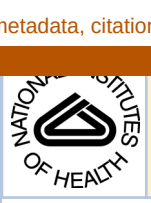

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Efficacy of Yoga for Vasomotor Symptoms: A Randomized Controlled Trial

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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; and Ellen W. Freeman, PhD, University of Pennsylvania.

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Abstract

Objective—To determine the efficacy of yoga in alleviating VMS frequency and bother.

Methods—Three by two factorial design, randomized, controlled. Eligible women were randomized to yoga (n=107), exercise (n=106), or usual activity (n=142), and were simultaneously randomized to double-blind comparison of omega-3 fatty acid (n=177) or placebo (n=178) capsules. Yoga intervention was twelve, weekly, 90-minute yoga classes with daily home practice. Primary outcomes were VMS frequency and bother assessed by daily diaries at baseline, 6, and 12 weeks. Secondary outcomes included insomnia symptoms (Insomnia Severity Index) at baseline and 12 weeks.

Results—Among 249 randomized women, 237 (95%) completed 12-week assessments. Mean baseline VMS frequency was 7.4/day (95% CI 6.6, 8.1) in the yoga group and 8.0/day (95% CI 7.3, 8.7) in the usual activity group. Intent-to-treat analyses included all participants with response data (n=237). There was no difference between intervention groups in change in VMS frequency from baseline to 6 and 12 weeks (mean difference (yoga – usual activity) from baseline −0.3 (95% CI −1.1, 0.5) at 6 weeks and −0.3 (95% CI −1.2, 0.6) at 12 weeks (p=0.119 across both time points). Results were similar for VMS bother. At week 12, yoga was associated with an improvement in insomnia symptoms (mean difference [yoga-usual activity] in change –Insomnia Severity Index, 1.3 [95% CI −2.5, −0.1][p=0.007]).

Conclusion—Among healthy women, 12 weeks of yoga class plus home practice compared with usual activity did not improve VMS frequency or bother, but reduced insomnia symptoms.

Keywords

clinical trials network; vasomotor symptoms; yoga; meditation; menopause; hot flashes

INTRODUCTION

Hormonal agents have been the predominant therapy for menopausal vasomotor symptoms (VMS: hot flashes plus night sweats), but their use decreased substantially with shifts in our understanding of the risk and benefits identified in the Women's Health Initiative. [1–3] However, no other treatments have Food and Drug Administration approval for VMS. Alternatives to hormone therapy (HT) have been explored. To date, selective serotonin reuptake inhibitors have demonstrated modest efficacy for relief of menopause symptoms,[4] while the search for mind-body therapies,[5] herbal treatments,[6] and supplements to lessen menopausal symptoms continues with limited success.

Yoga is a mind-body therapy that includes stretching, poses that require balance and core strength, deep breathing, and meditation.[7] In 2007, 6.1% of the adult U.S. population reported practicing yoga,[8] and women are almost four times as likely to practice yoga than men.[9] Population–based surveys indicate that some women use yoga in an attempt to manage their menopause symptoms.[10, 11] Yoga has been investigated as a therapy for VMS, but studies to date have been limited in size or methodology and results have been mixed.[12–17] We evaluated the efficacy of a yoga program designed to reduce the frequency and bother of vasomotor symptoms (VMS).

The rationale for evaluating yoga was based on hypothesized physiologic changes that occur with menopause (or estrogen withdrawal).[18] Menopause is associated with a narrowing in the range of core body temperatures at which physiologic responses to induce cooling or heating occur.[19] These changes appear to be regulated by central noradrenergic neurotransmitters and sympathetic nervous system (SNS) regulation, specifically an increase in norepinephrine.[18, 20, 21] The hypothesis that central noradrenergic neurotransmitters and sympathetic nervous system (SNS) regulation affect VMS is supported by clinical and anecdotal reports linking psychological stress and SNS regulation and VMS.[22–25] Yoga may decrease autonomic arousal through changes in the levels of circulating neurotransmitters and hormones.[26] These changes would reduce the SNS activation that has been implicated in VMS etiology. Behavioral interventions can impact both SNS and parasympathetic nervous system functioning and stress reactivity,[27–30] raising the possibility that yoga might decrease menopausal VMS through its impact on these finely balanced systems.

