REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Menopausal quality of life: RCT of yoga, exercise, and omega-3 supplements

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OBJECTIVE: The purpose of this study was to determine the efficacy of 3 nonhormonal therapies for the improvement of menopause-related quality of life in women with vasomotor symptoms.

STUDY DESIGN: We conducted a 12-week 3 × 2 randomized, controlled, factorial design trial. Peri- and postmenopausal women, 40-62 years old, were assigned randomly to yoga (n = 107), exercise (n = 106), or usual activity (n = 142) and also assigned randomly to a double-blind comparison of omega-3 (n = 177) or placebo (n = 178) capsules. We performed the following interventions: (1) weekly 90-minute yoga classes with daily at-home practice, (2) individualized facility-based aerobic exercise training 3 times/week, and (3) 0.615 g omega-3 supplement, 3 times/day. The outcomes were assessed with the following scores: Menopausal Quality of Life Questionnaire (MENQOL) total and domain (vasomotor symptoms, psychosocial, physical and sexual).

RESULTS: Among 355 randomly assigned women who average age was 54.7 years, 338 women (95%) completed 12-week assessments. Mean baseline vasomotor symptoms frequency was 7.6/day, and the mean baseline total MENQOL score was 3.8 (range, 1−8 from better to worse) with no between-group differences. For yoga compared to usual activity, baseline to 12-week improvements were seen for MENQOL total −0.3 (95% confidence interval, −0.6 to 0; $P = .02$), vasomotor symptom domain ($P = .02$), and sexuality domain ($P = .03$) scores. For women who underwent exercise and omega-3 therapy compared with control subjects, improvements in baseline to 12-week total MENQOL scores were not observed. Exercise showed benefit in the MENQOL physical domain score at 12 weeks ($P = .02$).

CONCLUSION: All women become menopausal, and many of them seek medical advice on ways to improve quality of life; little evidence-based information exists. We found that, among healthy sedentary menopausal women, yoga appears to improve menopausal quality of life; the clinical significance of our finding is uncertain because of the modest effect.

Key words: exercise, menopause, omega-3, quality of life, randomized controlled trial, yoga

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More than 38 million US women who are 45-64 years old (88%) experience daytime hot flashes or night sweats during the menopausal transition.[1] Hot flashes and night sweats or vasomotor symptoms (VMS) are the cardinal symptoms of menopause. However, other menopausal symptoms, which often are affected adversely by VMS frequency and bother[2] (such as sleep and mood disturbances, pain, difficulty concentrating, and diminished energy) can affect daily functioning in work and social, leisure and sexual activities.[3] Medical resources that have been expended to alleviate these problems are substantial,[4] and there is a compelling need for effective treatments to relieve menopausal symptoms in midlife women.

Among symptomatic peri- and postmenopausal women with VMS, hormone therapy has demonstrated an improvement in quality of life (QOL).[5] Because of the risks associated with hormone therapy among postmenopausal women,[6] alternative lower risk

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behavioral therapies have been proposed for the treatment of VMS. Studies regarding the benefit of behavioral interventions for improving menopause-related QOL are less robust but suggest that yoga[7-12] and exercise[13,14] may be beneficial. Findings across studies have been inconsistent, perhaps because of different measures and outcomes of interest.[14] Yoga findings, in particular, are limited by a paucity of studies, small sample sizes, and lack of control groups.

Nonphytoestrogenic supplements are used widely by midlife women but have not been examined specifically for improved midlife QOL.[15] Omega-3 supplements that contain polyunsaturated fatty acids are among the most widely consumed supplements for a variety of medical conditions.[16] Studies suggest that omega-3s modulate serotonergic and dopaminergic neurotransmission[17-19] and may alleviate VMS.[20] Two small randomized trials have examined the efficacy of omega-3s in the treatment of VMS[20,21] with conflicting results.

We conducted a factorial design randomized controlled trial to evaluate the efficacy of yoga, exercise, and omega-3s on VMS frequency and bother. We found no benefit from any of these interventions for VMS, but we found suggestive evidence that self-reported sleep quality and depressive symptoms improved slightly with exercise and yoga (findings previously reported, not adjusted for multiple comparisons).[22-25] In this analysis, we report findings on the impact of yoga, exercise, and omega-3s on menopause-related QOL.

MATERIALS AND METHODS

Study design

Details about the Menopause strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) Research Network, study design, and protocols have been published.[22-26] Briefly, we performed a multisite, 3 by 2 factorial randomized controlled trial. Eligible women were assigned randomly to 12 weeks of yoga, exercise, or usual activity and simultaneously were assigned randomly to 1.8 g/day of omega-3 or placebo capsules. The study was approved by the institutional review boards of all clinical sites and the Data Coordinating Center; all participants provided written informed consent. The Data Coordinating Center performed centralized training and monitored maintenance of the standardized protocol, fidelity to the intervention, and participant adherence.

