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Efficacy and Acceptability of Intermittent Aerobic Exercise on Polysomnography-Measured Sleep in People With Rheumatoid Arthritis With Self-Reported Sleep Disturbance: A Randomized Controlled Trial

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Objective. This study's objective was to investigate the efficacy and acceptability of intermittent aerobic exercise training on sleep parameters, fatigue, pain, depressive symptoms, physical function, and cardiorespiratory fitness in people with rheumatoid arthritis (RA).

Methods. Thirty-eight people with RA were assigned to intermittent aerobic exercise training (three sessions/week for 6 weeks; intervention group, n = 17) or usual care (control group, n = 21). The primary outcome was a change in polysomnography-assessed sleep efficiency from baseline to the end of the intervention. Secondary outcomes were sleep quality (Pittsburgh Sleep Quality Index), fatigue (Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire), depression (Center for Epidemiological Studies-Depression), and cardiorespiratory fitness (watt max test).

Results. No between-group differences were found in changes in polysomnography-assessed sleep efficiency (0.04; 95% confidence interval [CI]: −0.02 to 0.09, $P = 0.17$). In the intervention group, sleep efficiency was improved significantly from baseline (0.84; 95% CI: 0.80-0.88) compared with the end of the intervention (6 weeks) (0.88; 95% CI: 0.85-0.92); however, there was no significant difference in the control group. Fatigue and depression measures were significantly lower in the intervention group than in the control group. Between-group differences were overall fatigue (−16.1; 95% CI: −25.1 to −7.0, $P = 0.001$), physical fatigue (−5.0; 95% CI: −7.3 to −2.7, $P = 0.0001$), cognitive fatigue (−2.4; 95% CI: −4.2 to 0.6, $P = 0.009$), living with fatigue (−2.5; 95% CI: −4.5 to −0.5, $P = 0.01$), and depressive symptoms (−6.8; 95% CI: −12.4 to −1.1, $P = 0.02$).

Conclusion. The intervention yielded no significantly better sleep efficiency compared with usual care. However, aspects of fatigue, including physical and cognitive fatigue, and depressive symptoms were significantly improved in the intervention group.

INTRODUCTION

Approximately 50% to 70% of people with rheumatoid arthritis (RA) experience sleep disturbances (1,2) compared with 10% to 12% in the general population (3). In people with RA, these are generally characterized by difficulty falling asleep, frequent wakening from sleep, daytime sleepiness, and fatigue (1). Cross-sectional studies have shown associations between poor sleep and fatigue, pain, depression, and disease activity in people with

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SIGNIFICANCE & INNOVATIONS

- People with rheumatoid arthritis (RA) are able to engage in regular physical activity and exercise and achieve significant improvements in sleep parameters, fatigue, and depressive symptoms. Such experience provides new insight for people with RA and their ability to do high-intensity aerobic exercise.
- A significant proportion of people with RA report sleep disturbances. The study argues that intermittent physical exercise is a reasonable suggestion for a nonpharmacological treatment with a positive effect on sleep disturbances.
- Health professionals in rheumatological clinical practice should actively encourage and support people with RA to intermittent aerobic exercise training.
- Fatigue is one of the most pronounced daytime symptoms attributed to sleep disturbances in people with RA. Physical activity and exercise is a suitable intervention for reducing fatigue. The effect of reduced fatigue has important positive implications for the general well-being in peoples with RA.

RA (2,4,5), but evidence of effective treatments for sleep disturbances in people with RA still needs to be established. The recommended treatment for chronic sleep disturbances is cognitive behavioral therapy targeting insomnia (CBT-I) (6). However, CBT-I is not widely available because of the lack of trained professionals in hospitals—especially in rheumatology settings—and it is time-consuming and costly (7). A potentially more accessible alternative may be physical activity. Although cross-sectional studies have shown a positive association between regular physical activity and good sleep (8,9), only a few clinical trials, including one randomised controlled trial (RCT) (10), one feasibility study (11), and four pilot studies (12–14), have examined the effect of physical exercise on sleep in people with RA. However, these studies were characterized by the risk of a floor effect arising from a lack of screening for poor sleep at baseline and the limited descriptions of the content, intensity, and duration of the exercise interventions. Furthermore, sleep outcomes were primarily self-reported, whereas the gold standard method of polysomnography (PSG) was absent. Consequently, these studies did not yield information about the efficacy of exercise training on sleep architecture and other sleep parameters. Therefore, further research, especially definitive trials, is needed to determine the efficacy and relevance of this type of training in clinical practice. The aim of the present study was to examine the efficacy and acceptability of intermittent aerobic exercise on objectively and subjectively measured sleep (efficiency, quality, and disturbances) in people with RA who reported sleep disturbances. Furthermore, we aimed to examine the effects of the intervention on fatigue, pain, depressive symptoms, physical function, and cardiorespiratory fitness.

MATERIALS AND METHODS

Design. The study is a two-armed, single-blinded randomized controlled trial of people with RA who were allocated to a regime of intermittent aerobic exercise or of usual care (15). We obtained ethical approval from the Ethics Committee of the Capital Region of Denmark (no. H-1-2012-151), and the protocol was approved by the Danish Data Protection Agency (ref.no.711-1-08) and registered at ClinicalTrials.gov (NCT01966835). All participants gave their written informed consent before participating in any study procedures.

