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Efficacy of Exercise for Menopausal Symptoms: A Randomized Controlled Trial

Barbara Sternfeld, PhD[1], **Katherine A. Guthrie, PhD**[2], **Kristine E. Ensrud, MD, MPH**[3], **Andrea Z. LaCroix, PhD**[2], **Joseph C. Larson, MS**[2], **Andrea L. Dunn, PhD**[4], **Garnet L. Anderson, PhD**[2], **Rebecca A. Seguin, PhD**[5], **Janet S. Carpenter, PhD, RN, FAAN**[6], **Katherine M. Newton, PhD**[7], **Susan D. Reed, MD, MPH**[8], **Ellen W. Freeman, PhD**[9], **Lee S. Cohen, MD**[10], **Hadine Joffe, MD, MSc**[10], **Melanie Roberts, MS**[11], and **Bette J. Caan, DrPH**[1]

[1]Division of Research, Kaiser Permanente, Oakland, CA

[2]Fred Hutchison Cancer Research Center, Seattle, WA

[3]University of Minnesota and Minneapolis VA Health Care System, Minneapolis, MN

[4]Klein Buendel, Inc. Denver, CO

[5]Division of Nutritional Sciences, Cornell University, Ithaca, NY

[6]School of Nursing, Indiana University, Indianapolis, IN

[7]Group Health Research Institute, Seattle, WA

[8]University of Washington, Seattle, WA

[9]Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA

[10]Massachusetts General Hospital, Harvard University, Boston, MA

ADDRESS FOR CORRESPONDENCE: Barbara Sternfeld, PhD, Division of Research, 2000 Broadway, Oakland, CA 94612, 510-891-3717 (phone), 510-891-3836 (fax), Barbara.sternfeld@kp.org.

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Dr. Katherine 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.
The network sites that participated in this study were: Seattle, WA (Group Health Research Institute: Principal Investigators Katherine M. Newton, PhD and Susan D. Reed, MD, MPH); Indianapolis, IN (Indiana University; Principal Investigator: Janet S. Carpenter, PhD, RN, FAAN, Lee Learman, MD, PhD,); and Oakland, CA (Kaiser Permanente Division of Research; Principal Investigators: Barbara Sternfeld, PhD and Bette Caan, PhD). The Data Coordinating Center of the network is based at the Fred Hutchinson Cancer Research Center; Principal Investigators: Andrea Z. LaCroix, PhD and Garnet Anderson, PhD. The chairperson is Kris E. Ensrud, MD, University of Minnesota.
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/National Institutes of Health, Bethesda, MD.

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[11]National Institute for Fitness and Sport, Indianapolis, IN

Abstract

OBJECTIVE—To determine efficacy of exercise training for alleviating vasomotor and other menopausal symptoms.

METHODS—Late-peri and post-menopausal, sedentary women with frequent vasomotor symptoms (VMS) participated in a randomized controlled trial conducted at three sites: 106 to exercise and 142 to usual activity. The exercise intervention consisted of individual, facility-based aerobic exercise training 3 times/week for 12 weeks. VMS frequency and bother were recorded on daily diaries at baseline and weeks 6 and 12. Intent to treat analyses compared between group differences in changes in VMS frequency and bother, sleep symptoms (Insomnia Severity Index, Pittsburgh Sleep Quality Index) and mood (Patient Health Questionnaire-8 and Generalized Anxiety Disorder-7 questionnaire).

RESULTS—At the end of week 12, changes in VMS frequency in the exercise group (mean change of −2.4/day, 95% CI −3.0, −1.7) and VMS bother (mean change of −0.5 on a 4 point scale, 95% CI −0.6, −0.4) were not significantly different from those in the control group (−2.6 VMS/day, 95% CI −3.2, −2.0, p=0.43; −0.5 points, 95% CI −0.6, −0.4, p=0.75). The exercise group reported greater improvement in insomnia symptoms (p=0.03), subjective sleep quality (p=0.01), and depressive symptoms (p=0.04), but differences were small and not statistically significant when p values were adjusted for multiple comparisons. Results were similar when considering treatment-adherent women only.

CONCLUSION—These findings provide strong evidence that 12-weeks of moderate-intensity aerobic exercise does not alleviate VMS but may result in small improvements in sleep quality, insomnia and depression in midlife, sedentary women.