Eligibility, screening, randomization, and blinding

Participants were recruited from February 2011 through January 2012 primarily by mass-mailing to women who were 40-62 years old with the use of purchased lists and health-plan enrollment files at 3 sites (Indianapolis, IN, Oakland, CA, and Seattle, WA). Eligible women were in the menopausal or postmenopausal transition. Screening was performed centrally with standardized inclusion, exclusion, and final eligibility criteria across sites.[22,24]

Randomization was conducted in a secure central web-based database, with the use of a dynamic randomization algorithm to maintain comparability between study groups with respect to clinical site. An unequal allocation was used for the behavioral interventions (3:3:4; yoga:exercise:control), and equal allocation was used for omega-3 and placebo treatments, which were provided in masked identical capsules and containers.

Interventions

Yoga

The yoga intervention (studio and home practice)[24,26] emphasized a practice of "cooling" breathing exercises, 11-13 poses (Asana Yoga: restorative, inverted, lateral bends or twists, forward bends, and counter-poses), which had been suggested previously for VMS relief,[7,27] and guided meditation (Yoga Nidra). Instruction was provided during 12 weekly 90-minute classes. Daily home practice was expected for 20 minutes on days when class was not attended.

Exercise

The exercise intervention[23,24] consisted of 12 weeks of 3 individual cardiovascular conditioning training sessions/

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week at local fitness facilities that were supervised by trained, certified exercise trainers. The targeted training heart rate was 50-60% of the heart rate reserve for the first month and 60-70% for the remainder of the intervention (approximately 125-145 beats/minute). Women exercised 40-60 minutes per session to achieve the energy expenditure goal of 16 kcal/kg (approximately 1000-1500 kcals/week).

Usual activity

Women in the usual activity group[23,24,26] were instructed to follow their usual physical activity behavior and were asked not to begin yoga or a new exercise regimen.

Omega-3 and placebo capsules

To standardize the expectation of benefit, all women in both behavioral interventions and the usual activity group received either a placebo that contained olive oil or an active omega-3 capsule.[25] The omega-3 supplement contained 425 mg ethyl eicosapentaenoic acid, 100 mg docosahexaenoic acid, and 90 mg of other omega-3s. All capsules (placebo and omega-3) contained natural lemon oil, rosemary extract, and vitamin E.

Follow-up and compensation

Participants were contacted by study staff members who were masked to pill randomization assignment to encourage pill compliance and to evaluate tolerance at 2 and 6 weeks. Participants were compensated $50 after each clinic visit for a possible total of $150.

Data collection

Outcomes (baseline to 12-week change): Menopausal Quality of Life Questionnaire, total and specific domain scores

The Menopausal Quality of Life Questionnaire (MENQOL; range, 1−8) is a 29-item assessment of menopause-related QOL.[28] Scoring generates a total score and 4 domain scores (vasomotor, physical, psychosocial, sexual functioning); higher scores on all scales indicate poorer QOL. Women were asked whether an item was experienced in the past 4 weeks. Each item score includes nonendorsement "1" or endorsement "2" plus the bother score (0-6) for a maximum score of 8. The domain-specific score is the mean of the item scores within that domain. The total MENQOL score is the mean of the specific domain scores. Validity, internal consistency, reliability, and responsiveness to change are adequate to excellent.[28,29]

Other measures (covariates)

Demographic factors were assessed by a baseline questionnaire. Weight and height were measured at baseline and body mass index (kilograms/square meter) calculated. Frequency and severity of VMS were recorded retrospectively on daily diaries that were completed in the morning for night sweats and in the evening for daytime hot flashes. Standardized and validated baseline questionnaires (covariates and possible effect modifiers) included insomnia severity (7-item Insomnia Severity Index),[30] subjective sleep quality (Pittsburgh Sleep Quality Index),[31,32] depressive symptoms (8-item scale from the Patient Health Questionnaire),[33] and anxiety (7-item Generalized Anxiety Disorder scale).[34]

Additional individual validated MENQOL measures included the Hot Flash−Related Daily Interference Scale (HFRDIS),[35] Perceived Stress Scale,[32] Pain Intensity, Interference with Enjoyment of Life, and Interference with General Activity scale (PEG),[33] and Female Sexual Function Index (FSFI)[36]; the data were collected at baseline and 12 weeks.

Statistical analyses

The intent-to-treat analysis included all randomly assigned participants with response data that were collected regardless of intervention adherence. Baseline characteristics were compared between treatment groups with *t* tests or χ^2 tests.