METHODS

Study design

Details about the MsFLASH Research Network, study design, and protocols have been published.[31, 32] This study was a multi-site, 3 by 2 factorial, randomized, controlled trial. Eligible women were randomized to 12 weeks of yoga, exercise, or usual activity, and simultaneously randomized to 1.8 g/day of omega-3 fish oil capsules (EPA 1275 mg, DHA 300 mg) or placebo capsules. The factorial design was motivated by the desire to have all participants receive some intervention and hence have an expectancy of benefit (though participants taking pills knew they could be on either placebo or omega-3s), and to reduce costs. No head-to-head comparisons between yoga and exercise were planned. Interactions between the behavioral interventions and omega-3 fatty acids were hypothesized to be unlikely. This report describes the results of the yoga intervention compared to usual activity; results for the exercise and omega-3 comparisons are reported separately. The study was approved by the Institutional Review Boards of each clinical site and the Data Coordinating Center (DCC), and all participants provided written informed consent.

Yoga intervention

No single standardized yoga practice could be identified as most appropriate for relief of menopause symptoms. Investigators (KJS, CBL) worked with expert yoga instructors and consultants from the National Center for Complementary and Alternative Medicine to create a program that emphasized the practice of “cooling” breathing exercises and three groups of poses (Asanas) believed to be useful for relieving VMS.[12, 33] We sequenced poses according to the principles of Viniyoga[34] to promote safety.

Class Content—Yoga instruction was provided during 12 weekly 90-minute classes. Each class included breathing exercises, 11 to 13 poses (restorative, inverted, lateral bends, twists, forward bends, and counter poses), and deep relaxation featuring Yoga Nidra (a meditative practice). Three different sequences of poses were used to increase variety and maintain

participant interest. Women joined class as they were recruited. Before her first class, each woman met with the instructor for 30 minutes to discuss health concerns and learn the breathing exercises.

Home Practice—Home practice included breathing, poses, and Yoga Nidra. Participants were given written instructions, a DVD with the 3 sequences of poses, a CD for Yoga Nidra, and supplies (bolster, strap, blanket, and mat). Participants were instructed to practice at home 20 minutes each day they did not attend class, alternating poses one day with Yoga Nidra the next.

Classes were offered twice weekly. Yoga instructors had at least 5 years of teaching experience and 500 hours of training. Yoga consultants conducted two-day trainings at each study site. Instructors were taught to strictly adhere to the protocol. A research staff member attended every yoga class and completed a yoga protocol adherence log. Investigators (KJS, CBL) were in weekly contact with the instructors via email to discuss class experiences, adverse events, adherence, and other questions.

Usual activity comparison group

Women in the usual activity group were instructed to follow their usual routine and were asked not to engage in yoga or to change their exercise routines. At study end they were offered their choice of a 3-hour yoga workshop or a one-month gym membership.

Eligibility, screening, randomization and blinding

The trial was conducted at three MsFLASH sites – Indianapolis, Oakland, and Seattle. Participants were recruited from February 2011 through January 2012, primarily by mass mailing to age-eligible women using purchased lists and health-plan enrollment files. Eligible women were ages 40–62 years; in the menopausal transition or postmenopausal or had a hysterectomy with FSH >20 mIU/mL and estradiol ≤50 pg/mL; and in general good health. The VMS eligibility criteria were: ≥14 hot flashes/night sweats per week recorded on daily VMS diaries for 3 weeks; VMS rated as bothersome or severe on 4 or more occasions per week; and the VMS frequency in week 3 did not decrease >50% from the average weekly levels in weeks 1 and 2. Exclusion criteria included: BMI>37; use of hormonal contraceptives or hormones in the past month; use of prescription or over-the-counter treatments for VMS in the past month; unstable medical conditions; current user of one of the study interventions or a related activity (i.e., yoga, tai chi, qi gong, or meditation, regular exercise, omega-3 fatty acid supplements, frequent consumption of fish); contraindications to exercise (e.g., physical limitations), yoga, or omega-3 (e.g., allergy to soy or fish); or a major depressive episode in the past 3 months.

Data collection

Following telephone screening, women completed a two-week VMS diary and a questionnaire. Women who remained eligible attended an in-person visit that included a blood draw, physical measures, and an additional baseline questionnaire. Following that visit, women completed the week-3 VMS diary. Women then returned to the clinic for a final determination of eligibility and randomization.

