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Review article

Effect of omega-3 supplements on vasomotor symptoms in menopausal women: A systematic review and meta-analysis

Mina Mohammady[a], Leila Janani[b], Shayesteh Jahanfar[c,*], Mahsa Sadat Mousavi[a]

[a] Community Health Research Center, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran
[b] Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
[c] School of Health Sciences, Central Michigan University, Building 2212, Mount Pleasant, MI, 48859, USA

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ABSTRACT

Objective: We aimed to investigate the effect of omega-3 supplements on relief of vasomotor symptoms among menopausal women.

Study design: The Cochrane Library, MEDLINE, SCOPUS, EMBASE, ProQuest, Google Scholar, Web of Science, CINAHL, IranMedex and SID databases were searched until September 2017. Inclusion criteria were (1) women were experiencing vasomotor symptoms in the menopause period, (2) intervention was omega-3 supplements (3) randomized controlled trial (RCT) or quasi-RCT, and (4) outcome measures included changes in the frequency and severity of hot flush or night sweats, sleep problems and side effects.

Results: Three randomized controlled trials involving 483 women in the age range of 51 to 54.7 years were included in the review. Overall, the risk of bias in the included studies was moderate. All the participants were found to be blinded. Meta-analysis of the data showed no difference in the frequency and severity of hot flushes, insomnia severity, sleep quality, quality of life and adverse effects between the two groups. Compared to placebo group, women who received omega-3 supplements experienced lower frequency (mean difference: -1.82, 95% CI: -2.81, -0.83) and severity (mean difference: -.89, 95% CI: -1.25, -0.53) of night sweats.

Conclusions: RCTs which investigate the impact of omega-3 supplements on vasomotor symptoms in menopausal women are scarce. A comprehensive search in a wide range of databases found only three relevant papers. Our analysis suggests that omega-3 supplements may alleviate night sweats but have no benefit in reducing hot flushes, or improving sleep quality and quality of life during the menopausal period. We recommend high quality RCTs along with a longer follow-up period to investigate this important subject, as there was insufficient evidence to conclude that omega-3 supplements are of benefit in alleviating vasomotor symptoms in menopausal women.

Contents

* Corresponding author at: Central Michigan University, USA.
E-mail addresses: Mina.mohammady@khuisf.ac.ir (M. Mohammady), Janani.l@iums.ac.ir (L. Janani), Jahan2s@cmich.edu (S. Jahanfar), M.mousavi@khuisf.ac.ir (M.S. Mousavi).

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Introduction

Menopause is one of the most important events in a woman's life. It is a period of physiological changes that permanently affect the life of a woman [1]. Reduced estrogen levels during the menopause contribute to menopausal symptoms [2]. From perimenopause to the late postmenopausal stage of life, most women experience conditions such as vasomotor symptoms, vaginal dryness, sleep disturbance, somatic complaints, urinary complaints, depression and sexual dysfunction; these changes might affect their quality of life [3,4].Vasomotor symptoms are highly prevalent in most societies [5]. These symptoms affect two-thirds of women during the menopausal transition, and may continue for several years in some women after menopause [5,6].

The pathophysiology of vasomotor symptoms is not completely clear, though it is hypothesized that declining estrogen concentration may result in diminishing endorphin concentrations in the hypothalamus, which in turn may lead to enhancing the release of norepinephrine and serotonin [7,8]. Ultimately, these changes decrease the set point in the hypothalamic thermoregulatory center, leading to hot flushes [9]. Hot flushes are defined as a sudden onset of reddening of the skin and feeling of warmth over the face, neck and chest accompanied by sweating, palpitations and anxiety [10]. Some women find these symptoms very distressing; therefore, they look for treatments for vasomotor symptoms [11].

Oral hormone replacement therapy (HRT) is the oldest treatment for vasomotor symptoms of menopause, and is highly effective in decreasing hot flushes and night sweats [12]. Unfortunately, compared to other menopausal women, women taking estrogen plus progesterone may experience more venous thromboembolism [13], or breast cancer [14]. In addition to HRT, various nonhormonal therapies are recommended for the relief of menopausal hot flushes, such as selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors [8], clonidine [15] and gabapentin [16] medicines.

Given the potential health risks associated with use of HRT, and the adverse effects of the non-hormonal treatments, attention has been turned to other possible treatments to relieve hot flushes. Both complementary and alternative therapies have been investigated to reduce hot flashes among menopausal women [17,18]. It seems that natural therapies are popular among menopausal women [19]. However, there is a lack of sufficient research on the risks and benefits of these approaches.

