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CLINICAL TRIAL

Effects of exercise dose and type on sleep quality in breast cancer patients receiving chemotherapy: a multicenter randomized trial

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Abstract To examine the effects of different doses and types of exercise on sleep quality in breast cancer patients receiving chemotherapy. A multicenter trial in Canada randomized 301 breast cancer patients between 2008 and 2011 to thrice weekly, supervised exercise during chemotherapy consisting of either a standard dose of 25–30 min of aerobic exercise (STAN; $n = 96$), a higher dose of 50–60 min of aerobic exercise (HIGH; $n = 101$), or a combined dose of 50–60 min of aerobic and resistance exercise (COMB; $n = 104$). The secondary sleep outcomes in the trial were assessed by the Pittsburgh Sleep Quality Index (PSQI) at baseline, twice during chemotherapy, and postchemotherapy. We analyzed the global PSQI and the component scores. Repeated measures analyses of variance indicated that the HIGH group was statistically superior to the STAN group for global sleep quality (mean group difference = −0.90; 95 % CI −0.05 to −1.76; $p = 0.039$) as well as subjective sleep quality ($p = 0.028$) and sleep latency ($p = 0.049$). The COMB group was borderline statistically superior to the STAN group for global sleep quality (mean group difference = −0.76; 95 % CI +0.11 to −1.62; $p = 0.085$) as well as sleep duration ($p = 0.051$); and statistically superior for sleep efficiency ($p = 0.040$), and percentage of poor sleepers ($p = 0.045$). Compared to a standard volume of aerobic exercise, higher volumes of both aerobic and combined exercise improved some aspects of sleep quality during breast cancer chemotherapy. Exercise may be an attractive option to manage sleep dysfunction in cancer patients during chemotherapy.

Keywords Cancer survivor · Exercise · Physical activity · Sleep quality

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Introduction

Sleep problems are common in cancer patients [1], especially during chemotherapy [2]. Poor sleep quality can lead to fatigue, pain, depression, poor functioning, reduced quality of life, and even poor outcomes [3]. Pharmacological interventions have been shown to improve sleep problems in cancer patients but may have side effects [4]. Exercise may be an attractive option for managing sleep problems because of its favorable safety profile and its positive effects on other important health outcomes [5, 6]. The mechanisms for how exercise may improve sleep quality are unknown; however, possible mechanisms include changes in body weight, physical fitness, anxiety, depression, pain, circadian rhythms, and thermogenic regulation [7, 8].

Two recent systematic reviews of exercise interventions during [5] and after [6] cancer treatments identified 20 trials involving over 1,000 cancer patients that reported sleep quality as an endpoint. The overall findings suggested that exercise has a modest beneficial effect on sleep quality both during and after cancer treatment. Almost all of these trials, however, were pilot studies with small sample sizes under 100, heterogeneous samples of mixed cancer diagnoses, and unsupervised exercise interventions. Moreover, none of these trials compared different types or doses of exercise to identify the optimal exercise prescription for managing sleep problems in cancer patients [5, 6]. Here, we report what we believe to be the largest exercise trial to date to examine sleep quality in cancer patients, and the first to examine exercise dose and type effects.

The combined aerobic and resistance exercise (CARE) trial was designed to compare two different doses and types of exercise for improving physical functioning and symptoms in breast cancer patients receiving chemotherapy [9]. The CARE trial addressed the dose versus type question by comparing a thrice weekly standard dose of 25–30 min of aerobic exercise (STAN) to a higher dose of 50–60 min of aerobic exercise (HIGH) and a combined dose of 50–60 min of aerobic and resistance exercise (COMB). In the primary paper, we reported several positive effects of the higher dose interventions compared to the standard dose intervention for physical functioning and symptom management [9]. In the present paper, we report the sleep outcomes which were planned secondary outcomes. Based on previous research in postmenopausal women [10], we hypothesized that both HIGH and COMB (an exercise dose effect) would be superior to STAN for improving sleep quality. The comparison of HIGH to COMB (an exercise-type effect) was considered exploratory. Moreover, we examined potential moderators of the intervention effect to inform more targeted interventions in future research.