Randomization was conducted in a secure web-based database, maintained at the MsFLASH DCC utilizing a dynamic randomization algorithm to maintain comparability between study groups with respect to clinical site. For the behavioral interventions, a 3:3:4 (yoga:exercise:control) allocation was employed to improve power for intervention versus control contrasts while reducing costs. Local access to information on assignment to yoga,

exercise, or usual activity was limited to site staff involved in intervention delivery to assure masking of data collectors. Equal allocation was used for omega-3 and placebo treatments.

Follow-up

At week 2, participants were contacted by study staff blinded to omega-3 assignment to encourage compliance and to evaluate tolerance to the study capsules. During intervention weeks 6 and 12, participants completed 7-day VMS diaries. All other baseline measurements were repeated either during week 12 or at the week-12 clinic visit. Participants were compensated $50 for their time and effort after each clinic visit for a possible total of $150.

Measurements

The primary outcomes were VMS frequency and bother based on daily diaries[4] 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 on a 1–4 scale (none, a little, moderately, and a lot).

The secondary outcomes were subjective sleep quality and sleep disturbances (Pittsburgh Sleep Quality Index - PSQI) [35], insomnia symptoms (Insomnia Severity Index - ISI)[36], depressive symptoms (Patient Health Questionnaire depression domains - PHQ-8)[37] and anxiety (Generalized Anxiety Disorder questionnaire - GAD-7)[38].

Adverse events (AEs) were assessed using a self-reported questionnaire listing 15 common AEs related to yoga, physical activity, and omega-3 fatty acids. 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 the baseline reports.

Statistical analysis

Baseline characteristics were compared between treatment groups using t-tests or chi-square tests. The primary intent-to-treat analysis (ITT) included all randomized participants with response data, which were collected regardless of intervention adherence. Among 249 women who were randomized, 237 (95.2%) provided week-12 response data (Figure 1).

Baseline VMS frequency was calculated as the mean of the daily totals reported for the first two screening weeks. VMS frequency at weeks 6 and 12 were calculated as the mean of the daily frequencies for those weeks. Baseline, week 6, and week 12 bother were also defined as the means of the daily ratings. A categorical variable to indicate clinical VMS improvement was defined as ≥50% decrease in VMS frequency at 12 weeks from baseline.

Intervention arm contrasts were computed as Wald statistics from linear regression models summarizing the VMS frequency or bother at weeks 6 and 12 as a function of randomization assignment, adjusted for clinical site, visit (week 6 or 12), omega-3 intervention assignment, and baseline outcome value. Natural logarithmic transformations were applied to hot flash frequencies to accommodate modeling assumptions. Robust standard errors were calculated via generalized estimating equations to account for correlations between repeated measures from each participant.

Variables hypothesized *a priori* to modify treatment response on VMS frequency included prior experience with yoga and/or meditation, depressive symptoms (PHQ-8 continuous score), anxiety (GAD-7, continuous score), body mass index (BMI: < 25 kg/m^2, 25 to <30 kg/m^2, ≥ 30 kg/m^2), and race (African American, white). Tests for interaction between these variables and treatment assignment were performed within the linear regression model.

We defined adherence as completing 4 or more sessions in a week and tracked adherence weekly. The number of sessions completed per week (up to 4 maximum) was summed over 12 weeks and percent adherence was calculated as the total number of sessions divided by 48 (missing diaries were calculated as zero participation).

Secondary analyses also applied linear regression to model changes in measures of subjective sleep quality and sleep disturbances (PSQI [35]), insomnia symptoms (ISI [36]), depressive symptoms (PHQ-8 [37]), and anxiety (GAD-7[38]), as a function of treatment assignment, following a similar approach to that used with primary analyses. Incidence of newly emergent adverse events was compared between groups using Fisher's exact test.

Multiple comparisons determined our choice of what p values would be considered statistically significant. 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 less than 0.0125 was considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

A sample of 112 yoga participants and 150 usual activity participants was planned to provide 90% power to detect a mean difference of 1.9 VMS/day reduction between groups (a 0.49 standard deviation (SD) reduction in VMS/day, based on the variability observed in preliminary data from the first 97 participants enrolled in the MsFLASH escitalopram trial [4]. This calculation was based on a t-test with 2-sided significance level of 0.025 to account for two primary outcomes (VMS frequency, VMS bother), allowing for 10% loss to follow-up in both arms and an extra 10% in the exercise arm to address the potential for increased variability in outcomes due to differing adherence to the intervention.

