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Effect of Short-Term Interval Exercise Training on Fatigue, Depression and Fitness in Normal Weight vs. Overweight person with Multiple Sclerosis

Raof Negaresh ^a, Robert Motl ^b, Motahare Mokhtarzade ^{a*}, Rouholah Ranjbar ^c, Nastaran Majdinasab ^{d,e}, Mostafa Khodadoost ^f, Philipp Zimmer ^{g,h}, Julien S Baker ⁱ, Darpan Patel ^j

^a Department of sport physiology, Tarbiat Modares University, Tehran, Iran.

^b Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL, USA.

^c Department of sport physiology, Shahid Chamran University of Ahvaz, Ahvaz, Iran.

^d Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

^e Department of Neurology, Golstan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

^f Department of physical education, Abadan branch, Islamic Azad University, Abadan, Iran.

^g Department for Molecular and Cellular Sports Medicine, German Sport University Cologne, Cologne, Germany.

^h Division of Physical Activity, Prevention and Cancer, German Cancer Research Center, Heidelberg, Germany.

ⁱ Institute of Clinical Exercise and Health Sciences, School of Science and Sport, University of the West of Scotland, Hamilton, Lanarkshire, Scotland.

^j School of Nursing, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA.

Corresponding author: Motahare Mokhtarzade Department of Exercise Physiology, Tarbiat Modares University, Tehran, Iran.

Phone: +989164262029; Fax: +986153360839 E-mail: Motaharemokhtarzade@modares.ac.ir

Keywords: Fatigue; Depression; Excess weight; Fitness

Short Title (Running Head): Excess weight and exercise in MS

Conflict of Interest

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Abstract

Context: Excessive weight is a health problem that can exacerbate multiple sclerosis (MS) symptoms and its associated comorbidities such as depression and fatigue. In addition, weight may be a moderator of exercise effects on depression and fatigue symptoms.

Objective: This study aimed to investigate the effects of exercise training on fatigue and depression in normal and overweight individuals with MS.

Methods: Sixty-six persons with MS were randomly assigned into an exercise or control condition based on body weight status (overweight vs. normal-weight). The exercise conditions involved 8-weeks of interval exercise at 60-75% $Watt_{peak}$, while the control condition did not involve any exercise. Fatigue, depression, aerobic capacity, time up and go (TUG) and body mass index were measured before and following the 8-week period.

Results: There were no significant relationships revealed for weight status interactions for any of the variables examined. There were significant condition main effects for fatigue, depression, aerobic capacity and TUG, and significant improvements were noted for the exercise conditions, but not in the non-exercising control group.

Conclusion: The results from this study confirm that exercise is an effective therapeutic intervention for improving fatigue, depression and functional parameters, independent of initial weight status, in persons with MS.

Keywords: Fatigue; Depression; Excess weight; Fitness

INTRODUCTION

Fatigue and depression are two of the most common, debilitating, and poorly managed symptoms in persons with multiple sclerosis (MS) [1]. Cohort studies conducted on prevalence and incidence of fatigue in MS indicate that more than 50% of persons with MS experience symptoms of fatigue at least once a week [2, 3]. The prevalence of depression ranges between 10 and 54% among persons with MS [1, 3-5] and this is two to three times higher than healthy individuals and those with other chronic diseases [4]. A recent systemic review and meta-analysis of 58 studies with a total sample size of 87,756 persons with MS reported a prevalence of depression exceeding 30% [5]. Fatigue and depression symptoms are further related to the most commonly prescribed immune-modulatory medications in MS (i.e., interferon-beta) [3, 6]. Fatigue and depression are commonly accompanied by disability progression [2, 7], and fatigue and depression symptoms may reduce physical activity and quality of life in persons with MS [7]. The prevalence and impact of fatigue and depression underscore the importance of managing these symptoms in persons with MS [8, 9]. To date, pharmacological and psychological interventions have had limited positive effects in reducing fatigue symptoms and depression [10]. This supports the rationale for considering other behavioral strategies for reducing fatigue and depression in persons with MS.