Keywords

physical activity; intervention; hot flashes; sleep quality; insomnia symptoms; mood

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Although regular physical activity confers many short- and long-term health benefits, the evidence supporting the popularly held belief that exercise is helpful for alleviating vasomotor symptoms (VMS) (1) remains equivocal (2). Intervention studies are inconsistent (3–7), and about half the observational studies report no association (8–12), the remaining generally suggest a protective association (13–15), and a few report *increased* VMS with higher levels of activity (16; 17). This contradictory evidence, coupled with the many benefits and minimal risks of exercise for midlife women, suggests a clear need for a carefully designed randomized controlled trial (RCT) to test the efficacy of exercise for VMS.

Responding to this need, the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) Research Network conducted a 12-week RCT of aerobic exercise training with previously sedentary women. In this paper, we report the results of the test of the hypothesis that the exercise group would have significantly greater reduction in VMS frequency and bother than a usual activity control group. We also report results from secondary hypotheses exploring effects of exercise training on sleep and mood disturbances.

METHODS

Overview of Study Design

Details about the MsFLASH Research Network and the study design and protocol have been previously published (18; 19). Briefly, the exercise intervention, conducted at three of the five MsFLASH Clinical Centers (Indianapolis, Oakland, and Seattle), was one arm of a 12 week 3-by-2 factorial trial with women randomized in a 3:3:4 ratio to exercise, yoga, or usual activity, and then further randomized in a 1:1 ratio within each arm to 1.8 g/day of omega 3 fish oil or identical appearing placebo capsules. The factorial design ensured that all participants *could believe that they were receiving* some intervention and hence had an expectancy of benefit (20), and reduced the costs for testing several low-risk interventions through a shared control group. No head-to-head comparisons between yoga and exercise were planned, and interactions between the behavioral interventions and omega-3 were hypothesized to be unlikely. This report describes the results of the exercise intervention compared to usual activity; results of the yoga and omega-3 interventions are reported separately.

Following telephone screening, a 2-week VMS diary, and a baseline questionnaire, eligible women attended a baseline visit that included a blood draw, vital signs, a submaximal graded exercise treadmill test, and a second questionnaire. Women then completed a one-week VMS diary and wore a pedometer to assess daily activity behavior before returning for a second visit that included final determination of eligibility and randomization. At week 2, participants were contacted by study staff blinded to omega-3 assignment to encourage study compliance and evaluate tolerance to the study capsules. During weeks 6 and 12 of treatment, participants completed another one-week VMS diary. All other measures were repeated during week 12 or at the final week 12 visit.

Participants were compensated $50.00 after each clinic visit for a possible total of $150.00. The study was approved by the Institutional Review Boards of participating clinical sites and the Data Coordinating Center, and all participants provided written informed consent.

Sample Selection and Randomization

Initial recruitment into the study occurred primarily through mass mailings to age-eligible women, using purchased mailing lists and health-plan enrollment files. Inclusion criteria included being 40–62 years of age, in late peri- or post-menopause or having a hysterectomy with FSH >20 mIU/mL and estradiol ≤50 pg/mL, and in good general health. VMS eligibility criteria were ≥14 VMS/week in each of three consecutive weeks, based on daily diaries, VMS frequency between visits 1 and 2 no less than 50% of weekly mean in the two weeks before visit 1, and VMS rated as severe or bothersome on at least 4 occasions each week. 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; unstable medical conditions; current participation in regular exercise or yoga; current use of omega-3 supplements or frequent consumption of fish; contraindications to exercise training (e.g., physical limitations), yoga, or omega-3 (e.g., allergy to soy or fish; current use of anti-coagulants); or a major depressive episode in the past three months.

Randomization was accomplished through a secure Web-based database, maintained by the MsFLASH Data Coordinating Center, utilizing a dynamic randomization algorithm to maintain comparability between study groups with respect to clinical site. Data collectors were blinded to randomization assignment.

Exercise Training

The exercise intervention consisted of 12 weeks of three individualized cardiovascular conditioning training sessions per week conducted at local fitness facilities and supervised by a trained, certified exercise trainer. Women chose whether to exercise on a treadmill, elliptical trainer, or stationary bicycle. The target heart rate (THR), monitored throughout training with a heart rate monitor (RS100™ Cardiac Monitors, Polar Electro, Inc., Lake Success, NY) was 50–60% heart rate reserve (HRR) (21) for the first month and 60–70% HRR (approximately 125–145 bpm) for the remainder of the intervention. Trainers recorded the THR, workload, and perceived exertion (22) every 5–10 minutes.