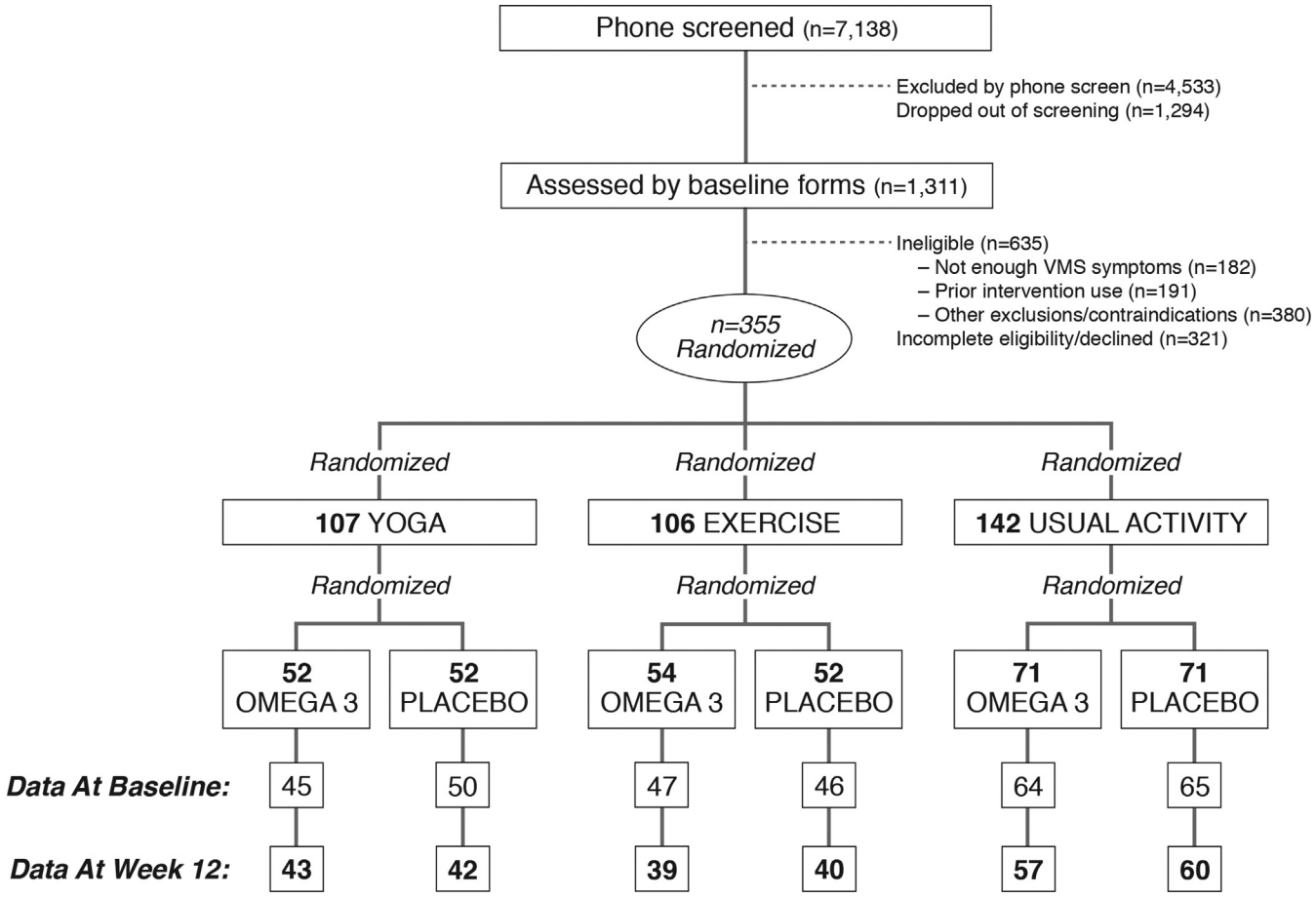
Primary analyses consisted of treatment group contrasts from linear regression models that summarized each outcome (total MENQOL and 4 domains) at 12 weeks as a function of treatment assignment; we adjusted each model for clinical center, concurrent intervention assignment, and baseline value of the outcome measure. Treatment group comparisons included yoga vs usual activity, exercise vs usual activity, and omega-3 vs placebo. Analyses that compared the treatment effects of yoga and exercise were adjusted for omega-3 assignment, and the omega-3 analyses were adjusted for the behavioral intervention assignment. Sensitivity analyses were conducted to determine whether the intervention effects differed among women who were adherent[22-24] to the intervention.

Additional analyses assessed treatment group contrasts from linear regression models that summarized the HFRDIS (hot flash interference), Perceived Stress Scale (stress), PEG (pain), and FSFI (sexual function) scores at 12 weeks as a function of treatment assignment. Each model was adjusted for clinical center, concurrent intervention assignment, and baseline value of the outcome measure.

