

Combined application of eicosapentaenoic acid and docosahexaenoic acid on depression in women: a meta-analysis of double-blind randomized controlled trials

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Objectives: Previous randomized controlled trials (RCTs) suggest that depression can be effectively treated by omega-3 polyunsaturated fatty acids (PUFAs). Therefore, we conducted this meta-analysis to systematically evaluate the clinical applicability of the combination of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are the two major bioactive types of PUFAs, in depressed women.

Methods: RCTs that compared the combination of DHA and EPA to placebo for short-course treatment of depression in women were systematically reviewed up to March 2015. Outcome measurement was the standardized difference in means in clinical measure of depression severity. Random effect model was performed. Meta-regression analysis was performed to assess the effects of baseline depression scores.

Results: Data were obtained from eight RCTs. In these RCTs, 182 patients received placebo and 185 patients received DHA and EPA. The pooled standardized difference in mean was 0.65 with 95% CI = [0.18, 1.12]. There was no relation between the efficacy and the baseline depression scores. The sensitivity analysis found that the combination of EPA and DHA as monotherapy yielded a standardized difference in means of 0.65 (95% CI = 0.41, 0.90) without heterogeneity.

Discussion: These results indicate a beneficial effect of the combination of EPA and DHA on depressed mood in women compared with placebo. The clinical applicability of EPA and DHA showed greater promise and should be further explored.

Keywords: depression, omega-3 polyunsaturated fatty acids, PUFAs, docosahexaenoic acid, DHA, eicosapentaenoic acid, EPA

Introduction

Depression is one of the most debilitating mental disorders in psychiatry field, which affects more than 10% of the population and results in more than 10% of the global disease burden.¹⁻³ There are about 10%–20% free-living elderly subjects and 20%–30% elderly hospitalized patients experiencing the depressive symptoms.⁴ Currently, despite a large number of established medication options for depression, about 19%–34% of patients fail to respond to the first-line treatments.⁵ On the other hand, the female preponderance of depression and its emergence in adolescence was reported by most of the studies.⁶ Studies reported that the prevalence of depression was doubled in girls than boys between 15 years and 19 years,⁷ and this trend persisted until 54 years.⁸ Some studies reported a higher prevalence of depression in women than men, even after menopause.⁹ This sex disparity indicated that gonadal hormones might play a

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potential role in the etiology of depression. Additionally, some data have raised the concern that using selective serotonin reuptake inhibitor antidepressants during the pregnancy may result in self-limited neonatal behavioral syndrome.¹⁰ Based on these results, there is an urgent need to identify a new treatment for depression in women.

Omega-3 polyunsaturated fatty acids (PUFAs), including the two major bioactive types: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are nutritional compounds, which are not synthesized by the human body.^{11,12} Omega-3 PUFAs are considered a necessary dietary component. Some studies reported that the deficit of DHA, EPA, or both in cell membranes or plasma was associated with an increased incidence of depression.^{13,14} The decreased levels of DHA and/or EPA were found in depressed patients.¹⁵ Furthermore, researchers found that PUFAs may be beneficial in individuals with diagnosed depressive illness.¹⁶ However, previous studies have demonstrated inconsistent findings regarding the efficacy of DHA and/or EPA in treating depression in women.^{17,18} Freeman et al reported that there was no significant difference between omega-3 PUFAs and placebo in treating depression in women.¹⁷ But Rondanelli et al reported that the supplementation of omega-3 PUFAs had therapeutic benefits in women with depression.¹⁸ These discrepant conclusions may be due to a lack of statistical power among some of the individual clinical trials.¹⁹ Therefore, this work seeks to examine the efficacy of DHA and EPA on treating depression in women. We hypothesized that the combined application of DHA and EPA could yield antidepressant effect on women with depression. This meta-analysis should obtain a more accurate conclusion by integrating the results from multiple studies.²⁰

Methods

Study selection

The first step of this meta-analysis was to identify eligible trials. Electronic searches were performed in international databases (PubMed, Cochrane Controlled Trials Register, Web of Science, Embase), two Chinese databases (China Biology Medicine disc, China National Knowledge Infrastructure), and relevant websites dated up to December 2014. The search terms used were “depress*” combined with “omega-3”, “PUFA”, “polyunsaturated fatty acids”, “DHA”, and “EPA”. In order to mitigate language bias, no language restriction was imposed. Reference documents listed in relevant papers, conference summaries, and the International Clinical Trials Registry Platform were also researched.

