Review

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Review

Effects of Omega-3 Polyunsaturated Fatty Acids Intake on Vasomotor Symptoms, Sleep Quality and Depression in Postmenopausal Women: A Systematic Review

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Abstract: The menopausal transition often accompanies distressing manifestations, including vasomotor symptoms, sleep disruptions, and depressive syndrome. Omega-3 fatty acids have emerged as a potential intervention to alleviate these symptoms. This review aimed to comprehensively assess the impact of omega-3 supplementation on vasomotor symptoms, sleep quality, and depression among postmenopausal women. We conducted a systematic search focusing on randomized control trials across the Cochrane Library, Web of Science, PubMed, CINAHL, EMBASE, and SCOPUS databases from inception to August 2023. Among the initial pool of 163 studies, 9 studies met the inclusion criteria and were incorporated into this review. Four studies suggested potential benefits of omega-3 intake for improving hot flashes and night sweats. Sleep quality outcomes displayed heterogeneity across the studies. Incorporating diverse scales such as the Hamilton Depression Rating Scale-21, the Patient Health Questionnaire depression scale, and Generalized Anxiety Disorder-7 for depression outcomes, the review found inconclusive evidence on omega-3's impact on depression. Overall, the combined analysis of these studies did not provide substantial evidence to support the efficacy of omega-3 fatty acids in improving vasomotor symptoms, sleep quality, and depression. Further well-designed RCTs with larger participant groups are crucial to validate and generalize these results.

Keywords: amenorrhea; depression; hot flashes; omega-3 PUFA; post-menopause; sleep quality; vasomotor symptoms

1. Introduction

Menopause, a phase marked by complex physiological changes in women, significantly impacts their well-being [1]. Defined as a cessation of menstruation for approximately one year after the last menstrual cycle, menopause spans 40 to 60 years, with an average age of 52 [2]. Vasomotor symptoms (VMS), encompassing hot flashes (HF), and night sweats, alongside various other manifestations such as sleep disturbances, anxiety, depression, vaginal dryness, muscular discomfort, and sexual dysfunction, collectively impair the quality of life during this period [3,4]. HF and major depressive

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disorder (MDD) emerge as prominent symptoms, with HF occurring in up to 80% of cases and MDD affecting over 20% of menopausal women. Consequently, more than 1/3rd of women obtain medical assistance due to the discomfort induced by HF [5]. Menopause-related depression needing medication has a substantial age of onset; it is more prevalent (10-15%) when symptoms begin before 45, but less common (5-6%) when symptoms begin at 48 or later [6].

The etiology of HF remains incompletely understood, hypothesized to stem from disturbances in temperature regulation due to factors including estrogen fluctuations and neurotransmitter perturbations [7,8]. Declining estrogen levels disrupt the hypothalamic-pituitary-adrenal (HPA) axis and serotonergic systems, triggering VMS characterized by HF and night sweats. These symptoms, in turn, disturb sleep patterns through stress-induced cortisol elevation and serotonin dysregulation. The interplay between hormonal changes, particularly reduced estrogen, and disrupted sleep contributes to depressive symptoms [9,10]. Hormone therapy (HT) remains the prevailing strategy for mitigating VMS, yet it harbors a spectrum of associated risks and potential adverse outcomes [11].

Omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA), represent essential dietary components with multiple double bonds [12]. Renowned for their therapeutic potential, these long-chain omega-3 supplements find utilization in treating diverse medical conditions such as cardiovascular disease, depression, and cognitive disorders [13,14]. Their efficacy in addressing menopausal symptoms and MDD in perimenopausal and postmenopausal women has also been investigated [15-17]. Human and animal investigations elucidating the mechanistic underpinnings of omega-3 indicate their engagement in the regulation of serotonergic and dopaminergic neurotransmitter systems. However, the definitive favorable impact of omega-3- 3 on menopausal transition-associated HF, depression, and cognitive symptoms remains inconclusive [18-20].

In a clinical investigation, the supplementation of ethyl eicosapentaenoic acid, an omega-3 derivative, resulted in reduced HF and improved hot flash scores compared to a placebo [21]. However, another study failed to observe alterations in VMS and sleep quality when compared to a placebo [22]. A comprehensive review of 32 studies underscored the vulnerability of menopausal women to depression and anxiety [23]. Exploring the interplay of HF, sleep patterns, and depression in women undergoing menopause induced by a Gonadotropin-releasing hormone (GnRH) agonist medication, a study revealed significant associations between increased sleep interruptions, nocturnal HF, and heightened depression scores [24]. Although certain studies propose the potential of omega-3 fatty acids in mitigating depression and HF [25,26], discrepant evidence arises from studies that found no support for the influence of omega-3 on depression scores, as assessed through diverse rating scales [22].

