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Efficacy of Omega-3 Treatment for Vasomotor Symptoms: A Randomized Controlled Trial:

Omega-3 treatment for vasomotor symptoms

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Dr. Katherine A. Guthrie had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors made substantial contributions to the study and this manuscript. None were compensated for the manuscript preparation.

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Abstract

Objective—To determine the efficacy and tolerability of omega-3 fatty acids in reducing VMS frequency and bother in peri- and postmenopausal women.

Methods—Three-by-two factorial, randomized, controlled 12-week trial. Eligible women were randomized to double-blind comparison of omega-3s (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 12 weeks of omega-3 dosage at a dose of 1.8 grams daily. Each capsule contained ethyl eicosapentaenoic acid (EPA; 425 mg) and docosahexaenoic acid (DHA; 100 mg) and other omega-3s (90mg). Primary outcomes were VMS frequency and bother. Secondary outcomes included sleep quality (Pittsburg 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/day was 7.6 (95% confidence interval [CI] 7.0, 8.2). After 12 weeks, reduction in VMS frequency for omega-3 (−2.5, 95% CI −3.0, −1.9) did not differ significantly from that in placebo (−2.7, 95% CI −3.3, −2.2), with a relative difference of 0.3 fewer hot flashes per day (95% CI −0.5, 1.0, p=0.28). Changes in VMS bother at 12 weeks were also similar between groups, with no relative difference on a 4-point scale (95% CI −0.1, 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).

Conclusion—Among healthy peri- and postmenopausal sedentary women, 12 weeks of omega-3 treatment compared with placebo did not improve VMS frequency, VMS bother, sleep, or mood compared to placebo.

Keywords

omega-3; fish oils; hot flashes; vasomotor symptoms; clinical trials network; menopause

INTRODUCTION

Vasomotor symptoms affect up to 80% of women during the menopausal transition, frequently last several years, and can be disruptive and compromise quality of life.¹ Many women seek alternative treatments to hormonal agents or selective serotonergic reuptake inhibitors (SSRIs) to manage VMS in light of demonstrated risks of hormonal interventions¹ and bothersome side effects of SSRIs.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 (NCCAM) indicated that over 40% of the adult population in the U.S. used at least one complementary or alternative medicine (CAM) treatment over the previous year, with women more likely than men to use CAM.^{3,4}

Omega-3 supplements are polyunsaturated fatty acids (PUFAs) that include the longer chain ω-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as alpha-linolenic acid (ALA), 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 in 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 3 times daily vs. 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, one of isoflavone vs. placebo and the other isoflavones+PUFA vs. placebo, results were inconclusive due to 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 the widespread use of this supplement for a spectrum of symptoms including VMS, there has been a need for a larger, more rigorously conducted trial to definitively delineate the role of omega-3s in the treatment of vasomotor symptoms.

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

METHODS

Study design

Details describing the MsFLASH Network, its protocols, and its overarching study procedures have been published elsewhere.¹¹ This study was a multi-center, 3 by 2 factorial design, randomized, controlled trial of 12 weeks duration testing the efficacy of 1.8 g/day of omega-3 supplementation from fish oil or a matching placebo from olive oil for reducing the frequency and/or relieving the bother of vasomotor symptoms (VMS). 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 DCC, utilizing 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 placebos pill or 1.8 g/day (3 pills/day, each containing 425 mg of EPA, 100 mg DHA and 90 mg of other omega-3s) of high-quality 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; women randomized to usual activity were asked to follow their usual physical activity routine and offered their choice of a 3-hour yoga workshop or a one-month gym membership at study end. Each woman participated for 15 weeks, including

a 3-week eligibility run-in period, 12-week intervention period, and a final clinic visit during week 12.

The study was approved by the institutional review boards at each participating site and the Data Coordinating Center (DCC), and all participants provided written informed consent 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 40-62 years; in the menopause transition (amenorrhea 60 days in the past year) or postmenopausal (12 months since last menstrual period or bilateral oophorectomy) or had a hysterectomy with FSH >20 mIU/mL and estradiol of 50 pg/mL; and in general good health.

VMS enrollment criteria were: 14 hot flashes/night sweats per week recorded on daily VMS diaries for 3 weeks; VMS rated as bothersome or severe during at least 4 or more 12-hour (day/night) blocks of times per week; and the VMS frequency in week 3 did not decrease >50% from the mean weekly levels in weeks 1 and 2. Exclusion criteria included: BMI>37; 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 (e.g., physical limitations), yoga, or omega-3 (allergy to soy or fish; current, regular use of anti-coagulants); current participation in regular exercise or yoga; current use of omega-3 supplements or frequent consumption of fish (4 or more servings a week); or a major depressive episode in the past three months.