We selected studies for subsequent analysis according to the following inclusion criteria: 1) randomized controlled trials (RCTs) comparing omega-3 fatty acid and placebo (active or not); 2) women patients over 18 years of age; 3) informed consent provided; 4) outcome assessed by Montgomery–Åsberg Depression Rating Scale, Hamilton Depression Rating Scale (HDRS), Clinical Global Impression, Beck Depression Inventory, or Geriatric Depression Scale; and 5) used EPA and DHA at the same time. Meanwhile, studies according with any of the following criteria were excluded: 1) nonrandom allocation; 2) case reports and reviews; and 3) duplicate studies.

Data extraction

Two reviewers independently verified all potentially suitable studies by the inclusion/exclusion criteria and completed the data abstraction. Any disagreement was solved by consensus, and if needed, a third reviewer was consulted. Data extracted from the included studies were recorded in a structured fashion as follows: 1) patients characteristics (ie, mean age, mean depression score, country, and outcome measurement); 2) treatment parameters (ie, treatment time, treatment strategy, and daily dose); and 3) outcome measures (ie, mean score of depression after the intervention and dropouts). When the trials reported results from different kinds of rating scales, HDRS was preferentially selected. For data that could not be directly extracted from the study, the data were retrieved through correspondence with the primary author or from other studies.

Bias risk assessment

Two reviewers independently assessed the quality of each included RCTs according to the Cochrane Collaboration criteria.²¹ Bias risk was assessed by the following items: the quality of randomization, using the allocation concealment, blinding the investigators and patients, and reporting incomplete data and similar baseline clinical characteristics. Studies with two or more bias risks were excluded from the subsequent meta-analysis.

Statistical analysis

RevMan 5.1 (Cochrane Information Management System [IMS]) and Stata software 8.0 (StataCorp LP, College Station, TX, USA) were used to do the statistical analyses. Continuous data were extracted as mean and standard deviations (SDs). All depression scales' means and SDs at the beginning of treatment and after treatment in two groups were combined.²² To correct for small sample bias, the standardized mean effect for included RCTs was calculated by using Hedges' g .²³

We used the Mantel–Haenszel random-effects model, as it was assumed that the included RCTs probably had varying true treatment effects.²⁴ But if there was no heterogeneity, the fixed-effects model was used. If needed, subgroup analysis and sensitivity analysis were conducted. Heterogeneity was investigated using the Q-statistic and I^2 .²⁵ The Egger test and funnel plots were conducted to assess the potential presence of publication bias. The protocol of this work followed the recommendations for conducting a meta-analysis.²⁶

Results

Totally, 254 potentially relevant studies were obtained in the initial Internet search. Among these, we first excluded 76 studies by reviewing the titles. Second, we excluded

167 additional studies by reviewing the abstract. Third, we excluded eleven additional studies by two reviewers independently reviewing the full texts. Finally, eight RCTs met all the inclusion/exclusion criteria and were used for the subsequent analysis (Figure 1). Although the references listed behind these studies were researched for possibly omitted RCTs, no more RCTs were found.

Characteristics of the eight studies

These eight RCTs contained an aggregate of 367 adult patients, composed of 182 patients receiving placebo and 185 patients receiving EPA and DHA.^{17,18,27–32} Three RCTs used paraffin oil as placebo;^{17,18,31} two RCTs used olive oil ethyl esters as placebo;^{27,32} and another three RCTs used sunflower