Methods

Setting and participants

The CARE trial methods have been reported elsewhere [9]. Briefly, the CARE trial was a multicenter trial with recruitment in Edmonton (coordinating center), Ottawa, and Vancouver, Canada. The trial received ethics approval from all three centers and written informed consent from all participants. Eligibility criteria included English or French speaking non-pregnant women ≥18 years old with stage I–IIIc breast cancer initiating adjuvant chemotherapy. Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominis muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, psychiatric illness, or otherwise were not approved by their oncologist. Eligible participants were identified by their treating oncologist prior to chemotherapy.

Randomization

After baseline assessments, participants were stratified by center and chemotherapy protocol (any Herceptin vs. no Herceptin/any taxane vs. no Herceptin/no taxane) and randomly assigned to STAN, COMB, or HIGH in a 1:1:1 ratio using a computer-generated program. The allocation sequence was generated in Edmonton and concealed from the project directors at each site who assigned participants to groups.

Exercise training interventions

The exercise training interventions have been described in detail elsewhere [9]. Briefly, participants exercised for the duration of their chemotherapy schedule. STAN followed the Physical Activity Guidelines for Americans [11] which have been endorsed for cancer survivors by the American College of Sports Medicine [12] and the American Cancer Society [13]. These guidelines recommend a minimum of 75 min/week of vigorous aerobic exercise spread over 3 days/week (i.e., 3 days/week for 25–30 min/session). HIGH followed double the minimum guidelines of 150 min/week of vigorous aerobic exercise per week (i.e., 3 days/week for 50–60 min/session). COMB followed the same aerobic exercise guideline as STAN plus a standard strength training program for 3 days/week, consisting of two sets of 10–12 repetitions of nine different strength exercises at 60–75 % of their estimated one repetition maximum (RM). COMB completed about 30–35 min of strength exercise for a total of about 50–60 min of combined exercise.

Assessment of primary and secondary sleep endpoints

Sleep quality was assessed at baseline (usually before chemotherapy but always before the second cycle of chemotherapy), approximately one-third and two-thirds of the way through chemotherapy, and postchemotherapy (3–4 weeks after chemotherapy) with the Pittsburgh Sleep Quality Index (PSQI) which has been validated in cancer patients [14, 15]. The PSQI is a 19-item self-report scale that measures sleep quality over the past month. Seven sleep components are assessed including subjective sleep quality, latency, duration, efficiency, disturbances, medication use, and daytime dysfunction [14]. Each component is rated on a 0–3 scale with lower scores indicating better sleep quality. The seven components can be summed to obtain a global sleep quality score ranging from 0 to 21. Scores >5 on the global sleep quality scale are indicative of poor sleep quality [14]. Given the length of the questionnaire in the CARE trial, we excluded the sleep disturbances component of the PSQI because it required 9 of the 19 items. Consequently, our global sleep quality score was based on the remaining six component scores. For comparison with other studies, we prorated the global sleep quality scale to range from 0 to 21 and used the standard cut-point for poor sleep quality of >5.0.

Selection and assessment of moderators

We selected ten moderators for analyses based on their scientific plausibility, clinical utility, and support in previous research [16, 17]. The moderators assessed by self-report consisted of age (<50 vs. ≥50 years), meeting aerobic exercise guidelines at baseline (< vs. ≥150 min of exercise/week), meeting strength exercise guidelines at baseline (< vs. ≥two sessions/week), and number of comorbidities (0 vs. ≥1). Body mass index (BMI) was measured objectively by body weight and height and dichotomized into non-obese (<29.9 kg/m^2) versus obese (≥30 kg/m^2). Baseline aerobic fitness was evaluated with a maximal treadmill protocol using gas exchange analyses and divided into a median split of low fitness (<27.5 ml/kg/min) versus high fitness (≥27.5 ml/kg/min). The medical moderators were abstracted from medical records and included disease stage (stages I/IIa vs. stages IIb/III), type of surgery (lumpectomy vs. mastectomy), and chemotherapy protocol (anthracyclines vs. no anthracyclines). We also examined baseline sleep quality by dichotomizing the baseline global sleep quality score into "good" sleepers and "poor" sleepers based on the recommended cut-point of ≤5 (good sleepers) versus >5 (poor sleepers).

