Regular Article

Psychotherapy and Psychosomatics

Psychother Psychosom 2008;77:167–174
DOI: 10.1159/000116610

Published online: February 14, 2008

A Randomized Controlled Trial of the Effect of Aerobic Exercise Training on Feelings of Energy and Fatigue in Sedentary Young Adults with Persistent Fatigue

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Key Words
Energy · Exercise · Fatigue · Mood · Profile of Mood States · Randomized controlled trial

Abstract
Background: There is growing evidence that chronic exercise is a promising intervention for combating feelings of low energy and fatigue. Although groups with well-defined medical conditions (for example cancer and heart disease) or unexplained fatigue syndromes consistently have reported improved feelings of energy and fatigue after chronic exercise, relatively few exercise training studies have been conducted with people who report persistent fatigue yet neither have a medical condition nor reach diagnostic criteria for an unexplained fatigue syndrome. The purpose of this investigation was to use a randomized controlled design to examine the effects of 6 weeks of chronic exercise training on feelings of energy and fatigue in sedentary, healthy young adults reporting persistent fatigue. ***Methods:*** Thirty-six healthy, young adults who reported persistent feelings of fatigue were randomly assigned to a moderate-intensity exercise, low-intensity exercise or no treatment control group. Participants in each condition then visited the exercise laboratory on 18 occasions over a 6-week period. Exercise laboratory visits occurred 3 days per week. Vigor and fatigue mood state scores were obtained at the beginning of the third exercise session each week for 6 weeks. Aerobic fitness was measured before and after intervention. ***Results:*** The effect of 6 weeks of exercise training on feelings of fatigue was dependent on exercise intensity; however, the effect on feelings of energy was similar for both the low- and moderate-intensity conditions. The changes in feelings of energy and fatigue were independent of changes in aerobic fitness. ***Conclusions:*** Six weeks of low and moderate exercise training performed by sedentary adults without a well-defined medical condition or an unexplained fatigue syndrome but reporting persistent feelings of fatigue resulted in similarly beneficial effects on feelings of energy. The effects for symptoms of fatigue were moderated by exercise intensity, and the more favorable outcome was realized with low-intensity exercise. Changes in feelings of energy and fatigue following exercise training were unrelated to changes in aerobic fitness.

Introduction

In community samples, persistent fatigue (that is symptom scores ≥half an SD from the population mean for ≥30 days) is a problem for 20% of adults in the community [1] and is associated with physical inactivity [2]. Sedentary groups with well-defined medical conditions

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(for example cancer and heart disease) or unexplained fatigue syndromes report improved feelings of fatigue after chronic exercise [3–6], but few studies have involved those with persistent fatigue who neither have a medical condition nor have reached diagnostic criteria for an unexplained fatigue syndrome [7–13]. Subsyndromal, persistent fatigue is one of the most common reasons for patients to seek medical advice and the prognosis, while not as bleak as those with chronic fatigue syndrome (CFS), is worse than those with more transient symptoms of fatigue [14].

Deconditioning following physical inactivity has been suggested as contributing to unexplained fatigue syndromes [15] and improved aerobic fitness might mediate improvements in quality of life including feelings of energy and fatigue [16–18]. However, few studies have addressed these issues in persistently fatigued individuals without a well-defined medical condition or an unexplained fatigue syndrome. It is possible that moderate-intensity exercise training is too intense to improve symptoms of low energy among sedentary, persistently fatigued, but otherwise healthy adults as has been suggested for patients with CFS [19]. Interestingly, low-intensity exercise has been more commonly used in studies of medical patients with CFS [20], while moderate-intensity exercise has been more frequently used in studies of healthy adults [8, 21].

This investigation had 2 primary aims. One was to use a randomized controlled trial design to examine the effects of 6 weeks of low and moderate exercise training on feelings of energy and fatigue in sedentary, healthy young adults reporting persistent fatigue. The second was to examine the association between changes in aerobic fitness and changes in feelings of energy and fatigue.