Inclusion and exclusion criteria. Patients were recruited from the outpatient clinic of the Center for Rheumatology and Spine Diseases. To be included, the patients had to fulfill the following inclusion criteria: aged 18 to 70 years, self-reported poor sleep, a Pittsburgh Sleep Quality Index (PSQI) global score of greater than or equal to 5, a disease activity score less than 3.2, normal 12-led electrocardiogram (ECG) findings, and the ability to understand Danish. Exclusion criteria were the following: documented sleep apnea (Apnea-Hypopnea Index [AHI] >15/hour) evaluated prior to inclusion, working at night during the intervention period, being pregnant or breastfeeding, being treated with antidepressants or antipsychotics, having cardiac symptoms corresponding to New York Heart Association (NYHA) functional classification of greater than 2, and being regularly physically active, which is taken as self-reporting doing aerobic exercise more than three times per week.

Screening. All eligible participants (n = 628) were screened before inclusion, initially for self-reported sleep quality and poor sleep with the PSQI (telephone screening). After the initial screening, participants were then screened for 1) sleep apnea and 2) cardiac symptoms. Sleep apnea screening was performed by cardiorespiratory monitoring (CRM) consisting of electromyography of the tibialis anterior muscles and ECG including channels of digital oximetry, nasal pressure, and respiratory movements (Xtrace thoracic and abdominal straps) (Figure 1). KL was responsible for monitoring the CRM equipment on the patients. All patients slept with CRM in their own homes one night. Then the patients returned the equipment to the Danish Center for Sleep Medicine (DCSM), Rigshospitalet, Glostrup, Denmark, and analyzed and managed at the DCSM. Patients with moderate to severe sleep apnea and an AHI of greater than 15/hour were excluded from the trial and referred to the DCSM to treat sleep apnea. Screening of cardiac symptoms were done according to NYHA criteria and ECG.

Group allocation and blinding. Participants were randomly allocated to the intervention or control group. Randomization was performed by computer-generated random numbers.

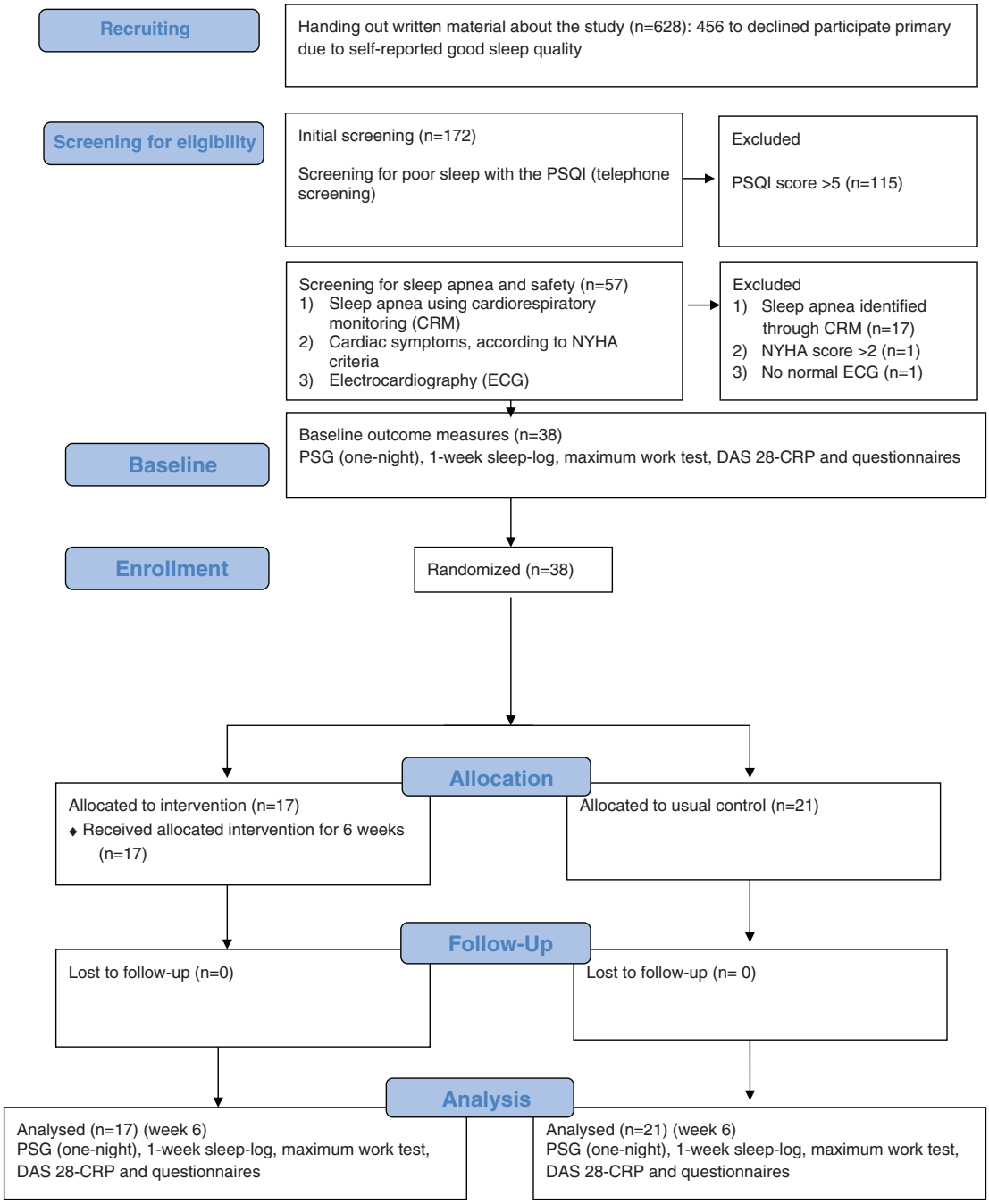

Figure 1. Flow of participants through the randomized controlled trial. CRM, cardiorespiratory monitoring; DAS28-CRP, disease activity score C-reactive protein; ECG, electrocardiography; NYHA, New York Heart Association; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index.

