Supplementary materials for Deane et al, “Omega 3 and polyunsaturated fat for prevention of depression and anxiety”.

Contents

Supplementary Text 1. Results section in greater detail

Characteristics of included studies
Characteristics of included studies and risk of bias are shown in Table 1 and in more detail in our database paper (1), risk of bias is itemised by domain for each study in Figure 1, flow diagram for this review in Supplementary Figure 1. The 32 RCTs (33 comparisons) randomised 46,467 participants, of which twelve were judged to be at low summary risk of bias (2-14), including twelve LCn3 comparisons, and the single ALA assessment (Figure 1). Thirty trials(2-33) (41,470 participants) assessed effects of LCn3, one assessed effects of ALA(2, 34) (4837 participants, these participants were part of a factorial trial so also included in an LCn3 trial) and one assessed effects of higher total PUFA(35) (4997 participants). We found no trials assessing effects of omega-6 fatty acids on depression or anxiety.

Fourteen RCTs assessed risk of serious depression symptoms, seventeen depression symptoms (assessed as a continuous measure in those without depression at baseline), one severity of depression in people with depression at baseline and five assessed anxiety. Participants were recruited with chronic illness or risk factors in 17 trials (6 with CVD, 3 diabetes or impaired glucose tolerance, 1 dyslipidaemia or hypertension, 2 with Huntingdon's disease, 1 each with multiple sclerosis, non-alcoholic fatty liver disease, macular degeneration, Parkinson's disease or colorectal tumours), memory deficit, cognitive impairment or Alzheimer's disease in 6 trials, mental health problems in 4 trials (two with schizophrenia, 1 young people at high risk of psychotic disorders, 1 mild to moderate depression), and healthy participants in 5 trials.

Of the 31 LCn3 trials, most gave supplementary capsules or medicinal oils, but two used supplemental foods (enriched margarine and fish sausages) (2, 21); one provided dietary advice (32); and one a combination.(7) The ALA trial provided enriched margarine (2), and the PUFA trial dietary advice plus nuts.(35) LCn3 doses ranged from 300mg/d (31) to 3360mg/d EPA+DHA (30), with 12 trial arms assessing doses of ≤1000mg/d, 13 arms >1000 to ≤2000mg/d, and seven arms doses of >2000mg/d EPA+DHA (one trial was unclear (32), two trials included two arms with different doses (12, 24)). Ratios of EPA to DHA varied, doses of EPA ranged from 96 to 2250mg/d, DHA from 120 to 1720mg/d. Seven RCTs randomised at least 1000 participants (2-4, 10, 13, 15, 35), so that more than1000 participants were involved in assessments of LCn3, ALA (2) and total PUFA (35). Control groups received olive, corn or sunflower oils, other fats, other 'inert' or ill-defined substances, different dietary advice, foods without omega-3 enrichment, or nothing. Trial authors provided some response to attempted contact for 16 trials.

Does increasing omega-3, omega-6 or total PUFA alter risk of depression or anxiety?
Key evidence is provided in the three GRADE tables summarising evidence on effects of LCn3, ALA and total PUFA on primary outcomes (Supplementary Tables 2, 5 and 6), in forest plots showing meta-analyses (Figures 2 and 3, Supplementary Figures 2-4, 6-8 and 10) and funnel plots (Supplementary Figures 5 and 9).

Risk of depression symptoms
Thirteen RCTs randomised 26,528 participants to higher vs lower LCn3 and reported on 1355 people found to have symptoms of depression (RR 1.01, 95% CI 0.92 to 1.10, I^2 0%, 5% incidence, Figure 2). In these trials mean LCn3 dose was 1.4g/d (SD 0.9), median dose was 0.95g/d (range 0.4 to 3.4), mean trial duration was 24.2 months (SD 25.1), median duration was 12 months (range 6 to 89 months). The four largest trials tended to be longer but lower dose than average. This lack of effect of LCn3 on risk of depression did not differ in sensitivity analyses by risk of bias, fixed effects or study size, though retaining only trials with good compliance suggested increased risk of depression diagnosis with increased LCn3 (RR 1.16, 95% CI 0.99 to 1.36, I^2 0%, Supplementary Table 1).

Over 90% of meta-analytic weight came from three trials that assessed depression using the Center for Epidemiologic Studies Depression Scale (CESD, score ≥16(3)), Becks Depression Inventory (BDI-II, score ≥14(10)) and General Health Questionnaire (GHQ-30, ≥5(11)). In these three trials the median LCn3 dose was 0.85g/d (range 0.4 to 1.0) and the median duration was 40 months (range 12 to 60 months). In other trials diagnosis resulted from Geriatric Depression scores (GDS-15, >10), reported adverse events or were unclear.

There was no suggestion of publication bias in visual inspection of the funnel plot (Supplementary Figure 5) or using statistical tests (Harbord test p=0.27 , Peters test p=0.29) (36-38). Similarly there were no clearly

missing data (although several of the ongoing trials detailed in Supplementary Table 9 would be expected to have finished by the start of 2017, so might be considered to constitute missing data, non-publication is most likely to equate to minimal effect sizes so would be likely to confirm rather than change our findings). The similarity of the random- and fixed-effects meta-analyses, which weight small studies differently (random effects: RR 1.01, 95% CI 0.92 to 1.10; fixed-effects: RR 1.02, 95% CI 0.93 to 1.12) also suggest that little small study bias is present.(39)

Subgrouping by intervention type, replacement nutrients, and LCn3 dose did not suggest important differences by subgroup, but subgrouping by baseline depression risk suggested increased depression risk in healthy adults with increased LCn3, and little or no effect in those with serious illnesses (no trials recruited participants with current depression or where ≥50% took antidepressants, Supplementary Table 1). As pre-specified LCn3 dose subgroupings did not divide included trials effectively, post-hoc we re-ran more even LCn3 dose subgroupings, and subgroupings by EPA and DHA dose. There was no suggestion of LCn3 dose effects (test for subgroup differences p=0.98), EPA (p=0.13) or DHA (p=0.87) effects, Supplementary Figures 2-4. GRADE assessment suggests that increasing LCn3 probably has little or no effect on risk of depression symptoms (moderate-quality evidence, downgraded once for imprecision, Supplementary Table 2).

Data were very limited from trials of ALA (RR 1.11, 95% CI 0.67 to 1.84, 1 trial, 59 people found to have depression symptoms (GDS-15 score >10), not altered in any sensitivity analysis, ALA dose 2g/d, trial duration 40 months, Figure 2 and Supplementary Table 3) and total PUFA (RR 0.75, 95% CI 0.54 to 1.03, 1 trial, 147 depression diagnoses – assessed via diagnosis by usual physician and reported by participants at study follow-up or reported habitual use of antidepressant drugs, total PUFA dose unclear, median duration 56 months, Figure 2 and Supplementary Table 4), and we found no data from trials of omega-6 (Figure 2). GRADE suggests that increasing ALA may increase the risk of depression symptoms very slightly (NNH 1000, low-quality evidence, downgraded twice for imprecision) and effects of increasing total PUFA on risk of depression symptoms are unclear as the evidence is of very low-quality (downgraded once each for risk of bias, indirectness and inconsistency, Supplementary Tables 5 and 6).

Depression severity and remission (in those with existing depression).

A single small trial assessed effects of 1.1g/d LCn3 for 6 months in poor Iranian men with mild or moderate depression symptoms at baseline (GDS-15 mean 7.2).(31) The study was not at low summary risk of bias, and found that GDS score fell by >10% of baseline, suggesting reduced severity of depression, in the higher LCn3 arm compared to control (MD -0.94, 95% CI -2.27 to 0.39, 61 participants) over 6 months. A further small study included participants with Parkinson's Disease(29), some of whom were depressed at baseline, and reported on remission, suggesting more remission in those on higher LCn3 (Supplementary Table 1). GRADE assessment suggests that effects of increasing LCn3 on depression severity was unclear as the evidence was of very low-quality (downgraded once each for risk of bias, indirectness and imprecision), and effects of increasing LCn3 on risk of remission in depression is unclear as the evidence was of very low-quality (downgraded once for risk of bias and twice for indirectness, Supplementary Table 2).

No trials of ALA, omega-6 or total PUFA included participants with depression at baseline.

Depression symptoms assessed on a continuous scale (in those not selected for depression at baseline)

Fifteen RCTs assessing depression symptoms on several scales (lower scores indicated less depression) were meta-analysed using SMD suggesting little or no effect of increased LCn3 (SMD 0.01, 95% CI -0.06 to 0.07, I^2 46%, mean LCn3 dose 1.2g/d, SD 0.6, median LCn3 dose 1.1g/d, range 0.3 to 2.4g/d, mean trial duration 18 months, SD 21, median duration 6 months, range 6 to 75 months, Supplementary Table 1). In the subgroup of seven trials that assessed depression using the Geriatric Depression Scale (GDS, short form scores from 0 to 15, 0-4 indicating no depression, 5-10 mild depression and 11+ severe depression) the mean difference with increased LCn3 was 0.03 (95% CI -0.10 to 0.16, I^2 35%, 8307 participants, mean control group GDS 3.4, mean dose 1.0g/d, SD 0.6, mean duration 17 months, SD 18, median duration 6 months, range 6 to 48 months).

There was no effect in any sensitivity analysis, and no differences between subgroups except for subgrouping by duration and depression scale. There was a suggestion of some benefit of LCn3 to

depression severity in trials of up to 24 months, no effect in trials of 24 to <48 months, and some harm in trials of at least 48 months. In the single trials using Hamilton, Self-rating and Calgary Depression Scales increasing LCn3 appeared to reduce depression scores (Supplementary Table 1). Post-hoc dose subgrouping using updated cut-offs did not suggest dose effects for LCn3 (test for subgroup differences p=0.36), EPA (p=0.50) or DHA (p=0.23), Supplementary Figures 6-8).

There was some evidence of small study bias. Data from two trials (33, 40) including 2389 participants could not be included in meta-analysis as no variance was provided but suggested similar final scores in both arms using the Beck Depression Inventory (Figure 3). A further three trials that assessed relevant outcomes provided no data (6, 15, 28), and the funnel plot suggests trials showing worsening of depression severity with increased LCn3 may be missing (Supplementary Figure 9). This suggestion of small study bias was confirmed by Egger's test for small study effects (p=0.029). If such studies were added into the analysis the SMD would tend to increase, suggesting some worsening of depression from increasing LCn3. However, the similarity of the random- and fixed-effects meta-analyses, which weight small studies differently (random effects: SMD 0.01, 95% CI -0.06 to 0.07; fixed-effects: SMD 0.02, 95% CI -0.02 to 0.06) suggest that the small study bias is not a very large problem.(39) Overall we believe that the effect of small study bias is small.

GRADE assessment suggests that increasing LCn3 probably has little or no effect on depression symptoms (moderate-quality evidence, downgraded once for publication bias, Supplementary Table 2).

A single large trial assessed effects of increasing ALA by 2g/d over 40 months on depression symptoms found little or no effect on the GDS (MD -0.02, 95% CI -0.14 to 0.10, 4068 participants, unaltered in sensitivity analyses, Supplementary Table 3). We found no data on effects of omega-6 or total PUFA on depression symptoms. GRADE assessment suggests that increasing ALA may have little or no effect on the severity of depression (low-quality evidence, downgraded once each for imprecision and risk of bias, Supplementary Table 6).

