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Efficacy and safety of *n*-3 fatty acids supplementation on depression: a systematic review and dose–response meta-analysis of randomised controlled trials

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Abstract

We aimed to investigate the effectiveness of *n*-3 fatty acids supplementation on the risk of developing depression, depressive symptoms and remission of depression. We searched PubMed, Scopus and Web of Science from inception to December 2022 to find randomised trials of *n*-3 fatty acids supplementation in adults. We conducted random-effects meta-analyses to estimate standardised mean differences (SMD) and 95 % CI for continuous outcomes and risk difference and 95 % CI for binary outcomes. A total of sixty-seven trials were included. Each 1 g/d *n*-3 fatty acids supplementation significantly improved depressive symptoms in adults with and without depression (moderate-certainty evidence), with a larger improvement in patients with existing depression. Dose–response analyses indicated a U-shaped effect in patients with existing depression, with the greatest improvement at 1·5 g/d. The analysis showed that *n*-3 fatty acid supplementation significantly increased depression remission by 19 more per 100 in patients with depression (low-certainty evidence). Supplementation with *n*-3 fatty acids did not reduce the risk of developing depression among the general population, but it did improve the severity of depression among patients with existing depression.

Keywords: **Fatty acids: *n*-3: Depression: Randomised control trials: Dose–response: Supplementation: Adult**

Depression is a common mental disorder around the world. According to the WHO, about 280 million adults (5 % of the world population) suffer from depression symptoms[1]. People with depression suffer from functional impairment and reduced quality of life[2]. Depression is also associated with a higher risk of CHD[3], stroke[4], and type 2 diabetes[5] and thereby affects both individuals[6] and societies[7].

Hence, it seems necessary to investigate various approaches to prevent depressive disorders among the general population or diminish depressive symptoms among people with existing depression. Currently, both pharmacological and non-pharmacological approaches are being used for treating depression. Even though there is improvement in developing antidepressant medications with lesser side effects, patients still experience residual symptoms[8]. Therefore, alternative non-pharmacological approaches for treating depressive symptoms may still be needed.

Evidence suggests that poor diet quality could be a risk factor for developing depression[9]. Of note, the optimum development of the central nervous system requires sufficient intake of *n*-3 PUFA such as EPA and DHA[10]. Evidence supports the protective effect of EPA and DHA in treating mental and mood disorders[10,11]. Over the past century, changes in the diet caused a noticeable decrease in the ratio of *n*-3 to *n*-6 fatty acids[11]. Epidemiologic studies have shown that patients with depression and mood disorders have a low dietary intake of long-chain *n*-3 fatty acids[12,13].

Previous pairwise meta-analyses have reported conflicting results about the effects of supplementation with *n*-3 fatty acids on depressive symptoms[14,15]. A recent network meta-analysis indicated that high-dose *n*-3 fatty acids might be superior to low-dose supplements in reducing depressive disorders in patients with major depressive disorders[16]. However, the optimum dose of *n*-3 fatty acids supplementation for reducing depressive symptoms has not been ascertained. Evaluating the potential dose-dependent effects of *n*-3 fatty acids on depressive symptoms can provide useful information for both patients and clinicians and, thus, may have important clinical implications. In addition, the potential efficacy of *n*-3 fatty acids on reversal of depression has not been well investigated. Therefore,

Abbreviations: GDS, Geriatric Depression Scale; RCT, randomised controlled trials; SMD, standardised mean differences.

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we conducted a systematic review and dose–response meta-analysis of randomised controlled trials (RCT) to investigate the effectiveness of *n*-3 fatty acids for the prevention of depression, as well as for treating depressive symptoms in adults.

Methods

The review was planned and conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[17] and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework[18]. The review protocol was registered with PROSPERO (CRD42022308241).

Data sources and searches

We searched PubMed, Scopus and Web of Science from inception to December 2022. Two investigators (RN and SZM) independently performed the literature search and screened the titles and abstracts and full texts. Disagreements were resolved by discussion with a third reviewer (SS-B). We also checked out the reference lists of published meta-analyses of RCT on the effect of *n*-3 fatty acids on depression and its symptoms. The systematic search was limited to articles published in English. The full search strategy is detailed in online Supplementary Table 2.

Study selection

Inclusion criteria for original controlled trials were as follows: (1) RCT (parallel or crossover design) with no limitation in intervention period, conducted in adults, regardless of medication use and health status, aged 18 years or older; (2) intervention with *n*-3 supplementation, including EPA and/or DHA or alpha-linolenic acid (ALA) in any type of advice, foodstuffs or oral supplements (oil, capsules or provided foodstuffs) against a control group; (3) considered one of these outcome including risk of depression as assessed by formal diagnosis or an appropriate scale, dichotomised to give risk of depression in participants without depression at baseline, or severity of depression as a continuous scale in participants with or without existing depression, and severity of depression or depression relapse in those with depression at baseline; and (4) provided the number of participants and events across study arms to estimate both relative and absolute effects for binary outcomes, or reported mean difference and its 95 % CI for continuous outcomes or reported required information to calculate these values.

Exclusion criteria

Trials that were conducted in adolescents (under 18 years of age), pregnant and lactating women were excluded from the analyses.

Outcomes

The primary outcomes of our systematic review were as follows (1) risk of developing depression among people without depression evaluated by formal diagnosis or a suitable scale (such as Geriatric Depression Scale (GDS), Becks' Depression Inventory (BDI), etc.), dichotomised to provide depression risk among individuals without depression before intervention, (2) depression symptoms as a continuous scale in people with or without depression, and (3) depression remission as a dichotomous scale among patients with existing depression. Our secondary outcomes included quality of life[19], medication reduction, and total and serious adverse events. Any scales that were used to measure depressive symptoms in the included trials were eligible for inclusion in the present meta-analysis.

