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Clinical impacts of *n*-3 fatty acids supplementation on depression symptoms: an umbrella review of meta-analyses

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Abstract

Several meta-analyses investigating the efficacy of *n*-3 PUFA in alleviating depression symptoms have reported conflicting findings. In the present study, we aimed to perform an umbrella meta-analysis to provide a definite conclusion. A comprehensive systematic search of PubMed, Scopus, Embase, Web of Science and Cochrane Central Library was performed up to June 2021. Meta-analysis studies evaluating the effects of *n*-3 PUFA on depression symptoms were included. The quality of the included meta-analyses was assessed using AMSTAR questionnaire. Out of 101 studies, twenty-two studies with twenty-six effect sizes (ES) were eligible for inclusion. Sixteen ES showed significant improving effect of *n*-3 supplementation on depression symptoms among which eleven ES had small ES. The other studies observed no significant effect. Available evidence suggests that *n*-3 PUFA (EPA, DHA) supplementation could be considered as an effective add-on therapeutic approach in relieving depression symptoms.

Keywords: ***n*-3: PUFA: DHA: EPA: Depression: Umbrella meta-analysis**

Depression is one of the relatively common mental disorders in today's society. Based on the evidence from the WHO, more than 264 million people are affected by depression worldwide[1,2]. Recent evidence has also shown that the prevalence of depression has increased in the current context of the corona epidemic[3]. The most obvious symptoms of depression include sadness, dissatisfaction with life, changes in appetite, low self-esteem, lack of motivation, anhedonia, low energy level, discomfort without a clear cause, changes in sleep, suicidal ideation, etc[4,5]. It has been shown that nutrition, genetic, environmental, immunologic and endocrine factors and neurogenesis have major roles in the pathogenesis of depression[6]. The levels of biogenic amines including serotonin, melatonin, dopamine,γ-aminobutyric acid and glutamate are altered in these patients[7]. Several mechanisms have been proposed for depression. As a known aetiopathological mechanism of depression, excessive release of glutamate under stressful conditions causes astrocyte apoptosis through over-stimulation of the N-methyl-D-aspartic acid (NMDA) receptor in the hippocampus. Depression is highly attributed to the overactivation of NMDA receptor in the brains[8].

While long-term concerns about their effectiveness and safety exist, antidepressants have been used for years to treat depression[9–11]. Furthermore, non-responsiveness to a wide range of pharmaceutical treatments[12] suggests that other mechanisms are involved in the pathogenesis of depression, including abnormalities in the neuroendocrine, immunological, neurotrophic and metabolic systems[13]. Despite these challenges, new complementary depression treatments are needed.

Dietary long-chain fatty acids (*n*-3 PUFA), namely EPA(C20:5*n*-3), DHA (22:6*n*-3) and α-linolenic acid (18:3*n*-3), have many beneficial effects like anti-inflammatory, pro-apoptotic, anti-tumour and anti-catabolic activities[14,15]. DHA, as an essential and structural *n*-3 fatty acid (FA), improves neurogenesis and repairs the myelin membrane[16]. *n*-3 FA suppress neuroinflammation via inhibition of expression of some of IL genes and cyclooxygenase enzymes[17–19]. Also, studies reported that *n*-3 FA have therapeutic potential in

Abbreviations: ES, effect size; FA, fatty acid.

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patients who show resistance to common medications[17]. On the other hand, Liao and *et al.* in a meta-analysis highlighted that composition of PUFA intake is important as EPA is more effective than DHA in the treatment of depression[20].

There are many clinical trial and meta-analysis articles investigating the relation between *n*-3 FA and depression. Most studies have shown the beneficial effects of *n*-3 FA on improving depressive symptoms[21–26]. Although various meta-analyses have been performed over the past years, they have not yet reached a clear conclusion about the effect of *n*-3 on treating depression and the results are still conflicting in some cases. Therefore, we tried to summarise and classify the effects of various unsaturated fatty acids (linolenic, EPA, DHA) on different symptoms of depression by conducting an umbrella review on published meta-analyses in this field to provide a comprehensive perspective.

