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Inflammation and psychosocial factors mediate exercise effects on sleep quality in breast cancer survivors: pilot randomized controlled trial

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Abstract

***Objective*: To improve mechanistic understanding, this pilot randomized controlled trial examined mediators of an exercise intervention effects on sleep in breast cancer survivors (BCS).**

***Methods*: Forty-six postmenopausal BCS (≤Stage II, off primary treatment) were randomized to a 3-month exercise intervention or control group. Intervention included 160 min/week of moderate intensity aerobic walking, twice weekly resistance training (resistance bands), and six discussion groups (to improve adherence). Blinded assessments at baseline and post-intervention included sleep disturbance (PSQI and PROMIS®), objective sleep quality (accelerometer), serum cytokines, accelerometer physical activity, cardiorespiratory fitness, body composition, fatigue, and psychosocial factors. Mediation was tested using Freedman–Schatzkin difference-in-coefficients tests.**

***Results*: When compared with control, the intervention group demonstrated a significant increase in PSQI sleep duration (i.e., fewer hours of sleep/night) ($d = 0.73$, $p = .03$). Medium to large but non-significant standardized effect sizes were noted for PSQI daytime somnolence ($d = -0.63$, $p = .05$) and accelerometer latency ($d = -0.49$, $p = .14$). No statistically significant mediators were detected for PSQI sleep duration score or accelerometer latency. Daytime somnolence was mediated by tumor necrosis factor-alpha (mediated 23% of intervention effect, $p < .05$), interleukin (IL)-6:IL-10 (16%, $p < .01$), IL-8:IL-10 (26%, $p < .01$), and fatigue (38%, $p < .05$). Mediating or enhancing relationships for several of the sleep outcomes were noted for accelerometer physical activity, PROMIS® fatigue, exercise social support, and/or physical activity enjoyment.**

***Conclusions*: Inflammation and psychosocial factors may mediate or enhance sleep response to our exercise intervention. Further study is warranted to confirm our results and translate our findings into more effective interventions aimed at improving sleep quality in BCS.**

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Introduction

Sleep disturbance is a common and persistent symptom suffered by cancer survivors, especially those with a history of breast cancer [1,2]. The majority of breast cancer survivors report sleep disturbances during the months after diagnosis [3] with 18% reporting persistent insomnia 3 to 4 years post-diagnosis [4]. Importantly, sleep disturbance predicts poorer quality of life [3].

According to the National Comprehensive Cancer Network (NCCN) guidelines, regular exercise is recommended as part of 'general sleep hygiene measures' and treatment of sleep disturbance among cancer survivors (http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf). Improved understanding of the mechanisms underlying exercise effects on sleep quality can be used to improve interventions aimed at reducing sleep disturbance after cancer diagnosis. The etiology of sleep disturbance is multifactorial with several theoretical models proposed [5]. Taken as a whole, a biobehavioral framework is warranted due to proposed mechanisms and associated factors [i.e. physiologic alterations (neurologic, endocrine, and immune), affective factors (e.g. personality traits), cognitive-behavioral (e.g. perceptions of the meaning of sleep quality), and comorbid disorders (e.g. depression, anxiety)] [5]. Examining inflammatory mechanisms underlying sleep quality response to exercise in breast cancer survivors is particularly relevant given that change in inflammation is proposed as an etiologic mechanism underlying exercise effects on cancer risk [6], sleep disturbances [7], and other symptoms such as fatigue [8]. Although our study protocol was developed with a focus on examining inflammation as a mediator of exercise effects on sleep, we also report psychosocial factors

(secondary study outcomes) because of the behavioral and affective factors contributing to sleep quality [5].

A recent meta-analysis of exercise effects after cancer reported a standardized mean difference for sleep disturbance of −0.46 (95% confidence interval: −0.72 to −0.20) when comparing 12-week follow-up values by comparison group [9] with the vast majority of the studies assessing sleep by self-report. Since the 2012 meta-analysis, five additional studies have reported sleep outcomes [10–14]. These studies have varied with regard to sample size (28 to 187 participants), cancer type (breast, lymphoma, multiple myeloma, lung, colorectal, prostate, other solid tumor), and treatment status (on primary treatment, off primary treatment, or a mix of both). Only two reported statistically significant intervention effects on sleep [i.e. self-reported sleep latency [10] and general perceived sleep quality [11]] with only two measuring sleep with a tool other than self-report (i.e. actigraphy) [10,14].