Data analyses

The CARE trial was originally powered to examine the effects of exercise on patient-reported physical functioning. A meaningful change on the PSQI has not been identified. Nevertheless, with 100 participants per group, the CARE trial had 80 % power to detect a standardized effect size (mean difference divided by standard deviation) of about 0.40 for patient-reported outcomes using a two-tailed alpha of 0.05. This effect size is consistent with the range of 0.33–0.50 that is suggested as meaningful for many patient-reported outcomes [18] and may be appropriate for the PSQI as a patient-reported outcome. The trial was not powered for interaction tests; consequently, these analyses are considered exploratory and hypothesis-generating. The primary sleep outcome for this study was the global sleep quality score, which was also used in all moderator analyses. Repeated measures analyses of variance were used to test the main effects as well as interaction effects. We modeled each sleep outcome at the three post-randomization time points to compare the average mean differences among arms, assumed to be common across the three time points [19]. Our primary analysis was adjusted for the baseline value of the outcome, age, education, previous exercise, BMI, disease stage, surgery type, and chemotherapy protocol except when a covariate was tested as the moderator. Standardized effect size d was reported for significant comparisons by dividing the mean between group differences by the pooled baseline SD for the entire sample. For all analyses, we employed the intention-to-treat principle and included all participants with complete follow-up data.

Results

Participant flow through the trial has been reported elsewhere [9]. Briefly, we randomized 301 of 728 (41 %) eligible patients between April 2008 and September 2011. We obtained patient-reported outcome data, including the sleep outcomes, on 299 (99.3 %) patients at midpoint #1, 298 (99.0 %) at midpoint #2, and 298 (99.0 %) at postintervention with complete data on 296 (98.3 %) patients. The distribution of the proposed moderators is reported in Table 1. The baseline mean global sleep quality score was 6.20 (SD = 4.10) with 154 (52.0 %) patients reporting poor sleep at baseline. Adherence to the exercise interventions is reported elsewhere [9]. Briefly, STAN, HIGH, and COMB completed 88 % (43/49), 82 % (40/49), and 78 % (39/50) of their prescribed aerobic exercise sessions, with 88 % supervised. Average duration of the aerobic exercise sessions was 28 (SD = 4), 48 (SD = 8), and 27 (SD = 3) min, respectively, for STAN, HIGH, and COMB and the resulting average weekly minutes of aerobic exercise were 73 (SD = 17), 120 (SD = 39), and 64 (SD = 19). COMB attended 66 % (33/50) of their resistance exercise sessions and completed ≥98 % of their weight training prescription each session.

Main effects of exercise dose and type on sleep quality

Table 2 reports the main effects of the exercise interventions on sleep quality. Figure 1 depicts the pattern of intervention effects on the primary sleep outcome of global sleep quality across the three postrandomization time points. The HIGH group was statistically superior to the STAN group for the primary sleep outcome of global sleep quality (mean group difference = −0.90; 95 % CI −0.05 to −1.76; $p = 0.039$; $d = 0.22$) as well as subjective sleep quality ($p = 0.028$; $d = 0.26$) and sleep latency ($p = 0.049$; $d = 0.18$). The

Table 1 Baseline Distribution of Proposed Moderators in the CARE Trial, Canada, 2008–2011

