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Efficacy of omega-3 for vasomotor symptoms treatment: a randomized controlled trial

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Abstract

Objective: This study aims to determine the efficacy and tolerability of omega-3 fatty acids in reducing vasomotor symptoms (VMS) frequency and bother in perimenopausal and postmenopausal women.

Methods: This study was a 12-week, three-by-two factorial, randomized controlled trial. Eligible women were randomized to a double-blind comparison of omega-3 (n = 177) or placebo (n = 178) capsules, and simultaneously to yoga (n = 107), aerobic exercise (n = 106), or their usual physical activity (n = 142). Participants received 1.8 g of omega-3 daily for 12 weeks. Each capsule contained ethyl eicosapentaenoic acid (425 mg), docosahexaenoic acid (100 mg), and other omega-3s (90 mg). Primary outcomes were VMS frequency and bother. Secondary outcomes included sleep quality (Pittsburgh Sleep Quality Index), insomnia symptoms (Insomnia Severity Index), depressive symptoms (Physician's Health Questionnaire-8), and anxiety (Generalized Anxiety Disorder-7).

Results: The mean baseline frequency of VMS per day was 7.6 (95% CI, 7.0 to 8.2). After 12 weeks, the reduction in VMS frequency with omega-3 (−2.5; 95% CI, −3.0 to −1.9) did not differ significantly from that with placebo (−2.7; 95% CI, −3.3 to −2.2), with a relative difference of 0.3 fewer hot flashes per day (95% CI, −0.5 to 1.0; $P = 0.28$). Changes in VMS bother at 12 weeks were also similar between groups, with no relative difference on a four-point scale (95% CI, −0.1 to 0.2; $P = 0.36$). Omega-3s compared with placebo showed no improvement in self-reported sleep or mood ($P > 0.09$ for all comparisons).

Conclusions: Among healthy, sedentary perimenopausal and postmenopausal women, a 12-week treatment with omega-3 does not improve VMS frequency, VMS bother, sleep, or mood compared with placebo.

Key Words: Omega-3 – Fish oils – Hot flashes – Vasomotor symptoms – Clinical Trials Network – Menopause.

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Vasomotor symptoms (VMS) affect up to 80% of women during the menopausal transition, frequently last several years, can be disruptive, and can compromise quality of life.[1] Many women seek alternative treatments to hormonal agents or selective serotonin reuptake inhibitors to manage VMS in light of the demonstrated risks of hormonal interventions[1] and the bothersome adverse effects of selective serotonin reuptake inhibitors.[2] Women who experience an array of menopausal symptoms frequently turn to complementary and alternative therapies, particularly herbal supplements. A recent report from the National Center for Complementary and Alternative Medicine indicated that more than 40% of the adult population in the United States used at least one complementary and alternative medicine treatment during the previous year, with women being more likely than men to use complementary and alternative medicine.[3,4]

Omega-3 supplements are polyunsaturated fatty acids (PUFAs) that include the longer-chain omega-3 fatty acids ethyl eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as α-linolenic acid, and are among the most widely consumed supplements for a variety of medical conditions (including cardiovascular disease, rheumatoid arthritis, depression, and other cognitive disorders).[5] Human and animal studies of omega-3s suggest mechanisms of action that include modulation of serotonergic and dopaminergic neurotransmission.[6-8]

To date, two small randomized trials have examined the efficacy of omega-3s for the treatment of VMS.[9,10] In an 8-week trial of an enriched EPA supplement containing 350 mg of EPA and 50 mg of DHA given three times daily versus placebo among 91 emotionally distressed women with VMS, hot flash frequency and intensity improved significantly in the active treatment group relative to the placebo group.[9] In a second trial (n = 28) that included two studies (isoflavone vs placebo and other isoflavones + PUFA vs placebo), results were inconclusive owing to the small number of participants investigated and a large number of women who failed to complete the study.[10] Given small sample sizes, conflicting results, and widespread use of this supplement for a spectrum of symptoms including VMS, there is a need for a larger, more rigorously conducted trial to definitively delineate the role of omega-3s in the treatment of VMS.

In the current study, we report the results of a randomized placebo-controlled study testing the efficacy of omega-3s for the reduction of VMS frequency and bother in perimenopausal and postmenopausal women. We also examine the effects of omega-3s versus placebo on other menopausal symptoms, including self-reported measures of sleep, depressive symptoms, and anxiety symptoms—all of which commonly co-occur with VMS.