We hypothesized that the intervention effects on the total MENQOL might be modified by symptom thresholds that were measured at baseline: anxiety (Generalized Anxiety Disorder scale continuous), depressive symptoms (Patient Health Questionnaire, continuous), poor sleep quality (Pittsburgh Sleep Quality Index, >8), or moderate-to-severe insomnia (Insomnia Severity Index, >14). Tests of interaction between treatment assignment and each of these 4 variables were performed within the linear regression models with an estimate of mean 12-week MENQOL as a function of the treatment arm, the covariate of interest, and the interaction between treatment assignment and covariate; models were adjusted for clinical center, concurrent intervention assignment, and baseline outcome value. Nominal probability values were calculated for the 8 potential interactions that were examined. Thus, less than 1 probability value would be expected to be statistically significant at the .05 level by chance alone.

Reported probability values were based on the Wald statistic, with a 2-sided probability value $\leq$ .05 considered

FIGURE
Participant recruitment, randomization, and data collected



Participants were assigned randomly to yoga, exercise, and usual activity in a 3:3:4 ratio and also to omega-3 and placebo pills in a 1:1 ratio. Some women had multiple reasons for ineligibility. Week-12 data totals include only those participants who also have baseline data.

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statistically significant. Analyses were conducted with SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Sample sizes by intervention assignments, available MENQOL data for analyses, and study completion are shown in the Figure. Overall, 78% of the women met the yoga adherence threshold; 83% of the women met the threshold for adherence to exercise[22-24]; and 82% of women assigned randomly to omega-3 and 79% assigned randomly to placebo took at least 80% of dispensed pills.[25]

There were no significant differences between the randomized treatment groups in baseline characteristics (Table 1), with the exception of age (exercise group older than usual activity group) and ethnicity (omega-3 group more likely to be white than the placebo group).

Additional factors that might affect menopause-related QOL were compared at baseline (Table 2). There were no differences among groups, with the exception that women who were assigned randomly to exercise had a higher mean PEG score than did the women in the usual activity group and that women who were assigned randomly to receive omega-3s had a lower mean FSFI score than did the women in the placebo group. Overall, 35% of the women had mild/moderate depressive symptoms; 27% of them had mild/moderate anxiety, and 40% of them had poor sleep quality. Mean hot flash interference score was 32.4 (HFRDIS; range, 0–100). Stress levels were relatively low, with an overall mean Perceived Stress Scale score of 13.8 ± 7.0 (SD) that was similar to the standard norm of 13.7 ± 6.6.[37] The mean PEG score was low at 1.1 ± 1.8. Sexual function was relatively poor with a mean FSFI score of 18.4 ± 10.5.

The mean total MENQOL score was 3.8 (range, 1–8) at baseline, with no between-group differences at baseline (Tables 3 and 4). The yoga intervention resulted in significantly greater improvement in MENQOL scores at 12 weeks, compared with the usual activity group in adjusted linear regression models ($P = .02$), but there were no group differences between exercise and usual activity or omega-3 and placebo. The mean

TABLE 1
Baseline demographic and clinical characteristics by intervention arm

Baseline Characteristic	Total participant, n	Behavioral intervention, %			Omega-3, %	
		Yoga (n = 107)	Exercise (n = 106)	Usual activity (n = 142)	Active (n = 177)	Placebo (n = 178)
Age at screening, y[a]	355	54.3 ± 3.9	55.8 ± 3.6	54.2 ± 3.5	54.4 ± 3.6	55.0 ± 3.8
<50	19	6.5	1.9	7.0	5.6	5.1
50-54	162	46.7	40.6	48.6	49.2	42.1
55-59	130	36.4	37.7	35.9	35.6	37.6
≥60	44	10.3	19.8	8.5	9.6	15.2
Race						
White	228	63.6	66.0	63.4	70.6	57.9
African American	93	23.4	25.5	28.9	25.4	27.0
Other[b]	34	13.1	8.5	7.7	4.0	15.2
College graduate	221	64.5	54.7	66.2	64.4	60.1
Employment status						
Retired or no employment	49	13.1	16.0	12.7	15.3	12.4
Full/part-time	267	72.0	77.4	76.1	76.3	74.2
Other	38	14.0	6.6	11.3	8.5	12.9
Married/living with partner	236	68.2	62.3	68.3	70.1	62.9
Current smoker	32	7.5	7.5	11.3	9.0	9.0
≥7 alcohol drinks/wk	60	13.1	17.9	19.0	21.5	12.4
Body mass index, m/kg^2[a]		27.1 ± 4.6	26.8 ± 3.9	26.9 ± 4.6	26.8 ± 4.4	27.1 ± 4.3
≥30	88	27.1	23.6	23.9	23.7	25.8
Menopause status						
Postmenopausal	286	74.8	84.9	81.7	82.5	78.7
Perimenopausal	69	25.2	15.1	18.3	17.5	21.3
Hot flashes/ day at screening[a]		7.4 ± 3.8	7.3 ± 3.3	8.0 ± 4.1	7.7 ± 3.9	7.6 ± 3.8
≥9	114	29.9	30.2	35.2	33.9	30.3
Hysterectomy	64	15.9	23.6	15.5	19.8	16.3
Bilateral oophorectomy	32	7.5	10.4	9.2	10.2	7.9
Self-reported health						
Excellent/very good	220	58.9	59.4	66.2	61.6	62.3
Good	119	36.4	37.7	28.2	33.9	33.1
Fair	15	4.7	1.9	5.6	4.5	3.9