Variable	Overall ($N = 296$)	STAN ($n = 95$)	HIGH ($n = 99$)	COMB ($n = 102$)
Age (mean, SD) no. (%)	50.0 (8.7)	49.5 (8.0)	49.9 (8.7)	50.5 (9.4)
<50 years	148 (50.0)	50 (52.6)	55 (55.6)	43 (42.2)
≥50 years	148 (50.0)	45 (47.4)	44 (44.4)	59 (57.8)
Disease stage, no. (%)				
I/IIa	203 (68.6)	62 (65.3)	70 (70.7)	71 (69.6)
IIb/IIIa	93 (31.4)	33 (34.7)	29 (29.3)	31.(30.4)
Surgical protocol, no. (%)				
Lumpectomy	167 (56.4)	47 (49.5)	57 (57.6)	63 (61.8)
Mastectomy	129 (43.6)	48 (50.5)	42 (42.4)	39 (38.2)
Chemotherapy regimen, no. (%)				
No anthracyclines	214 (72.3)	62 (65.3)	74 (74.7)	78 (76.5)
Anthracyclines	82 (27.7)	33 (34.7)	25 (25.3)	24 (23.5)
Comorbidities, no. (%)				
None	132 (44.6)	49 (51.6)	45 (45.5)	38 (37.3)
≥1	164 (55.4)	46 (48.4)	54 (54.5)	64 (62.7)
Baseline aerobic exercise, no. (%)				
Not meeting guidelines	207 (69.9)	66 (69.5)	71 (71.7)	70 (68.6)
Meeting guidelines	89 (31.1)	29 (30.5)	28 (28.3)	32 (31.4)
Baseline strength exercise, no. (%)				
Not meeting guidelines	234 (79.1)	75 (78.9)	81 (81.8)	78 (76.5)
Meeting guidelines	62 (20.9)	20 (21.1)	18 (18.2)	24 (23.5)
Baseline aerobic fitness, no. (%)				
<27.5 ml/kg/min	145 (49.0)	43 (45.3)	43 (43.4)	59 (57.8)
≥27.5 ml/kg/min	151 (51.0)	52 (54.7)	56 (56.6)	43 (42.2)
Body mass index (mean, SD) no. (%)	26.5 (5.6)	26.1 (4.9)	25.2 (4.5)	28.3 (6.6)
Non-obese	227 (76.7)	79 (83.2)	84 (84.8)	64 (62.7)
Obese	69 (23.3)	16 (16.8)	15 (15.2)	38 (37.3)
Baseline sleep quality[1], (mean, SD) no. (%)	6.20 (4.10)	6.14 (3.91)	6.23 (4.35)	6.22 (4.07)
Poor sleepers	154 (52.0)	46 (48.4)	52 (52.5)	56 (54.9)
Good sleepers	142 (48.0)	49 (51.6)	47 (47.5)	46 (45.1)

STAN standard aerobic exercise program, *HIGH* high volume aerobic exercise program, *COMB* combined aerobic and resistance exercise program

[1] Defined as a global PSQI > 5 (poor sleepers) versus ≤5 (good sleepers)

COMB group was borderline statistically superior to STAN for global sleep quality (mean group difference = −0.76; 95 % CI +0.11 to −1.62; $p = 0.085$; $d = 0.19$) as well as sleep duration ($p = 0.051$; $d = 0.22$); and statistically superior for sleep efficiency ($p = 0.040$; $d = 0.24$), and percentage of poor sleepers ($p = 0.045$; $d = 0.20$). The HIGH group was statistically superior to COMB for sleep latency ($p = 0.040$; $d = 0.20$).

Moderators of the effects of exercise dose and type on sleep quality

There were statistically significant or borderline significant interactions for five of the ten moderators including type of surgery (p for interaction = 0.002; Fig. 2a), baseline aerobic fitness (p for interaction = 0.037; Fig. 2b), baseline aerobic exercise guidelines (p for interaction = 0.093; Fig. 2c), baseline strength exercise guidelines (p for interaction = 0.058; Fig. 2d), and number of comorbidities (p for interaction = 0.068; Fig. 2e). Overall, the effect of HIGH compared to STAN on global sleep quality was stronger for patients treated with lumpectomy ($p < 0.001$; $d = 0.60$), with no comorbidities ($p = 0.002$; $d = 0.50$), meeting aerobic exercise guidelines at baseline ($p = 0.005$; $d = 0.63$), and aerobically fitter at baseline ($p = 0.008$; $d = 0.40$). The effects of COMB versus STAN were stronger for patients treated with lumpectomy ($p = 0.009$; $d = 0.39$), meeting strength exercise guidelines at baseline

Table 2 Effects of exercise dose and type on sleep quality in breast cancer patients receiving chemotherapy, Canada, 2008–2011