One of these natural therapies is omega-3 fatty acids. Omega-3 fatty acids are a type of polyunsaturated fatty acids (PUFAs) found in fish oil and other seafood, nuts and green-leafed vegetables. Omega-3 fatty acids consist of docosapentaenoic acid (DPA), eicosapentaenoic acid (EPA) and alpha-linolenic acid (ALA) [20]. They are essential nutrients, as the human body cannot produce omega-3 fatty acids [21]. Nowadays, omega-3 supplements are among the most extensively consumed supplements for different medical disorders such as cardiovascular diseases, depression and cognitive disorders [22–24]. However, the mechanisms by which omega-3 might affect vasomotor symptoms are not completely clear. Both human and animal studies on omega-3 support the existence of mechanisms that raise omega-3 fatty acid levels that may change the levels of some neurotransmitters such as serotonin and dopamine in the brain [25,26]. Furthermore, because of positive effects of omega-3 on different aspects of health, this suplementary drug has a high acceptiblity among people [27].

Some clinical studies have suggested that omega-3 supplements are associated with benefits in alleviating the frequency and severity of vasomotor symptoms [28]. In contrast, a randomized, double-blind, placebo-controlled trial found that omega-3 supplements had no effect on the frequency or severity of vasomotor symptoms [29]. We found an absence of conclusive evidence supporting the effects of omega-3 supplements on vasomotor symptoms in the literature. Thus, the aim of this systematic review is to synthesize all the available evidence on the effect of omega-3 supplements on the relief of vasomotor symptoms in menopausal women.

Methods

Types of participants

Women who were experiencing menopause and had vasomotor symptoms due to peri-menopausal, menopausal or postmenopausal stages, or women experiencing vasomotor symptoms after spontaneous or surgical menopause at the baseline.

Types of interventions and comparisons

Studies included if they assessed the effect of supplements of omega-3 fatty acids compared to placebo, no treatment, omega-6 fatty acids, or combined omega-3 fatty acids plus omega-6 fatty acids. Supplementation could involve with any dosage, frequency, duration and form (such as capsules, oil or powders). We excluded those studies in which (1) the intervention was defined as consumption of a diet enriched with fish products, (2) there were mixed interventions in one arm of study, and (3) there was no placebo control group.

Types of outcome measures

Primary outcome measures included changes in (1) the frequency of vasomotor menopausal symptoms consisting of hot flushes or night sweats that were evaluated subjectively by self-report using daily symptom diaries, (2) the severity of vasomotor symptoms was also recorded if it was measured by self-report (e.g., graded scale or a compound measure such as multiplication of frequency by severity) [8], (3) vasomotor symptoms scores that were measured by Kupperman Index or any other general

menopausal symptom scores. Secondary outcome measures included quality of sleep, quality of life, and the incidence of adverse effects.

Types of study designs

We included randomized controlled trials (RCTs) and quasi-RCTs published in any language in the review. We excluded cross over studies and all types of observational studies.

Literature search

The CENTRAL in the Cochrane Library (Issue 9, 2017), MEDLINE via Ovid SP, SCOPUS, Embase and ProQuest Dissertations were searched in September 2017 using free text and Medical Subject Headings (MeSH) terms includes "Fish Oils", "fatty acids omega-3", "PUFA", "menopause", "climacteric", "hot flashes", "vasomotor" and "clinical trial". In addition, we searched Web of Science, CINAHL, Google Scholar and two Persian medical databases: IranMedex (www.health.barakatkns.com) and SID (www.sid.ir). The World Health Organization international clinical trials registry, ClinicalTrials.gov and Current Controlled Trials were also searched to identify ongoing or unpublished studies. The references of the retrieved articles were checked to find additional articles. There were no restrictions on the language of publications, time of publication or publication status. The search strategy in MEDLINE is presented in Appendix 1.

Selection of studies, data extraction and quality assessment

In stage one of screening, one reviewer screened the titles and abstracts (MM, LJ). Controversies were resolved by a third person (SJ). In stage two, full papers extracted from the earlier stage were screened independently by two reviewers. (NM, LI) Eleven papers were selected first to identify the consistency between reviewers. The Kappa score was more than 0.7.

The Cochrane Collaboration Risk of Bias Assessment Tool [30] was used to evaluate the quality of included studies. The Cochrane seven domains of assessment were used to assess the quality of studies: randomization, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Data were then extracted from the papers and entered in Revman for analysis. Data extraction was conducted in duplicates to ensure quality.