Intervention. The aerobic exercise intervention was developed on the following explanatory mechanisms. Aerobic exercise can improve thermoregulation, which positively impacts sleep duration and sleep onset (16), which positively impact sleep structure, sleep–wake, and circadian rhythmicity. There may also be a particular sleep potential for the patients through the antidepressant effects of physical exercise. Compelling data support that depression is linked to high systemic levels of the substance kynurenine, which is converted in the skeletal muscle during muscular work, especially during moderate aerobic exercise (17). Thus, this exercise intervention was designed to achieve an increased thermoregulation effect, increase the systemic reduction of kynurenine, and improve sleep.

The intervention consisted of 18 intermittent aerobic exercise training sessions: 3 sessions of 20 to 30 minutes per week for 6 weeks. The sessions were performed on bicycle ergometers (Kettler), supervised by trained physiotherapists. Each session was initiated by a 5-minute warm-up, followed by four blocks of

5- to 7.5-minute alternating periods of continuous moderate intensity (40%-50%) and intermittent high-intensity aerobic exercise (70%-80% watt max), and finally a 5-minute cooldown period. The intervention is described in greater detail elsewhere (15). The exercise workload (watts) was determined individually by an indirect watt max test conducted on a bicycle at baseline (16) and was calculated from the maximum load reached adjusted for the number of seconds performed at the highest load. In each exercise session, any changes from the prescribed intensity were noted, the participant's heart rate was monitored (with a polar watch device) for each training block, and the mean and maximum heart rates were recorded for each session. The patients' cardiorespiratory fitness was assessed by an incremental maximum work test on a bicycle ergometer as described by Andersen et al (18). The test was modified to accommodate the participants' fitness level to obtain a test period of 5 minutes or more. Following a 5-minute warm-up period on individual steady-state work intensity, the workload increased by 20 watts each minute until exhaustion was reached. Thus, maximum workload (watts), maximum heart rate (beats per minute), and time to exhaustion were recorded as test results. Previous studies have shown this test to be suitable when estimating cardiorespiratory fitness in clinical populations (19).

Control group. The control group received usual care, during which the participants were encouraged to maintain their normal everyday activities. No types of exercise training or treatment for sleep disturbances were included as part of usual care.

Outcome measures. The primary outcome measure was change in sleep efficiency between baseline and the end of the intervention (week 6), as measured by PSG. Measurements from a one-night PSG were taken at baseline and at the end of the intervention at each participant's home using Trackit Ambulatorium PSG (Lifelines Ltd). PSG measurements were evaluated following the guidelines of the 2007 standard of the American Academy of Sleep Medicine (20).

Secondary outcomes were changes between baseline and the end of the intervention in sleep efficiency (sleep log), sleep latency, total sleep time, wake after sleep onset (minutes; PSG and sleep log), sleep quality (PSQI), sleepiness (Epworth Sleepiness Scale), pain (visual analog scale [VAS]), fatigue (Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire), depression (Center for Epidemiological Studies-Depression [CES-D]), cardiorespiratory fitness (measured by an incremental maximum work test on a bicycle ergometer), and physical function (Health Assessment Questionnaire). In the sleep log, we collected information on the patients' daytime functioning, sleep during the daytime, hypnotics, time getting up in the morning, time going to sleep, sleep onset latency, and number of awakenings during the night. This information was registered daily for 2 weeks.

Demographic and lifestyle information was assessed by means of self-reported questionnaires, and disease-specific information was obtained from the national clinical quality registry DANBIO. The measurements are reported in detail elsewhere (15).

Acceptability of the intervention. To offer a qualitative perspective on the acceptability of the intervention, all participants in the intervention group were asked to participate in a semistructured, telephone-based interview (range 18-41 minutes, median 32 minutes). The interview guide was built on previous literature about motivation and barriers to physical activity among patients with RA. It covered six overall themes: motivation, first experience/meeting with the training, physical well-being, mental well-being, the role of the professionals, and future/retention.

Blinding. The polysomnographic technician who interpreted the PSG analyses was blinded to the group allocation. However, it was not possible to blind participants and project staff who supervised the aerobic exercise training.

Sample size calculation. The sample size was calculated based on sleep efficiency. A previous RCT (21) examining the effect of a nonpharmacological intervention in people with insomnia and using PSG as a measure of sleep efficiency reported a mean value of 81.4% (SD, 7.4%). Because the threshold for good clinical sleep efficiency is greater than or equal to 85%, the aim was to improve sleep efficiency by at least 5% to achieve a level of at least 86.4% in the intervention group. Thus, with a significance level (α) of 5% and a statistical power of 80%, we estimated that 36 participants were needed to complete the trial. Allowing for an estimated 20% loss to follow-up, a minimum of 44 participants was therefore required.