No prior study has reported a mediation analysis examining the mechanisms underlying the effects of exercise on sleep after a cancer diagnosis. One prior randomized exercise trial reported the associations between changes in serum markers of inflammation (i.e. serum cytokines) and changes in sleep quality in a randomized controlled exercise and cancer trial but no formal mediation analysis was performed [15]. In this study of 38 breast and prostate cancer patients receiving radiation therapy, no significant associations among the change scores were found for individuals randomized to the exercise group. In the control group, the change in tumor necrosis factor (TNF)-alpha from baseline to post-intervention (i.e. 4 week home-based pedometer with resistance bands intervention) was positively associated with a change in sleep latency ($r = 0.50$, $p = .03$) and sleep medication use ($r = 0.58$, $p = .009$).

Given the limited and inconsistent data related to exercise effects on sleep and the mechanistic mediators of these effects, our primary study aim was to investigate inflammatory mechanisms that may underlie the effects of an exercise intervention on subjective and accelerometer-measured sleep outcomes. Our secondary aim was to examine non-inflammatory mediators collected as secondary outcomes.

Methods

Study design and participants

This randomized controlled trial has been described in a previous publication reporting mediators of fatigue [16] with a brief summary provided here. A 3-month exercise intervention was compared with the control group; outcomes were obtained at baseline (pre-intervention; M0) and 3 months (post-intervention; M3) with a small monetary incentive paid to the participants after completion of each assessment. Randomization was stratified by ductal carcinoma in situ (DCIS) versus Stage I or II and done in blocks of four using computer generated numbers. Staff members and investigators were unaware of group allocation until the opaque envelopes containing the group assessment were opened after the participant completed baseline testing. Participants were randomized in the order in which they completed baseline testing.

Local institutional review board approval was obtained, and all participants provided informed consent before initiating study activities. An individual was included if she was a post-menopausal woman between the ages of 30 and 70 years with a history of breast cancer [i.e. DCIS, Stage I, or Stage II]. Participants had to be ≥4 weeks post primary treatment but could be currently receiving longer term therapies such as anti-estrogen agents. Other inclusion criteria include ≥8 weeks post-cancer surgery, able to speak English, and able to obtain medical clearance for study participation from their physician. To facilitate avoiding a 'floor effect', participants were required to report either an average fatigue ≥3 on a 1 to 10 Likert scale [17] or sleep disturbance ≥1 on a 0 to 3 Likert scale [18]. Because serum cytokine levels were the primary mediators being examined, participants had to be willing to abstain from 'as needed' medications for 7 days prior to each blood draw. Individuals were excluded if they had metastatic or recurrent breast cancer, required assistance to ambulate, were currently taking steroids, had been advised by a physician to only do exercise prescribed by a physician, were exercising >20 min on ≥2 days per week (on average over the past six months), lived or worked >50 miles from the study site, or did not have transportation to the study site. Individuals were also excluded if they anticipated any of the following during study participation: (a) moving residence outside local area, (b) changes in usual medications, (c) elective surgery, or (d) travel outside local area during the first 4 weeks of the intervention or for >1 week during the last 8 weeks of the intervention. Participants with health conditions that increased exercise risk, prevented ability to comply with study activities, or significantly altered systemic inflammation were excluded [16] .

Exercise intervention

The exercise intervention has been described in detail in a previous publication [16]. In brief, this combined aerobic with strength training intervention included supervised, on-site sessions twice a week (treadmill aerobic walking of moderate intensity and resistance bands) and unsupervised, home-based sessions twice a week (aerobic walking, not necessarily on a treadmill). The total weekly goal for aerobic minutes was 160 min (i.e. four sessions of 40 min each spread out throughout the week). Moderate exercise intensity was based on the Karvonen method (i.e. 48% to 52% of heart rate reserve). The weekly goal

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for resistance bands was two sessions (supervised) which included eight different resistance exercises focused on the major muscle groups with up to 2 sets of 15 repetitions per exercise. Behavioral support for improving adherence was provided in the format of six discussion group meetings based on a prior successful behavior change intervention [19]. These groups were led by a clinical psychologist (or psychology intern under the supervision of a clinical psychologist), and the group dynamics were facilitated by enrolling participants in cohorts or 'waves'.