RESULTS

Among 249 women, 107 were randomly assigned to receive yoga and 142 were assigned to usual activity (Figure 1). There were no significant differences in baseline characteristics between the two intervention groups. The mean age of participants was 54 years, 63% were white, most were postmenopausal and well educated, mean BMI was 27 kg/m^2, and few were smokers (Table 1). Follow-up rates among the intervention and usual activity groups were 96% and 95% at 6 weeks, and 94% and 95% at 12 weeks, respectively, with no differences between groups.

Vasomotor symptom frequency and bother

The mean baseline VMS frequency was 7.4/day (95% CI 6.6, 8.1) in the yoga group and 8.0/day (95% CI 7.3, 8.7) in the usual activity group with a range of 2.1–21.4 VMS per day (Table 2). Yoga did not significantly reduce the frequency of VMS relative to usual activity, adjusted for site, visit (week 6 or 12), omega-3 capsule assignment, or baseline VMS frequency (Figure 2). In the yoga group, mean hot flash frequency at week 12 decreased to 4.6 (95%CI 3.9, 5.3) VMS/day, a 35% decrease or a mean of 2.9 fewer VMS/day compared to baseline. The placebo group decreased to 5.4 (95%CI 4.8, 6.1) VMS/day, a 27% decrease or a mean of 2.6 fewer VMS per day. The mean difference between yoga and usual activity in the reduction of VMS from baseline to both weeks 6 and 12 was −0.3 VMS/day (6-week 95% CI −1.1,0.5, 12-week 95% CI −1.2, 0.6), overall p=0.119. The mean baseline rating for VMS bother was 2.9 (95% CI 2.8, 3.0) in the yoga group and 3.0 (95%CI 2.9, 3.1) in the usual activity group (Table 2). There were no statistically significant differences in change in VMS bother between baseline and 6 and 12 weeks comparing yoga to usual activity (overall p=0.417).

There were no statistically significant interactions between treatment effects and baseline characteristics on VMS frequency including prior participation in yoga or meditation (p=0.67), depressive symptoms (p=0.44), BMI (< 25 kg/m^2, 25 to ≥30 kg/m^2, > 30 kg/m^2) (p=0.37), or race (p=0.48) (Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A60).

Secondary outcomes

Clinical improvement in VMS at week 12 (≥50% decrease from baseline in VMS frequency) occurred at a similar rate between the yoga and usual care groups, 36% and 30%, respectively (p=0.31). The yoga intervention significantly improved insomnia symptoms, but had no significant impact on anxiety, sleep quality, or depressive symptoms (Table 2). The mean change in ISI score between baseline and 12 weeks was −4.4 for the yoga intervention and −3.1 for usual activity (p=0.007).

Among women assigned to yoga, 68% reported at the end of the trial that yoga helped their menopause symptoms with minimal side effects, 66% reported being satisfied with their hot flash relief, and 87% said they would like to continue practicing yoga.

Intervention adherence

Participants attended an average of 8.5 ± 3.5 of the 12 scheduled yoga sessions, ranging from 0 to 13. Women practiced at home an average of 4.1 ± 2.3 times per week. On average, women did poses 2.6 ± 1.1 times per week and Yoga Nidra 2.3 ± 1.2 times per week. Results were not altered when analyses were limited to women who were 80% adherent (attended at least 80% of the yoga classes).

Adverse events

Newly-emergent AEs were reported by 33.7% in the yoga group and 39.3% in the usual activity group (p=0.41). There were no differences in emergent AEs between groups at any time point, including muscle aches and strains (6.7% yoga, 10.3% usual activity), low back pain (4.2% yoga, 3.1% usual activity), or changes in strength or sensation in the arms or legs (5.5% yoga, 8.9% usual activity). There were no reported serious AEs. Tolerability of treatment was high; no participants stopped the intervention due to AEs.

DISCUSSION

Based upon the intent-to-treat analysis of this randomized controlled trial we found that a 12-week program of yoga had no effect on VMS frequency or bother when compared to usual activity. VMS decreased equally in the yoga and usual activity groups over 12 weeks of intervention. Secondary analyses found no difference in clinical improvement in VMS frequency but did demonstrate that the yoga intervention improved insomnia symptoms.