Statistical analysis. Data analyses were based on the intention-to-treat principle. All available data were included, and missing observations were treated as missing-at-random. The main analyses of primary outcome and numerical secondary outcomes were based on a linear mixed-effects model including a random effect of subject and fixed effects of allocation group, assessment time (at baseline or week 6), and their interaction. Estimates and 95% confidence intervals (CIs) are reported for 1) each combination of assessment time and allocation group, 2) within-group changes over time, and 3) between-group difference of changes over time. Probabilities associated with the testing of null hypotheses that within-group changes over time are zero and that within-group changes differ between groups are presented. Residuals were examined to justify the use of a mixed model based on the assumption of normally distributed outcome values. For clarity, all the results are based on models

that use untransformed outcomes. However, residual plots suggested that statistical analyses for sleep latency should preferably be performed on logarithmically transformed outcomes. Here we report the relative (median) percentage change in sleep latency obtained by back-transformation of results from the subsequent, more appropriate analysis. Characteristics of the study population at baseline are illustrated by means and standard deviations for continuous outcomes and as frequencies and percentages for categorical outcomes. The linear mixed-effects models were derived using the lmer function of the lme4 package in R (22).

Qualitative analysis. For the qualitative data analysis of acceptability of the intervention, the interviews were recorded, transcribed verbatim, and analyzed thematically by means of editing style (23).

RESULTS

Recruitment and study flow are presented in Figure 1. Among the people with RA who were interested in participating in the study, 115 were excluded after telephone screening because they had a global PSQI score of less than 5, indicating no sleep disturbance. Additional reasons for exclusion are shown in Figure 1. Participants excluded because of sleep apnea, measured by CRM, were referred for treatment at the Danish Center for Sleep Medicine. All participants in the intervention group completed all 18 training sessions, except for one participant, who completed 16 sessions. All participants performed all their training sessions at the planned intensity. No adverse events were observed during the exercise training period. Further characteristics of participants are presented in Table 1.

Participants in the intervention group (n = 17) had clinically poor sleep efficiency (<85%) at baseline. For participants in the

Table 1. Demographic, health-related, and disease-related baseline characteristics of participants, by allocated group

Characteristic	Control group (n = 21)	Intervention group (n = 17)
Women, n (%)	20 (95)	13 (76)
Age (year), mean (SD)	54.8 (9.6)	57.8 (9.8)
RA duration (year), mean (SD)	17.9 (12.8)	10.1 (5.9)
Positive anti-CCP, n (%)	18 (86)	17 (100)
Positive IgM-RF, n (%)	18 (86)	17 (100)
DAS-28, mean (SD)	2.0 (0.5)	2.3 (0.6)
Hemoglobin, mean (SD)	8.4 (0.6)	8.7 (0.6)
C-reactive protein, mean (SD)	4.2 (4.0)	7.0 (6.0)
Current comorbidity, n (%)	2 (9)	0
Living with partner, n (%)	18 (86)	10 (59)
Highest attained education, n (%)		
Short (basic school 7-9 years)	7 (33)	6 (35)
Medium (youth education 9-12 years)	10 (48)	9 (53)
Long (higher education >12 years)	4 (19)	2 (12)
Occupation, n (%)		
Unemployed	2 (10)	2 (12)
Employed	12 (57)	9 (53)
Age-related retirement	7 (33)	6 (35)
Smoking (current), n (%)	1(5)	4(24)
Alcohol consumption, n (%)		
≤5 units per week	17 (81)	11 (65)
>5 units per week	4 (19)	6 (35)
Caffeine, n (%)		
<5 cups per day	10 (48)	9 (53)
≥5 cups per day	11 (52)	8 (47)
Leisure time physical activity, n (%)		
Sedentary	13 (62)	14 (82)
Moderately physically active	8 (38)	3 (18)
Vigorously physically active	0	0
Sleep apnea (PSG), n (%)		
AHI ≤15	6 (33)	4 (25)
AHI >15	12 (67)	12 (75)
LM (PSG), n (%)		
LM ≤10	3 (17)	5 (31)
LM >10	15 (83)	11 (69)

Abbreviations: AHI, Apnea-Hypopnea Index; anti-CCP, anticyclic citrullinated peptide antibody; DAS-28, Disease Activity Score 28 Joints; IGM-RF, immunoglobulin M rheumatoid factor; LM, leg movement; PSG, polysomnography; RA, rheumatoid arthritis.

control group (n = 21), the baseline sleep efficiency was 88%. Five participants reported that they were using sleep medication more than once a week. For the intervention and control groups, participants' sleep was characterized by approximately 15% of stage one sleep (N1) (light sleep) through the night, 50% of stage two sleep (N2), and about 10% of stage three sleep (N3). More than 50% of the participants had severe sleep apnea and 10% to 15% had an index score greater than 10 for leg movements through the night, indicating a pathological condition.