All women had the same, progressive energy expenditure goal relative to body weight: 4 kcals/kg in week 1, 8 kcals/kg in week 2, 12 kcals/kg in week 3, and 16 kcals/kg in weeks 4–12 (about 1,000–1,500 kcal/week for most women). Duration typically ranged from 40–60 minutes/session, depending on the workload required to achieve the THR and caloric expenditure, including a short warm-up and cool-down. The progressive energy expenditure and THR goals were based on the need for sedentary women to adapt gradually to exercise over a 4-week period and on the ACSM guidelines for exercise training (21; 23).

Centralized training, weekly observation of trainers, exercise training logs, site visits, and regular conference calls were used to maintain intervention fidelity across trainers and clinical sites.

Usual Activity Control Group

The control group was asked not to change physical activity behavior during the study. At the end, they were given a choice of a one-month membership at a local fitness center or a free yoga workshop, materials, and equipment.

Measurement of VMS

Primary outcomes were VMS frequency and bother based on daily diaries in which participants entered the number of nighttime symptoms upon awakening and daytime symptoms before going to sleep. VMS bother was rated each day on a scale of 1–4 (none, a little, moderately, and a lot). Baseline frequency was calculated from the mean number of VMS reported in a 24-hour period over 14 consecutive days before the first clinic visit. VMS frequency during weeks 6 and 12 was defined similarly, using the corresponding 7-day diaries. Baseline, week 6, and week 12 bother was defined as the means of the daily ratings.

Secondary Outcomes

Self-reported sleep quality and sleep disturbances (Pittsburgh Sleep Quality Index - PSQI (24), insomnia symptoms (Insomnia Severity Index – ISI (25), depressive symptoms (Patient Health Questionnaire - PHQ-8) (26) and anxiety (Generalized Anxiety Disorder questionnaire - GAD-7) (27) were assessed at baseline and week 12. *The PSQI assesses overall sleep quality and sleep disturbances regardless of underlying cause (insomnia and other possible sleep disorders) while the ISI measures severity of insomnia symptoms only.* Higher scores on all scales indicated greater symptomatology.

Covariates

Potential demographic and behavioral correlates of treatment response included self-reported age, race, smoking status, alcohol intake, menopausal status, overall health status, education, employment, and marital status. Body mass index was calculated as kg/m^2, from measured height and weight. Fitness was defined as time to 85% of HRR on a graded

exercise treadmill test conducted at baseline and week 12. Physical activity behavior outside of the intervention was defined as steps/min recorded on a pedometer (NL-1000, New Lifestyles, Lees Summit, MO) worn for one week at baseline and in week 12 and averaged over all minutes of recording over the relevant time period.

Adherence

Adherence was defined in three ways: attendance at ≥80% of training sessions, achievement of ≥80% weekly energy expenditure goal, and achievement of THR (±10 bpm) for ≥50% of exercise time. Documented home-based training sessions were counted for women unable to attend a facility-based session.

Adverse Events

Adverse events were assessed at baseline, during training sessions, and at the final 12-week study visit with a checklist of specific expected side effects of exercise that included back pain, muscle aches and pains, heart palpitations, dizziness, and fainting. Newly emergent adverse events were symptoms or side effects reported in week 12 that were not present at baseline.

Statistical Analysis

A sample of 112 exercise participants and 150 usual activity participants was planned to provide 90% power to detect *a mean difference of 1.9 VMS/day* (a 0.49 standard deviation (SD) reduction in VMS/day, *based on the effect size observed in preliminary data from the first 97 participants enrolled in the MsFLASH escitalopram trial* (28)). *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), and 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.

Outcome analyses included all women randomized to either exercise or usual activity who provided follow-up data, regardless of adherence to study intervention, according to the intention-to-treat principle. Primary analyses compared mean frequency or bother of VMS at 6 and 12 weeks for treatment and control groups using linear regression models adjusted for clinical site, visit (week 6 or 12), omega-3 randomization, and baseline outcome measure. *Because VMS frequency was skewed to the right, raw values raw values were* transformed via natural logarithm to meet model assumptions *or a normally distributed outcome.* Robust standard errors were calculated using generalized estimating equations to account for the correlation between repeated measures of the outcome from each participant. Additional analyses were conducted to assess sensitivity of the model results to a) adjustment for other baseline characteristics that varied between the two groups (age, race, baseline fitness); or b) exclusion of participants who were not adherent to exercise.

