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

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## 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<sup>2</sup> 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<sup>2</sup> 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  $\geq 16(3)$ ), Becks Depression Inventory (BDI-II, score  $\geq 14(10)$ ) and General Health Questionnaire (GHQ-30,  $\geq 5(11)$ ). 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

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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  $\geq$ 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 of remission in depression is unclear as the evidence was of very low-graded 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<br>(test for<br>subgroup<br>differences) | SA or Subgroup  | Studies | Participants | <b>Effect Estimate (</b> Risk Ratio, M-H,<br>Random, 95% CI)* | ²,<br>% |
|--|---|---------|--------------|---|---------|
| Risk of  | Main  | 13      | 26528        | 1.01 [0.92, 1.10]   | 0       |
| depression<br>symptoms                           | Summary risk of bias (SA)                                   | 6       | 24618        | 1.05 [0.90, 1.22]   | 33      |
| symptoms   | Fixed effects (SA)  | 13      | 26528        | 1.02 [0.93, 1.12]<br>(Risk Ratio, M-H, Fixed, 95% CI)         | 0       |
|  | Compliance (SA)   | 5       | 7210         | 1.16 [0.99, 1.36]   | 0       |
|  | Larger trials (≥100<br>randomised, SA)                      | 12      | 26436        | 1.01 [0.92, 1.10]   | 0       |
| Intervention                                     | Dietary advice  | 1       | 101          | 4.90 [0.24, 99.66]  | -       |
| type,  | Supplemental foods  | 1       | 4068         | 0.98 [0.59, 1.63]   | -       |
| subgrouping<br>(p=0.68)                          | Supplement or capsule                                       | 10      | 22154        | 1.00 [0.92, 1.10]   | 0       |
| (p 0.00)   | Any combination   | 1       | 205          | 2.91 [0.12, 70.71]  | -       |
| Replacement,                                     | n3 vs SFA   | 0       | 0            | Not estimable   | -       |
| subgrouping                                      | n3 vs MUFA  | 5       | 22456        | 1.16 [0.99, 1.36]   | 0       |
| (p=0.10)   | 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,  | LCn3 ≤150mg/d   | 0       | 0            | Not estimable   | -       |
| subgroup   | LCn3 >150 to ≤250mg/d                                       | 0       | 0            | Not estimable   | -       |
| (p=0.68)   | 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,  | Duration 6 to <12 months                                    | 4       | 1361         | 1.15 [0.63, 2.11]   | 0       |
| subgroup   | Duration 12 to <24 months                                   | 4       | 3331         | 1.18 [1.00, 1.40]   | 0       |
| (p=0.12)   | 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<br>risk, subgroup                     | Previous or current<br>depression                           | 0       | 0            | Not estimable   | -       |
| (p=0.03)   | Other serious illness                                       | 10      | 25278        | 0.97 [0.88, 1.07]   | 0       |
|  | Healthy   | 3       | 1250         | 1.35 [1.02, 1.79]   | 0       |
| Antidepressant                                   | antidepressants used  | 0       | 0            | Not estimable   | -       |
| use, subgroup                                    | no antidepressant use                                       | 13      | 26528        | 1.01 [0.92, 1.10]   | 0       |
| <b>Depression</b><br>severity<br>(participants   | Main, assessed using GDS<br>(Geriatric Depression<br>Score) | 1       | 61           | -0.94 [-2.27, 0.39]<br>MD (IV, Random, 95% CI)                | -       |
| have<br>depression at                            | Low summary risk of bias<br>(SA)                            | 0       | 0            | Not estimable   | -       |
| baseline)  | Fixed effects (SA)  | 1       | 61           | -0.94 [-2.27, 0.39]<br>MD (IV, Random, 95% CI)                | -       |
|  | Compliance (SA)   | 1       | 61           | -0.94 [-2.27, 0.39]<br>MD (IV, Random, 95% CI)                | -       |

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

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

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

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

|   | Anticipat  | ed absolute                    |                                |                               |   |   |  |
|---|--|--------------------------------|--------------------------------|-------------------------------|---|---|--|
|   |  | * (95% CI)                     |                                | Nº of                         | Certainty of                            |   |  |
| Outcomes  | Risk with<br>low LCn3<br>(primary<br>outcomes<br>) | Risk with<br>High LCn3         | Relative<br>effect<br>(95% CI) | participa<br>nts<br>(studies) | the<br>evidence<br>(GRADE)              | Comments  |  |
| Risk of anxiety<br>symptoms   | 1 per<br>1,000                                     | <b>1 per 1,000</b><br>(0 to 2) | <b>RR 1.00</b> (0.32 to 3.10)  | 15480<br>(1 RCT)              | ⊕◯◯◯<br>VERY<br>LOW º,p,q               | The effect of increasing<br>LCn3 on anxiety<br>incidence is unclear as<br>the evidence is of very<br>low quality. Downgraded<br>once for indirectness and<br>twice for imprecision. |  |
| Anxiety severity<br>(in those with<br>anxiety at<br>baseline)       | Not pooled   | Not pooled                     | not<br>pooled                  | (0 RCTs)                      | -                                       | We found no studies that<br>assessed effects of LCn3<br>on severity of anxiety in<br>those with anxiety at<br>baseline.   |  |
| Anxiety<br>remission (50%<br>reduction)                             | not pooled   | not pooled                     | not<br>pooled                  | (0 RCTs)                      | -                                       | We found no studies that assessed effects of LCn3 on anxiety remission.   |  |
| Anxiety<br>symptoms (in<br>those without<br>anxiety at<br>baseline) | -  | -                              | -                              | 1378<br>(5 RCTs)              | ⊕⊕⊕⊖<br>MODERAT<br>E <sup>b,r,s,t</sup> | Increasing LCn3 probably<br>has little or no effect on<br>anxiety symptoms in<br>those without anxiety at<br>baseline. Downgraded<br>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. I. 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,<br>Random, 95% CI)* |
|--------------------------------|--|---------|--------------|---|
| Risk of                        | Main                                   | 1       | 4068         | 1.11 [0.67, 1.84]                                     |
| depression                     | Summary risk of bias (SA)              | 1       | 4068         | 1.11 [0.67, 1.84]                                     |
| symptoms                       | Fixed effects (SA)                     | 1       | 4068         | 1.11 [0.67, 1.84]<br>(Risk Ratio, M-H, Fixed, 95% CI) |
|                                | Compliance (SA)                        | 1       | 4068         | 1.11 [0.67, 1.84]                                     |
|                                | Larger trials (≥100<br>randomised, SA) | 1       | 4068         | 1.11 [0.67, 1.84]                                     |
| Depression<br>symptoms (in     | Main, GDS                              | 1       | 4068         | -0.02 [-0.14, 0.10]<br>MD (IV, Random, 95% CI)        |
| those without<br>depression at | Summary risk of bias (SA)              | 1       | 4068         | -0.02 [-0.14, 0.10]<br>MD (IV, Random, 95% CI)        |
| baseline)                      | Fixed effects (SA)                     | 1       | 4068         | -0.02 [-0.12, 0.09]<br>MD (IV, Fixed, 95% CI)         |
|                                | Compliance (SA)                        | 1       | 4068         | -0.02 [-0.14, 0.10]<br>MD (IV, Random, 95% CI)        |
|                                | Larger trials (≥100<br>randomised, SA) | 1       | 4068         | -0.02 [-0.14, 0.10]<br>MD (IV, Random, 95% CI)        |
| Depression<br>remission        | Main                                   | 0       | 0            | Not estimable   |
| Risk of anxiety<br>symptoms    | Symptomatic                            | 0       | 0            | Not estimable   |
| Anxiety<br>symptoms            |  | 0       | 0            | Not estimable   |
| Anxiety<br>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,<br>Random, 95% CI)* |
|---|--|---------|--------------|---|
| Risk of   | Main                                   | 1       | 2739         | 0.75 [0.54, 1.03]                                     |
| depression  | Summary risk of bias (SA)              | 0       | 0            | Not estimable   |
| symptoms  | Fixed effects (SA)                     | 1       | 2739         | 0.75 [0.54, 1.03]<br>(Risk Ratio, M-H, Fixed, 95% CI) |
|   | Compliance (SA)                        | 0       | 0            | Not estimable   |
|   | Larger trials (≥100<br>randomised, SA) | 1       | 2739         | 0.75 [0.54, 1.03]                                     |
| Depression<br>symptoms (in<br>those without<br>depression at<br>baseline) | Main                                   | 0       | 0            | Not estimable   |
| Depression<br>remission   | Main                                   | 0       | 0            | Not estimable   |
| Risk of anxiety<br>symptoms   | Symptomatic                            | 0       | 0            | Not estimable   |
| Anxiety<br>symptoms   | Main                                   | 0       | 0            | Not estimable   |
| Anxiety<br>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<br>absolute<br>effects <sup>*</sup> (95%<br>CI) |  | Relative<br>effect<br>(95%<br>CI)             | № of<br>participants<br>(studies) | Certainty<br>of the<br>evidence<br>(GRADE) | Comments  |
|---|---|--|---|-----------------------------------|--|---|
|   | Risk<br>with<br>lower<br>total<br>PUFA                      | Risk<br>with<br>higher<br>total<br>PUFA        |   |                                   |  |   |
| Risk of<br>depression<br>symptoms   | 61<br>per<br>1,000  | <b>46 per</b><br><b>1,000</b><br>(33 to<br>63) | <b>RR</b><br><b>0.75</b><br>(0.54 to<br>1.03) | 2739<br>(1 RCT)                   | ⊕○○○<br>VERY<br>LOW abc                    | We are uncertain of the effect of<br>increasing total PUFA as the<br>evidence is of very low-quality.<br>Downgraded once each for risk of<br>bias, inconsistency and<br>indirectness. |
| Depression<br>severity  |   |  | -   | (0 RCTs)                          | -  | No RCTs assessed this outcome.  |
| Depression<br>remission (50%<br>reduction)  |   |  |   | (0 RCTs)                          | -  | No RCTs assessed this outcome.  |
| <b>Depression</b><br><b>symptoms</b> (in<br>those without<br>depression at<br>baseline) |   |  |   | (0 RCTs)                          | -  | No RCTs assessed this outcome.  |
| Risk of anxiety<br>symptoms   |   |  |   | (0 RCTs)                          | -  | No RCTs assessed this outcome.  |
| Anxiety severity  |   | -  | -   | (0 RCTs)                          | -  | No RCTs assessed this outcome.  |
| <b>Anxiety remission</b> (50% reduction)  |   |  |   | (0 RCTs)                          | -  | No RCTs assessed this outcome.  |
| Anxiety<br>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<br>absolute<br>effects <sup>*</sup> (95%<br>CI) |   | solute effect participant<br>fects* (95% (95% (studies) | participants | <br>Comments |
|----------|---|---|---|--------------|--------------|
|          | with N<br>lower l   | Risk<br>with<br>higher<br>total<br>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<br>effects <sup>*</sup> (95% CI)   |   | Relative<br>effect<br>(95%                    | Nº of<br>participants | Certainty<br>of the        | Comments  |
|  | Risk<br>with<br>Iower<br>ALA                            | Risk with<br>Higher ALA   | (95%<br>CI)                                   | (studies)             | evidence<br>(GRADE)        |   |
| Risk of<br>depression<br>symptoms  | 14 per<br>1,000   | <b>15 per 1,000</b><br>(9 to 25)  | <b>RR</b><br><b>1.11</b><br>(0.67 to<br>1.84) | 4068<br>(1 RCT)       | ⊕⊕⊖⊖<br>LOW ª              | Increasing ALA may<br>increase the risk of<br>diagnosis of depression very<br>slightly, NNH 1000.<br>Downgraded twice for<br>imprecision. |
| <b>Depression</b><br><b>severity</b> in<br>those with<br>depression at<br>baseline   | not<br>pooled   | -   |   | (0 RCTs)              | -                          | No RCTs assessed this outcome.  |
| Depression<br>remission<br>(50% reduction)   | not<br>pooled   | not pooled  | not<br>pooled                                 | (0 RCTs)              | -                          | No RCTs assessed this outcome.  |
| Depression<br>symptoms (in<br>those without<br>depression at<br>baseline) -<br>assessed with<br>GDS (Geriatric<br>Depression<br>Scale) | The<br>mean<br>GDS at<br>baseline<br>was<br><b>1.49</b> | The mean<br>GDS in the<br>intervention<br>group was -<br>0.02 lower<br>(0.14 lower to<br>0.10 higher) | -   | 4068<br>(1 RCT)       | ⊕⊕⊖⊖<br>LOW <sup>b,c</sup> | Increasing ALA may have<br>little or no effect on<br>depression symptoms.<br>Downgraded for imprecision<br>and risk of bias.              |
| Risk of<br>anxiety<br>symptoms   | not<br>pooled   | not pooled  | not<br>pooled                                 | (0 RCTs)              | -                          | No RCTs assessed this outcome.  |
| Anxiety<br>severity in<br>those with<br>anxiety at<br>baseline   | not<br>pooled   | -   | -   | (0 RCTs)              | -                          | No RCTs assessed this outcome.  |
| Anxiety<br>remission<br>(50% reduction)  | not<br>pooled   | not pooled  | not<br>pooled                                 | (0 RCTs)              | -                          | No RCTs assessed this outcome.  |
| Anxiety<br>symptoms in<br>those without<br>anxiety at<br>baseline  | not<br>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

| effects <sup>*</sup> (95% CI) |                         |             | participants | of the              | Comments |
|-------------------------------|-------------------------|-------------|--------------|---------------------|----------|
| Risk<br>with<br>Iower<br>ALA  | Risk with<br>Higher ALA | (95%<br>CI) | (studies)    | evidence<br>(GRADE) |          |

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

|                                      | Bleeding                             | 4  | 3290 | Risk Ratio (M-H,<br>Random, 95% CI) | 1.35 [0.82, 2.20] |
|--------------------------------------|--------------------------------------|----|------|-------------------------------------|-------------------|
|                                      | Skin problems<br>(itching, rashes)   |    | 6831 | Risk Ratio (M-H,<br>Random, 95% CI) | 0.80 [0.49, 1.32] |
|                                      | Infections                           | 2  | 2905 | Risk Ratio (M-H,<br>Random, 95% CI) | 0.90 [0.77, 1.06] |
|                                      | Brain and<br>Nervous<br>System       | 6  | 3834 | Risk Ratio (M-H,<br>Random, 95% CI) | 0.97 [0.80, 1.17] |
|                                      | Headache or<br>worsening<br>migraine | 3  | 651  | Risk Ratio (M-H,<br>Random, 95% CI) | 0.77 [0.33, 1.82] |
|                                      | Insomnia or<br>fatigue               | 3  | 712  | Risk Ratio (M-H,<br>Random, 95% CI) | 1.11 [0.71, 1.73] |
|                                      | Sense organs                         | 2  | 2905 | Risk Ratio (M-H,<br>Random, 95% CI) | 0.96 [0.70, 1.31] |
|                                      | Hormonal                             | 2  | 2385 | Risk Ratio (M-H,<br>Random, 95% CI) | 1.11 [0.73, 1.70] |
| Drop outs                            |                                      | 11 | 5654 | Risk Ratio (M-H,<br>Random, 95% CI) | 0.94 [0.82, 1.09] |
| Dropouts due<br>to adverse<br>events |                                      | 6  | 4976 | Risk Ratio (M-H,<br>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       |              | Risk Ratio (M-H,<br>Random, 95% CI) | 0.93 [0.38, 2.28] |
| Dropouts due to adverse events   | 1       |              | Risk Ratio (M-H,<br>Random, 95% CI) | 0.89 [0.47, 1.65] |