METHODS

Study design

Details describing the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) Network, its protocols, and its overarching study procedures have been published elsewhere.[11] This study was a 12-week, multicenter, three-by-two factorial, randomized controlled trial testing the efficacy of 1.8 g/day omega-3 supplementation from fish oil or a matching placebo from olive oil in reducing VMS frequency and/or relieving VMS bother. Concurrent with randomization to omega-3s or placebo, participants were also cross-randomized to aerobic exercise, yoga, or their usual physical activity. Randomization was accomplished through a secure Web-based database, maintained by the MsFLASH Data Coordinating Center, that uses a dynamic randomization algorithm to maintain comparability between study groups with respect to clinical site. Data collectors were blinded to randomization assignment. The current study reports the results of the omega-3 intervention; results for the exercise and yoga interventions are reported separately.

Within each behavioral intervention group (yoga, exercise, or regular physical activity), women were randomized to receive placebo pills or 1.8 g/day high-quality omega-3s (three pills per day, each containing 425 mg of EPA, 100 mg of DHA, and 90 mg of other omega-3s). Women randomized to yoga attended a weekly class with a trained instructor and practiced at home on other days; those randomized to exercise attended supervised aerobic exercise sessions three times per week; and women randomized to usual activity were asked to follow their usual physical activity routine and were offered their choice of a 3-hour yoga workshop or a 1-month gym membership at study end. Each woman participated for 15 weeks, including a 3-week eligibility run-in period, a 12-week intervention period, and a final clinic visit on week 12.

The study was approved by the institutional review boards at each participating site and by the Data Coordinating Center. All participants provided a written informed consent form and authorization to use protected health information.

Study population

The trial was conducted at three MsFLASH Network sites (Indianapolis, Seattle, and Oakland). Participants were recruited from February 2011 through January 2012 primarily by mass mailings to age-eligible women, using purchased mailing lists and health plan enrollment files. Eligible women were aged 40 to 62 years; were in the menopausal transition (amenorrhea ≥60 d in the past year) or in postmenopause (≥12 mo since the last menstrual period or had had bilateral oophorectomy) or had had hysterectomy with follicle-stimulating hormone levels higher than 20 mIU/mL and estradiol levels of 50 pg/mL or less; and were in generally good health.

VMS enrollment criteria were as follows: 14 or more hot flashes/night sweats per week recorded on daily VMS diaries for 3 weeks; VMS rated as bothersome or severe during at least four or more 12-hour (day/night) blocks of times per week; and VMS frequency on week 3 failing to decrease by more than 50% from the mean weekly levels on weeks 1 and 2. Exclusion criteria included the following: body mass index higher than 37 kg/m^2; use of hormones or hormonal contraceptives in the past 2 months; use of prescription or over-the-counter treatments for VMS in the past month; any unstable medical conditions; contraindications to exercise training (eg, physical limitations), yoga, or omega-3 (allergy to soy or fish; current

regular use of anticoagulants); current participation in regular exercise or yoga; current use of omega-3 supplements or frequent consumption of fish (four or more servings a week); or a major depressive episode in the past 3 months.

Treatment

The omega-3 study supplement contained omega-3 ($n - 3$) fatty acids from fish oils (also described as PUFAs; Nordic Naturals, Watsonville, CA). Each gel capsule had a total omega-3 dose of 615 mg, which included the two major omega-3 components EPA (425 mg) and DHA (100 mg), along with other assorted omega-3s (90 mg). Vitamin E (15 IU), an antioxidant, was added to each gel capsule of active treatment and placebo to preserve freshness. Participants assigned to placebo took identical gel capsules containing olive oil. Gel capsules (placebo and omega-3) contained natural lemon oil and rosemary extract to enhance taste. Participants, study clinicians, and staff were blinded to study pill treatment assignment. Participants were instructed to take three capsules of omega-3s or placebo per day for 12 weeks.

Screening and baseline data collection

Women found to be eligible after a telephone screen completed a 2-week hot flash diary and a questionnaire. Women who continued to meet eligibility criteria came to a clinic visit during which we collected additional information, including vital signs, blood draw, and baseline questionnaire. Women were given an additional hot flash diary to be completed before the next clinic visit a week later, at which time final eligibility was assessed and randomization occurred.