There is a growing body of evidence indicating that physical activity is an effective strategy for reducing fatigue and depression in clinical populations including person with MS [2, 9, 11]. Indeed, a meta-analysis of 17 studies reported the positive effects of exercise training on fatigue in persons with MS (effect size=0.45, standard error= 0.12, 95% CI = 0.22-0.68) [2]. A further meta-analysis of 13 studies reported that exercise training improved depressive symptoms

among persons with MS (effect size=0.36, standard error= 0.09, 95% CI = 0.18-0.54) [7]. Both meta-analyses confirmed the positive effects of exercise on fatigue and depression in persons with MS, but the effect sizes were modest and heterogeneous, and support further research for factors that moderate the effects of exercise training.

There are several factors that may moderate the beneficial effect of exercise training on fatigue and depression in persons with MS. Body composition and weight status may be one of the most salient moderating factors. Weight gain is a major public health concern that increases the risk of MS [12]. Previous studies clearly report a high prevalence of overweight and obesity in persons with MS indicating that more than 40% of persons with MS were overweight and nearly half were obese [13, 14]. Overweight and obese individuals frequently report experiencing fatigue and depression more frequently than people of normal weight [15]. Body weight is further associated with a decrease in walking ability and aerobic capacity in persons with MS [16]. The theory that weight can be a moderating factor for exercise effect has been outlined in previous research[17, 18]. These studies confirm the role of initial weight and weight loss on adaptation following an exercise program intervention. Even when no significant weight loss has been observed, this moderating weight effect has been investigated in cardiovascular disease and aerobic fitness[17], walking ability[17], and psychological parameters [18]. Collectively, body weight can be considered as an important and influential moderator of exercise training, but the moderating role of weight has not been investigated in persons with MS.

The present study examined the hypothesis that body weight may be a moderator of exercise training effects on the outcomes of fatigue and depression, based on individual adaptations in aerobic capacity, in person with MS. We further examined the likelihood of a link between functional changes in fatigue and depression in overweight and normal weight persons with MS.

METHODS

Study design and procedure

This study was a randomized controlled trial with a blinded outcome assessment. The study was approved by the Ethics Committee of Abadan University, Abadan, Iran, but and did not have a clinical trials registration. All participants gave written informed consent prior to commencement of the study. The consolidated standards of reporting trial (CONSORT) diagram describing participant interaction during the study is presented in Fig. 1. An invitation letter was sent to all persons with relapsing-remitting MS (RRMS) that were registered at the MS center of Khuzestan (Iran). We screened 108 volunteers diagnosed with RRMS for inclusion based on the following criteria; a) RRMS type (revised McDonald criteria [19]), b) general body mass index (BMI) ranging between 20 to 30 kg/m², c) $0 < \text{Expanded Disability Status Scale (EDSS)} \leq 4$, and d) age > 22 years. There were 103 RRMS participants who were eligible to participate in the study based on exclusion criteria (54 normal weight and 49 overweight persons with MS). The exclusion criteria were as follows: a) those engaged in regular moderate to heavy exercise during the study or activity within the previous year; b) smoking; c) documented relapses or acute multiple sclerosis exacerbation during the study or within the last six months; d) volunteers with orthopedic limitations; or e) presence of chronic diseases (i.e. kidney disease) other than MS.

We randomly selected 66 RRMS person (33 normal weight and 33 overweight persons with MS) from 103 eligible MS participants to participate in the current study (Fig. 1).

All measures including fatigue, depression, time up and go test (TUG), aerobic capacity and body composition (weight, BMI) were measured prior to starting the intervention and were

repeated post intervention. Fatigue, depression, aerobic capacity and BMI were assessed by authors (RN and MM); EDSS scores were determined by a neurologist (NM).