### 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)<br>who initially participated in the first Beyond Ageing Project  |
| Interventions       | Each for 12 months:<br>Arm 1: omega-3 (4 capsules, total 2g/d: 1200mg EPA and 800mg DHA) and<br>placebo microcrystalline cellulose (1 capsule)<br>Arm 2: paraffin oil placebo (4 capsules) and sertraline hydrochloride (1 capsule,<br>50mg)<br>Arm 3: paraffin oil placebo (4 capsules) and placebo microcrystalline cellulose (1<br>capsule) |
| Outcomes            | Primary: depressive symptoms (PHQ-9)<br>Secondary: cognitive decline, MMSE, brain metabolism, hippocampal volume,<br>anxiety (GAD-7), disability (WHODAS-II), sleeping problems (PSQI), exercise<br>(Active Australian Survey)   |
| Starting date       | Registered on Trials Registry: 12 Jan 2010<br>Study start date: June 2011<br>Study completion date est: Main results expected in 2017  |
| Contact information | Ian Hickie (PI), Brain and Mind Centre, University of Sydney,<br>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<br>disease and depressive symptoms (Center for Epidemiological Studies<br>Depression Scale, CES-D) and low fish/fish oil intakes.   |
| Interventions | Intervention: Four 1 gram capsules of eicosapentaenoic acid (EPA)-rich fish oil<br>per day for 6 months. Each capsule will contain 500mg of eicosapentaenoic acid<br>(EPA) and 25 mg of docosahexaenoic acid (DHA).<br>Placebo: Four 1 gram capsules of soybean/corn oil per day for 6 months. Each<br>capsule will contain 500mg of soybean oil and 500 mg of corn oil. |
| Outcomes      | Primary: Depression (Hamilton Rating Scale For Depression)<br>Secondary: Quality of Life (Short Form (SF)-36)<br>Angina frequency (Seattle Angina Questionnaire)<br>Degree of change in vasodilator function assessed by flow mediated dilatation<br>(FMD) in the brachial artery<br>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,<br>Nutrition and Activity, Sansom Institute for Health Research, University of South<br>Australia, PO Box 2471, Adelaide, South Australia. <u>Alison.coates@unisa.edu.au</u> |
|---------------------|---|
| Notes               | ACTRN12608000598381<br>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<br>eicosapentanoic acid (20:5n-3), 400 mg of docosahexanoic acid (22:6n-3),<br>tertiary-butylhydroquinone 0.2 mg/g and tocopherols 2 mg/g.<br>Placebo: three identical capsules per day. All capsules included olive oil. |
| Outcomes            | Recurrence of depression<br>Change of cognitive function   |
| Starting date       | Study start date: May 2007<br>Study Completion Date: September 2010  |
| Contact information | Chih-Chiang Chiu, Department of Psychiatry, Taipei City Psychiatric Center,<br>Taipei City Hospital, No. 309, Sungde Road, Taipei 110, Taiwan.<br>Email: eric.ccchiu@gmail.com   |
| Notes               | NCT01235533  |

### DO Health

| Study name    | Vitamin D3- Omega3- Home Exercise- Healthy Ageing and Lengevity Trial (DO-<br>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:<br>Arm 1: omega 3 (1g/d, ratio EPA:DHA = 1:2) and vitamin D3 (2000 IU/d)<br>capsules and strength home exercise (3x30 mins/week)<br>Arm 2: omega 3 (1g/d, ratio EPA:DHA = 1:2) and vitamin D3 (2000 IU/d)<br>capsules and flexibility home exercise (3x30 mins/week)<br>Arm 3: omega 3 (1g/d, ratio EPA:DHA = 1:2) and placebo capsules and strength<br>home exercise (3x30 mins/week)<br>Arm 4: omega 3 (1g/d, ratio EPA:DHA = 1:2) and placebo capsules and<br>flexibility home exercise (3x30 mins/week)<br>Arm 5: placebo and vitamin D3 (2000 IU/d) capsules and strength home<br>exercise (3x30 mins/week)<br>Arm 6: placebo and vitamin D3 (2000 IU/d) capsules and flexibility home<br>exercise (3x30 mins/week)<br>Arm 7: placebo and placebo capsules and strength home exercise (3x30 mins/week)<br>Arm 7: placebo and placebo capsules and strength home exercise (3x30 mins/week)<br>Arm 8: placebo and placebo capsules and flexibility home exercise (3x30 mins/week) |

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

### InTrePad

| Study name          | Intervention of Testosterone & Fish Oil for the Prevention of Alzheimer's<br>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:<br>Arm 1: DHA capsules (1720mg/d) and testosterone undecanoate (intramuscular<br>injection 1000mg/4ml every 8 weeks)<br>Arm 2: placebo DHA and testosterone undecanoate (intramuscular injection<br>1000mg/4ml every 8 weeks)<br>Arm 3: placebo DHA and placebo testosterone       |
| Outcomes            | Primary: PiB score<br>Secondary: neuropsychological, mood and daily functioning questionnaires,<br>beta amyloid levels, fluorodeoxyglucose to assess brain glucose metabolism,<br>inflammatory and oxidative biomarkers, hippocampal volume, quality of life,<br>safety and tolerability of treatment |
| Starting date       | Registered on Trials Registry: 14 Jan 2013<br>Study start date: 28 Feb 2013<br>Study completion date est: unclear   |
| Contact information | Ralph Martins (PI), Sir James McCusker Alzheimer's Disease Research Unit,<br>Hollywood Medical Centre, Nedlands, Australia, r.martins@ecu.edu.au  |
| Notes               | ACTRN12613000034730<br>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<br>Cont: 200ml juice drink without omega 3 (no fish taste in either) |
| Outcomes      | Primary: transition to psychosis<br>Secondary: fatty acid changes   |
| Starting date | Registered on Trials Registry: 25 July 2016   |
|               | Supplementary file for Deane et al, PUFA for depression, page 24  |

|                     | 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<br>Methods | n-3 PUFA for Vascular Cognitive Aging<br>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:<br>Arm 1: omega 3 fish oil (1.65g/d EPA+DHA)<br>Arm 2: soybean oil placebo (1.65g/d)  |
| Outcomes              | Primary: total cerebral white matter volume<br>Secondary: biomarkers of endothelial health, total brain atrophy, medial<br>temporal lobe atrophy, ventricular expansion, trail making test part B, digit<br>symbol WAIS-R, cerebral blood flow, fractional anisotropy within frontal gyri |
| Starting date         | Registered on Trials Registry: 24 Sept 2013<br>Study start date: May 2014<br>Study completion date est: March 2019  |
| Contact information   | Alena Borgatti, borgatti@ohsu.edu; James Dursch, dursch@ohsu.edu; Gene<br>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:<br>Intervention: 1.2 g/day concentrated marine fish oil (2 capsules/d together<br>providing 720 mg/d EPA & 480 mg/d DHA)<br>Control: matched soft gel capsules, content unclear<br>Both plus or minus minocycline tablet (2x2) |
| Outcomes                     | Primary: transition to psychotic disorder<br>Secondary: severity of depression symptoms (Montgomery-Åsberg Depression<br>Rating Scale, MADRS), ARMS symptoms, social and occupational function,<br>cognitive scores, medication, adverse effects  |
| Starting date                | Registered on Trials Registry: October 2015<br>Study start date: October 2015<br>Study completion date est: December 2018   |
| Contact information<br>Notes | Inti Qurashi, Manchester University, Inti.Qurashi@merseycare.nhs.uk<br>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:<br>Arm 1: phosphatidylserine omega 3 (DHA enriched)<br>Arm 2: placebo cellulose capsules   |
| Outcomes            | Primary: selective reminding test (SRT)<br>Secondary: mini mental state examination (MMSE), neurological battery test<br>(NBT), dementia (DSM-4 criteria), mini sleep questionnaire (MSQ), Hamilton<br>Anxiety rating scale (HAM-A), safety and adverse events |
| Starting date       | Registered on Trials Registry: 6 Aug 2014<br>Study start date: Sept 2014<br>Study completion date est: Sept 2019   |
| Contact information | Nadia Niemerzyanski, nadiaN@enzymotec.com; Yael Richter,<br>yaelr@enzymotec.com  |
| Notes               | NCT02211560<br>Terminated due to difficulties in participant recruitment – not known whether results exist for those participating   |

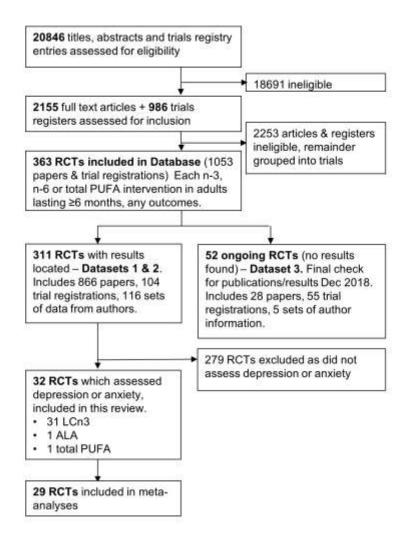
### Stoll 2001

| Study name<br>Methods      | Omega 3 fatty acids in bipolar disorder prophylaxis<br>RCT   |  |  |  |  |  |  |  |  |  |
|----------------------------|--|--|--|--|--|--|--|--|--|--|
| Participants               | People aged 18 to 65 with bipolar disorder   |  |  |  |  |  |  |  |  |  |
| Interventions              | Each for 12 months:<br>Arm 1: omega 3<br>Arm 2: placebo  |  |  |  |  |  |  |  |  |  |
| Outcomes                   | Prophylactic efficacy  |  |  |  |  |  |  |  |  |  |
| Starting date              | Trial Registration entry: 2 Feb 2001<br>Trial start date: July 2000<br>Estimated study completion: July 2004   |  |  |  |  |  |  |  |  |  |
| <b>Contact information</b> | Andrew Stoll, Mclean Hospital  |  |  |  |  |  |  |  |  |  |
| Notes                      | NCT00010868<br>The PI, Andrew Stoll, appears to have been struck off the medical register in<br>Massachusetts in 2011 (Commonwealth of Massachusetts Board of Registration<br>in Medicine, Adjudicatory Case number 2011-026) so it has not been possible to<br>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-<br>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:<br>Arm 1: omega 3 (Omacor fish oil, EPA+DHA 1g/d: 465mg EPA; 375mg DHA)<br>and placebo  |

|                     | Arm 2: placebo and vitamin D3 (1/d, 2000IU)<br>Arm 3: omega 3 (Omacor fish oil, EPA+DHA 1g/d: 465mg EPA; 375mg DHA)<br>and vitamin D3 (1/d, 2000IU)<br>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<br>Trial start date: July 2010<br>Estimated study completion: May 2020  |
| Contact information | Olivia I. Okereke, MD, SM, Principal Investigator, Brigham and Women's<br>Hospital, Brigham and Women's Hospital   |
| Notes               | NCT01696435  |



Supplementary Figure 1. Study flow diagram.

| Study or Subgroup  | Higher on<br>Events        | iega 3<br>Total | Lower om<br>Events                     |            | Moight       | Risk Ratio<br>M-H, Random, 95% Cl       | Risk Ratio<br>M-H, Random, 95% Cl            |
|--|----------------------------|-----------------|--|------------|--------------|---|--|
| Study or Subgroup<br>1.37.1 LCn3 ≤500mg/d                | Evenis                     | TULAI           | Evenie                                 | TULAI      | weight       | M-H, Kaluuli, 95% Ci                    | M-H, Rahuohi, 95% Ci                         |
| AlphaOmega 2010 EPA+DHA                                  | 29                         | 2016            | 30                                     | 2052       | 3.1%         | 0.98 [0.59, 1.63]                       |  |
| DIPP-Tokudome 2015                                       | 23                         | 104             | 0                                      | 101        | 0.1%         | 2.91 [0.12, 70.71]                      | <b>.</b>                                     |
| Subtotal (95% CI)  |                            | 2120            |  | 2153       | 3.2%         | 1.01 [0.61, 1.67]                       |  |
| Total events   | 30                         |                 | 30                                     |            |              |   |  |
| Heterogeneity: Tau² = 0.00; Chi²                         | ²= 0.43, df=               | 1 (P = 0.       | .51); I² = 0%                          | ,          |              |   |  |
| Test for overall effect: Z = 0.04 (I                     | P = 0.97)                  |                 |  |            |              |   |  |
| 1.37.2 LCn3 >500 to ≤1000mg                              | /d                         |                 |  |            |              |   |  |
| AREDS2 2014  | 360                        | 971             | 402                                    | 1011       | 64.6%        | 0.93 [0.83, 1.04]                       | <b></b>                                      |
| ASCEND 2018  | 13                         | 7740            | 15                                     | 7740       | 1.5%         | 0.87 [0.41, 1.82]                       |  |
| OMEGA - Senges 2009                                      | 158                        | 1046            | 142                                    | 1035       | 18.3%        | 1.10 [0.89, 1.36]                       |  |
| OPAL - Dangour 2010                                      | 88                         | 367             | 62                                     | 359        | 9.5%         | 1.39 [1.04, 1.86]                       |  |
| TREND-HD 2008  | 14                         | 158             | 11                                     | 158        | 1.4%         | 1.27 [0.60, 2.72]                       |  |
| Subtotal (95% CI)  | 633                        | 10282           | 600                                    | 10303      | 95.3%        | 1.08 [0.90, 1.28]                       | <b>T</b>                                     |
| Total events<br>Heterogeneity: Tau² = 0.02; Chi²         |                            | 4 (P = 0        | 632<br>10\:I≷ - 40'                    | ov.        |              |   |  |
| Test for overall effect: Z = 0.80 (                      |                            | 4 (F - 0.       | 10),1 = 48                             | <i>1</i> 0 |              |   |  |
| 10010101010101010102.2 - 0.00 (i                         | - 0.42/                    |                 |  |            |              |   |  |
| 1.37.3 LCn3 >1000 to ≤2000m                              | -                          |                 |  |            |              |   |  |
| Ferreira 2015<br>Subtatal (05% CI)                       | 6                          | 147             | 6                                      | 143<br>143 | 0.7%         | 0.97 [0.32, 2.95]                       |  |
| Subtotal (95% CI)<br>Total events                        | 6                          | 147             | 6                                      | 145        | 0.7%         | 0.97 [0.32, 2.95]                       |  |
| Heterogeneity: Not applicable                            | 0                          |                 | 0                                      |            |              |   |  |
| Test for overall effect: Z = 0.05 (                      | P = 0.96)                  |                 |  |            |              |   |  |
| 10011010101010101012 = 0.00 (i                           | - 0.007                    |                 |  |            |              |   |  |
| 1.37.4 LCn3 >2000mg/d                                    |                            |                 |  |            |              |   |  |
| Derosa 2016  | 1                          | 138             | 1                                      | 143        | 0.1%         | 1.04 [0.07, 16.40]                      |  |
| EPE-A - Sanyal 2014                                      | 8<br>0                     | 168<br>46       | 4                                      | 75         | 0.6%         | 0.89 [0.28, 2.87]                       |  |
| OFAMS - Torkildsen 2012<br>Pratt 2009                    | 1                          | 332             | 1<br>0                                 | 46<br>331  | 0.1%<br>0.1% | 0.33 [0.01, 7.98]<br>2.99 [0.12, 73.16] | ·  |
| Subtotal (95% CI)  |                            | 684             | 0                                      | 595        | 0.9%         | 0.93 [0.35, 2.45]                       |  |
| Total events   | 10                         |                 | 6                                      |            |              |   |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> |                            | 3 (P = 0.       | .82); I² = 0%                          | ,          |              |   |  |
| Test for overall effect: Z = 0.15 (I                     | P = 0.88)                  |                 |  |            |              |   |  |
| 1.37.6 Unknown dose                                      |                            |                 |  |            |              |   |  |
| THIS DIET - Tuttle 2008                                  | 2                          | 51              | 0                                      | 50         |              | Not estimable                           |  |
| Subtotal (95% Cl)  | -                          | 0               | -                                      | 0          |              | Not estimable                           |  |
| Total events   | 0                          |                 | 0                                      |            |              |   |  |
| Heterogeneity: Not applicable                            |                            |                 |  |            |              |   |  |
| Test for overall effect: Not applic                      | able                       |                 |  |            |              |   |  |
| Total (95% CI)   |                            | 13233           |  | 13194      | 100.0%       | 1.00 [0.92, 1.10]                       |  |
| Total events   | 679                        |                 | 674                                    |            |              |   |  |
| Heterogeneity: Tau² = 0.00; Chi²                         | ²= 9.22, df=               | 11 (P = 1       | 0.60); I <sup>z</sup> = 0 <sup>.</sup> | %          |              |   | 0.05 0.2 1 5 20                              |
| Test for overall effect: Z = 0.10 (I                     | ,                          |                 |  |            |              |   | Favours higher omega 3 Favours lower omega 3 |
| Test for subgroup differences: (                         | Chi <sup>2</sup> = 0.16, ( | lf = 3 (P :     | = 0.98), I <sup>2</sup> =              | 0%         |              |   | · · · · · · · · · · · · · · · · · · ·        |