Based on *a priori* hypotheses, the possibility of treatment effect modification on VMS frequency by age, race, and baseline values of VMS frequency, BMI, fitness, activity behavior, and overall health was examined by entering appropriate cross product terms into linear regression models with no adjustment for multiple testing.

Secondary analyses also applied linear regression to model changes in sleep and mood as a function of treatment assignment, following a similar approach to that used with primary analyses.

Baseline characteristics, treadmill duration, and pedometer steps of those in the exercise group were compared with those in the usual activity group with t tests for continuous

variables and Chi square tests for categorical variables. A 2-sided p value < 0.025 was considered statistically significant for the two primary outcomes. For the four outcomes examined in 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).

RESULTS

Figure 1 shows the accrual flow with 248 women randomized in a 3:4 ratio as designed: 106 to exercise and 142 to usual activity. Outcome data were available for 97% of participants in each arm. Women randomized to exercise were older (p<0.001) and marginally less fit (p=0.09), but otherwise comparable in terms of menopausal status, race, education, employment status, marital status, body mass index, smoking status, alcohol use, activity behavior, and self-reported overall health (Table 1).

By week 12, the mean increase in treadmill duration was 1.66 minutes in the exercise group compared with 0.05 minutes in the usual activity group (p<0.001). Activity behavior outside of exercise training decreased by 1.5 steps/min in the exercise group compared with an increase of 0.22 steps/min in the usual activity group (p=0.02). Both groups had little change in BMI (−0.12 kg/m^2, 95% CI −0.26, 0.02 in exercise group vs.−0.09 kg/m^2, 95% CI −0.24, 0.06 in control group, p=0.73).

Effect on Vasomotor Symptoms

The exercise group reported a mean decrease of 2.4 hot flashes/day (95% CI 1.7, 3.0), but the usual activity group reported a similar decrease (2.6, 95% CI 2.0, 3.2), and the difference between them was not significant (p=0.43) (Table 2). The exercise group also reported declines in VMS bother, but the between group difference was minimal and not significant (p=0.75). Limiting the analysis to women who adhered to the intervention, defined in terms of training sessions (N=74, Table 2), achievement of energy expenditure goal (N=66, data not shown), or achievement of target heart rate goal (N=75, data not shown), did not change the results.

The effect of exercise on VMS frequency varied significantly by race (p for interaction = 0.03, Table 3), with white women in the exercise group experiencing a decrease relative to usual activity, and African Americans experiencing no benefit. The intervention effect also tended to vary by baseline fitness (p for interaction = 0.06), indicating larger decreases in VMS frequency in the exercise group relative to the control group with higher levels of fitness. There was no evidence of interaction with other baseline characteristics.

Sleep and mood outcomes

The exercise group reported a greater improvement in insomnia symptoms (ISI, p=0.025) and subjective sleep quality (PSQI, p=0.007) between baseline and week 12 than the control group (Table 4). However, group differences were small, and only the improvement in perceived sleep quality, but not insomnia symptoms, was significant at a p level of <0.0125 that accounted for multiple comparisons. The exercise group also experienced a greater decrease in depressive symptoms (PHQ-8) compared to usual activity (p=0.028), but this difference did not meet the defined level of significance set at p<0.0125. There was little evidence that change in anxiety differed between groups. Limiting analyses to adherent women by any of the three definitions did not change the findings (data not shown).

Adverse events and reactions to study

The number of incident adverse events was similar for both groups (17% vs. 18%). No serious adverse events related to the study occurred in either group.

Among women assigned to exercise, 56% were satisfied with the VMS relief they experienced, and 60% thought exercise helped. Ninety five percent wanted to continue to exercise.

DISCUSSION

This study provides strong evidence that 12 weeks of individual, facility-based, moderate-intensity aerobic exercise does not reduce either frequency or bother of VMS more than usual activity in initially sedentary women, and suggests that lack of adherence did not account for the null finding. The results suggest possible, but small, improvements in subjective sleep quality, insomnia symptoms, and depressive symptoms with exercise training, although comparisons were generally not significant at a p level that accounted for multiple comparisons.