Anxiety incidence and remission. One study at low summary risk of bias provided data on effects of 0.84g/d LCn3 on risk of anxiety symptoms over 74 months, with only 12 evenly distributed cases in 15480 participants (RR 1.00, 95% CI 0.32 to 3.10)(4), none on remission. No studies provided data on effects of ALA, omega-6 or total PUFA on anxiety incidence or remission.

Anxiety symptoms assessed on continuous scales (in those not selected for anxiety at baseline)
Five studies assessed effects of increasing LCn3 on anxiety symptoms using four different scales (SMD 0.15, 95% CI 0.05 to 0.26, I^2 0%, 1378 participants, mean does 1.4g/d, SD 0.7, median dose 1.1g/d, range 0.5 to 2.4g/d LCn3, mean trial duration 26 months, SD 30, median 6 months, range 6 to 35 months, Supplementary Figure 10). No included studies were at low summary risk of bias, but other sensitivity analyses reflected the main analysis. Subgrouping and funnel plots were not attempted as there were too few trials, we are not aware of missing data. No trials of ALA, omega-6 or total PUFA reported on anxiety symptoms. GRADE assessment suggests that increasing LCn3 probably has little or no effect on anxiety symptoms (moderate-quality evidence, downgraded once for risk of bias, Supplementary Table 2).

Effects of LCn3 vs omega-6
We assessed effects of LCn3 vs omega-6 to help understand whether omega-3 is helpful, while omega-6 is harmful. If this were the case we would expect to see a greater effect of LCn3 when it replaces omega-6. There was no indication that effects of replacing omega-6 with LCn3 differed from replacement of any other dietary component for depression incidence or severity (Supplementary Table 1).

Secondary outcomes
We found no outcome data on effects of increasing LCn3 on social participation, psychosis, self-harm, costs or fidelity of the intervention. Data on quality of life, carer stress, suicidality, adverse events, drop outs and drop outs due to adverse events are reported in Supplementary Table 9. Data are sparse, often poorly reported and may suffer from reporting bias (we are aware of missing quality of life data for one trial(41)). Drawing conclusions simply on statistical significance of the SMD analyses, one trial suggested improvements in the Life Satisfaction Index with higher LCn3, but another did not suggest changes in SF-36 mental or physical components. Caregiver burden was assessed in two trials, suggesting a reduction in caregiver burden in one small trial, but no change in emotional or economic burden in another. There were

no important differences in acceptability of LCn3 or its control when assessed through dropouts, and no effect of increasing LCn3 on dropouts due to adverse effects. Adverse events reported by at least 4 trials suggested no effect on gastrointestinal side effects, respiratory or nervous systems, an increased risk of urogenital problems and bleeding, and reduced risk of skin problems with increased LCn3 but these are based on few reports. We have formally systematically reviewed effects of omega-3, omega-6 and total PUFA on cancer, diabetes, cognition, inflammatory bowel disease, cardiovascular disease, functional outcomes, mortality, adiposity and lipids in sister reviews. (1, 42-49)

There was little or no effect of being randomised to increased ALA on gastrointestinal side effects, but fewer dropouts due to adverse side effects (Supplementary Table 8). Trials of omega-6 and total PUFA did not provide data on secondary outcomes.

Ongoing trials

We identified eleven ongoing trials of polyunsaturated fats that appear likely to have assessed depression or anxiety outcomes (detailed in Supplementary Table 9). Some are overdue for publication and may constitute missing data, others are due to complete and be published over the next few years.

Supplementary Table 1. High vs low long-chain omega 3 (primary outcomes)

Outcome (test for subgroup differences)	**SA or Subgroup**	**Studies**	**Participants**	**Effect Estimate (**Risk Ratio, M-H, Random, 95% CI)*	**I^2, %**
Risk of depression symptoms	Main	13	26528	1.01 [0.92, 1.10]	0
	Summary risk of bias (SA)	6	24618	1.05 [0.90, 1.22]	33
	Fixed effects (SA)	13	26528	1.02 [0.93, 1.12] (Risk Ratio, M-H, Fixed, 95% CI)	0
	Compliance (SA)	5	7210	1.16 [0.99, 1.36]	0
	Larger trials (≥100 randomised, SA)	12	26436	1.01 [0.92, 1.10]	0
Intervention type, subgrouping (p=0.68)	Dietary advice	1	101	4.90 [0.24, 99.66]	-
	Supplemental foods	1	4068	0.98 [0.59, 1.63]	-
	Supplement or capsule	10	22154	1.00 [0.92, 1.10]	0
	Any combination	1	205	2.91 [0.12, 70.71]	-
Replacement, subgrouping (p=0.10)	n3 vs SFA	0	0	Not estimable	-
	n3 vs MUFA	5	22456	1.16 [0.99, 1.36]	0
	n3 vs n6	2	755	0.99 [0.10, 9.43]	0
	n3 vs non-fat, nil or low n3	6	3317	0.94 [0.84, 1.05]	0
Dose, subgroup (p=0.68)	LCn3 ≤150mg/d	0	0	Not estimable	-
	LCn3 >150 to ≤250mg/d	0	0	Not estimable	-
	LCn3 >250 to ≤400mg/d	1	4068	0.98 [0.59, 1.63]	-
	LCn3 >400 to ≤2400mg/d	10	21696	1.00 [0.92, 1.10]	0
	LCn3 >2.4 to ≤4.4g/d	1	663	2.99 [0.12, 73.16]	-
	LCn3 >4.4g/d	0	0	Not estimable	-
Duration, subgroup (p=0.12)	Duration 6 to <12 months	4	1361	1.15 [0.63, 2.11]	0
	Duration 12 to <24 months	4	3331	1.18 [1.00, 1.40]	0
	Duration 24 to <48 months	3	4374	1.05 [0.64, 1.73]	0
	Duration ≥48months	2	17462	0.93 [0.83, 1.04]	0
Depression risk, subgroup (p=0.03)	Previous or current depression	0	0	Not estimable	-
	Other serious illness	10	25278	0.97 [0.88, 1.07]	0
	Healthy	3	1250	1.35 [1.02, 1.79]	0
Antidepressant use, subgroup	antidepressants used	0	0	Not estimable	-
	no antidepressant use	13	26528	1.01 [0.92, 1.10]	0
Depression severity (participants have depression at baseline)	Main, assessed using GDS (Geriatric Depression Score)	1	61	-0.94 [-2.27, 0.39] MD (IV, Random, 95% CI)	-
	Low summary risk of bias (SA)	0	0	Not estimable	-
	Fixed effects (SA)	1	61	-0.94 [-2.27, 0.39] MD (IV, Random, 95% CI)	-
	Compliance (SA)	1	61	-0.94 [-2.27, 0.39] MD (IV, Random, 95% CI)	-

	Larger trials (≥100 randomised, SA)	0	0	Not estimable	-
Depression symptoms (in those without depression at baseline)	main	15	9908	0.01 [-0.06, 0.07] SMD (IV, Random, 95% CI)	46
	Low summary risk of bias (SA)	6	8044	0.00 [-0.08, 0.08] SMD (IV, Random, 95% CI)	62
	Fixed effects (SA)	15	9908	0.02 [-0.02, 0.06] SMD (IV, Fixed, 95% CI)	46
	Compliance (SA)	11	7832	-0.01 [-0.10, 0.07] SMD (IV, Random, 95% CI)	56
	Larger trials (≥100 randomised, SA)	10	9697	0.03 [-0.01, 0.07] SMD (IV, Random, 95% CI)	0
Assessment scale (p=0.02 in SMD analysis) Note: all available studies used for each subgroup	GDS (Geriatric Depression Scale)	7	8307	0.03 [-0.10, 0.16] MD (IV, Random, 95% CI)	35
	MADRS (Montgomery–Åsberg Depression Rating Scale)	3	698	-0.12 [-0.61, 0.37] MD (IV, Random, 95% CI)	0
	HAM-D (Hamilton Depression Scale)	1	24	-2.70 [-6.34, 0.94] MD (IV, Random, 95% CI)	-
	HADS (Hospital Anxiety & Depression Scale); depression subscore	1	449	0.30 [-0.21, 0.81] MD (IV, Random, 95% CI)	-
	GHQ (General Health Questionnaire); depression subscore	1	218	0.03 [-0.26, 0.32] MD (IV, Random, 95% CI)	-
	SDS (Self-rating Depression Scale)	1	48	-3.96 [-7.85, -0.07] MD (IV, Random, 95% CI)	-
	CDS (Calgary Depression Scale for Schizophrenia)	1	71	-1.58 [-2.66, -0.50] MD (IV, Random, 95% CI)	-
	Derogatis tool	1	392	1.55 [-0.42, 3.52] MD (IV, Random, 95% CI)	-
Intervention type, subgroup (p=0.28)	Dietary advice	0	0	Not estimable	-
	Supplemental foods	2	4116	-0.03 [-0.15, 0.08] SMD (IV, Random, 95% CI)	58
	Supplement or capsule	12	5400	0.00 [-0.08, 0.09] SMD (IV, Random, 95% CI)	43
	Any combination	1	392	0.16 [-0.04, 0.35] SMD (IV, Random, 95% CI)	-
Replacement, subgrouping (p=0.15)	n3 vs SFA	0	0	Not estimable	-
	n3 vs MUFA	5	4704	-0.05 [-0.17, 0.07] SMD (IV, Random, 95% CI)	61
	n3 vs n6	6	1152	-0.09 [-0.30, 0.13] SMD (IV, Random, 95% CI)	56
	n3 vs non-fat, nil or low n3	4	4052	0.06 [0.00, 0.12] SMD (IV, Random, 95% CI)	0
Dose, subgrouping (p=0.81)	LCn3 ≤150mg/d	0	0	Not estimable SMD (IV, Random, 95% CI)	-
	LCn3 >150 to ≤250mg/d	0	0	Not estimable SMD (IV, Random, 95% CI)	-

	LCn3 >250 to ≤400mg/d	1	4068	-0.01 [-0.08, 0.06] SMD (IV, Random, 95% CI)	-
	LCn3 >400 to ≤2400mg/d	14	5840	0.00 [-0.08, 0.09] SMD (IV, Random, 95% CI)	48
	LCn3 >2.4 to ≤4.4g/d	0	0	Not estimable	-
	LCn3 >4.4g/d	0	0	Not estimable	-
Duration, subgrouping (p=0.02)	Duration 6 to <12months	8	1481	-0.11 [-0.28, 0.07] SMD (IV, Random, 95% CI)	58
	Duration 12 to <24 months	2	83	-0.51 [-0.95, -0.06] SMD (IV, Random, 95% CI)	0
	Duration 24 to <48months	3	5952	0.01 [-0.04, 0.06] SMD (IV, Random, 95% CI)	0
	Duration ≥48months	2	2392	0.08 [0.00, 0.16] SMD (IV, Random, 95% CI)	0
Depression risk, subgrouping (p=0.36)	Previous or current depression	1	61	-0.35 [-0.86, 0.15] SMD (IV, Random, 95% CI)	-
	Other serious illness	11	9077	0.01 [-0.06, 0.07] SMD (IV, Random, 95% CI)	47
	Healthy	4	831	-0.05 [-0.30, 0.21] SMD (IV, Random, 95% CI)	55
Antidepressant use, subgrouping	antidepressants used	0	0	Not estimable	-
	no antidepressants used	15	9908	0.01 [-0.06, 0.07] SMD (IV, Random, 95% CI)	46
Depression remission	50% reduction HAM-D	1	24	8.00 [1.17, 54.50] SMD (IV, Random, 95% CI)	-
	Summary risk of bias (SA)	0	0	Not estimable	-
	Compliance (SA)	0	0	Not estimable	-
	Larger trials (≥100 randomised, SA)	0	0	Not estimable	-
Risk of anxiety symptoms	Main	1	15480	1.00 [0.32, 3.10]	-
	Low summary risk of bias (SA)	1	15480	1.00 [0.32, 3.10]	-
	Fixed effects (SA)	1	15480	1.00 [0.32, 3.10]	-
	Compliance (SA)	0	0	Not estimable	-
	Larger trials (≥100 randomised, SA)	1	15480	1.00 [0.32, 3.10]	-
Anxiety remission	50% reduction	0	0	Not estimable	-
Anxiety severity (participants have anxiety at baseline)		0	0	Not estimable	-
Anxiety symptoms (participants without anxiety at baseline)	Main	5	1378	0.15 [0.05, 0.26] SMD (IV, Random, 95% CI)	0
	Summary risk of bias (SA)	0	0	Not estimable	-
	Fixed effects (SA)	5	1378	0.15 [0.05, 0.26] SMD (IV, Fixed, 95% CI)	0
	Compliance (SA)	3	962	0.14 [0.01, 0.27]	0