Methods

Search strategy and study selection

PICO criteria for the current study were as follows: Population/Patients (P: adults of 18 > years of age, who were supplemented with *n*-3 PUFA); Intervention (I: *n*-3 PUFA); Comparison (C: control or placebo group) and Outcome (O: depression symptoms). A comprehensive systematic search of the international scientific databases including PubMed, Scopus, Embase, Web of Science and Cochrane Central Library was carried out up to June 2021. The search strategy was developed using the following MeSH terms and keywords: (depress* OR dysthymi OR 'affective disorder' OR 'affective symptom' OR 'mood disorder' OR 'mental health)' AND ('DHA' OR docosahex OR eicosapent OR 'EPA' OR 'fatty acid' OR fish OR linolenic OR omega OR '*n*-3' OR 'ω-3' OR 'PUFA' OR 'cod liver oil') AND 'systematic review' OR 'meta-analysis') (online Supplementary file 1). The wild-card term '*' was used to increase the sensitivity of the search strategy. The articles in English language only were included in the study. The protocol of the study has been registered on PROSPERO (registration code: CRD42021282975).

Inclusion and exclusion criteria

Meta-analysis studies examining the effects of *n*-3 FA supplementation on depression symptoms while reporting the effect sizes (ES) and corresponding CI were included in the current umbrella meta-analysis. *In vitro*, *in vivo* and *ex vivo* studies, case reports, observational studies, quasi-experimental studies, clinical trials and also the studies that did not achieve the least quality score were excluded from this meta-analysis of meta-analyses.

Quality assessment

Two reviewers (D.Q, J.M) independently assessed the methodological quality of the eligible articles using the AMSTAR questionnaire[27]. The eleven questions in the questionnaire are completed with yes, no, can't answer or not applicable and has a maximum of eleven points. Articles with a score of over 7 were considered as high quality.

Data extraction

Articles were screened based on the eligibility criteria by two independent reviewers (D.Q, J.M). At first, the abstract and title of the articles were reviewed. Then, the full text of screened papers was evaluated to ascertain the suitability of the study to include in the umbrella meta-analysis. The judgement of the third author (Y.L) resolved any disagreement.

The first authors' name, year, sample size, study location, the dose and duration range of supplementation, ES and CI for depression symptoms were extracted from the selected studies.

Results

Systematic review

The flow diagram of the literature search process is summarised in Fig. 1. The initial search identified 101 records of which sixty were duplicates. After screening titles and abstracts, fifty-one studies were considered potentially relevant and included for full-text evaluation. Twenty-nine articles after a full-text review were excluded and at the end, twenty-two studies published between 2007 and 2021 were included in the current analysis. The characteristics of eligible studies are described in Table 1. Five studies were performed in UK[23,28–31], five in China[21,32–35], three in Netherlands[22,36,37], two in USA[38,39],one in Australia[40], one in Columbia[41], two in Korea[24] and Italy[42] and three in Thailand[26], Germany[43] and Taiwan[44]. The duration of interventions varied from 4 to 160 weeks in included studies. Six meta-analyses were conducted exclusively on women[26,45–49] and the remaining studies on both sexes. The pooled number of participants per meta-analysis ranged from 201 to 10 297. Two meta-analyses reported two ES, each[50,51]. Included meta-analyses have used Cochrane Risk of Bias Tool[52] and Jadad scores[53] to assess the quality of clinical trials. Most of the meta-analyses included high-quality trials. The quality of the original randomized controlled trial (RCT) studies is presented in Table 1.

Risk of bias assessment

Almost all of the included meta-analyses had high quality. On average, the meta-analyses achieved a mean of 10 scores. The results of quality assessment of meta-analyses were done according to the AMSTAR questionnaire and summarised in Table 2.