Follow-up

Study staff blinded to treatment assignment contacted participants on week 2 to encourage compliance and to evaluate pill tolerance. Six and 12 weeks after randomization, participants completed additional 7-day VMS diaries. Other baseline measurements were repeated during the week 12 postrandomization clinic visit. Treatment adherence was assessed by counting the number of pills returned at the last visit. Participants received US$50 after each of three clinic visits for their time and effort, for a possible total of US$150.

Study outcomes

Primary outcomes

The primary outcomes were VMS frequency and bother based on daily diaries at baseline and on weeks 6 and 12, in which participants entered the number of VMS they had experienced upon awakening (for nighttime symptoms) and before going to sleep (for daytime symptoms). They rated VMS bother for each day and night on a scale from 1 to 4 (1, none; 2, a little; 3, moderately; 4, a lot).

Secondary outcomes

The secondary outcomes were each measured at baseline and 12 weeks, and were evaluated as continuous scores: subjective sleep quality (Pittsburgh Sleep Quality Index),[12] insomnia symptoms (Insomnia Severity Index [ISI]),[13] depressive symptoms (Physician's Health Questionnaire-8 [PHQ-8] depression domain),[14] and anxiety (Generalized Anxiety Disorder-7 [GAD-7]).[15]

Adverse events

Adverse events (AEs) were assessed at each visit using a self-administered questionnaire listing common yoga, exercise, and omega-3 AEs. Participants were instructed to call the study nurse to report any potential AEs during the study. Newly emergent AEs were identified by comparing AE reports during treatment to each woman's baseline report.

Statistical analysis

A sample size of 176 participants in each of the omega-3 and placebo groups was planned to provide 90% power to detect a mean difference (reduction) of 1.6 hot flashes per day between treatment groups (a 0.40-SD reduction in hot flashes per day based on preliminary data). This calculation was based on a t test with a two-sided significance level of 0.025 to account for two primary outcomes and allowance for a 10% loss to follow-up.

All analyses of treatment effects were based on the intent-to-treat principle, where all randomized participants who provided diary data at any point during follow-up were included and analyzed by randomized treatment assignment, regardless of their adherence to treatment assignment. Baseline hot flash frequency was calculated as the mean of the daily (24 h) totals reported in the first two screening weeks. Hot flash frequencies on weeks 6 and 12 were calculated as the mean of the daily (24 h) frequencies for the prior week. Hot flash bother scores were calculated similarly. A categorical variable indicating clinical VMS improvement was defined as a 50% or more decrease in VMS frequency at 12 weeks from baseline.

Treatment group contrasts were computed as Wald statistics from linear regression models summarizing the frequency or bother of VMS on weeks 6 and 12 as a function of randomization assignment, adjusting for clinical site, visit (week 6 or 12), behavioral intervention assignment, and baseline value of the outcome measure. Because VMS frequency values were skewed to the right, raw values were transformed via natural logarithm to meet model assumptions of a normally distributed outcome. Robust standard errors were calculated via generalized estimating equations to account for correlations between repeated measures from each participant.

Ten baseline variables were hypothesized a priori to modify hot flash frequency treatment response: smoking status, body mass index, menopause status, depressive symptoms (PHQ-8), anxiety (GAD-7), insomnia symptoms (ISI), alcohol use, age, race, and baseline hot flash frequency. Tests for interaction between these variables and treatment assignment were performed within the linear regression model, with continuous variables analyzed as such for interaction tests. Secondary outcomes were also analyzed by linear regression to model changes in sleep and mood as a function of treatment assignment, following an approach similar to that used with primary outcomes.

Baseline characteristics between treatment groups were compared using t test (for continuous variables) and χ^2 test

(for categorical variables). The incidence of newly emergent AEs was compared between treatment groups via Fisher's exact test.

A two-sided P value less than 0.025 was considered statistically significant for the two primary outcomes. For the four outcomes examined as secondary analyses, $P < 0.0125$ was considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute Inc Cary, NC).

RESULTS

Three hundred fifty-five women were randomly assigned to receive omega-3s (n = 177) or placebo (n = 178; Fig. 1). Follow-up data collection retention was high: 173 women each in the omega-3 group (98%) and placebo group (97%) provided diary data on week 6 and/or week 12.