	Baseline *M* (SD)	Adjusted mean follow-up score[1,2] *M* (SE)	Adjusted between group differences during follow-up[1,2]		
			COMB versus STAN *M* [95 % CI]; *p* value	HIGH versus STAN *M* [95 % CI]; *p* value	HIGH versus COMB *M* [95 % CI]; *p* value
Global sleep quality (0–21)					
STAN	6.14 (3.91)	7.61 (0.31)	−0.76 [+0.11 to −1.62];0.085	−0.90 [−0.05 to −1.76]; 0.039	−0.15 [+0.71 to −1.00]; 0.74
HIGH	6.23 (4.35)	6.71 (0.31)			
COMB	6.22 (4.07)	6.86 (0.30)			
Subjective sleep quality (0–3)					
STAN	1.15 (0.64)	1.34 (0.06)	−0.08 [+0.08 to −0.25]; 0.31	−0.18 [−0.02 to −0.34]; 0.028	−0.10 [+0.06 to −0.26]; 0.24
HIGH	1.25 (0.73)	1.15 (0.06)			
COMB	1.06 (0.73)	1.25 (0.06)			
Sleep latency (0–3)					
STAN	0.71 (0.84)	0.86 (0.06)	+0.01 [+0.17 to −0.16]; 0.93	−0.16 [−0.00 to −0.33]; 0.049	−0.17 [−0.01 to −0.34]; 0.040
HIGH	0.69 (0.86)	0.70 (0.06)			
COMB	0.82 (0.89)	0.87 (0.06)			
Sleep duration (0–3)					
STAN	0.91 (0.91)	1.13 (0.07)	−0.21 [+0.00 to −0.41]; 0.051	−0.17 [+0.04 to −0.37]; 0.11	+0.04 [+0.24 to −0.17]; 0.72
HIGH	0.97 (0.95)	0.96 (0.07)			
COMB	0.99 (0.96)	0.93 (0.07)			
Sleep efficiency (0–3)					
STAN	0.95 (1.07)	1.26 (0.09)	−0.25 [−0.01 to −0.49]; 0.040	−0.14 [+0.10 to −0.38]; 0.24	+0.11 [+0.34 to −0.13]; 0.37
HIGH	0.90 (1.09)	1.12 (0.08)			
COMB	0.91 (1.03)	1.01 (0.08)			
Sleep medication (0–3)					
STAN	0.79 (1.18)	0.91 (0.08)	−0.07 [+0.16 to −0.30]; 0.55	−0.04 [+0.19 to −0.27]; 0.73	+0.03 [+0.26 to −0.20]; 0.80
HIGH	0.75 (1.21)	0.87 (0.08)			
COMB	0.77 (1.18)	0.84 (0.08)			
Daytime dysfunction (0–3)					
STAN	0.77 (0.66)	1.01 (0.05)	−0.05 [+0.08 to −0.18]; 0.47	−0.04 [+0.10 to −0.17]; 0.60	+0.01 [+0.15 to −0.12]; 0.85
HIGH	0.79 (0.70)	0.98 (0.05)			
COMB	0.77 (0.69)	0.96 (0.05)			
Poor sleepers (%)[3]					
STAN	51.6 (50.2)	64.0 (3.5)	−10.0 [−0.2 to +19.8]; 0.045	−7.3 [+2.5 to −17.0]; 0.14	+2.8 [+12.5 to −7.0]; 0.58
HIGH	47.5 (50.2)	56.7 (3.5)			
COMB	45.1 (50.0)	54.0 (3.4)			

STAN standard aerobic exercise program, *HIGH* high volume aerobic exercise program, *COMB* combined aerobic and resistance exercise program

[1] Follow-up score is the average for midpoint #1, midpoint #2, and postintervention based on repeated measures analyses

[2] Analyses are adjusted for baseline value of the outcome, age, education, baseline exercise, comorbidities, body mass index, disease stage, surgery type, and chemotherapy protocol

[3] Poor sleepers defined as a global PSQI > 5

($p = 0.064$; $d = 0.45$), and aerobically fitter at baseline ($p = 0.003$; $d = 0.50$).