Control group instructions

Participants randomized to the control group were asked to avoid changing their exercise behavior during the study when compared with what they were doing at time of study enrollment.

Measures: general

As previously described [16], demographic and medical characteristics were self-reported. Unless otherwise specified, measures were obtained at baseline (pre-intervention) and 3 months (post-intervention). Carbohydrate ingestion which might act as a covariate [20] was assessed with a 3-day diet record [FoodWorks 13 (Long Valley, NJ)]. Exercise adherence was assessed with attendance records and weekly exercise logs (intervention group only; every week of the intervention). Both control and intervention participants wore a MTI/Actigraph accelerometer for seven days at baseline and 3 months [four valid days were required for analysis; cutpoints were sedentary = 0–99 [21], inactive = 100–499, light activity = 500–1951, moderate activity = 1952–5724, vigorous $\geq$ 5725 [22]].

Measures: sleep

Self-reported sleep disturbance was measured using the Pittsburgh Sleep Quality Index [PSQI; subjective sleep quality, latency, sleep duration, efficiency, sleep disturbances, use of sleep medications, daytime somnolence, and global score (sum of subscales)]. The PSQI was scored according to published protocol (i.e. higher score indicates greater sleep disturbance) [18]. To improve interpretation of the sleep duration subscore, we also report the number of self-reported hours of sleep per night. In addition, sleep quality was self-reported using the Patient Reported Outcomes Measurement Information System (PROMIS®) sleep/wake disturbances scale [16 items; all items use a 1 to 5 Likert scale (http://www.nihpromis.org/default.aspx)]. Items were summed and then converted to T scores using conversion tables published on the PROMIS® website; higher scores indicate greater sleep/wake disturbances.

During the 7-day physical activity monitoring, the same accelerometer used for measuring physical activity was transferred to the wrist when the participant went to bed each evening. Actigraphs used for physical activity have been reported to be a valid sleep measure when transferred to the wrist at night [23], and the brand used in this study (Actigraph®) has demonstrated validity when compared with polysomnography [24]. The participant recorded the time in and out of bed on a record sheet. At least three valid nights of monitoring were required. Sleep data was analyzed using ActiLife version 6.7.1 and the default algorithm (i.e. Sadeh [25]). The objective, accelerometer outcomes of sleep latency, and efficiency are described in this report.

Measures: potential mediators

Our primary objective was to assess inflammatory mediators of sleep response to our exercise intervention. To that end, we obtained fasting serum samples for interleukin (IL)-6, IL-8, IL-10, and TNF-alpha between 7:45 AM and 10:00 AM. Prior to the blood draw, the participant was given the following instructions: (a) do not take sporadic or 'as needed' medications for preceding seven days, (b) abstain from exercise, smoking, and alcohol for the preceding 24 h, and (c) complete 7-day medication log in the preceding week. The medication log was examined by a licensed physician (Rogers) for changes which might influence cytokine levels. Standard operating procedures consistent with expert consensus recommendations were used to collect, process, and store blood samples [26]. Samples were batch analyzed by an investigator unaware of the participants' group allocations. Luminex® technology using the High Sensitivity Human cytokine assay (Cat # HSCYTO-60SK, Millipore Corp. Billerica, MA) measured serum levels of IL-6, IL-8, IL-10, and TNF-alpha.

Individuals obtaining the physical measures were blinded to the study group allocation of the participant. Body mass index [BMI; (weight in pounds / height in inches squared) multiplied by 703] and waist-to-hip ratio were calculated. Percent body fat was estimated with bioelectric impedance (i.e. Quantum X by RJL Systems; fasting and same time of day for each measurement). Back and leg dynamometer (Takei, model T.K.K. 5002) assessed extensor leg strength. Submaximal treadmill test estimated cardiorespiratory fitness [modified Naughton protocol [27]].