Effects of n-3 PUFA on depression

The results of five meta-analyses reported standardized mean difference (SMD) ranging from −0·61 to −0·94 that *n*-3 PUFA supplementation significantly reduced depressive symptoms[46,49,54–56]. The results also indicated that a more pronounced improving effect was observed on depression symptoms when EPA with DHA were supplemented, average dose of *n*-3 PUFA was > 3 g/d and intervention period was > 15 weeks. The findings from eleven other meta-analyses showed that *n*-3 PUFA supplementation significantly improved depression symptoms, although the clinical significance was negligible[21,31,42,50,51,57–62]. The remaining meta-analyses reported no significant effect of *n*-3 supplementation on

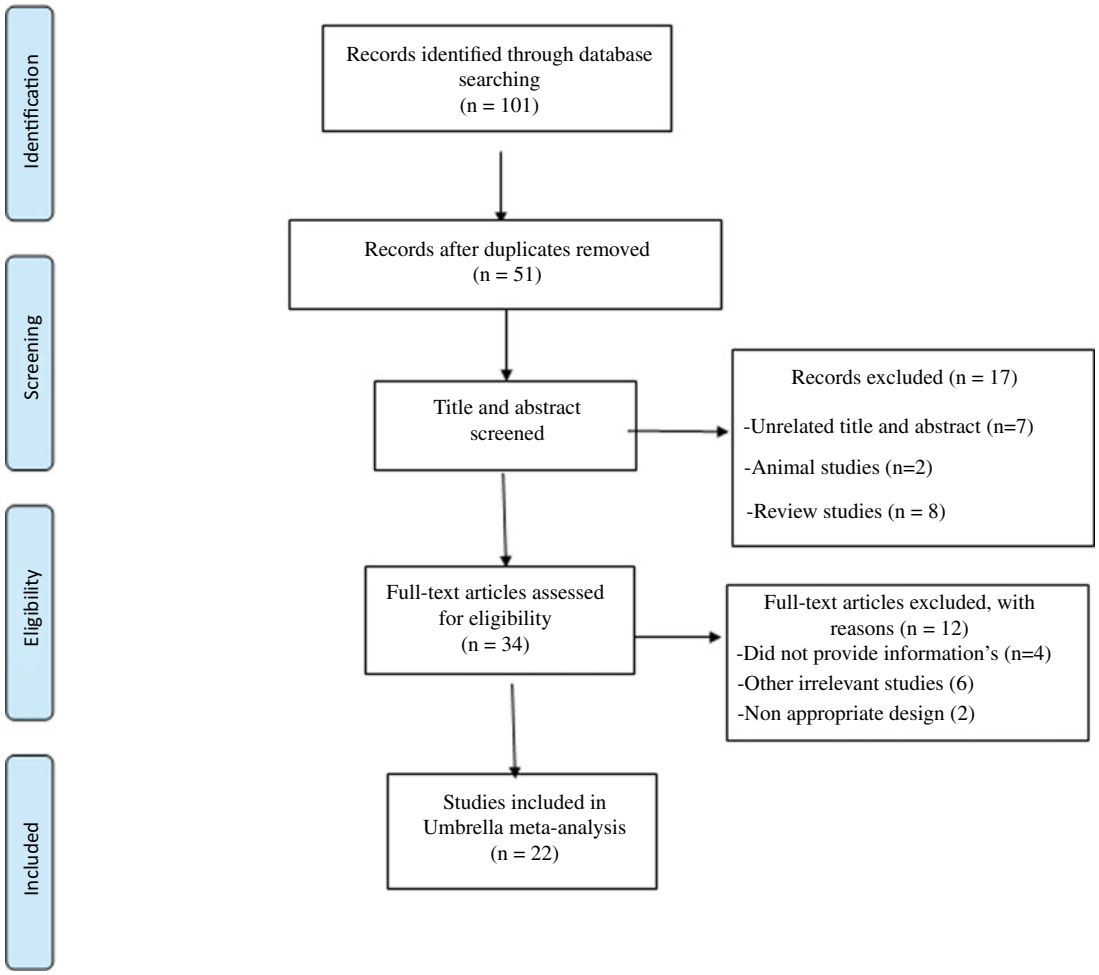

Fig. 1. Flow diagram of study selection.

depression symptoms, as almost half of the included RCT had low quality and with high significant between-study heterogeneity[26,38,45,47,50,63,64]. Seven meta-analyses had large heterogeneity ($I^2 > 50\,\%$)[21,31,38,42,51,58,60], and seven had very large heterogeneity ($I^2 > 75\,\%$)[47,49,54,56,57,59,61]. In addition, three meta-analyses did not report information on heterogeneity between studies[50,63,64]. The quality assessment process of the RCT included in the five meta-analyses was not explained in detail, which could affect their overall quality[50,51,55,60,64]. The results of included meta-analyses are presented in Table 1.