The only nominally significant differences in baseline characteristics between the omega-3 group and the placebo group were found for race ($P < 0.001$) and baseline VMS bother score ($P = 0.019$). A somewhat higher proportion of white women were randomized to the omega-3 group compared with the placebo group (Table 1). Overall, the mean (SD) age was 54.7 (3.7) years; 64% were white, 26% were African American, and 10% were of another race. A small proportion of women (8%) had substantial depressive symptoms (PHQ-8 >9), and a similar percentage of participants had high levels of anxiety symptoms (GAD-7); 33% of participants had moderate to severe insomnia (ISI), as defined by a baseline ISI score higher than 14.

Hot flash frequency and bother

The mean baseline hot flash frequency was 7.6 per day (95% CI, 7.0 to 8.2). As seen in Figure 2, omega-3s did not significantly reduce hot flash frequency compared with placebo ($P = 0.28$; Table 2). In the omega-3 group, the mean hot flash frequency on week 12 decreased to 5.2 VMS/day (95% CI, 3.0 to 1.9), corresponding to a 32% decrease or a mean of 2.5 fewer VMS per day compared with baseline. The placebo group decreased to 4.9 VMS/day (95% CI, 3.3 to 2.2) on week 12, a 36%

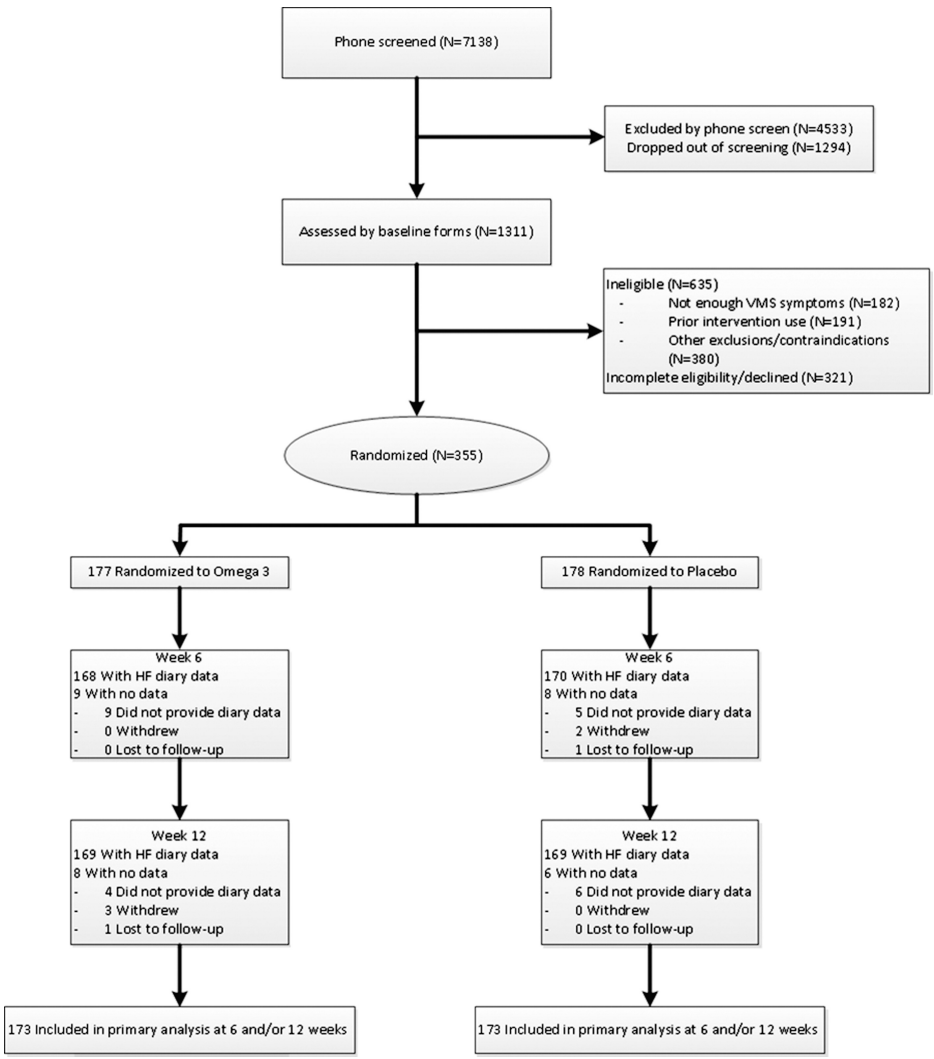

FIG. 1. Participant recruitment. Randomization to yoga (n = 107), exercise (n = 106), or usual activity (n = 142) occurred concurrently. VMS, vasomotor symptoms; HF, hot flash.