Data extraction

Two authors (RN and SZM) independently and in duplicate conducted literature screening for eligibility. From studies that were considered eligible, the same two reviewers independently extracted the following data: author name, year of publication, population location, study design and duration, characteristics of the population (% female, mean age +/–SD, baseline BMI and health status), total sample size, intervention characteristics (dose of *n*-3 supplementation in the intervention group), weight status, drop-out, the scale used for evaluating depressive symptoms, baseline depression severity, comparison group, antidepressant usage (yes/no), physical activity (yes/no), behavioural support (yes/no), outcome measures and main results for the outcomes included.

Risk of bias assessment

To determine the risk of bias of the trials, we used the RoB 2.0 tools for individually randomised parallel-group and crossover trials[20]. Two authors (RN and SZM) independently evaluated the study's risk of bias. Disagreements were resolved by consulting a third investigator (SS-B).

Strategy for data synthesis

For reporting the results of the present systematic review, the effect size was considered as standardised mean difference (SMD) and its 95 % CI for continuous outcomes, and both relative (OR and its 95 % CI) and absolute (risk difference (RD) and its 95 % CI) effects for binary outcomes. Since included trials used different scale to measure depressive symptoms, we used SMD to standardise the effect estimates obtained from different scales.

For the analyses of continuous outcomes, we first extracted the mean and SD of changes from baseline to the end of the intervention in each study arm in each trial. If a trial did not report these changes, we used the reported means and SD of outcomes before and after the intervention using the Cochrane Handbook guidelines[21]. For trials that reported standard errors instead of SD, we converted them to SD[22]. If neither SDs nor standard errors were reported in the trials, we used the average SD obtained from other trials for the analyses[23]. Second, we calculated SMD and its 95 % CI of change in continuous outcomes for each 1 g/d increment in *n*-3 fatty acids intake in each trial using the method introduced by Crippa and Orsini[24]. Trial-specific changes in outcomes per each 1 g/d increment in *n*-3 fatty acids intake were pooled using the DerSimonian and Laird random-effects model[25]. For the analyses of binary outcomes (depression risk, depression remission and medication reduction), we calculated both relative and absolute effects using the number of participants

British Journal of Nutrition

and events in the intervention and control groups. With regard to trials that had multiple study arms, we included trials that implemented two or three study arms with different doses since dose–response meta-analysis allows to include these trials. With regard to trials that had two study arms, one with co-intervention and another without co-intervention, we selected those without co-intervention for inclusion. For trials that implemented several study arms as intervention that were eligible for inclusion, we combined their results using the methods described below[26]. In order to rule out a possible placebo effect of *n*-3 fatty acids, we also showed the effects of the control groups (without *n*-3 fatty acids) for comparison. To report the results in the control group, we calculated the change in depressive symptoms in the control groups (final values minus baseline values) divided by baseline SD to compare the effect in the control groups with pooled SMD.

We performed prespecified subgroup analyses based on baseline depression risk, defined as: (1) high risk, defined as people with clinically diagnosed depression, using any diagnostic criteria; (2) medium risk, defined as people with depression risk factors such as long-term conditions; and (3) low risk, defined as all other populations); duration of intervention ($\leq$ 12, 12–24, $\geq$ 24 weeks for the severity of depression and ≤ 1 *v.* > 1 years for risk of depression); health status; and study risk of bias (low risk *v.* high risk/some concerns. Moreover, *post hoc* subgroup analyses were conducted based on supplement type (EPA, EPA + DHA, EPA + DHA + ALA), sex (men, women and both), weight status (normal weight, overweight/obese and not reported), and medication use (yes, no, mixed and not reported). According to eight criteria determined by the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN), we examined the credibility of subgroup differences[27]. We used meta-regression analysis to compute the *P*-values for subgroup differences. We applied Egger's[28] and Begg's test[29] for publication bias and evaluated the funnel plots for asymmetry. For assessing the heterogeneity across trials, we used the I^2 statistic and performed a χ^2 test ($P_{heterogeneity} > 0{\cdot}10$)[30]. Finally, we conducted a dose–response meta-analysis to determine the dose-dependent effects of *n*-3 fatty acids (g/d) on depression risk and its symptoms[24]. We used a '1-stage' natural cubic spline regression model on the basis of a random-effects model[31], assessing heterogeneity with the I^2 statistic[32]. The 1-stage method, consisting of a weighted mixed effects model, was recently developed and[33] allowed us to make inferences about the average dose–response relationship between supplementation with *n*-3 fatty acids and depressive symptoms. Having no specific parametric assumptions about the shape of the association, we used restricted cubic splines of potassium with three knots at fixed percentiles (10%, 50% and 90 %)[34]. Estimates of the parameters were obtained using restricted maximum likelihood[34]. We used STATA software version 17.0 for our analyses. A two-tailed *P*-value less than 0·05 was considered statistically significant.

Grading the evidence

To evaluate the certainty of the evidence, we applied the GRADE approach[35]. According to the GRADE, evidence acquired from RCT starts at high certainty that can be downregulated or upregulated based on predefined criteria. Detailed criteria used to apply the GRADE approach are explained in online Supplementary Table 14. In order to interpretation of the magnitude of effect sizes, the estimated SMD were interpreted as a trivial effect (0·0–0·2), a small effect (0·2–0·6), a moderate effect (0·6–1·2), a large effect (1·2–2·0), a very large effect (2·0–4·0) and an extremely large effect ($\geq$ 4·0)[36,37].

Results

Systematic search

An outline of the search strategy is presented in online Supplementary Fig. 1. Our search in databases identified a total of 2611 records. After excluding 363 duplicates, and exclusion of twenty-one studies, we reviewed the rest of the records for eligibility, and of those, sixty-seven trials met the eligibility criteria[38–104] (online Supplementary Table 4). Reasons for exclusions are provided in online Supplementary Table 6.