Reports from three previous trials of the effects of yoga practice on menopausal symptoms are generally consistent with our VMS results. Elavsky and colleagues[39] studied 4 months of Iyengar yoga, walking, or usual activity (n=164). There were no significant between group differences in VMS at 4 months. Positive affect increased in both the walking and yoga groups compared to the control. In a trial conducted by Afonson and colleagues, 61 postmenopausal women aged 50–65 years with insomnia were randomized to biweekly 1-hour yoga classes, bi-weekly passive stretching, or usual care.[16] They found that compared to usual care, women assigned to yoga had significant improvement in the Kupperman Menopause Index, the Insomnia Severity Index, the Menopause-Specific Quality of Life Questionnaire, and the Inventory of Stress Symptoms for Adults; hot flash frequency was not measured.[16] However, given the extremely high withdrawal rate (23% overall, 63%

yoga group) these results must be viewed cautiously.[40] compared a yoga intervention that included breathing practices, sun salutation, and cyclic meditation to simple physical exercises (both 1 hour per day, 5 days a week for 8 weeks) in a randomized controlled trial of 120 women aged 40–55 years with FSH≥15mIU/ml. At 8 weeks there were no significant group differences in the change in daytime hot flashes, night sweats, or disturbed sleep. However yoga resulted in a significant improvement in Greene Climacteric Scale vasomotor subscale scores.[15] In contrast, two small non-randomized yoga studies comparing VMS symptoms pre and post yoga intervention reported that yoga reduced VMS frequency, severity, and bother[12] as well as severity of menopause-related symptoms, hot-flash daily interference, and sleep efficiency, disturbances, and quality.[14] Interpretation of the results of these two studies are limited by the lack of a randomized control trial design.

We found that yoga modestly reduced insomnia symptoms, which are common among women during the menopausal transition[41–50] and which can prompt women to seek therapy.[51, 52] While our findings also suggest beneficial effects of yoga on sleep quality and depressive symptoms, these differences did not reach the level of significance required in our analyses of the four secondary outcomes. In general, these findings are consistent with numerous other studies that have found yoga to exert beneficial effects on insomnia,[16, 53–56] sleep disturbances,[55, 56] and depressive symptoms.[13, 57–59]

Several limitations are noteworthy. Although this was a community-based sample, the participants may be a select group motivated to seek treatment and thus our results may not be generalizable to all women. We examined several potential moderating factors of treatment response, but other factors likely exist. The overall effect was modest for all outcomes. The 12-week treatment interval was brief, but data indicate that this interval is sufficient to determine long-term efficacy of non-hormonal treatments.[60, 61] While participants did keep a home practice log, short of video taping their practice at home it was impossible to know if their home practice was of equal intensity to the yoga class. We also cannot rule out the possibility that other yoga approaches might decrease menopause symptoms. Finally, the “dose” of yoga required to have an effect is not known, including effects on physiologic parameters of sympathetic/parasympathetic tone. Studies in which frequency and dose are carefully regulated would be required to answer this question.

Study strengths include the adherence to state-of-the-science randomized trial design, the design and strict standardization of the yoga intervention, the large sample size, the inclusion of peri- and postmenopausal women, reasonable adherence to therapy, the prospective assessment of VMS, and the low dropout rate. The low rates of AEs provide reassurance that similar yoga programs are safe for midlife women.

CONCLUSIONS

In conclusion, in this randomized controlled trial we found that yoga had no effect on VMS frequency or bother. However yoga modestly improved insomnia symptoms, another menopausal symptom important to midlife women. Future trials designed to address the dose of yoga required to detect meaningful effects on insomnia symptoms, subjective sleep quality, and depressive symptoms are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The National Institutes of Health had no role in the collection, analysis, and interpretation of the data. NIH staff critically reviewed the study protocol and drafts of the manuscript prior to journal submission.