TABLE 1. *Baseline demographic and clinical characteristics by omega-3 arm*

	Omega-3 (n = 177)	Placebo (n = 178)
Age at screening, mean (SD), y	54.39 (3.55)	54.98 (3.79)
Age at screening, n (%)		
<50 y	10 (5.6)	9 (5.1)
50-54 y	87 (49.2)	75 (42.1)
55-59 y	63 (35.6)	67 (37.6)
≥60 y	17 (9.6)	27 (15.2)
Race, n (%)		
White	125 (70.6)	103 (57.9)
African American	45 (25.4)	48 (27.0)
Other	7 (4.0)	27 (15.2)
Clinical center, n (%)		
Indianapolis	58 (32.8)	60 (33.7)
Oakland	55 (31.1)	55 (30.9)
Seattle	64 (36.2)	63 (35.4)
Education, n (%)		
High school diploma/GED or less	14 (7.9)	7 (3.9)
School/training after high school	49 (27.7)	63 (35.4)
College graduate	114 (64.4)	107 (60.1)
Employment status, n (%)		
Retired or no employment	27 (15.3)	22 (12.4)
Full time	107 (60.5)	108 (60.7)
Part time	28 (15.8)	24 (13.5)
Homemaker	7 (4.0)	6 (3.4)
Other	8 (4.5)	17 (9.6)
Marital status, n (%)		
Never married	13 (7.3)	21 (11.8)
Divorced	36 (20.3)	40 (22.5)
Widowed	4 (2.3)	3 (1.7)
Married/living with partner	124 (70.1)	112 (62.9)
Smoking, n (%)		
Never	112 (63.3)	120 (67.4)
Past	48 (27.1)	41 (23.0)
Current	16 (9.0)	16 (9.0)
Alcohol use, n (%)		
0 drinks/wk	60 (33.9)	77 (43.3)
1 to <7 drinks/wk	78 (44.1)	78 (43.8)
≥7 drinks/wk	38 (21.5)	22 (12.4)
BMI, mean (SD), kg/m^2	26.81 (4.42)	27.09 (4.33)
BMI, n (%)		
<25 kg/m^2	63 (35.6)	60 (33.7)
25 to 29 kg/m^2	72 (40.7)	72 (40.4)
≥30 kg/m^2	42 (23.7)	46 (25.8)
Menopause status, n (%)		
Postmenopause	146 (82.5)	140 (78.7)
Late transition	28 (15.8)	34 (19.1)
Early transition	3 (1.7)	4 (2.2)
Hysterectomy, n (%)	35 (19.8)	29 (16.3)
Bilateral oophorectomy, n (%)	18 (10.2)	14 (7.9)
Self-reported health, n (%)		
Excellent	31 (17.5)	27 (15.2)
Very good	78 (44.1)	84 (47.2)
Good	60 (33.9)	59 (33.1)
Fair	8 (4.5)	7 (3.9)
Depression score, mean (SD)	3.63 (3.48)	4.37 (4.03)
Depression score, n (%)		
No depression (0-4)	118 (66.7)	107 (60.1)
Mild depression (5-9)	49 (27.7)	48 (27.0)
Moderate+ depression (10+)	10 (5.6)	19 (10.7)
Anxiety score, mean (SD)	2.89 (3.43)	3.46 (3.77)
Anxiety score, n (%)		
No anxiety (0-4)	134 (75.7)	126 (70.8)
Mild anxiety (5-9)	33 (18.6)	34 (19.1)
Moderate+ anxiety (10+)	10 (5.6)	18 (10.1)
PSQI, mean (SD)	7.87 (3.29)	8.16 (3.37)
PSQI, n (%)		
Good sleep quality	23 (13.0)	27 (15.2)
Poor sleep quality	149 (84.2)	145 (81.5)
ISI, mean (SD)	11.76 (5.16)	12.03 (5.69)
ISI, n (%)		
No clinically significant insomnia (≤7)	42 (23.7)	44 (24.7)
Subthreshold insomnia (8-14)	75 (42.4)	73 (41.0)
Moderate clinical insomnia (15-21)	52 (29.4)	50 (28.1)
Severe clinical insomnia (≥22)	5 (2.8)	9 (5.1)

BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index.

decrease or a mean of 2.7 fewer VMS per day. Similarly, there was no difference in VMS bother reduction between the two groups (P = 0.36). The incidence of clinical improvement in VMS on week 12 (≥50% decrease from baseline in VMS frequency) also did not differ between the omega-3 group and the placebo group (34% and 38%, respectively; P = 0.43).

The lack of effect of omega-3s on hot flash frequency was consistent across the strata of baseline characteristics. There was no evidence of an interaction between treatment assignment and any of the baseline factors specified for testing (Table, Supplemental Digital Content, http://links.lww.com/MENO/A59).

Secondary outcomes

Compared with placebo, the omega-3 intervention did not significantly improve any secondary measures of sleep or mood, including sleep quality, insomnia symptoms, depressive symptoms, or anxiety symptoms (Table 2). The mean ISI reduction was 3.8 for the omega-3 group and 3.7 for the placebo group (P = 0.73). The mean Pittsburgh Sleep Quality Index reduction was 2.1 for the omega-3 group and 1.7 for the placebo group (P = 0.09). There was no PHQ-8 change in the omega-3 group, and there was negligible change (−0.8) in the placebo group (P = 0.10). The mean reduction in GAD-7 score was 0.2 for the omega-3 group and 0.9 for the placebo group (P = 0.19).

Adherence

During the entire treatment period, 80% of participants (285 of 355) adhered to omega-3 or placebo pills (defined as

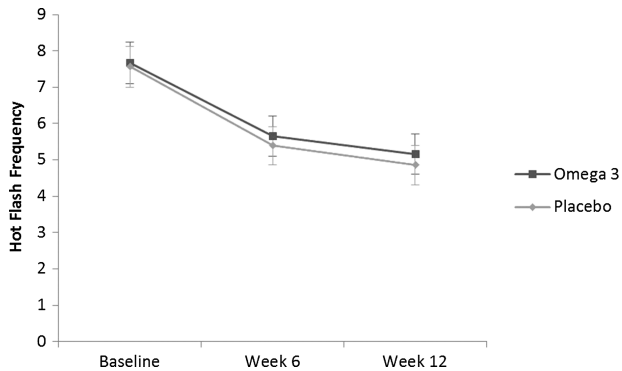

FIG. 2. Hot flash frequency over time by omega-3 assignment. Mean difference in the number of hot flashes per day from baseline to week 12: baseline, 0.1 (95% CI, −0.7 to 0.9); week 6 to baseline, 0.2 (95% CI, −0.5 to 0.9); week 12 to baseline, 0.3 (95% CI, −0.5 to 1.0).