[a] Data are given as mean ± SD; [b] 18% Hispanic, 23% American Indian, 35% Asian/Pacific Islander, and 24% other groups (with <5 individuals).

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difference in change from baseline to 12 weeks in the total MENQOL score for the yoga intervention, compared with the usual activity group, was −0.3 (95% CI, −0.6 to 0). Statistically significant differences in MENQOL domain scores that favored the yoga intervention group were observed for the vasomotor (−0.3; 95% CI, −0.8 to 0.2; $P = .02$) and sexual domains (−0.5; 95% CI, −1.0 to 0; $P = .03$). For exercise and omega-3 groups, evaluation of the 4 MENQOL domains showed only a statistically significant treatment group difference that favored the exercise group for the physical domain (−0.2; 95% CI, −0.5 to 0; $P = .02$), and no domain scores varied between the omega-3 and placebo groups.

There was no significant difference between the yoga and usual activity groups when sexual function was

TABLE 2
Baseline factors that are related to menopausal quality of life

Baseline characteristic	Total participant, n	Behavioral intervention			Omega-3	
		Yoga (n = 107)	Exercise (n = 106)	Usual activity (n = 142)	Active (n = 177)	Placebo (n = 178)
Depression score[a,b]		4.0 ± 3.6	4.0 ± 4.2	4.1 ± 3.6	3.6 ± 3.5	4.4 ± 4.0
Mild+ depression: ≥5, %	126	38.3	34.0	34.5	33.3	37.6
Anxiety score[a,c]		3.2 ± 3.8	3.4 ± 4.1	3.0 ± 3.0	2.9 ± 3.4	3.5 ± 3.8
Mild+ anxiety: ≥5, %	95	27.1	27.4	26.1	24.3	29.2
Insomnia Severity Index score[a,d]		11.8 ± 5.4	11.5 ± 5.9	12.2 ± 5.2	11.8 ± 5.2	12.0 ± 5.7
Moderate+ insomnia: >14, %	264	32.7	31.1	33.8	32.2	33.1
Pittsburgh Sleep Quality Index score[a,e]		7.7 ± 3.4	7.8 ± 3.4	8.4 ± 3.3	7.9 ± 3.3	8.2 ± 3.4
Poor sleep quality: >8, %	294	34.6	40.6	43.7	35.6	44.4
Hot Flash–Related Daily Interference Scale[a,f]	336	31.7 ± 21.3	31.8 ± 22.5	33.6 ± 21.4	32.4 ± 20.0	32.5 ± 23.2
Perceived Stress Score[a,g]	347	13.5 ± 7.0	14.1 ± 7.3	13.6 ± 6.9	13.5 ± 7.1	14.0 ± 6.9
Pain Intensity, Interference with Enjoyment of Life, and Interference with General Activity scale score[a,h]	353	1.2 ± 2.0	0.8 ± 1.1	1.3 ± 2.0	1.0 ± 1.7	1.3 ± 1.8
Female Sexual Function Index score[a,i]	290	18.5 ± 10.5	16.8 ± 10.6	19.6 ± 10.4	20.0 ± 10.3	16.8 ± 10.6
Treadmill test duration, min[a]	355	10.4 ± 3.1	9.6 ± 2.9	10.3 ± 2.9	10.3 ± 2.9	9.9 ± 3.1

[a] Data are given as mean ± SD; [b] Patient Health Questionaire-8 (range, 0–20); [c] Generalized Anxiety Disorder-7 (range, 0–17); [d] Range, 0–27; [e] Range, 1–17; [f] Range, 0–100; [g] Range, 0–32; [h] Range, 0–10; [i] Range, 2–36.

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evaluated by the validated and more detailed FSFI ($P = .58$; Table 5). HFRDIS scores declined (ie, improved) in the yoga group relative to the usual activity group by 12 weeks (group difference, −3.4; 95% CI, −9.0 to 2.3; $P = .03$), but changes in stress and pain did not differ between the yoga and usual activity groups. Hot flash interference, stress, pain, and sexual function showed no improvement with exercise or omega-3 interventions over usual care or placebo, respectively.