Primary outcome. In the intervention group, sleep efficiency as measured objectively by PSG was improved significantly from baseline (mean, 0.84; 95% CI: 0.80-0.88) compared with the end of the intervention at week 6 (mean, 0.88; 95% CI: 0.85-0.92), composing a within-group difference of 0.04 (95%

Table 2. Changes in sleep parameters from baseline to postintervention (week 6) of participants by allocated group

	Baseline		Postintervention		Within-group difference in change			Between-group difference in change		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	*P*	Estimate	95% CI	*P*
Primary outcome										
Sleep efficiency (%)										
PSG										
Intervention	0.84	0.80 to 0.88	0.88	0.85 to 0.92	0.04	0.00 to 0.08	0.03	0.04	−0.02 to 0.09	0.17
Control	0.88	0.85 to 0.92	0.89	0.85 to 0.92	0.01	−0.03 to 0.04	0.78			
Secondary outcomes										
Sleep efficiency (%)										
Sleep-log										
Intervention	0.79	0.71 to 0.87	0.81	0.74 to 0.89	0.02	−0.01 to 0.06	0.19	−0.01	−0.06 to 0.04	0.70
Control	0.78	0.71 to 0.85	0.81	0.74 to 0.89	0.03	−0.00 to 0.07	0.06			
Sleep latency (minutes)										
PSG										
Intervention	8.2	2.8 to 3.6	8.5	3.2 to 13.9	0.3	−6.8 to 7.5	0.92	7.0	−3.0 to 17.0	0.16
Control	11.9	6.8 to 16.9	5.3	0.0 to 10.4	−6.6	−13.5 to 0.2	0.05			
Sleep-log										
Intervention	29.6	18.9 to 40.4	24.6	14.0 to 35.1	−5.1	−14.3 to 4.2	0.27	−4.5	−17.4 to 8.4	0.47
Control	21.9	12.1 to 31.6	21.3	11.1 to 31.5	−0.5	−9.5 to 8.4	0.90			
Total sleep time (hours)										
PSG										
Intervention	6.2	5.72 to 6.70	6.8	6.32 to 7.30	0.59	−0.03 to 1.21	0.06	0.32	−0.54 to 1.18	0.45
Control	6.3	5.87 to 6.80	6.6	6.13 to 7.08	0.27	−0.32 to 0.86	0.36			
Sleep-log										
Intervention	6.5	5.7 to 7.2	6.9	6.17 to 7.64	0.41	0.04 to 0.77	0.02	0.21	−0.29 to 0.72	0.39
Control	6.2	5.5 to 6.9	6.4	5.77 to 7.15	0.19	−0.16 to 0.54	0.27			
Wake after sleep onset (minutes)										
PSG										
Intervention	49.9	35.2 to 64.6	41.6	26.9 to 56.3	−8.3	−18.2 to 1.6	0.09	−11.7	−25.5 to 2.0	0.09
Control	24.5	10.6 to 38.4	27.9	13.8 to 41.9	3.4	−6.1 to 13.0	0.47			
Sleep-log										
Intervention	67.9	49.8 to 86.0	54.6	36.7 to 72.4	−13.3	−25.7 to −0.9	0.04	−11.0	−28.3 to 6.3	0.20
Control	45.1	28.6 to 61.5	42.8	25.7 to 59.8	−2.29	−14.3 to 9.7	0.69			
Sleep stage (% of total sleep time)										
PSG										
N1										
Intervention	0.19	0.15 to 0.23	0.18	0.14 to 0.22	−0.01	−0.04 to 0.02	0.56			
Control	0.13	0.10 to 0.17	0.11	0.08 to 0.15	−0.02	−0.04 to 0.02	0.23	0.01	−0.03 to 0.05	0.67
N2										
Intervention	0.58	0.54 to 0.62	0.55	0.51 to 0.59	−0.03	−0.06 to 0.01	0.13			
Control	0.56	0.52 to 0.60	0.56	0.52 to 0.60	0.00	−0.03 to 0.04	0.94	−0.03	−0.08 to 0.02	0.25
N3										
Intervention	0.08	0.04 to 0.12	0.09	0.05 to 0.13	0.01	−0.03 to 0.04	0.67			
Control	0.10	0.06 to 0.14	0.10	0.06 to 0.14	−0.00	−0.04 to 0.03	0.84	0.01	−0.04 to 0.06	0.66
REM										
Intervention	0.15	0.13 to 0.18	0.18	0.16 to 0.20	0.03	0.00 to 0.05	0.03			
Control	0.21	0.18 to 0.23	0.23	0.20 to 0.25	0.02	−0.01 to 0.04	0.10	0.01	−0.03 to 0.04	0.63

Abbreviations: CI, confidence interval; N1, sleep stage 1; N2, sleep stage 2; N3, sleep stage 3; PSG, polysomnography; REM, rapid eye movement.

CI: 0.00-0.08; P = 0.03). There was no statistically significant within-group change in the control group between baseline (mean, 0.88; 95% CI: 0.85-0.92) and week 6 (mean, 0.89; 95% CI: 0.85-0.92) because the within-group difference was only 0.01 (95% CI: −0.03 to 0.04) (Table 2).

For the primary outcome, ie, the between-group difference in change in objectively measured sleep efficiency from baseline to week 6, no statistically significant difference was observed between the intervention and control groups (0.04, 95% CI: −0.02 to 0.09; P = 0.17) (Table 2).

Secondary outcomes. No statistically significant changes were observed between the intervention and control groups in any of the outcomes of sleep latency, total sleep time, wake after sleep onset, and sleep stages (N1, N2, N3, rapid eye movement) (Table 2). However, total sleep time (as recorded in the sleep log) improved significantly in the intervention group, with a within-group change of 0.41 hour (95% CI: 0.04-0,77; P = 0.02), and waking after sleep onset (also as recorded in the sleep log) showed a statistically significant reduction in the intervention group, with a within-group decrease of −13.3 minutes (95% CI: −25.7 to 0.89; P = 0.04) (Table 2), whereas no statistically significant improvements were observed in the control group. No statistically significant changes were observed for any sleep measurements by PSQI (Table 3).