Discussion

A higher dose of aerobic exercise was statistically superior to a standard dose of aerobic exercise for managing global sleep quality, subjective sleep quality, and sleep latency in breast cancer patients receiving chemotherapy. Combined exercise was statistically superior for sleep duration and % of poor sleepers; and borderline significant for global sleep quality and sleep duration. The PSQI does not identify a clinically important difference but our effect size of ≈ -0.90 points on the global sleep quality scale translates into a standardized effect size d of ≈ -0.20. This effect

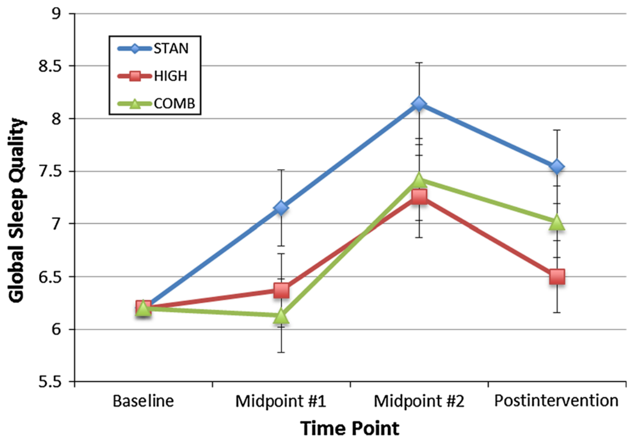

Fig. 1 Effects of exercise dose and type on global sleep quality during breast cancer chemotherapy. *Note* Means and standard errors are based on adjusted analyses. *STAN* standard aerobic exercise program, *HIGH* high volume aerobic exercise program, *COMB* combined aerobic and resistance exercise program. Lower sleep quality scores indicate better sleep quality

size would be considered small; however, the modest effect was obtained over and above a standard aerobic exercise program. Two recent systematic reviews of exercise interventions and sleep quality in cancer patients reported a standardized effect size d of ≈ -0.40 when comparing exercise to no intervention [5, 6]. The comparison of higher dose exercise programs with a standard dose of aerobic exercise provides a more rigorous test of the causal effects of exercise on sleep quality because it controls for the many non-exercise-related factors that may improve sleep quality including travel to the fitness center, interactions with the trainer or other participants, expectation of benefit, and cognitive dissonance. Moreover, if the small effect of the higher dose exercise interventions is added to the medium effect reported in trials that compared exercise to no intervention, it is possible that the total effect of the higher dose exercise interventions on sleep quality could be $d = -0.60$, which would be meaningful.

Moreover, our results are also comparable to a recent large-scale yoga trial in cancer survivors. Mustian et al. [20] compared 4 weeks of group-based yoga classes to a wait-list control group in 410 cancer survivors with at least moderate sleep disturbance within 2–24 months after primary treatment. The effect of the yoga intervention on global sleep quality was approximately −0.80 points on the PSQI, roughly equivalent to our trial. These data suggest that the benefits of higher dose exercise compared to standard dose exercise are comparable to the benefits of yoga compared to no intervention. A comparative effectiveness trial of exercise versus yoga for sleep outcomes may shed light on the relative merit of these two interventions.

The temporal effects of the higher dose exercise interventions on sleep quality during chemotherapy are also informative (Fig. 1). Consistent with previous research [2], sleep quality in general worsened over the course of chemotherapy with some improvement after chemotherapy but not back to baseline levels. Consequently, the effect of the higher dose exercise interventions was to mitigate some of the decline in sleep quality during chemotherapy. Importantly, the benefits of the higher dose exercise interventions were already evident one-third of the way through chemotherapy and were maintained two-thirds of the way through chemotherapy and 3–4 weeks postchemotherapy. These data suggest that the modest effects of higher dose exercise on sleep quality are fast-acting and durable and, therefore, experienced throughout the entire course of chemotherapy.

In terms of the sleep components most affected by higher dose exercise, the HIGH group was superior to STAN for subjective sleep quality and sleep latency. Conversely, the COMB group was superior to STAN for sleep efficiency and borderline superior for sleep duration. Moreover, the only "exercise-type" effect was for sleep latency with HIGH being superior to COMB. Mishra et al. [5, 6] did not report the separate effects of exercise on the sleep components in their systematic reviews with cancer patients. In a systematic review of six trials involving 305 older adults with sleep problems, Yang et al. [21] reported that exercise had positive effects on subjective sleep quality, sleep latency, and sleep medication use, but not on sleep duration, sleep efficiency, sleep disturbance, and daytime dysfunction. These systematic review findings are most consistent with the effects of our higher dose aerobic exercise intervention, which is not be surprising given that 5 of the 6 studies in the systematic review tested aerobic exercise interventions. It is possible that different types and doses of exercise may have differential effects on the different sleep components.