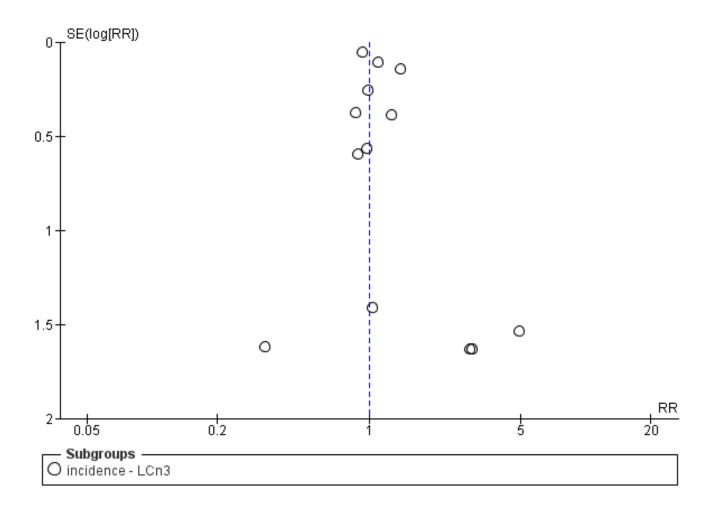
Supplementary Figure 2. Meta-analysis of effects of higher LCn3 vs lower LCn3 on risk of depression symptoms, sub-grouped by LCn3 dose.