Methods and Materials

Participants

Healthy male and female college students between the ages of 18 and 35 were recruited from the University of Georgia via electronic mail sent to several campus groups. An a priori statistical power analysis showed that a sample of 36 participants would provide a statistical power of ≥ 0.80 for the main and interaction effects of the study design assuming a two-tailed α value of 0.05, a high correlation across repeated measures ($r = 0.80$) and an expected Cohen's d effect size of 0.60 [22].

Exclusion criteria were: (a) the absence of persistent fatigue defined as a raw score of 17 or higher on the vitality scale of the SF-36 Health Survey using the time frame 'during the past 4 weeks'; a raw score of 16 is approximately half an SD below US population norms [23], (b) the presence of contraindications to maximal exercise based on professional guidelines [24], (c) a physically active lifestyle defined as a weekly energy expenditure greater than half an SD below college-aged norms as measured by the 7-Day Physical Activity Recall (7dPAR) questionnaire [25, 26], (d) the self-reported use of any antidepressant medication within the last month, (e) the presence of a well-defined medical condition, (f) meeting criteria for an unexplained fatigue syndrome, and (g) scores at or above a cutoff suggesting any of the following DSM-IV psychiatric disorders measured by the Psychiatric Diagnostic Screening Questionnaire [27, 28]: generalized anxiety disorder, panic disorder, social anxiety disorder, major depressive disorder and substance abuse.

Design and Procedures

Thirty-six participants were randomly assigned to 1 of 3 conditions: moderate-intensity aerobic exercise, low-intensity aerobic exercise or no treatment control. Blocked randomization, which assured 12 participants in each condition, was performed using Research Randomizer (www.randomizer.org).

Following randomization and the week before the intervention began, mood, physical activity, exercise expectancy and medication/nutritional supplement data were obtained. Exercise expectancy was measured with a modified questionnaire (1 item about feelings of energy was added) that examined the expected benefits associated with being physically active [29]. Week-to-week changes in the use of medications and nutritional supplements were monitored with an author-created questionnaire. All participants visited the exercise lab on 18 occasions, 3 days per week at about the same time each day. Fitness testing occurred the week before the start and the week after the end of the 6-week study period.

Aerobic Fitness Testing

All participants performed an incremental exercise test on an electronically braked, computer-driven cycle ergometer (Lode BV, Groningen, The Netherlands) in order to measure peak oxygen consumption (VO_{2peak}). The purpose of the VO_{2peak} test was to examine changes in fitness and ensure that subsequent exercise training bouts were completed at the appropriate relative intensity for each participant.

Participants were fitted to the ergometer and provided with standardized, tape-recorded instructions [30] for providing overall ratings of perceived exertion using a 6–20 scale [31]. The participants performed a 5-min warm-up at 25 W. The initial work rate for the exercise test was 50 W and the work rate continuously increased at a rate of 24 W/min until volitional exhaustion [32]. Pedal rate was maintained at 50–70 rotations/min. Ventilation, oxygen consumption and carbon dioxide production were measured (Parvo Medics TrueOne 2400) and respiratory exchange ratio calculated every 15 s. Heart rate was measured using a Polar S120 monitor (Polar Electro Oy, Kempele, Finland). Heart rate and perceived exertion were recorded during the last 10 s of every minute during the test. VO_{2peak} was defined as the highest VO_2 value when 2 of the 3 following criteria were satisfied: (a) respiratory exchange ratio ≥ 1.10, (b) heart rate within 10 beats/min of age-predicted maximum (that is 220 – age) or (c) rating of perceived exertion ≥ 18.

Intervention Conditions

Participants in the moderate-intensity aerobic exercise condition performed 20 min of moderate-intensity (75% VO_{2peak}) cycle ergometry after a 5-min warm-up cycling at 25 W. During minutes 4 and 14 of exercise, VO_2 data were collected and then adjustments made to the work rate to maintain an intensity of 75% VO_{2peak}. Participants cooled down by cycling at 25 W for 5 min. Exercise sessions were held in a small room with the door closed in the presence of a single investigator. Social interactions were kept to a minimum in order to avoid the possible effects of social interactions on mood and to standardize the exercise setting. Ten minutes before the start of the third training session of each week, mood, physical activity and medication/nutritional supplement data were obtained.