Comment

Little evidenced-based information is available for women with menopausal symptoms considering behavioral changes to improve QOL. We found that, relative to usual activity, a 12-week program of yoga slightly improved menopause-related QOL and reduced the extent to which hot flashes interfered with a woman's daily function among women with VMS but that exercise and omega-3 supplements had no effect on these measures. Among the individual MENQOL domains, we found a slight benefit for VMS and sexual function domains (but not for the physical and psychosocial domains) from the yoga intervention and benefit for only the physical domain for the exercise intervention.

All of the significant menopause-related QOL differences and the difference that was observed in the hot flash daily interference measure with the yoga intervention were small; therefore, the clinical relevance of our findings may be modest at best. For example, the mean total MENQOL score at baseline was 3.8 (range, 1–8), with a mean diminution of 0.9 in the yoga intervention and a decrease of 0.6 in the usual activity group at 12 weeks. Significant MENQOL domain-specific differences that were observed (VMS, physical, sexual) were of similarly small magnitudes and were not supported by other individual validated measures of factors that potentially were related to QOL: pain (PEG), sexual function (FSFI), and VMS daily diaries.[22] Although similar questionnaires may purport to measure the same outcomes, differences in the way they are delivered (eg, diary vs global scale) may lead women to respond differently (counts vs global impression). Aside from these differences, the statistically significant differences that we found could be because of chance alone.

Few studies have evaluated menopause-related QOL in menopausal women who practice yoga. Most studies were conducted in special populations, such as women with insomnia symptoms[11] or breast cancer[12] and women who specifically took aromatase inhibitors.[38] All of the studies found benefit, but they were limited by an extremely high withdrawal rate (overall, 23%; yoga group, 63%),[11] and wait-list[12] or no control subjects[38]; the results should be interpreted with caution. A 3-arm trial (n = 162 women) found a "positive affect" on QOL in both walking and yoga intervention groups compared with wait-list control subjects.[39] We previously reported that, among healthy women, 12 weeks of yoga class plus home practice did not improve VMS frequency or bother

TABLE 3
Menopausal quality of life: yoga vs usual activity and exercise vs usual activity

	Intervention arm						Difference			
	Yoga		Exercise		Usual activity		Yoga vs usual activity		Exercise vs usual activity	
MENQOL score[a]	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	*P* value[b]	Mean (95% CI)	*P* value[b]
Total								.02		.32
Baseline	95	3.8 (3.6–4.0)	93	3.8 (3.5–4.1)	129	3.8 (3.6–4.0)	0 (−0.3 to 0.3)		0 (−0.3 to 0.3)	
Week 12-baseline	85	−0.9 (−1.2 to −0.7)	79	−0.8 (−1.0 to −0.6)	117	−0.6 (−0.8 to −0.5)	−0.3 (−0.6 to 0)		−0.1 (−0.4 to 0.1)	
DOMAINS										
Vasomotor								.02		.52
Baseline	104	5.3 (5.0–5.6)	105	5.3 (5.0–5.6)	141	5.6 (5.4–5.8)	−0.3 (−0.7 to 0)		−0.3 (−0.7 to 0.1)	
Week 12-baseline	97	−1.5 (−1.9 to −1.2)	99	−1.2 (−1.5 to −0.9)	133	−1.2 (−1.5 to −0.9)	−0.3 (−0.8 to 0.2)		0 (−0.4 to 0.5)	
Psychosocial								.78		.57
Baseline	105	3.3 (3.0–3.6)	106	3.3 (3.0–3.6)	140	3.3 (3.1–3.5)	0 (−0.4 to 0.3)		0 (−0.4 to 0.4)	
Week 12-baseline	98	−0.6 (−0.8 to −0.4)	98	−0.6 (−0.9 to −0.4)	130	−0.6 (−0.7 to −0.4)	0 (−0.3 to 0.3)		−0.1 (−0.4 to 0.2)	
Physical								.13		.02
Baseline	98	3.2 (2.9–3.5)	100	3.2 (2.9–3.4)	137	3.3 (3.1–3.5)	−0.1 (−0.4 to 0.3)		−0.1 (−0.4 to 0.2)	
Week 12-baseline	90	−0.6 (−0.8 to −0.4)	91	−0.7 (−0.9 to −0.5)	129	−0.5 (−0.6 to −0.3)	−0.1 (−0.4 to 0.1)		−0.2 (−0.5 to 0)	
Sexual								.03		.41
Baseline	102	3.2 (2.7–3.6)	100	3.4 (2.9–3.9)	137	3.3 (2.9–3.7)	−0.1 (−0.7 to 0.5)		0.1 (−0.5 to 0.8)	
Week 12-baseline	95	−0.9 (−1.3 to −0.5)	88	−0.6 (−0.9 to −0.3)	127	−0.4 (−0.7 to −0.1)	−0.5 (−1.0 to 0)		−0.2 (−0.6 to 0.2)	

CI, confidence interval; *MENQOL*, Menopausal Quality of Life Questionnaire.

