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Research Article

A Randomized Trial of Aerobic Exercise and Sleep Quality in Lymphoma Patients Receiving Chemotherapy or No Treatments

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Abstract

Background: Patients with lymphoma experience sleep problems that may be managed with aerobic exercise but no previous study has examined this issue.

Methods: We randomized 122 patients with lymphoma to usual care ($n = 62$) or 12 weeks of supervised aerobic exercise training (AET; $n = 60$). Our primary sleep endpoint was global sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI). Secondary endpoints were the PSQI component scores. Planned subgroup analyses were also conducted.

Results: Intention-to-treat analyses indicated that AET resulted in a nonsignificant ($P = 0.16$) improvement in global sleep quality compared with usual care [mean group difference = −0.64; 95% confidence interval (CI), −1.56 to +0.27]. In planned subgroup analyses, statistically significant or borderline significant interactions were identified for type of lymphoma ($P_{interaction} = 0.006$), current treatment status ($P_{interaction} = 0.036$), time since diagnosis ($P_{interaction} = 0.010$), body mass index ($P_{interaction} = 0.075$), and baseline sleep quality ($P_{interaction} = 0.041$). Specifically, AET improved global sleep quality in patients with lymphoma who had indolent non–Hodgkin lymphoma ($P = 0.001$), were receiving chemotherapy ($P = 0.013$), were <2 years post-diagnosis ($P = 0.005$), were obese ($P = 0.025$), and were poor sleepers at baseline ($P = 0.007$).

Conclusions: AET did not significantly improve sleep quality in this heterogeneous sample of patients with lymphoma; however, clinically identifiable subgroups appeared to benefit. Future exercise trials targeting these responsive subgroups are needed to confirm these findings.

Impact: If replicated in larger and more focused trials, aerobic exercise may be an attractive option to manage sleep dysfunction in patients with cancer because of its favorable safety profile and other documented health benefits. *Cancer Epidemiol Biomarkers Prev; 21(6); 887–94. ©2012 AACR.*

Introduction

Sleep disturbance is a common problem in patients with cancer (1) that is associated with deleterious outcomes including fatigue, pain, depression, poor functioning, reduced quality of life, and worse prognosis (2). Many cancer patient groups experience sleep difficulties including patients with lymphoma (3). Few interventions have been shown to improve sleep outcomes in patients with cancer including pharmacologic interventions (2). Moreover, pharmacologic interventions for sleep problems may be associated with higher risks of death and cancer incidence (4). For non pharmacologic interventions, a recent systematic review of 47 studies in more than 3,200 patients with cancer concluded that cognitive behavioral therapy is moderately effective for improving sleep outcomes whereas evidence for other interventions such as complementary medicine, education/information, and exercise remains limited (5).

Exercise may be a particularly attractive option for managing sleep disturbances in patients with cancer because of its favorable safety profile and its positive effects on other important health outcomes including physical functioning (6), fatigue (7), depression (8), and quality of life (9). Exercise may improve sleep quality through various mechanisms including alterations in body weight, physical fitness, anxiety, depression, pain, circadian rhythms, and thermogenic regulation (10, 11). Seven randomized controlled trials (RCT) have examined the effects of exercise on sleep quality in patients with cancer (10, 12–15); however, these trials have largely been pilot studies limited by small sample sizes under 75 (10, 12, 14–17), heterogeneous samples with mixed cancer

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diagnoses (9, 12, 15), unsupervised exercise interventions (10, 12–14, 16, 17), and short exercise interventions of <12 weeks (10, 16, 17). Three of these trials have shown significant improvements in sleep quality (10, 14, 17) whereas 4 have not (12, 13, 15, 16).

Here, we report what we believe to be the largest exercise RCT to date to examine sleep quality in patients with cancer and the first to examine sleep quality in patients with lymphoma. The Healthy Exercise for Lymphoma Patients (HELP) Trial was an RCT comparing 12 weeks of supervised aerobic exercise training (AET) with usual care (UC) in 122 patients with lymphoma receiving chemotherapy or no treatments. We included patients receiving chemotherapy or off-treatments to explore potential differences in response by treatment status. We previously reported the main outcomes of the HELP Trial showing that AET was superior to UC for improving physical functioning, quality of life, fatigue, depression, cardiovascular fitness, and body composition (18). In the present study, we report the secondary sleep outcomes. We hypothesized that AET would be superior to UC for improving sleep quality. Moreover, we examined potential moderators of the intervention effects on the basis of clinically relevant indicators.