Participants in the low-intensity condition cycled at 40% VO_{2peak}. Participants in the no treatment control condition sat on the cycle ergometer for 30 min. Controls were asked to maintain their current physical activity level for the duration of the study. Otherwise, procedures and measures were identical to those described above for the moderate-intensity aerobic exercise condition.

Outcome Measures

Vigor and fatigue mood states were measured using the 30-item Profile of Mood States Short Form (POMS-SF) [33]. Participants were asked to respond as to how they felt during the last week. A large body of evidence indicates that scores from the POMS-SF vigor and fatigue scales can be interpreted as measures of the intensity of energy and fatigue mood states [33, 34]. In the present study, the stability of the weekly vigor [ICC (3,6) = 0.89, 95% CI = 0.83–0.94] and fatigue [ICC (3,6) = 0.87, 95% CI = 0.79–0.93] scores was high across the 6-week testing period.

Changes in physical activity not associated with the intervention were documented using the 7dPAR questionnaire [25]. This questionnaire provided self-reported estimates of the time spent sleeping and engaged in moderate, hard and very hard physical activities over the prior 7-day period. Raw data from the questionnaire were used to calculate energy expenditure. The 7dPAR questionnaire provides a reliable and valid measure of weekly energy expenditure among college students [26]. The stability of the 7dPAR scores across 6 weeks was high [ICC (3,6) = 0.91, 95% CI = 0.86–0.95] and similar to prior reports based on college-aged samples [26].

Statistical Analyses

Data analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics are presented in text and tables as means with SD in parentheses. Statistical significance was based on $p \leq 0.05$. One-way ANOVA were used to compare preintervention participant characteristics, exercise expectancy, intervention intensity measures and exercise adherence rates among the 3 groups of participants. Aerobic fitness data were analyzed with a mixed model 3 (group: moderate-intensity exercise training, low-intensity exercise training and no treatment control) × 2 (time: before and after intervention) ANOVA with repeated measures on the time variable.

The first aim of the study (effect of exercise on vigor and fatigue) was analyzed with a 3 (group) × 6 (time: 1, 2, 3, 4, 5 and 6 weeks) trend analysis. Preintervention vigor and fatigue scores were used as covariates in the vigor and fatigue trend analyses, respectively. The second aim of the study (relationships between changes in aerobic fitness and changes in feelings of energy and fatigue) was analyzed with a mixed model 3 (group) × 2 (time: before intervention and week 6) ANCOVA with repeated measures on the time variable and VO_{2peak} used as a time-varying covariate. All mixed model analyses were based on the F-statistic. Effect sizes for F-statistics were expressed as partial η^2. Degrees of freedom were adjusted (Greenhouse-Geisser) when the sphericity assumption was violated. The family-wise error rate was controlled using the Bonferroni adjustment when tests of simple effects were conducted.

Results

No participants discontinued the intervention during the course of the study and all participant data were used in the analysis (fig. 1). There were no significant group differences in expected benefits of exercise including those specific to feelings of energy and fatigue. The average number of medications and supplements taken was 1. Birth control pills and over-the-counter pain relievers or cold medicines were the most common medications. Multivitamins were the most common supplement. There were no significant group, time or group-by-time interactions for the number of medications or supplements taken. Other baseline characteristics are summarized in table 1.

Manipulation Checks

The moderate-intensity exercise, low-intensity exercise and no treatment control groups completed an average of 97.2, 98.3 and 99.4% of the 18 prescribed sessions, respectively. During the 20-min exercise period, the moderate-intensity group was characterized by an overall mean VO_2 of 76% (10), a heart rate of 154 beats/min (13) and a perceived exertion rating of 13 (1). The results for the low-intensity group were 43% (9), 110 beats/min (10) and 8 (1), respectively, and those for the no treatment group were 14% (2), 80 beats/min (8) and 6 (0), respectively. There was a significant group-by-time interaction for aerobic fitness ($F_{2,33} = 7.87$, $p = 0.05$, $\eta^2 = 0.16$; table 2). The interaction showed the increase in fitness was larger for the moderate-intensity group compared to the low-intensity and no treatment groups ($F_{1,34} = 6.32$, $p = 0.02$, $\eta^2 = 0.16$).

