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Efficacy of exercise for menopausal symptoms: a randomized controlled trial

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Abstract

Objective: This study aims to determine the efficacy of exercise training for alleviating vasomotor and other menopausal symptoms.

Methods: Late perimenopausal and postmenopausal sedentary women with frequent vasomotor symptoms (VMS) participated in a randomized controlled trial conducted in three sites: 106 women randomized to exercise and 142 women randomized to usual activity. The exercise intervention consisted of individual facility-based aerobic exercise training three times per week for 12 weeks. VMS frequency and bother were recorded on daily diaries at baseline and on weeks 6 and 12. Intent-to-treat analyses compared between-group differences in changes in VMS frequency and bother, sleep symptoms (Insomnia Severity Index and 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, −2.4 VMS/d; 95% CI, −3.0 to −1.7) and VMS bother (mean change on a four-point scale, −0.5; 95% CI, −0.6 to −0.4) were not significantly different from those in the control group (−2.6 VMS/d; 95% CI, −3.2 to −2.0; $P = 0.43$; −0.5 points; 95% CI, −0.6 to −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.

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

Key Words: Physical activity – Intervention – Hot flashes – Sleep quality – Insomnia symptoms – Mood.

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Although regular physical activity confers many short-term and long-term health benefits, 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]: about half of observational studies report no association,[8-12] the remaining studies generally suggest a protective association,[13-15] and a few studies 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 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 randomized controlled trial of aerobic exercise training with previously sedentary women. In this article, we report the results of hypothesis testing (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 the 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 in three of five MsFLASH Clinical Centers (Indianapolis, Oakland, and Seattle), was one arm of a 12-week 3 × 2 factorial trial, with women randomized (3:3:4) to exercise, yoga, or usual activity and further randomized (1:1) within each arm to 1.8 g/day ω-3 fish oil or identically 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 it also 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 behavioral interventions and ω-3 were hypothesized to be unlikely. This report describes the results of the exercise intervention compared with usual activity. The results of the yoga and ω-3 interventions are reported separately.

After telephone screening, a 2-week VMS diary, and a baseline questionnaire, eligible women attended a baseline visit, which included a blood draw, vital signs, a submaximal graded exercise treadmill test, and a second questionnaire. Women completed a 1-week VMS diary and wore a pedometer to assess daily activity behavior before returning for a second visit, which included final determination of eligibility and randomization. On week 2, participants were contacted by study staff blinded to ω-3 assignment to encourage study compliance and evaluate tolerance to the study capsules. During weeks 6 and 12 of treatment, participants completed another 1-week VMS diary. All other measures were repeated during week 12 or at the final week 12 visit.

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

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 the following: aged 40 to 62 years, late perimenopausal or postmenopausal or had had hysterectomy with follicle-stimulating hormone levels higher than 20 mIU/mL and estradiol levels of 50 pg/mL or less, and in good general health. VMS eligibility criteria were as follows: 14 or more VMS/week in each of three consecutive weeks, based on daily diaries; VMS frequency between visits 1 and 2 no less than 50% of the weekly mean in the 2 weeks before visit 1; and VMS rated as severe or bothersome on at least four occasions each week. Exclusion criteria included the following: body mass index (BMI) higher than 37 kg/m^2; use of hormones or hormonal contraceptives in the past 2 months; use of prescription or over-the-counter treatments for VMS in the past month; unstable medical conditions; current participation in regular exercise or yoga; current use of ω-3 supplements or frequent consumption of fish; contraindications to exercise training (eg, physical limitations), yoga, or ω-3 (eg, allergy to soy or fish; current use of anticoagulants); or a major depressive episode in the past 3 months.

Randomization was accomplished through a secure Web-based database, maintained by the MsFLASH Data Coordinating Center, using 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, an elliptical trainer, or a stationary bicycle. Target heart rate (THR), monitored throughout training with a heart rate monitor (RS100™ Cardiac Monitors; Polar Electro Inc, Lake Success, NY), was 50% to 60% of heart rate reserve (HRR)[21] for the first month and 60% to 70% of HRR (approximately 125-145 beats/min) for the remainder of the intervention. Trainers recorded THR, workload, and perceived exertion[22] every 5 to 10 minutes.