Depression, anxiety, and fatigue were measured using the PROMIS® scales (i.e. 8 items, 7 items, and 7 items, respectively) with all items using a Likert scale (1 = rarely to 5 = always) (http://www.nihpromis.org/default.aspx). Responses for each scale were summed (higher scores indicates greater symptomatology). Conversion tables published on the PROMIS® website were used to convert the raw scores to T scores for the analysis. For walking

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self-efficacy, participants rated their confidence in their ability to walk at a moderately fast pace without stopping for 5 min up to 30 min in 5-min increments (i.e. 6 items) [28]. Confidence was rated on a scale from 0% to 100% (10% increments) with a mean of responses calculated for the analysis. Four items assessed exercise social support [i.e. how often family or friends offered to exercise with the participant or encouraged the participant to exercise; 5-point Likert responses (0 = rarely to 4 = very often), responses summed for the analysis] [29]. A single item assessed physical activity enjoyment [i.e. indicate agreement with the following statement 'I enjoy engaging in regular physical activity' (1 = disagree to 5 = agree)] [30].

Data analysis

The two study groups were compared at baseline using independent groups *t*-test or chi-square. Cytokines were analyzed individually and as pro-inflammatory to anti-inflammatory ratios (i.e. IL-6:IL-10, IL-8:IL-10, and TNF-alpha:IL-10). Data was analyzed regardless of intervention adherence. Paired *t*-test and independent groups *t*-test analyzed within group changes over time and between group differences, respectively. Mediation of intervention effects on sleep outcomes was tested using the Freedman and Schatzkin difference-in-coefficients test, a procedure known to optimize study power when analyzing mediation in small randomized trials [31]. This procedure was chosen because of the pilot (and hypotheses generating) nature of our study in which we wanted to reduce the likelihood of missing an important mediation relationships which warranted further study. Relevant to this objective, Freedman and Schatzkin procedures do not require that the relationship between the intervention and mediator and the relationship between the mediator and outcome be significant while also resulting in the most accurate Type I error rates when these relationships are null [32]. With regard to interpretation, a statistically significant reduction in the relationship between the intervention and outcome (e.g. sleep) when the mediator is included in the final model indicates mediation and is reported as the positive proportion (or percentage) of the intervention effect that is due to the change in the mediator. At times, inclusion of the potential mediator in the final model will result in a stronger statistical relationship between the intervention and outcome. When this is the case, the relationship is described as a negative percent change and interpreted as indicating that the potential mediator is influencing the intervention-outcome relationship rather than mediating the relationship. Statistical significance was defined as p value of $<.05$ with p values $<.10$ and standardized effect sizes also noted due to the pilot nature of the study.

Results

Participant flow through the study, reasons for exclusion and drop out, adverse events, and intervention adherence rates have been previously reported [16]. In brief, 46 breast cancer survivors enrolled from July 2010 to February 2012 were randomized with 44 (96%) retained (i.e. complete or partial data) and 42 (91%) providing complete data. Of the 44 retained in the study, two participants (both in the intervention group) developed cancer recurrence during the intervention. Although these women completed the intervention and follow-up assessment, they were dropped from the analysis due to the potential effect of cancer recurrence on the primary mediator outcomes related to serum cytokines. Therefore, the final analyses reported here include 42 participants (20 in the intervention and 22 in the control; 91% of the 46 randomized).

Sample characteristics have been previously reported [16]. In brief, mean age was 56.2 ± 7.7 and education was 14.0 ± 2.2 years with 42 (95.5%) being White. With regard to cancer stage, 18.2% had DCIS, 47.7% had Stage I, and 34.1% had Stage II. Among the 40.9% who had received chemotherapy, the mean months since treatment completion was 70.3 ± 65.5. Among the 63.6% receiving radiation therapy, the mean months since treatment completion was 44.1 ± 41.8. Current anti-estrogen therapy was reported by 52.3%. Mean number of comorbidities was 2.1 ± 1.6, and mean grams of carbohydrate ingested was 200 ± 77. Medication change with the potential to influence cytokine levels was noted on review of medication logs for 48.8% of the participants. Sleep disturbance was reported by 93% at the time of screening. Adjustment for the only factor which differed for the two study groups at baseline (i.e. percent who never smoked cigarettes = 75% in control versus 45% in the intervention group, $p = .04$) did not change our results; therefore, we report the unadjusted analysis.