Statistical analysis

RevMan software (version 5.3) was used to analyze the data. We used the Mantel–Haenszel fixed-effect model to combine dichotomous outcomes (adverse effects) and present them as odds ratios (OR) with 95% confidence intervals (CI). The continuous outcomes were compared with the inverse-variance method to achieve the mean difference (MD) and 95%CI with a random-effect model. As the severity of hot flushes was measured using different scales, the standardized mean difference (SMD) was calculated with 95% CI to pool the data.

Moreover, any heterogeneity across individual studies was quantified by the I^2 test. Low, moderate or high degrees of heterogeneity were approximated by I^2 values of 25%, 50% and 75%, respectively. If the I^2 value was larger than 50%, random-effect model was estimated.

Heterogeneity was assessed by subgrouping the different dosages of omega-3 supplements. We planned to investigate heterogeneity by subgroup analysis of different forms of omega-3 supplements (raw, capsule, powder, enteric coated, etc.), age groups and stage of menopause (peri-menopausal, menopausal transition and postmenopausal).

The authors of the included studies were contacted to obtain the missing data or information to assess the risk of bias. Only one author replied via email and provided more data [31]. We planned to plot funnel plots if we encountered more than 10 studies for each forest plot; however, the number of studies was not found to be adequate for such plotting.

It is recommended that assessment of publication bias via funnel plot asymmetry should be used when at least 10 studies are included in a systematic review [30]. We planned to detect publication bias, as only three studies were included in the review, therefore; it was not possible to prepare a funnel plot.

Results

Study selection

We identified 1051 references from our electronic and hand searches. After the removal of duplicate articles and checking the study titles and abstracts, 11 full papers were retrieved and three studies were included (Fig. 1).

Included and excluded studies

We included three studies included 483 participants [28,31,32]. Moghadam's [31,33] and Cohen's [29,32] studies were published in two reports. The range of age for the participants was between 51 and 54.7 years (Table 1).

Four studies were excluded because of non-RCT design [34–36], one due to usage of other supplements in addition to omega-3 supplements in the intervention group [37] and one due to including women with moderate and severe psychological disorders where the participants were assessed for hot flushes after randomization [38]. One study applied a cross-over design [39] and one compared omega-3 supplements versus soybean isoflavones without a control group [40]. In addition, we found two registered trials and contacted the authors for more information, but with no success. One of the authors noted that the trial was not published because of negative results [41] and so he was not willing to share the results.

Effect of omega-3 fatty acids on vasomotor symptoms

All included studies assessed the frequency and severity of hot flushes based on daily diaries. All studies assessed climacteric symptoms by a menopause rating scale but reported them in different ways, including mean reduction in the number of hot flushes and the severity of hot flushes from the baseline to the end [32], mean and standard deviation of daily hot flushes during a week-long period [31] and median and range of daily hot flushes during the same period [28]. To facilitate data pooling the mean and SD were calculated [42].

Meta-analysis of the three studies showed no difference in the frequency of hot flushes among the women who received omega-3 supplements compared to the placebo group (MD: -0.5, 95% CI (-1.58, 0.58), P = 0.37, Fig. 2). Hot flush severity was evaluated according to different rating scales ranging from 1 to 3 (mild, moderate and severe symptoms) and 1 to 4 (none, a little, moderately and a lot). Meta-analysis of the data showed no difference in the severity of hot flushes in the omega-3 group compared to the placebo group (SMD: -0.18, 95% CI (-0.64, 0.28), P = 0.44). Subgroup analysis was performed in order to determine hot flush severity according to different dosages of omega-3 and different scales; the results showed there was a statistically significant effect on hot flush severity (P = 0.02), I^2 = 81.9%). This