Discussion

Assessment of twenty-two meta-analyses including eighty-three RCT in the current umbrella systematic review revealed that *n*-3 PUFA (EPA, DHA and combination of these FA) supplementation has a significant improvement effect on depression indices in most studies. However, some contradictory results have also been reported[22,26,30,32,36,38,39,41]. The first important factor leading to these contradictory results is the degree of depression. Some studies have indicated that *n*-3 PUFA supplementation led to a non-significant or small effect on depression indicators in people with mild symptoms of depression or normal conditions. While in people with major depressive disorder, this supplement has a major positive effect[22,28,29,31,58]. The next item is the supplementary dose. Most of the studies performing subgroup and meta-regression analysis based on dose have pointed out that there is a direct relationship between dose and ES on depression[32,38]. However, Lin *et al.* reported that the association between *n*-3 PUFA and depression is not dose-dependent[44]. The next important point is the control group. Appleton *et al.* who compared the effects of *n*-3 PUFA with placebo or antidepressants showed that *n*-3 PUFA have a better effect than placebo, although, compared with antidepressants, they do not have a superior effect[58]. In addition to the mentioned factors, the type of *n*-3 FA is important. Some studies have indicated that EPA had superior effect on depression indices compared with DHA[20,29,34,39,41]. Moreover, the substantial inefficacy of *n*-3 PUFA supplementation on depressive disorders in some studies might be related to their studied participants. Grosso *et al.* reported that *n*-3 PUFA was not effective in alleviating of depressive symptoms in patients suffering from depression as a secondary outcome[42].

There are the broad types of scales to measure the depression in the investigated studies including Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Depression Anxiety Stress Scale (DASS), Hospital Anxiety

Table 1. Study characteristics of included studies. (95 % confidence intervals)