The highest and lowest weekly mean nonintervention energy expenditure values (kcals·kg·week) for the moderate intensity group were 250.2 (31.3) and 243.4 (18.4), respectively. Results were 253.2 (22.6) and 243.6 (13.0), respectively, for the low-intensity group and 250.9 (34.4) and 243.0 (13.7), respectively, for the no treatment group. These scores are about half an SD below college-aged norms and such scores have categorized individuals as

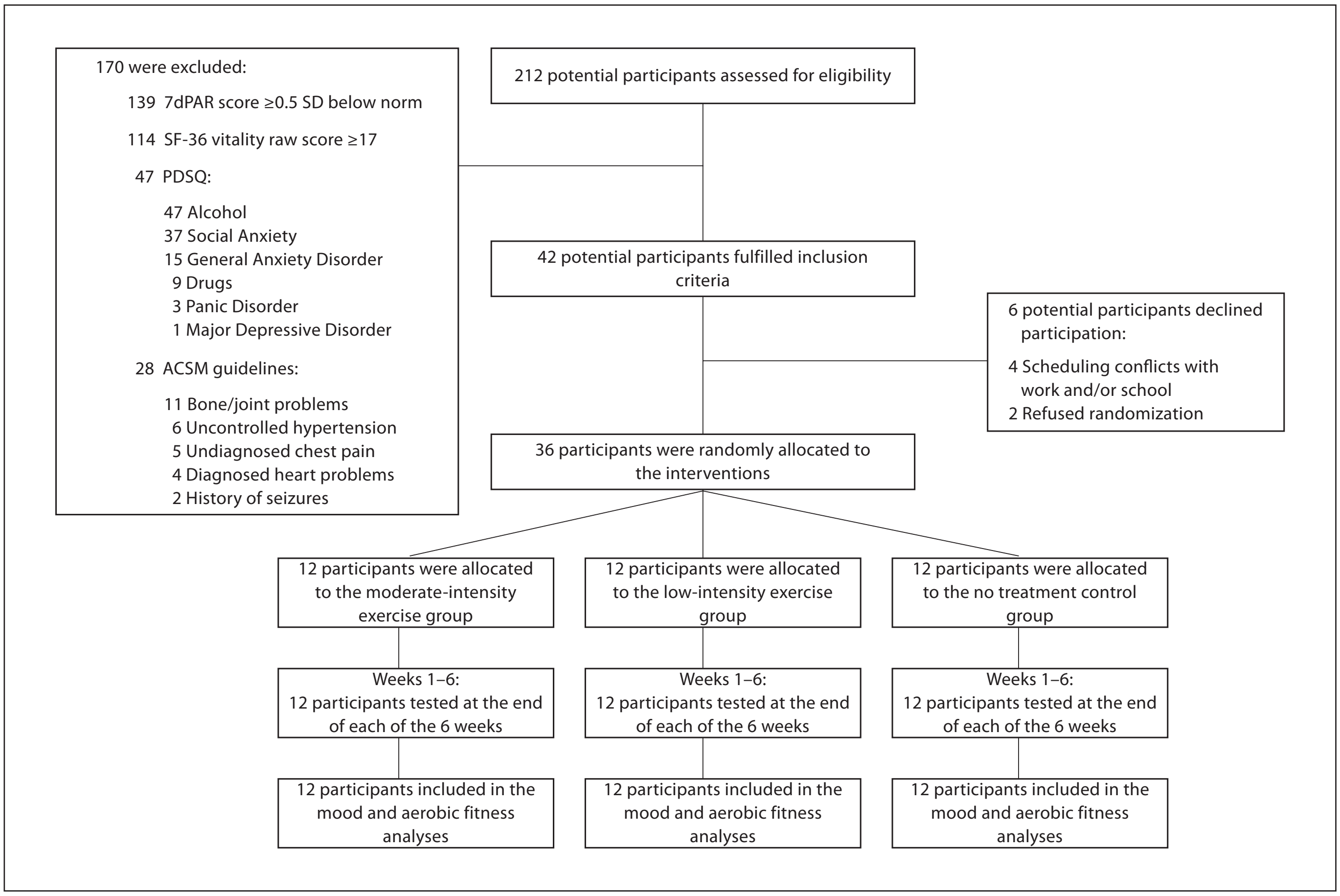

Fig. 1. The flow of participants throughout the 6-week randomized controlled trial.