Characteristics of original trials

Fifty-three trials reported information on depression severity, of those, seven trials reported information on depression remission (online Supplementary Table 7). Of the fifty-three studies, ten trials were carried out on healthy participants[53,55,58,62,64,67,94,101–103], twenty-five trials were carried out in depressed populations[39,41,43–45,49,51,56,65,66,70,73,76,79–81,87,88,90,92,93,96,98,99,105], one study in Alzheimer's disease patients[38], two in participants with borderline personality disorder[40,104], one in those with stress[42], one in patients with myocardial infarction[57,60], one in patients with self-harm experience[61], one in those with mild cognitive impairment[69], one in those with psychological distress[71], one in people at risk for psychotic disorders[77], two in those with bipolar disorders[78,79], one in those with schizophrenia[82], two in patients with Parkinson's disease[83,89], one in patients with ischemic stroke[84], one in women with premenstrual syndrome[95] and one those with cognitive decline[103]. Twelve trials had a low risk of bias[39,41,42,58,66,70,71,74,77,83,89,101], sixteen trials were rated to have some concerns [46,53,55,65,76,78,79,81,82,84,90,92–94,98,102,103] and the other twenty-five trials considered to have a high risk of bias[38,40,43–45,48,49,51,56,57,60–62,64,67,69,73,80,87,88,95,96,99,104]. In total, twenty trials were carried out in populations with overweight or obesity (BMI $\geq$ 25 kg/m^2)[38,41–43,45,48,57,58,65–67,69,71,84,94,98,99,101], eight trials were conducted in participants with normal weight (18 < BMI < 25 kg/m^2)[39,61,62,64,81,89,90,95] and the other twenty-seven trials did not report the weight status of the participants[40,49,51,53,55,56,60,67,70,73,74,76–80,82,83,87,88,92,93,96,102–105]. The intervention duration was 12 weeks or shorter in thirty-one trials[39–44,48,49,60,61,64–67,70,71,73,74,76,80,81,84,87,88,90,93,95,96,99,104,105], between 12 and 24 weeks in nine trials[51,56,58,83,89,92,94,98,103], and longer than 24 weeks in thirteen trials[38,43,53,55,57,62,69,77–79,82,101,102]. Four clinical trials used DHA for supplementation[73,79,93,103], four trials used EPA[41,44,79,80,104], thirty-seven trials used a combination of DHA and EPA[38–40,42,43,49,51,53,56,58,60–62,66,67,69–71,77–79,81–84,87–89,

[92,94,96,98,99,101,102,105] and eight trials used EPA + DHA + ALA for supplementation[45,48,55,57,65,74,76,95].

Thirteen trials (fourteen effect sizes) reported information about the effects of n-3 supplementation on depression risk (online Supplementary Table 8). These trials were published between 2008 and 2019. Four trials implemented behavioural support[52,68,72,106], while the other ten trials did not[47,50,54,59,63,75,85,86,91,100]. Nine trials had a low risk of bias[50,52,54,59,68,75,86,91,100], and four trials were considered to have a high risk of bias[47,63,72,85] (online Supplementary Table 9). The primary studies used different scales to recognise participants with depression or at risk of depression. For instance, GDS[38,57,69,72,88,90,94,98,101,103], BDI[39,43–46,51,56,58,60,61,65,66,75,76,79,87,93,99], Hamilton Depression Rating Scale (HAMD)[40,43,44,46,66,73,76,83,97], Montgomery–Asberg Depression Rating Scale (MADRS)[49,65,70,92,101,104], Clinical Global Impression (CGI)[49], Hospital Anxiety and Depression Scale (HDRS)[78–80,93], Calgary Depression Scale (CDS)[82], Brief Psychiatric Rating Scale (BPRS)[89], Center for Epidemiologic Studies Depression Scale (CES-D)[67,81,99,101], The Depression, Anxiety and Stress Scale (DASS)[42,64], Patient Health Questionnaire (PHQ)[48,53,87,102], The General Health Questionnaire[84], The Diagnostic and Statistical Manual of Mental Disorders (DSM)[73,80,92], Zagazig Depression Scale (ZDS)[53], Self-Rating Depression Scale (SDS)[62], and Young Mania Rating Scale (YMRS)[78] in the form of continuous or dichotomised scales were commonly used to assess the outcomes.

The definition of depression remission also varied considerably across trials. For example, one trial defined depression remission as the GDS score less than 11[90], two trials defined it as the BDI-II score ≤ 8[43,44] and the other four trials defined it as the Hamilton Rating Scale for Depression score ≤ 7[55,79,83,107].

Primary outcomes

Fourteen trials with 16 412 participants in the intervention group and 16 343 in the control group reported data about the effect of n-3 fatty acids on the risk of depression[47,50,52,54,59,63,68,72,75,85,86,91,100,106]. Supplementation with n-3 fatty acid did not significantly reduce the risk of depression (OR: 0·95, 95 % CI 0·79, 1·15; GRADE = moderate) (Fig. 1, online Supplementary Fig. 2 and Table 1).

Online Supplementary Table 10 shows the subgroup analyses of the effects of n-3 fatty acids supplementation on the risk of depression based on risk of bias, intervention duration, physical activity, behavioural support and degree of adherence to the intervention. The results remained non-significant in all subgroups (online Supplementary Table 10). The ICEMAN tool revealed no credible difference between the subgroups (online Supplementary Table 11)[27]. Figure 2 showed the dose-dependent effects of n-3 fatty acids on the risk of depression. The analysis showed that the risk of depression did not change materially with the increase of the dosage of intervention ($P_{nonlinearity} = 0{\cdot}71$, $P_{dose\text{-}response} = 0{\cdot}49$; n 14, Table 2).

Fifty-three trials with 5110 participants in the intervention group and 5057 in the control group reported data about the effect of n-3 fatty acids (each 1 g/d) on the severity of depression[38–46,48,49,51,53,55–58,60–62,64–66,69–71,73,74,76–84,87–90,92–96,98,99,101–104]. Each 1 g/d n-3 fatty acid supplementation resulted in a large improvement in the severity of depression (SMD: −1·38, 95 % CI −1·69, −1·07; $I^2 = 97\,\%$, GRADE = moderate) (online Supplementary Fig. 3 and Table 1).