The null findings with regard to VMS are consistent with many observational studies. Those studies, however, were generally limited by inadequate statistical power, heterogeneity in menopause status (12; 14; 15; 29), few women with frequent and severe symptoms (14; 15; 30), few women participating in regular, moderate intensity activity (8; 17), lack of adequate control over confounding (16; 29), and inability to establish temporality (31), which hinder drawing strong inferences. Previous randomized trials also do not provide a strong or consistent evidence base related to exercise and VMS. A recent Cochrane review of 3 trials (total of 59 women in exercise) reported an overall standardized mean difference in VMS frequency of −0.14 (95% CI = −0.55, 0.26) for exercise vs. control groups and concluded that no evidence existed to support use of exercise as an effective treatment for VMS (32). In addition, overall findings from a recent Finnish trial also failed to show any effect of 6 months of exercise training on hot flashes or night sweats based on the trial's primary assessment of VMS, although there was a significant decline in night sweats based on a secondary outcome measure (7; 33). With the addition of the present trial, the evidence moves more convincingly towards the conclusion that exercise does not alleviate menopausal VMS in previously sedentary women.

One unanswered question is whether a single bout of exercise has a beneficial acute effect on VMS. A reported decrease in subjectively and objectively measured hot flashes following a single bout of exercise (34) provides partial support for this hypothesis. Also unanswered is whether there is inter-individual variability in the effect of acute or chronic exercise on VMS attributable to physiological or psychological factors, as suggested by Elavsky et al (35). In the current study, the significant interaction between race and treatment group in which exercise reduced VMS frequency in white women but not African Americans may be due to racial differences in cardiovascular, metabolic, and neuroendocrine responses to exercise (36–42). *Also, the border line significant effect modification by baseline fitness in which exercise training appeared to have a positive effect on VMS frequency in those who were most fit may be attributable to genetic variability in the response to exercise* (43). Other factors that may modify the effect of exercise on VMS are self-efficacy and perceived symptom control (3; 35), which were not examined here, but deserve further research.

The current trial suggests that exercise may have potential benefits, albeit small in magnitude, on subjective sleep quality and insomnia and depressive symptoms. Many previous observational studies and trials of physical activity and menopausal symptoms have reported similar findings (5; 10; 14; 29; 44–46), and are consistent with observed exercise effects in other population groups (47–50). Interestingly, many of the proposed biological mechanisms for a positive effect of exercise on sleep and mental health, including increased release of neurotransmitters, increased parasympathetic activation, distraction from stressful stimuli, decreased body weight, and increased fitness (45; 51), have also been proposed as

mechanisms by which exercise could positively impact VMS. Since the MsFLASH trial observed small improvements in sleep and mood with exercise, but not in VMS, the results suggest that poor sleep and depressive symptoms in midlife women may be less a consequence of VMS and more age-related, independent, though frequently co-occurring, symptoms.

One limitation of the MsFLASH trial is the reliance on self-report of VMS. Although objective measurement of VMS might provide a more precise physiological assessment, currently available measures are not recommended for ambulatory clinical trials (52). Also, the current trial tested only one dose of exercise; a higher intensity or greater frequency or more individualized prescription may have had a different effect. *The fact that the exercise group received more attention from the trainer than the control group may be another limitation in terms of the inferences* that can be drawn from the finding of a greater improvement in depressive symptoms. Finally, the findings may only be generalizable to sedentary women with frequent VMS.

Strengths of the MsFLASH trial include the large and adequately powered sample, the factorial design that included omega-3 vs. placebo to control for expectancy of benefit *by offering all participants the possibility of believing they were receiving a treatment*, and the careful monitoring of exercise dose, and high rates of adherence. These strengths reinforce the credibility of the findings.

CONCLUSION

In conclusion, this MsFLASH trial provides strong evidence that aerobic exercise training in previously sedentary women does not significantly alleviate frequent or bothersome VMS. However, exercise training improved fitness level, was safe and well-tolerated, and may have slightly improved subjective sleep quality and symptoms of insomnia and depression. Given these positive outcomes, along with the established health benefits of regular physical activity, the public health implications of this trial are clear: midlife women cannot expect exercise to relieve VMS, but may reasonably expect it to improve how they feel and their overall health.

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NIH staff critically reviewed the study protocol and drafts of the manuscript prior to journal submission.