				SMD (IV, Random, 95% CI)	
	Larger trials (≥100 randomised, SA)	4	1354	0.16 [0.05, 0.27] SMD (IV, Random, 95% CI)	0
Assessment scale (p=0.72 in SMD analysis)	HARS (Hamilton Anxiety Rating Scale)	1	24	-1.20 [-5.58, 3.18] MD (IV, Random, 95% CI)	-
	HADS (Hospital Anxiety & Depression Scale) -Anxiety	2	744	0.43 [0.06, 0.79] MD (IV, Random, 95% CI)	0
	GHQ (General Health Questionnaire) - Anxiety	1	218	0.24 [-0.55, 1.03] MD (IV, Random, 95% CI)	-
	Derogatis Stress Profile	1	392	1.94 [0.04, 3.84] MD (IV, Random, 95% CI)	-

Supplementary Table 2: GRADE assessment: Summary of findings for effects of long-chain omega-3 (LCn3) on depression and anxiety

Patient or population: People at any baseline risk of depression and anxiety
Setting: Trials of at least 6 months duration of LCn3 in any country or context
Intervention: Higher LCn3 intake
Comparison: lower LCn3 intake

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low LCn3 (primary outcomes)	**Risk with High LCn3**				
Risk of depression symptoms	51 per 1,000	**51 per 1,000** (47 to 56)	**RR 1.01** (0.92 to 1.10)	26528 (13 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d,e]	Increasing LCn3 probably has little or no effect on depression diagnosis. Downgraded once for imprecision.
Depression severity in those with depression at baseline assessed with: GDS (Geriatric Depression Scale)	The mean depression severity in those with depression at baseline was **7.2** GDS score	The mean depression severity in those with depression at baseline in the intervention group was 0.94 GDS score lower (2.27 lower to 0.39 higher)	-	61 (1 RCT)	⊕◯◯◯ VERY LOW [f,g,h]	The effect of increasing LCn3 on depression severity is unclear as the evidence is of very low quality. Downgraded once each for risk of bias, indirectness and imprecision.
Depression remission assessed with: 50% reduction in HAM-D	83 per 1,000	**667 per 1,000** (97 to 1,000)	**RR 8.00** (1.17 to 54.50)	24 (1 RCT)	⊕◯◯◯ VERY LOW [i,j,k]	The effect of increasing LCn3 on risk of remission in depression is unclear as the evidence is of very low quality. Downgraded once for risk of bias and twice for indirectness.
Depression symptoms (in those without depression at baseline)	-	-	-	9908 (15 RCTs)	⊕⊕⊕◯ MODERATE [b,c,l,m,n]	Increasing LCn3 probably has little or no effect on depression symptoms in people without depression at baseline. Downgraded once for publication bias.

Patient or population: People at any baseline risk of depression and anxiety
Setting: Trials of at least 6 months duration of LCn3 in any country or context
Intervention: Higher LCn3 intake
Comparison: lower LCn3 intake

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low LCn3 (primary outcomes)	**Risk with High LCn3**				
Risk of anxiety symptoms	1 per 1,000	**1 per 1,000** (0 to 2)	**RR 1.00** (0.32 to 3.10)	15480 (1 RCT)	⊕◯◯◯ VERY LOW [o,p,q]	The effect of increasing LCn3 on anxiety incidence is unclear as the evidence is of very low quality. Downgraded once for indirectness and twice for imprecision.
Anxiety severity (in those with anxiety at baseline)	Not pooled	Not pooled	not pooled	(0 RCTs)	-	We found no studies that assessed effects of LCn3 on severity of anxiety in those with anxiety at baseline.
Anxiety remission (50% reduction)	not pooled	not pooled	not pooled	(0 RCTs)	-	We found no studies that assessed effects of LCn3 on anxiety remission.
Anxiety symptoms (in those without anxiety at baseline)	-	-	-	1378 (5 RCTs)	⊕⊕⊕◯ MODERATE [b,r,s,t]	Increasing LCn3 probably has little or no effect on anxiety symptoms in those without anxiety at baseline. Downgraded once for risk of bias.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Risk of bias: Main analysis and most sensitivity analyses suggest little or no effect, but limiting to trials at low risk of compliance problems suggests increased risk of depression with increased LCn3. Not downgraded.
b. Inconsistency: I2 <50%, not downgraded.
c. Indirectness: men and women with a variety of baseline health conditions included, from several regions of the world. Not downgraded
d. Imprecision: 95% confidence intervals include increased risk of depression with more LCn3. Downgraded once.
e. Publication bias: funnel plot appears symmetrical, we are not aware of missing data. Not downgraded
f. Risk of bias: the single study was not at low summary risk of bias. Downgraded once.

g. Indirectness: Single trial assessing 61 Iranian men, women and other countries not represented. Downgraded once.
h. Imprecision: 95% CI includes both important benefits and some harm. Downgraded once.
i. Risk of bias: the single trial was not at low summary risk of bias. Downgraded once.
j. Indirectness: single trial in 24 Italians with Parkinson's Disease. Downgraded twice.
k. Imprecision: Although there were only 8 events, the 95% CI included only benefits. Not downgraded.
l. Risk of bias: effect did not differ in trials at low summary risk of bias, or in other sensitivity analyses. Not downgraded.
m. Imprecision: 95% CI included only little or no effect. Not downgraded.
n. Publication bias: Funnel plot suggests that some small studies with higher SMDs may be missing. Adding these back would tend to suggest slightly worse outcomes with LCn3. Downgraded once.
o. Risk of bias: the single study was at large and at low summary risk of bias. Not downgraded.
p. Indirectness: the single trial was conducted in UK diabetics. Downgraded once.
q. Imprecision: the 95% CI included both important harms and important benefits. Downgraded twice.
r. Risk of bias: no included trials were at low summary risk of bias. Downgraded once.
s. Indirectness: included men and women with a variety of health conditions, though mainly from Europe. Not downgraded.
t. Imprecision: 95% CI included only little or no effect. Not downgraded.

Supplementary Table 3. High vs low ALA (primary outcomes)

Outcome	SA or Subgroup	Studies	Participants	**Effect Estimate** (Risk Ratio, M-H, Random, 95% CI)*
Risk of depression symptoms	Main	1	4068	1.11 [0.67, 1.84]
	Summary risk of bias (SA)	1	4068	1.11 [0.67, 1.84]
	Fixed effects (SA)	1	4068	1.11 [0.67, 1.84] (Risk Ratio, M-H, Fixed, 95% CI)
	Compliance (SA)	1	4068	1.11 [0.67, 1.84]
	Larger trials (≥100 randomised, SA)	1	4068	1.11 [0.67, 1.84]
Depression symptoms (in those without depression at baseline)	Main, GDS	1	4068	-0.02 [-0.14, 0.10] MD (IV, Random, 95% CI)
	Summary risk of bias (SA)	1	4068	-0.02 [-0.14, 0.10] MD (IV, Random, 95% CI)
	Fixed effects (SA)	1	4068	-0.02 [-0.12, 0.09] MD (IV, Fixed, 95% CI)
	Compliance (SA)	1	4068	-0.02 [-0.14, 0.10] MD (IV, Random, 95% CI)
	Larger trials (≥100 randomised, SA)	1	4068	-0.02 [-0.14, 0.10] MD (IV, Random, 95% CI)
Depression remission	Main	0	0	Not estimable
Risk of anxiety symptoms	Symptomatic	0	0	Not estimable
Anxiety symptoms		0	0	Not estimable
Anxiety remission	50% reduction	0	0	Not estimable

Supplementary Table 4. High vs low total PUFA (primary outcomes)

Outcome	SA or Subgroup	Studies	Participants	**Effect Estimate** (Risk Ratio, M-H, Random, 95% CI)*
Risk of depression symptoms	Main	1	2739	0.75 [0.54, 1.03]
	Summary risk of bias (SA)	0	0	Not estimable
	Fixed effects (SA)	1	2739	0.75 [0.54, 1.03] (Risk Ratio, M-H, Fixed, 95% CI)
	Compliance (SA)	0	0	Not estimable
	Larger trials (≥100 randomised, SA)	1	2739	0.75 [0.54, 1.03]
Depression symptoms (in those without depression at baseline)	Main	0	0	Not estimable
Depression remission	Main	0	0	Not estimable
Risk of anxiety symptoms	Symptomatic	0	0	Not estimable
Anxiety symptoms	Main	0	0	Not estimable
Anxiety remission	50% reduction	0	0	Not estimable

Supplementary Table 5: GRADE assessment: Summary of findings for effects of total PUFA on depression and anxiety

Patient or population: People at any baseline risk of depression and anxiety
Setting: Trials of at least 6 months duration in any country or context
Intervention: Higher total PUFA intake
Comparison: lower total PUFA intake

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower total PUFA	**Risk with higher total PUFA**				
Risk of depression symptoms	61 per 1,000	**46 per 1,000** (33 to 63)	**RR 0.75** (0.54 to 1.03)	2739 (1 RCT)	⨁◯◯◯ VERY LOW [a b c]	We are uncertain of the effect of increasing total PUFA as the evidence is of very low-quality. Downgraded once each for risk of bias, inconsistency and indirectness.
Depression severity			-	(0 RCTs)	-	No RCTs assessed this outcome.
Depression remission (50% reduction)				(0 RCTs)	-	No RCTs assessed this outcome.
Depression symptoms (in those without depression at baseline)				(0 RCTs)	-	No RCTs assessed this outcome.
Risk of anxiety symptoms				(0 RCTs)	-	No RCTs assessed this outcome.
Anxiety severity		-	-	(0 RCTs)	-	No RCTs assessed this outcome.
Anxiety remission (50% reduction)				(0 RCTs)	-	No RCTs assessed this outcome.
Anxiety symptoms				(0 RCTs)	-	No RCTs assessed this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

Patient or population: People at any baseline risk of depression and anxiety
Setting: Trials of at least 6 months duration in any country or context
Intervention: Higher total PUFA intake
Comparison: lower total PUFA intake

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower total PUFA	**Risk with higher total PUFA**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias: the included study was not at low summary risk of bias (or at low risk for compliance). Downgraded once.
b. Inconsistency: only one trial, downgraded once.
c. Indirectness: the single trial that provided data for this assessment compared increased nut intake (high in PUFA) with increased olive oil intake (high in MUFA). However, nuts are also rich sources of many vitamins and minerals including magnesium, selenium, zinc and B vitamins, so it is unclear whether the decrease in depression risk is due to PUFA or other dietary components.