| Study or Subgroup         Events         Total         Verints         Total         Verints         Multiple           AlphaDmega 2010 EPA-DHA         29         2016         30         2052         3.1%         0.98 (0.59, 1.63)           DIPP-Tokudome 2015         1         10.4         0         101         0.1%         2.91 (0.12, 70.71)           DIPP-Tokudome 2015         1         10.4         0         101         0.1%         2.91 (0.12, 70.71)           OPAL-Dangour 2010         88         367         62         399         9.5% (1         1.28 (1.00, 1.65)           Total events         118         92         12.8         1.28 (1.00, 1.65)         1.28 (1.00, 1.65)           Total events         118         92         12.8         1.28 (1.00, 1.65)         1.28 (1.00, 1.65)           Total events         118         97         1.5%         0.87 (0.41, 1.82)         1.28 (1.00, 1.65)           Subtotal (95% CI)         8786         8775         19.3%         1.10 (0.89, 1.36)         1.06 (0.89, 1.32)           Total events         1.1         157         Heterogenely, Tau*=0.000; Ch*= 0.37, d*= 1 (P = 0.54); P = 0%         1.08 (0.83, 1.04)         1.04 (0.07, 16.40)           Trestor overall effect Z = 0.76 (P = 0.45)   |                                      | Higher om      | -         | Lower om                  | -     |        | Risk Ratio          | Risk Ratio   |
|--|--------------------------------------|----------------|-----------|---------------------------|-------|--------|---------------------|--|
| Alphaomega 2010 EPA+DHA 29 2016 30 2052 3.1% 0.98 [0.59, 1.63]<br>DIPP-Tokudome 2015 1 104 0 101 0.1% 2.91 [0.12, 70.71]<br>OPAL - Dangour 2010 88 367 62 259 9.9% 1.391 [0.4, 1.86]<br>Subtotal (95% C) 2487 2512 12.8% 1.28 [1.00, 1.65]<br>Total events 118 92<br>Heterogeneity: Tau" = 0.00; Chi" = 1.60; dir = 2 (P = 0.45); P = 0%<br>Test for overall effect Z = 1.93 (P = 0.05)<br><b>1.38.2 EPA &gt; 250 to ≤500mgid</b><br>ASCEND 2018 13 7740 15 7740 1.5% 0.87 [0.41, 1.82]<br>OMEGA- Senges 2009 158 1046 142 1035 18.3% 1.10 [0.88, 1.32]<br>Total events 171 157<br>Heterogeneity: Tau" = 0.00; Chi" = 0.37; dir = 1 (P = 0.54); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.54); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.45)<br><b>1.38.3 EPA &gt; 500 to ≤1000mgid</b><br>AREDS2 2014 360 971 402 1011 64.6% 0.93 [0.83, 1.04]<br>Derosa 2016 1 138 11 158 1.4% 1.27 [0.60, 2.72]<br>Subtotal (95% C) 1267 1312 66.1% 0.94 [0.84, 1.05]<br><b>1.38.4 EPA &gt; 100</b> ; Chi" = 0.4; dir = 2 (P = 0.73); P = 0%<br>Test for overall effect Z = 1.12 (P = 0.26)<br><b>1.38.4 EPA &gt; 100</b> ; Chi" = 0.84, dir = 2 (P = 0.73); P = 0%<br>Test for overall effect Z = 1.12 (P = 0.28)<br><b>1.38.4 EPA &gt; 100</b> ; Chi" = 0.84, dir = 2 (P = 0.73); P = 0%<br>Test for overall effect Z = 1.12 (P = 0.28)<br><b>1.38.4 EPA &gt; 100</b> ; Chi" = 0.84, dir = 2 (P = 0.73); P = 0%<br>Test for overall effect Z = 1.12 (P = 0.28)<br><b>1.38.4 EPA &gt; 100</b> ; Chi" = 0.92; P = 0%<br>Test for overall effect Z = 0.16 (P = 0.82); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.82); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.82); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.82); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.87)<br><b>1.38.6 Unknown dose</b>   |                                      | Events         | Total     | Events                    | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl                                |
| DiPP-Tokudome 2015 1 104 0 101 0.1% 2.91 [0.12, 70.71]<br>OPAL- Dangour 2010 88 367 62 359 9.5% 1.39 [1.0.4, 1.86]<br>Subtotal (95% C) 2487 2512 12.8% 1.28 [1.0.0, 1.65]<br>Total events 118 92<br>Heterogeneity, Tau <sup>2</sup> = 0.0, ChP <sup>2</sup> = 1.80, df = 2 (P = 0.45); P = 0%<br>Test for overall effect $Z = 1.93$ (P = 0.45); P = 0%<br>Test for overall effect $Z = 1.93$ (P = 0.45); P = 0%<br>Total events 171 157<br>Total events 171 157<br>Total events 171 157<br>Total events 171 158 1.4% 0.93 [0.83, 1.04]<br>Derosa 2016 1 138 1 143 0.1% 1.04 [0.07, 16.40]<br>TREND-HD 2008 14 158 11 156 1.4% 1.27 [0.60, 2.72]<br>Subtotal (95% C) 1267 1312 66.1% 0.94 [0.28, 2.87]<br>Total events 375 414<br>Heterogeneity, Tau <sup>2</sup> = 0.012 0.10 46 1 46 0.1% 0.33 [0.01, 7.86]<br>Total events 375 414<br>Heterogeneity, Tau <sup>2</sup> = 0.12 (P = 0.73); P = 0%<br>Test for overall effect $Z = 1.12$ (P = 0.37); P = 0%<br>Test for overall effect $Z = 1.12$ (P = 0.37); P = 0%<br>Test for overall effect $Z = 1.12$ (P = 0.37); P = 0%<br>Total events 375 414<br>Heterogeneity, Tau <sup>2</sup> = 0.012 0 46 1 46 0.1% 0.33 [0.01, 7.86]<br>Pratizo09 1 332 0 331 0.1% 2.99 [0.12, 2.37]<br>Total events 15 6 11<br>Heterogeneity, Tau <sup>2</sup> = 0.07, P = 0.84, df = 2 (P = 0.73); P = 0%<br>Test for overall effect $Z = 1.12$ (P = 0.32); P = 0%<br>Test for overall effect $Z = 1.12$ (P = 0.32); P = 0%<br>Test for overall effect $Z = 1.02$ (P = 0.73); P = 0%<br>Test for overall effect $Z = 1.02$ (P = 0.32); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.82); P = 0%<br>Test for overall effect $Z = 0.16$ (P = 0  | -                                    |                | 0040      | ~~                        |       | ~      | 0.00 10 50 4.00     |  |
| OPAL-Dangour 2010       88       367       62       359       9.5%       1.38 [1.04, 1.86]         Subtotal (95% C)       2487       2512       12.8%       1.28 [1.00, 1.65]         Total events       118       92         Heterogeneity, Tau"= 0.00; Chi"= 1.60, df= 2 (P = 0.45); P = 0%         Testfor overall effect Z = 1.93 (P = 0.05)         1.38.2 EPA >250 to ≤500mgid         ASCEND 2018       13       7740       1.5%       0.87 [0.41, 1.82]         OMEGA-Senges 2009       158       1046       142       1035       18.3%         Subtotal (95% C)       8775       19.8%       1.08 [0.88, 1.32]         Total events       171       157         Heterogeneity, Tau" = 0.00; Chi" = 0.37, df = 1 (P = 0.54); P = 0%         Testfor overall effect Z = 0.76 (P = 0.45)         Testfor overall effect Z = 0.76 (P = 0.45)         Total events       375         1.38       143       0.1%       1.04 [0.07, 16.40]         Testfor overall effect Z = 1.12 (P = 0.23); P = 0%       1312       66.1%       0.93 [0.83, 1.04]       0.94 [0.84, 1.05]       0.94 [0.84, 1.05]         Total events       375       414       158       1.4%       0.27 [0.32, 2.85]       0.94 [0.84, 1.05]       0.94 [0.84, 2.07]       0.94 [0.8  | . 2                                  |                |           |                           |       |        | • • •               |  |
| Stubtoral (95% CI)       2487       2512       12.8 (1.00, 1.65)         Total events       118       92         Heterogeneity: Tau* = 0.00; Ch* = 1.60, df = 2 (P = 0.45); P = 0%         Test for overall effect Z = 1.93 (P = 0.05)         1.38.2 EPA > 250 to ≤500mg/d         ASCEND 2018       13       7740       1.5 %       0.87 [0.41, 1.82]         OMEGA - Senges 2009       158       1046       142       1035       18.3 %       1.10 [0.89, 1.36]         Stubtotal (95% CI)       8786       8775       19.8 %       1.08 [0.88, 1.32]       -         Total events       171       157       157       1400 (0.7, 16.40]       -         Test for overall effect Z = 0.76 (P = 0.45)       -       -       0.93 [0.83, 1.04]       -         AREDS2 2014       360       971       402       1011       64.6%       0.93 [0.83, 1.04]         Derosa 2016       1       158       1.4%       0.27 [0.60, 2.72]       -       -         Stubtoral (95% CI)       1267       1312       66.1%       0.39 [0.28, 2.87]       -         Total events       375       414       -       66.1%       0.33 [0.01, 7.86]       -         1284 EPA >1000mg/d       EPEA - Samyal 2014       6147 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td> '</td>   |                                      |                |           |                           |       |        |                     | '  |
| Total events       118       92         Heterogeneity: Tau" = 0.00; Ch" = 1.60, df = 2 (P = 0.45); P = 0%         Test for overall effect Z = 1.93 (P = 0.05)         1.38.2 EPA >250 to ≤500mgid         ASCEND 2018       13       7740       1.5%       0.87 [0.41, 1.82]         OMEGA- Senges 2009       158       1046       142       1035       18.3%       1.10 [0.89, 1.36]         Subtotal (95% Cl)       8785       8775       19.8%       1.08 [0.88, 1.32]       •         Test for overall effect Z = 0.76 (P = 0.45)       1.38       1.71       157       19.8%       1.08 [0.88, 1.32]         Test for overall effect Z = 0.76 (P = 0.45)       1.38       1.42       1.01       64.6%       0.93 [0.83, 1.04]         Derosa 2016       1       138       1       143       0.1%       1.04 [0.07, 16.40]         Test for overall effect Z = 0.76 (P = 0.45)       1.32       66.1%       0.93 [0.83, 1.04]       •         Total events       375       414       1.42       1.012 (D.60, 2.72]       •         Total events       375       414       1.43       0.7%       0.97 [0.32, 2.95]       •         Total events       375       614       1.43       0.7%       0.97 [0.32, 2.95]       •   |                                      | 00             |           | 02                        |       |        |                     | •  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.60, df = 2 (P = 0.45); P = 0%<br>Test for overall effect Z = 1.93 (P = 0.05)<br><b>1.38.2EPA &gt; 250 to <math>\leq</math> 500mg/d<br/>ASCEND 2018 13 7740 15 7740 15% 0.87 [0.41, 1.82]<br/>OMEGA - Senges 2009 158 1046 142 1035 18.3% 1.10 [0.89, 1.36]<br/>Subtotal (9% CI) 8776 8775 13.8% 1.08 [0.88, 1.32]<br/>Total events 171 157<br/>Heterogeneity: Tau<sup>2</sup> = 0.00; Ch<sup>2</sup> = 0.37, df = 1 (P = 0.54); P = 0%<br/>Test for overall effect Z = 0.76 (P = 0.45)<br/><b>1.38.3 EPA &gt; 500 to</b> <math>\leq</math> 1000mg/d<br/>AREDS 2014 138 1 143 0.1% 1.04 [0.07, 16.40]<br/>Derosa 2016 1 138 1 143 0.1% 1.04 (0.76, 40]<br/>Derosa 2016 1 138 1 143 0.1% 0.94 [0.84, 1.05]<br/><b>1.38.4 EPA &gt; 1000</b> (Ch<sup>2</sup> = 0.40; df = 2 (P = 0.73); P = 0%<br/>Test for overall effect Z = 1.12 (P = 0.26)<br/><b>1.38.4 EPA &gt; 1000mg/d</b><br/>EPE-A - Sanyal 2014 8 168 4 75 0.6% 0.99 [0.28, 2.87]<br/>Ferreira 2015 6 147 6 143 0.7% 0.97 [0.32, 2.95]<br/><b>1.38.4 EPA &gt; 1000mg/d</b><br/>EPE-A - Sanyal 2014 8 168 4 75 0.6% 0.99 [0.12, 7.316]<br/>OFAMS - Torkidisen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br/>Prat 2009 1 332 0 331 0.1% 2.99 [0.12, 7.316]<br/>OFAMS - Torkidisen 2012 0 46 1 44 0.1% 0.33 [0.01, 7.98]<br/>Prat 2009 1 332 0 5 1.4% 0.94 [0.44, 2.01]<br/>Total events 1 5 11<br/>Heterogeneity: Tau<sup>2</sup> = 0.00; Ch<sup>2</sup> = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br/>Test for overall effec</b> |                                      | 118            |           | 92                        |       |        |                     | •  |
| Test for overall effect. Z = 1.93 (P = 0.05)<br><b>1.32.2 EPA &gt; 250 to ≤500mg/d</b><br>ASCEND 2018 13 7740 15 7740 1.5% 0.87 [0.41, 1.82]<br>OMEGA- Senges 2009 158 1046 142 1035 18.3% 1.10 [0.89, 1.36]<br><b>Subtotal (95% CI)</b> 8796 8775 19.8% 1.08 [0.88, 1.32]<br>Total events 171 157<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.37, 0'1 + (P = 0.54); P <sup>=</sup> 0 %<br>Test for overall effect. Z = 0.76 (P = 0.45)<br><b>1.33.3 EPA &gt; 500 to ≤1000mg/d</b><br>AREDS2 2014 360 971 402 1011 64.6% 0.93 [0.83, 1.04]<br>Derosa 2016 1 138 1 143 0.1% 1.04 [0.07, 16.40]<br>Derosa 2016 1 138 11 158 1.4% 0.94 [0.84, 1.05]<br>Total events 375 414<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); P <sup>=</sup> 0%<br>Test for overall effect Z = 1.12 (P = 0.26)<br><b>1.38.4 EPA &gt; 1000mg/d</b><br>EPE-A- Sanyal 2014 8 168 4 75 0.6% 0.89 [0.28, 2.87]<br>Ferreira 2015 6 147 6 143 0.7% 0.97 [0.32, 2.95]<br>OFAMS- Torkidsen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br>Prat 2009 1 332 0 331 01% 2.99 [0.12, 7.31]<br><b>5</b> 11<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.82); P <sup>=</sup> 0%<br>Test for overall effect Z = 1.12 (P = 0.82); P <sup>=</sup> 0%<br>Test for overall effect Z = 0.16 (P = 0.87); P <sup>=</sup> 0%<br>Total events 15 11<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); P <sup>=</sup> 0%<br>Test for overall effect Z = 0.16 (P = 0.87); P <sup>=</sup> 0%  |                                      | = 1.60, df = 1 | 2 (P = 0. | .45); I <sup>2</sup> = 0% |       |        |                     |  |
| ASCEND 2018 13 7740 15 7740 1.5% 0.87 [0.41, 1.82]<br>OMEGA-senges 2009 158 10.46 142 1035 18.3% 1.10 [0.89, 1.36]<br>Subtotal (95% CI) 8786 8775 19.8% 1.08 [0.88, 1.32]<br>Total events 171 157<br>Heterogeneity: Tau" = 0.00; Chi" = 0.37, df = 1 (P = 0.54); P = 0%<br>Test for overall effect Z = 0.76 (P = 0.45)<br>Test for overall effect Z = 0.76 (P = 0.45)<br>Tas 3.EPA >500 to ≤ 1000mgid<br>AREDs 2 2014 360 971 402 1011 64.6% 0.93 [0.83, 1.04]<br>Derosa 2016 1 138 1 143 0.1% 1.04 [0.07, 16.40]<br>TREND-HD 2008 14 158 11 158 1.4% 1.27 [0.60, 2.72]<br>Subtotal (95% CI) 1267 1312 66.1% 0.94 [0.84, 1.05]<br>Total events 375 414<br>Heterogeneity: Tau" = 0.00; Chi" = 0.84, df = 2 (P = 0.73); P = 0%<br>Test for overall effect Z = 1.12 (P = 0.26)<br><b>1.38.4 EPA &gt;1000mgid</b><br>EPE-A- Saryal 2014 8 168 4 75 0.6% 0.89 [0.28, 2.97]<br>Ferreira 2015 6 147 6 143 0.7% 0.97 [0.32, 2.95]<br>OFAMS-Torkidsen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br>Prat 2009 1 332 0 331 0.1% 2.99 [0.12, 7.316]<br>Subtotal (95% CI) 693 595 1.4% 0.94 [0.44, 2.01]<br>Total events 15 11<br>Heterogeneity: Tau" = 0.00; Chi" = 0.82); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.87)<br><b>1.38.6 Unknown dose</b>   | Test for overall effect: Z = 1.93 (F | P = 0.05)      |           |                           |       |        |                     |  |
| ASCEND 2018 13 7740 15 7740 1.5% 0.87 [0.41, 1.82]<br>OMEGA-senges 2009 158 10.46 142 1035 18.3% 1.10 [0.89, 1.36]<br>Subtotal (95% CI) 8786 8775 19.8% 1.08 [0.88, 1.32]<br>Total events 171 157<br>Heterogeneity: Tau" = 0.00; Chi" = 0.37, df = 1 (P = 0.54); P = 0%<br>Test for overall effect Z = 0.76 (P = 0.45)<br>Test for overall effect Z = 0.76 (P = 0.45)<br>Tag. 2014 360 971 402 1011 64.6% 0.93 [0.83, 1.04]<br>Derosa 2016 1 138 1 143 0.1% 1.04 [0.07, 16.40]<br>TREND-HD 2008 14 158 11 158 1.4% 1.27 [0.60, 2.72]<br>Subtotal (95% CI) 1267 1312 66.1% 0.94 [0.84, 1.05]<br>Total events 375 414<br>Heterogeneity: Tau" = 0.00; Chi" = 0.84, df = 2 (P = 0.73); P = 0%<br>Test for overall effect Z = 1.12 (P = 0.26)<br><b>1.38.4 EPA &gt; 1000mg/d</b><br>EPE-A- Saryal 2014 8 168 4 75 0.6% 0.89 [0.28, 2.97]<br>Ferreira 2015 6 147 6 143 0.7% 0.97 [0.32, 2.95]<br>OFAMS- Torkidsen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br>Prat 2009 1 332 0 331 0.1% 2.99 [0.12, 7.316]<br>Subtotal (95% CI) 693 595 1.4% 0.94 [0.44, 2.01]<br>Total events 15 15 11<br>Heterogeneity: Tau" = 0.00; Chi" = 0.82); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.87); P = 0%<br>Test for overall effect Z = 0.16 (P = 0.87); P = 0%  | 1.38.2 EPA >250 to ≤500mg/d          |                |           |                           |       |        |                     |  |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $   | -                                    | 13             | 7740      | 15                        | 7740  | 1.5%   | 0.87 [0.41, 1.82]   |  |
| Subtotal (95% CI)       8786       8775       19.8%       1.08 [0.88, 1.32]         Total events       171       157         Heterogeneity: Tau" = 0.00; Chi" = 0.37; df = 1 (P = 0.54); P = 0%         Test for overall effect: $Z = 0.76$ (P = 0.45) <b>1.38.3 EPA &gt;500 to ≤ 1000mg/d</b> AREDS2 2014       360       971       402       1011       64.6%       0.93 [0.83, 1.04]         Derosa 2016       1       138       1       43       0.1%       1.04 [0.07, 16.40]         TREND-HD 2008       14       158       1.4%       1.27 [0.60, 2.72]         Subtotal (95% CI)       1267       1312       66.1%       0.94 [0.84, 1.05]         Total events       375       414         Heterogeneity: Tau" = 0.00; Chi"= 0.64, df = 2 (P = 0.73); P = 0%       0.94 [0.38, 1.05]  |                                      |                |           |                           |       |        |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.37, df = 1 ( $P = 0.54$ ); $P = 0\%$<br>Test for overall effect $Z = 0.76$ ( $P = 0.45$ )<br><b>1.38.3 EPA &gt;500 to ≤ 1000mg/d</b><br>AREDS2 2014 360 971 402 1011 64.6% 0.93 [0.83, 1.04]<br>Derosa 2016 1 138 1 143 0.1% 1.04 [0.07, 16.40]<br>TREND-HD 2008 14 158 11 158 1.4% 1.27 [0.60, 2.72]<br><b>Subtotal (95% CI)</b> 1267 1312 66.1% 0.94 [0.84, 1.05]<br>Total events 375 414<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 ( $P = 0.73$ ); $P = 0\%$<br>Test for overall effect $Z = 1.12$ ( $P = 0.26$ )<br><b>1.38.4 EPA &gt;1000mg/d</b><br>EPE-A - Sanyal 2014 8 168 4 75 0.6% 0.89 [0.28, 2.97]<br>Ferreira 2015 6 147 6 143 0.7% 0.97 [0.32, 2.95]<br>OFAMS - Torkildsen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br>Pratt 2009 1 332 0 331 0.1% 2.99 [0.12, 73.16]<br><b>Subtotal (95% CI)</b> 693 595 1.4% 0.94 [0.44, 2.01]<br>Total events 15 11<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 ( $P = 0.82$ ); $P = 0\%$<br>Test for overall effect $Z = 0.16$ ( $P = 0.87$ )<br><b>1.38.6 Unknown dose</b>   |                                      |                | 8786      |                           | 8775  | 19.8%  |                     | *  |
| Test for overall effect $Z = 0.76$ (P = 0.45)<br><b>1.38.3 EPA &gt;500 to</b> ≤ <b>1000mg/d</b><br>AREDS2 2014 360 971 402 1011 64.6% 0.93 [0.83, 1.04]<br>Derosa 2016 1 138 1 143 0.1% 1.04 [0.07, 16.40]<br>TREND-HD 2008 14 158 11 158 1.4% 1.27 [0.60, 2.72]<br><b>5.000 tot</b> (95% CI) 1267 1312 66.1% 0.94 [0.84, 1.05]<br>Total events 375 414<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); i <sup>2</sup> = 0%<br>Test for overall effect $Z = 1.12$ (P = 0.26)<br><b>1.38.4 EPA &gt;1000 mg/d</b><br>EPE-A · Sanyal 2014 8 168 4 75 0.6% 0.89 [0.28, 2.87]<br>Ferreira 2015 6 147 6 143 0.7% 0.97 [0.32, 2.95]<br>OFAMS · Torkildsen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br>Pratt 2009 1 332 0 331 0.1% 2.99 [0.12, 73.16]<br><b>Subtotal (95% CI)</b> 693 595 1.4% 0.94 [0.44, 2.01]<br>Total events 15 11<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); i <sup>2</sup> = 0%<br>Test for overall effect $Z = 0.16$ (P = 0.87)<br><b>1.38.6 Unknown dose</b>   | Total events                         | 171            |           | 157                       |       |        |                     |  |
| 1.38.3 EPA >500 to ≤1000mg/d         AREDS2 2014       360       971       402       1011       64.6%       0.93 [0.83, 1.04]         Derosa 2016       1       138       1       143       0.1%       1.04 [0.07, 16.40]         TREND-HD 2008       14       158       11       158       1.4%       1.27 [0.60, 2.72]         Subtoal (95% CI)       1267       1312       66.1%       0.94 [0.84, 1.05]         Total events       375       414         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); P = 0%         Test for overall effect Z = 1.12 (P = 0.26)         1.38.4 EPA >1000mg/d         EPE-A - Sanyal 2014       8       168       4       75       0.6%       0.99 [0.28, 2.87]         Ferreira 2015       6       147       6       143       0.7%       0.97 [0.32, 2.95]  |                                      |                | 1 (P = 0. | .54); I² = 0%             |       |        |                     |  |
| AREDS2 2014 $360$ $971$ $402$ $1011$ $64.6\%$ $0.93 [0.83, 1.04]$ Derosa 2016       1 $138$ $143$ $0.1\%$ $1.04 [0.07, 16.40]$ TREND-HD 2008 $14$ $158$ $11$ $158$ $1.27 [0.60, 2.72]$ Subtotal (95% CI)       1267 $1312$ $66.1\%$ $0.94 [0.84, 1.05]$ Total events $375$ $414$ Heterogeneily: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); P = 0\%         Test for overall effect Z = $1.12$ (P = $0.26$ ) <b>138.4 EPA &gt;1000mg/d</b> EPE-A- Sanyal 2014       8 $168$ 4 $75$ $0.6\%$ $0.89 [0.28, 2.87]$ Ferreira 2015       6 $147$ 6 $143$ $0.7\%$ $0.97 [0.32, 2.95]$ OFAMS - Torkildsen 2012       0 $46$ 1 $46$ $0.1\%$ $0.33 [0.01, 7, 38]$ Pratt 2009       1 $332$ $0$ $311$ $0.1\%$ $0.94 [0.44, 2.01]$ Total events       15       11       Heterogeneity: Tau <sup>2</sup> = $0.00$ ; Chi <sup>2</sup> = $0.92$ , df = $3$ (P = $0.82$ ); P = $0\%$ Test for overall effect Z = $0.16$ (P = $0.87$ ) <b>1.38.6 Unknown dose 1.4</b> %  | Test for overall effect: Z = 0.76 (F | ° = 0.45)      |           |                           |       |        |                     |  |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $   | 1.38.3 EPA >500 to ≤1000mg/d         | I              |           |                           |       |        |                     |  |
| TREND-HD 2008       14       158       11       158       1.4%       1.27       10.60, 2.72]         Subtotal (95% Cl)       1267       1312       66.1%       0.94 [0.84, 1.05]         Total events       375       414         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); P = 0%       0.94 [0.84, 1.05]         Test for overall effect: $Z = 1.12$ (P = 0.26)       138.4 EPA > 1000mg/d         EPE-A - Sanyal 2014       8       168       4       75       0.6%       0.89 [0.28, 2.87]         OFAMS - Torkildsen 2012       0       46       1       46       0.1%       0.33 [0.01, 7.98]         Pratt 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtotal (95% Cl)       693       595       1.4%       0.94 [0.44, 2.01]         Total events       15       11         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92; df = 3 (P = 0.82); I <sup>2</sup> = 0%       75       0.94 [0.44, 2.01]         Total events       15       11         Heterogeneity: Tau <sup>2</sup> = 0.16 (P = 0.87)       138.6 Unknown dose       138.6 Unknown dose   | AREDS2 2014                          | 360            | 971       | 402                       | 1011  | 64.6%  | 0.93 [0.83, 1.04]   |  |
| Subtotal (95% Cl)       1267       1312       66.1% $0.94 [0.84, 1.05]$ Total events       375       414         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); l <sup>2</sup> = 0%         Test for overall effect: $Z = 1.12$ (P = 0.26) <b>1.38.4 EPA &gt;1000mg/d</b> EPE-A - Sanyal 2014       8       168       4       75       0.6%       0.89 [0.28, 2.87]         Ferreira 2015       6       147       6       143       0.7%       0.97 [0.32, 2.95]         OFAMS - Torkildsen 2012       0       46       1       46       0.1%       0.33 [0.01, 7.98]         Pratl 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtotal (95% Cl)       693       595       1.4%       0.94 [0.44, 2.01]       4         Total events       15       11       11       11       11         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); l <sup>2</sup> = 0%       7       0.94 [0.44, 2.01]       13         Total events       15       11       14       14       14       14       14       15       14         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); l <sup>2</sup> = 0%       15       14       14       14  | Derosa 2016                          | 1              | 138       | 1                         | 143   | 0.1%   | 1.04 [0.07, 16.40]  |  |
| Total events $375$ $414$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); l <sup>2</sup> = 0%         Test for overall effect: $Z = 1.12$ (P = 0.26) <b>1.38.4 EPA &gt; 1000mg/d</b> EPE-A - Sanyal 2014       8       168       4       75       0.6%       0.89 [0.28, 2.87]         Ferreira 2015       6       147       6       143       0.7%       0.97 [0.32, 2.95]         OFAMS - Torkildsen 2012       0       46       1       46       0.1%       0.33 [0.01, 7.98]         Pratt 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtotal (95% CI)       693       595       1.4%       0.94 [0.44, 2.01]       46         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); l <sup>2</sup> = 0%       Test for overall effect: $Z = 0.16$ (P = 0.87) <b>1.38.6 Unknown dose</b>   | TREND-HD 2008                        | 14             | 158       | 11                        | 158   | 1.4%   | 1.27 [0.60, 2.72]   |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.64, df = 2 (P = 0.73); i <sup>2</sup> = 0%<br>Test for overall effect: Z = 1.12 (P = 0.26)<br><b>1.38.4 EPA &gt; 1000mg/d</b><br>EPE-A - Sanyal 2014 8 168 4 75 0.6% 0.89 [0.28, 2.87]<br>Ferreira 2015 6 147 6 143 0.7% 0.97 [0.32, 2.95]<br>OFAMS - Torkildsen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br>Pratt 2009 1 332 0 331 0.1% 2.99 [0.12, 73.16]<br><b>Subtoal (95% Cl)</b> 693 595 1.4% 0.94 [0.44, 2.01]<br>Total events 15 11<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); i <sup>2</sup> = 0%<br>Test for overall effect: Z = 0.16 (P = 0.87)<br><b>1.38.6 Unknown dose</b>   | Subtotal (95% CI)                    |                | 1267      |                           | 1312  | 66.1%  | 0.94 [0.84, 1.05]   | •  |
| Test for overall effect: $Z = 1.12$ (P = 0.26) <b>1.38.4 EPA &gt; 1000mg/d</b> EPE-A - Sanyal 2014       8       168       4       75       0.6%       0.89 [0.28, 2.87]         Ferreira 2015       6       147       6       143       0.7%       0.97 [0.32, 2.95]         OFAMS - Torkildsen 2012       0       46       1       46       0.1%       0.33 [0.01, 7.98]         Pratt 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtoal (95% CI)       693       595       1.4%       0.94 [0.44, 2.01]       644, 2.01]         Total events       15       11         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); i <sup>2</sup> = 0%       Test for overall effect: Z = 0.16 (P = 0.87) <b>1.38.6 Unknown dose</b> 5       14   |                                      |                |           |                           |       |        |                     |  |
| 1.38.4 EPA >1000mg/d         EPE-A - Sanyal 2014       8       168       4       75       0.6%       0.89 [0.28, 2.87]         Ferreira 2015       6       147       6       143       0.7%       0.97 [0.32, 2.95]         OFAMS - Torkildsen 2012       0       46       1       46       0.1%       0.33 [0.01, 7.98]         Pratt 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtoal (95% CI)       693       595       1.4%       0.94 [0.44, 2.01]       ●         Total events       15       11       Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 3 (P = 0.82); i² = 0%       ●         Test for overall effect: Z = 0.16 (P = 0.87)       ■       ■       ■       ■         1.38.6 Unknown dose       ■       ■       ■       ■       ■  |                                      |                | 2 (P = 0. | .73); I* = 0%             |       |        |                     |  |
| EPE-A- Sanyal 2014       8       168       4       75       0.6%       0.89 [0.28, 2.87]         Ferreira 2015       6       147       6       143       0.7%       0.97 [0.32, 2.95]         OFAMS - Torkildsen 2012       0       46       1       46       0.1%       0.33 [0.01, 7.98]         Prati 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtoal (95% CI)       693       595       1.4%       0.94 [0.44, 2.01]  | lest for overall effect: Z = 1.12 (F | 9 = 0.26)      |           |                           |       |        |                     |  |
| Ferreira 2015       6       147       6       143       0.7%       0.97 [0.32, 2.95]         OFAMS - Torkildsen 2012       0       46       1       46       0.1%       0.33 [0.01, 7.98]         Prati 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtotal (95% CI)       693       595       1.4%       0.94 [0.44, 2.01]         Total events       15       11         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); i <sup>2</sup> = 0%         Test for overall effect: Z = 0.16 (P = 0.87) <b>1.38.6 Unknown dose</b>   |                                      |                |           |                           |       |        |                     |  |
| OFAMS - Torkildsen 2012 0 46 1 46 0.1% 0.33 [0.01, 7.98]<br>Pratt 2009 1 332 0 331 0.1% 2.99 [0.12, 73.16]<br>Subtotal (95% CI) 693 595 1.4% 0.94 [0.44, 2.01]<br>Total events 15 11<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); l <sup>2</sup> = 0%<br>Test for overall effect: Z = 0.16 (P = 0.87)<br>1.38.6 Unknown dose   | · ·                                  |                |           |                           |       |        |                     |  |
| Pratt 2009       1       332       0       331       0.1%       2.99 [0.12, 73.16]         Subtotal (95% CI)       693       595       1.4%       0.94 [0.44, 2.01]         Total events       15       11         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); l <sup>2</sup> = 0%         Test for overall effect: Z = 0.16 (P = 0.87) <b>1.38.6 Unknown dose</b>   |                                      |                |           |                           |       |        |                     |  |
| Subtotal (95% CI)         693         595         1.4%         0.94 [0.44, 2.01]           Total events         15         11           Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); l <sup>2</sup> = 0%         Test for overall effect: Z = 0.16 (P = 0.87)           1.38.6 Unknown dose         5   |                                      |                |           |                           |       |        | • • •               | · · · · · · · · · · · · · · · · · · ·              |
| Total events 15 11<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); i <sup>2</sup> = 0%<br>Test for overall effect: Z = 0.16 (P = 0.87)<br><b>1.38.6 Unknown dose</b>  |                                      | 1              |           | U                         |       |        |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.92, df = 3 (P = 0.82); i <sup>2</sup> = 0%<br>Test for overall effect: Z = 0.16 (P = 0.87)<br><b>1.38.6 Unknown dose</b>  |                                      | 15             | 095       | 11                        | 393   | 1.4 70 | 0.94 [0.44, 2.01]   |  |
| Test for overall effect: Z = 0.16 (P = 0.87)  1.38.6 Unknown dose  |                                      |                | 3 (P = n  |                           |       |        |                     |  |
|  |                                      |                |           | -,,,.                     |       |        |                     |  |
|  | 1 38 6 Unknown doeo                  |                |           |                           |       |        |                     |  |
| 1110 DIE 1- 14116 2000 Z 31 0 30 NULESUITABLE  |                                      | 2              | 64        | 0                         | 60    |        | Not octimable       |  |
| Subtotal (95% CI) 0 0 Not estimable  |                                      | 2              |           | U                         |       |        |                     |  |
| Total events 0 0   |                                      | 0              | -         | 0                         | -     |        |                     |  |
| Heterogeneity: Not applicable  |                                      | Ŭ              |           | Ŭ                         |       |        |                     |  |
| Test for overall effect: Not applicable  |                                      | able           |           |                           |       |        |                     |  |
| Total (95% CI) 13233 13194 100.0% 1.00 [0.92, 1.10]  | Total (95% CI)                       |                | 13233     |                           | 13194 | 100.0% | 1.00 [0.92, 1.10]   |  |
| Total events 679 674   |                                      | 679            |           | 674                       |       |        |                     |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 9.22, df = 11 (P = 0.60); l <sup>2</sup> = 0%   |                                      |                | 11 (P = I | - · ·                     | ж     |        |                     |  |
| Test for overall effect: Z = 0.10 (P = 0.92) U.05 U.2 1 5 20<br>Favours higher omega 3 Favours lower omega 3   |                                      |                | •         |                           |       |        |                     |  |
| Test for subgroup differences: Chi <sup>2</sup> = 5.60, df = 3 (P = 0.13), l <sup>2</sup> = 46.4%  | Test for subgroup differences: C     | ≿hi² = 5.60, d | f=3(P:    | = 0.13), I <b>²</b> =     | 46.4% |        |                     | r avoars nighter onnega 5 in avoars tower onnega 5 |