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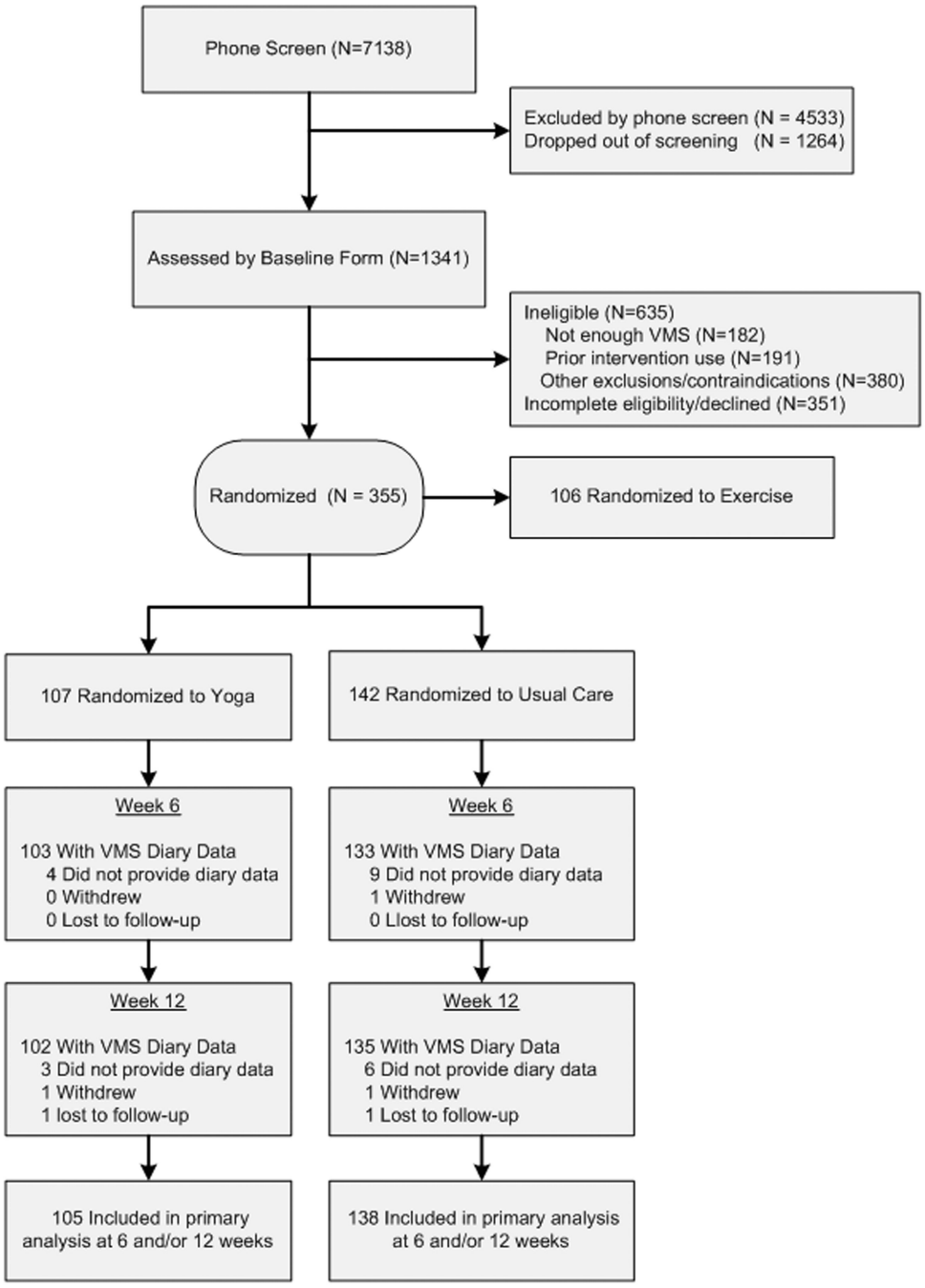