[a] MENQOL total score range, 1–8; domain scores range, 1–8; [b] *P* values from contrasts comparing active vs control in a linear model of outcome as a function of the intervention arm and adjusted for clinical center, baseline outcome value, and concurrent interventions.

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TABLE 4
Menopausal quality of life: omega-3 vs placebo capsule

	Intervention arm					
	Omega-3		Placebo		Difference	
MENQOL score[a]	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	*P* value[b]
Total						.12
Baseline	156	3.8 (3.6–3.9)	161	3.9 (3.7–4.0)	−0.1 (−0.3 to 0.2)	
Week 12-baseline	139	−0.7 (−0.8 to −0.5)	142	−0.9 (−1.0 to −0.7)	0.2 (−0.1 to 0.4)	
DOMAINS						
Vasomotor						.06
Baseline	173	5.5 (5.3–5.7)	177	5.3 (5.1–5.6)	0.2 (−0.1 to 0.5)	
Week 12-baseline	164	−1.2 (−1.5 to −1.0)	165	−1.4 (−1.7 to −1.1)	0.2 (−0.2 to 0.6)	
Psychosocial						.29
Baseline	175	3.2 (3.0–3.4)	176	3.3 (3.2–3.6)	−0.2 (−0.5 to 0.1)	
Week 12-baseline	163	−0.5 (−0.7 to −0.3)	163	−0.7 (−0.8 to −0.5)	0.2 (−0.1 to 0.4)	
Physical						.91
Baseline	167	3.2 (3.0–3.4)	168	3.2 (3.0–3.4)	0 (−0.3 to 0.3)	
Week 12-baseline	156	−0.6 (−0.8 to −0.4)	154	−0.5 (−0.7 to −0.4)	0 (−0.3 to 0.2)	
Sexual						.31
Baseline	167	3.1 (2.8–3.5)	172	3.4 (3.0–3.8)	−0.3 (−0.8 to 0.3)	
Week 12-baseline	154	−0.5 (−0.7 to −0.2)	156	−0.7 (−1.0 to −0.4)	0.3 (−0.1 to 0.6)	

CI, confidence interval; *MENQOL*, Menopausal Quality of Life Questionnaire.

[a] MENQOL total score range, 1–8, domain scores range, 1–8; [b] *P* values from contrasts comparing active vs control in a linear model of outcome as a function of intervention arm and adjusted for clinical center, baseline outcome value, and concurrent interventions.

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compared with usual activity, but yoga was associated with minor improvements in sleep quality, insomnia symptoms, and depressive symptoms.[22] In the analyses reported here, we found modest diminished hot flash interference with daily activities, comparing yoga with usual activity; the findings were consistent with 2 smaller studies that lacked control groups.[7,9] The inclusion of control groups in our study with opportunity for expectation of benefit (all women received placebo pills or omega-3 fatty acid tablets) is critical for interpreting these mixed findings.

Consistent with other studies on exercise in midlife, we found that the exercise intervention improved the MENQOL physical function domain compared with usual activity but that exercise was not associated with improvement in overall menopause-related QOL.[40,41] Two studies that reported on health-related QOL among postmenopausal women found benefit with increased physical activity; however, specifics as to whether women had significant VMS, as in our study population, were lacking in one study,[13] and the other study evaluated breast cancer survivors with a home-based exercise program.[42] In addition, both studies used a different QOL measure that is not specific to menopause-related symptoms. Consistent with the lack of menopause-related QOL benefit from exercise, we did not observe improvement in hot flash interference, stress, pain, or sexual function.

In our study, omega-3 supplements were not associated with improvements in menopausal QOL, hot flash interference, stress, pain, or sexual function.

The rationale for evaluating whether yoga and/or exercise improves QOL is based on the hypothesis that sympathetic nervous system and parasympathetic nervous system imbalances occur at midlife. Behavioral interventions impact both sympathetic nervous system and parasympathetic nervous system function and stress reactivity, which supports the hypothesis that yoga and/or exercise might shift the balance toward sympathetic dominance and improve perceived QOL. Yoga or exercise could also decrease autonomic arousal through changes in circulating neurotransmitters and hormone concentrations[43] that lead to improved perceived QOL. In addition, improved QOL with exercise is hypothesized to occur through increasing circulation of beta endorphins or potentially as a relief or distraction from worries or stress.[44,45] Analyses of

TABLE 5
Hot flash interference, stress, pain, and sexual function by intervention arm