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

|  | Higher on            | nega 3      | Lower om                  | iega 3  |        | Risk Ratio                     | Risk Ratio  |
|--|----------------------|-------------|---------------------------|---------|--------|--------------------------------|---|
| Study or Subgroup  | Events               | Total       | Events                    | Total   | Weight | M-H, Random, 95% Cl            | M-H, Random, 95% Cl                               |
| 1.39.1 DHA ≤250mg/d                                      |                      |             |                           |         |        |                                |   |
| AlphaOmega 2010 EPA+DHA                                  | 29                   | 2016        | 30                        | 2052    | 3.1%   | 0.98 [0.59, 1.63]              |   |
| EPE-A - Sanyal 2014                                      | 8                    | 168         | 4                         | 75      | 0.6%   | 0.89 [0.28, 2.87]              |   |
| Ferreira 2015  | 6                    | 147         | 6                         | 143     | 0.7%   | 0.97 [0.32, 2.95]              |   |
| TREND-HD 2008  | 14                   | 158         | 11                        | 158     | 1.4%   | 1.27 [0.60, 2.72]              | <u> </u>  |
| Subtotal (95% CI)  |                      | 2489        |                           | 2428    | 5.8%   | 1.04 [0.71, 1.50]              | <b>•</b>  |
| Total events   | 57                   |             | 51                        |         |        |                                |   |
| Heterogeneity: Tau² = 0.00; Chi²                         |                      | 3 (P = 0    | .94); I <sup>z</sup> = 0% |         |        |                                |   |
| Test for overall effect: Z = 0.18 (F                     | P = 0.85)            |             |                           |         |        |                                |   |
| 1.39.2 DHA >250 to ≤500mg/d                              |                      |             |                           |         |        |                                |   |
| AREDS2 2014  | 360                  | 971         | 402                       | 1011    | 64.6%  | 0.93 [0.83, 1.04]              |   |
| ASCEND 2018  | 13                   | 7740        | 15                        | 7740    | 1.5%   | 0.87 [0.41, 1.82]              |   |
| DIPP-Tokudome 2015                                       | 1                    | 104         | 0                         | 101     | 0.1%   | 2.91 [0.12, 70.71]             | <b>_</b>  |
| OMEGA - Senges 2009                                      | 158                  | 1046        | 142                       | 1035    | 18.3%  | 1.10 [0.89, 1.36]              | _ <b>_</b>  |
| OPAL - Dangour 2010                                      | 88                   | 367         | 62                        | 359     | 9.5%   | 1.39 [1.04, 1.86]              |   |
| Subtotal (95% CI)  | 00                   | 10228       | 02                        | 10246   | 94.0%  | 1.07 [0.89, 1.29]              | •   |
| Total events   | 620                  |             | 621                       |         |        |                                | -   |
| Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> |                      | 4 (P = 0)   |                           | %       |        |                                |   |
| Test for overall effect: Z = 0.72 (F                     |                      |             | ,                         |         |        |                                |   |
|  |                      |             |                           |         |        |                                |   |
| 1.39.3 DHA >500 to ≤1000mg/d                             |                      |             |                           |         |        |                                |   |
| OFAMS - Torkildsen 2012                                  | 0                    | 46          | 1                         | 46      | 0.1%   | 0.33 [0.01, 7.98]              | •   |
| Subtotal (95% CI)  |                      | 46          |                           | 46      | 0.1%   | 0.33 [0.01, 7.98]              |   |
| Total events   | 0                    |             | 1                         |         |        |                                |   |
| Heterogeneity: Not applicable                            |                      |             |                           |         |        |                                |   |
| Test for overall effect: Z = 0.68 (F                     | <sup>2</sup> = 0.50) |             |                           |         |        |                                |   |
| 1.39.4 DHA >1000mg/d                                     |                      |             |                           |         |        |                                |   |
| Derosa 2016  | 1                    | 138         | 1                         | 143     | 0.1%   | 1.04 [0.07, 16.40]             |   |
| Pratt 2009   | 1                    | 332         | 0                         | 331     | 0.1%   | 2.99 [0.12, 73,16]             |   |
| Subtotal (95% CI)  |                      | 470         |                           | 474     | 0.2%   | 1.63 [0.20, 13.18]             |   |
| Total events   | 2                    |             | 1                         |         |        |                                |   |
| Heterogeneity: Tau² = 0.00; Chi²                         | = 0.24, df=          | 1 (P = 0    | .62); I <sup>2</sup> = 0% | ,       |        |                                |   |
| Test for overall effect: Z = 0.46 (F                     | ° = 0.65)            |             |                           |         |        |                                |   |
| 1 20 E Unknown dooo                                      |                      |             |                           |         |        |                                |   |
| 1.39.5 Unknown dose                                      | ~                    | -           | ~                         |         |        | bl=4414 *                      |   |
| THIS DIET - Tuttle 2008<br>Subtotal (95% CI)             | 2                    | 51<br>0     | 0                         | 50<br>0 |        | Not estimable<br>Not estimable |   |
|  |                      | 0           |                           | 0       |        | Notestimable                   |   |
| Total events   | 0                    |             | 0                         |         |        |                                |   |
| Heterogeneity: Not applicable                            | oblo                 |             |                           |         |        |                                |   |
| Test for overall effect: Not applic                      | apie                 |             |                           |         |        |                                |   |
| Total (95% CI)   |                      | 13233       |                           | 13194   | 100.0% | 1.00 [0.92, 1.10]              |   |
| Total events   | 679                  |             | 674                       |         |        |                                |   |
| Heterogeneity: Tau² = 0.00; Chi²                         | = 9.22, df=          | 11 (P =     | 0.60); I <b>²</b> = 0'    | %       |        |                                | 0.05 0.2 1 5 20                                   |
| Test for overall effect: Z = 0.10 (F                     | ° = 0.92)            |             |                           |         |        |                                | Favours higher omega 3 Favours lower omega 3      |
| Test for subgroup differences: C                         | hi² = 0.70, t        | df = 3 (P : | = 0.87), I <sup>z</sup> = | 0%      |        |                                | r avoaro nigrior ontoga o Travoaro tomor ontoga o |
|  |                      |             |                           |         |        |                                |   |