The exercise intervention effects on sleep outcomes in our study and the within group change are reported in Table 1. For the PSQI subscales, only sleep duration (i.e. higher score indicates fewer hours slept per night; range = 0 to 3) demonstrated a significant between group difference for the intervention compared with control group (+0.2 versus −0.4. $d = 0.73$, $p < .05$). The next largest effect size among the PSQI subscales was daytime somnolence (i.e. higher score indicates greater somnolence during the day; range = 0 to 3) with the between group difference for the intervention versus control group being −0.5 versus −0.1, $d = -0.63$, $p = .05$). No significant between group differences were noted for the remaining PSQI outcomes, PROMIS® sleep disturbance, accelerometer efficiency, and accelerometer latency. To improve interpretation of the sleep duration score, the mean number of self-reported hours of sleep per night are also reported in

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Table 1. Effects of a walking program plus resistance exercise on sleep in breast cancer survivors post-primary treatment (participants with complete data, $n = 42$)

		Month 0		Month 3		Change over time		Between group difference		
Variable	**Group**	**Mean**	**(SD[a])**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Effect Size**
PSQI[b] sleep quality	Intervention	1.2	(0.5)	0.7	(0.6)	−0.4***	(0.5)			
	Control	1.5	(0.9)	1.2	(0.6)	−0.4*	(0.9)	0.0	(0.7)	−0.01
PSQI latency	Intervention	1.3	(0.9)	1.2	(1.0)	0.0	(0.7)			
	Control	1.5	(0.9)	1.0	(0.7)	−0.5*	(1.2)	0.5	(1.0)	0.45
PSQI sleep duration[c]	Intervention	1.0	(0.8)	1.1	(0.8)	0.2	(0.8)			
	Control	1.5	(0.9)	1.2	(0.8)	−0.4**	(0.7)	0.6	(0.8)	0.73**
PSQI efficiency	Intervention	0.8	(1.0)	0.6	(0.8)	−0.1	(1.2)			
	Control	1.0	(1.1)	0.6	(1.0)	−0.5**	(1.0)	0.3	(1.1)	0.32
PSQI sleep disturbances	Intervention	1.7	(0.6)	1.5	(0.6)	−0.2**	(0.4)			
	Control	1.6	(0.6)	1.3	(0.6)	−0.3**	(0.7)	0.1	(0.6)	0.18
PSQI sleep medication[d]	Intervention	1.2	(1.4)	0.8	(1.3)	−0.2	(0.9)			
	Control	0.9	(1.3)	0.7	(1.2)	−0.1	(0.7)	−0.1	(0.8)	−0.10
PSQI daytime somnolence	Intervention	1.2	(0.5)	0.7	(0.6)	−0.5***	(0.6)			
	Control	1.2	(0.8)	1.0	(0.7)	−0.1	(0.8)	−0.4	(0.7)	−0.63*
PSQI global	Intervention	8.2	(3.4)	6.7	(3.7)	−1.3	(3.2)			
	Control	9.2	(4.8)	7.1	(3.2)	−2.2**	(4.4)	1.0	(3.9)	0.25
Self-reported hours of sleep per night	Intervention	7.0	(0.9)	7.0	(0.9)	−0.1	(0.8)			
	Control	6.1	(1.1)	6.6	(0.9)	0.6**	(1.1)	−0.7	(1.0)	0.68**
PROMIS® sleep dysfunction[e]	Intervention	49.4	(7.1)	46.2	(8.0)	−3.7*	(8.6)			
	Control	53.4	(9.2)	51.1	(7.4)	−1.9	(7.6)	−1.8	(8.1)	−0.22
Accelerometer efficiency[f]	Intervention	82.3	(6.2)	82.9	(5.7)	0.1	(4.9)			
	Control	82.4	(8.6)	84.9	(6.0)	2.7**	(6.2)	−2.6	(5.6)	−0.46
Accelerometer latency[g]	Intervention	10.3	(10.5)	7.4	(5.6)	−3.0	(12.9)			
	Control	7.1	(6.8)	8.9	(6.6)	2.1	(7.7)	−5.1	(10.4)	−0.49

[a]SD = standard deviation.
[b]PSQI = Pittsburg Sleep Quality Index (higher scores for all PSQI measures = greater sleep disturbance).
[c]Higher score = fewer hours slept per night.
[d]Higher score = more frequent medication use.
[e]Results previously reported [16].
[f]Higher score = beneficial.
[g]Lower score = beneficial.
*$p < .10$.
**$p < .05$.
***$p < .01$.