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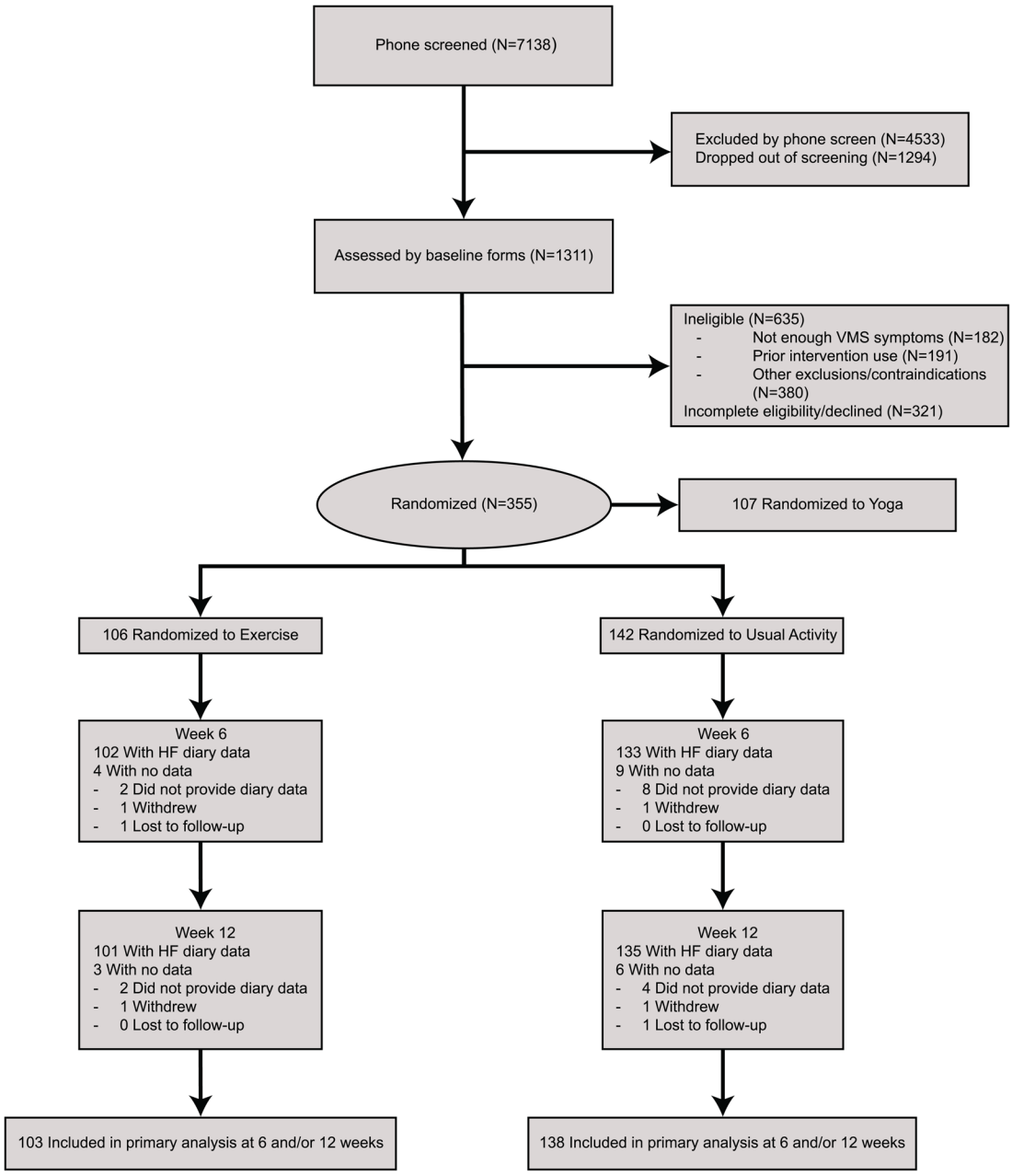

Figure 1.
Recruitment, enrollment, and compliance in the MsFLASH trial of exercise, yoga, and omega-3 supplementation for menopausal symptoms