Materials and Methods

The HELP Trial methods have been reported elsewhere (18). Briefly, the study was a single-center, two-armed RCT. Ethical approval was obtained from the University of Alberta (Edmonton, AB, Canada) and the Alberta Cancer Board, and all participants provided written informed consent.

Setting and participants

Participants were recruited in Edmonton (AB, Canada) and were eligible if they were English speaking, ≥18 years old, had histologically confirmed Hodgkin lymphoma (HL) or non–Hodgkin lymphoma (NHL), and were receiving chemotherapy or no treatments. Patients were excluded if they had uncontrolled hypertension or cardiac illness, lived >80 km from the facility, or were not approved by their oncologist. Eligible patients were identified in clinic by oncologists or through a mailed invitation using the Alberta Cancer Registry.

Randomization

After baseline tests, participants were stratified by type of lymphoma (HL vs. indolent NHL vs. aggressive NHL) and current treatment status (receiving chemotherapy vs. no treatments) and randomized to AET or UC using a computer-generated program with an independently generated allocation sequence that was concealed from the study coordinator.

Intervention

The AET group received a 12-week supervised exercise program that consisted of 3 exercise sessions per week on a cycle ergometer (Life Fitness). Intensity began at 60% of peak power output that corresponded to peak oxygen consumption (V_{O_2}peak) and was increased by 5% each week to 75% by the fourth week. Duration began at 15 to 20 minutes for the first 4 weeks and increased by 5 minutes per week until 40 to 45 minutes in the ninth week. Threshold and peak interval training sessions were introduced at weeks 7 and 9, respectively. Adherence was supported by flexible hours, scheduled exercise sessions, telephone follow-up after missed sessions, positive reinforcement, and paid parking. Unsupervised exercise was not encouraged but prescriptions for unsupervised exercise were provided for the few patients unable or unwilling to attend supervised exercise sessions. These unsupervised sessions were not counted in the adherence calculation. UC participants were asked not to increase their exercise from baseline but were offered 4 weeks of supervised exercise after post-intervention assessments. Adherence was measured objectively by tracking attendance.

Assessment of primary and secondary sleep endpoints

Sleep quality was assessed at baseline (1–2 weeks before randomization) and post-intervention (within 1–2 weeks after the 12-week exercise intervention) with the validated Pittsburgh Sleep Quality Index (PSQI; ref. 19) which has also been validated in patients with cancer (20). 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 (19). Each component is rated on a 0 to 3 scale with lower scores indicating better sleep quality. The 7 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 (19). Given the length of the questionnaire in the HELP 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 6 component scores and ranged from 0 to 18. Accordingly, we prorated the cutoff point for poor sleep quality to ≥4.3.

Selection and assessment of moderators

We selected 9 moderators for analyses on the basis of their scientific plausibility, clinical use, and support in previous research (21, 22). The demographic and behavioral moderators were assessed by self-report and consisted of age (<50 years vs. ≥50 years), sex, and meeting physical activity guidelines at baseline based on 150 minutes of exercise per week (23) as measured by the Leisure Time Exercise Questionnaire (24). Body mass index (BMI) was assessed objectively by measured body mass and height and dichotomized into nonobese (<29.9 kg/m^2) and obese (≥30 kg/m^2) patients. The medical moderators were abstracted from medical records and included the 2 stratification variables of type of lymphoma (aggressive NHL vs. indolent NHL vs. HL) and current

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treatment status (no treatments vs. receiving chemotherapy). Disease stage was divided into no evidence of disease, stage I/II, and stage III/IV. Time since diagnosis was divided into <2 versus ≥2 years. We also examined baseline sleep quality by dichotomizing the baseline global sleep quality score into "good" sleepers and "poor" sleepers on the basis of our prorated cutoff point of <4.3 (good sleepers) versus ≥4.3 (poor sleepers).

Data analyses

The HELP Trial was powered to detect a medium standardized effect size (*d*) of approximately 0.50 SDs on the primary patient-reported outcome of physical functioning (17). For a power of 0.80 and 2-tailed α <0.05, 60 patients per group were required. This level of power remains intact for the main effects analyses of the present study. The trial was not originally powered to detect interactions or subgroup effects. The primary sleep outcome in the present study was the global sleep quality score (0–18), which was also used in all moderator analyses. Analysis of covariance was used to test the main effects of AET on sleep quality as well as interaction effects. All analyses were adjusted for baseline value of the outcome, type of lymphoma, disease stage, current treatment status, age, sex, and baseline exercise except when a covariate was tested as the moderator. Reductions in sleep quality scores indicate improved sleep quality. Standardized effect size *d* was reported for all comparisons by dividing the mean between group difference by the pooled baseline SD for the entire sample (for main effects) or the subgroup of interest (for interaction effects). For all analyses, we used the intention-to-treat principle for all participants with post-intervention data but we did not use a missing data strategy due to the minimal missing data at post-intervention. In total, our analytic strategy resulted in 17 statistical tests based on one test of a primary sleep endpoint (the global sleep quality score), 7 tests of secondary sleep endpoints (the 6 PSQI component scores and the percentage of poor sleepers), and 9 interaction tests. We made no adjustment for the multiple secondary comparisons or interaction tests because our trial was not originally powered for multiple comparisons.