Online Supplementary Table 12 shows the subgroup analyses of the effects of n-3 fatty acids (each 1 g/d) supplementation on the severity of depression. Of note, supplementation with n-3 fatty acids resulted in a larger reduction in depressive symptoms among those with existing depression (SMD: -3·03, 95 % CI −4·27, −1·79; n 25 trials with 1830 participants). There was no significant subgroup difference based on risk of bias, length of intervention, baseline depression risk and type of supplement (EPA *v.* DHA *v.* combined). There was no credible differences across subgroups (online Supplementary Table 13)[27]. The funnel plot and Egger's test ($P = 0{\cdot}01$) and Begg's test ($P = 0{\cdot}001$) showed some evidence of publication bias (online Supplementary Fig. 4).

Figure 3 indicates the dose-dependent effects of n-3 fatty acids on the severity of depression. The analysis showed that supplementation of n-3 fatty acids up to 2 g/d resulted in a large reduction in the severity of depression ($SMD_{2\ g/d}$: −1·98; 95 % CI −2·88, −1·08), followed by a trivial decrease in the severity of depression at higher doses ($P_{dose\text{-}response} < 0{\cdot}001$, $P_{nonlinearity} = 0{\cdot}021$; n 53, Table 2).

Figure 4 indicates a sensitivity analysis of the dose-dependent effects of n-3 fatty acids on the severity of depression in patients with existing depression. The analysis indicated a modest U-shaped effect, with the highest decline in the severity of depression at a dose of 1·5 g/d ($MD_{1.5\ g/d}$: −4·32; 95 % CI −6·50, −2·14) ($P_{dose\text{-}response} < 0{\cdot}001$, $P_{nonlinearity} = 0{\cdot}002$; n 33, Table 2). A sensitivity analysis of participants without depression indicated a linear reduction in depressive symptoms along with the increase in dose of intervention (($P_{dose\text{-}response} < 0{\cdot}001$, $P_{nonlinearity} = 0{\cdot}08$; n 20, Fig. 5).

Seven trials with 113 participants in the intervention group and 128 participants in the control group reported data about the effect of n-3 fatty acids on depression remission[43,44,55,61,79,83,90]. The follow-up duration was between 8 to 52 weeks (median follow-up duration: 12 weeks). n-3 fatty acid supplementation significantly increased the odds of depression remission by 148 % (OR: 2·48, 95 % CI 1·12, 5·46; $I^2 = 63\,\%$, GRADE = low) (online Supplementary Fig. 5 and Table 1).

Secondary outcomes

The effects of n-3 fatty acids on secondary outcomes are shown in online Supplementary Fig. 6–22 and Table 1. Supplementation with n-3 fatty acids did not increase adverse events but improved overall quality of life and some aspects of quality of life such as role emotion and vitality (Table 1).

Grading of the evidence

The certainty of evidence was rated moderate for the effects of supplementation with n-3 fatty acids on the risk of depression and severity of depression. The certainty of evidence was rated very low to low for other outcomes (online Supplementary Table 14).

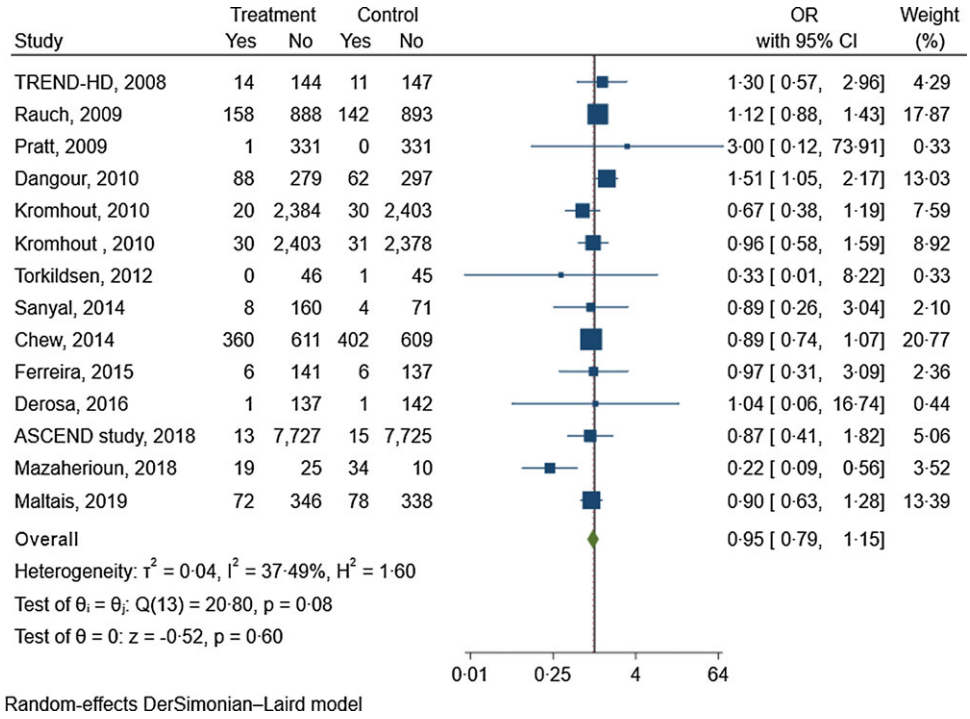

Fig. 1. The effects of *n*-3 fatty acids supplementation on depression risk.