Table 1. Preintervention participant characteristics

	Overall (n = 36)	Moderate intensity (n = 12)	Low intensity (n = 12)	Control (n = 12)	F value	p value
Physical						
Female	27 (75%)	8 (67%)	9 (75%)	10 (83%)	0.42	0.66
Age, years	23 (4.2)	24 (4.7)	24 (4.4)	21 (2.4)	2.53	0.10
Height, m	1.47 (0.1)	1.49 (0.1)	1.45 (0.1)	1.49 (0.1)	0.79	0.46
Weight, kg	71.1 (13.1)	71.4 (13.8)	69.5 (12.9)	72.2 (13.6)	0.13	0.88
BMI	24.4 (3.7)	24.1 (3.3)	24.8 (4.8)	24.4 (3.2)	0.12	0.89
VO_{2peak}, ml•kg•min^{-1}	27.8 (7.2)	29.6 (8.8)	26.5 (6.6)	27.5 (6.1)	0.55	0.58
Psychological						
POMS vigor	8.17 (3.4)	7.42 (2.6)	8.33 (3.1)	8.75 (4.4)	0.47	0.63
POMS fatigue	6.58 (4.6)	7.75 (4.5)	5.8 (4.0)	6.25 (5.4)	0.59	0.56
Physical Activity						
7dPAR, kcal•kg•week	243.39 (13.7)	239.34 (13.23)	245.9 (13.0)	244.94 (15.0)	0.55	0.58

Data are presented as means with SD in parentheses for continuous variables and frequencies with percentages in parentheses for categorical variables. BMI = Body mass index.

Table 2. Change in aerobic fitness over 6 weeks

Intervention	Participants	VO_{2peak}		Group × time		Group		Time	
		preintervention	postintervention	F value	p value	F value	p value	F value	p value
Moderate intensity	12	29.6 (8.8)	32.6 (8.1)	7.78	0.05	1.02	0.37	22.27	<0.01
Low intensity	12	26.5 (6.6)	27.8 (6.6)						
Control	12	27.5 (6.1)	28.4 (6.9)						

Data are presented as means with SD in parentheses.

Table 3. Changes in POMS-SF vigor and fatigue scores over 6 weeks

Intervention	Participants	Week 1	2	3	4	5	6	Group × trend F value	Group × trend p value	Group F value	Group p value	Time F value	Time p value
Vigor scores								3.21	0.05[a]	1.36	0.27	0.63	0.44
Moderate intensity	12	8.63 (2.4)	7.97 (2.9)	8.08 (2.6)	8.43 (2.4)	8.92 (2.5)	10.09 (3.4)						
Low intensity	12	7.57 (2.4)	7.03 (2.9)	6.92 (2.6)	7.07 (2.4)	7.66 (2.4)	8.86 (3.4)						
Control	12	6.39 (2.4)	6.66 (2.9)	6.99 (2.5)	7.33 (2.4)	8.0 (2.4)	6.80 (3.4)						
Fatigue scores								3.61	0.04[b]	1.53	0.23	0.13	0.72
Moderate intensity	12	3.35 (3.2)	3.24 (3.7)	3.34 (3.1)	3.38 (3.2)	2.97 (3.3)	3.68 (3.1)						
Low intensity	12	4.68 (3.2)	4.80 (3.6)	3.05 (3.1)	3.18 (3.2)	2.99 (3.2)	2.17 (3.1)						
Control	12	4.56 (3.2)	4.20 (3.7)	4.87 (3.1)	4.19 (3.2)	4.96 (3.3)	4.90 (3.1)						

Data are presented as means with SD in parentheses. Scores have been statistically adjusted using preintervention vigor and fatigue scores as covariates for vigor and fatigue scores, respectively.
[a] Significant group by quadratic trend interaction.
[b] Significant group by linear trend interaction.

inactive [26]. There was no significant group, time or group-by-time interactions.