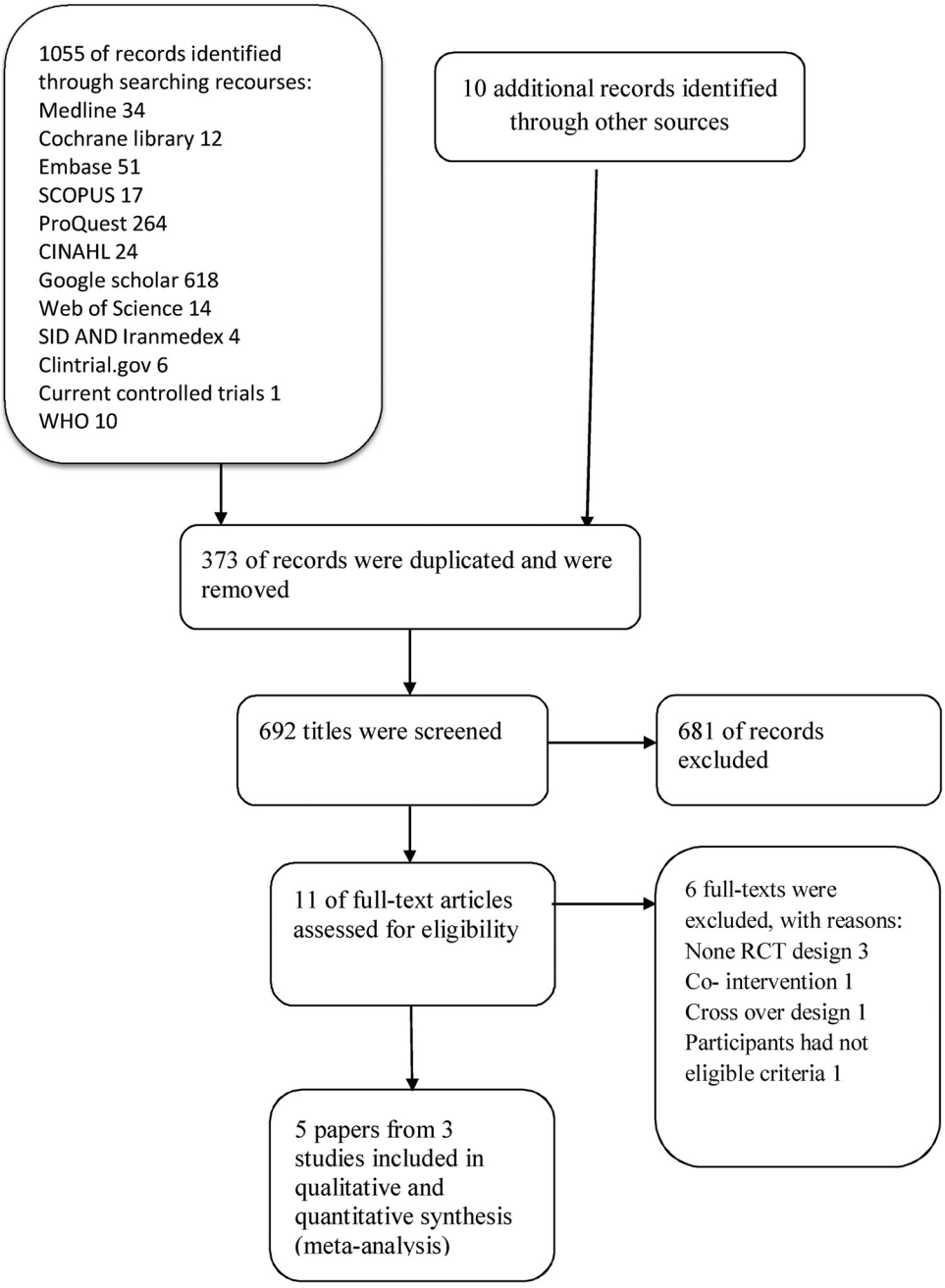

Fig. 1. Study flow diagram.

suggests that these factors may be potential sources of heterogeneity on hot flush severity (Fig. 3). Frequency and severity of night sweats were reported in only one study [31]. This study reported that compared to the placebo group, women who received omega-3 supplement experienced lower night sweat frequency (mean difference: -1.82, 95% CI: -.81, -0.83, P = 0.0003) and severity (mean difference: -.89, 95% CI: -1.25, -0.53, P = 0.00001).

Effect of omega-3 fatty acids on sleep and quality of life

Insomnia severity and sleep quality were assessed by one study [32] and the results showed no statistically significant difference between the two groups (MD: -0.27, 95% CI (-1.40, 0.86), P = 0.64), (MD: -0.29, 95% CI (-.098 to 0.40), P = 0.41) respectively. Quality of life was evaluated by Cohen et al., in the second portion of their publication of the same study [29] using MENQOL. The results showed that there was no statistically significant difference between two groups (MD: -0.2, 95% CI (-0.48 to 0.80), P = 0.163).

Adverse events

One study [32] reported adverse events frequency as 36.9% in the placebo group and 38.5% in the omega-3 group (P = 0.82). The incidence of gastrointestinal upset consisting of nausea, vomiting, diarrhea and constipation was higher in the omega-3 group (18%) compared to the placebo group (12%). In addition, there were no statistically significant differences between the two groups in the incidence of burping, bad breath, heartburn, heart palpitation, dizzying, skin rash, flu-like symptoms, muscle aches, strengths changes, back pain, bruising and bleeding. No participants were withdrawn because of adverse events in this study. Another study [31] reported that only 2 out of the 34 participants experienced

Table 1
Characteristics of the included studies.