Several significant and borderline significant interaction effects identified that the higher dose exercise interventions may be more beneficial for certain subgroups. The subgroups identified in the present study suggest additional benefit for patients with *better* physical functioning at baseline (e.g., lumpectomy, no comorbidities, regular exerciser, aerobically fitter). This pattern of findings is in contrast to our healthy exercise for lymphoma patients (HELP) trial where we found that a standard aerobic exercise intervention compared to no exercise provided greater sleep benefits to lymphoma patients with *worse* physical functioning at baseline (e.g., obese, receiving chemotherapy, newly diagnosed, existing disease) [22]. Taken together, these data suggest that standard exercise volumes and yoga programs may be most beneficial to exercise-naïve patients with modest functioning. Conversely, higher dose exercise interventions may be most

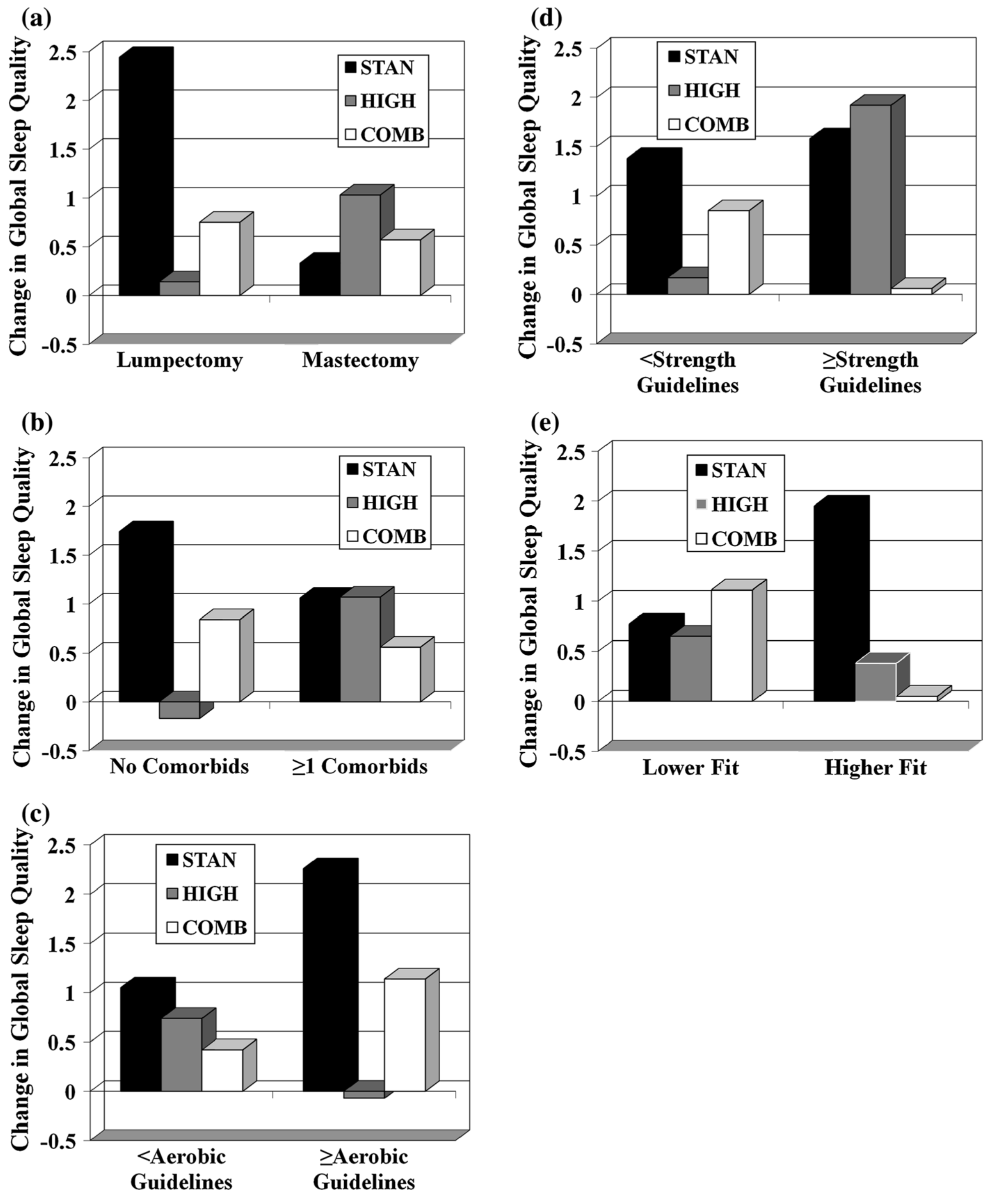

Fig. 2 Effects of exercise dose and type on change in global sleep quality during breast cancer chemotherapy by **a** type of surgery, **b** number of comorbidities, **c** baseline aerobic exercise, **d** baseline strength exercise, and **e** baseline aerobic fitness. *STAN* standard aerobic exercise program, *HIGH* high volume aerobic exercise program, *COMB* combined aerobic and resistance exercise program. Lower sleep quality scores indicate better sleep quality

beneficial to exercise-savvy patients with good functioning because they have the necessary capacity to complete and respond to such higher dose exercise interventions. Additional research identifying which cancer patients respond best to which type and dose of exercise intervention is warranted.

Several factors may explain the generally positive effects of our higher dose exercise interventions on sleep quality in the CARE trial. First, we previously reported positive effects of the higher dose exercise interventions on endocrine symptoms [9]. Previous studies have suggested that endocrine symptoms, including vasomotor symptoms and hot flashes, are related to sleep disturbance during chemotherapy [23, 24]. Second, we also reported positive effects on bodily pain which has also been shown to be a strong predictor of sleep problems in cancer patients [25, 26]. Finally, improvements in aerobic fitness and muscular strength might also be related to improved sleep quality [27, 28]. Research on the mechanisms of how exercise may improve sleep quality is needed.