Supplementary Table 6: GRADE assessment: Summary of findings for effects of ALA on depression and anxiety

Patient or population: People at any baseline risk of depression and anxiety
Setting: Trials of at least 6 months duration of ALA in any country or context
Intervention: Higher ALA intake
Comparison: lower ALA intake

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower ALA	**Risk with Higher ALA**				
Risk of depression symptoms	14 per 1,000	**15 per 1,000** (9 to 25)	**RR 1.11** (0.67 to 1.84)	4068 (1 RCT)	⨁⨁◯◯ LOW [a]	Increasing ALA may increase the risk of diagnosis of depression very slightly, NNH 1000. Downgraded twice for imprecision.
Depression severity in those with depression at baseline	not pooled	-		(0 RCTs)	-	No RCTs assessed this outcome.
Depression remission (50% reduction)	not pooled	not pooled	not pooled	(0 RCTs)	-	No RCTs assessed this outcome.
Depression symptoms (in those without depression at baseline) - assessed with GDS (Geriatric Depression Scale)	The mean GDS at baseline was **1.49**	The mean GDS in the intervention group was -0.02 lower (0.14 lower to 0.10 higher)	-	4068 (1 RCT)	⨁⨁◯◯ LOW [b,c]	Increasing ALA may have little or no effect on depression symptoms. Downgraded for imprecision and risk of bias.
Risk of anxiety symptoms	not pooled	not pooled	not pooled	(0 RCTs)	-	No RCTs assessed this outcome.
Anxiety severity in those with anxiety at baseline	not pooled	-	-	(0 RCTs)	-	No RCTs assessed this outcome.
Anxiety remission (50% reduction)	not pooled	not pooled	not pooled	(0 RCTs)	-	No RCTs assessed this outcome.
Anxiety symptoms in those without anxiety at baseline	not pooled	-		(0 RCTs)	-	No RCTs assessed this outcome.

Patient or population: People at any baseline risk of depression and anxiety
Setting: Trials of at least 6 months duration of ALA in any country or context
Intervention: Higher ALA intake
Comparison: lower ALA intake

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower ALA	**Risk with Higher ALA**				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Imprecision: 95% CI include both important harms and important benefits. Downgraded twice.
b. Risk of bias: the included study was not at low summary risk of bias (or at low risk for compliance). Downgraded once.
c. Imprecision: 95% CI included benefit of over 10% improvement in GDS score. Downgraded once.

Supplementary Table 7. High vs low long-chain omega 3 (secondary outcomes)

Outcome	Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Social participation		0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
Quality of life measures	Life satisfaction index (LSI)	1	352	Mean Difference (IV, Random, 95% CI)	1.10 [0.14, 2.06]
	SF36 - mental	1	91	Mean Difference (IV, Random, 95% CI)	-0.60 [-3.10, 1.90]
	SF36 - physical	1	91	Mean Difference (IV, Random, 95% CI)	1.10 [-2.12, 4.32]
Carer stress	Caregiver burden (Zarit Burden Interview)	1	48	Mean Difference (IV, Random, 95% CI)	-3.49 [-7.02, 0.04]
	Emotional overload	1	174	Mean Difference (IV, Random, 95% CI)	0.00 [-0.91, 0.91]
	Economic overload	1	174	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
Healthcare and patient costs		0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
Psychosis, suicidality, suicide or self-harm	Suicide	3	16433	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.13, 7.73]
Fidelity		0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
Adverse events	Any GI side effect	12	11609	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.12]
	Nausea	3	651	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.64, 2.05]
	Abdominal pain or discomfort	3	271	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.11, 9.21]
	Diarrhoea	3	849	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.43, 1.00]
	Malignancy	1	2081	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.15, 0.32]
	Urogenital system	4	3063	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.83, 1.48]
	Respiratory system	5	3577	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.61, 1.66]
	Musculoskeletal disorders	3	2997	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.45, 1.18]
	Falls or injuries	3	2687	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.88, 2.62]
	Cardiovascular system	3	2971	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.83, 1.68]

	Bleeding	4	3290	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.82, 2.20]
	Skin problems (itching, rashes)	4	6831	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.49, 1.32]
	Infections	2	2905	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.06]
	Brain and Nervous System	6	3834	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.17]
	Headache or worsening migraine	3	651	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.33, 1.82]
	Insomnia or fatigue	3	712	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.71, 1.73]
	Sense organs	2	2905	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.31]
	Hormonal	2	2385	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.73, 1.70]
Drop outs		11	5654	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
Dropouts due to adverse events		6	4976	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.42]

Supplementary Table 8. High vs low ALA (secondary outcomes)

Outcome	Studies	Participants	Statistical Method	Effect Estimate
Any gastrointestinal side effect	1	2433	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.38, 2.28]
Dropouts due to adverse events	1	2433	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.47, 1.65]

Supplementary Table 9. Characteristics of ongoing trials that appear to have assessed relevant outcomes for this review

Beyond Aging Project (50)

Study name	The Beyond Ageing Project Phase 2: A selective prevention trial using novel pharmacotherapies in an older age cohort at risk for depression
Methods	RCT
Participants	Older adults (60+ years) at risk of depression (K-10 score ranging from 16-29) who initially participated in the first Beyond Ageing Project
Interventions	Each for 12 months: Arm 1: omega-3 (4 capsules, total 2g/d: 1200mg EPA and 800mg DHA) and placebo microcrystalline cellulose (1 capsule) Arm 2: paraffin oil placebo (4 capsules) and sertraline hydrochloride (1 capsule, 50mg) Arm 3: paraffin oil placebo (4 capsules) and placebo microcrystalline cellulose (1 capsule)
Outcomes	Primary: depressive symptoms (PHQ-9) Secondary: cognitive decline, MMSE, brain metabolism, hippocampal volume, anxiety (GAD-7), disability (WHODAS-II), sleeping problems (PSQI), exercise (Active Australian Survey)
Starting date	Registered on Trials Registry: 12 Jan 2010 Study start date: June 2011 Study completion date est: Main results expected in 2017
Contact information	Ian Hickie (PI), Brain and Mind Centre, University of Sydney, ian.hickie@sydney.adu.au
Notes	ACTRN12610000032055

Cai 2017 (51)

Study name	Omega-3 fatty acid supplementation for symptoms of depression in patients with cardiovascular disease
Methods	RCT, parallel groups. Both the participants and the researchers were blinded to whether they were in the fish oil or placebo groups.
Participants	91 patients (65 males and 26 females, mean age 59.2 (10.3) years) with heart disease and depressive symptoms (Center for Epidemiological Studies Depression Scale, CES-D) and low fish/fish oil intakes.
Interventions	Intervention: Four 1 gram capsules of eicosapentaenoic acid (EPA)-rich fish oil per day for 6 months. Each capsule will contain 500mg of eicosapentaenoic acid (EPA) and 25 mg of docosahexaenoic acid (DHA). Placebo: Four 1 gram capsules of soybean/corn oil per day for 6 months. Each capsule will contain 500mg of soybean oil and 500 mg of corn oil.
Outcomes	Primary: Depression (Hamilton Rating Scale For Depression) Secondary: Quality of Life (Short Form (SF)-36) Angina frequency (Seattle Angina Questionnaire) Degree of change in vasodilator function assessed by flow mediated dilatation (FMD) in the brachial artery Changes in cerebral blood flow measured by transcranial Doppler ultrasound
Starting date	Participants were recruited in 2009-2013. Trial was registered 1/12/2008

Contact information	Alison Coates, School of Health Sciences, Alliance for Research in Exercise, Nutrition and Activity, Sansom Institute for Health Research, University of South Australia, PO Box 2471, Adelaide, South Australia. Alison.coates@unisa.edu.au
Notes	ACTRN12608000598381 The authors confirm that the main outcomes are still being analysed.

Chiang Chiu 2010

Study name	The Assessment for the Effects of Health Products on Depression and Cognitive Function: Fish Oil in Patients With Late-life Depression
Methods	RCT, parallel groups, double-blind
Participants	Older people with major depression
Interventions	Intervention: three capsules of n-3 fatty acids. Each capsule included 600mg eicosapentanoic acid (20:5n-3), 400 mg of docosahexanoic acid (22:6n-3), tertiary-butylhydroquinone 0.2 mg/g and tocopherols 2 mg/g. Placebo: three identical capsules per day. All capsules included olive oil.
Outcomes	Recurrence of depression Change of cognitive function
Starting date	Study start date: May 2007 Study Completion Date: September 2010
Contact information	Chih-Chiang Chiu, Department of Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital, No. 309, Sungde Road, Taipei 110, Taiwan. Email: eric.ccchiu@gmail.com
Notes	NCT01235533

DO Health

Study name	Vitamin D3- Omega3- Home Exercise- Healthy Ageing and Lengevity Trial (DO-HEALTH)
Methods	RCT
Participants	Community dwelling adults 70 years and older, 50% of seniors enrolled based on a fall in the year before enrollment
Interventions	Each for 3 years: Arm 1: omega 3 (1g/d, ratio EPA:DHA = 1:2) and vitamin D3 (2000 IU/d) capsules and strength home exercise (3x30 mins/week) Arm 2: omega 3 (1g/d, ratio EPA:DHA = 1:2) and vitamin D3 (2000 IU/d) capsules and flexibility home exercise (3x30 mins/week) Arm 3: omega 3 (1g/d, ratio EPA:DHA = 1:2) and placebo capsules and strength home exercise (3x30 mins/week) Arm 4: omega 3 (1g/d, ratio EPA:DHA = 1:2) and placebo capsules and flexibility home exercise (3x30 mins/week) Arm 5: placebo and vitamin D3 (2000 IU/d) capsules and strength home exercise (3x30 mins/week) Arm 6: placebo and vitamin D3 (2000 IU/d) capsules and flexibility home exercise (3x30 mins/week) Arm 7: placebo and placebo capsules and strength home exercise (3x30 mins/week) Arm 8: placebo and placebo capsules and flexibility home exercise (3x30 mins/week)

Outcomes	Primary: non-vertebral fractures, functional decline, blood pressure, cognitive decline, rate of any infection Secondary: other fractures, falls, pain in knee osteoarthritis, musculoskeletal changes, gastro-intestinal symptoms, mental and oral health, quality of life, life-expectancy, cardiovascular events, cancer, glucose measures, cost-benefit. All endpoints supported by a DO-HEALTH biomarker study
Starting date	Registered on Trials Registry: 6 Dec 2012 Study start date: Dec 2012 Study completion date est: Nov 2017
Contact information	Heike Bischoff-Ferrari (PI), Centre on Aging and Mobility, University of Zurich
Notes	NCT01745263 EudraCT: 2012-001249-41 www.do-health.eu