Citation (First author *et al.*, year)	Number of studies in meta-analysis	Location duration	Number of participants in meta-analysis	Daily dose (*n*-3 PUFA)	Quality assessment scale and outcome	Effect size (95 %CI)/I^2, *P*-heterogeneity	Outcome measure
Appleton *et al.* 2006	12	UK 4–26 weeks	1360	0·09–3·4 g DHA 0·14–6·2 g EPA	Yes (Cochrane) 8/12 high	SMD: −0·13(−0·25, −0·01) 79 %, $P < 0·001$	Four-point Likert scale, HDRS-SF, POMS (depression),CDI, CGI, BDI, HDRS, MADRS, IDS-C, MADRS, DSP (depression)
Appleton *et al.* 2010	35	UK 4–28 weeks	2704	0·09–3·4 g DHA 0·14–6·2 g EPA	Yes (Cochrane) 21/35 high	SMD: −0·1(−0·17, −0·02) 65 %, $P < 0·001$	Four-point Likert scale, HDRS-SF, POMS (depression),CDI, CGI, BDI, HDRS, MADRS, IDS-C, MADRS, DSP (depression), CDRS, NPI, GHQ, MINI, PPBQ, PGWB, HSCL-D-20
Appleton *et al.* 2016	26	UK 4–16 weeks	1373	0·144–2·4 g DHA 0·18–4·4 g EPA	Yes (Cochrane) 14/26 high	SMD: −0·32(−0·52, −0·12) 59 %, $P < 0·001$	MADRS, BDI, HDRS, GDS, HDRS-SF
Bae *et al.* 2018	6	South Korea 8–24 weeks	4605	0·3–2·5 g EPA + DHA 2 g ALA	Yes (Cochrane) 6/6 high	SMD: −0·94(−1·37, −0·5) 84·1 %, $P < 0·001$	GDS-15, CES-D, HAMD
Bai *et al.* 2018	9	China 8–160 weeks	3432	0·12–1·72 g DHA 0·18–1·67 g EPA 0·4–1·8 g EPA + DHA	Yes (Cochrane) 9/9 high	SMD: −0·202(−0·463, 0·06) NR	MADRS, GDS, SDS, CES-D
Bloch *et al.* 2012	13	USA 4–16 weeks	731	0·15–2·4 g DHA 0·4–4·4 g EPA	Yes (Jadad) 10/13 high	SMD: 0·11(−0·04, 0·26) 73 %, $P < 0·001$	HAM-D-17, HAM-D-SF, BDI, DASS, MADRS
Grosso *et al.* 2014	55	Italy 4–16 weeks	10 297	0·09–3·4 g DHA 0·14–6 g EPA	Yes (Cochrane) 50/55 high	SMD: −0·38(−0·59, −0·18) 65 %, $P < 0·001$	MADRS, HDRS, BDI, GDS, four-point Likert scale, HDRS-SF, DASS, PGWB, HSCL-D-20, VAS, IDS-C, CDRS-R, CPRS, CGI-BP, EPDS, MMSE, NPI, LOT-R, POMS, LEIDS-R, CES-D
Hallahan *et al.* 2016	15	USA 12 weeks	3381	DHA-predominant formulations (NR dose)	No	SMD: −0·03(−0·19, 0·12) 35 %, $P < 0·66$	GDS, DASS, MADRS, HDRS, PHQ, YMRS, EPDS, BDI, CGI, CGI-BP, PSS, YMRS, CES-D, HADS-A
Hallahan *et al.* 2016	39	USA 12 weeks	6292	EPA-predominant formulations (NR dose)	No	SMD: −0·34(−0·47, −0·21) 61 %, $P < 0·001$	GDS, DASS, MADRS, HDRS, PHQ, YMRS, EPDS, BDI, CGI, CGI-BP, PSS, YMRS, CES-D, HADS-A
Jans *et al.* 2010	7	Netherlands 6–35 weeks	612	0·2–2·24 g DHA 0·5–2·2 g EPA	Yes (Cochrane) 5/7 high	SMD: −0·03(−0·18, 0·13) 40·89 %, $P = 0·064$	EPDS, BDI, HAM-D, MADRS
Liao *et al.* 2019	27	China 4–16 weeks	2160	0·12–2 g DHA 0·18–4 g EPA	Yes (Cochrane)	SMD: −0·28(−0·47, −0·09) 75 %, $P < 0·001$	HDRS-17, MADRS, BDI, DASS, GDS
Lin *et al.* 2007	10	Taiwan 4–16 weeks	329	2·2–3·4 g DHA 0·6–6·2 g EPA	No	SMD: −0·61(−1·01, −0·21) 23·91 %, $P = 0·142$	HAM-D, MADRS, BDI
Liu *et al.* 2017	4	China 6–8 weeks	201	0·8–1·64 g DHA 0·42–2·2 g EPA	Yes (Cochrane) 4/4 high	SMD: −0·75(−1·04, −0·47) 0 %, $P = 0·874$	HDRS, CGI, EPDS, MADRS, BDI
Martins *et al.* 2009	28	UK 4–36 weeks	1961	0·088–3·4 g DHA 0·136–6·2 g EPA	Yes (Jadad) 15/28 low	SMD: −0·291(−0·463, −0·012) 76·1 %, $P < 0·001$	HDRS, SCID-IV, EPDS, MADRS, BDI, HDRS-SF, POMS, IDS-C, CDI, DASS, HSCL-D-20

Table 1. (*Continued*)