Table 1. The effect of *n*-3 fatty acids supplementation on primary and secondary outcomes

Outcome (s)	Number of trials	Participants	Type of effect size	Effect size	95 % CI	GRADE certainty
Severity of depression	53	10 273	Change in the control group	−0·15	−0·20, −0·10	Moderate
	53	10 273	Standardised mean difference (per 1 g/d)	−1·38	−1·69, −1·07	
Risk of depression	14	32 755	OR	0·95	0·79, 1·15	Moderate
			Risk difference	−0·00	−0·00, 0·00	
Depression remission	7	467	OR	2·48	1·12, 5·46	Low
			Risk difference	0·19	0·05, 0·34	Low
Adverse event	29	4387	OR	1·10	0·86, 1·39	Low
			Risk difference	0·02	−0·03, 0·07	Low
Serious adverse event	2	2010	OR	1·01	0·89, 1·15	Very low
			Risk difference	0·00	−0·02, 0·03	Very low
Overall quality of life (per 1 g/d)	2	112	Standardised mean difference	0·88	0·41, 1·35	Low
Emotional well-being (per 1 g/d)	1	72	Standardised mean difference	−0·23	−0·69, 0·23	Low
General health (per 1 g/d)	2	106	Standardised mean difference	−0·13	−0·51, 0·25	Low
Mental health (per 1 g/d)	2	136	Standardised mean difference	0·25	−0·74, 1·24	Very low
Pain (per 1 g/d)	2	106	Standardised mean difference	0·14	−0·84, 1·12	Very low
Physical health (per 1 g/d)	3	208	Standardised mean difference	−0·57	−1·26, 0·12	Very low
Role-emotion (per 1 g/d)	1	34	Standardised mean difference	1·93	1·13, 2·73	Low
Role-function (per 1 g/d)	2	338	Standardised mean difference	1·05	−1·20, 3·31	Very low
Social function (per 1 g/d)	4	445	Standardised mean difference	0·54	−0·12, 1·19	Very low
Social-occupational function (per 1 g/d)	1	304	Standardised mean difference	0·02	−0·20, 0·25	Low
Vitality (per 1 g/d)	1	34	Standardised mean difference	1·74	0·96, 2·52	Low
Medication reduction	2	163	OR	1·21	0·87, 1·68	Low
			Risk difference	0·03	−0·07, 0·12	Low

Discussion

Herein, we investigated the RCT of the effect of *n*-3 fatty acids supplementation on the risk of depression among the general population, as well as the effects of *n*-3 supplementation on depression symptoms. The analyses indicated that supplementation with *n*-3 fatty acids did not reduce the risk of developing depression among those without depression but resulted in a large improvement in depressive symptoms and increased remission rate among patients with existing depression.

British Journal of Nutrition

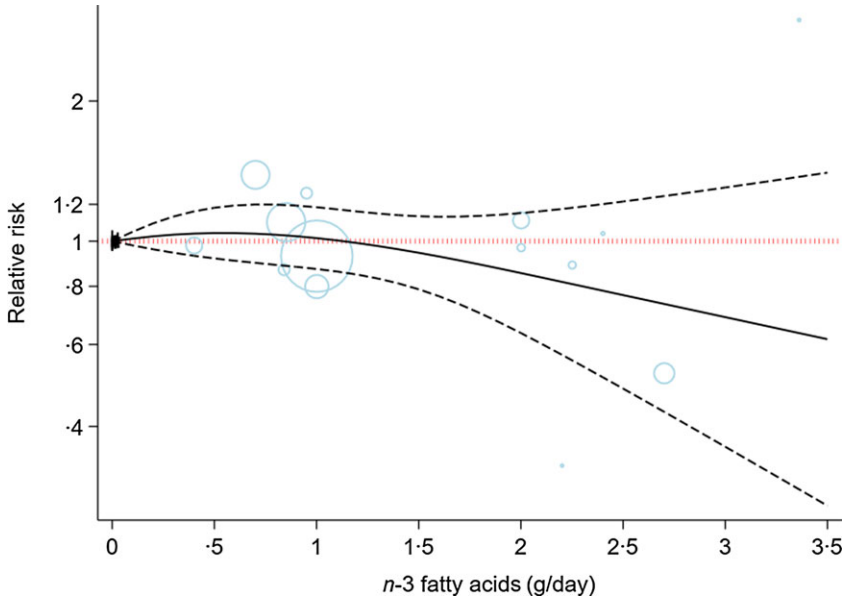

Fig. 2. Dose-dependent effect of *n*-3 fatty acids on risk of depression. Solid lines represent standardised mean difference and dashed lines represent 95 % CI.

Comparison with previous reviews

Evidence regarding the effects of *n*-3 fatty acids supplementation on depressive symptoms is conflicting. A meta-analysis of twenty-eight trials suggested that supplementation with *n*-3 fatty acids improved depressive symptoms in adults[108]. A meta-analysis of twenty-six trials with 2160 participants indicated that supplementation with *n*-3 fatty acids did not significantly affect depressive symptoms in adults; however, they found some evidence of a significant improvement in trials that implemented EPA supplementation[14]. Another meta-analysis of thirty-one randomised trials with 41 470 adults with or without depression indicated that supplementation with *n*-3 fatty acids did not reduce the risk of depression severity when assessed as a binary outcome[15]. In comparison with previous reviews, we included a larger number of trials and evaluated the dose-dependent effects.

Subgroup analyses

In the subgroup analyses of depression severity, there was a significant subgroup difference by health status, where trials that were conducted among patients with existing depression indicated a larger improvement than those conducted in other populations, especially healthy populations. Previous reviews demonstrated that supplementation with EPA had stronger effects on improving depression symptoms than DHA[14,107,109]. Although our subgroup analysis by type of intervention indicated a larger effects in trials that implemented EPA supplementation, there was no significant difference across subgroups by type of intervention (EPA *v.* DHA *v.* combined). In any case, because comparisons between EPA + DHA *v.* pure EPA or DHA in clinical investigations are limited, comparative effects of EPA and DHA in depression therapy needs to be more investigated in future research.