InTrePad

Study name	Intervention of Testosterone & Fish Oil for the Prevention of Alzheimer's Disease: InTrePad
Methods	RCT
Participants	PiB-PET (Pittsburgh compound B) positive men aged 60 years and over with Subjective Memory Complaints
Interventions	Each for 56 weeks: Arm 1: DHA capsules (1720mg/d) and testosterone undecanoate (intramuscular injection 1000mg/4ml every 8 weeks) Arm 2: placebo DHA and testosterone undecanoate (intramuscular injection 1000mg/4ml every 8 weeks) Arm 3: placebo DHA and placebo testosterone
Outcomes	Primary: PiB score Secondary: neuropsychological, mood and daily functioning questionnaires, beta amyloid levels, fluorodeoxyglucose to assess brain glucose metabolism, inflammatory and oxidative biomarkers, hippocampal volume, quality of life, safety and tolerability of treatment
Starting date	Registered on Trials Registry: 14 Jan 2013 Study start date: 28 Feb 2013 Study completion date est: unclear
Contact information	Ralph Martins (PI), Sir James McCusker Alzheimer's Disease Research Unit, Hollywood Medical Centre, Nedlands, Australia, r.martins@ecu.edu.au
Notes	ACTRN12613000034730 Ralph Martins written to in 2016- no response

Irish Omega-3 NCT02848469

Study name	Irish Omega-3 Study
Methods	RCT, 2 arms (LCn3 vs placebo), 6 months
Participants	Participants at ultra high risk of psychosis (aged 13 to 45 years)
Interventions	Int: 200ml juice drink including 1g EPA and 1g DHA Cont: 200ml juice drink without omega 3 (no fish taste in either)
Outcomes	Primary: transition to psychosis Secondary: fatty acid changes
Starting date	Registered on Trials Registry: 25 July 2016

	Study start date: Sept 2013 Estimated study completion date: February 2018
Contact information	M Rooney (PI), University College Cork
Notes	NCT02848469

n-3 for Vascular Cognitive Aging-NCT01953705 (52)

Study name	n-3 PUFA for Vascular Cognitive Aging
Methods	RCT
Participants	Older adults (80 years and older) at high risk for cognitive decline and dementia of Alzheimer's type
Interventions	Each for 3 years: Arm 1: omega 3 fish oil (1.65g/d EPA+DHA) Arm 2: soybean oil placebo (1.65g/d)
Outcomes	Primary: total cerebral white matter volume Secondary: biomarkers of endothelial health, total brain atrophy, medial temporal lobe atrophy, ventricular expansion, trail making test part B, digit symbol WAIS-R, cerebral blood flow, fractional anisotropy within frontal gyri
Starting date	Registered on Trials Registry: 24 Sept 2013 Study start date: May 2014 Study completion date est: March 2019
Contact information	Alena Borgatti, borgatti@ohsu.edu; James Dursch, dursch@ohsu.edu; Gene Bowman and Lynne Shinto (PIs), Oregon Health and Science University
Notes	NCT01953705

NAYAB Qurashi 2017 (53)

Study name	Minocycline and/or omega-3 fatty acids added to treatment as usual for at-risk mental states (NAYAB)
Methods	RCT (2x2)
Participants	People aged 16 to 35 years with at-risk mental state (ARM)
Interventions	Each for 6 months: Intervention: 1.2 g/day concentrated marine fish oil (2 capsules/d together providing 720 mg/d EPA & 480 mg/d DHA) Control: matched soft gel capsules, content unclear Both plus or minus minocycline tablet (2x2)
Outcomes	Primary: transition to psychotic disorder Secondary: severity of depression symptoms (Montgomery-Åsberg Depression Rating Scale, MADRS), ARMS symptoms, social and occupational function, cognitive scores, medication, adverse effects
Starting date	Registered on Trials Registry: October 2015 Study start date: October 2015 Study completion date est: December 2018
Contact information	Inti Qurashi, Manchester University, Inti.Qurashi@merseycare.nhs.uk
Notes	NCT02569307

Phosphatidylserine for Mild Cognitive Impairment

Study name	Investigating a phosphatidylserine based dietary approach for the management of mild cognitive impairment
Methods	RCT
Participants	People with mild cognitive impairment (MCI) aged 65 to 85 years
Interventions	Each for 24 months: Arm 1: phosphatidylserine omega 3 (DHA enriched) Arm 2: placebo cellulose capsules
Outcomes	Primary: selective reminding test (SRT) Secondary: mini mental state examination (MMSE), neurological battery test (NBT), dementia (DSM-4 criteria), mini sleep questionnaire (MSQ), Hamilton Anxiety rating scale (HAM-A), safety and adverse events
Starting date	Registered on Trials Registry: 6 Aug 2014 Study start date: Sept 2014 Study completion date est: Sept 2019
Contact information	Nadia Niemerzyanski, nadiaN@enzymotec.com; Yael Richter, yaelr@enzymotec.com
Notes	NCT02211560 Terminated due to difficulties in participant recruitment – not known whether results exist for those participating

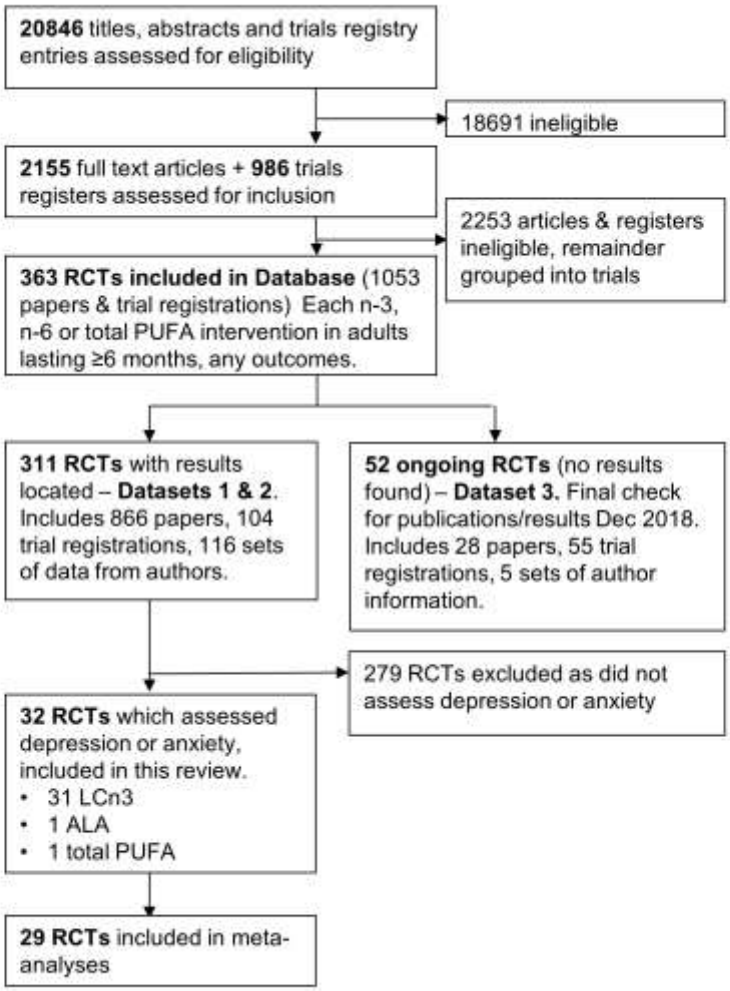
Stoll 2001

Study name	Omega 3 fatty acids in bipolar disorder prophylaxis
Methods	RCT
Participants	People aged 18 to 65 with bipolar disorder
Interventions	Each for 12 months: Arm 1: omega 3 Arm 2: placebo
Outcomes	Prophylactic efficacy
Starting date	Trial Registration entry: 2 Feb 2001 Trial start date: July 2000 Estimated study completion: July 2004
Contact information	Andrew Stoll, Mclean Hospital
Notes	NCT00010868 The PI, Andrew Stoll, appears to have been struck off the medical register in Massachusetts in 2011 (Commonwealth of Massachusetts Board of Registration in Medicine, Adjudicatory Case number 2011-026) so it has not been possible to contact him and no publication of results has been found

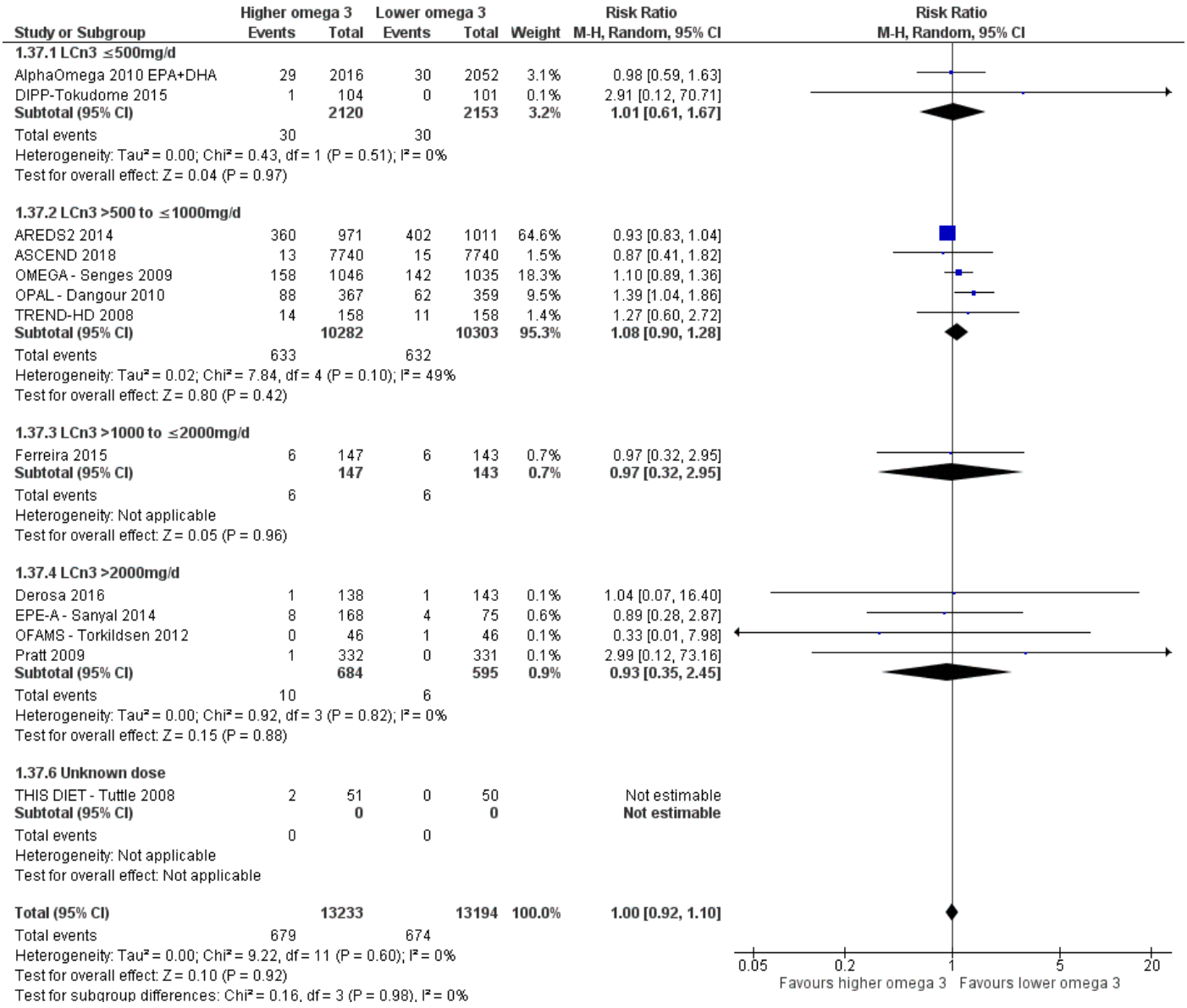
VITAL-DEP 2018 (54)