Figure 1.
Participant recruitment

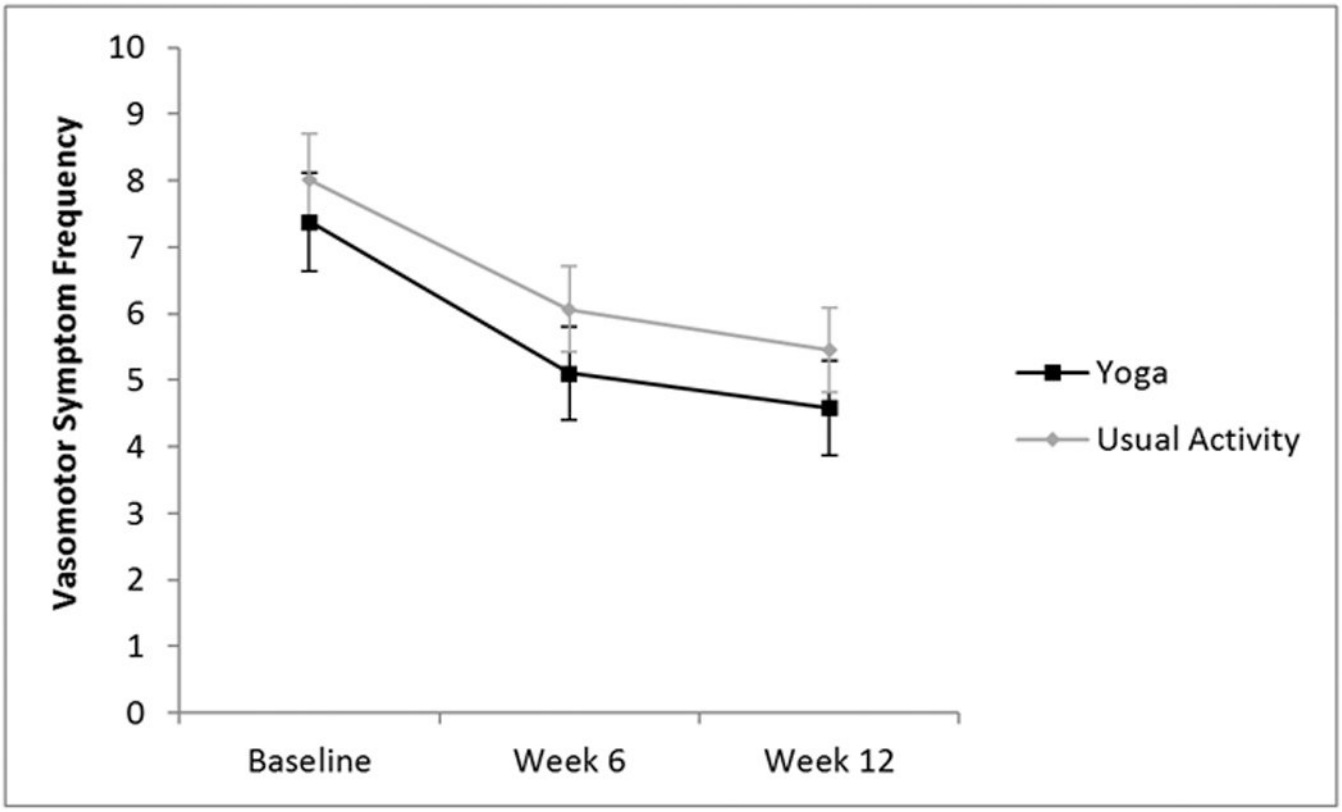

Figure 2.
Vasomotor symptom frequency over time by intervention arm, presented as mean +/− standard error at baseline, week 6, and week 12.

Table 1

Baseline demographic and clinical characteristics by intervention arm, yoga versus usual activity

	Yoga (N =107)		Usual Activity (N =142)	
	N	%	N	%
Age at screening (years), mean (SD)	54.3 (3.9)		54.2 (3.5)	
< 50	7	6.5	10	7.0
50 – 54	50	46.7	69	48.6
55 – 59	39	36.4	51	35.9
60+	11	10.3	12	8.5
Race				
White	68	63.6	90	63.4
African American	25	23.4	41	28.9
Other	14	13.1	11	7.7
Clinical Center				
Indianapolis	36	33.6	48	33.8
Oakland	33	30.8	44	31.0
Seattle	38	35.5	50	35.2
Education				
≤ High school diploma/GED	7	6.5	8	5.6
School/training after high school	31	29.0	40	28.2
College graduate	69	64.5	94	66.2
Employment status				
Retired or no employment	14	13.1	18	12.7
Full-time	60	56.1	91	64.1
Part-time	17	15.9	17	12.0
Homemaker	4	3.7	7	4.9
Other	11	10.3	9	6.3
Married/living with partner	73	68.2	97	68.3
Smoking				
Never	73	68.2	89	62.7
Past	25	23.4	36	25.4
Current	8	7.5	16	11.3
Alcohol use (drinks/week)				
0	45	42.1	51	35.9
1-<7	48	44.9	62	43.7
7+	14	13.1	27	19.0
BMI (m/kg^2), mean (SD)	27.1 (4.6)	26.9 (4.6)		