Risk of depression

Although our findings indicated that supplementation with *n*-3 can significantly improve depressive symptoms, we could not find any significant relation between supplementation with *n*-3 fatty acids and the risk of depression among the general population. Similarly, a recent systematic review and meta-analysis of thirteen trials suggested that increasing *n*-3 fatty acids intake probably has little or no effect on the risk of developing depression among those without depression at baseline[15]. Of thirteen trials that were included in the previous meta-analysis, most of the meta-analysis weight (over 90 %) came from three trials that assessed depression symptoms dichotomously[47,50,86]. The other ten trials reported depression events based on a 15-score GDS, mainly in the form of an adverse event. However, unlike the clinical trials, a pooled analysis of thirty-one observational studies in 255 076 participants with 20 000 cases of depression indicated that highest *v.* lowest category of fish intake was associated with a 22 % lower risk of depression among the general population[110]. With regard to no effects in healthy population, we think that although supplementation with *n*-3 fatty acids did not reduce the risk of developing depression, this finding does not imply on no effects of *n*-3 fatty acids on depressive symptoms. Indeed, meta-analyses of prospective cohort studies indicated that higher intake of *n*-3 fatty acids and fish, their main dietary sources, was associated with a lower risk of depression[110,111]. Null effect of supplementation with *n*-3 fatty acids may be due the fact that individuals in the included trials did not have *n*-3 fatty acids deficiency or had sufficient serum *n*-3 fatty acids concentrations. Due to inadequate information, we could performed subgroup analyses by baseline *n*-3 fatty acids intake or their serum concentrations.

Depression remission

Besides improvement in depressive symptoms, our findings indicated that supplementation with *n*-3 could result in depression remission among patients with existing depression.

British Journal of Nutrition

Table 2. The effects of *n*-3 fatty acids supplementation on severity of depression in the non-linear dose–response meta-analysis (standardised mean difference and 95 % CI)

n-3 fatty acids supplementation (g/d)	0		0·5		1		1·5		2		2·5		3		3·5		4	
	(ref)	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI	Standardised mean difference	95 % CI
All participants	0	−1·70	−2·82, −0·58	−2·38	−3·77, −0·99	−2·36	−3·51, −1·20	−1·98	−2·88, −1·08	−1·54	−2·68, −0·41	−1·11	−2·81, 0·59	−0·67	−3·03, 1·69	−0·24	−3·30, 2·82
Participants with depression	0	−2·82	−4·41, −1·23	−4·24	−6·53, −1·95	−4·32	−6·50, −2·14	−3·52	−5·18, −1·86	−2·27	−3·65, −0·90	−0·95	−2·83, 0·92	0·37	−2·41, 3·15	1·69	−2·13, 5·50

A recent meta-analysis of trials with an intervention duration longer than 6 months did not find an evidence of the effect of supplementation with *n*-3 on depression remission[15]. However, they included only one trial for depression remission. It is suggested that the assessment of depression remission needs participants with depression at baseline and at least 6 months of intervention with *n*-3 fatty acids to equilibrate fatty acids throughout our bodies[112]. However, the average intervention duration of the trials in the present meta-analysis was 12 weeks, the certainty of evidence was rated low, and the definition on depression remission varied considerably across trials. One trial defined depression remission as the GDS score less than 11[90], two trials defined it as the BDI-II score ≤ 8[43,44], and the other four trials defined it as the Hamilton Rating Scale for Depression score ≤ 7[55,79,83,107]. Therefore, our findings on depression remission are not conclusive and need to be examined in more long-term RCT.

Dose–response analyses

In the present dose–response meta-analysis, we observed that supplementation with *n*-3 fatty acids could significantly decrease the severity of depression, with the greatest reduction at a dose of 1 g/d ($MD_{1\ g/d}$: −2·38) in the main analysis. A sensitivity analysis among patients with existing depression showed a modest U-shaped effect, with the highest decline in the severity of depression at a dose of 1·5 g/d of *n*-3 fatty acid ($MD_{1.5\ g/d}$: −4·32). Taken together, our findings suggest that the beneficial effect of *n*-3 fatty acids supplementation was more evident between the doses of 1 and 1·5 g/d and, as a result, higher doses could not confer additional benefits.

In case of safety of high-dose *n*-3 fatty acids in short terms, it has been reported that doses up to 4 g of *n*-3 PUFA daily are not associated with an increased risk of major bleeding[113]. Moreover, it has been illustrated that even when patients receive antiplatelet and anticoagulants, there is no risk of excessive bleeding from *n*-3 fatty acids[114]. Of course, there are minor side effects such as fishy smell, hiccups and nausea, rather than any serious ones[115]. Higher dosages of supplementation with *n*-3 fatty acids (3–6 g/d) in several trials did not result in any serious adverse effect [116–121].

In case of safety of high-dose *n*-3 fatty acids in long terms, a RCT with 52 weeks of intervention with 4 g/d *n*-3 fatty acids revealed that this dosage was safe and tolerated by hepatitis C virus patients[97]. Evidence from a RCT on patients at high cardiovascular risk, after 5 years of intervention with 4 g/d *n*-3 fatty acids *v.* corn oil, the adverse events were more commonly observed in the *n*-3 fatty acids group than the comparator group[122]. However, to make conclusion with certainty, more studies with long-term follow-ups are needed.