All women had the same progressive energy expenditure goal relative to body weight: 4 kcal/kg on week 1, 8 kcal/kg on week 2, 12 kcal/kg on week 3, and 16 kcal/kg on weeks 4 to 12 (about 1,000-1,500 kcal/wk for most women). Duration typically ranged from 40 to 60 minutes/session, depending on the workload required to achieve THR and energy expenditure,

including a short warm-up and cool-down. The progressive energy expenditure and THR goals were based on sedentary women's need to adapt gradually to exercise during a 4-week period and on the American College of Sports Medicine 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 choices: a 1-month membership at a local fitness center or 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 the number of daytime symptoms before going to sleep. VMS bother was rated each day on a scale from 1 to 4 (1, none; 2, a little; 3, moderately; 4, a lot). Baseline frequency was calculated from the mean number of VMS reported in a 24-hour period for 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 were defined as the means of 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-8),[26] and anxiety symptoms (Generalized Anxiety Disorder-7 questionnaire [GAD-7])[27] were assessed at baseline and on week 12. The PSQI assesses overall sleep quality and sleep disturbances regardless of underlying cause (insomnia and other possible sleep disorders), whereas the ISI measures the severity of insomnia symptoms only. Higher scores on all scales indicated greater symptoms.

Covariates

Potential demographic and behavioral correlates of treatment response included self-reported age, race, smoking status, alcohol intake, menopause status, overall health status, education, employment, and marital status. BMI was measured from measured height and weight (calculated as kg/m^2). Fitness was defined as time to 85% of HRR on a graded exercise treadmill test conducted at baseline and on week 12. Physical activity behavior outside the intervention was defined as steps per minute recorded on a pedometer (NL-1000; New Lifestyles, Lees Summit, MO) worn for 1 week at baseline and on week 12 and averaged across all minutes of recording during the relevant period.

Adherence

Adherence was defined in three ways: attendance at 80% or more of training sessions, achievement of 80% or more of weekly energy expenditure goal, and achievement of THR (+10 beats/min) for 50% or more of exercise time. Documented home-based training sessions were counted for women who were 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 adverse effects of exercise, including back pain, muscle aches and pains, heart palpitations, dizziness, and fainting. Newly emergent adverse events were symptoms or adverse effects reported on 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-SD reduction in VMS per 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 a two-sided significance level of 0.025 to account for two primary outcomes (VMS frequency and VMS bother) and allowed for 10% loss to follow-up in both arms and an extra 10% loss to follow-up 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 intent-to-treat principle. Primary analyses compared the 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), ω-3 randomization, and baseline outcome measure. Because VMS frequency was skewed to the right, raw values were transformed via natural logarithm to meet model assumptions or a normally distributed outcome. Robust standard errors were calculated with generalized estimating equations to account for the correlation between repeated measures of the outcome from each participant. Additional analyses were conducted to assess the sensitivity of the model results to (a) adjustment for other baseline characteristics that varied between the two groups (age, race, and 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 an approach similar 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, using t tests for continuous variables and χ^2 tests for categorical variables. Two-sided $P < 0.025$ was considered statistically significant for the two primary outcomes. For the four outcomes examined in secondary analyses, $P < 0.0125$ was considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Figure 1 shows accrual flow with 248 women randomized (106 randomized to exercise and 142 randomized to usual activity) in a 3:4 ratio, as designed. 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 on menopause status, race, education, employment status, marital status, BMI, 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 exercise training decreased by 1.5 steps/minute in the exercise group compared with an increase of 0.22 steps/minute in the usual-activity group ($P = 0.02$). There was little change in BMI in the exercise group (-0.12 kg/m^2; 95% CI, -0.26 to 0.02) and the control group (-0.09 kg/m^2; 95% CI, -0.24 to 0.06; $P = 0.73$).

Effect on VMS

The exercise group reported a mean decrease of 2.4 hot flashes/day (95% CI, 1.7 to 3.0), but the usual-activity group reported a similar decrease (2.6; 95% CI, 2.0 to 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 by training sessions