Results

Participant flow through the trial has been reported elsewhere (18). Briefly, we randomized 122 of 474 (26%) eligible patients between May 2005 and May 2008. The main reasons for refusal were too busy ($n = 83$), not interested ($n = 40$), and transportation issues ($n = 40$). Post-intervention sleep data were obtained from 117 of 122 (96%) patients. The AET group attended 78% (28.0 of 36) of their supervised exercise sessions and significantly improved their aerobic fitness by >20% (18). No serious adverse events were observed during the trial. The baseline distribution of the proposed moderators was balanced between groups (Table 1). The baseline mean global sleep quality score was 4.97 (SD = 3.41) and 47.0% were considered poor sleepers at baseline. The AET group had worse global sleep quality ($P = 0.007$) and more poor sleepers ($P = 0.021$) at baseline but these differences were adjusted for in the analyses.

Main effects of aerobic exercise on sleep quality

AET resulted in a small ($d = -0.19$) but nonsignificant ($P = 0.16$) improvement in global sleep quality compared with UC [mean group difference = −0.64; 95% confidence interval (CI), −1.56 to +0.27; Table 2). There was a small ($d = -0.27$) borderline significant ($P = 0.086$) reduction in the percentage of poor sleepers in the AET group compared with UC group (mean group difference = −14.2; 95% CI, −30.5 to +2.1). There were no significant effects of AET on any of the 6 component scores (Table 2). The only sleep component to reach a small standardized effect size ($d = -0.22$) was daytime dysfunction (mean group difference = −0.18; 95% CI, −0.41 to +0.06; $P = 0.14$).

Moderators of the effects of aerobic exercise on sleep quality

There were statistically significant or borderline significant interactions for 5 of the 9 moderators including BMI ($P_{interaction} = 0.075$), type of lymphoma ($P_{interaction} = 0.006$), time since diagnosis ($P_{interaction} = 0.010$), current treatment status ($P_{interaction} = 0.036$), and baseline sleep quality ($P_{interaction} = 0.041$; Table 3). For BMI (Fig. 1A), AET improved global sleep quality in obese patients by −1.96 points ($P = 0.025$; $d = -0.52$) but had no effect in nonobese patients ($P = 0.76$). For type of lymphoma (Fig. 1B), AET improved global sleep quality in patients with indolent NHL by −2.35 points ($P = 0.001$; $d = -0.80$) but had no effect in patients with aggressive NHL ($P = 0.27$) or HL ($P = 0.93$). For time since diagnosis (Fig. 1C), AET improved global sleep quality in patients <2 years post-diagnosis by −1.78 points ($P = 0.005$; $d = -0.50$) compared with no effect in patients ≥2 years post-diagnosis ($P = 0.34$). For current treatment status (Fig. 1D), AET improved global sleep quality in patients receiving chemotherapy by −1.71 points ($P = 0.013$; $d = -0.50$) but not for patients off-treatment ($P = 0.72$). Finally, for baseline sleep quality (Fig. 1E), AET improved global sleep quality by −1.95 points in patients who were poor sleepers at baseline ($P = 0.007$; $d = -0.74$) compared with no effect in patients who were good sleepers at baseline ($P = 0.92$).

To determine whether differences in adherence may explain these subgroup effects in sleep outcomes, we compared the subgroups on their exercise adherence levels. We found no evidence of this effect and, in fact, adherence was slightly lower in the subgroups that benefited. Specifically, obese patients had a nonsignificantly lower adherence than nonobese patients (74% vs. 84%; $P = 0.21$); patients with indolent NHL had nonsignificantly lower adherence than patients with aggressive NHL (79% vs. 86%; $P = 0.38$); patients <2 years post-diagnosis had borderline significantly lower adherence than patients ≥2 years post-diagnosis (75% vs. 88%; $P = 0.066$); patients receiving chemotherapy had significantly lower adherence than patients off-treatment (73% vs. 88%;

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Table 1. Baseline distribution of moderators in patients with lymphoma in Edmonton, Canada, 2005–2008