Citation (First author *et al.*, year)	Number of studies in meta-analysis	Location duration	Number of participants in meta-analysis	Daily dose (*n*-3 PUFA)	Quality assessment scale and outcome	Effect size (95 %CI)/I^2, *P*-heterogeneity	Outcome measure
Mocking *et al.* 2016	13	Netherlands NR	1233	NR	No	SMD: −0·398(−0·682, −0·114) 73·36 %, $P < 0·001$	HDRS, BDI
Mocking *et al.* 2020	14	Netherlands 6–40	3554	0·008–2·24 g DHA 0·009–2·2 g EPA	Yes (Cochrane) 8/14 high	SMD: −0·309(−0·619, 0·001) 89·63 %, $P < 0·001$	EPDS, BDI, HAM-D, MADRS, PDSS, SCID
Sublette *et al.* 2011	10	Columbia 4–16 week	304	0·2–2·2 g DHA 0·4–4·4 g EPA	No NR	SMD: −0·558(−0·838, −0·277)	BDI, HAM-D, MADRS, CDRS, DASS
Sublette *et al.* 2011	7	Columbia 6–16 week	612	0·75–2·4 g DHA 0·414–1·1 g EPA	No NR	SMD: −0·026(−0·148, 0·2)	BDI, HAM-D, MADRS, CDRS, DASS
Suradom *et al.* 2021	11	Thailand 6–32 weeks	920	0·22–1·02 g DHA 0·1–2·15 g EPA	Yes (Cochrane) 11/11 high	SMD: −0·05(−0·2, 0·1) 21 %, $P = 0·328$	BDI, EPDS, HAM-D, PDSS
Wolters *et al.* 2021	25	Germany 3–160	5836	0·12–1·55 g 0·09–2 g	Yes (Cochrane) 14/25 low	SMD: −0·34(−0·55, −0·12) 86 %, $P < 0·001$	BDI, MADRS, GDS, GDI, HDRS
Yang *et al.* 2015	8	China 6–8 weeks	367	0·15–2·2 g DHA 0·42–4·4 g EPA	Yes (Cochrane) 8/8 high	SMD: −0·65(−1·12, −0·18) 78 %, $P < 0·001$	HSCL-D-20, HDRS, GDS, BDI, EPDS
Zhang *et al.* 2021	8	China 4–14 weeks	638	0·12–1·638 g DHA 0·18–2·2 g EPA	Yes (Cochrane) 8/8 high	SMD: −0·65(−1·2, −0·1) 91 %, $P < 0·001$	EPDS, HRSD, BDI
Sarris *et al.* 2012	6	Australia 4–16 weeks	291	3·4 g DHA 6·2 mg EPA 6·6 g ALA	Yes (Jadad) 5/6 high	SMD: −0·338(−0·641, −0·035) 30 %, $P = 0·213$	HDRS, YMRS, IDS-C, CDRS-R
Martins *et al.* 2012		UK 4–16 weeks	NR	0·15–2·2 g 0·42–4·4 g	No	SMD: 0·11(−0·04, 0·26) NR	HDRS, MADRS, BDI, DASS, EPDS, HSCL-D-20, IDS-SR, GDS

BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; IDS-C, Inventory of Depressive Symptomatology; DSP, Derogatis Stress Profile; HDRS-SF, HDRS short form; POMS, Profile of Mood States; CDRS, Children's Depression Rating Scale; CDI, Children's Depression Inventory; CGI, Clinical Global Impression; IDS-C, Inventory of Depressive Symptomatology; MMSE, Mini-Mental State Examination; EPDS, Edinburgh Postnatal Depression Scale; NPI, Neuropsychiatric Inventory; DASS, Depression, Anxiety and Stress Scales; GHQ, General Health Questionnaire; CES-D, Center for Epidemiologic Studies–Depression scale; GDS-15, Geriatric Depression scale (15 items); LEIDSR, Leiden Index of Depression Sensitivity; PPBQ, Postpartum Blues Questionnaire; PGWB, Psychological General Well-Being Index; HSCL-D-20, Hopkins Symptom Checklist Scale (20 items); ALA, α-linolenic acid.