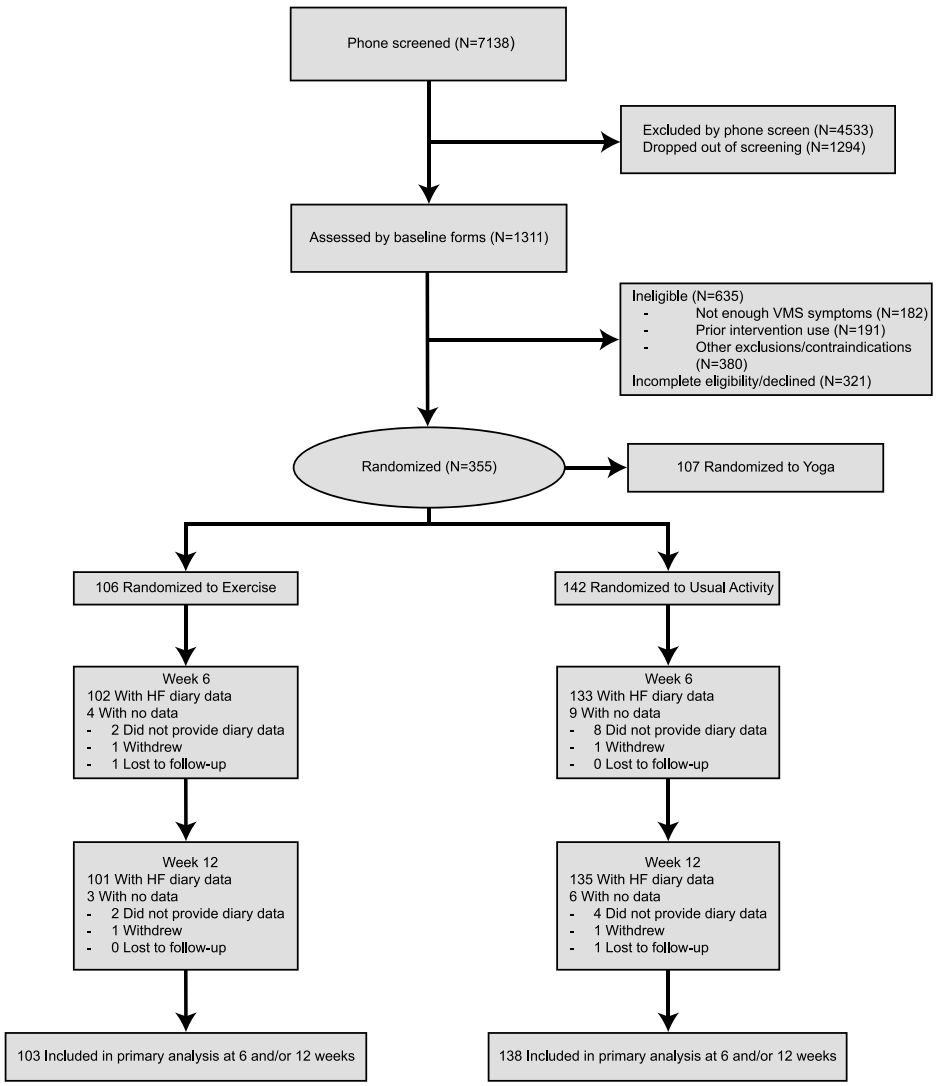

FIG. 1. Recruitment, enrollment, and compliance in the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) trial of exercise, yoga, and ω-3 supplementation for menopausal symptoms. VMS, vasomotor symptoms; HF, hot flushes.

TABLE 1. *Baseline demographic and clinical characteristics by exercise arm*

	Exercise (n = 106)	Usual activity (n = 142)
Age at screening, mean (SD), y	55.8 (3.6)	54.2 (3.5)
Age at screening, n (%)		
<50 y	2 (1.9)	10 (7.0)
50-54 y	43 (40.6)	69 (48.6)
55-59 y	40 (37.7)	51 (35.9)
≥60 y	21 (19.8)	12 (8.5)
Menopause status, n (%)		
Postmenopause	90 (84.9)	116 (81.7)
Late transition	15 (14.2)	23 (16.2)
Early transition	1 (0.9)	3 (2.1)
Race, n (%)		
White	70 (66.0)	90 (63.4)
African American	27 (25.5)	41 (28.9)
Other	9 (8.5)	11 (7.7)
Education, n (%)		
High school diploma/GED or less	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, n (%)		
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, n (%)		
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)
Body mass index, mean (SD), kg/m^2	26.8 (3.9)	26.9 (4.6)
Body mass index, n (%)		
<25 kg/m^2	35 (33.0)	49 (34.5)
25-29 kg/m^2	46 (43.4)	59 (41.5)
≥30 kg/m^2	25 (23.6)	34 (23.9)
Smoking, n (%)		
Never	70 (66.0)	89 (62.7)
Past	28 (26.4)	36 (25.4)
Current	8 (7.5)	16 (11.3)
Alcohol use, n (%)		
0	41 (38.7)	51 (35.9)
1 to <7 drinks/wk	46 (43.4)	62 (43.7)
≥7 drinks/wk	19 (17.9)	27 (19.0)
Treadmill test duration, mean (SD), min	9.63 (2.94)	10.26 (2.90)
Usual activity, mean (SD), steps/min	8.41 (4.52)	7.91 (4.08)
Self-reported health, n (%)		
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, n (%)		
Indianapolis	34 (32.1)	48 (33.8)
Oakland	33 (31.1)	44 (31.0)
Seattle	39 (36.8)	50 (35.2)

(n = 74; Table 2), achievement of energy expenditure goal (n = 66; data not shown), or achievement of THR 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 with African-American women 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 greater improvement in insomnia symptoms (ISI; $P = 0.025$) and subjective sleep quality (PSQI; $P = 0.007$) between baseline and week 12 compared with 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 $P < 0.0125$, accounting for multiple comparisons. The exercise group also experienced a greater decrease in depressive symptoms (Patient Health Questionnaire-8) compared with 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 the analyses to adherent women by any of the three definitions did not change the findings (data not shown).