First author year/ country	Baseline characteristics	Control	Intervention	Number of capsules/day	Duration (weeks)	Outcomes
Cohen 2014 US	355 participants, Mean age: CG: 54.98 ± 3.79 IG: 54.39 ± 3.55 Postmenopausal period: CG: 78.8% IG: 82.5%	Placebo (Capsules containing Olive oil, 15 IU Vitamin E, antioxidant, lemon oil and rosemary extract)	Capsules containing 425 mg EPA, 100 mg DHA, 90 mg, other assorted omega-3 s, 15 IU Vitamin E, antioxidant, lemon oil and rosemary extract	1.8 g/day (3 Capsules /day	12 weeks	-Frequency of hot flushes and night sweats -Severity of hot flushes and night sweats -Sleep quality -Insomnia symptoms - Quality of life -Adverse events
Moghadam 2012 Iran	68 participants, Mean age: CG: 51.09 ± 2.84 IG: 52.15 ± 3.03 Menopause time (years): CG: 2.54 ± 2.3 IG: 2.66 ± 2.58	Placebo (Capsules 1 gr. containing oral, non-absorbable paraffin)	Capsules 1 gr. containing 120 mg EPA and 180 mg DHA	1 capsule /day	8 weeks	-Frequency of hot flushes and night sweats -Severity of hot flushes and night sweats -Adverse events
Ghasemi 2012 Iran	60 participants, Mean age: CG: 51.1 ± 5.9 IG: 51.07 ± 5.9 Menopause time (months): CG: 10.8 ± 3.8 IG: 11 ± 7. 4	Placebo (Capsules containing gelatin)	Capsules 1 gr. containing omega-3	1capsule /day	12 weeks	-Frequency of hot flushes -Severity of hot flushes

IG, intervention group; CG, control group.

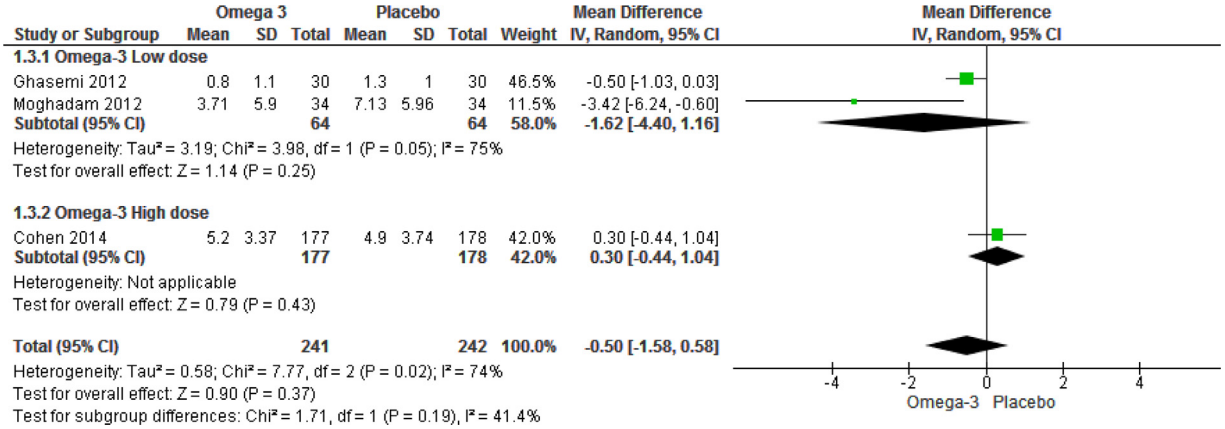

Fig. 2. Mean difference and 95% confidence interval of hot flush frequency in omega-3 supplement versus placebo groups.