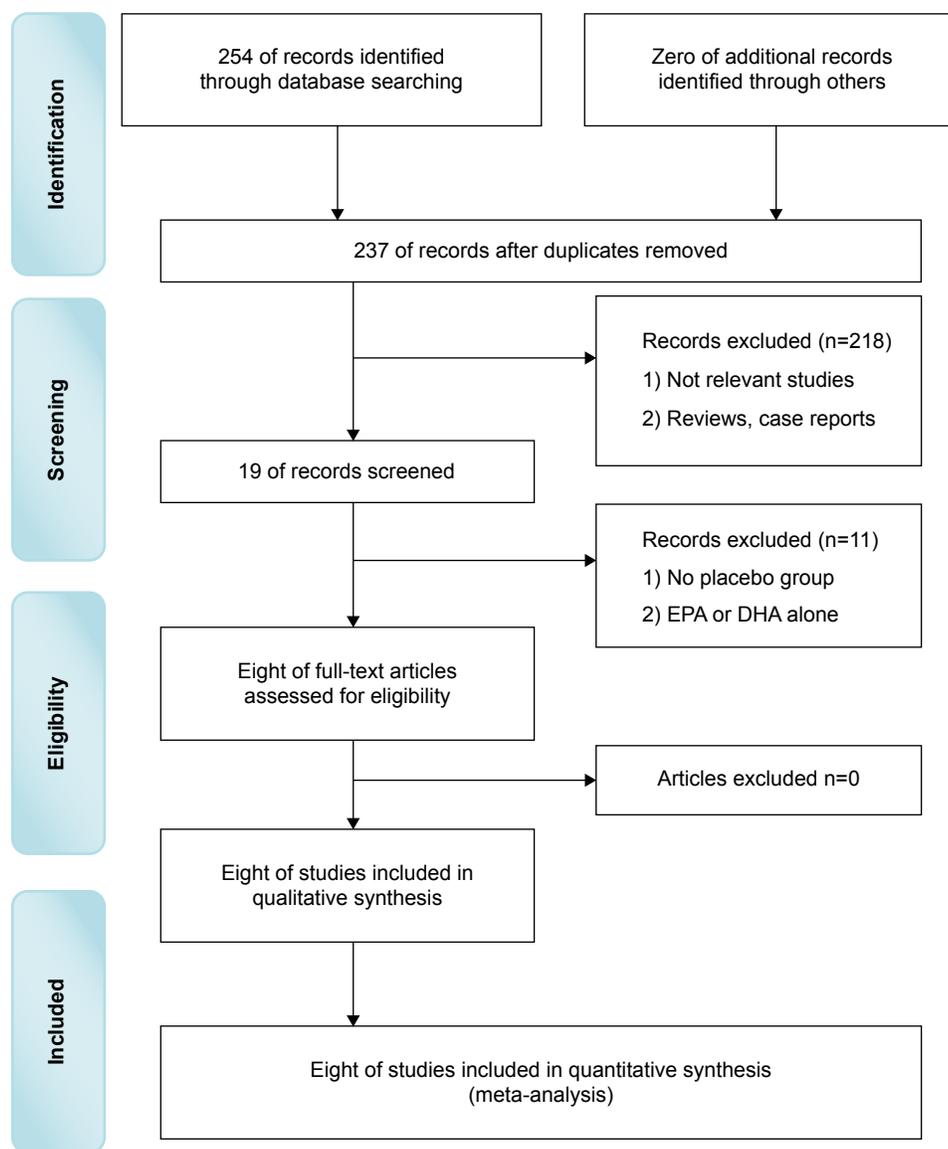


Figure 1 Literature search.

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Table 1 Demographic and clinical characteristics of included subjects

Study	Subjects, n (I/C)	Age, (SD) (I/C)	Outcome	Depression	Ethnic group
Rizzo et al ³¹	46 (22/24)	84.9 (6.9)/83.0 (7.3)	GDS	MDD	Caucasian white
Rondanelli et al ²⁸	46 (22/24)	84.9 (6.9)/83.0 (7.3)	GDS, SF-36	MDD	Caucasian white
Rondanelli et al ¹⁸	46 (22/24)	84.9 (6.9)/83.0 (7.3)	GDS, SF-36	MDD	Caucasian white
Lucas et al ³⁰	120 (59/61)	48.4 (4.0)/49.1 (3.9)	HDRS, CGI, HSCL-D-20	MDD	Caucasian white
Freeman et al ¹⁷	59 (31/28)	31.0 (5.8)/29.7 (6.2)	HDRS, CGI, EPDS	MDD ^b	Caucasian white
Rees et al ²⁹	26 (13/13)	31.2 (4.4)/34.5 (3.8)	HDRS, MADRS, EPDS	MDD ^b	Caucasian white
Su et al ²⁷	36 (18/18)	30.9 (3.9)/31.3 (5.7)	HDRS, EPDS, BDI-21	MDD ^b	Asian
Su et al ^{32a}	22 (12/10)	35.2 (11.6)/42.3 (10.7)	HDRS	MDD	Asian

Notes: ^aTen of 12 in the intervention group were women, and eight of ten in the control group were women. ^bMDD during pregnancy.