Table 2. Results of assessing the methodological quality of meta-analysis

Study	A priori design	Selection and data extraction	Literature search	Publication type	List of studies	Characteristics of the included studies	Assessed scientific quality	Scientific quality formulating conclusions	Methods used to combine the findings	Assessed publication bias	Conflict of interest stated	Quality score
Appleton *et al.* 2006	+	+	+	+	+	+	+	−	+	+	+	10
Appleton *et al.* 2010	+	+	+	+	+	+	+	+	+	+	+	11
Appleton *et al.* 2016	+	+	+	+	+	+	+	+	+	+	+	11
Bae *et al.* 2018	+	+	+	+	+	+	+	+	+	+	+	11
Bai *et al.* 2018	+	+	+	+	+	+	+	+	+	−	+	10
Bloch *et al.* 2012	+	+	−	+	−	+	+	+	+	+	+	9
Grosso *et al.* 2014	+	+	+	+	+	+	+	+	+	+	+	11
Hallahan *et al.* 2016	+	+	+	+	+	+	+	+	+	+	−	10
Jans *et al.* 2010	+	+	+	+	+	+	+	−	+	+	+	10
Liao *et al.* 2019	+	+	+	+	+	+	−	+	+	+	+	10
Lin *et al.* 2007	+	+	+	+	+	+	−	+	+	+	−	9
Liu *et al.* 2017	+	+	+	+	+	+	+	−	−	+	−	8
Martins *et al.* 2009	+	+	−	+	+	+	+	+	+	+	−	9
Mocking *et al.* 2020	+	+	+	+	+	+	+	+	+	+	+	11
Mocking1 *et al.* 2016	+	+	+	+	+	−	+	+	+	+	+	10
sublette *et al.* 2011	+	+	−	+	+	+	−	+	+	+	−	8
Suradom *et al.* 2021	+	+	+	+	+	+	+	+	+	+	+	11
Wolters *et al.* 2021	+	+	+	+	+	+	+	−	+	+	+	10
Yang *et al.* 2015	+	+	+	+	+	+	+	−	+	+	+	10
Zhang *et al.* 2020	+	+	+	+	+	+	+	−	+	+	+	10
Sarris *et al.* 2012	+	?	+	+	+	+	+	+	+	+	−	9
Martins *et al.* 2012	+	?	−	+	+	+	−	+	+	+	+	8

The result of assess the methodological quality using AMSTAR: each item for included studies (?: can't answer; -: means no; +: means yes).

and Depression Scale (HADS), Hamilton Depression Rating Scale, Edinburgh Postnatal Depression Scale (EPDS), Leiden Index of Depression, Geriatric Depression Scale (GDS), Profile of Mood States and Quick Inventory of Depressive Symptomatology (QIDS). Following purposes have been defined for these scales: screening, diagnosis, differentiated diagnosis, severity, treatment effect judgement and processing observation[65]. Regarding inconsistency between these questionnaire, QIDS and BDI dedicated less than 10 % to 'Mood and Outlook' while the MADRS, DASS, EPDS and GDS dedicated 15 %+ to this category. Regarding 'Confidence and Self Judgement', BDI and GDS dedicated most and lowest to this category, respectively. The other categories such as sleeping, appetite, anxiety, self-harm and distress were even more heterogeneously distributed across the questionnaires[66]. Consequently, the conflicting results in some studies could be due to the different scales used in the clinical trials they analysed.

It must be noted that the baseline levels of EPA and DHA and levels achieved have been traditionally ignored in intervention trials. Therefore, positive effect of *n*-3 PUFA on depression in included meta-analysis studies might be an underestimated result. It has been reported that DHA synthesis from ingested *α*-linolenic acid is typically < 1 % of the oral *α*-linolenic acid dose[67]. Therefore, many studies ignore the endogenous biosynthesis of *n*-3 PUFA. Many studies have recorded *n*-3 PUFA intake as self-reports, which can be inaccurate in some cases. Therefore, it is recommended that future studies measure the serum or tissue level of *n*-3 PUFA to accurately determine their positive effects.