Overall, between-group difference in fatigue scores during the study favored the intervention group. General fatigue (measured by VAS) was significantly improved in the intervention group compared with the control group, with a reduction of −16.0 points (95% CI: −25.1 to −7.0). The same patterns were evident for physical fatigue (−4.9 points; 95% CI: −7.25 to −2.74), cognitive fatigue (−2.43 points; 95% CI: −4.22 to −0.63), living with fatigue (−2.50 points; 95% CI: −4.45 to −0.54), and total Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire score (−11.1 points; 95% CI: −16.6 to −5.6). The between-group difference for depressive symptoms also

Table 3. Changes in sleep parameters measured by Pittsburgh Sleep Quality Index of participants, by allocated group

	Control group		Intervention group	
	Baseline, n (%)	Postintervention, n (%)	Baseline, n (%)	Postintervention, n (%)
Sleep quality				
Very good	13 (62)	13 (72)	15 (88)	11 (65)
Fairly good	5 (24)	4 (22)	0	4 (23)
Fairly bad	2 (9)	0	1 (6)	0
Very bad	1(5)	1 (6)	1 (6)	2 (12)
Sleep latency (minutes)				
≤15	9 (53)	3 (17)	3 (21)	2 (12.5)
16-30	3 (18)	8 (44)	8 (58)	8 (50)
31-60	5 (29)	5 (28)	3 (21)	4 (25)
>60	0	2 (11)	0	2 (12.5)
Sleep duration (hours)				
>7	1 (5)	0	3 (18)	5 (29)
6-7	7 (35)	7 (39)	0	3 (17)
5-6	7 (35)	8 (44)	11 (64)	7 (42)
<5	5 (25)	3 (17)	3 (18)	2 (12)
Sleep efficiency (%)				
≥85	6 (38)	6 (33)	3 (19)	6 (35)
75-84	5 (31)	8 (44)	5 (31)	7 (41)
65-74	2 (12)	3 (17)	2 (12)	2 (12)
<65	3 (19)	1 (6)	6 (38)	2 (12)
Sleep disturbances				
0	7 (33)	7 (41)	5 (29)	6 (35)
1-9	12 (57)	9 (53)	11 (65)	11 (65)
10-18	2 (10)	1 (6)	1 (6)	0
19-27	0	0	0	0
Use of sleep medication				
Not during the past month	17 (81)	12 (67)	14 (82)	15 (88)
Less than once a week	1 (5)	5 (28)	1 (6)	1 (6)
Once or twice a week	3 (14)	0	1 (6)	1 (6)
Three or more times a week	0	1 (5)	1 (6)	0
Daytime dysfunction				
Not a problem	2 (10)	2 (11)	0	3 (18)
Only a very slight problem	6 (28)	6 (33)	8 (47)	7 (41)
Somewhat of a problem	5 (24)	4 (23)	6 (35)	4 (23)
A very big problem	8 (38)	6 (33)	3 (18)	3 (18)

Table 4. Changes in fatigue, sleepiness, pain, depression, physical function, watt max from baseline to post-intervention (week 6) of participants by allocated group