Abbreviations: SD, standard deviation; I/C, intervention/control; GDS, Geriatric Depression Scale; MDD, major depression disorder; SF-36, Short-Form 36-Item Health Survey; HDRS, Hamilton Depression Rating Scale; CGI, Clinical Global Impression; HSCL-D-20, 20-item Hopkins Symptom Checklist Depression Scale; EPDS, Edinburgh Postnatal Depression Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; BDI, Beck Depression Inventory.

oil, corn oil, and Sunola oil as placebo.^{24,29,30} The dose of EPA was higher than that of DHA in seven RCTs, but the dose of DHA (1.64 g) was higher than that of EPA (0.42 g) in Rees et al.²⁹ Six RCTs used EPA and DHA as monotherapy,^{18,27-31} and two RCTs used them as an augmentation agent (supportive psychotherapy,¹⁷ tert-butylhydroquinone and tocopherols³²). Patients in seven RCTs received 8 weeks of treatment, but patients in Rees et al received 6 weeks of treatment.²⁹ The age of all patients in three RCTs was more than 65 years.^{18,28,31} The detailed information is described in Tables 1 and 2.

Bias risk assessment

In this review, the eight studies used randomization and conducted allocation concealment. All studies reported the similar baseline characteristics and incomplete data. As far as we know, in clinical studies, the double-blind was difficult, but all these included RCTs blinded the investigators and patients. Thus, the eight RCTs in this review were consistently of high quality. As these RCTs displayed no bias risk, all RCTs were used in this meta-analysis (Table 3).

Standardized difference in means

All the included RCTs reported the data at the treatment end point.^{17,18,27-32} The pooled standardized difference in means was 0.52 (95% CI =0.31, 0.73) for the fixed-effects model

and 0.65 (95% CI =0.18, 1.12) for the random-effects model (Figure 2), which indicated a beneficial effect of the combination of EPA and DHA on depressed mood compared with placebo. But, significant heterogeneity in effect size existed ($P < 0.0001$, $I^2 = 78\%$). In order to check whether or not the depression scores on baseline played a role in the efficacy of the combination of EPA and DHA, we performed a meta-regression analysis. The results indicated that there was no relation between the efficacy and the baseline depression scores (regression coefficient =0.015; 95% CI =-0.007, 0.034; $P = 0.24$). No significant asymmetry in the inverted funnel plots of these RCTs appeared. Meantime, the Egger test was conducted, and the result showed that the outcome was not influenced by the publication bias ($P = 0.32$).

Sensitivity analysis

Two RCTs used the combination of EPA and DHA as an augmentation agent.^{17,32} Then, we excluded these two RCTs to investigate the efficacy of EPA and DHA as monotherapy. The results showed that the pooled standardized difference in means was 0.65 (95% CI =0.41, 0.90) for the fixed-effects model (Figure 3). This exclusion did not significantly affect the initial effect size estimates for the whole sample, but no significant heterogeneity existed ($P = 0.33$, $I^2 = 13\%$). One study recruited four (18%) men with major depression disorder

Table 2 Treatment parameters of included randomized controlled trials

Study	Intervention	Placebo	Daily dose	Duration	Strategy
Rizzo et al ³¹	EPA + DHA	Paraffin oil	1.67 g EPA +0.83 g DHA	8 weeks	Monotherapy
Rondanelli et al ²⁸	EPA + DHA	Paraffin oil	1.67 g EPA +0.83 g DHA	8 weeks	Monotherapy
Rondanelli et al ¹⁸	EPA + DHA	Paraffin oil	1.67 g EPA +0.83 g DHA	8 weeks	Monotherapy
Lucas et al ³⁰	EPA + DHA	Sunflower oil	1.05 g EPA +0.15 g DHA	8 weeks	Monotherapy
Freeman et al ¹⁷	EPA + DHA	Corn oil +1% fish oil	1.1 g EPA +0.8 g DHA	8 weeks	Augmentation
Rees et al ²⁹	EPA + DHA	Sunola oil	0.42 g EPA +1.64 g DHA	6 weeks	Monotherapy
Su et al ²⁷	EPA + DHA	Olive oil ethyl esters	2.2 g EPA +1.2 g DHA	8 weeks	Monotherapy
Su et al ³²	EPA + DHA	Olive oil ethyl esters	4.4 g EPA +2.2 g DHA	8 weeks	Augmentation