Presently, the precise impact of omega-3 supplementation on VMS remains elusive. Convergent research in both animal and human subjects suggests that omega-3 may modulate neurotransmitter levels, including serotonin and dopamine, within the brain by elevating levels of these fatty acids [19,27]. Consequently, the definitive impact of omega-3 supplements on VMS, sleep quality, and depression scores lacks empirical validation. As such, this systematic review endeavors to synthesize existing evidence to elucidate the efficacy of omega-3 supplementation in ameliorating VMS, enhancing sleep quality, and reducing depression scores in the context of postmenopausal women.

2. Materials and Methods

2.1. Study Participants

The study focused on women at both menopausal and post-menopausal stages, who were experiencing VMS and depression due to menopause, or women undergoing surgical menopause who were also experiencing VMS and depression.

2.2. Type of Intervention and Control

Included studies evaluated the omega-3 fatty acid supplementation in any dosage, frequency, and form (capsule, oil, powder) compared to placebo or other control groups. Studies involving fish

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consumption, use of antidepressants, hormone replacement therapy, use of anticoagulants, and those lacking placebo or adequate control groups, were excluded from consideration.

2.3. Study Search and Selection

A comprehensive search strategy was executed to identify pertinent studies for this systematic review. Multiple databases including the Cochrane Library, Web of Science, PubMed, Embase, CINAHL, and SCOPUS were utilized. The search employed both free text and Medical Subject Headings (MeSH) terms, such as "omega-3," "fish oils," "PUFA," "menopause," "hot flashes," "night sweats," "vasomotor," "sleep quality," "insomnia," and "depression." Supplementary sources, such as Google Scholar and ClinicalTrials.gov, were also consulted to identify ongoing or unpublished research. The search encompassed studies published in English from inception to the present, without imposing restrictions on publication time or status. The study's registration in PROSPERO was completed under registration number CRD42023421922.

The systematic review adhered to the following inclusion criteria: (1) randomized controlled trials (RCTs) determine the effect of omega-3 fatty acid supplements on postmenopausal symptoms in women; (2) studies encompassing both naturally postmenopausal and surgically postmenopausal women; (3) studies reporting outcomes pertinent to postmenopausal symptoms such as HF, night sweats, mood swings, sleep quality, and depression; (4) studies comparing omega-3 fatty acid intake with a placebo or control group. Exclusion criteria encompassed: (1) studies lacking relevant outcome reporting, and (2) studies published in languages other than English.

2.4. Outcome Measures

The primary outcomes targeted VMS, including the frequency and intensity of HF and night sweats, which were assessed through patient-maintained diaries or measured using scales such as the Hot Flash-Related Daily Interference Score Kupermann index, and menopause rating scale. Additional primary outcomes included sleep quality and depression, measured using established scales including the Pittsburgh Sleep Quality Index, Insomnia Severity Index, Beck's Depression Inventory, Montgomery-Asberg Depression Rating Scale, Generalized Anxiety Disorder Questionnaire, and Physician's Health Questionnaire depression domains. Secondary outcomes encompass menopause-specific quality of life scores and the monitoring of adverse events.

2.5. Data Extraction

The initial screening involved the assessment of titles and abstracts in the first stage, with disagreements resolved by a third reviewer. In the subsequent stage, all papers extracted from the previous phase were individually evaluated by two reviewers. An initial subset of nine papers was chosen to establish reviewer consistency.

3. Results

3.1. Selected Studies

Figure 1 depicts the results of the screening process. The database searches yielded a total of 163 studies; after eliminating 58 duplicate entries, 107 publications were reviewed. After selection based on the title and abstract, 44 publications were selected. Finally, this systematic review identified nine relevant papers that contained randomized controlled trials (RCTs) with sample sizes ranging from 60 to 546 people. These studies evaluated how omega-3 supplements affected menopausal symptoms, sleep quality, and depression in menopausal women. The participants in the RCTs were given varying amounts of EPA and DHA, the omega-3 fatty acids of interest. Depending on the trial design, the placebo groups got soybean oil, sunflower oil, or olive oil. Furthermore, some research used interventions other than the aforementioned placebos, extending the types of interventions used.