To precisely designate the effect of *n*-3 fatty acids supplementation, we need to access data that present the effects of *n*-3 fatty acids supplementation solely and yet several trials in our meta-analysis used antidepressant alongside the *n*-3 fatty acids supplements. In comparison with *n*-3 monotherapy, taking *n*-3 supplements with antidepressants may be more effective[109], suggesting that combined supplementation with *n*-3 fatty acids and antidepressant medications may potentiate the

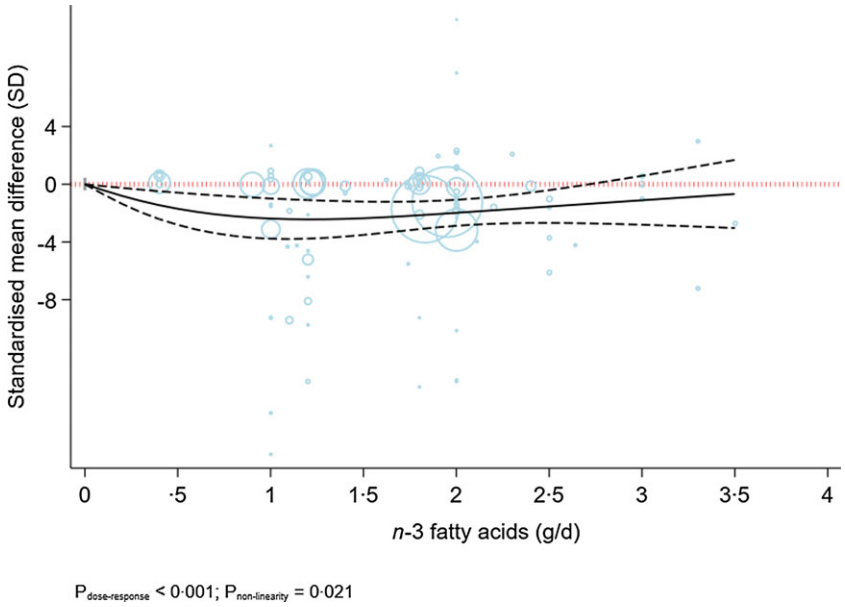

Fig. 3. Dose-dependent effect of *n*-3 fatty acids on severity of depression. Solid lines represent standardised mean difference and dashed lines represent 95 % CI.

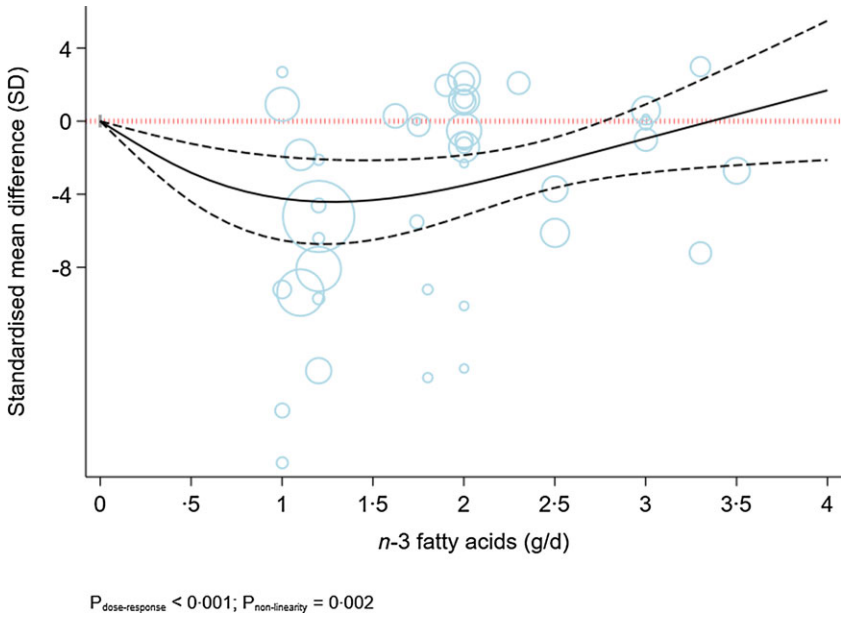

Fig. 4. Dose-dependent effect of *n*-3 fatty acids on severity of depression in depressed individuals. Solid lines represent standardised mean difference and dashed lines represent 95 % CI.

efficacy of drugs. PUFA have the ability to modulate neuronal membrane–antidepressant interactions and inflammatory pathways[123]. On the other hand, *n*-3 fatty acids have the potential to disrupt the functioning of serotonin neurotransmitters[124]. Deeper analysis into the interaction between *n*-3 PUFA and antidepressants is needed. We performed subgroup analysis of the effects of *n*-3 fatty acids supplementation on the severity of depression on medication use (online Supplementary Table 12) The subgroup analysis showed that the severity of depression did not change significantly across different categories of medication use (medication use, no medication use, mixed and not reported) and results were significant in all subgroups.

What is to be done? If studies involve both groups of participants – those who use antidepressant medications and those who do not –, they should include a large sample data so that analysis can be conducted separately. It should be clear what type of antidepressants participants used.

Placebo effect

In general, in trials evaluating the effects of a specific intervention on depressive symptoms, in comparison with a placebo or sham intervention, the effects of placebo on depressive symptoms should be considered[125]. The placebo

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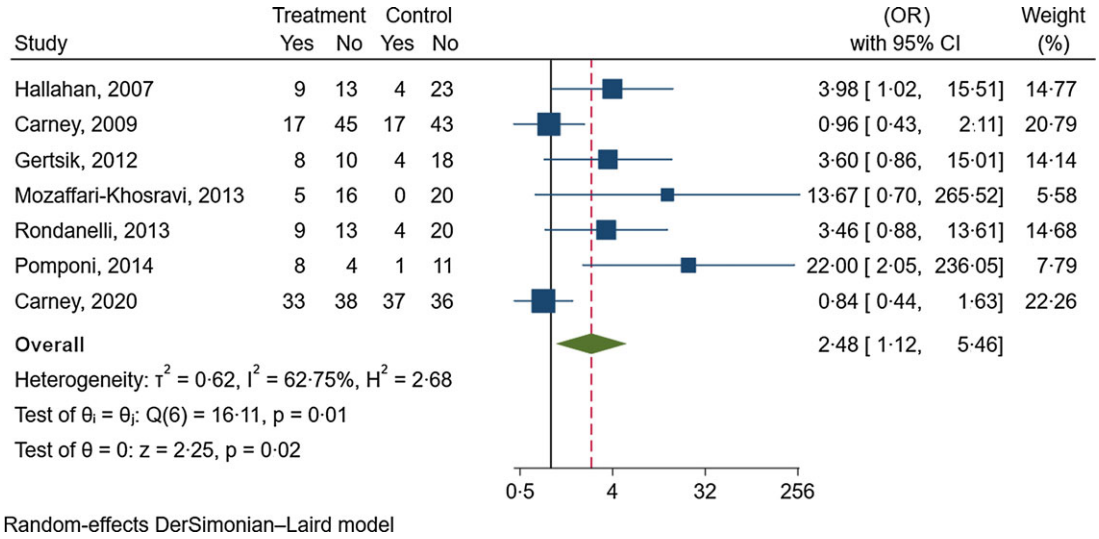