Both sexes benefited from *n*-3 PUFA to improve depression. However, major depression is more prevalent among females. It may be related to hormonal changes, particularly oestrogen in women during the different periods of their life such as prior to menstruation, puberty, following pregnancy and at perimenopause[68]. Gordon *et al.* suggested that hormone replacement therapy especially could be effective in the treatment of premenopausal depression[69]. In addition, improving efficacy of *n*-3 PUFA on maternal depression has been investigated in some studies[49,70,71]. In the male brain, oestrogen could be produced from testosterone via endogenous aromatase (CYP19). Oestrogen could exert its protective properties against depression via oestrogen receptors expressed in the male brain[72]. Therefore, improving effect of *n*-3 PUFA on the females might be related to their beneficial effects on hormonal changes among them[73].

The mechanism of action of *n*-3 FA on depression has been explained in many studies. *n*-3 PUFA have been proven to influence the activity and structure of brain through affecting adult neurogenesis and synaptogenesis by increasing the signalling factors involved in neurogenesis, such as brain-derived neurotrophic factor, cAMP response element-binding protein or calcium/calmodulin-dependent protein kinase II[74]. It must be added that DHA is a component of neural membrane phospholipids[75]. Moreover, *n*-3 PUFA boost the blood flow of brain[76]. Therefore, decrease or increase in their intakes could affect the brain functions. *n*-3 PUFA through different pathways could improve depression. In one pathway, *n*-3 PUFA might increase the expression of dopamine receptor, thereby increasing the dopamine activity as a neurotransmitter in restoring the mood[77]. In addition, *n*-3 PUFA were effective in balancing the low level of brain-derived neurotrophic factor among depressed patients[78]. Brain-derived neurotrophic factor could boost the action of antidepressant agents[79]. In addition, *n*-3 PUFA act as an potent anti-inflammatory agent to supress the production of inflammatory cytokines such as IL-1 and TNF-*α*, which are involved in the pathogenesis of the depression[80]. In addition, *n*-3 PUFA were inversely associated with depression in patients with the increased levels of oxidative stress biomarkers[81]. Koponen *et al.* reported that depressed patients had impaired glucose metabolism, and this could result in pathological effects on the brain[82]. Yeum *et al.* showed that *n*-3 PUFA tended to improve the metabolism of glucose[83]. In depressive disorders, the hypothalamic–pituitary–adrenal axis tended to be up-regulated. Besides, negative feedback controls of this axis were down-regulated in depression. This led to increased secretion of corticotropin-releasing factor from the hypothalamus and subsequently adrenocorticotropic hormone from the pituitary and cortisol from the adrenal cortex[84]. Excessive cortisol desensitises cortisol receptors, thereby increasing the activity of macrophage as well as the level of proinflammatory cytokines. Moreover, this desensitisation led to disturbances in noradrenaline and serotonin transmission[85]. Kim *et al.* reported that *n*-3 PUFA could reduce the circulating adrenocorticotropin hormone, corticosterone and corticotropin-releasing factor, as well as elevate serotonin and brain-derived neurotrophic factor levels in a rat model[86].

Present umbrella systematic review is the first umbrella study that could collect and evaluate various and inconsistent results of published meta-analyses and reach to a decisive conclusion. Second, high quality of included meta-analyses and their included RCT helped us to obtain more reliable results. However, it had some limitations too that must be noted. First, subgroup analyses were limited in terms of dose, duration of supplementation, sex, depression screening tool and population in the included studies. As a result, no definite conclusions can be drawn about these terms. Second, the heterogeneity of some studies was high (Table 1), which can reduce the validity of the results. Therefore, results should be interpreted with precaution. Third, none of the studies has done a GRADE assessment. As a result, no conclusion can be drawn about the certainty of the evidence.

Conclusion

n-3 PUFA (EPA, DHA and combination of these FA) supplementation has a significant improvement effect on depression indices in most studies. This result was more pronounced in major depressive disorder. There is a direct relationship between dose of *n*-3 PUFA and ES on depression. *n*-3 PUFA have not a superior effect on depression compared with anti-depressant drugs. However, EPA has more anti-depressive effects than DHA. In conclusion, *n*-3 PUFA supplementation could be considered as an effective therapeutic adjuvant approach in relieving depression symptoms.

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Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S000711452300226X

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