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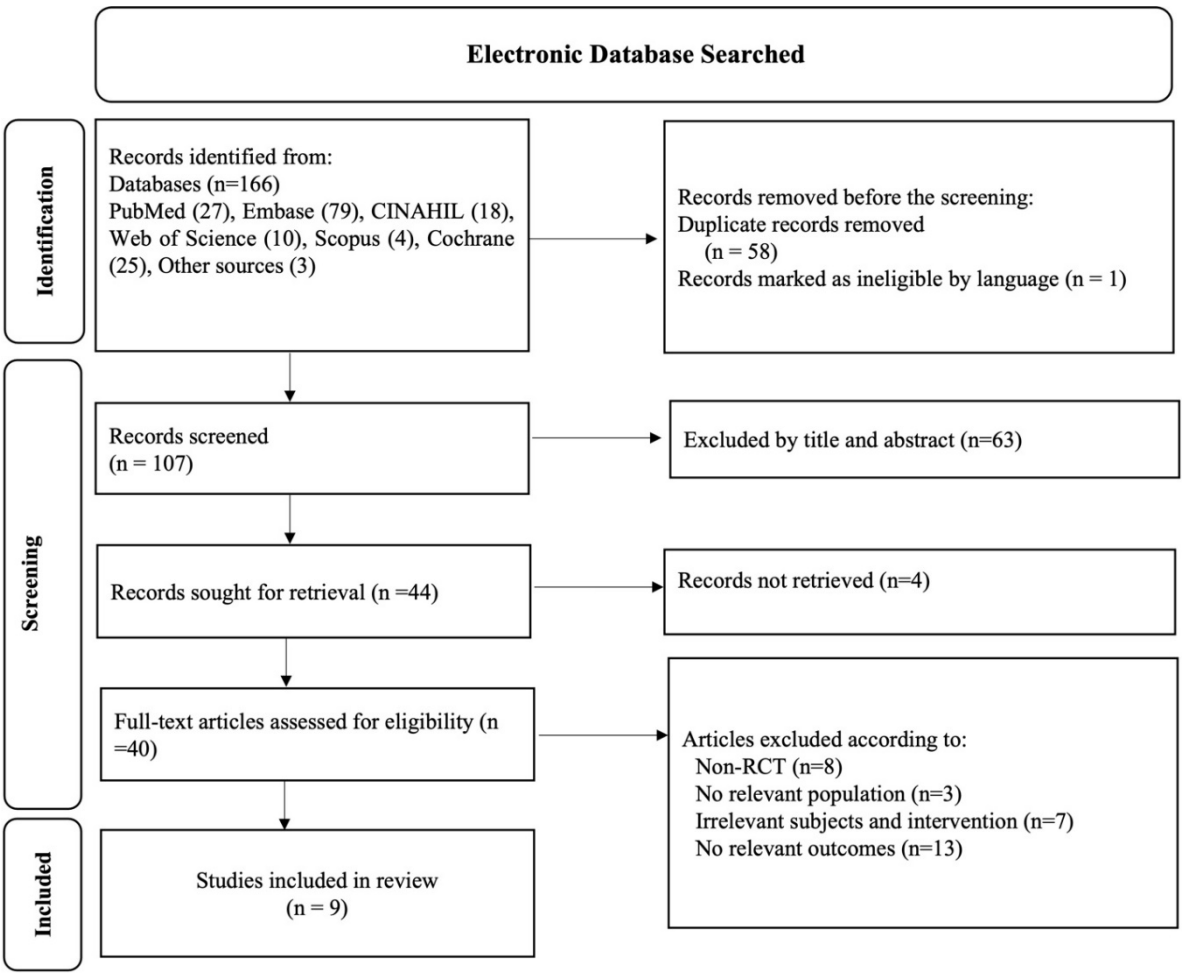

Figure 1. Flowchart for study search and screening.

3.2. The effect of omega-3 fatty acids on vasomotor symptoms

The studies evaluating the impact of omega-3 supplementation on menopausal symptoms are summarized in Table 1. Two randomized control trials outlined no significant difference in the frequency of vasomotor symptoms (VMS) with omega-3 supplementation [22,28], whereas others found a decrease in both VMS and HF frequency and intensity [21,29,30]. Moreover, a separate study found a decrease in HF frequency but no effect on the intensity [31]. Overall, the systematic review indicates that omega-3 supplementation may have a variable impact on menopausal symptoms, with some studies showing a decrease in symptoms and others reporting no significant change.