TABLE 2. *Changes in primary and secondary outcomes by omega-3 arm*

	Omega-3		Placebo		Difference	
	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	*P*
Primary outcomes						
Hot flashes per day[a]						0.283[b]
Baseline	177	7.7 (7.1 to 8.2)	178	7.6 (7.0 to 8.1)	0.1 (−0.7 to 0.9)	
Week 6 to baseline	168	−2.0 (−2.5 to −1.5)	170	−2.2 (−2.7 to −1.7)	0.2 (−0.5 to 0.9)	
Week 12 to baseline	169	−2.5 (−3.0 to −1.9)	169	−2.7 (−3.3 to −2.2)	0.3 (−0.5 to 1.0)	
Bother (1-4)						0.359[b]
Baseline	177	3.0 (2.9 to 3.1)	178	2.9 (2.8 to 3.0)	0.1 (0.0 to 0.2)	
Week 6 to baseline	167	−0.4 (−0.5 to −0.3)	168	−0.4 (−0.5 to −0.3)	0.0 (−0.1 to 0.1)	
Week 12 to baseline	168	−0.5 (−0.6 to −0.4)	165	−0.5 (−0.6 to −0.4)	0.0 (−0.1 to 0.2)	
Secondary outcomes						
ISI sleep						0.729[c]
Baseline	174	11.8 (11.0 to 12.5)	176	12.0 (11.2 to 12.9)	−0.3 (−1.4 to 0.9)	
Week 12 to baseline	164	−3.8 (−4.5 to −3.2)	164	−3.7 (−4.5 to −2.9)	−0.2 (−1.2 to 0.8)	
PSQI sleep						0.093[c]
Baseline	172	7.9 (7.4 to 8.4)	172	8.2 (7.7 to 8.7)	−0.3 (−1.0 to 0.4)	
Week 12 to baseline	162	−2.1 (−2.6 to −1.7)	162	−1.7 (−2.2 to −1.3)	−0.4 (−1.0 to 0.2)	
Depression (PHQ-8)						0.097[c]
Baseline	177	3.6 (3.1 to 4.1)	174	4.4 (3.8 to 5.0)	−0.7 (−1.5 to 0.1)	
Week 12 to baseline	168	0.0 (−0.5 to 0.6)	161	−0.8 (−1.4 to −0.3)	0.8 (0.1 to 1.6)	
Anxiety (GAD-7)						0.191[c]
Baseline	177	2.9 (2.4 to 3.4)	178	3.5 (2.9 to 4.0)	−0.6 (−1.3 to 0.2)	
Week 12 to baseline	169	−0.2 (−0.7 to 0.3)	168	−0.9 (−1.4 to −0.3)	0.7 (−0.1 to 1.4)	

ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; PHQ-8, Physician's Health Questionnaire-8; GAD-7, Generalized Anxiety Disorder-7.
[a]Hot flash frequency values were log-transformed for modeling.
[b]*P* values from contrasts comparing omega-3 with placebo in a repeated-measures linear model of outcome as a function of intervention arm and adjusted for clinical center, visit (week 6 or 12), active intervention assignment (exercise, yoga, or usual activity), and baseline outcome value. $P < 0.025$ was considered statistically significant to account for the two primary outcome comparisons of interest.
[c]*P* values from contrasts comparing omega-3 with placebo in a linear model of outcome as a function of intervention arm and adjusted for clinical center, active intervention assignment (exercise, yoga, or usual activity), and baseline outcome value. $P < 0.0125$ was considered statistically significant to account for the four secondary outcome comparisons of interest.

taking at least 80% of dispensed pills), with no significant difference in adherence between intervention groups (omega-3, 82%; placebo, 79%; $P = 0.44$).

Adverse events

Newly emergent AEs were reported by 39.0% of participants in the omega-3 group and by 36.9% of participants in the placebo group ($P = 0.82$; Table 3), with no statistically significant differences in the incidence of individual symptoms between treatment groups; in particular, there was no difference in gastrointestinal AEs. All newly emergent symptoms were reported by fewer than 10% of participants in the omega-3 group. There were no serious AEs requiring medical intervention or study withdrawals due to study treatment. Tolerability of study treatment was very high: only one participant stopped treatment because of a protocol-mandated reason (omega-3).

Fewer women in the omega-3 group reported being satisfied with their hot flash relief (38%) compared with women in the placebo group (49%; $P = 0.04$). There was no difference in the proportion of women who wanted to continue their study pills between the omega-3 group (42%) and the placebo group (44%; $P = 0.61$).

DISCUSSION

In this large, multicenter, three-by-two factorial, randomized controlled trial of three low-risk interventions (omega-3 supplementation, exercise, and yoga), omega-3 supplementation did not reduce VMS frequency or bother, as compared with placebo, in healthy perimenopausal and postmenopausal women. Although there are at least some data to support the salutary effects of omega-3 supplementation with respect to some health outcomes in other populations (including cardiovascular disease, rheumatoid arthritis, depression, and other cognitive disorders),[16,17] data with respect to the efficacy of this VMS treatment in postmenopausal women have been incomplete and inconsistent.[5]

Despite the absence of conclusive data supporting the efficacy of omega-3 supplementation for the treatment of VMS, the use of this particular supplement is frequent among midlife women experiencing VMS.[9] Our results are consistent with those noted in the Herbal Alternative for Menopause (HALT)[16] trial, where an herbal intervention widely used to treat VMS failed to demonstrate efficacy when studied under strict conditions. As in the current study, that investigation underscored a public health need for a careful study of agents whose efficacy is often assumed versus agents whose efficacy is confirmed by systematic examination.