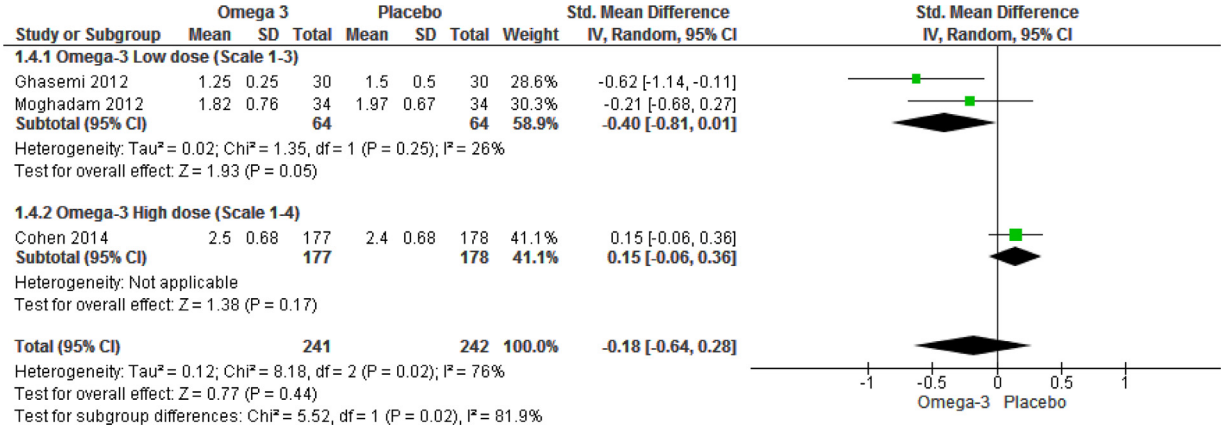

Fig. 3. Standardized mean difference and 95% confidence interval of hot flush severity in omega-3 supplement versus placebo groups.

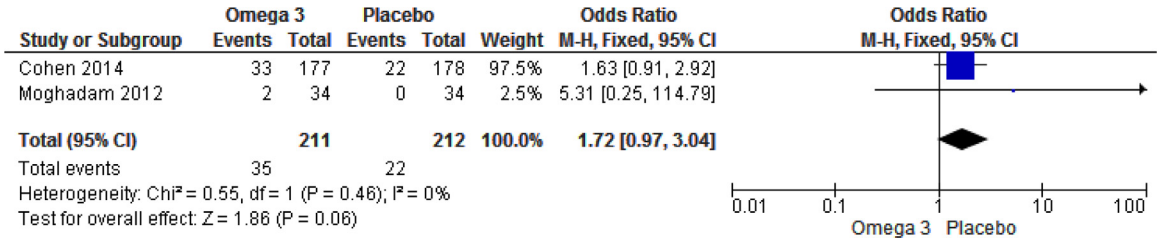

Fig. 4. Odds ratio and 95% confidence interval of overall adverse events in omega-3 supplement and placebo groups.

stomachache in the omega-3 group. In the pooled analyses, there was no statistically significant difference between the two groups in the overall incidence of gastrointestinal upset (OR: 1.72, 95% CI (0.97, 3.04), P = 0.06, Fig. 4).

Risk of bias in included studies

We evaluated the quality of the trials in seven domains as shown in Fig. 5. Overall, the risk of bias in the included studies was moderate.

Sequence generation: All included studies described the method of random sequence generation adequately as computer-generated randomization software [31], fixed blocked randomization [28] and Web-based randomization [32].

Allocation concealment: The methods of allocation concealment were unclear in all included studies.

Blinding of participants and personnel: participants were blinded in all included studies as researchers used identical capsules in intervention and control groups. In addition, clinicians and staff involved in research process were blinded in two studies [28,32], whereas, it was unclear in Moghadam (2012) study.

Blinding of outcome assessment: only in one trial outcome assessor blinding was mentioned [32].

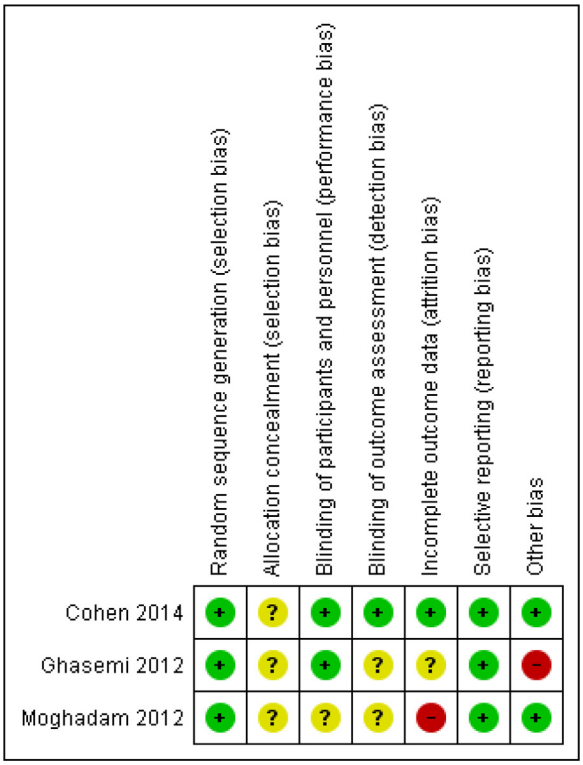

Fig. 5. Risk of bias summary.