Changes in Feelings of Vigor and Fatigue

There was a significant group-by-trend interaction for the quadratic change in feelings of vigor over the intervention period ($F_{2,32}$ = 3.61, p = 0.04, η^2 = 0.18; table 3). The interaction showed that the no treatment group had a different rate of change than the low-intensity ($F_{1,21}$ = 4.87, p = 0.04, η^2 = 0.19) and moderate-intensity ($F_{1,21}$ = 4.67, p = 0.04, η^2 = 0.18) exercise groups. There was no significant difference in the rate of change in feelings of vigor for the moderate- and low-intensity exercise groups. Baseline and unadjusted vigor scores have been provided for descriptive purposes (table 4).

There was a significant group-by-trend interaction for the linear change in feelings of fatigue over the intervention period ($F_{2,32}$ = 3.21, p = 0.05, η^2 = 0.17; table 3). The interaction showed that the low-intensity group had a different rate of change than the moderate-intensity ($F_{1,21}$ = 5.24, p = 0.03, η^2 = 0.20) and no treatment ($F_{1,21}$ = 6.29, p = 0.02, η^2 = 0.23) groups. There was no difference in the rate of change in feelings of fatigue for the moderate-intensity or no treatment groups. Baseline and unadjusted fatigue scores have been provided for descriptive purposes (table 4).

Associations with Changes in Fitness and Changes in Vigor and Fatigue

ANCOVA was used to assess whether the changes in feelings of vigor and fatigue in the intervention groups were independent of the changes in aerobic fitness. There was a significant group-by-time interaction for vigor ($F_{2,33}$ = 3.63, p = 0.04, η^2 = 0.18). The interaction showed that the increase in vigor was larger for the moderate-intensity group compared to the low-intensity and no treatment groups ($F_{1,34}$ = 4.81, p = 0.04, η^2 = 0.12). This interaction remained significant after accounting for the

Table 4. Changes in POMS-SF vigor and fatigue scores over 6 weeks

Intervention	Participants	Pre-intervention	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Vigor scores								
Moderate intensity	12	7.42 (2.6)	8.17 (3.7)	7.75 (3.0)	7.75 (3.2)	8.00 (3.1)	8.50 (2.2)	9.83 (3.1)
Low intensity	12	8.33 (3.1)	7.67 (3.3)	7.08 (3.7)	7.08 (2.8)	7.17 (3.7)	7.75 (3.9)	8.92 (3.5)
Control	12	8.75 (4.4)	6.75 (4.3)	6.83 (4.3)	6.83 (4.1)	7.67 (4.3)	8.33 (4.6)	7.00 (3.2)
Fatigue scores								
Moderate intensity	12	7.75 (4.5)	3.83 (2.6)	3.67 (2.8)	3.75 (3.4)	3.75 (2.5)	3.42 (2.7)	3.92 (3.6)
Low intensity	12	5.75 (4.0)	4.33 (1.7)	4.50 (3.8)	2.75 (2.5)	2.92 (2.4)	2.67 (2.9)	2.00 (2.2)
Control	12	6.25 (5.5)	4.42 (4.3)	4.08 (3.2)	4.75 (3.1)	4.08 (3.3)	4.83 (3.4)	4.83 (4.3)

Data are presented as means with SD in parentheses.

change in feelings of vigor explained by aerobic fitness ($F_{2,33} = 3.49$, $p = 0.04$, $\eta^2 = 0.18$).

There was no significant group-by-time interaction for changes in feelings of fatigue ($F_{2,33} = 0.90$, $p = 0.42$, $\eta^2 = 0.05$). There was a main effect for time ($F_{1,33} = 12.96$, $p = 0.001$, $\eta^2 = 0.28$), but not for group ($F_{2,33} = 1.25$, $p = 0.30$, $\eta^2 = 0.07$). There was a reduction in fatigue for all 3 groups from before to after intervention. The main effect for time remained significant after accounting for the change in feelings of fatigue explained by aerobic fitness ($F_{2,33} = 8.03$, $p = 0.01$, $\eta^2 = 0.20$).