Variable	Overall ($n = 117$)	UC ($n = 60$)	AET ($n = 57$)	*P*
Age				0.839
<50 y	38 (32.5)	20 (33.3)	18 (31.6)	
≥50 y	79 (67.5)	40 (66.7)	39 (68.4)	
Sex				0.603
Male	69 (59.0)	34 (56.7)	35 (61.4)	
Female	48 (41.0)	26 (43.3)	22 (38.6)	
Baseline exercise				0.206
Not meeting guidelines	84 (71.8)	40 (66.7)	44 (77.2)	
Meeting guidelines	33 (28.2)	20 (33.3)	13 (22.8)	
BMI				0.558
Nonobese	85 (72.6)	45 (75.0)	40 (70.2)	
Obese	32 (27.4)	15 (25.0)	17 (29.8)	
Type of lymphoma				0.994
NHL aggressive	49 (41.9)	25 (41.7)	24 (42.1)	
NHL indolent	47 (40.2)	24 (40.0)	23 (40.4)	
HL	21 (17.9)	11 (18.3)	10 (17.5)	
Disease stage at study entry				0.723
No evidence of disease	32 (27.4)	17 (28.3)	15 (26.3)	
Stage I/II	40 (34.2)	22 (36.7)	18 (31.6)	
Stage III/IV	45 (38.5)	21 (35.0)	24 (42.1)	
Current treatment status				0.661
Off-treatment	64 (54.7)	34 (56.7)	30 (52.6)	
Receiving chemotherapy	53 (45.3)	26 (43.3)	27 (47.4)	
Time since diagnosis				0.954
<2 y	66 (56.4)	34 (56.7)	32 (56.1)	
≥2 y	51 (43.6)	26 (43.3)	25 (43.9)	
Baseline sleep quality[a]				0.021
Poor sleepers	55 (47.0)	22 (36.7)	33 (57.9)	
Good sleepers	62 (53.0)	38 (63.3)	24 (42.1)	

NOTE: All values are expressed as *n* (%).

[a]Based on global sleep quality score of ≥4.3.

$P = 0.037$); and adherence was slightly higher for patients who were poor versus good sleepers at baseline (84% vs. 77%; $P = 0.34$).

Discussion

Twelve weeks of supervised AET that resulted in substantial improvements in cardiorespiratory fitness and other patient-reported outcomes (18) did not significantly improve sleep quality in this heterogeneous sample of patients with lymphoma. The overall standardized effect size of *d* approximately −0.20 suggests that the null effect was not likely due to insufficient power. Planned subgroup analyses suggested that the null effect may have resulted from a heterogeneous patient population. In particular, patients who were obese, had indolent NHL, were receiving chemotherapy, were within 2 years of diagnosis, or were poor sleepers at baseline appeared to benefit. These subgroup effects do not appear to be explained by better exercise adherence. No previous study has examined the effects of exercise on sleep quality in patients with lymphoma. In other cancer patient groups, results have been mixed with 3 studies showing benefit (10, 14, 17) and 4 studies showing no benefit (12, 13, 15, 16).

Payne and colleagues (14) observed significant improvements in sleep quality from 12 weeks of home-based walking in 20 older patients with breast cancer (≥55 years) receiving hormone therapy. Our trial did not find benefit in older patients with lymphoma (≥50 years). Tang and colleagues (10) found significant improvements in sleep quality from 8 weeks of home-based walking in 71 mixed patients with cancer selected for poor sleep quality at baseline (PSQI global score ≥5). Our subgroup analysis corroborate this finding showing benefit in patients with poor sleep quality at baseline. Finally, Wang and colleagues (17) reported significant improvements in sleep quality from 6 weeks of home-based walking in 72 newly diagnosed patients with breast cancer selected for non-obesity (BMI < 30). Our subgroup analysis actually contradicts this finding, suggesting benefit only in obese patients with cancer.

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Table 2. Effects of aerobic exercise on sleep quality in patients with lymphoma, Edmonton, Canada, 2005–2008