	Yoga (N =107)		Usual Activity (N =142)	
	N	%	N	%
<25	39	36.4	49	34.5
25 – 29	39	36.4	59	41.5
≥ 30	29	27.1	34	23.9
Menopause status				
Postmenopausal	80	74.8	116	81.7
Late transition	24	22.4	23	16.2
Early transition	3	2.8	3	2.1
Hysterectomy	17	15.9	22	15.5
Bilateral Oophorectomy	8	7.5	13	9.2
Self-reported health				
Excellent	18	16.8	24	16.9
Very Good	45	42.1	70	49.3
Good	39	36.4	40	28.2
Fair	5	4.7	8	5.6
Depression score, mean (SD)	4.0 (3.6)		4.1 (3.6)	
No depression (0–4)	65	60.7	91	64.1
Mild depression (5–9)	32	29.9	38	26.8
Moderate+ depression (10+)	9	8.4	11	7.7
Anxiety score, mean (SD)	3.2 (3.8)		3.0 (3.0)	
No anxiety (0–4)	78	72.9	105	73.9
Mild anxiety (5–9)	21	19.6	30	21.1
Moderate+ anxiety (10+)	8	7.5	7	4.9

BMI = Body Mass Index

Table 2

Change in primary and secondary outcomes by intervention arm, yoga versus usual activity

	Yoga		Usual Activity		Difference	
Primary Outcomes	**N**	**Mean (95% CI)**	**N**	**Mean (95% CI)**	**Mean (95% CI)**	**p-value[a]**
Hot flashes / day[c]						0.119
Baseline	107	7.4 (6.6, 8.1)	142	8.0 (7.3, 8.7)	−0.6 (−1.7, 0.4)	
Week 6 – baseline	103	−2.3 (−2.9, −1.6)	133	−2.0 (−2.5, −1.4)	−0.3 (−1.1, 0.5)	
Week 12 – baseline	102	−2.9 (−3.6, −2.2)	135	−2.6 (−3.2, −2.0)	−0.3 (−1.2, 0.6)	
Bother (1–4)						0.417
Baseline	107	2.9 (2.8, 3.0)	142	3.0 (2.9, 3.1)	−0.1 (−0.3, 0.0)	
Week 6 – baseline	101	−0.4 (−0.5, −0.3)	132	−0.4 (−0.5, −0.3)	0.0 (−0.1, 0.2)	
Week 12 – baseline	100	−0.6 (−0.7, −0.4)	133	−0.5 (−0.6, −0.4)	0.0 (−0.2, 0.1)	
	Yoga		**Usual Activity**		**Difference**	
Secondary Outcomes	**N**	**Mean (95% CI)**	**N**	**Mean (95% CI)**	**Mean (95% CI)**	**p-value[b]**
ISI Sleep						0.007
Baseline	106	11.8 (10.8, 12.8)	140	12.2 (11.4, 13.1)	−0.4 (−1.8, 0.9)	
Week 12 – baseline	99	−4.4 (−5.4, −3.4)	130	−3.1 (−3.9, −2.4)	−1.3 (−2.5, −0.1)	
PSQI Sleep						0.049
Baseline	102	7.7 (7.1, 8.4)	139	8.4 (7.8, 8.9)	−0.7 (−1.5, 0.2)	
Week 12 – baseline	95	−2.1 (−2.7, −1.4)	131	−1.6 (−2.1, −1.1)	−0.5 (−1.2, 0.3)	
Depression (PHQ-8)						0.028
Baseline	106	4.0 (3.3, 4.7)	140	4.1 (3.5, 4.6)	−0.1 (−1.0, 0.8)	
Week 12 – baseline	99	−0.8 (−1.5, −0.1)	133	0.1 (−0.5, 0.7)	−0.9 (−1.8, 0.1)	
Anxiety (GAD-7)						0.182
Baseline	107	3.2 (2.5, 3.9)	142	3.0 (2.5, 3.5)	0.2 (−0.7, 1.1)	
Week 12 – baseline	101	−0.7 (−1.5, 0.0)	135	−0.1 (−0.7, 0.4)	−0.6 (−1.5, 0.3)	

[a] p-values from contrasts comparing yoga vs. usual activity in a repeated measures linear model of outcome as a function of intervention arm, clinical center, visit (week 6 or 12), omega-3 intervention assignment, and baseline outcome value; $p < 0.025$ was considered statistically significant to account for the two primary outcome comparisons of interest.

[b] p-values from contrasts comparing yoga vs. usual activity in a linear model of outcome as a function of intervention arm, clinical center, omega-3 intervention assignment, and baseline outcome value; $p < 0.0125$ was considered statistically significant to account for the four secondary outcome comparisons of interest.

[c] hot flash frequency values were log transformed for modeling

ISI = Insomnia Severity Index, PSQI = Pittsburgh Sleep Quality Index, PHQ-8= Patient Health Questionaire-8, GAD-7 = Generalized Anxiety Disorder-7