Table 1. The main characteristics of nine included studies evaluating the effect of omega-3 PUFA intake on vasomotor symptoms, sleep quality, and depression in postmenopausal women.

Authors & Year	Study Design	Participants, No.	Intervention	Duration	Vasomotor Symptoms	Sleep Quality	Depression	Other Outcomes
[32]	Triple-Blind Randomized Controlled Trial	Menopause women, n=60; Intervention group, n=30; Control group, n=30	**Intervention group:** 20 mg citalopram and 1g of omega-3 PUFAs per day **Placebo group:** 20 mg citalopram along with a placebo per day	4 weeks	--------	--------	BDI-II ($p < 0.001$)	------
[33]	Double-blind placebo-controlled, RCT	Postmenopausal women, n=188 Intervention group, n=; 95 Control group, n= 93	**Intervention group:** 1.8 g omega-3 fatty acids per day Placebo group: 3 capsules per day containing olive oil	12 weeks	--------	PSQ-I (0.0933) ISI = (0.729)	------	------
[22]	Double-Blind, Randomized Clinical Trial	Menopause women, n=355; Intervention group, n=177; Placebo group, n=178	**Intervention group:** 615 mg omega-3 PUFAs (EPA= 425 mg, DHA=100 mg) 3 capsules per day **Placebo group:** 3 capsules per day containing olive oil	12 weeks	VMS frequency = (p=0.283)	PSQ-I (0.0933) ISI = (0.729)	PHQ-8 (0.097) GAD-7 = (0.191)	No Adverse Effect

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[25]	Double-blind placebo-controlled, RCT	Menopause women, n=120; Intervention group, n=59; Placebo group, n=61	**Intervention group:** 500 mg omega-3 PUFAs (EPA= 350 mg and DHA= 50 mg in ethyl esters form) / day **Placebo group:** 500 mg capsule containing sunflower oil per day 0.2% of regular fish oil (18% EPA/12% DHA) 3 times daily	8 weeks	-------	-----	PGWB (p = 0.034) HSCL-D-20 (p = 0.040) HAM-D-21 (p = 0.030)	------
[21]	Double-blind placebo-controlled, RCT	Menopause women, n=120; Intervention group, n=59; Placebo group, n=61	**Intervention group:** 500 mg omega-3 PUFAs (EPA= 350 mg and DHA= 50 mg in ethyl esters form) / day **Placebo group:** 500 mg capsule containing sunflower oil per day 0.2% of regular fish oil (18% EPA/12% DHA) 3 times daily	8 weeks	HF and night sweats Frequency (p= 0.005) and Intensity (0.64)	------	-------	MENQOL (p=0.2) No Adverse Effect

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[28]	Randomized control trial	Menopause women, n=355; Intervention group, n=177; Placebo group, n=178	**Intervention group:** Omega-3 supplement contained 425 mg ethyl EPA, 100 mg DHA acid per day **Placebo group:** 90 mg placebo containing olive oil per day	12 weeks	VMS frequency = (p=0.06)	PSQ-I (0.0933) ISI = (0.729) PSS = (0.08)	PHQ-8 (0.097) GAD-7 = (0.191)	MENQOL = (0.12)
[29]	Randomized, Prospective, Two-Arm Study	Menopause women, n=76; Omega-3 group, n=40; Isoflavone group, n=36	**Intervention group:** omega-3 PUFAs (425 mg of omega-3/capsule), 2 capsules per day **Placebo group:** Soybean isoflavones (54.4 mg of isoflavones/ tablet), 2 tablets per day	16 weeks	VMS Frequency and HF ($p < .001$)	-----	------	No Adverse Effect
[30]	Double-Blind, Placebo-Controlled, Randomized Clinical Trial	Menopause women, n=180; Soy group, n=60; Omega-3 group, n=60; Placebo group, n=60	**Intervention group:** 1000 mg Omega-rex soft gel Soygan 500 mg capsule **Placebo group:** placebo	3 months	MRS (p = 0.03)	-----	-----	No Adverse Effect
[31]	Double-blind, randomized	Menopause women, n=68; Omega-3 group, n=38; Control, n=38	**Intervention group:**	8 weeks	HF frequency (p=0.003) but	-----	-------	No Adverse Effect