	Intervention arm											
	Yoga	Usual activity	Difference[a]		Exercise	Usual activity	Difference[a]		Omega-3	Placebo	Difference[a]	
Outcome	n	n	Mean (95% CI)	*P* value[b]	n	n	Mean (95% CI)	*P* value[b]	n	n	Mean (95% CI)	*P* value[b]
Daily interference[c]				.03				.14				.59
Baseline	103	133	−1.9 (−7.4 to 3.6)		100	133	−1.8 (−7.5 to 3.9)		167	169	−0.1 (−4.8 to 4.5)	
Week 12-baseline	95	122	−3.4 (−9.0 to 2.3)		95	122	−2.0 (−7.7 to 3.7)		158	154	−1.6 (−6.2 to 3.0)	
Stress[d]				.19				.97				.08
Baseline	102	139	−0.1 (−1.9 to 1.7)		106	139	0.5 (−1.3 to 2.3)		172	175	−0.6 (−2.0 to 0.9)	
Week 12-baseline	95	132	0.9 (−0.6 to 2.4)		101	132	−0.2 (−1.8 to 1.4)		164	164	1.1 (−0.2 to 2.5)	
Pain[e]				.75				> .99				.64
Baseline	105	142	−0.1 (−0.6 to 0.4)		106	142	−0.5 (−0.9 to −0.1)		175	178	−0.3 (−0.6 to 0.1)	
Week 12-baseline	99	135	0 (−0.5 to 0.5)		100	135	0.3 (−0.2 to 0.7)		166	168	0 (−0.4 to 0.5)	
Sexual function[f]				.58				.31				.61
Baseline	86	119	−1.1 (−4.1 to 1.8)		85	119	−2.9 (−5.8 to 0.1)		147	143	3.2 (0.8–5.6)	
Week 12-baseline	76	104	0.8 (−1.1 to 2.6)		75	104	−0.5 (−2.7 to 1.6)		129	126	−1.0 (−2.7 to 0.6)	

CI, confidence interval.

[a] Active vs control differences for each outcome; [b] *P* values from contrasts comparing active vs control in a linear model of outcome as a function of intervention arm and adjusted for clinical center, baseline outcome value, and concurrent interventions; [c] Daily interference measured by Hot Flash-Related Daily Interference Scale (range, 0–100); [d] Stress measured by Perceived Stress Score (range, 0–32); [e] Pain measured by Pain Intensity, Interference with Enjoyment of Life, and Interference with General Activity scale (range, 0–10); [f] Sexual function measured by Female Sexual Function Index (range, 2–36).

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physiologic measures of the sympathetic nervous system and parasympathetic nervous system balance (heart rate variability and salivary cortisol) among our participants are ongoing to guide biologic interpretation of our findings.

Limitations of our study deserve mention. Although women were recruited from community-based samples, participants primarily were sedentary, had at least 2 hot flashes per day, and were compensated for their participation. Generalizability to other populations must be considered thoughtfully. The impact of reimbursement is uncertain. Women who self-selected and paid for similar classes in the community might be more (because of their financial investment) or less (because of lack of reimbursement) motivated to adhere to the program. They may have been a select group that was motivated to seek treatment and had treatment expectations. Mean total baseline MENQOL scores for all groups were 3.8 (yoga, exercise, and usual activity), comparable with another MsFLASH study that evaluated a selective serotonin reuptake inhibitor vs placebo (MENQOL scores 3.7-3.9),[46] but lower than a study evaluating hormonal therapies (MENQOL scores 4.4-4.5).[47] The 12-week treatment interval was brief but most likely was sufficient for the determination of long-term nonhormonal treatment efficacy.[42] We examined multiple potential moderating factors of treatment response, but other factors likely exist. We cannot rule out the possibility that other more intensive yoga or exercise regimens or a different omega-3 formulation might have a more salutary effect on menopause-related QOL. This study analyzed multiple outcomes; thus, significant findings may be due to chance.

Study strengths are that the interventions were designed specifically for midlife women, both peri- and postmenopausal women, that the omega-3 formulation had excellent quality control data, that the sample size was large with a low dropout rate, and that participants were adherent to therapy. All participants took either omega-3 or placebo capsules, which provided the expectancy of benefit in all women. Validated measures for VMS, sleep, stress, pain, sexual function, and mood assisted in the interpretation of MENQOL findings. Most VMS intervention trials have not evaluated treatment effects on menopause-related QOL. For those that have, the available QOL measures are numerous and of variable quality.[48] Our rationale for using the MENQOL for the MsFLASH trials was based on the breadth of its domains, salutary psychometric properties, brevity, and sensitivity to change over time.

All women become menopausal, and many seek medical advice on ways to improve QOL; little evidence-based information exists. Future studies are needed to better understand the physiologic basis for and maximization of benefit from behavioral therapies for menopausal symptoms. Providers may advise women that yoga slightly improves menopause QOL and that exercise and omega-3 supplements do not. ■

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