Table 1

Baseline demographic and clinical characteristics by exercise arm

	Exercise (N =106)		Usual Activity (N =142)	
	N	%	N	%
Age at screening (years), mean (SD)	55.8 (3.6)		54.2 (3.5)	
< 50	2	1.9	10	7.0
50 – 54	43	40.6	69	48.6
55 – 59	40	37.7	51	35.9
60+	21	19.8	12	8.5
Menopause status				
Postmenopausal	90	84.9	116	81.7
Late transition	15	14.2	23	16.2
Early transition	1	0.9	3	2.1
Race				
White	70	66.0	90	63.4
African American	27	25.5	41	28.9
Other	9	8.5	11	7.7
Education				
≤High school diploma/GED	6	5.7	8	5.6
School/training after high school	41	38.7	40	28.2
College graduate	58	54.7	94	66.2
Employment status				
Retired or no employment	17	16.0	18	12.7
Full-time	64	60.4	91	64.1
Part-time	18	17.0	17	12.0
Homemaker	2	1.9	7	4.9
Other	5	4.7	9	6.3
Marital status				
Never married	9	8.5	14	9.9
Divorced	28	26.4	27	19.0
Widowed	2	1.9	3	2.1
Married/living with partner	66	62.3	97	68.3
BMI (m/kg^2), mean (SD)	26.8 (3.9)		26.9 (4.6)	
<25	35	33.0	49	34.5
25 – 29	46	43.4	59	41.5
≥ 30	25	23.6	34	23.9
Smoking				
Never	70	66.0	89	62.7
Past	28	26.4	36	25.4

	Exercise (N =106)		Usual Activity (N =142)	
	N	%	N	%
Current	8	7.5	16	11.3
Alcohol use (drinks/week)				
0	41	38.7	51	35.9
1–<7	46	43.4	62	43.7
7+	19	17.9	27	19.0
Treadmill test duration (min), mean (SD)	9.63 (2.94)		10.26 (2.90)	
Usual activity (steps/min), mean (SD)	8.41 (4.52)		7.91 (4.08)	
Self-reported health				
Excellent	16	15.1	24	16.9
Very good	47	44.3	70	49.3
Good	40	37.7	40	28.2
Fair	2	1.9	8	5.6
Clinical center				
Indianapolis	34	32.1	48	33.8
Oakland	33	31.1	44	31.0
Seattle	39	36.8	50	35.2

Table 2

Change in vasomotor symptoms by exercise arm

Intent to Treat Analysis[1]	N	Exercise Mean (95% CI)	N	Usual Activity Mean (95% CI)	Difference Mean (95% CI)	p-value[2]
Hot flashes / day[3]						0.434
Baseline	106	7.3 (6.7, 7.9)	142	8.0 (7.3, 8.7)	−0.7 (−1.6, 0.2)	
Week 6 – baseline	102	−2.0 (−2.6, −1.4)	133	−2.0 (−2.5, −1.4)	−0.1 (−0.9, 0.7)	
Week 12 – baseline	101	−2.4 (−3.0, −1.7)	135	−2.6 (−3.2, −2.0)	0.2 (−0.6, 1.1)	
Bother (1–4)						0.745
Baseline	106	2.9 (2.8, 3.0)	142	3.0 (2.9, 3.1)	−0.1 (−0.2, 0.0)	
Week 6 – baseline	102	−0.4 (−0.5, −0.3)	132	−0.4 (−0.5, −0.3)	0.0 (−0.1, 0.1)	
Week 12 – baseline	100	−0.5 (−0.6, −0.4)	133	−0.5 (−0.6, −0.4)	0.0 (−0.1, 0.2)	
Sensitivity Analysis[4]	**N**	**Exercise Mean (95% CI)**	**N**	**Usual Activity Mean (95% CI)**	**Difference Mean (95% CI)**	**p-value[2]**
Hot flashes / day[3]						0.708
Baseline	106	7.3 (6.7, 7.9)	142	8.0 (7.3, 8.7)	−0.7 (−1.6, 0.2)	
Week 6 – baseline	79	−1.9 (−2.6, −1.2)	133	−2.0 (−2.5, −1.4)	0.0 (−0.9, 0.9)	
Week 12 – baseline	74	−2.5 (−3.2, −1.7)	135	−2.6 (−3.2, −2.0)	0.1 (−0.8, 1.1)	
Bother (1–4)						0.628
Baseline	106	2.9 (2.8, 3.0)	142	3.0 (2.9, 3.1)	−0.1 (−0.2, 0.0)	
Week 6 – baseline	79	−0.4 (−0.5, −0.3)	132	−0.4 (−0.5, −0.3)	0.0 (−0.1, 0.2)	
Week 12 – baseline	74	−0.5 (−0.6, −0.4)	133	−0.5 (−0.6, −0.4)	0.0 (−0.2, 0.2)	

[1] includes all participants with follow-up measures, regardless of adherence to intervention

[2] p-values from contrasts comparing exercise 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. A p-value < 0.025 was considered statistically significant when accounting for the 2 primary outcome comparisons of interest.