## 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.

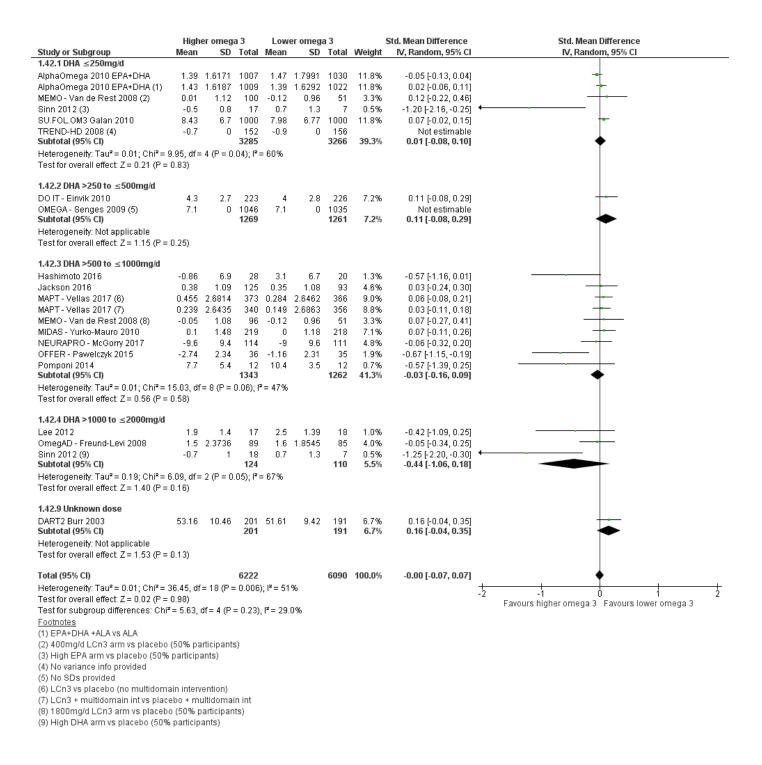
|  | Higher omega 3 Lower omega 3 Std. Mean Differ |             |             |                      |        |                   | :                     | Std. Mean Difference                                | fference Std. Mean Difference                |  |  |
|--|---|-------------|-------------|----------------------|--------|-------------------|-----------------------|---|--|--|--|
| Study or Subgroup  | Mean  | SD          | Total       | Mean                 | SD     | Total             | Weight                | IV, Random, 95% Cl                                  | IV, Random, 95% Cl                           |  |  |
| 1.40.1 LCn3 ≤500mg/d   |   |             |             |                      |        |                   |                       |   |  |  |  |
| AlphaOmega 2010 EPA+DHA  |   | 1.6171      | 1007        |                      | 1.7991 | 1030              | 13.1%                 | -0.05 [-0.13, 0.04]                                 | -  |  |  |
| AlphaOmega 2010 EPA+DHA (1)  |   | 1.6187      | 1009        |                      | 1.6292 | 1022              | 13.1%                 | 0.02 [-0.06, 0.11]                                  | +  |  |  |
| DART2 Burr 2003  | 53.16   | 10.46       | 201         | 51.61                | 9.42   | 191               | 6.4%                  | 0.16 [-0.04, 0.35]                                  |  |  |  |
| MEMO - Van de Rest 2008 (2)<br>Subtotal (05% CI)   | 0.01  | 1.12        | 100<br>2317 | -0.12                | 0.96   | 51<br>2294        | 2.9%<br><b>35.4</b> % | 0.12 [-0.22, 0.46]                                  |  |  |  |
| Subtotal (95% Cl)  | 1.04 46-                                      | - 2 (m - 0  |             | 2000                 |        | 2294              | 33.470                | 0.02 [-0.06, 0.09]                                  | Ť  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 4<br>Test for overall effect: Z = 0.42 (P = |   | - 3 (F = 0  | .24), 173   | - 2970               |        |                   |                       |   |  |  |  |
| 1.40.2 LCn3 >500 to ≤1000mg/d  |   |             |             |                      |        |                   |                       |   |  |  |  |
| MIDAS - Yurko-Mauro 2010   | 0.1   | 1.48        | 219         | 0                    | 1.18   | 218               | 6.9%                  | 0.07 [-0.11, 0.26]                                  | - <del> </del>                               |  |  |
| OMEGA - Senges 2009 (3)  | 7.1   | 0           | 1046        | 7.1                  | 0      | 1035              |                       | Not estimable                                       |  |  |  |
| SU.FOL.OM3 Galan 2010  | 8.43  | 6.7         | 1000        | 7.98                 | 6.77   | 1000              | 13.0%                 | 0.07 [-0.02, 0.15]                                  |  |  |  |
| TREND-HD 2008 (4)  | -0.7  | 0           | 152         | -0.9                 | 0      | 156               |                       | Not estimable                                       |  |  |  |
| Subtotal (95% CI)  |   |             | 2417        |                      |        | 2409              | <b>19.9</b> %         | 0.07 [-0.01, 0.15]                                  | •  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0<br>Test for overall effect: Z = 1.68 (P = |   | = 1 (P = 0  | .94); I²:   | = 0%                 |        |                   |                       |   |  |  |  |
| 1.40.3 LCn3 >1000 to ≤2000mg/d   |   |             |             |                      |        |                   |                       |   |  |  |  |
| DO IT - Einvik 2010  | 4.3   | 2.7         | 223         | 4                    | 2.8    | 226               | 7.0%                  | 0.11 [-0.08, 0.29]                                  |  |  |  |
| Hashimoto 2016   | -0.86   | 6.9         | 28          | 3.1                  | 6.7    | 20                | 1.1%                  | -0.57 [-1.16, 0.01]                                 |  |  |  |
| Jackson 2016   | 0.38  | 1.09        | 125         | 0.35                 | 1.08   | 93                | 4.2%                  | 0.03 [-0.24, 0.30]                                  |  |  |  |
| Lee 2012   | 1.9   | 1.4         | 17          | 2.5                  | 1.39   | 18                | 0.8%                  | -0.42 [-1.09, 0.25]                                 |  |  |  |
| MAPT - Vellas 2017 (5)   | 0.239   | 2.6435      | 340         | 0.149                | 2.6863 | 356               | 8.8%                  | 0.03 [-0.11, 0.18]                                  | +  |  |  |
| MAPT - Vellas 2017 (6)   |   | 2.6814      |             | 0.284                |        | 366               | 9.1%                  | 0.06 [-0.08, 0.21]                                  |  |  |  |
| MEMO - Van de Rest 2008 (7)  | -0.05   | 1.08        | 96          | -0.12                | 0.96   | 51                | 2.9%                  | 0.07 [-0.27, 0.41]                                  |  |  |  |
| NEURAPRO - McGorry 2017  | -9.6  | 9.4         | 114         | -9                   | 9.6    | 111               | 4.4%                  | -0.06 [-0.32, 0.20]                                 |  |  |  |
| Pomponi 2014   | 7.7   | 5.4         | 12          | 10.4                 | 3.5    | 12                | 0.6%                  | -0.57 [-1.39, 0.25]                                 |  |  |  |
| Sinn 2012<br>Subtotal (95% CI)   | 3.2   | 1.516       | 18<br>1346  | 4.6                  | 1.516  | 15<br><b>1268</b> | 0.7%<br><b>39.6</b> % | -0.90 [-1.62, -0.18]<br>- <b>0.03 [-0.14, 0.09]</b> |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 1   |   | '= 9 (P =   |             | ²= 42%               |        | 1200              | 55.070                | -0.05 [-0.14, 0.05]                                 | Ť  |  |  |
| Test for overall effect: Z = 0.43 (P =   | 0.67)   |             |             |                      |        |                   |                       |   |  |  |  |
| 1.40.4 LCn3 >2000mg/d  |   |             |             |                      |        |                   |                       |   |  |  |  |
| OFFER - Pawelczyk 2015   | -2.74   | 2.34        | 36          | -1.16                | 2.31   | 35                | 1.6%                  | -0.67 [-1.15, -0.19]                                |  |  |  |
| OmegAD - Freund-Levi 2008<br>Subtotal (95% CI)   | 1.5   | 2.3736      | 89<br>125   | 1.6                  | 1.8545 | 85<br>120         | 3.6%<br><b>5.2</b> %  | -0.05 [-0.34, 0.25]<br>- <b>0.33 [-0.94, 0.28]</b>  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 4   | 4 73 df=                                      | = 1 (P = 0  |             | = 79%                |        |                   | 01270                 | 0.00 [ 0.0 1, 0.20]                                 |  |  |  |
| Test for overall effect: Z = 1.06 (P =   |   |             | ,,.         |                      |        |                   |                       |   |  |  |  |
| 1.40.9 Unknown dose<br>Subtotal (95% Cl)   |   |             | 0           |                      |        | 0                 |                       | Not estimable                                       |  |  |  |
| Heterogeneity: Not applicable  |   |             |             |                      |        |                   |                       |   |  |  |  |
| Test for overall effect: Not applicable  | le  |             |             |                      |        |                   |                       |   |  |  |  |
| Total (95% CI)   |   |             | 6205        |                      |        | 6001              | 100.0%                | 0.01 [-0.05, 0.07]                                  |  |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 0   | 20 60 44                                      | - 17 /D -   |             | IZ - 400             | 6      | 0031              | 100.076               | 0.01[-0.05, 0.07]                                   | ++   |  |  |
| Test for overall effect: Z = 0.29 (P =   |   | - 17 (F -   | - 0.03),    | 1 - 435              | 0      |                   |                       |   | -2 -1 0 1 2                                  |  |  |
| Test for subgroup differences: Chi <sup>2</sup>  |   | df = 3 (P)  | = 0.36)     | I <sup>2</sup> = 5.9 | 96     |                   |                       |   | Favours higher omega 3 Favours lower omega 3 |  |  |
| Footnotes  | - 0.10,                                       | ui - 0 (i - | - 0.00)     | 1 = 0.0              |        |                   |                       |   |  |  |  |
| (1) EPA+DHA +ALA vs ALA  |   |             |             |                      |        |                   |                       |   |  |  |  |
| (2) 400mg/d LCn3 arm vs placebo  | (50% pa                                       | articipants | 5)          |                      |        |                   |                       |   |  |  |  |
| (3) No SDs provided  |   |             |             |                      |        |                   |                       |   |  |  |  |
| (4) No variance info provided  |   |             |             |                      |        |                   |                       |   |  |  |  |
| (5) LCn3 + multidomain int vs place  | ebo+m   | ultidomai   | in int      |                      |        |                   |                       |   |  |  |  |
| (6) LCn3 vs placebo (no multidoma  |   | -           |             |                      |        |                   |                       |   |  |  |  |
| (7) 1800mg/d LCn3 arm vs placeb  | o (50% p                                      | participan  | its)        |                      |        |                   |                       |   |  |  |  |
|  |   |             |             |                      |        |                   |                       |   |  |  |  |

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

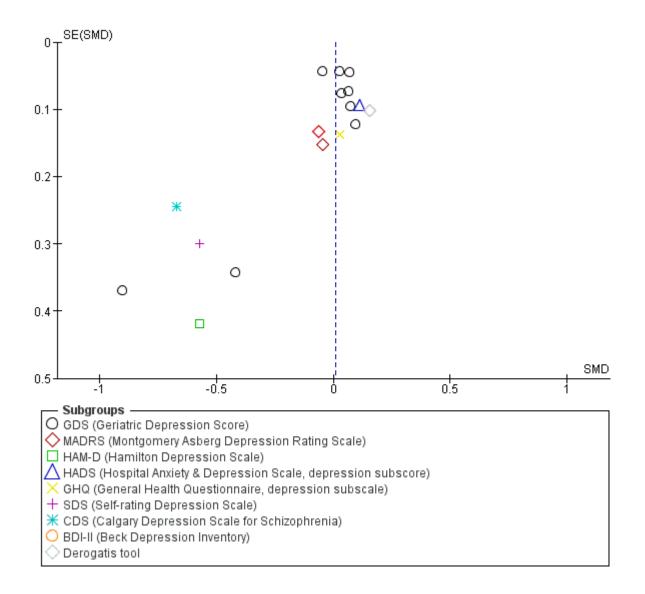
## dose.