Table 1 [e.g. between group difference = -0.7 ± 1.0 ($d = .68$, $p < .05$)]. Lastly, of the 14 participants in the intervention group reporting PSQI global scores >5 at baseline (cutpoint for classification as a 'poor sleeper' [18]), four no longer reported global scores >5 at 3 months.

Because our objective was to generate hypotheses related to potential mediators warranting further study, we tested mediation using all sleep outcomes and inflammatory markers regardless of intervention effect. The remaining potential mediators were chosen based on statistical significance (or close to significance) on between or within group differences as previously reported [16]. In brief, the effect sizes for the inflammatory markers were IL-6 $d = 0.16$ [p = not significant (NS)], IL-8 $d = -0.40$ (p = NS), IL-10 $d = -0.17$ (p = NS), TNF-alpha $d = 0.50$ (p = NS), IL-6:IL-10 $d = -0.13$ (p = NS), IL-8:IL-10 $d = -0.04$ (p = NS), and TNF-alpha:IL-10 $d = -0.23$ (p = NS). The significant between group differences for the intervention compared with control group included weekly minutes of ≥moderate intensity physical activity (103 ± 89, $p < .01$), walking self-efficacy (12.8 ± 19.5, $p < .05$), exercise social support (2.9 ± 3.4, $p < .01$), and physical activity enjoyment (0.8 ± 1.2, $p < .05$). The potential mediators that did not have significant between group differences but did demonstrate a significant within intervention group change (paired t-test) included percent body fat (-1.1 ± 2.2, $p < .05$), cardiorespiratory fitness (2.8 ± 4.9 ml/kg/min, $p < .05$), anxiety (-4.0 ± 6.5), and PROMIS® fatigue (-3.8 ± 4.1, $p < .01$). The intervention effects on factors not tested as mediators can be found in the previous publication [16].

Freedman and Schatzkin results are provided in Tables 2 and 3. Inflammatory markers and/or pro- to anti-inflammatory ratios significantly mediated PSQI latency (49% to 63%), PSQI efficiency (99% to 129%), PSQI sleep disturbance (37% to 68%), daytime somnolence (16% to 26%), PSQI global sleep disturbance (209% to 284%), number of self-reported hours of sleep per night (88% to 212%), and accelerometer efficiency (21% to

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Table 2. Potential mediators: Correlation of residualized change score with intervention and percent of intervention effect mediated (positive percent) or enhanced (negative percent) by the mediator: Pittsburg Sleep Quality Index (PSQI) subscales and global

	Percent of intervention effect mediated							
Potential mediator[a]	**Sleep quality**	**Latency**	**Sleep duration**	**Efficiency**	**Sleep disturbance**	**Sleep medication**	**Daytime somnolence**	**Global**
IL[b] -6 ($n = 41$)	−5%	14%	2%	36%	9%	−101%	−1%	205%
IL-8 ($n = 42$)	1%	19%	−10%	28%	−27%	−54%	4%	17%
IL-10 ($n = 38$)	−29%**	36%*	18%	116%**	68%***	163%	−3%	335%*
TNF[c]-alpha ($n = 41$)	−7%	16%	26%	129%***	.6%	−357%**	23%**	248%*
IL-6:IL-10 ($n = 38$)	−19%***	49%***	.9%	99%***	37%***	−1%	16%***	209%***
IL-8:IL-10 ($n = 38$)	−28%***	63%***	20%	112%***	26%	−137%	26%***	284%**
TNF-alpha:IL-10 ($n = 38$)	−29%***	24%	0%	127%***	28%	86%	23%**	139%
Weekly minutes ≥ moderate intensity physical activity ($n = 42$)	56%*	−62%	−108%*	−425%***	−41%	263%	−10%	−939%**
Percent body fat ($n = 42$)	−12%	15%	18%	46%	−17%	24%	4%	110%
Fitness ($n = 42$)	36%*	30%	−26%	−156%*	28%	317%	−14%	−229%
Anxiety ($n = 41$)	−4%	−3%	−17%	10%	−33%	−304%	6%	−57%
PROMIS® fatigue ($n = 41$)	34%*	−27%	−60%*	−87%	−114%***	135%	38%**	−595%**
Walking self-efficacy ($n = 41$)	−20%	−7%	20%	−4%	−68%	−74%	−21%	24%
Exercise social support ($n = 41$)	−24%	4%	14%	−179%	−16%	456%	−55%**	63%
Physical activity enjoyment ($n = 41$)	30%	−2%	−53%	−187%**	−33%	459%	17%	−540%*

[a]Total *n* varies due to missing survey on one participant and undetectable levels of IL-6 ($n = 1$), IL-10 ($n = 3$), and TNF-alpha ($n = 1$).
[b]Interleukin.
[c]Tumor necrosis factor.
*$p < .10$.
**$p < .05$.
***$p < .01$.