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	controlled clinical trial		300 mg (contain EPA=120 mg and DHA= 180 mg) per day **Placebo group:** Placebo containing paraffin		no intensity (p=0.2)			

Abbreviations: PUFAs, Polyunsaturated Fatty Acids; BDI, Beck's Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; EPA, Eicosapentaenoic Acid; DHA, Docosahexaenoic acid; VMS, Vasomotor Symptoms; ISI, Insomnia Severity Index; PHQ-8, Physician's Health Questionnaire depression domains; GAD-7, Generalized Anxiety Disorder questionnaire; PGWB, Psychological General Well-Being Schedule; HSCL-D-20, 20-item Hopkins Symptom Checklist Depression Scale; HAM-D- 21, 21-item Hamilton Depression Rating Scale; HF, Hot flashes; MENQOL, Menopause-specific quality of life score; MRS, Menopause Rating Score.

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3.2. The effect of omega-3 fatty acids on sleep quality

Three studies examining how postmenopausal women's sleep quality is affected by omega-3 supplementation were included in the review. They were all evaluated using the PSQI and ISI measures. The study by Reed et al. found that omega-3 supplementation had no influence on the sleep quality among 355 menopausal women compared to the placebo group [28]. Similar to this, a double-blind, randomized clinical trial by Cohen et al. found no effect in menopausal women taking 615 mg of omega-3 daily for 12 weeks [22]. Moreover, an increased daily intake of 1.8 g of omega-3 fatty acids also had no impact on sleep quality, according to research by Guthrie et al. According to a thorough study of the research, omega-3 supplements do not appear to have a substantial impact on postmenopausal women's sleep quality [33]. Based on the existing research, the comprehensive review concludes that omega-3 supplementation does not appear to have a substantial impact on sleep quality in postmenopausal women.

3.4. The effect of omega-3 fatty acids on depression

The systematic review included four studies investigating the effects of omega-3 supplementation on depression in menopausal women. Masoumi et al.'s triple-blind, randomized controlled trial demonstrated that menopausal women who received a combination of 20 mg citalopram and 1g of omega-3 showed a decrease in depression as measured by the BDI-II [32]. However, The double-blind, randomized clinical trial conducted by Cohen et al. and Reed et al. observed no statistically significant alterations in depression levels, as evaluated through the PHQ-8 and GAD-7 scales, following a 12-week regimen of 1.8 g/day omega 3 supplementation (425 mg of EPA, 100 mg DHA and 90 mg of other omega-3s, 3 pills/day) [22,28]. In contrast, the double-blind, placebo-controlled study conducted by Lucas et al. revealed a reduction in depression scores (measured using PGWB, HSCL-D-20, and HAM-D-21) among menopausal women administered with 500 mg omega-3 capsules (350 mg EPA and 50 mg DHA) thrice daily over 8 weeks [25]. Overall, the comprehensive review reveals that omega-3 supplementation may improve depressive symptoms in menopausal women, as indicated by several of the included studies, but not all studies showed meaningful changes.

3.5. Other Outcomes

Out of the nine studies, the majority of the studies found no adverse effects associated with omega-3 supplementation [21,22,29-31]. In addition, as indicated by the Menopause-specific quality of life score (MENQOL), two studies found increases in quality of life specifically related to menopause, suggesting a potential positive impact of omega-3 supplementation [21,28]. These findings highlight the safety and potential benefits of omega-3 supplementation for menopausal women.

4. Discussion

The study aimed to evaluate the impact of omega-3 fatty acid supplementation on menopausal symptoms in postmenopausal women. The review encompassed nine pertinent randomized controlled trials (RCTs) that exhibited diversity in terms of sample sizes and treatment approaches. The trials were comprehensive in investigating a range of menopause-related issues, including VMS, sleep quality, depression, and various indicators of quality of life.