Treatment

The omega-3 study supplement contained omega-3 (ω -3, n-3) fatty acids from fish oils (also described as polyunsaturated fatty acids (PUFAs), manufactured by Nordic Naturals, Watsonville, CA). Each gel capsule had a total omega-3 dosage of 615 mg, which included the two major omega-3 components of ethyl eicosapentaenoic acid (EPA; 425 mg) and docosahexaenoic acid (DHA; 100 mg) along with other assorted omega-3s (90mg). Vitamin E (15 IU), an antioxidant, was added to each gel capsule of active treatment and placebo in order 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 per day of omega-3s or placebo for 12 weeks.

Screening and baseline data collection

Women who were eligible after a telephone screen completed a two-week hot flash diary and a questionnaire. Women who continued to meet eligibility criteria came to a clinic visit during which additional information was collected, 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 at week 2 to encourage compliance and evaluate pill tolerance. Six weeks and 12 weeks post-randomization participants completed additional 7-day VMS diaries. Other baseline measurements were repeated at the week 12 post-randomization clinic visit. Treatment adherence was assessed by counting the number of pills returned at the last visit. Participants received \$50 after each of 3 clinic visits for their time and effort, for a possible total of \$150.

Study outcomes

Primary outcomes—The primary outcomes were VMS frequency and bother based on daily diaries at baseline and 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 1-4 scale (none, a little, moderately, and 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 – PSQI),¹² insomnia symptoms (Insomnia Severity Index – ISI),¹³ depressive symptoms (Physician's Health Questionnaire depression domains – PHQ-8),¹⁴ and anxiety (Generalized Anxiety Disorder questionnaire – GAD-7)¹⁵.

Adverse Events—Adverse events (AE) were assessed at each visit using a self-administered questionnaire listing common yoga, exercise, and omega-3 adverse events. Participants were instructed to call the study nurse to report any potential AEs during the study. Newly emergent adverse events were identified by comparing adverse event 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 of 1.6 HF per day reduction between treatment groups (a 0.40 standard deviation (SD) units reduction in HF/day based on preliminary data). This calculation was based on a t-test with 2-sided significance level of 0.025 to account for two primary outcomes, and allowance for 10% loss to follow-up.

All analyses of treatment effect were based on the intention-to-treat principle where all randomized participants who provided diary data at any point in 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 hour) totals reported in the first two screening weeks. Hot flash frequency at weeks 6 and 12 were calculated as the mean of the daily (24 hour) frequencies for the week prior. Hot flash bother scores were calculated in a similar way. A categorical variable to indicate

clinical VMS improvement was defined as 50% 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 at weeks 6 and 12 as a function of randomization assignment, adjusting for clinical site, visit (week 6 or 12), behavioral intervention assignment, and the baseline value of the outcome measure. Because VMS frequency values were skewed to the right, the 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 correlation 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 (BMI), menopausal 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 a similar approach to that used with primary outcomes.

Baseline characteristics were compared between treatment groups using t-tests for continuous variables and χ^2 tests for categorical variables. Incidence of newly emergent adverse events was compared between treatment groups via Fisher exact test.

A 2-sided p-value <0.025 was considered statistically significant for the two primary outcomes. For the four outcomes examined as secondary analyses, a p-value <0.0125 was considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

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

The only nominally significant differences between the omega-3 and placebo groups in baseline characteristics were 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 than the placebo group (Table 1). Overall, the mean age was 54.7 (SD 3.7); 64% were white, 26% were African-American, and 10% were of another race group. 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 > 14 .

Hot flash frequency and bother

The mean baseline hot flash frequency was 7.6, with 95% confidence interval (CI) 7.0-8.2, per day. As seen in Figure 2, omega-3s did not significantly reduce hot flash frequency compared to placebo ($p=0.28$, Table 2). In the omega-3 group, mean hot flash frequency at week 12 decreased to 5.2 (95% CI 3.0-1.9) VMS/day corresponding to a 32% decrease or a mean of 2.5 fewer VMS/day compared to baseline. The placebo group decreased to 4.9 (95% CI 3.3-2.2) VMS/day at week 12, a 36% 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 at week 12 (50% decrease from baseline in VMS frequency) also did not differ between the omega-3 and placebo groups, 34% and 38%, respectively ($p=0.43$).