	Baseline		Postintervention		Within-group difference in change			Between-group difference in change		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	*P*	Estimate	95% CI	*P*
Physical fatigue (BRAF) (score 0-22)										
Intervention	14.27	11.5 to 16.9	10.8	8.20 to 13.5	−3.38	−5.03 to −1.74	0.0002			
Control	10.95	8.53 to 13.3	12.5	10.1 to 15.0	1.60	0.06 to 3.15	0.04	−4.99	−7.25 to −2.74	0.0001
Living with fatigue (BRAF) (score 0-21)										
Intervention	5.88	4.27 to 7.49	3.11	1.50 to 4.72	−2.76	−4.17 to −1.35	0.0003			
Control	4.47	3.02 to 5.92	4.21	2.69 to 5.73	−0.26	−1.61 to −1.08	0.69	−2.50	−4.45 to −0.54	0.01
Cognitive fatigue (BRAF) (score 0-15)										
Intervention	5.41	3.92 to 6.89	3.58	2.10 to 5.07	−1.82	−3.11 to −0.53	0.007			
Control	4.14	2.80 to 5.48	4.74	3.24 to 6.15	0.60	−0.63 to 1.84	0.32	−2.43	−4.22 to −0.63	0.009
Emotional fatigue (BRAF) (score 0-12)										
Intervention	3.29	2.18 to 4.39	2.0	0.89 to 3.10	−1.29	−2.20 to −0.38	0.006			
Control	2.52	1.53 to 3.51	2.3	1.25 to 3.33	−0.22	−1.09 to 0.64	0.59	−1.06	−2.32 to 0.19	0.09
BRAF total (score 0-70)										
Intervention	28.9	22.8 to 35.1	19.5	13.5 to 25.6	−9.36	−13.3 to −5.37	0			
Control	22.1	16.6 to 27.5	23.8	18.2 to 29.4	1.72	−2.02 to 5.46	0.35	−11.1	−16.5 to −5.6	0.0002
Overall fatigue (VAS) (score 0-100)										
Intervention	58.5	43.2 to 73.7	48.2	32.9 to 63.4	−10.3	−16.7 to −3.8	0.002			
Control	46.0	32.3 to 59.7	51.8	37.8 to 65.7	5.75	−0.50 to 12.0	0.07	−16.0	−25.1 to −7.04	0.001
Sleepiness (ESS) (score 0-24)										
Intervention	7.5	5.36 to 9.69	6.23	4.00 to 8.45	−1.29	−2.91 to 0.31	0.11			
Control	9.9	7.95 to 11.8	10.5	8.48 to 12.5	0.59	−0.87 to 2.06	0.41	−1.89	−4.07 to 0.29	0.08
Pain (VAS) (score 0-100)										
Intervention	27.9	16.7 to 39.1	28.0	16.8 to 39.3	0.12	−5.80 to 6.03	0.96			
Control	25.5	15.4 to 35.6	27.8	17.5 to 38.2	2.28	−3.43 to 8.00	0.42	−2.16	−10.4 to 6.07	0.59
Depression (CES-D) (score 0-60)										
Intervention	13.7	10.0 to 17.4	10.7	7.2 to 14.3	−2.99	−6.83 to 0.85	0.12			
Control	8.6	5.2 to 12.1	12.4	8.5 to 16.2	3.75	−0.38 to 7.90	0.07	−6.75	−12.4 to −1.1	0.02
Physical function (HAQ) (score 0-3)										
Intervention	0.57	0.32 to 0.82	0.58	0.33 to 0.84	0.01	−0.10 to 0.13	0.79			
Control	0.74	0.51 to 0.97	0.65	0.42 to 0.88	−0.08	−0.20 to 0.02	0.12	0.10	−0.05 to 0.26	0.20
Cardiorespiratory fitness (VO_2 max)										
Intervention	2.09	1.78 to 2.40	2.40	2.09 to 2.71	0.31	0.20 to 0.42	0			
Control	2.09	1.82 to 2.35	2.04	1.77 to 2.31	−0.04	−0.14 to 0.05	0.39	0.35	0.21 to 0.50	0

Abbreviations: BRAF, Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; ESS, Epworth Sleepiness Scale; HAQ, Health Assessment Questionnaire; VAS, visual analog scale; VO_2 max, watt max test.

favored the intervention group (–6.75 points; 95% CI: –12.4 to –1.1). No between-group difference was observed for cardiorespiratory fitness, pain, sleepiness, or physical function (Table 4).

Acceptability of the intervention. Qualitative analysis of interviews with participants in relation to the acceptability of the intermittent aerobic exercise training revealed four themes (motivation, compliance with the exercise intervention, impact, and adoption) covering 12 subthemes. The participants' motivation for enrollment in the trial included hopes and expectations that the exercise training would increase their strength and energy, whereas adherence was primarily related to access to professional supervision by physiotherapists. Moreover, some participants described that the exercise training improved their energy and sleep, whereas others did not experience any changes. Theme adoption included descriptions of gaining new insight in relation to their ability to do high-intensity aerobic exercise. An overview of themes and subthemes complemented by selected quotes is presented in Table 5.

Table 5. Trial participants' (qualitative) acceptability of the intervention, organized into superordinate and subordinate themes with illustrative quotes

Superordinate themes	Subordinate themes	Selected illustrative quotes
Motivation	Unknown terrain	"I've been exercising before but not in this way where you're supposed to really push yourself and get short of breath the way you do on a bike."
	Finding my strength	"I know that I'm able to walk longer when I'm in shape than I'm able to when I'm out of shape. When I'm in shape, it's easier for me to carry myself erect and I have more energy both physically and mentally."
	Altruism	"Something good will come out of (the research), if not for me personally then for those who come after me."
Compliance with the exercise intervention	Positive attention	"They showed a lot on interest in what we were doing on that bike and they cheered and praised us and did all they could to back us up."
	Person-centered care	"They quickly came to know you—who you are and your personal preferences. For example, I get irritated if somebody's cheering too much, so they didn't do that with me."
	Commitment	"I'm very conscientious and when I've decided to say yes to something, then I know that I'll do what it takes and complete the job. Moreover, some very clever and nice people were counting on me and I just knew that it was good for me."
Impact	Surprised by own capacity	"I can do so much more than I think I can. It really took me by surprise that I was able to cycle for that long, that fast, and with that intensity."
		"I was surprised that I didn't feel more pain after working out on the bike."
	Sleep quality	"It didn't take me long to notice some positive changes in how well I sleep, and it has made me think that perhaps I need to allow myself to get physically exhausted a few times per week to sleep better. I really feel more energized, and my sleep has improved."
		"I don't know if the quality of my sleep has anything to do at all with my illness or if it's just my age. I wake up every two hours and it's not because I'm in pain."
	Transfer to daily life	"I've been doing some renovation in my apartment together with my children, which—a year back—I wouldn't have thought that I would be able to. It has made me think that I've let myself be lulled into the idea that there is so much that I can't do."
	Efforts recognized	"I can tell that my children, who are all teenagers, are impressed when I tell them how fast I've been riding on the bike and what power I achieved. I know that some of the boys are thinking 'wow,' and that has given us a different approach to some things. That has been a good experience for us."
Adoption	New insight	"I'm glad that I joined the trial because now I know how important it is to get your pulse rate up. I'll try to ride the bike more often now because I know that it's not enough to take a walk or lie on the floor stretching your legs or doing sit-ups."
	On your own	"I'm not yet up to the same speed as I was when I was in the program, but then again there's no longer someone standing beside me to serve me water or get me a chair if I need one. I'm riding more slowly, but the fact that I'm actually getting (exercise) done is great, I think."