|  | Higher omega 3 |             | Lower omega 3       |                        |        | Std. Mean Difference |                        | Std. Mean Difference                       |   |  |  |
|--|----------------|-------------|---------------------|------------------------|--------|----------------------|------------------------|--|---|--|--|
| Study or Subgroup  | Mean           | SD          | Total               | Mean                   | SD     | Total                | Weight                 | IV, Random, 95% Cl                         | IV, Random, 95% Cl  |  |  |
| 1.41.1 EPA ≤250mg/d  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| AlphaOmega 2010 EPA+DHA (1)  | 1.43           | 1.6187      | 1009                | 1.39                   | 1.6292 | 1022                 | 11.8%                  | 0.02 [-0.06, 0.11]                         | +   |  |  |
| AlphaOmega 2010 EPA+DHA  | 1.39           | 1.6171      | 1007                | 1.47                   | 1.7991 | 1030                 | 11.8%                  | -0.05 [-0.13, 0.04]                        |   |  |  |
| Hashimoto 2016   | -0.86          | 6.9         | 28                  | 3.1                    | 6.7    | 20                   | 1.3%                   | -0.57 [-1.16, 0.01]                        |   |  |  |
| Jackson 2016   | 0.38           | 1.09        | 125                 | 0.35                   | 1.08   | 93                   | 4.6%                   | 0.03 [-0.24, 0.30]                         |   |  |  |
| MAPT - Vellas 2017 (2)   |                | 2.6814      |                     |                        | 2.6462 | 366                  | 9.0%                   | 0.06 [-0.08, 0.21]                         |   |  |  |
| MAPT - Vellas 2017 (3)   | 0.239          | 2.6435      |                     |                        | 2.6863 | 356                  | 8.8%                   | 0.03 [-0.11, 0.18]                         |   |  |  |
| MEMO - Van de Rest 2008 (4)  | 0.01           | 1.12        | 100                 |                        | 0.96   | 51                   | 3.3%                   | 0.12 [-0.22, 0.46]                         |   |  |  |
| MIDAS - Yurko-Mauro 2010   | 0.1            | 1.48        | 219                 | 0                      | 1.18   | 218                  | 7.1%                   | 0.07 [-0.11, 0.26]                         |   |  |  |
| Sinn 2012 (5)<br>Subtotal (95% Cl)   | -0.7           | 1           | 18<br>3219          | 0.7                    | 1.3    | 7<br>3163            | 0.5%<br><b>58.2</b> %  | -1.25 [-2.20, -0.30]<br>0.01 [-0.07, 0.08] | •   |  |  |
| Heterogeneity: Tau² = 0.00; Chi² = 13.72, df = 8 (P = 0.09); I² = 42%<br>Test for overall effect: Z = 0.20 (P = 0.84)                                    |                |             |                     |                        |        |                      |                        |  |   |  |  |
| 1.41.2 EPA >250 to ≤500mg/d  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| DART2 Burr 2003  | 53.16          | 10.46       | 201                 | 51.61                  | 9.42   | 191                  | 6.7%                   | 0.16 [-0.04, 0.35]                         | +   |  |  |
| Lee 2012   | 1.9            | 1.4         | 17                  | 2.5                    | 1.39   | 18                   | 1.0%                   | -0.42 [-1.09, 0.25]                        |   |  |  |
| OMEGA - Senges 2009 (6)  | 7.1            | 0           | 1046                | 7.1                    | 0      | 1035                 |                        | Not estimable                              |   |  |  |
| Pomponi 2014   | 7.7            | 5.4         | 12                  | 10.4                   | 3.5    | 12                   | 0.7%                   | -0.57 [-1.39, 0.25]                        |   |  |  |
| SU.FOL.OM3 Galan 2010<br>Subtotal (95% CI)   | 8.43           | 6.7         | 1000<br><b>2276</b> | 7.98                   | 6.77   | 1000<br><b>2256</b>  | 11.8%<br><b>20.2</b> % | 0.07 [-0.02, 0.15]<br>0.04 [-0.13, 0.21]   | <br>◆   |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 5.13, df = 3 (P = 0.16); I <sup>2</sup> = 41%<br>Test for overall effect: Z = 0.50 (P = 0.61) |                |             |                     |                        |        |                      |                        |  |   |  |  |
| 1.41.3 EPA >500 to ≤1000mg/d   |                |             |                     |                        |        |                      |                        |  |   |  |  |
| DO IT - Einvik 2010  | 4.3            | 2.7         | 223                 | 4                      | 2.8    | 226                  | 7.2%                   | 0.11 [-0.08, 0.29]                         | +   |  |  |
| NEURAPRO - McGorry 2017  | -9.6           | 9.4         | 114                 | -9                     | 9.6    | 111                  | 4.8%                   | -0.06 [-0.32, 0.20]                        |   |  |  |
| OmegAD - Freund-Levi 2008  | 1.5            | 2.3736      | 89                  | 1.6                    | 1.8545 | 85                   | 4.0%                   | -0.05 [-0.34, 0.25]                        |   |  |  |
| TREND-HD 2008 (7)<br>Subtotal (95% CI)   | -0.7           | 0           | 152<br>578          | -0.9                   | 0      | 156<br>578           | 16.0%                  | Not estimable<br>0.03 [-0.10, 0.17]        | •   |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1<br>Test for overall effect: Z = 0.46 (P =   |                | 2 (P = 0    |                     | = 0%                   |        |                      |                        |  |   |  |  |
| 1.41.4 EPA >1000 to ≤2000mg/d  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| MEMO - Van de Rest 2008 (8)  | -0.05          | 1.08        | 96                  | -0.12                  | 0.96   | 51                   | 3.3%                   | 0.07 [-0.27, 0.41]                         |   |  |  |
| OFFER - Pawelczyk 2015   | -2.74          | 2.34        | 36                  | -1.16                  | 2.31   | 35                   | 1.9%                   | -0.67 [-1.15, -0.19]                       |   |  |  |
| Sinn 2012 (9)  | -0.5           | 0.8         | 17                  | 0.7                    | 1.3    | 7                    | 0.5%                   | -1.20 [-2.16, -0.25]                       |   |  |  |
| Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = 0.29; Chi <sup>2</sup> = 1  | I0 15 df       | = 2 (P =    | 149<br>0.006\*      | I <sup>2</sup> = 809   | 6      | 93                   | 5.6%                   | -0.51 [-1.20, 0.19]                        |   |  |  |
| Test for overall effect: Z = 1.43 (P =   |                | -20-        | 0.000),             | 1 - 00,                | •      |                      |                        |  |   |  |  |
| 1.41.9 Unknown dose  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| Subtotal (95% Cl)  |                |             | 0                   |                        |        | 0                    |                        | Not estimable                              |   |  |  |
| Heterogeneity: Not applicable<br>Test for overall effect: Not applicabl  | е              |             |                     |                        |        |                      |                        |  |   |  |  |
| Total (95% CI)   |                |             | 6222                |                        |        | 6090                 | 100.0%                 | -0.00 [-0.07, 0.07]                        |   |  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 3   | 36.45, df      | = 18 (P =   | = 0.006             | ); I <sup>2</sup> = 51 | %      |                      |                        |  | + $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$                       |  |  |
| Test for overall effect: Z = 0.02 (P =   | 0.98)          |             |                     |                        |        |                      |                        |  | -2 -1 U I 2<br>Favours higher omega 3 Favours lower omega 3 |  |  |
| Test for subgroup differences: Chi <sup>2</sup>  | = 2.35,        | df = 3 (P : | = 0.50)             | , I² = 0%              | 1      |                      |                        |  | r avours nigher onlega 5 T avours lower onlega 5            |  |  |
| <u>Footnotes</u>   |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (1) EPA+DHA +ALA vs ALA  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (2) LCn3 vs placebo (no multidomain intervention)  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (3) LCn3 + multidomain int vs placebo + multidomain int  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (4) 400mg/d LCn3 arm vs placebo (50% participants)   |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (5) High DHA arm vs placebo (50% participants)   |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (6) No SDs provided  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (7) No variance info provided  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (8) 1800mg/d LCn3 arm vs placebo (50% participants)<br>(9) High EPA arm vs placebo (50% participants)  |                |             |                     |                        |        |                      |                        |  |   |  |  |
| (9) High EPA aim vs placebo (50%   | particip       | ants)       |                     |                        |        |                      |                        |  |   |  |  |

# 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.

|  |                       | her LCn3    |             |                       | wer LCn          |            |                          | Std. Mean Difference                      | Std. Mean Difference  | Risk of Bias  |
|--|-----------------------|-------------|-------------|-----------------------|------------------|------------|--------------------------|---|---|---|
| Study or Subgroup<br>9.2.1 GDS (Geriatric Depression S   | Mean                  | SD          | Total       | Mean                  | SD               | Total      | Weight                   | IV, Random, 95% CI                        | IV, Random, 95% Cl  | ABCDEFGHI   |
| AlphaOmega 2010 EPA+DHA (1)  |                       | 1.6171      | 1007        | 1.47                  | 1.7991           | 1030       | 19.9%                    | -0.05 [-0.13, 0.04]                       |   |   |
| AlphaOmega 2010 EPA+DHA (2)  |                       | 1.6187      |             | 1.39                  |                  |            | 19.8%                    | 0.02 [-0.06, 0.11]                        | +   |   |
| Lee 2012   | 1.9                   |             | 17          | 2.5                   | 1.39             | 18         | 0.9%                     | -0.42 [-1.09, 0.25]                       | • • • • •   | $\bullet ? ? \bullet \bullet ? \bullet \bullet \bullet$   |
| MAPT - Vellas 2017 (3)<br>MAPT - Vellas 2017 (4)   | 0.239<br>0.455        |             | 340<br>373  |                       | 2.6863<br>2.6462 | 356<br>366 | 11.5%<br>11.9%           | 0.03 [-0.11, 0.18]<br>0.06 [-0.08, 0.21]  |   |   |
| MEMO - Van de Rest 2008  | -0.0194               |             | 196         | -0.12                 | 2.0402           | 103        | 5.7%                     | 0.10 [-0.14, 0.33]                        |   |   |
| MIDAS - Yurko-Mauro 2010   | 0.1                   | 1.48        | 219         | 0                     | 1.18             |            | 8.3%                     | 0.07 [-0.11, 0.26]                        | _ <del>_</del>  |   |
| Sinn 2012 (5)  | 3.2                   |             |             | 4.6                   | 1.516            | 15         | 0.7%                     | -0.90 [-1.62, -0.18]                      | •   | ••••  |
| SU.FOL.OM3 Galan 2010  | 8.43                  |             |             | 7.98<br>-0.3          | 6.77<br>2.77     | 1000<br>29 | 19.7%<br>1.5%            | 0.07 [-0.02, 0.15]                        |   |   |
| Tajalizadekhoob 2011 (6)<br>Subtotal (95% CI)  | -1.24                 | 2.5         | 4211        | -0.3                  | 2.11             | 4157       | 100.0%                   | -0.35 [-0.86, 0.15]<br>0.02 [-0.05, 0.08] | •   |   |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =   | 14.43, df=            | 9 (P = 0.   | 11); l²=    | 38%                   |                  |            |                          |   | ſ   |   |
| Test for overall effect: Z = 0.51 (P =   |                       |             |             |                       |                  |            |                          |   |   |   |
| 9.2.2 MADRS (Montgomery Asber  | a Doproce             | sion Datir  | a Scal      | a)                    |                  |            |                          |   |   |   |
| MEMO - Van de Rest 2008 (7)  |                       | 3 5674      | -           | -0.83                 | 3.39             | 103        | 40.4%                    | -0.03 [-0.26, 0.21]                       |   |   |
| NEURAPRO - McGorry 2017  | -9.6                  | 9.4         | 114         | -9                    | 9.6              |            | 33.6%                    | -0.06 [-0.32, 0.20]                       |   | •••••   |
| OmegAD - Freund-Levi 2008  | 1.5                   | 2.3736      |             | 1.6                   | 1.8545           | 85         | 26.0%                    | -0.05 [-0.34, 0.25]                       |   | • ? ? ? • • • • ?   |
| Subtotal (95% CI)  | 0.04.46               |             | 399         |                       |                  | 299        | 100.0%                   | -0.04 [-0.20, 0.11]                       | -   |   |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =<br>Test for overall effect: Z = 0.57 (P =   |                       | 2 (P = 0.9  | 18); I* = 1 | 0%                    |                  |            |                          |   |   |   |
|  | 0.017                 |             |             |                       |                  |            |                          |   |   |   |
| 9.2.3 HAM-D (Hamilton Depressio  | n Scale)              |             |             |                       |                  |            |                          |   | _   |   |
| Pomponi 2014   | 7.7                   | 5.4         | 12<br>12    | 10.4                  | 3.5              |            | 100.0%                   | -0.57 [-1.39, 0.25]                       | <b>↓</b>  | •???•?•?•   |
| Subtotal (95% CI)<br>Heterogeneity: Not applicable   |                       |             | 12          |                       |                  | 12         | 100.0%                   | -0.57 [-1.39, 0.25]                       |   |   |
| Test for overall effect: Z = 1.37 (P =   | 0.17)                 |             |             |                       |                  |            |                          |   |   |   |
|  |                       |             |             |                       |                  |            |                          |   |   |   |
| 9.2.4 HADS (Hospital Anxiety & D   | -                     |             | -           |                       |                  |            |                          |   | _   |   |
| DO IT - Einvik 2010<br>Subtotal (95% CI)   | 4.3                   | 2.7         | 223<br>223  | 4                     | 2.8              | 226<br>226 | 100.0%<br><b>100.0</b> % | 0.11 [-0.08, 0.29]<br>0.11 [-0.08, 0.29]  |   | $\bullet ? ? \bullet \bullet ? \bullet \bullet \bullet$   |
| Heterogeneity: Not applicable  |                       |             | 225         |                       |                  | 220        | 100.076                  | 0.11[-0.00, 0.25]                         |   |   |
| Test for overall effect: Z = 1.15 (P =   | 0.25)                 |             |             |                       |                  |            |                          |   |   |   |
| 0.0.5 CHO. Democratica (Compared   |                       |             |             |                       |                  |            |                          |   |   |   |
| 9.2.5 GHQ - Depression (General<br>Jackson 2016  | ieann Qui<br>0.38     |             |             | 0.35                  | 1.08             | 0.2        | 100.0%                   | 0.03 (-0.24, 0.30)                        |   |   |
| Subtotal (95% CI)  | 0.30                  | 1.08        | 125         | 0.50                  | 1.00             | 93         | 100.0%                   | 0.03 [-0.24, 0.30]                        |   |   |
| Heterogeneity: Not applicable  |                       |             |             |                       |                  |            |                          |   |   |   |
| Test for overall effect: Z = 0.20 (P =   | 0.84)                 |             |             |                       |                  |            |                          |   |   |   |
| 9.2.6 SDS (Self-rating depression  | scale)                |             |             |                       |                  |            |                          |   |   |   |
| Hashimoto 2016   | -0.86                 | 6.9         | 28          | 3.1                   | 6.7              | 20         | 100.0%                   | -0.57 [-1.16, 0.01]                       | ← <b>–</b>  | ????@?@?  |
| Subtotal (95% CI)  |                       |             | 28          |                       |                  | 20         | 100.0%                   | -0.57 [-1.16, 0.01]                       |   |   |
| Heterogeneity: Not applicable  |                       |             |             |                       |                  |            |                          |   |   |   |
| Test for overall effect: Z = 1.91 (P =   | 0.06)                 |             |             |                       |                  |            |                          |   |   |   |
| 9.2.7 CDS (Calgary Depression S  | ale for Sc            | hizophre    | enia)       |                       |                  |            |                          |   |   |   |
| OFFER - Pawelczyk 2015   | -2.74                 | 2.34        | 36          | -1.16                 | 2.31             | 35         | 100.0%                   | -0.67 [-1.15, -0.19]                      |   |   |
| Subtotal (95% CI)  |                       |             | 36          |                       |                  | 35         | 100.0%                   | -0.67 [-1.15, -0.19]                      |   |   |
| Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.75 (P =  | (800.0                |             |             |                       |                  |            |                          |   |   |   |
| reactor overall ellect. Z = 2.75 (r =  | 0.000)                |             |             |                       |                  |            |                          |   |   |   |
| 9.2.8 BDI-II (Beck Depression Inve   | entory)               |             |             |                       |                  |            |                          |   |   |   |
| OMEGA - Senges 2009 (8)  | 7.1                   |             | 1046        | 7.1                   | 0                |            |                          | Not estimable                             |   |   |
| TREND-HD 2008 (9)<br>Subtotal (95% CI)   | -0.7                  | 0           | 152         | -0.9                  | 0                | 156<br>0   |                          | Not estimable<br>Not estimable            |   | $\bullet \bullet \circ \circ \bullet \bullet \circ \circ \circ \bullet \bullet \bullet \circ \bullet \bullet \bullet \bullet \bullet \bullet \bullet$ |
| Heterogeneity: Not applicable  |                       |             |             |                       |                  | 0          |                          | Notestimusic                              |   |   |
| Test for overall effect: Not applicat  | le                    |             |             |                       |                  |            |                          |   |   |   |
| 0.2.0 Decentio to al   |                       |             |             |                       |                  |            |                          |   |   |   |
| 9.2.9 Derogatis tool<br>DART2 Burr 2003  | 53.16                 | 10.46       | 201         | 51.61                 | 9.42             | 101        | 100.0%                   | 0.16 [-0.04, 0.35]                        |   | 22888282828   |
| Subtotal (95% CI)  | 05.10                 | 10.40       | 201         | 51.01                 | 9.42             |            | 100.0%                   | 0.16 [-0.04, 0.35]                        |   |   |
| Heterogeneity: Not applicable  |                       |             |             |                       |                  |            |                          |   | -   |   |
| Test for overall effect: Z = 1.53 (P =   | 0.13)                 |             |             |                       |                  |            |                          |   |   |   |
|  |                       |             |             |                       |                  |            |                          |   |   | _   |
|  |                       |             |             |                       |                  |            |                          |   | -0.5 -0.25 0 0.25 0.5   |   |
| Test for subgroup differences: Chi   | <sup>2</sup> = 17.21, | df = 7 (P = | = 0.02),    | I <sup>2</sup> = 59.3 | 3%               |            |                          |   | Favours higher LCn3 Favours lower LCn3  |   |
| Footnotes  |                       |             |             |                       |                  |            |                          |   | Risk of bias legend   |   |
| (1) EPA+DHA vs control   |                       |             |             |                       |                  |            |                          |   | (A) Random sequence generation (selection   | n bias)   |
| (2) EPA+DHA +ALA vs ALA<br>(3) LCn3 + multidomain int vs plac  | aho + mu              | tidomais    | int         |                       |                  |            |                          |   | <ul> <li>(B) Allocation concealment (selection bias)</li> <li>(C) Blinding of participants and personnel (p)</li> </ul> | erformance hias)  |
| (4) LCn3 vs placebo (no multidom   |                       |             |             |                       |                  |            |                          |   | (D) Blinding of outcome assessment (detec   |   |
| (5) DHA vs control (unable to com  |                       |             | arms)       |                       |                  |            |                          |   | (E) Incomplete outcome data (attrition bias)  |   |
| (6) Change data used (F) Selective reporting (reporting bias)  |                       |             |             |                       |                  |            |                          |   |   |   |
| (7) Omitied in meta-analysis to prevent MEMO participants appearing twice in the analysis (G) Attention (2) Ne water and the second sec |                       |             |             |                       |                  |            |                          |   |   |   |
| (8) No variance info provided<br>(9) No variance info provided   |                       |             |             |                       |                  |            |                          |   | (H) Compliance<br>(I) Other bias  |   |
|  |                       |             |             |                       |                  |            |                          |   |   |   |
|  |                       |             |             |                       |                  |            |                          |   |   |   |