	Baseline, mean (SD)	Post-test, mean (SD)	Adjusted mean change,[a] mean (95% CI)	Adjusted between group difference in mean change,[a] mean (95% CI); *P*	Cohen *d*
Global sleep quality (0–18)					
UC	4.15 (3.04)	4.15 (3.19)	−0.35 (−0.98 to +0.28)		
AET	5.84 (3.58)	4.47 (3.13)	−1.00 (−1.64 to −0.35)	−0.64 (−1.56 to +0.27); $P = 0.167$	−0.19
Subjective sleep quality (0–3)					
UC	0.97 (0.61)	0.87 (0.62)	−0.14 (−0.28 to 0.00)		
AET	1.14 (0.67)	0.89 (0.62)	−0.20 (−0.35 to −0.06)	−0.06 (−0.27 to +0.14); $P = 0.556$	−0.09
Sleep latency (0–3)					
UC	0.60 (0.85)	0.68 (0.89)	+0.04 (−0.16 to +0.23)		
AET	0.84 (0.90)	0.68 (0.89)	−0.11 (−0.31 to +0.09)	−0.14 (−0.43 to +0.14); $P = 0.321$	−0.16
Sleep duration (0–3)					
UC	0.63 (0.78)	0.67 (0.80)	−0.03 (−0.19 to +0.13)		
AET	0.91 (0.76)	0.72 (0.70)	−0.13 (−0.29 to +0.04)	−0.09 (−0.33 to +0.14); $P = 0.419$	−0.12
Sleep efficiency (0–3)					
UC	0.70 (1.01)	0.65 (0.99)	−0.19 (−0.41 to +0.03)		
AET	1.12 (1.18)	0.67 (0.91)	−0.31 (−0.54 to −0.09)	−0.13 (−0.44 to +0.19); $P = 0.432$	−0.12
Sleep medication (0–3)					
UC	0.37 (0.90)	0.35 (0.90)	−0.09 (−0.29 to +0.11)		
AET	0.77 (1.15)	0.67 (1.14)	−0.03 (−0.23 to +0.17)	+0.06 (−0.22 to +0.35); $P = 0.658$	+0.06
Daytime dysfunction (0–3)					
UC	0.88 (0.76)	0.93 (0.78)	+0.01 (−0.15 to +0.17)		
AET	1.05 (0.85)	0.84 (0.68)	−0.17 (−0.33 to +0.00)	−0.18 (−0.41 to +0.06); $P = 0.143$	−0.22
Poor sleepers[b] (%)					
UC	36.7 (48.6)	41.7 (49.7)	−0.0 (−12.0 to +10.4)		
AET	57.9 (49.8)	36.8 (48.7)	−15.0 (−26.5 to −3.5)	−14.2 (−30.5 to +2.1); $P = 0.086$	−0.28

[a]Adjusted for baseline value of the outcome, type of lymphoma, disease stage, current treatment status, age, sex, and baseline exercise.
[b]Based on global sleep quality score of $\geq$4.3.

The null effects on sleep quality from the other 4 exercise trials consisted of 6 months of home-based combined exercise in 24 patients with multiple myeloma receiving stem cell transplant therapy (12), a home-based aerobic exercise program started either during or after treatment in 119 mixed patients with cancer (13), a partially supervised 12-week aerobic exercise program in 41 patients with breast cancer on hormone therapy (15), and a 4 week home-based walking and strength training program in 38 patients with breast or prostate cancer receiving radiation therapy (16). These mixed results from exercise and sleep quality trials in patients with cancer could be attributable to numerous factors including patient characteristics, treatment status, and the exercise prescription. Nevertheless, the primary criticism of exercise and sleep trials is that the majority of participants in these trials are good sleepers (11). In our trial, almost 50% of patients with lymphoma were poor sleepers at study entry.

The significant moderators identified in the present study appear to represent a consistent theme of identifying patients with poor sleep quality or with clinical features that place them at higher risk for poor sleep quality (e.g., obese, receiving chemotherapy, newly diagnosed, with existing disease). One of the largest subgroup effects in our trial was for patients with lymphoma with poor baseline sleep quality. These patients experienced an improvement in sleep quality of almost 0.80 SDs, consistent with the report from Tang and colleagues (10) which is the only exercise study to select patients with poor sleep quality. Speck and colleagues (6) reviewed more than 80 exercise trials involving almost 7,000 cancer survivors and noted that few exercise trials targeted participants based on their need for improvement in the primary outcome (e.g., fatigued, depressed, poor quality of life, poor sleep). Consequently, most exercise trials and subsequent meta-analyses have likely underestimated the benefit of exercise for a given outcome.