Table 3. Potential mediators: Correlation of residualized change score with intervention and percent of intervention effect mediated (positive percent) or enhanced (negative percent) by the mediator: Self-reported hours of sleep per night, PROMIS® sleep disturbance, and accelerometer efficiency and latency

	Percent of intervention effect mediated			
Potential mediator	**Self-reported hours of sleep per night**	**PROMIS® sleep disturbance**	**Accelerometer efficiency**	**Accelerometer latency**
IL[b] -6 ($n = 41$)	90%	−39%***	20%*	−22%
IL-8 ($n = 42$)	−39%	12%	6%	−25%
IL-10 ($n = 38$)	212%**	−65%***	36%**	−7%
TNF[c]-alpha ($n = 41$)	180%**	−21%*	8%	−39%*
IL-6:IL-10 ($n = 38$)	88%**	−38%***	21%***	−13%
IL-8:IL-10 ($n = 38$)	201%**	−20%*	23%**	−10%
TNF-alpha:IL-10 ($n = 38$)	135%	−22%*	33%***	−31%
Weekly minutes ≥ moderate intensity physical activity ($n = 42$)	−525%**	92%**	25%	−66%
Percent body fat ($n = 42$)	57%	.7%	−.3%	18%
Fitness ($n = 42$)	−257%*	19%	−2%	62%
Anxiety ($n = 41$)	−58%	9%	14%	−13%
PROMIS® fatigue ($n = -41$)	−278%**	82%***	32%	−47%
Walking self-efficacy ($n = 41$)	9%	52%*	48%*	−16%
Exercise social support ($n = 41$)	−8%	−75%**	11%	80%
Physical activity enjoyment ($n = 41$)	−244%	27%	21%	−58%

[a]Total *n* varies due to missing survey on one participant and undetectable levels of IL-6 ($n = 1$), IL-10 ($n = 3$), and TNF-alpha ($n = 1$).
[b]Interleukin.
[c]Tumor necrosis factor.
*$p < .10$.
**$p < .05$.
***$p < .01$.

36%). Inflammatory changes enhanced the intervention relationship with PSQI sleep quality (−19% to −29%), sleep medication use (−357%), and PROMIS® sleep disturbance (−38% to −65%). Physical activity mediated PROMIS® sleep disturbance (92%) and enhanced the relationship between the intervention and PSQI efficiency

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(−425%), PSQI global (−939%), and hours of sleep per night (−525%). Neither anxiety nor walking self-efficacy was a significant mediator or enhancer for any sleep outcomes. PROMIS® fatigue mediated PSQI daytime somnolence (38%) and PROMIS® sleep disturbance (82%) while enhancing the relationship between the intervention and PSQI sleep disturbance (−114%), PSQI global (−595%), and hours of sleep per night (−278%). Exercise social support was not a significant mediator but enhanced the intervention's relationship with daytime somnolence (−55%) and PROMIS® sleep disturbance (−75%). No significant mediators or enhancers were noted for PSQI sleep duration subscale score and accelerometer latency.

Discussion

Our exercise intervention demonstrated significant effects on the PSQI sleep duration indicating an increase in hours of sleep per night in the control group compared with a minimal decrease in hours of sleep per night for the intervention group. Although not statistically significant, medium standardized effect sizes suggest promising and beneficial exercise intervention effects on PSQI daytime somnolence and accelerometer latency that warrant further study. Inflammation and fatigue mediated and enhanced the intervention relationship with several of the sleep outcomes. Exercise social support and physical activity enjoyment did not mediate but did enhance the intervention relationship with a few of the sleep outcomes.