Discussion

Chronic exercise has promise for improving fatigue among the sedentary [2, 4, 16]. The present study used a randomized controlled trial design and found that (a) the rate at which feelings of fatigue changed over the course of 6 weeks of exercise training was dependent on exercise intensity, (b) the rate at which feelings of energy changed over the course of 6 weeks of exercise training was similar for the low- and moderate-intensity conditions and both exercise conditions differed from the control, and (c) changes in feelings of energy and fatigue were independent of changes in aerobic fitness.

Exercise training effects on feelings of fatigue were moderated by exercise intensity. After adjusting for baseline scores, there was a trend for improved fatigue with low-intensity exercise training. Moderate-intensity exercise often results in better health outcomes compared to low-intensity exercise [35]. For instance, moderate-intensity exercise has been found to reduce symptoms of depression to a greater extent than low-intensity exercise [36]. However, the greater benefits of moderate-intensity exercise may not extend to people with persistent fatigue who do not have a well-defined medical condition or an unexplained fatigue syndrome. It has been suggested that moderate-intensity exercise may be too intense for patients with CFS because they experience severe fatigue symptoms after moderate-intensity exercise [19]. The fatigue results here are consistent with the idea that low-intensity exercise may minimize training-induced increases in fatigue symptoms among people with persistent fatigue.

Training effects on feelings of energy were not moderated by exercise intensity. After adjusting for baseline vigor scores, the rate of change in vigor scores across the 6-week study period did not differ between low and moderate exercise training groups; however, the rate of change for both exercise groups differed from the no treatment control. Vigor scores for the exercise groups, but not the control group, were increased from baseline and reached their highest point during the final week of the investigation. The vigor score results are consistent with results from large cross-sectional studies suggesting that increased feelings of energy should accompany small increases in regular physical activity [2].

The magnitudes of increase in vigor scores (by an average of 20% for the low and moderate exercise conditions) and decrease in fatigue scores (by 65% in the low-intensity condition) from baseline to week 6 were large and clinically meaningful [37], but unrelated to changes in aerobic fitness. The absence of a strong relationship between changes in aerobic fitness and changes in feelings of energy and fatigue is consistent with prior exercise training experiments with CFS patients [17, 38] and a growing body of evidence showing that symptoms of fatigue are mediated by central nervous system mechanisms [39].

The reason for the different pattern of results for feelings of energy compared to feelings of fatigue is unclear. Factor-analytic studies of mood questionnaires have yielded distinct energy and fatigue factors [33, 40] and experiments with depressants and stimulants show different patterns and magnitudes of effects on feelings of energy compared to fatigue [41]. Chronic exercise also can have different effects on feelings of energy compared to fatigue. For example, a 27% increase in the amount of exercise training performed by competitive athletes resulted in larger and faster increases in feelings of fatigue compared to the reductions in feelings of energy that also occurred during the increased training period [42].

In conclusion, our study showed that 6 weeks of low and moderate exercise training performed by sedentary adults reporting persistent fatigue but no well-defined medical illness and not meeting criteria for an unexplained fatigue syndrome resulted in similar beneficial effects on feelings of energy. The effects for symptoms of fatigue are moderated by exercise intensity, and the more favorable outcome is realized with low-intensity exercise. Changes in feelings of energy and fatigue following exercise training are unrelated to changes in aerobic fitness. The findings point to the need for future investigations aimed at understanding the behavioral and neurophysiological consequences of low-intensity exercise that improves feelings of energy and fatigue.

Acknowledgements

The authors have no conflicts of interest and received no external financial support to conduct this investigation. The authors thank the participants for their time and effort and Brittany Beasley, Stella Hondros, Kristen Moles, Amanda Reichert, Tabitha Sharber and Matt Steele for assistance in supervising the exercise training of the participants.

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