We also found a medium effect ($d = -0.50$) of AET on sleep quality in patients with lymphoma receiving chemotherapy. This finding contrasts with a recent meta-analysis suggesting larger exercise effects in the post-adjuvant setting than in the adjuvant setting for many patient-reported outcomes (6). These meta-analyses, however, are based almost entirely on breast cancer

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Table 3. Moderators of the effects of aerobic exercise on global sleep quality in patients with lymphoma, Edmonton, Canada, 2005–2008

	Baseline, mean (SD)	Post-test, mean (SD)	Adjusted mean change,[a] mean (95% CI)	Adjusted group difference in mean change,[a] mean (95% CI); *P*	Cohen *d*
Type of lymphoma ($P_{interaction} = 0.006$)					
NHL aggressive					
UC ($n = 25$)	4.12 (3.18)	3.92 (3.07)	−0.47 (−1.44 to +0.50)		
AET ($n = 24$)	6.63 (4.09)	6.17 (3.36)	+0.28 (−0.71 to +1.27)	+0.75 (+2.10 to −0.61); $P = 0.276$	+0.20
NHL indolent					
UC ($n = 24$)	4.33 (2.70)	4.96 (3.56)	+0.18 (−0.77 to +1.12)		
AET ($n = 23$)	5.96 (2.98)	3.57 (2.57)	−2.17 (−3.17 to −1.18)	−2.35 (−3.72 to −0.98); $P = 0.001$	−0.80
Hodgkin lymphoma					
UC ($n = 11$)	3.82 (3.66)	2.91 (2.21)	−1.26 (−2.75 to +0.23)		
AET ($n = 10$)	3.70 (2.94)	2.50 (1.43)	−1.34 (−2.91 to +0.24)	−0.08 (−2.08 to +1.92); $P = 0.939$	−0.02
Current treatment status ($P_{interaction} = 0.036$)					
Off-treatment					
UC ($n = 34$)	4.38 (3.45)	3.59 (2.76)	−1.28 (−2.14 to −0.42)		
AET ($n = 30$)	5.60 (3.38)	4.50 (3.21)	−1.07 (−1.97 to −0.17)	+0.21 (−0.99 to +1.42); $P = 0.727$	+0.06
Receiving chemotherapy					
UC ($n = 26$)	3.85 (2.44)	4.88 (3.59)	+0.83 (−0.16 to +1.81)		
AET ($n = 27$)	6.11 (3.85)	4.44 (3.11)	−0.89 (−1.86 to +0.09)	−1.71 (−3.06 to −0.37); $P = 0.013$	−0.50
Time since diagnosis ($P_{interaction} = 0.010$)					
<2 y					
UC ($n = 34$)	3.74 (2.56)	4.29 (3.53)	−0.29 (−1.14 to +0.56)		
AET ($n = 32$)	6.13 (3.43)	3.97 (2.85)	−2.07 (−3.02 to −1.12)	−1.78 (−0.56 to −3.00); $P = 0.005$	−0.55
≥2 y					
UC ($n = 26$)	4.69 (3.55)	3.96 (2.73)	−0.35 (−1.33 to +0.64)		
AET ($n = 25$)	5.48 (3.81)	5.12 (3.42)	+0.29 (−0.77 to +1.35)	+0.64 (−0.69 to +1.96); $P = 0.344$	+0.17
BMI ($P_{interaction} = 0.075$)					
Nonobese					
UC ($n = 45$)	3.80 (2.91)	3.89 (3.17)	−0.43 (−1.16 to +0.29)		
AET ($n = 40$)	5.33 (3.26)	4.58 (3.36)	−0.59 (−1.34 to +0.16)	−0.16 (−1.21 to +0.90); $P = 0.769$	−0.05
Obese					
UC ($n = 15$)	5.20 (3.28)	4.93 (3.22)	−0.05 (−1.29 to +1.19)		
AET ($n = 17$)	7.06 (4.10)	4.24 (2.61)	−2.00 (−3.19 to −0.82)	−1.96 (−3.67 to −0.25); $P = 0.025$	−0.52
Baseline global sleep quality ($P_{interaction} = 0.041$)					
Good sleepers					
UC ($n = 38$)	2.21 (1.21)	2.61 (2.22)	+0.39 (−0.44 to +1.22)		
AET ($n = 24$)	2.67 (1.20)	2.96 (2.01)	+0.46 (−0.59 to +1.51)	+0.07 (−1.26 to +1.40); $P = 0.920$	+0.06
Poor sleepers					
UC ($n = 22$)	7.50 (2.20)	6.82 (2.84)	−0.72 (−1.81 to +0.38)		
AET ($n = 33$)	8.15 (2.90)	5.58 (3.36)	−2.67 (−3.57 to −1.76)	−1.95 (−0.54 to −3.36); $P = 0.007$	−0.74

[a]Adjusted for baseline value of the outcome, major lymphoma type, disease stage, current treatment status, age, sex, and baseline exercise.

trials and have not included sleep outcomes. Interestingly, current treatment status did not moderate the effects of AET on other patient-reported outcomes in the HELP Trial including quality of life, depression, and fatigue (18), suggesting a unique interaction of exercise and treatment status for sleep outcomes.

