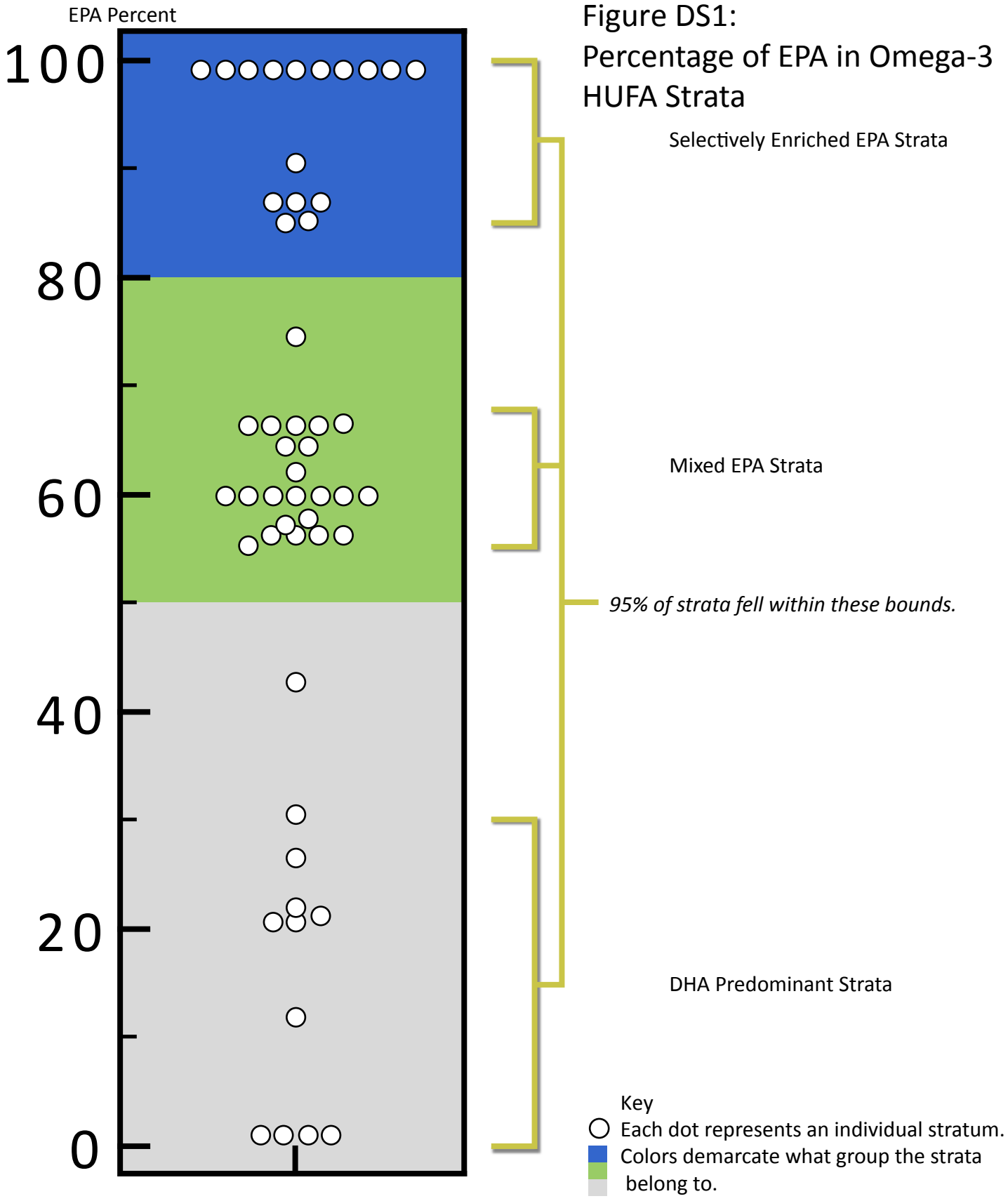

Figure DS1:
Percentage of EPA in Omega-3 HUFA Strata