Adverse events and reactions to the 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 of the women wanted to continue exercising.

DISCUSSION

This study provides strong evidence that 12 weeks of individual, facility-based, moderate-intensity aerobic exercise do not reduce either VMS frequency or VMS bother more than usual activity in initially sedentary women and suggests that lack of adherence did not account for the null findings. 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 on 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 on confounding,[16,29] and inability to establish temporality,[31] which hinder drawing of 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 three trials (total of 59 women in exercise) reported an overall standardized mean difference in VMS frequency of −0.14 (95% CI, −0.55 to 0.26) for exercise versus control groups and concluded that there was no evidence to support the use of exercise as an effective treatment of 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

TABLE 2. *Changes in vasomotor symptoms by exercise arm*

	Exercise		Usual activity		Difference	
	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	P^a
Intent-to-treat analysis[b]						
Hot flashes per day[c]						0.434
Baseline	106	7.3 (6.7 to 7.9)	142	8.0 (7.3 to 8.7)	−0.7 (−1.6 to 0.2)	
Week 6 to baseline	102	−2.0 (−2.6 to −1.4)	133	−2.0 (−2.5 to −1.4)	−0.1 (−0.9 to 0.7)	
Week 12 to baseline	101	−2.4 (−3.0 to −1.7)	135	−2.6 (−3.2 to −2.0)	0.2 (−0.6 to 1.1)	
Bother (1-4)						0.745
Baseline	106	2.9 (2.8 to 3.0)	142	3.0 (2.9 to 3.1)	−0.1 (−0.2 to 0.0)	
Week 6 to baseline	102	−0.4 (−0.5 to −0.3)	132	−0.4 (−0.5 to −0.3)	0.0 (−0.1 to 0.1)	
Week 12 to baseline	100	−0.5 (−0.6 to −0.4)	133	−0.5 (−0.6 to −0.4)	0.0 (−0.1 to 0.2)	
Sensitivity analysis[d]						
Hot flashes per day[c]						0.708
Baseline	106	7.3 (6.7 to 7.9)	142	8.0 (7.3 to 8.7)	−0.7 (−1.6 to 0.2)	
Week 6 to baseline	79	−1.9 (−2.6 to −1.2)	133	−2.0 (−2.5 to −1.4)	0.0 (−0.9 to 0.9)	
Week 12 to baseline	74	−2.5 (−3.2 to −1.7)	135	−2.6 (−3.2 to −2.0)	0.1 (−0.8 to 1.1)	
Bother (1-4)						0.628
Baseline	106	2.9 (2.8 to 3.0)	142	3.0 (2.9 to 3.1)	−0.1 (−0.2 to 0.0)	
Week 6 to baseline	79	−0.4 (−0.5 to −0.3)	132	−0.4 (−0.5 to −0.3)	0.0 (−0.1 to 0.2)	
Week 12 to baseline	74	−0.5 (−0.6 to −0.4)	133	−0.5 (−0.6 to −0.4)	0.0 (−0.2 to 0.2)	

[a]*P* values from contrasts comparing exercise with usual activity in a repeated-measures linear model of outcome as a function of intervention arm, clinical center, visit (week 6 or 12), ω-3 intervention assignment, and baseline outcome value. $P < 0.025$ was considered statistically significant when the two primary outcome comparisons of interest were accounted for.
[b]Includes all participants with follow-up measures, regardless of adherence to intervention.
[c]Hot flash frequency values were log-transformed for modeling.
[d]Includes only participants with 80% or more total session attendance for the given time interval.