A large ($d = -0.80$) and reliable effect was also found for patients with indolent NHLs. One possible explanation for this finding is that HL and aggressive patients with NHL are often treated with curative intent and are probably disease-free when off-therapy which may negate the impact of exercise on any sleep problems. Conversely, indolent patients with NHLs often have residual disease which may affect sleep in a way that can be improved with exercise. Time since diagnosis was also an important modifier of the effects of AET on sleep quality in our trial. Patients within 2 years of diagnosis experienced a medium-to-large improvement of approximately 0.60 SDs.

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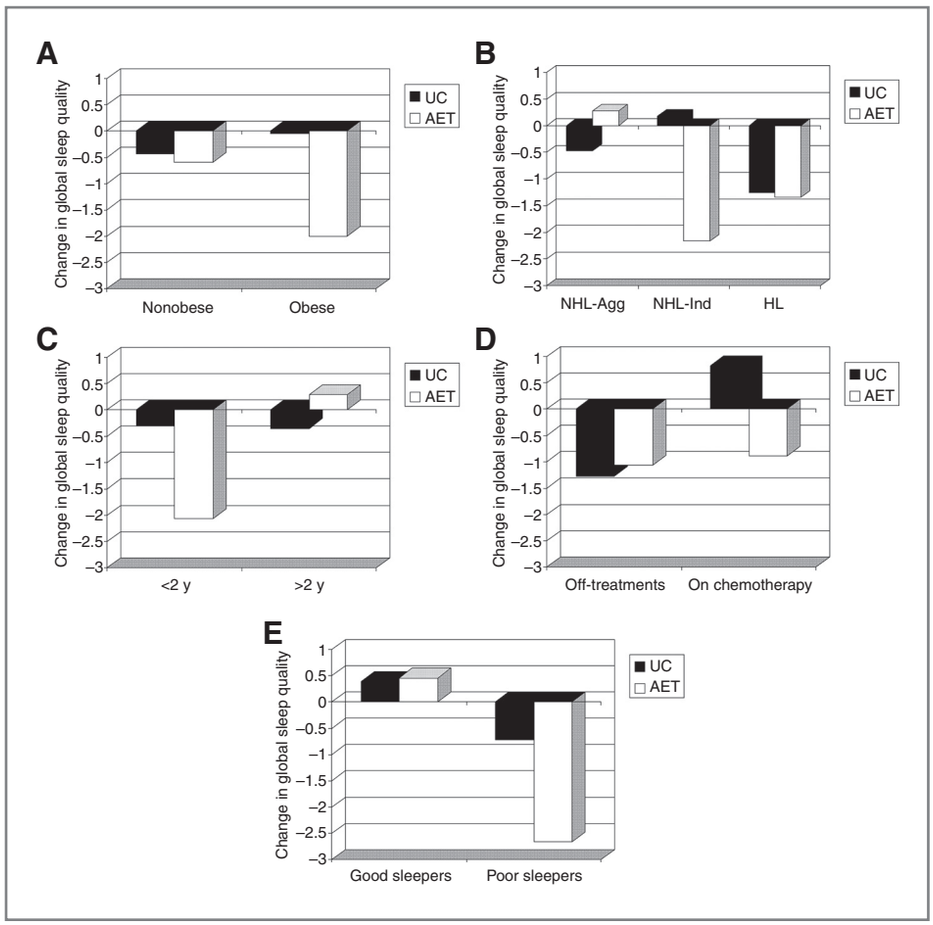

Figure 1. Effects of aerobic exercise on change in global sleep quality in patients with lymphoma by (A) BMI (B) type of lymphoma, (C) time since diagnosis, (D) current treatment status, and (E) baseline sleep quality. Agg, aggressive; Ind, indolent. Reductions in sleep quality scores indicate improved sleep quality.

Previous research has shown that the (i) greatest sleep problems occur in the first year after diagnosis and portend the worst prognosis and (ii) sleep problems improve with time although remain evident. Given the exploratory nature of these findings, replication is needed before they can be considered reliable.

Finally, BMI was a borderline significant moderator with the beneficial effects of exercise on sleep quality restricted to obese patients. This finding is not in agreement with the trial by Wang and colleagues (17) that reported significant improvements in sleep quality in patients with breast cancer selected for nonobesity. This inconsistent finding may be due to differences in the population group and the exercise prescription. Nevertheless, obesity is a strong risk factor for sleep disturbance in patients with cancer (1) and exercise may be particularly helpful for obese patients (11).