The lack of an effect of omega-3s on hot flash frequency was consistent across 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 measure of sleep or mood, including sleep quality, insomnia symptoms, depressive symptoms, or anxiety (Table 2). The mean ISI reduction for the omega-3 group was 3.8 and 3.7 for the placebo ($p=0.73$). The mean PSQI reduction was 2.1 in the omega-3 group and 1.7 in the placebo group ($p=0.09$). There was no PHQ-8 change in the omega-3 group and a negligible change (-0.8) in the placebo group ($p=0.10$). The mean reduction for the GAD-7 score was 0.2 for the omega-3 group and 0.9 for the placebo group ($p=0.19$).

Adherence

Over the entire treatment period, 80% of participants (285/355) adhered to omega-3 or placebo pills defined as 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 36.9% in the placebo group ($p=0.82$, Table 3), with no statistically significant differences between treatment groups in the incidence of individual symptoms; in particular, there was no difference in GI adverse events. All newly emergent symptoms were reported by fewer than 10% of participants in the omega-3 group. There were no serious AEs that required medical intervention or study withdrawal due to the study treatment. Tolerability of study treatment was very high: only 1 participant stopped treatment due to a protocol mandated reason (omega-3).

Fewer women in the omega-3 group reported being satisfied with their hot flash relief (38%) compared to 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 multi-center, 3 by 2 factorial design, 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 to placebo in healthy peri- and postmenopausal women. While 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 efficacy of this treatment for VMS in menopausal women have been incomplete and inconsistent.⁵

Despite the absence of conclusive data supporting 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 in theme to those noted in the Herbal Alternative for Menopause (HALT)¹⁶ trial, where testing of a widely used herbal intervention to treat vasomotor symptoms failed to demonstrate efficacy when studied under strict conditions. As in the current study, that investigation underscored the public health need for the careful study of agents whose efficacy is often assumed versus confirmed by systematic examination.

A previous randomized controlled study of omega-3 supplementation conducted in 91 women supported efficacy of this treatment for management of 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 or more on the Psychological Well-Being Scale) with improvement in the emotional domain constituting the primary outcome. Our 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 was a chance finding.

Omega-3 fatty acids have been studied as a treatment for major depressive disorder and in several¹⁸⁻²⁰ 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 has been described in several reports,²³⁻²⁵ including new onset major depressive episode.^{25,26} Whether 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.

Study strengths include the large sample size, the inclusion of peri- and postmenopausal women, excellent adherence to therapy, a double-blinded, prospective assessment of VMS, and high compliance with follow-up data collection requirements. However, the trial has limitations. Although recruitment to all women in the sampling frame was community-based (i.e., 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 dose of omega-3s that was used may have been too low or may not have contained the optimal

quantities of each constituent to see the full effect, although previous studies that demonstrated a decrease in VMS used a similar or a lower dose of omega-3s.^{9,10}

CONCLUSION

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Other investigators of the MsFLASH Network that contributed to this study include Lee Cohen, MD and Hadine Joffe, MD, MSc, Massachusetts General Hospital; Ellen W. Freeman, PhD, University of Pennsylvania; and Sheryl Sherman, PhD: National Institute on Aging/US National Institutes of Health, Bethesda, MD.

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Figure 1.
Participant recruitment ¹

1. Randomization occurred concurrently to Yoga (n=107), Exercise (n=106), or Usual Activity (n=142).

Figure 2.

Hot flash frequency over time by omega-3 assignment ¹

1. Mean difference in number of hot flashes/day from baseline to week 12; Baseline = 0.1 (−0.7, 0.9); Week 6-baseline = 0.2 (−0.5, 0.9); Week 12-baseline = 0.3 (−0.5, 1.0)

Table 1

Baseline demographic and clinical characteristics by Omega-3 arm

	Omega-3 (N =177)		Placebo (N =178)	
	N	%	N	%
Age at screening (yrs), mean (SD)	54.39 (3.55)		54.98 (3.79)	
< 50	10	5.6	9	5.1
50 - 54	87	49.2	75	42.1
55 - 59	63	35.6	67	37.6
60+	17	9.6	27	15.2
Race				
White	125	70.6	103	57.9
African American	45	25.4	48	27.0
Other	7	4.0	27	15.2
Clinical Center				
Indianapolis	58	32.8	60	33.7
Oakland	55	31.1	55	30.9
Seattle	64	36.2	63	35.4
Education				
High school diploma/GED	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				
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				
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				
Never	112	63.3	120	67.4
Past	48	27.1	41	23.0
Current	16	9.0	16	9.0
Alcohol use (drinks/week)				
0	60	33.9	77	43.3
1-<7	78	44.1	78	43.8