With regard to mediators, inflammation demonstrated a strong and consistent mediation role for our exercise intervention effects on sleep. The individual markers of inflammation mediating the largest number of sleep outcomes were IL-10 and TNF-alpha. The pro- to anti-inflammatory ratios demonstrated more frequent mediation roles than the individual markers with the IL-6:IL-10 ratio mediating seven of the outcomes. It is also interesting that IL-8 alone did not mediate any of the sleep outcomes but the IL-8:IL-10 ratio mediated six outcomes. This suggests the importance of considering the balance between individual cytokines rather than individual levels alone. Also, it is possible that inconsistent findings related to individual cytokines and sleep in non-cancer populations may be due, in part, to failure to consider the interplay between individual cytokines when examining associations with sleep (e.g. higher serum IL-6 was significantly associated with habitual sleep duration in U.S. adults [33] but no association was noted among British civil service employees [34]).

The medium standardized effect size increase in TNF-alpha is consistent with prior research indicating an association between TNF-alpha and reduced sleep duration [33]. Although the lack of mediation of the PSQI sleep duration subscore by TNF-alpha does not support this relationship, it is noteworthy that when we converted the PSQI sleep duration score to the actual self-reported hours of sleep per night, the intervention effect size was −.68 ($p < .05$) and TNF-alpha was a significant mediator (i.e. 180%, $p = .027$). Also related, a decrease in hours of sleep per night is considered a measure of poorer sleep when interpreting the PSQI scoring. However, the participants' reductions in daytime somnolence in the face of a negative intervention effect on hours of sleep suggests that the sleep, although less, may have felt more restorative to the participant. Further research is needed to evaluate this possibility. Also, the fact that not all sleep outcomes changed in a direction that is typically interpreted as beneficial indicates a complex relationship between sleep and exercise which may partially explain the inconsistent results in prior studies examining the effects of exercise on sleep quality after cancer diagnosis.

The mediating and enhancing effects of fatigue are consistent with the clustering of fatigue and sleep disturbance seen in cancer survivors [35]. It is also not surprising that fatigue mediated the more general measures of sleep which include feelings that could be interpreted as fatigue (i.e. PSQI daytime somnolence and PROMIS® sleep disturbance). Further study is needed to determine if lower fatigue improves sleep and/or if the improved sleep reduces fatigue.

As with many outcomes with a perceived or subjective aspect, measurement is a major challenge in sleep-related research. We did not use the polysomnography for budgetary reasons and in an effort to avoid further increasing the participant study burden. However, perceptions of sleep quality may differ from polysomnography [36], suggesting that perceived sleep quality is a valid and worthwhile measure. Future studies should include accelerometer and self-report measures while also considering the addition of polysomnography to better define changes in sleep architecture which may occur and explain the observed mediating and enhancing relationships.

Because of the pilot nature of our study, our report is limited by the small sample size which was based on budgetary and logistical restraints. However, our study suggests novel and important relationships warranting further research. Future studies should account for the timing of exercise bouts relative to bedtime, measure time asleep during the day (and not just at night), and obtain assessments at ≥ 3 time points to examine the potential reciprocal relationships between sleep and fatigue. Moreover, our results only apply to breast cancer survivors who have completed primary treatment. Testing is needed to determine if our results can be generalized to patients who are on-treatment or suffer from other cancer types. Last, we acknowledge that our study is limited by the inability to differentiate between the effects of exercise distinct from psychosocial effects that may have resulted from our discussion groups and staff support (i.e. no attentional control was used). Nevertheless, our study is among the few to assess sleep response to exercise using an objective sleep measure and the only randomized controlled

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exercise and cancer trial to date to use mediation analyses to examine the mediating roles of inflammation and psychosocial factors in sleep response to an exercise intervention.

The effect of exercise on sleep quality in cancer survivors continues to be perceived as beneficial, but the topic is understudied and results to date have been inconsistent. Our results support continued investigation of inflammation as an underlying mechanism explaining exercise effects on sleep. Whether this mechanism contributes to the inter-relationships among sleep disturbance, exercise, and cancer risk warrants further study. Future research should also examine which exercise types, intensities, and durations result in inflammatory profiles most likely to improve sleep quality and moderators of exercise response (e.g. age). Exercise interventions aimed at treating poor sleep quality in breast cancer survivors should consider behavioral interventions for psychosocial factors that may play a role. In addition, an improved understanding of the sleep dimensions most likely to respond to exercise can be used to target those survivors most apt to experience sleep improvements with an exercise intervention.

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Conflict of interest

The authors have declared no conflict of interest.

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