Our trial's strengths include being the largest RCT to date of exercise and sleep quality in patients with cancer and the first to examine sleep quality in patients with lymphoma, the supervised exercise intervention, excellent adherence, substantial improvements in aerobic fitness, use of the gold standard self-report measure of sleep quality, intention-to-treat analysis, and minimal loss to follow-up. Limitations include the 25% recruitment rate from a single center, the secondary focus on sleep outcomes, the exclusion of the sleep disturbances subcomponent of the PSQI, failure to include an objective sleep measure, and the 17 statistical comparisons which would likely result in one false discovery if all comparisons were null. In terms of dissemination, this exercise intervention could be implemented at other cancer centers and community-based fitness centers with the necessary facilities and qualified staff. Given its complexity in terms of exercise training principles, it is unclear whether such a program could be self-directed by patients with minimal or no supervision.

In summary, the results from this secondary analysis of the HELP Trial suggest no overall benefit to sleep quality from AET in a heterogeneous sample of patients with lymphoma. Nevertheless, there is suggestive evidence that AET may improve sleep quality in patients with lymphoma with poor sleep quality or clinical features that increase the risk of poor sleep quality (i.e., obesity, receiving chemotherapy, diagnosis with indolent NHL, or within 2 years of diagnosis). Given the possibility of false-positive findings from multiple subgroup analyses, definitive trials targeting patients with lymphoma with poor sleep quality or these clinical risk factors are needed to confirm these findings. If

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replicated in larger and more focused trials, aerobic exercise may be a particularly attractive intervention to manage sleep disturbances in patients with cancer because of its favorable safety profile and its documented positive effects on other health outcomes such as physical functioning, fatigue, depression, and quality of life (18). Additional research on the optimal exercise prescription to improve sleep quality in diverse cancer patient groups is needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. J Clin Oncol 2011;29:3580–6.
2. Berger AM. Update on the state of the science: sleep-wake disturbances in adult patients with cancer. Oncol Nurs Forum 2007;36: 165–77.
3. Johansson E, Wilson B, Brunton L, Tishelman C, Molassiotis A. Symptoms before, during, and 14 months after the beginning of treatment as perceived by patients with lymphoma. Oncol Nurs Forum 2010;37:105–13.
4. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open 2012;2: e000850.
5. Langford DJ, Lee K, Miaskowski C. Sleep disturbance interventions in oncology patients and family caregivers: a comprehensive review and meta-analysis. Sleep Med Rev. 2011 Nov 4. [Epub ahead of print].
6. Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv 2010;4: 87–100.
7. Brown JC, Huedo-Medina T, Pescatello LS, Pescatello SM, Ferrer RA, Johnson B. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2011;20:123–33.
8. Craft L, Vanlterson EH, Helenowski IB, Rademaker AW, Courneya KS. Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2012;21:3–19.
9. Ferrer RA, Huedo-Medina T, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. Ann Behav Med 2011;41:32–47.
10. Tang MF, Liou TH, Lin CC. Improving sleep quality for cancer patients: benefits of a home-based exercise intervention. Support Care Cancer 2010;18:1329–39.
11. Youngstedt SD. Effects of exercise on sleep. Clin Sports Med 2005; 24:355–65.
12. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B. Feasibility of exercise during treatment for multiple myeloma. Cancer Nurs 2003;26:410–9.
13. Dodd MJ, Cho MH, Miaskowski C, Painter PL, Paul SM, Cooper BA, et al. A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. Cancer Nurs 2010;33:245–57.
14. Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum 2008;35:635–42.
15. Rogers LQ, Hopkins-Price P, Vicari S, Markwell S, Pamenter R, Courneya KS, et al. Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects. Cancer Epidemiol Biomarkers Prev 2009;18:1410–8.
16. Sprod LK, Palesh OG, Janelsins MC, Peppone LJ, Heckler M, Jacob Adams GR, et al. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. Community Oncol 2010;7:463–71.
17. Wang Y, Boehmke M, Wu YB, Dickerson SS, Fisher N. Effects of a 6-week walking program on Taiwanese women newly diagnosed with early-stage breast cancer. Cancer Nurs 2011;34:1–13.
18. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Fridenreich CM, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. J Clin Oncol 2009;27:4605–12.
19. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
20. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh sleep quality index in cancer patients. J Pain Symptom Manage 2004;27:140–8.
21. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. Cancer 2008;112:1845–53.
22. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Friedenreich CM, Peddle CJ, et al. Moderator effects in a randomized controlled trial of exercise training in lymphoma patients. Cancer Epidemiol Biomarkers Prev 2009;18:2600–7.
23. US Department of Health and Human Services (USDHHS). 2008 Physical activity guidelines for Americans. Washington, DC: USDHHS; 2008.
24. Godin G, Shepard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 1985;10:141–6.

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