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

[4] includes only participants with ≥ 80% total session attendance for the given time interval

Table 3

Change in frequency of vasomotor symptoms from baseline to week 12 by exercise arm: subgroup analysis by selected baseline characteristics

	Exercise		Usual Activity				
Characteristic	**N**	**Difference[1]**	**N**	**Difference[1]**	**% Change[2] (95% CI)**		**p for interaction[3]**
BMI (kg/m^2)							0.375
< 25	33	−2.27	49	−3.10	−3.5	(−20.5, 17.1)	
25 - <30	43	−2.67	53	−2.40	−7.5	(−24.0, 12.6)	
≥30	25	−1.96	33	−2.19	−1.2	(−21.6, 24.3)	
GXT Treadmill Duration							0.056
≤8.5 minutes	37	−2.07	36	−2.95	7.6	(−12.0, 31.5)	
8.5 –11 minutes	31	−2.06	54	−2.97	−3.5	(−22.5, 20.1)	
> 11 minutes	33	−2.98	45	−1.88	−16.2	(−31.8, 3.0)	
Race							0.028
African American	27	−2.38	38	−3.64	18.4	(−7.2, 50.9)	
White	66	−2.30	86	−2.07	−14.5	(−26.1, −1.0)	
Age							0.939
< 55	41	−3.07	74	−2.42	−10.1	(−24.8, 7.5)	
≥55	60	−1.88	61	−2.83	0.1	(−14.2, 18.7)	
Self Reported Health							0.338
Excellent / VG	60	−2.37	90	−2.46	−9.2	(−21.6, 5.2)	
Good / Fair	40	−2.39	45	−2.89	2.9	(−16.3, 26.6)	
Hot Flashes/day							0.192
< 9	71	−1.40	87	−1.73	−4.6	(−19.0, 12.5)	
≥ 9	30	−4.63	48	−4.19	−13.6	(−29.4, 5.9)	
Pedometer Steps/min							0.379
< 7	39	−1.91	64	−2.39	−6.8	(−22.7, 12.5)	
≥ 7	55	−2.64	63	−2.74	−3.7	(−17.7, 12.8)	

[1] Week 12 – baseline difference

[2] percentage change in hot flashes in the exercise group relative to the usual activity group

[3] interaction p-values for continuous variables are computed from the interaction term between the continuous subgroup variable of interest and treatment arm in a separate model.

Table 4

Change in secondary outcomes (sleep and mood) by exercise arm

Intent to Treat Analysis[1]	N	Exercise Mean (95% CI)	N	Usual Activity Mean (95% CI)	Difference Mean (95% CI)	p-value[2]
ISI Sleep						0.025
Baseline	104	11.5 (10.4, 12.7)	140	12.2 (11.4, 13.1)	−0.7 (−2.1, 0.7)	
Week 12 – baseline	80	−4.0 (−5.1, −2.9)	130	−3.1 (−3.9, −2.4)	−0.9 (−2.2, 0.4)	
PSQI Sleep						0.007
Baseline	103	7.8 (7.1, 8.5)	139	8.4 (7.8, 8.9)	−0.6 (−1.4, 0.2)	
Week 12 – baseline	79	−2.4 (−3.1, −1.7)	131	−1.6 (−2.1, −1.1)	−0.8 (−1.6, 0.0)	
Depression (PHQ-8)						0.028
Baseline	105	4.0 (3.2, 4.8)	140	4.1 (3.5, 4.6)	−0.1 (−1.1, 0.9)	
Week 12 – baseline	78	−0.9 (−1.6, −0.1)	133	0.1 (−0.5, 0.7)	−1.0 (−2.0, 0.0)	
Anxiety (GAD-7)						0.156
Baseline	106	3.4 (2.6, 4.2)	142	3.0 (2.5, 3.5)	0.4 (−0.5, 1.3)	
Week 12 – baseline	82	−0.8 (−1.6, −0.1)	135	−0.1 (−0.7, 0.4)	−0.7 (−1.6, 0.2)	

[1] includes all participants with follow-up measures, regardless of adherence to intervention

[2] p-values from contrasts comparing exercise 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. A p-value < 0.0125 was considered statistically significant when accounting for the 4 secondary outcome comparisons of interest.

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