Study name	The VITamin D and OmegA-3 TriaL - Depression Endpoint Prevention (VITAL-DEP)
Methods	RCT
Participants	Multi-ethnic population of apparently healthy adults (men 50 years plus, women 55 years plus) without cancer, cardiovascular disease or depression at baseline
Interventions	Each for mean 5 years: Arm 1: omega 3 (Omacor fish oil, EPA+DHA 1g/d: 465mg EPA; 375mg DHA) and placebo

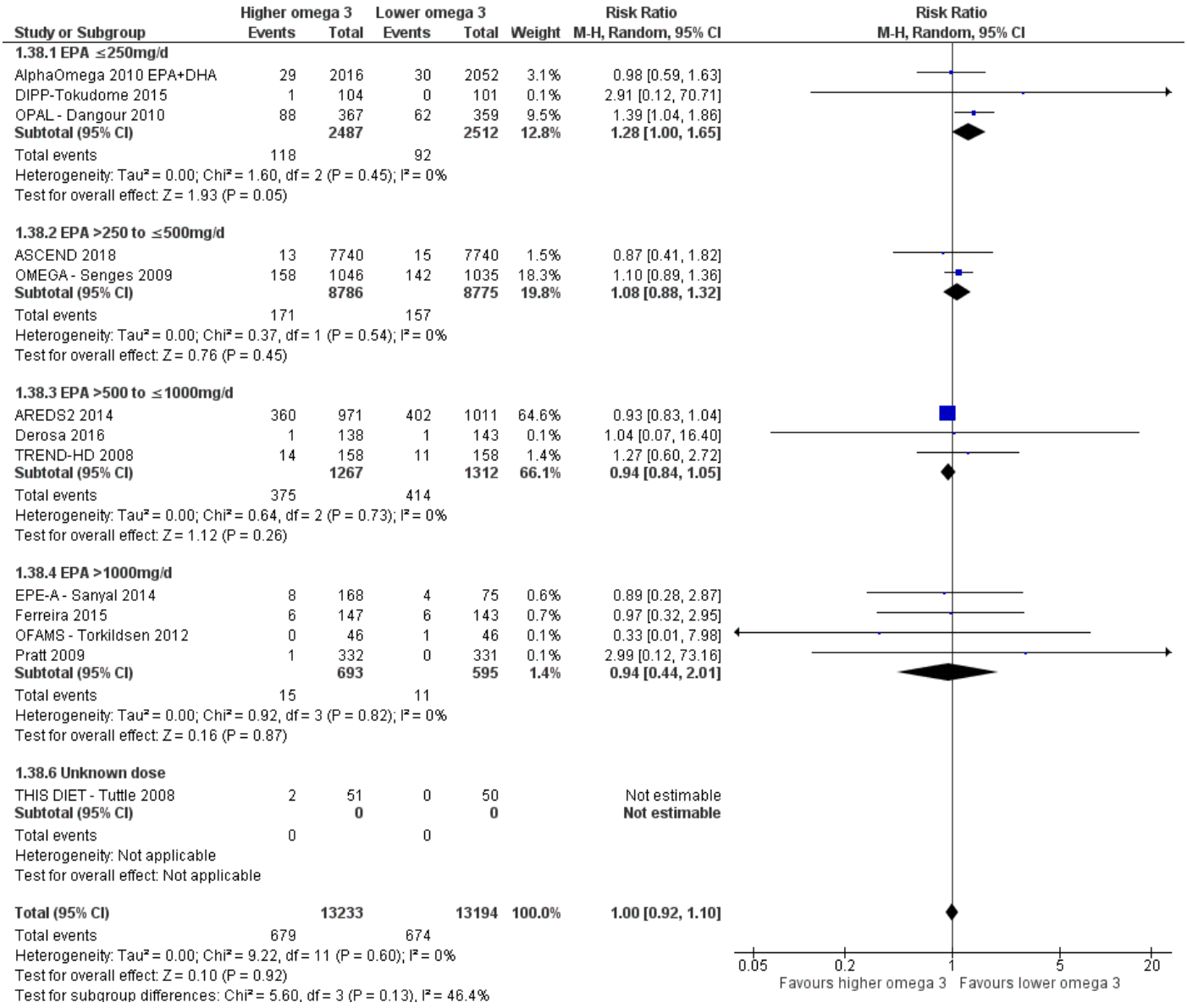
	Arm 2: placebo and vitamin D3 (1/d, 2000IU) Arm 3: omega 3 (Omacor fish oil, EPA+DHA 1g/d: 465mg EPA; 375mg DHA) and vitamin D3 (1/d, 2000IU) Arm 4: placebo and placebo
Outcomes	Patient Health Questionnaire 8 (PHQ8), other self-reported depression measures and health service use measures related to depression (plus additional measures in participants at high risk of depression)
Starting date	Trial Registration entry: 1 Oct 2012 Trial start date: July 2010 Estimated study completion: May 2020
Contact information	Olivia I. Okereke, MD, SM, Principal Investigator, Brigham and Women's Hospital, Brigham and Women's Hospital
Notes	NCT01696435



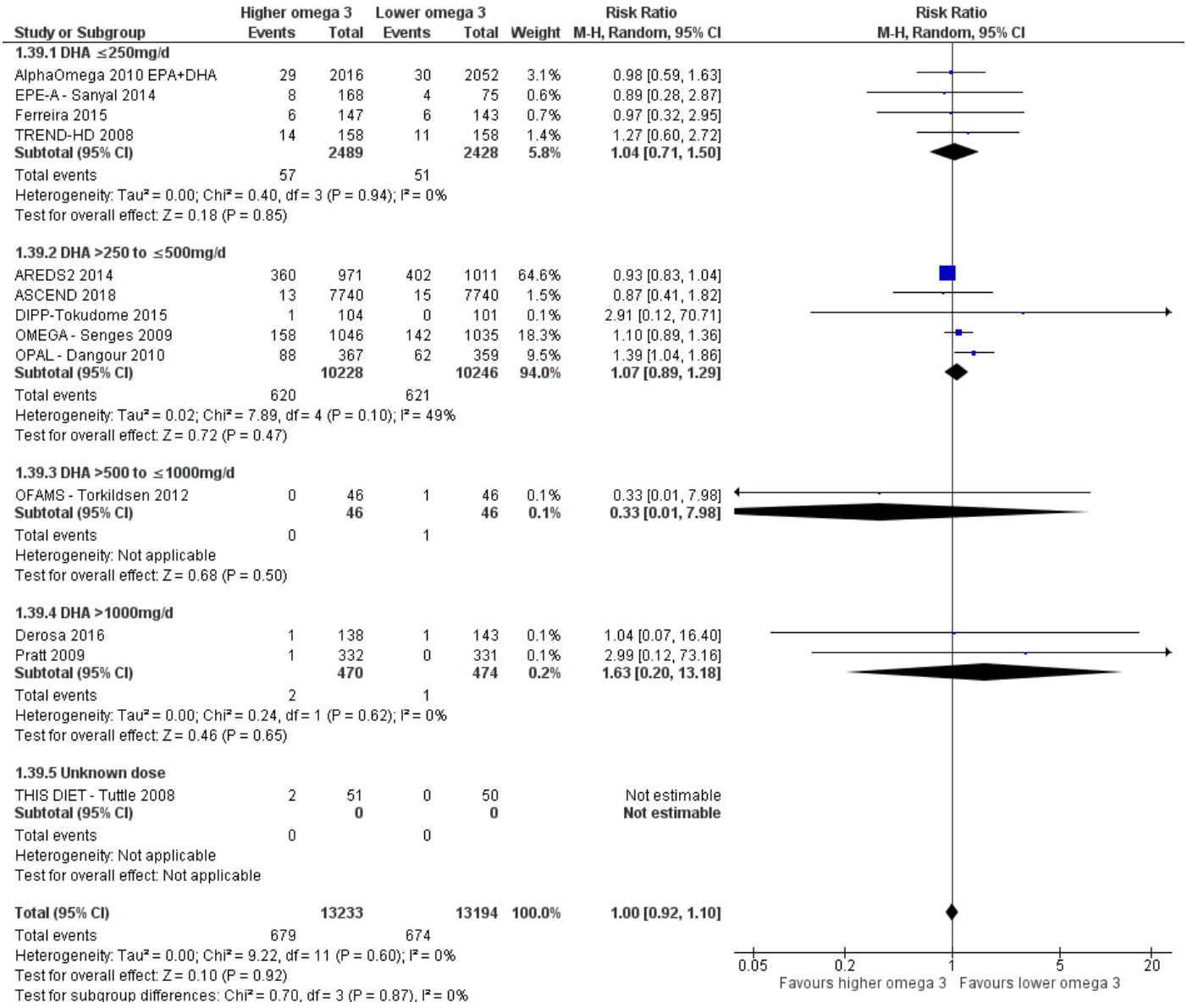
Supplementary Figure 1. Study flow diagram.



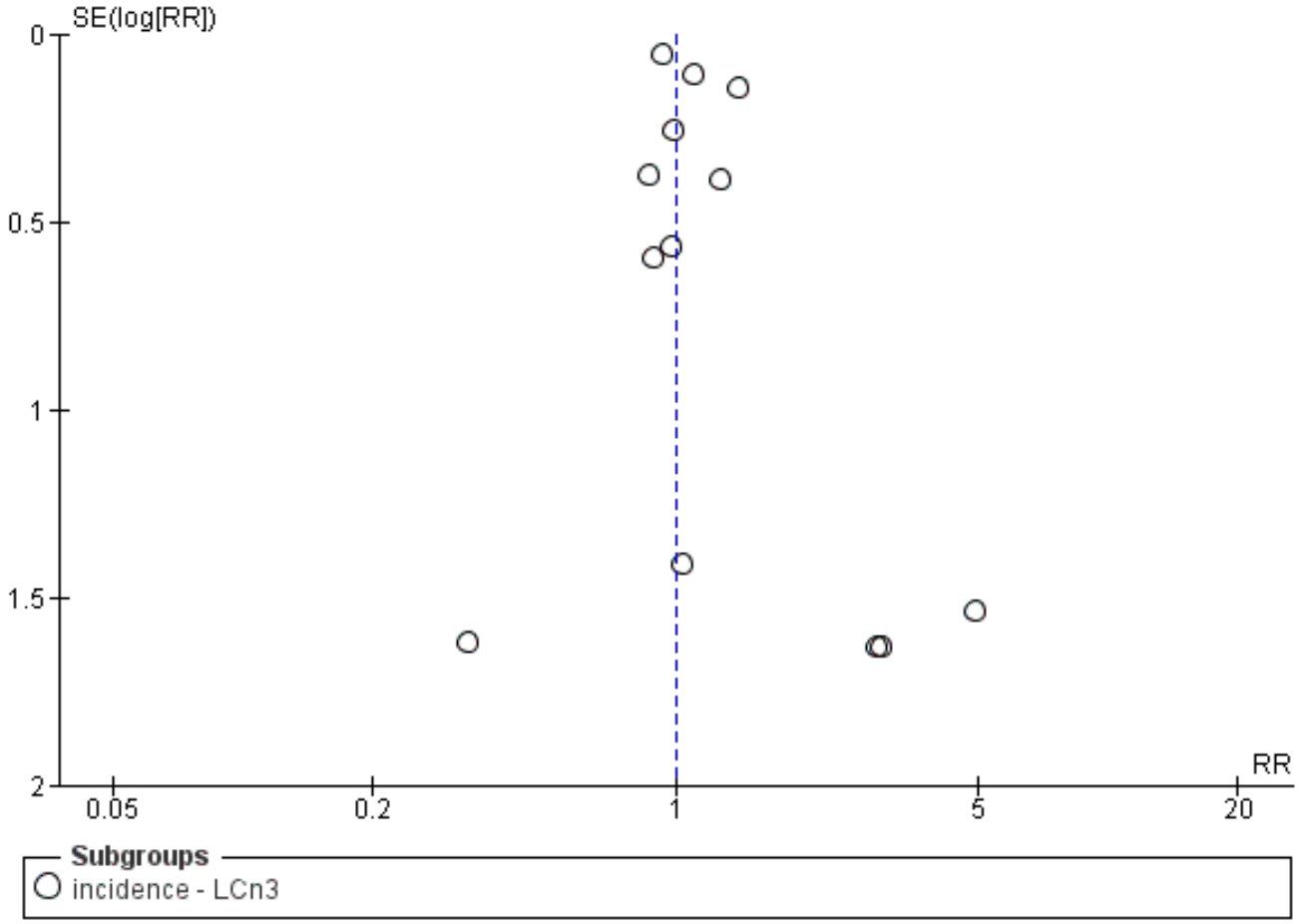
Supplementary Figure 2. Meta-analysis of effects of higher LCn3 vs lower LCn3 on risk of depression symptoms, sub-grouped by LCn3 dose.