Our trial's strengths include being the largest exercise RCT to examine sleep quality in cancer patients, the innovative design that simultaneously examined exercise dose and type effects, the well-defined population, multi-center recruitment, supervised exercise, good adherence rates, use of a validated self-report measure of sleep quality at multiple time points, intention-to-treat analysis, and trivial loss-to-follow-up. Limitations include the 41 % recruitment rate, the fact that sleep quality was not our primary outcome, the exclusion of the sleep disturbances component of the PSQI which may have affected the overall validity of the scale, and the failure to include an objective sleep measure. Moreover, the primary criticism of the exercise and sleep quality literature is that the majority of participants in these trials are good sleepers [8]. Although we did not target breast cancer patients with sleep problems at baseline in the CARE trial, over 50 % of our study patients were poor sleepers at baseline and this percentage increased during chemotherapy. Moreover, we found no interaction between baseline sleep quality and the effectiveness of the higher dose exercise interventions, suggesting that the interventions were equally beneficial to patients with clinical levels of poor sleep quality. In terms of dissemination, this exercise intervention could be implemented at other cancer centers and community-based fitness centers with appropriate facilities and qualified staff. Given its sophisticated exercise training principles and required motivation, it is unclear if such a program could be self-directed by breast cancer patients receiving chemotherapy.

In summary, our analyses of the secondary sleep outcomes from the CARE trial suggest that higher doses of aerobic or combined exercise improve sleep quality compared to a standard dose of aerobic exercise, especially for patients with better baseline physical functioning (e.g., breast-conserving surgery, no other comorbidities, previous exercise experience). Given the benefits of exercise on other outcomes in cancer patients, higher dose exercise interventions may be an attractive intervention to manage sleep disturbances in breast cancer patients with good functioning. Additional research on the optimal exercise prescription to improve sleep quality in diverse cancer patient groups is needed.

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