DISCUSSION

This is the first RCT to examine the efficacy of an exercise intervention into sleep in people with RA using a mixture of objective and subjective measurements. It assessed a 6-week intermittent aerobic exercise intervention and found no statistically significant effect on the primary outcome or change in objectively measured sleep efficiency for the intervention group compared with the control group. However, the intervention group showed statistically significant reductions in aspects of fatigue (general, physical, and cognitive fatigue and living with fatigue) and in depressive symptoms.

Although the participants in the intervention group achieved numerical increases in the measures of sleep efficiency, longer sleep duration, and less time awake during the night, none of these improvements were significantly improved from the values in the control group. However, the findings do indicate that people with RA can achieve improved sleep through physical exercise training. In contrast, the authors of a systematic review concluded that no consistent or incontrovertible evidence exists of the impact of exercise on sleep in people with RA (24). Thus, despite our study, little is still known about the dose of exercise (type, frequency, duration, and intensity) needed to improve sleep in people with RA. This highlights the need for further studies to explore exercise training as a treatment option for improving sleep in people with RA.

Measuring PSG made it possible to identify the sleep architecture in this RA population, and although we did not find that aerobic exercise affected the sleep stages, it is notable that the sleep in this population was characterized by lighter (N1) and shallower (N3) sleep than the norm (25). Another observation in this RA population was that the prevalence of sleep apnea was higher than in the general population of similar age (26), highlighting the

importance of identifying undiagnosed sleep apnea in people with RA who experience sleep disturbances.

Fatigue was significantly lower in the intervention group than in the control group in terms of the general level of fatigue and the specific fatigue domains (eg, physical and cognitive fatigue and living with fatigue). This may have important implications because fatigue is one of the most pronounced daytime symptoms attributed to sleep disturbances and generally for people with RA. More studies of types and intensities are needed to establish the effect of physical exercise on sleep, but the present and previous studies have documented that exercise is an appropriate intervention for reducing fatigue. Thus, in accordance with our results, a meta-analysis had previously shown that moderate- to high-intensity exercise has a positive effect on fatigue in people with RA (27).

Depressive symptoms were significantly reduced in the intervention group compared with the control group. Because depression is a major mental health problem associated with arthritis (28) and one that is associated with sleep disturbances, this result may have important implications for the population with RA with and without sleep disturbances.

We found better cardiorespiratory fitness in the intervention group than in the control group, although the difference was not statistically significant. The finding is nevertheless important because even a modest improvement in oxygen uptake is known to be a strong independent predictor of survival in healthy people (29) and in people with RA and low cardiorespiratory fitness (22). Furthermore, our study showed high rates of adherence to the intermittent aerobic exercise regime and of achieving the planned intensity, including high-intensity aerobic exercise corresponding to 70% to 80% of the maximum wattage. This finding means that people with RA can undertake high-intensity exercise without the risk of any adverse events.

One of the limitations of the study is that the majority of potential participants did not wish to take part in the study or was excluded after screening. This affects the generalizability of the study. In interpreting the results, it is necessary to consider the differences between the intervention and control groups despite randomization. For example, the intervention group had a smaller percentage of women, shorter disease duration, higher percentage of smokers, greater alcohol consumption, and a higher percentage who were sedentary, all of which might affect sleep parameters. On the other hand, for the control group, the baseline sleep efficiency was better, and the baseline fatigue and CES-D scores were lower. One explanation may be that the sample size was smaller than what our power calculation recommended. The sex imbalance may also affect the generalizability, but this study is relevant for people with insomnia, most of whom are women (30), and for people with RA, about 75% of whom are women (31). Also, it might be a limitation in our study that participants did not have a PSG adaption night prior to the first PSG as baseline measurement. However, instead we considered CRM to be an adaption night. CRM is a less comprehensive measurement method, but several electrodes and equipment are attached to the patient. In this way, the participants tried to sleep with electrodes on before the PSG was applied. At the same time, it is a strength that this applied to both the intervention group and the control group, which means that it was the same conditions for both groups.

The strengths of the current study include the randomized design and the initial screening for sleep disturbances. Furthermore, this is the first study of an RA population that uses comprehensive measurement methods, including the gold standard reference (PSG), for objective measurement of sleep and sleep architecture, subjective sleep measurements, and detailed information about the content, duration, and intensity of the intermittent aerobic exercise training intervention. Furthermore, the high degree of adherence to the exercise intervention is a significant strength.

Our results have important clinical implications. The participants in this study were suboptimally physically active at the time of inclusion in the study, which is known to be the case for most people with RA (32–34). The qualitative data suggest that an intermittent aerobic exercise program including high-intensity physical activity is acceptable for patients with RA and may facilitate substantive improvements in mental well-being, including the patient's recognition of their own strength and capacity.

In conclusion, the intervention did not yield any statistically significant effect on the primary outcome of objectively measured sleep efficiency in people with RA compared with those receiving usual care. However, there were statistically significant between-group differences in aspects of fatigue, including physical and cognitive fatigue and living with fatigue, and in depressive symptoms.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Esbensen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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