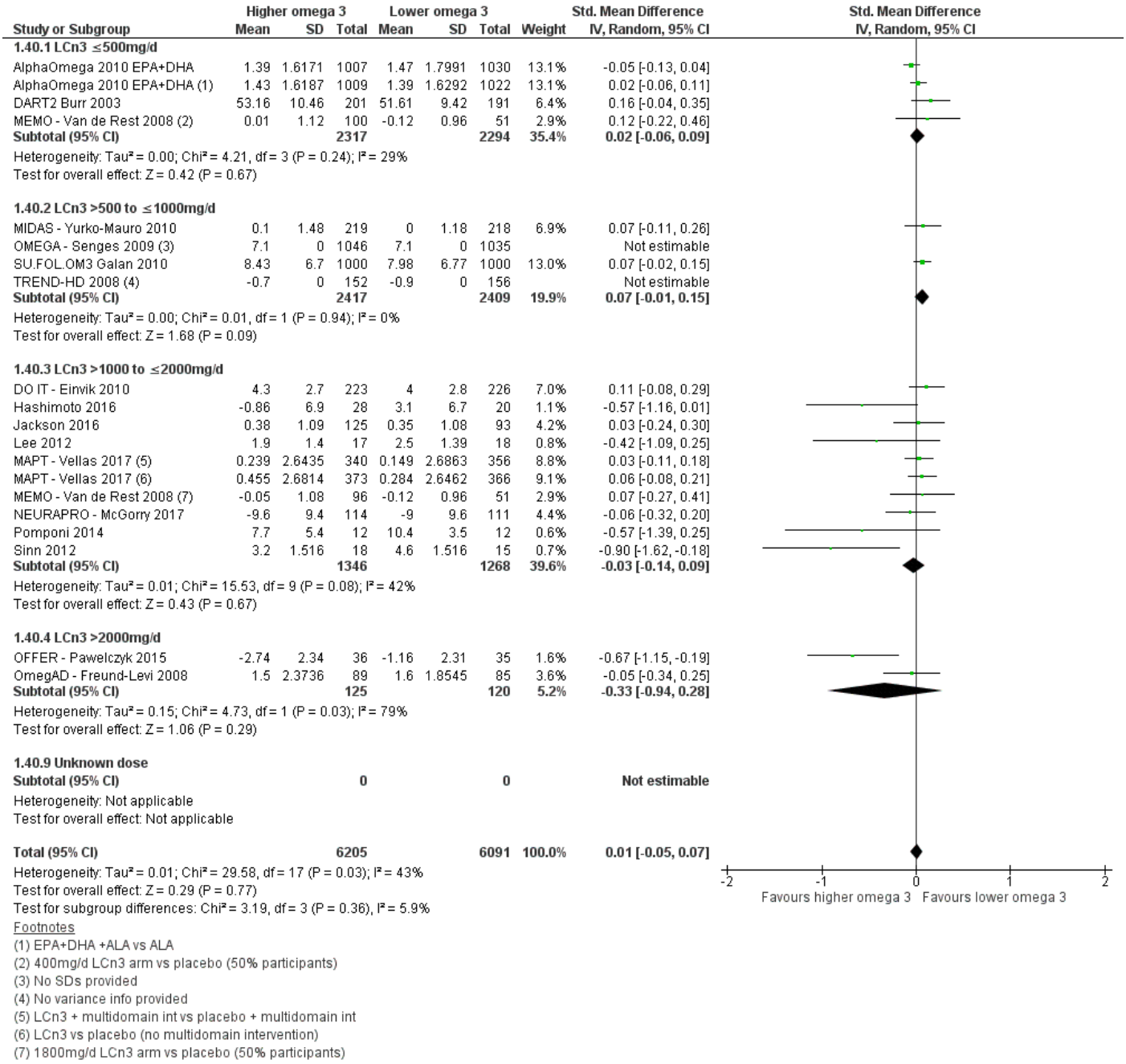
Supplementary Figure 3. Meta-analysis of effects of higher LCn3 vs lower LCn3 on risk of depression symptoms, sub-grouped by EPA dose.



Supplementary Figure 4. Meta-analysis of effects of higher LCn3 vs lower LCn3 on risk of depression symptoms, sub-grouped by DHA dose.



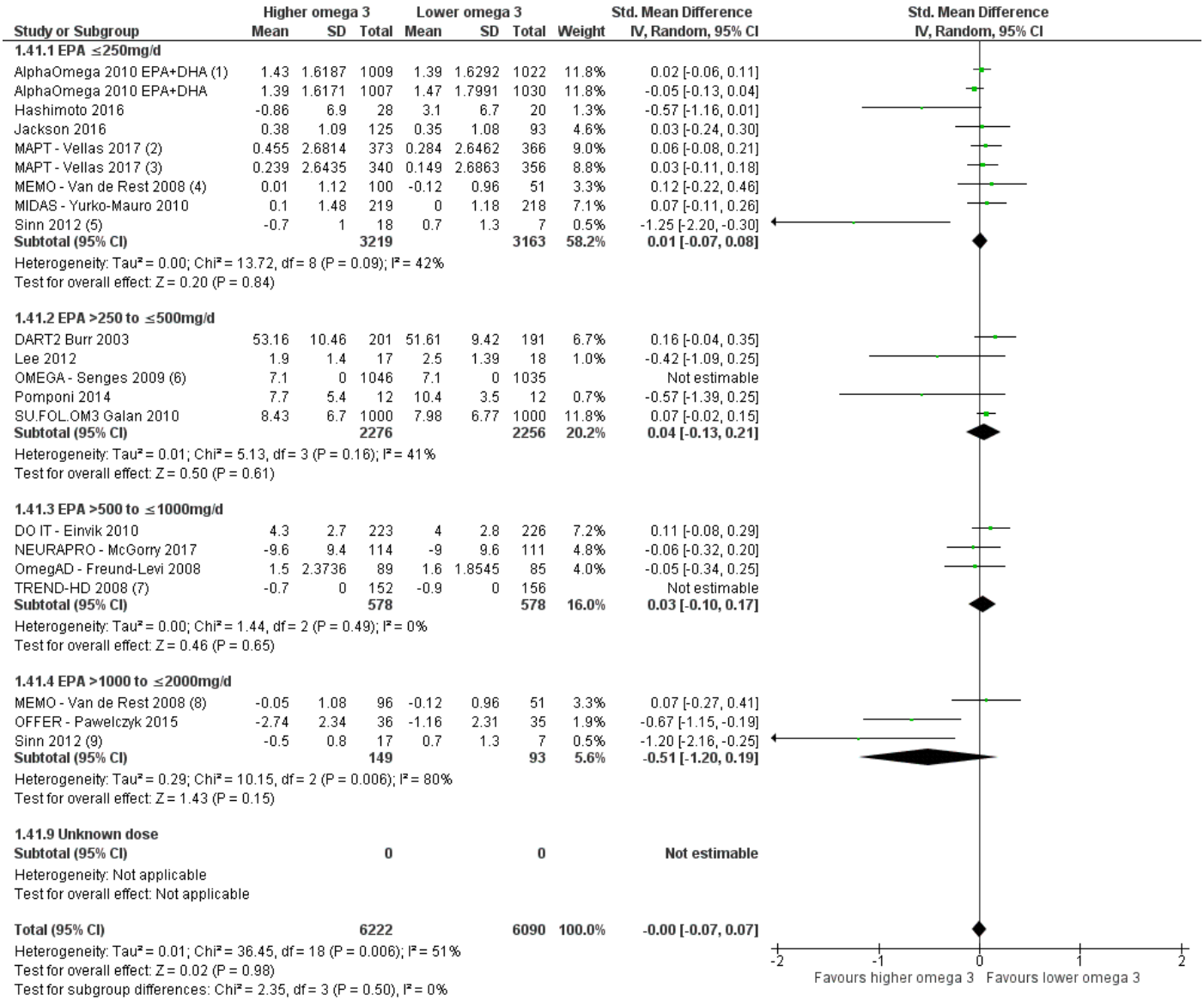
Supplementary Figure 5. Funnel plot of the analysis of effects of higher LCn3 vs lower LCn3 on risk of depression.