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 toward 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 short-term effect on VMS. A reported

TABLE 3. *Changes in the frequency of vasomotor symptoms from baseline to week 12 by exercise arm: subgroup analysis by selected baseline characteristics*

	Exercise		Usual activity			
Characteristic	n	Difference[c]	n	Difference[c]	% Change[a] (95% CI)	*P* for interaction[b]
Body mass index						0.375
<25 kg/m^2	33	−2.27	49	−3.10	−3.5 (−20.5 to 17.1)	
25 to <30 kg/m^2	43	−2.67	53	−2.40	−7.5 (−24.0 to 12.6)	
≥30 kg/m^2	25	−1.96	33	−2.19	−1.2 (−21.6 to 24.3)	
GXT treadmill duration						0.056
≤8.5 min	37	−2.07	36	−2.95	7.6 (−12.0 to 31.5)	
8.6-11 min	31	−2.06	54	−2.97	−3.5 (−22.5 to 20.1)	
>11 min	33	−2.98	45	−1.88	−16.2 (−31.8 to 3.0)	
Race						0.028
African American	27	−2.38	38	−3.64	18.4 (−7.2 to 50.9)	
White	66	−2.30	86	−2.07	−14.5 (−26.1 to −1.0)	
Age						0.939
<55 y	41	−3.07	74	−2.42	−10.1 (−24.8 to 7.5)	
≥55 y	60	−1.88	61	−2.83	0.1 (−14.2 to 18.7)	
Self reported health						0.338
Excellent/very good	60	−2.37	90	−2.46	−9.2 (−21.6 to 5.2)	
Good/fair	40	−2.39	45	−2.89	2.9 (−16.3 to 26.6)	
Hot flashes per day						0.192
<9	71	−1.40	87	−1.73	−4.6 (−19.0 to 12.5)	
≥9	30	−4.63	48	−4.19	−13.6 (−29.4 to 5.9)	
Pedometer						0.379
<7 steps/min	39	−1.91	64	−2.39	−6.8 (−22.7 to 12.5)	
≥7 steps/min	55	−2.64	63	−2.74	−3.7 (−17.7 to 12.8)	

[a]Percentage change in hot flashes in the exercise group relative to the usual-activity group.
[b]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.
[c]Week 12 to baseline difference.

TABLE 4. *Changes in secondary outcomes (sleep and mood) by exercise arm*

	Exercise		Usual activity		Difference	P^b
Intent-to-treat analysis[a]	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	
Insomnia Severity Index sleep						0.025
Baseline	104	11.5 (10.4 to 12.7)	140	12.2 (11.4 to 13.1)	−0.7 (−2.1 to 0.7)	
Week 12 to baseline	80	−4.0 (−5.1 to −2.9)	130	−3.1 (−3.9 to −2.4)	−0.9 (−2.2 to 0.4)	
Pittsburgh Sleep Quality Index sleep						0.007
Baseline	103	7.8 (7.1 to 8.5)	139	8.4 (7.8 to 8.9)	−0.6 (−1.4 to 0.2)	
Week 12 to baseline	79	−2.4 (−3.1 to −1.7)	131	−1.6 (−2.1 to −1.1)	−0.8 (−1.6 to 0.0)	
Depression (Patient Health Questionnaire-8)						0.028
Baseline	105	4.0 (3.2 to 4.8)	140	4.1 (3.5 to 4.6)	−0.1 (−1.1 to 0.9)	
Week 12 to baseline	78	−0.9 (−1.6 to −0.1)	133	0.1 (−0.5 to 0.7)	−1.0 (−2.0 to 0.0)	
Anxiety (Generalized Anxiety Disorder-7 questionnaire)						0.156
Baseline	106	3.4 (2.6 to 4.2)	142	3.0 (2.5 to 3.5)	0.4 (−0.5 to 1.3)	
Week 12 to baseline	82	−0.8 (−1.6 to −0.1)	135	−0.1 (−0.7 to 0.4)	−0.7 (−1.6 to 0.2)	

[a]Includes all participants with follow-up measures, regardless of adherence to intervention.
[b]*P* values from contrasts comparing exercise with usual activity in a linear model of outcome as a function of intervention arm, clinical center, ω-3 intervention assignment, and baseline outcome value. $P < 0.0125$ was considered statistically significant when the four secondary outcome comparisons of interest were accounted for.

decrease in subjectively and objectively measured hot flashes after a single bout of exercise[34] provides partial support for this hypothesis. Another unanswered question is whether there is interindividual variability in the effects of short-term or long-term 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 in African-American women, may be attributable to racial differences in cardiovascular, metabolic, and neuroendocrine responses to exercise.[36-42] Furthermore, the borderline significant effect modification by baseline fitness, where exercise training seemed to have a positive effect on VMS frequency in those who were fittest, 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—on subjective sleep quality, insomnia symptoms, 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 on 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. Because 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 a consequence of age-related, independent, but frequently co-occurring symptoms.

One limitation of the MsFLASH trial is its reliance on self-reports of VMS. Although objective measurements 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, a greater frequency, or a 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.

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

CONCLUSIONS

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 improves fitness level, is safe and well-tolerated, and may slightly improve 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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