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Table 3 Bias risk of included studies

Study	Randomization	Allocation	Blinding	Incomplete data	Baseline
Rizzo et al ³¹	None	None	None	None	None
Rondanelli et al ²⁸	None	None	None	None	None
Rondanelli et al ¹⁸	None	None	None	None	None
Lucas et al ³⁰	None	None	None	None	None
Freeman et al ¹⁷	None	None	None	None	None
Rees et al ²⁹	None	None	None	None	None
Su et al ²⁷	None	None	None	None	None
Su et al ³²	None	None	None	None	None

(MDD), and one study treated the recruited patients for six weeks. Then, we excluded these two RCTs to do sensitivity analysis, respectively. The results showed that the exclusion did not significantly affect the initial effect size estimates.

Subgroup analysis

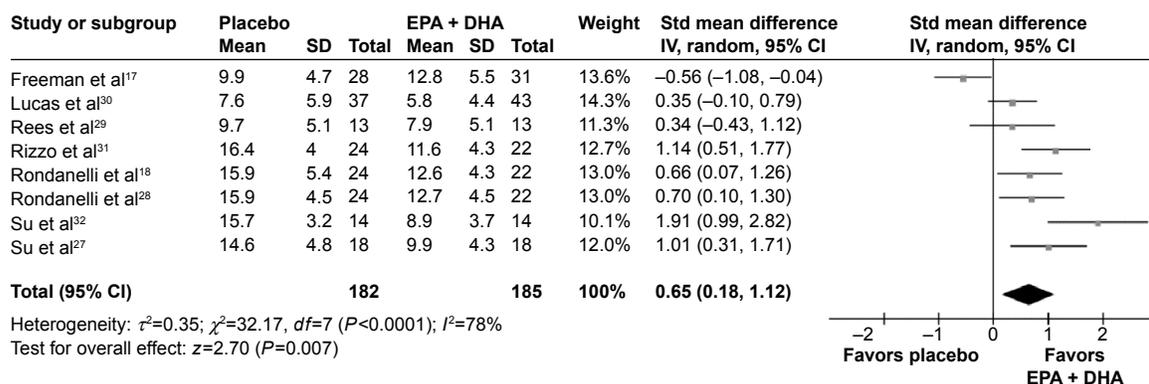
Three RCTs mainly used Geriatric Depression Scale to assess the outcome,^{18,28,31} and five RCTs mainly used HDRS to assess the outcome.^{17,27,29,30,32} Then we did subgroup analysis according to the outcome measurement. The results showed that the five RCTs and three RCTs yielded the standardized difference in means of 0.34 (95% CI =0.07, 0.61) and 0.82 (95% CI =0.47, 1.17), respectively. Three RCTs recruited patients with an average age of above 80 years^{18,28,31} and five RCTs recruited patients with an average age of 30–50 years.^{17,27,29,30,32} Then we did subgroup analysis according to the age. The results showed that the three RCTs and five RCTs yielded the standardized difference in means of 0.34 (95% CI =0.07, 0.61) and 0.82 (95% CI =0.47, 1.17), respectively. These results indicated that the different outcome measurement methods and age did not influence the outcomes.

Discussion

This meta-analysis first investigated the efficacy of EPA and DHA in the treatment of depressed women. Compared to

the placebo, the combination of EPA and DHA had significantly better efficacy with pooled standardized difference in means of 0.65 (95% CI =0.18–1.12, $z=2.70$, $P=0.007$), but significant heterogeneity existed ($P<0.0001$, $I^2=78\%$). After excluding the two studies that used the combination of EPA and DHA as an augmentation agent, the pooled standardized difference in means had no changed, but significant heterogeneity non-existed ($P=0.33$, $I^2=13\%$). These results showed that the combination of EPA and DHA could effectively treat the depression in women.