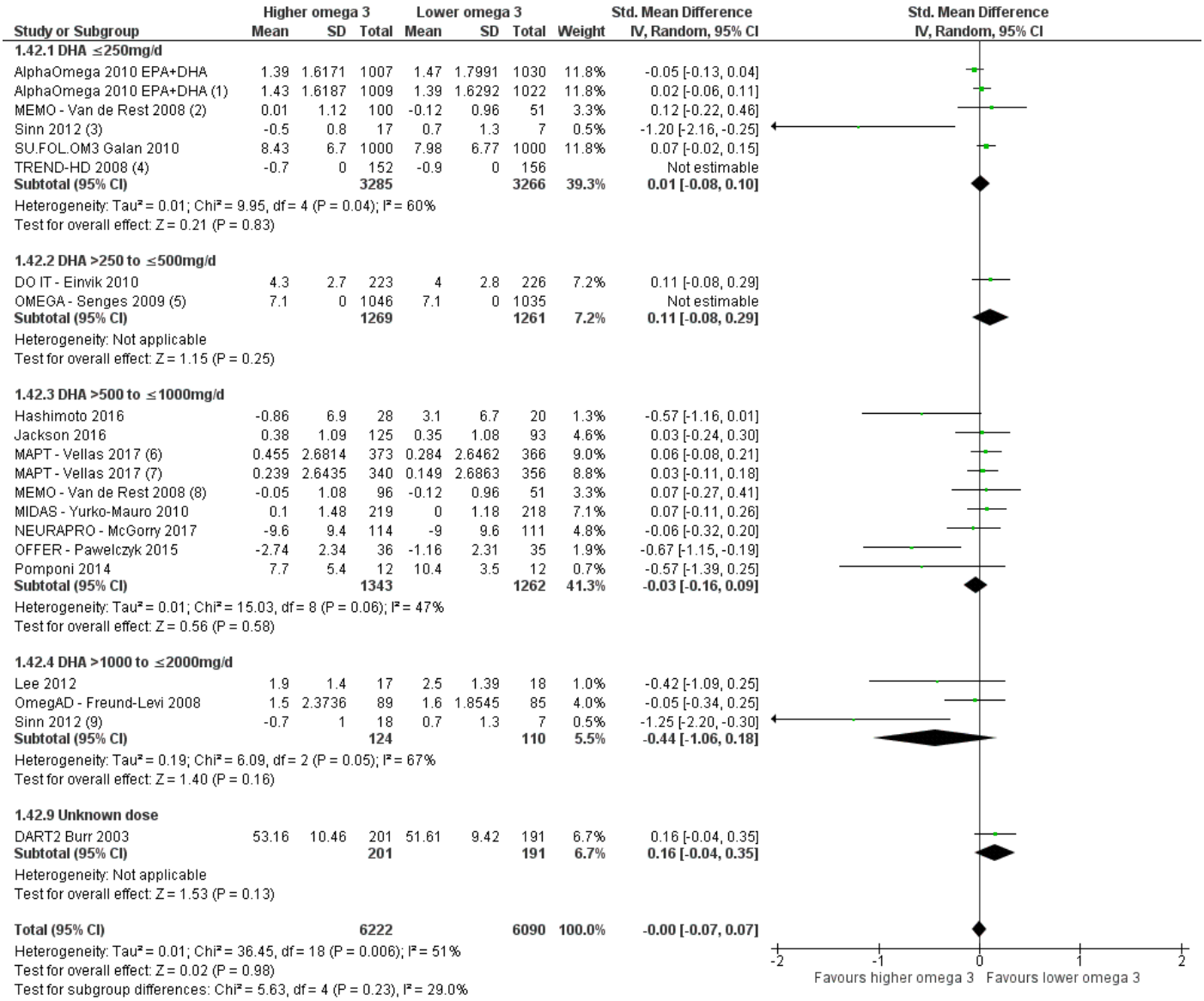
Footnotes

(1) EPA+DHA +ALA vs ALA
(2) 400mg/d LCn3 arm vs placebo (50% participants)
(3) No SDs provided
(4) No variance info provided
(5) LCn3 + multidomain int vs placebo + multidomain int
(6) LCn3 vs placebo (no multidomain intervention)
(7) 1800mg/d LCn3 arm vs placebo (50% participants)

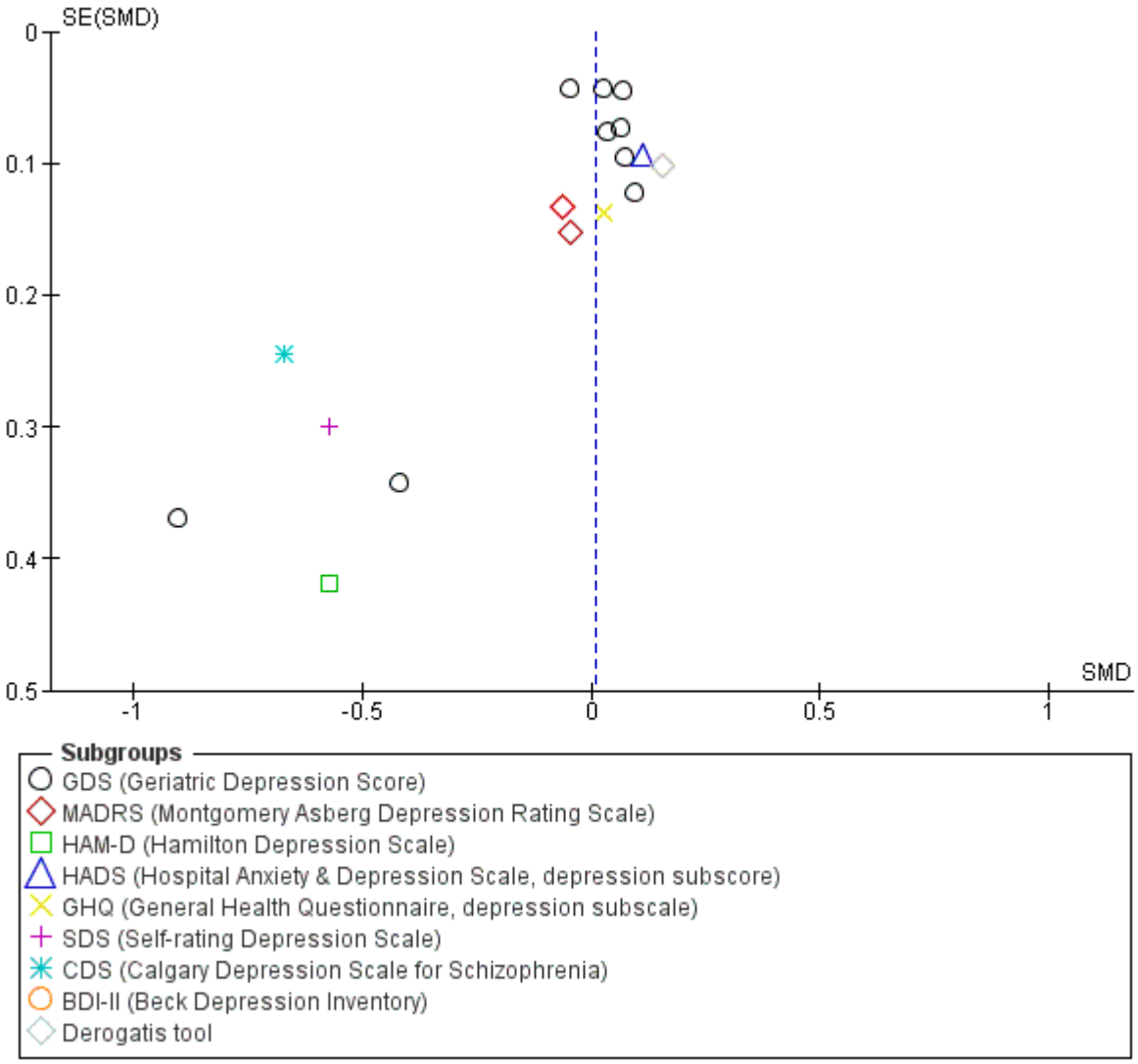
Supplementary Figure 6. Meta-analysis of effects of higher LCn3 vs lower LCn3 on depression symptoms, analysed using SMD, sub-grouped by LCn3 dose.



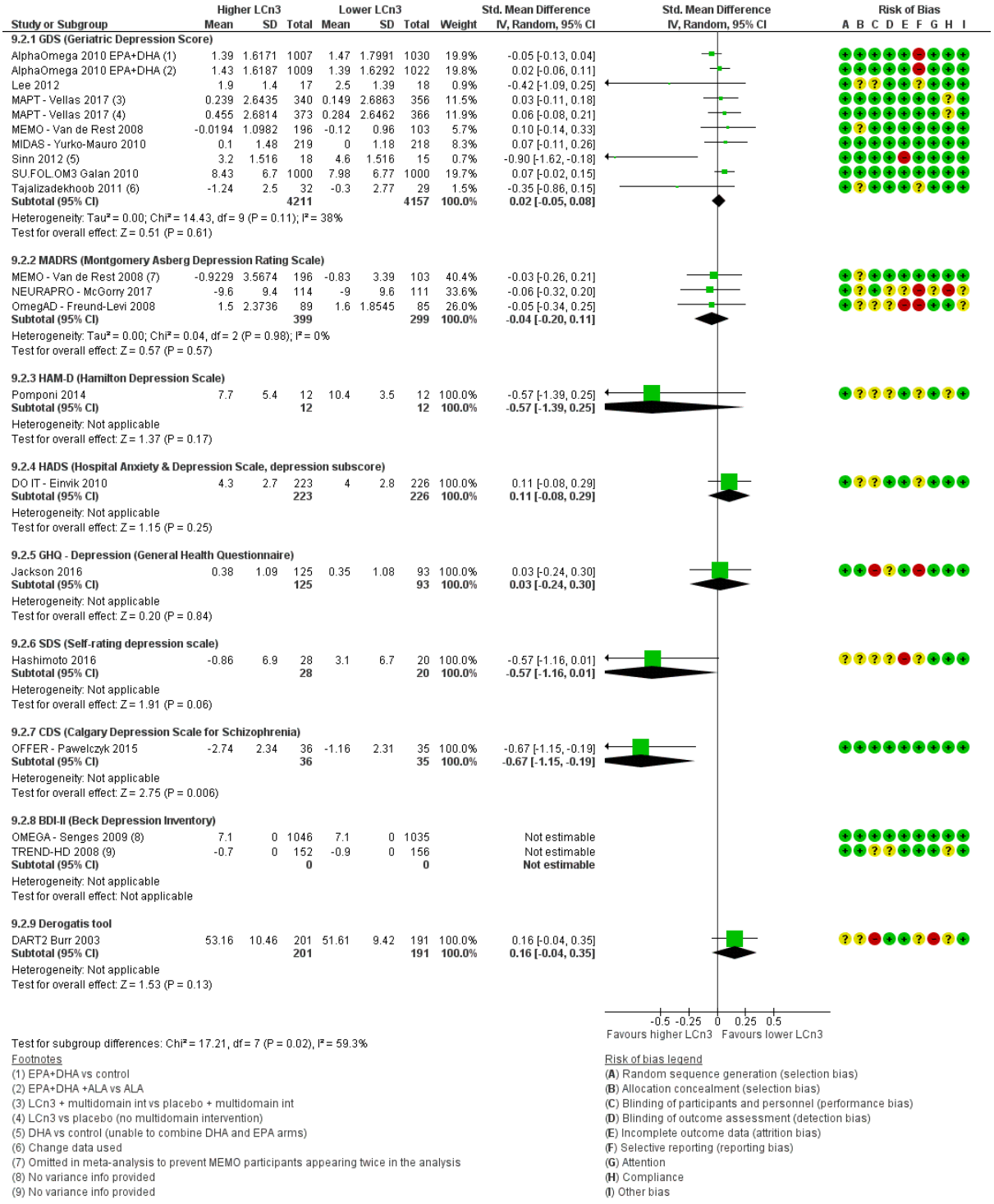
Supplementary Figure 7. Meta-analysis of effects of higher LCn3 vs lower LCn3 on depression symptoms, analysed using SMD, sub-grouped by EPA dose.



Supplementary Figure 8. Meta-analysis of effects of higher LCn3 vs lower LCn3 on depression symptoms, analysed using SMD, sub-grouped by DHA dose.



Supplementary Figure 9. Funnel plot of the analysis of effects of higher LCn3 vs lower LCn3 on depression symptoms, using SMD, sub-grouped by depression rating scale.



Supplementary Figure 10. Forest plot of trials randomising to higher vs lower LCn3 intake and assessing depression symptoms (on a continuous scale) in those without depression at baseline, subgrouping by scale and displayed in native scales. For meta-analysis data were combined using SMD (not shown, SMD 0.01, 95% CI -0.06 to 0.07, I^2 46%).

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