The menopausal transition signifies a profound period of transformation for women. This natural progression involves a decline in estrogen levels, potentially leading to modifications in brain neurochemicals and instability within the hypothalamus – the brain region responsible for regulating body temperature. These changes are often attributed to the emergence of VMS, encompassing HF and night sweats [34]. The ingestion of a diet rich in omega-3 fatty acids exhibited a capacity to diminish VMS, suggesting the potential utility of omega-3 fatty acids in addressing such symptoms [35]. Within the scope of this study, the trials included demonstrated a heterogeneous nature, with certain trials indicating a decrease in VMS (including HF and night sweats) following omega-3

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intervention, while others did not exhibit such effects. For example, Lucas et al. documented a reduction in both frequency and intensity of HF and night sweats in menopausal women who consumed omega-3 capsules [21]. In contrast, Cohen et al. and Reed et al. did not observe substantial effects on VMS through omega-3 treatment. The divergent outcomes might potentially be attributed to variations in dosages, treatment durations, and participant characteristics [28,36].

Sleep disturbances frequently afflict postmenopausal women, often linked to the presence of HF and night sweats [37]. Several studies have revealed a graduated correlation between the frequency and severity of HF and the intensity of insomnia symptoms, accompanied by quantifiable measures of disrupted sleep patterns [38,39]. An intriguing randomized controlled trial (RCT) displayed noteworthy results: when Omega-3 PUFA supplementation was employed alongside conventional medication, it led to improved outcomes spanning depression symptoms, anxiety, sleep dimensions, and emotional self-regulation, surpassing placebo effects [40]. However, our comprehensive systematic analysis did not yield robust evidence supporting the notion that omega-3 supplementation significantly enhances sleep quality in postmenopausal women. In line with this, Guthrie et al., Cohen et al., and Reed et al. all concurred by reporting no substantial impact on sleep quality through diverse sleep assessment scales, including the PSQI and ISI [28,33,36]. Despite the common occurrence of sleep issues in menopausal women, it appears that omega-3 supplementation does not offer discernible efficacy in augmenting sleep quality within this cohort. In contrast, a distinct study highlighted that DHA/EPA supplementation did enhance sleep quality in middle-aged and elderly individuals, even at the lower doses employed in earlier investigations [41]. These disparities in outcomes could potentially be attributed to suboptimal omega-3 doses or an imbalance in the optimal quantities of individual components needed for a comprehensive effect.

Depression, characterized by persistent low mood and reduced interest in daily activities for more than two weeks, is notably more prevalent among females, with 1.5 to 3 times higher incidence rates compared to males [42,43]. In seeking relief from depressive symptoms, individuals often turn to antidepressants, particularly selective serotonergic reuptake inhibitors (SSRIs), despite potential side effects such as sexual dysfunction and weight gain if used over extended periods [44,45]. In contrast, emerging research has spotlighted the polyunsaturated fatty acids role, including omega-3s, in mitigating depression symptoms [46-48]. An intriguing study underscored the clinical efficacy of endocannabinoids derived from ω–3 polyunsaturated fatty acids in the treatment of major depressive disorder (MDD), opening avenues for innovative therapeutic approaches [49]. However, the impact of omega-3 supplementation on depression among postmenopausal women remains equivocal. Masoumi et al. demonstrated reduced depression scores through combined citalopram and omega-3 supplementation [32]. In contrast, Cohen et al. and Reed et al. did not observe significant changes in depression scores with omega-3 supplementation alone [22,28]. Lucas et al., on the other hand, reported lowered depression scores in women who received omega-3 capsules, suggesting potential benefits in alleviating depressive symptoms [25]. Notably, due to the diverse range of outcomes, prudence is necessary when drawing definitive conclusions about the antidepressant effects of omega-3 supplementation in menopausal women.

Vasomotor symptoms, which can significantly compromise women's quality of life, have often been linked to the menopausal transition. Although prior epidemiological studies have primarily associated this transition with somatic symptoms, the connection to other areas of quality of life remains unclear [50]. A study within this review demonstrated improvements in the MENQOL score among the omega-3-supplemented group, indicating a potential positive impact on overall well-being during menopause [21]. Additionally, our comprehensive analysis affirms the general safety of omega-3 supplementation in menopausal women, as adverse effects were not prominently noted.

5. Conclusions

In summary, the outcomes of our investigation indicate that the impact of omega-3 supplementation on menopausal symptoms in postmenopausal women is varied. While certain studies highlight benefits for vasomotor symptoms (VMS) and mood disturbances, others do not corroborate these effects. The data suggesting a positive influence of omega-3 supplementation on

sleep quality in menopausal women is limited. Nonetheless, the safety profile of such supplementation remains promising. Therefore, we propose that future research should entail extended follow-up periods, encompass larger cohorts, and explore combined therapeutic approaches with other medications aimed at enhancing the management of menopausal symptoms.

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