Mischoulon et al hypothesized that subjects with diets low in PUFAs would have higher baseline severity of depression.³³ The association between depression and PUFAs has been reported by several studies.^{34,35} One study reported that the DHA levels were particularly lower in the postmortem orbitofrontal cortex of female patients with major depressive disorder than their male counterparts.³⁶ Another study using adipose tissue, which reflects long-term dietary fat intake, also found a significantly lower DHA concentrations in female MDD patients than male MDD patients.³⁷ The reason might be the conversion of alpha-linolenic acid to DHA, positively regulated by estrogen.³⁸ Meanwhile, many evidences have implicated estrogen in the pathophysiology of MDD in women.^{39,40} Furthermore, another study found that the low levels of DHA could predict the low levels of 5-hydroxytryptamine, which

**Figure 2** Meta-analysis of the combination of EPA and DHA versus placebo.

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Std, standard; SD, standard deviation; IV, intravenous; CI, confidence interval.

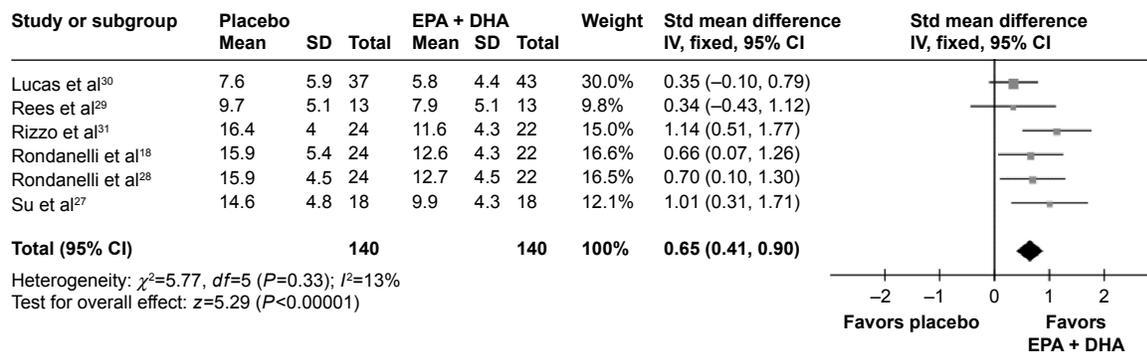


Figure 3 Meta-analysis of the combination of EPA and DHA as monotherapy versus placebo.

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Std, standard; SD, standard deviation; IV, intravenous; CI, confidence interval.

was implicated in the pathophysiology of depression.⁴¹ This work found that the supplementation of PUFAs could yield better efficacy for women with depression. Moreover, all the included studies showed that PUFAs were well tolerated by postpartum and pregnant women.

Seven of eight studies in this meta-analysis used the larger dose of EPA than DHA. Previous study showed that EPA had an effect on core depressive symptoms, such as guilt feelings, depressed mood, and worthlessness as well as insomnia.⁴² Mischoulon et al reported that the observed decrease in HAM-D-17 score was significant for the EPA group, but not for the placebo group.³³ They also found that the administration of EPA resulted in a significant increase in mean plasma EPA, but had limited effect on plasma DHA. The mechanism of EPA and DHA was different. The EPA might influence mood by acting through eicosanoid mechanisms to increase cerebral blood flow. The brains contained much more DHA than EPA, which might partly explain why many studies used the larger dose of EPA than DHA.

Depression comorbidity with other diseases, such as cardiovascular diseases and dementia, in the elderly population often lower the effects of antidepressive treatments. This might be caused by the age or the comorbidity. In this meta-analysis, we found that the combined application of EPA and DHA in younger women with depression yielded a better antidepressant effect than that in elderly women with depression (standardized difference in means, 0.82 versus 0.34). Although these results were limited by the relatively small studies, the treatments for elderly women with depression needed more attention.

Several limitations should be addressed here: 1) the number of included RCTs and depressed patients were relatively small; 2) the dose of EPA and DHA, the age of included patients, and the used placebo were not exactly the same and there were also the general problems for metastudies to solve; 3) four of 367 included patients were men; and

4) whether or not it is appropriate to apply this conclusion to postpartum depression and male with depression or vascular depression is unknown. However, this pooled analysis of eight double-blinded RCTs found that the clinical applicability of EPA and DHA showed greater promise and should be further explored.

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Disclosure

The authors declare no conflicts of interest in this work.

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