A previous randomized controlled study of omega-3 supplementation conducted in 91 women supported the efficacy of this treatment for managing VMS.[9] However, in contrast to the current study, participants were selected based on the presence of emotional distress (defined as a score of ≥72 on the Psychological Well-Being Scale), with improvement in the emotional domain constituting the primary outcome. Our

TABLE 3. *Participants reporting newly emergent adverse events during treatment by omega-3 arm*

	Omega-3		Placebo		
Symptom	n (%)	n[b]	n (%)	n[b]	*P*[a]
Burping/belching	9 (5.6)	162	12 (7.7)	156	0.50
Bad breath or aftertaste	5 (3.1)	162	4 (2.5)	160	1.00
Heartburn	9 (5.7)	158	8 (5.3)	150	1.00
Nausea	10 (6.0)	168	6 (3.7)	164	0.44
Vomiting	1 (0.6)	168	1 (0.6)	168	1.00
Diarrhea	14 (8.7)	161	9 (5.5)	164	0.29
Constipation	6 (3.8)	160	6 (3.9)	156	1.00
Mild flu-like symptoms	8 (5.0)	159	9 (5.6)	162	1.00
Dizziness or fainting	1 (0.6)	164	4 (2.4)	166	0.37
Heart palpitations	0 (0.0)	162	7 (4.2)	158	0.02
Rash	6 (3.8)	159	6 (3.7)	163	1.00
Muscle aches/strains	12 (7.8)	154	17 (11.8)	144	0.33
Change in strength/ sensation of arms/legs	6 (3.6)	167	5 (3.2)	158	1.00
Back pain	14 (9.2)	152	11 (7.1)	154	0.54
Bruising or bleeding	2 (1.2)	168	3 (1.8)	164	0.68
Other symptoms	8 (5.7)	140	4 (3.0)	132	0.38
Any new symptom	65 (38.5)	169	62 (36.9)	168	0.82

[a]Two-sided *P* value from Fisher's exact test.
[b]Participants not reporting the given symptom at baseline.

study population differed from that previous study in that psychological distress, as measured by depressive and anxiety symptoms, in our participants was low. The population differences between studies raise questions of whether response to omega-3 supplementation with respect to VMS is mediated by other factors (including those associated with emotional well-being) or is a chance finding.

Omega-3 fatty acids have been studied as treatment of major depressive disorder. In several[18-20]—but not all—studies,[21,22] omega-3 fatty acids have been demonstrated to be more efficacious than placebo when added to the treatment regimen. The association between depressed mood and VMS,[23-25] including new-onset major depressive episode,[25,26] has been described in several reports. Whether the results of the current study would have been different in a population of women with a greater degree of depressive or anxiety symptoms is unknown and warrants further study.

This study's strengths include its large sample size, the inclusion of perimenopausal and postmenopausal women, excellent adherence to therapy, a double-blind prospective assessment of VMS, and high compliance with follow-up data collection requirements. However, the trial has limitations. Although the recruitment of all women in the sampling frame was community-based (ie, recipients were not selected on any basis other than age and geography), participants may have self-selected to be highly motivated to seek treatment. Furthermore, the omega-3 dose used may have been too low or may not have contained the optimal quantities of each constituent to derive the full effect, although previous studies that demonstrated a decrease in VMS used a similar or lower dose of omega-3s.[9,10]

CONCLUSIONS

In this randomized, double-blind, placebo-controlled trial, omega-3 supplementation has been shown to have no effect on VMS frequency or bother. Midlife women experience a wide array of menopausal symptoms that can impact quality of life. Investigators examining the potential efficacy of a wide spectrum of pharmacologic and nonpharmacologic treatments in managing these bothersome symptoms must identify therapies that not only are acceptable to women but also afford clear evidence of efficacy.

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Other investigators of the MsFLASH Network who contributed to this study include L.S.C. and H.J. (Massachusetts General Hospital); E.W.F. (University of Pennsylvania); and Sheryl Sherman, PhD (National Institute on Aging/National Institutes of Health, Bethesda).

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