Fig. 5. The effects of *n*-3 fatty acids supplementation on depression remission.

effect is defined as the therapeutic effect caused by a placebo that is not due to any inherent properties of the placebo. This phenomenon is a challenge for researchers and may result in an overestimated effect estimate when evaluating the effects of a specific intervention, in comparison with the placebo, on depressive symptoms. Previous meta-analyses of randomised trials on depression suggested that the magnitude of the effect due to the placebo was about 35–40 %, suggesting a large effect estimate[126,127]. Therefore, the magnitude of the effect estimates found in the present meta-analyses may have been overestimates and, thus, should be interpreted with caution.

When comparing intervention and placebo group, making sure that blinding is correctly taking place is a must. Are participants and research crew actually blind? In a study by Rabkin *et al.*, depressed patients who were given imipramine, phenelzine or a placebo were asked to identify which group they had been placed in. Most patients and doctors were able to tell whether the patients had received an active medication or a placebo[128]. It is a fact that patients are being told that there are possible side effect at the beginning of the study, and they (and by extension research crew) could identify the assigned group. Patients respond better to medications when they are aware they are receiving them than when they suspect they could be receiving a placebo[129]. Moreover, when patients are aware that they could be receiving a placebo, the placebo reaction is less pronounced than when they are made to believe they are receiving the real medication[130]. This could be one possible reason for the marginally different results between the medication and placebo.

Mechanisms

One possible mechanism for *n*-3 fatty acids is its vital role in fluidity and preserving the function of cell membrane[131] through displacing cholesterol from the membrane[132], which is crucial for neurotransmitter binding and the signalling within the cell[133].

Another role for *n*-3 fatty acids is in the production of pro-inflammatory immune chemicals such as IL-1β, −2 and −6, interferon-γ (IFN-γ) and TNF-α. Such cytokines can lower neurotransmitter precursor availability, activate the hypothalamic–pituitary axis, and alter the metabolism of neurotransmitters and neurotransmitter mRNA[134]. Overexpression of monocyte-associated pro-inflammatory cytokines and chemokines has been seen in depressed patients[135]. An elevation in such inflammatory cytokines by psychological stress could be inhibited by *n*-3 fatty acids as antidepressant[134]. Moreover, *n*-3 fatty acids could be beneficial in reducing the severity of depression by modulating brain-derived neurotrophic factor, which supports the survival and growth of neurons through development and adulthood[136].

Is there a sole solution? To fairly respond to this question, we should be asking, is there a sole cause for depression. There are two main category relating depression: biology and psychology, that each one contains multiple domains (e.g. neuroticism, cognitive fusion, emotional clarity, rumination, and so on). Different combinations of reasons are linked to various types of depression, requiring different types of intervention for patients. It is important for clinicians to go through the diagnosing process cautiously and prescribe psychosocial therapies, when needed, alongside the biochemical ones.

Strengths and limitations

Our systematic review and meta-analysis was the first study to evaluate the dose-dependent effects of *n*-3 supplementation on the severity of depression and depression risk. Our broad search included participants at different baselines of depression severity. In comparison with previous reviews, we included a high number of RCT with considerable participants regardless of their health status, estimated both relative and absolute effects for binary outcomes, used the GRADE approach for evaluating the certainty of the evidence, and used the minimal clinically important difference (MCID) thresholds (0·0–≥ 4·0) for evaluating whether the results were clinically important.

As for limitations of our study, the geographical and ethnic variables affecting depression were not examined in the present

meta-analysis. The variety of methods that were used for the assessment of depression symptoms and also high levels of heterogeneity, which persisted even after subgroup analysis, may also limit clinical interpretation. The large heterogeneity in the data may be due to the variation in participant's characteristics, intervention duration and type of outcome assessment. The number of trials that used EPA or DHA supplementation as monotherapy was limited (four trials for each), which made it difficult to interpret the efficacy of EPA and DHA singularly. In addition, for depression remission, we had limited data obtained from short-term trials, and thus, our findings about the effects of *n*-3 fatty acids on depression remission should be interpreted with caution.

Conclusions

Based on moderate-certainty evidence, our study showed that supplementation with *n*-3 fatty acids could lead to a large and clinically important improvement in the severity of depression among patients with existing depression. The greatest reduction was seen at 1–1·5 g/d, with no additional benefits for higher dosages of *n*-3 fatty acids supplementation. Supplementation with *n*-3 fatty acids had no effects on the risk of developing depression among participants without baseline depression. Based on low-certainty evidence obtained from short-term trials, supplementation with *n*-3 fatty acids may increase remission rate in patients with existing depression, finding that needed to be confirmed in future research.

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S. S-B. designed the research; R. N. and S. Z-M. conducted research; A. J. analysed data; S. Z-M. and A. J. revised the tables and images; R. N. and S. Z-M. wrote the first draft of the manuscript; S. S-B. and A. J. provided important revisions for the final content. All authors reviewed and approved the study content.

There are no conflicts of interest.

The data sets generated or analysed during the current study are not publicly available but are available from the corresponding author at reasonable request.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114523002052

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British Journal of Nutrition

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