Incomplete outcome data: two of the studies had an adequate description of the numbers of drop-outs. Moghadam et al. (2012) noted of 18% loss to follow-up because of none adherences of participants from the intervention. This study reported that the participants who were loss to follow up were excluded from analysis and leading us to believe that intention-to-treat-analysis (ITT) was not applied. The other study by Cohen et al. (2014) had 5% loss to follow up. However, they reported all analyses were based on the ITT principle regardless of participant's adherence to the treatment assignment.

Selective outcome reporting: The protocols of all studies were previously registered on the clinical trial registry websites. We considered to have a' low' risk of bias as they reported all pre-specified outcomes.

Other bias: There is a potential bias in one of the studies as the authors did not report the actual dose of EPA and DHA prescribed [28].

Discussion

There are relatively few RCTs that have investigated the effectiveness of omega-3 supplements on vasomotor symptoms. We incorporated data from three trials enrolling 483 women to evaluate the effectiveness of omega-3 fatty acid supplements on vasomotor symptoms in menopausal women. Despite overall no statistically significant results in our systematic review, positive findings of omega-3 supplementation were reported in one small trial, which shows that omega-3 supplements may reduce the frequency and severity of night sweats. The other results suggest that the omega-3 supplements had no effect on the frequency or severity of hot flushes, severity of insomnia, sleep quality or quality of life in menopausal women compared with the placebo.

In the RCTs of hot flush therapy, one of the problems that should be considered is the potential placebo effects. In other words, all the participants compared with the baseline experienced lower hot flush frequency and severity after completing the study. While this seems to be an observer effect (Hawthorne effect) on participants, it may be due to the natural reduction of vasomotor symptoms over time [43]. This change in measured outcomes in the placebo group can lead to few differences between the intervention and placebo groups, and ultimately non-statistically significant results.

All studies were conducted for duration of 12 weeks or less, and most of the participants were followed up for 12 weeks or less. Because our brain needs at least three months to improve chronic PUFAs deficiency [44], the majority of these studies can be considered too short for the benefits of PUFAs on neurotransmitters to materialize, leading to alleviation of the vasomotor symptoms.

Overall, the risk of bias in the trials was moderate. Most of the studies reported the method of sequence generation, but they did not describe the method of allocation concealment. All the included studies had participant blinding; however, a major problem with omega-3 supplementation is participant blinding because the specific smell and taste of fish oil might reveal the

capsules' content. Adherence may also have been an important issue in these trials because the participants were expected to take one to three large capsules, which some participants might not have been able to swallow.

Two out of three included studies did not follow the ITT principles. This may lead to an overestimation of the benefits associated with omega-3 supplements. None of the included studies were sponsored by the companies that produced the omega-3 supplements under investigation.

The review had several strengths. We performed a comprehensive search of several international and national databases without any language restriction. We also searched the gray literature and included only randomized and quasi-randomized trials. We did not find another systematic review to compare the results to.

The potential limitation of our review was the small number of identified studies. Although we tried to identify all eligible studies, some studies might still have been overlooked. In addition, there were methodological flaws in some studies, and the risk of bias was unclear in some domains due to inadequate reporting. Another limitation of our meta-analysis was the considerable heterogeneity among the results of hot flush frequency and severity measures. The studies were not alike in terms of dose and constituents of PUFAs, duration of therapy, follow-up period, and sample size. This can partly explain the considerable heterogeneity that was found in our results.

Conclusion

RCTs investigating the impact of omega-3 on vasomotor symptoms of menopausal women are scarce. A comprehensive search in a wide range of databases found only three relevant papers. Our analysis suggests that omega-3 supplements may alleviate night sweats but have no benefit in reducing hot flushes, or improving sleep quality and quality of life during the menopausal period. We recommend high quality RCTs with longer follow-up periods to investigate this important subject, as there was insufficient evidence to conclude that omega-3 supplements are of benefit for alleviating vasomotor symptoms in menopausal women.

Funding

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Conflict of interest

The authors report no conflict of interest.