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<sup>2</sup> 46%).

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## **Supplementary References**

1. Hooper L, Abdelhamid A, Brainard J, Deane KHO, Song F. Creation of a database to assess effects of omega-3, omega-6 and total polyunsaturated fats on health: database and methodology for a set of reviews. BMJ Open. 2019; 9(5): e029554. DOI: 10.1136/bmjopen-2019-029554

2. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010; 363(21): 2015-26.

3. Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS, et al. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. JAMA. 2015; 314(8): 791-801.

4. ASCEND Study Collaborative Group. Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med. 2018; 379(16): 1540-50. 10.1056/NEJMoa1804989

5. Derosa G, Cicero AF, D'Angelo A, Borghi C, Maffioli P. Effects of n-3 PUFAs on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance. BioFactors. 2016; 42(3): 316-22.

6. Danthiir V, Hosking D, Burns NR, Wilson C, Nettelbeck T, Calvaresi E, et al. Cognitive performance in older adults is inversely associated with fish consumption but not erythrocyte membrane n-3 fatty acids. J Nutr. 2014; 144(3): 311-20.

7. Vellas B, Carrie I, Guyonnet S, Touchon J, Dantoine T, Dartigues JF, et al. MAPT (multi-domain Alzheimer's prevention trial): Results at 36 months. Alzheimer's dement. 2015; 1): 331.

8. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimer's dement. 2010; 6(6): 456-64.

9. Pawelczyk T, Grancow-Grabka M, Kotlicka-Antczak M, Trafalska E, Pawelczyk A. A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. J Psychiatr Res. 2016; 73: 34-44.

10. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010; 122(21): 2152-9.

11. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr. 2010; 91(6): 1725-32.

12. Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. Br J Nutr. 2012; 107(11): 1682-93.

13. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. Br Med J. 2010; 341: c6273.

14. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017; 16(5): 377-89. DOI: 10.1016/S1474-4422(17)30040-6

15. Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(6): 1538-44.

16. Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr. 2003; 57(2): 193-200.

17. Tokudome S, Kuriki K, Yokoyama Y, Sasaki M, Joh T, Kamiya T, et al. Dietary n-3/long-chain n-3 polyunsaturated fatty acids for prevention of sporadic colorectal tumors: a randomized controlled trial in polypectomized participants. Prostaglandins Leukot Essent Fatty Acids. 2015; 94: 1-11.

18. Einvik G, Ekeberg O, Lavik JG, Ellingsen I, Klemsdal TO, Hjerkinn EM. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. J Psychosom Res. 2010; 68(6): 567-72.

19. Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M, Group E. No significant effects of ethyleicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology. 2014; 147(2): 377-84. 20. Ferreira JJ, Rosser A, Craufurd D, Squitieri F, Mallard N, Landwehrmeyer B. Ethyl-eicosapentaenoic acid treatment in Huntington's disease: A placebo-controlled clinical trial. Mov Disord. 2015; 30(10): 1426-9.

21. Hashimoto M, Kato S, Tanabe Y, Katakura M, Mamun AA, Ohno M, et al. Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function and mental health of the oldest elderly in Japanese care facilities and nursing homes. Geriatr Gerontol Int. 2016; 17(2): 330-7.

22. Jackson PA, Forster JS, Bell JG, Dick JR, Younger I, Kennedy DO. DHA Supplementation Alone or in Combination with Other Nutrients Does not Modulate Cerebral Hemodynamics or Cognitive Function in Healthy Older Adults. Nutrients. 2016; 8: 86-.

Lee SP, Dart AM, Walker KZ, O'Dea K, Chin-Dusting JP, Skilton MR. Effect of altering dietary n-6:n-3 PUFA ratio on cardiovascular risk measures in patients treated with statins: a pilot study. Br J Nutr. 2012; 108(7): 1280-5.
 Van De Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG, et al. Effect of fish oil

on cognitive performance in older subjects: a randomized, controlled trial. Neurology. 2008; 71(6): 430-8. 25. McGorry PD, Nelson B, Markulev C, Yuen HP, Schäfer MR, Mossaheb N, et al. Effect of  $\omega$ -3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders: The NEURAPRO Randomized Clinical Trial. JAMA Psychiatry. 2017; 74(1): 19-27.

26. Torkildsen O, Wergeland S, Bakke S, Beiske AG, Bjerve KS, Hovdal H, et al. omega-3 fatty acid treatment in multiple sclerosis (OFAMS Study): a randomized, double-blind, placebo-controlled trial. Arch Neurol. 2012; 69(8): 1044-51.

27. Freund-Levi Y, Basun H, Cederholm T, Faxen-Irving G, Garlind A, Grut M, et al. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. Int J Geriatr Psychiatry. 2008; 23(2): 161-9.

28. Palma C. Omega 3 fatty acids supplementation in Schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2015; 265(Supplement 1): S122-S.

29. Pomponi M, Loria G, Salvati S, Di Biase A, Conte G, Villella C, et al. DHA effects in Parkinson disease depression. Basal Ganglia. 2014; 4(2): 61-6.

30. Pratt CM, Reiffel JA, Ellenbogen KA, Naccarelli GV, Kowey PR. Efficacy and safety of prescription omega-3acid ethyl esters for the prevention of recurrent symptomatic atrial fibrillation: a prospective study. Am Heart J. 2009; 158(2): 163-9.

31. Tajalizadekhoob Y, Sharifi F, Fakhrzadeh H, Mirarefin M, Ghaderpanahi M, Badamchizade Z, et al. The effect of low-dose omega 3 fatty acids on the treatment of mild to moderate depression in the elderly: a double-blind, randomized, placebo-controlled study. Eur Arch Psychiatry Clin Neurosci. 2011; 261(8): 539-49.

32. Tuttle KR, Shuler LA, Packard DP, Milton JE, Daratha KB, Bibus DM, et al. Comparison of low-fat versus Mediterranean-style dietary intervention after first myocardial infarction (from The Heart Institute of Spokane Diet Intervention and Evaluation Trial). Am J Cardiol. 2008; 101(11): 1523-30.

33. Huntington Study Group. Randomized controlled trial of ethyl-eicosapentaenoic acid in Huntington disease: the TREND-HD study. Arch Neurol. 2008; 65(12): 1582-9.

34. Geleijnse J, Giltay E, Kromhout D. Effects of n-3 fattyacids on cognitive decline: A randomized double-blind, placebo-controlled trial in stable myocardial infarction patients. Alzheimer's dement. 2011; 1): S512.

35. Estruch R, Ros E, Salas-Salvadó J, Covas M, Corella D, Arós F et al. Retraction and republication: Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013; 368:1279-90. N Engl J Med. 2018; 378: 25-.

36. Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Statistics in Medicine. 2006; 25(20): 3443-57. DOI: 10.1002/sim.2380

37. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Br Med J. 2011; 343: d4002. DOI: 10.1136/bmj.d4002

38. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of Two Methods to Detect Publication Bias in Meta-analysis. JAMA. 2006; 295(6): 676-80. DOI: 10.1001/jama.295.6.676

39. Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. Draft version (29 Janaury 2019) for inclusion in. In: Cochrane Handbook for Systematic Reviews of Interventions (eds JPT HIggins, J Thomas, J Chandler, M Cumpston, T Li, MJ Page, et al.). Cochrane, 2019.

40. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010; 122(21): 2152-9.

41. Van De Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Hoefnagels WH, Beekman AT, et al. Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2008; 88(3): 706-13.

42. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018; 11: CD003177. DOI: 10.1002/14651858.CD003177.pub4

43. Abdelhamid AS, Martin N, Bridges C, Brainard JS, Wang X, Brown TJ, et al. Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018; 11: CD012345. DOI: 10.1002/14651858.CD012345.pub3

44. Hooper L, Al-Khudairy L, Abdelhamid AS, Rees K, Brainard JS, Brown TJ, et al. Omega-6 fats for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018; 11: CD011094. DOI: 10.1002/14651858.CD011094.pub4

45. Abdelhamid A, Hooper L, Sivakaran R, Hayhoe RPG, Welch A, The PUFAH Group. The Relationship Between Omega-3, Omega-6 and Total Polyunsaturated Fat and Musculoskeletal Health and Functional Status in Adults: A Systematic Review and Meta-analysis of RCTs. Calcified Tissue International. 2019. DOI: 10.1007/s00223-019-00584-3

46. Brainard J, Jimoh OF, Deane K, Biswas P, Donaldson D, Maas K, et al. Omega-3, omega-6 and total polyunsaturated fat for cognition and dementia: Systematic review and meta-analysis of RCTs. submitted. 2019.

47. Brown TJ, Brainard J, Song F, Wang X, Abdelhamid A, Hooper L. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. Br Med J. 2019; 366: I4697. DOI: 10.1136/bmj.I4697

Hanson S, Thorpe G, Winstanley L, Abdelhamid AS, Hooper L. Omega-3, omega-6 and total dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials. submitted. 2019.
Thorpe G, Ajabnoor S, Ahmed Z, Abdelhamid A, Hooper L. Dietary polyunsaturated fat for prevention and treatment of inflammatory bowel disease. PROSPERO. 2017: CRD42017068704.

50. Cockayne NL, Duffy SL, Bonomally R, English A, Amminger PG, Mackinnon A, et al. The Beyond Ageing Project Phase 2--a double-blind, selective prevention, randomised, placebo-controlled trial of omega-3 fatty acids and sertraline in an older age cohort at risk for depression: study protocol for a randomized controlled trial. Trials. 2015; 16: 247.

51. Cai S, Coates AM, Buckley JD, Berry NM, Burres L, Beltrame J, et al. There is No Association Between the Omega-3 Index and Depressive Symptomsin Patients With Heart Disease Who Are Low Fish Consumers. Heart Lung Circ. 2017; 26: 276-84.

52. Bowman LG, Silbert CL, Dodge HH, Lahna D, Hagen K, Murchison FC, et al. Randomized Trial of Marine n-3 Polyunsaturated Fatty Acids for the Prevention of Cerebral Small Vessel Disease and Inflammation in Aging (PUFA Trial): Rationale, Design and Baseline Results. Nutrients. 2019; 11(4). DOI: 10.3390/nu11040735

53. Qurashi I, Chaudhry IB, Khoso AB, Farooque S, Lane S, Husain MO, et al. A randomised, double-blind, placebo-controlled trial of minocycline and/or omega-3 fatty acids added to treatment as usual for at-risk mental states (NAYAB): study protocol. Trials. 2017; 18(1): 524. DOI: 10.1186/s13063-017-2275-y

54. Okereke OI, Reynolds CF, III, Mischoulon D, Chang G, Cook NR, Copeland T, et al. The VITamin D and OmegA-3 TriaL-Depression Endpoint Prevention (VITAL-DEP): Rationale and design of a large-scale ancillary study evaluating vitamin D and marine omega-3 fatty acid supplements for prevention of late-life depression. Contemp Clin Trials. 2018; 68: 133-45. DOI: 10.1016/j.cct.2018.02.017