	Omega-3 (N =177)		Placebo (N =178)	
	N	%	N	%
7+	38	21.5	22	12.4
BMI (m/kg ²), mean (SD)	26.81 (4.42)		27.09 (4.33)	
<25	63	35.6	60	33.7
25 – 29	72	40.7	72	40.4
30	42	23.7	46	25.8
Menopause status				
Postmenopausal	146	82.5	140	78.7
Late transition	28	15.8	34	19.1
Early transition	3	1.7	4	2.2
Hysterectomy	35	19.8	29	16.3
Bilateral Oophorectomy	18	10.2	14	7.9
Self-reported health				
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)	
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)	
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)	
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)	
No clinically significant insomnia (< 7)	42	23.7	44	24.7
Subthreshold insomnia (8-14)	75	42.4	73	41.0
Clinical insomnia (moderate, 15-21)	52	29.4	50	28.1
Clinical insomnia (severe, 22+)	5	2.8	9	5.1

Table 2

Change in primary and secondary outcomes by Omega-3 arm

Primary Outcomes	N	Omega-3 Mean (95% CI)	N	Placebo Mean (95% CI)	Difference Mean (95% CI)	p-value ^a
Hot flashes / day ^c						0.283
Baseline	177	7.7 (7.1, 8.2)	178	7.6 (7.0, 8.1)	0.1 (−0.7, 0.9)	
Week 6 – baseline	168	−2.0 (−2.5, −1.5)	170	−2.2 (−2.7, −1.7)	0.2 (−0.5, 0.9)	
Week 12 – baseline	169	−2.5 (−3.0, −1.9)	169	−2.7 (−3.3, −2.2)	0.3 (−0.5, 1.0)	
Bother (1–4)						0.359
Baseline	177	3.0 (2.9, 3.1)	178	2.9 (2.8, 3.0)	0.1 (0.0, 0.2)	
Week 6 – baseline	167	−0.4 (−0.5, −0.3)	168	−0.4 (−0.5, −0.3)	0.0 (−0.1, 0.1)	
Week 12 – baseline	168	−0.5 (−0.6, −0.4)	165	−0.5 (−0.6, −0.4)	0.0 (−0.1, 0.2)	

Secondary Outcomes	N	Omega-3 Mean (95% CI)	N	Placebo Mean (95% CI)	Difference Mean (95% CI)	p-value ^b
ISI Sleep						0.729
Baseline	174	11.8 (11.0, 12.5)	176	12.0 (11.2, 12.9)	−0.3 (−1.4, 0.9)	
Week 12 – baseline	164	−3.8 (−4.5, −3.2)	164	−3.7 (−4.5, −2.9)	−0.2 (−1.2, 0.8)	
PSQI Sleep						0.093
Baseline	172	7.9 (7.4, 8.4)	172	8.2 (7.7, 8.7)	−0.3 (−1.0, 0.4)	
Week 12 – baseline	162	−2.1 (−2.6, −1.7)	162	−1.7 (−2.2, −1.3)	−0.4 (−1.0, 0.2)	
Depression (PSQ-8)						0.097
Baseline	177	3.6 (3.1, 4.1)	174	4.4 (3.8, 5.0)	−0.7 (−1.5, 0.1)	
Week 12 – baseline	168	0.0 (−0.5, 0.6)	161	−0.8 (−1.4, −0.3)	0.8 (0.1, 1.6)	
Anxiety (GAD-7)						0.191
Baseline	177	2.9 (2.4, 3.4)	178	3.5 (2.9, 4.0)	−0.6 (−1.3, 0.2)	
Week 12 – baseline	169	−0.2 (−0.7, 0.3)	168	−0.9 (−1.4, −0.3)	0.7 (−0.1, 1.4)	

^a p-values from contrasts comparing omega-3 vs. 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, usual activity), and baseline outcome value. A p-value < 0.025 was considered statistically significant to account for the 2 primary outcome comparisons of interest.

^b p-values from contrasts comparing omega-3 vs. placebo in a linear model of outcome as a function of intervention arm and adjusted for clinical center, active intervention assignment (exercise, yoga, usual activity), and baseline outcome value. A p-value < 0.0125 was considered statistically significant to account for the 4 secondary outcome comparisons of interest.

^c hot flash frequency values were log transformed for modeling

Table 3

Participants reporting newly-emergent adverse events during treatment by Omega-3 arm

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

^a Participants not reporting the given symptom at baseline^b 2-sided p-value from a Fisher's Exact test