Appendix 1 Cochrane Library (CENTRAL) search strategy

#1 MeSH descriptor Fish Oils explode all trees
#2 MeSH descriptor Fatty Acids, Omega-3 explode all trees
#3 (Acids, Omega-3 Fatty OR Fatty Acids, Omega 3 OR Omega-3 Fatty Acids OR Omega 3 Fatty Acids OR n-3 PUFA OR n-3 Fatty Acids OR Fatty Acids, n-3 OR n 3 Fatty Acids OR n-3 Polyunsaturated Fatty Acid OR n 3 Polyunsaturated Fatty Acid): ti,ab
#4 (*eicosapentaen* OR icosapentaenoic OR docosahexaeno*): ti,ab
#5 (*eicosapentanoic OR docosahexanoic OR docosapentanoic OR alpha-linolenic): ti,ab
#6 FISH near3 oil*: ti,ab
#7 (PUFA OR EPA OR E-EPA OR DHA OR DPA OR ALA): ti,ab
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9 MeSH descriptor: [Menopause] explode all trees
#10 MeSH descriptor: [Menopause, Premature] explode all trees
#11 MeSH descriptor: [Premenopause] explode all trees
#12 MeSH descriptor: [Postmenopause] explode all trees
#13 MeSH descriptor: [Perimenopause] explode all trees
#14 (Premature menopaus* OR Premenopaus* OR Perimenopause* OR postmenopaus* OR menopaus*): ti,ab
#15 MeSH descriptor: [Climacteric] explode all trees
#16 Climacteri*: ti,ab
#17 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18 MeSH descriptor: [Hot Flashes] explode all trees
#19 Hot Fl?sh*: ti,ab
#20 Vasomotor*: ti,ab
#21 Night* sweat*: ti,ab
#22 #18 OR #19 OR #20 OR #21
#23 #8 AND #17 AND #22

Appendix 2 MEDLINE search strategy via Ovid SP

1. exp Fish Oils/
2. exp Fatty Acids, Omega-3/
3. (Acids, Omega-3 Fatty or Fatty Acids, Omega 3 or Omega-3 Fatty Acids or Omega 3 Fatty Acids or n-3 PUFA or n-3 Fatty Acids or Fatty Acids, n-3 or n 3 Fatty Acids or n-3 Polyunsaturated Fatty Acid or n 3 Polyunsaturated Fatty Acid).ti,ab.
4. (?eicosapentaen? or icosapentaenoic or docosahexaeno?).ti,ab.
5. (eicosapentanoic or docosahexanoic or docosapentanoic or alpha-linolenic).ti,ab.
6. (Oils, Fish or Fish Oil or Oil, Fish or Fish Liver Oils or Liver Oils, Fish or Oils, Fish Liver).ti,ab.
7. (PUFA or EPA or E-EPA or DHA or DPA or ALA).ti,ab.
8. or/1-7
9. exp menopause/
10. exp menopause, premature/
11. exp premenopause/
12. exp postmenopause/
13. exp perimenopause/
14. (premature menopaus? or premenopaus? or perimenopause? or postmenopaus? or menopaus?).ti,ab.
15. exp climacteric/
16. climacteric?.ti,ab.
17. or/ 9-16
18. exp hot flashes/
19. hot fl?sh?.ti,ab.
20. vasomotor.ti,ab.
21. night sweat?.ti,ab.
22. or/18-21
23. randomi?ed controlled trial?.pt.
24. controlled clinical trial?.pt.
25. randomi?ed.ab.
26. placebo.ab.
27. drug therapy.fs
28. random?.ab.
29. trial.ab.
30. groups.ab.
31. or/23-30
32. exp animals/ not humans.sh.
33. 31 not 32
34. 8 and 17 and 22 and 34

SCOPUS 2017/9/11

((TITLE-ABS ((acids, AND omega-3 AND fatty) OR (fatty AND acids, AND omega 3) OR (omega-3 AND fatty AND acids) OR (n-3 AND pufa) OR (n-3 AND fatty AND acids) OR (polyunsaturated 5

AND fatty AND acid) OR (n 3 polyunsaturated AND fatty AND acid))) OR (TITLE-ABS (*eicosapentanoic OR docosahexanoic OR docosapentanoic OR alpha-linolenic OR pufa OR epa OR e-epa OR dha OR dpa OR ala))) AND (TITLE-ABS ((hot AND fl?sh*) OR vasomotor* OR (night* AND sweat*))) AND (TITLE-ABS ((premature AND menopaus*) OR premenopaus* OR perimenopause* OR postmenopaus* OR menopaus* OR climacteric)) ...	4
	3
(TITLE-ABS ((acids, AND omega-3 AND fatty) OR (fatty AND acids, AND omega 3) OR (omega-3 AND fatty AND acids) OR (n-3 AND pufa) OR (n-3 AND fatty AND acids) OR (polyunsaturated AND fatty AND acid) OR (n 3 polyunsaturated AND fatty AND acid))) OR (TITLE-ABS (*eicosapentanoic OR docosahexanoic OR docosapentanoic OR alpha-linolenic OR pufa OR epa OR e-epa OR dha OR dpa OR ala))	2
	1
	0

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