Randomization and masking

A concealed randomization procedure was carried out by classifying participants based on initial BMI. Sixty-six RRMS participants were then randomly selected and assigned into two conditions (exercise or control condition). BMI was calculated from body mass (kg, Seca515, Sweden) divided by the square of height (m) of an individual. Therefore, normal weight and overweight participants are referred to as participants with $20 \text{ kg/m}^2 < \text{BMI} < 25 \text{ kg/m}^2$ and $25 \text{ kg/m}^2 < \text{BMI} < 30 \text{ kg/m}^2$, respectively. Based on BMI measures, each group was divided into two sub-groups, which yielded four groups including overweight control (OC, n=15), overweight exercise (OE, n=18), normal weight controls (NC, n=15), and normal exercise (NE, n=18) groups. During the study, 5 participants withdrew due to a relapse (1 participant from NE) and reluctance to continue the program (4 participants).

Primary end point

Fatigue

The fatigue severity scale (FSS) measured the primary end point of fatigue. The FSS has captured the effects of exercise on fatigue in previous studies involving persons with MS [2] and the reliability and validity of the Persian version of FSS has been established previously [20].

The questionnaire consists of 9 questions; each question is rated on a scale from 1 (representing

minimal fatigue) to 7 (representing maximal fatigue). The overall FSS score consists of an average of the 9 items and assesses the severity of fatigue on a scale between 1 and 7 in persons with MS [2, 20].

Depression

The Beck depression inventory (BDI) measured the primary end point of depression severity. The BDI has been widely used as a valid psychometric test of depression status in previous MS studies [21] and the reliability and validity of the Persian version of BDI has been established previously [22]. The BDI is a 21-item question tool (each question ranging between 0 and 3), and overall scores ranged between 0 (represents minimal depression) and 63 (represents maximal depression) [7].

Secondary end point

Timed up and go

The TUG was administered as a measure of mobility [23]. The TUG test requires both static and dynamic balance ability. Participants on hearing the command go, raise from a seated position and walk 3 meters forward, turn and walk back and sit in a chair [23]. The investigator then records the TUG test time in seconds.

Exercise program and aerobic capacity test

The exercise program for both exercise groups consisted of 8 weeks (3 days per week) of upper- and lower-limb cycling (Monark 891E and 894E ergometers, Sweden). The exercise program was administered in the exercise physiology lab under the supervision of exercise physiologists (RN and MM). The interval exercise program was chosen because it (1) has been demonstrated to be well tolerated by persons with MS [24, 25], (2) has many benefits [25-27], and (3) includes intervals of rest and exercise that are suitable for person with MS who have fatigue [25].

Exercise sessions started with a warm up (10 min) and finished with cool down (10 min). The main body of the exercise program in the first week consisted of three intervals (two min) cycling separately for upper- and lower-limbs. Following exercise, there were two min of inactive rest between intervals. The number of intervals gradually increased progressively over the course of the 8 week period. This concluded in participants undertaking six intervals separately for the upper and lower limbs in week 8. The training intensity was adjusted by watt peak (W_{peak}) determined by the aerobic capacity (VO_{2peak}) test [28, 29]. Training intensity started at 60% W_{peak} (percent peak work rate) during week 1 and increased gradually to 75% W_{peak} in week 8. During all sessions, the pedal rate was fixed at 50 rpm. The session duration was 42 min in week 1 and increased gradually to 66 min in week 8. During the intervention program, the control groups only completed pre and post outcome assessments and did not participate in any additional exercise program. The exercise program used has been previously studied in MS patients, and reports indicate that the exercise program was well-tolerated [24, 25].

Statistical analysis

To test our hypothesis, we used a two-factor ANOVA (weight status: 2 levels of normal weight or overweight, condition: 2 levels of exercise or control) (SPSS Statistics 21[®], IBM[®] Armonk, NY, USA) on change scores computed on the difference between pre- and post-test scores. We reported partial eta squared (η^2) for documenting the effect size associated with the ANOVA tests. Pearson correlation coefficients were used to determine the relationship between changes in $V_{O_{2peak}}$ fatigue, depression and TUG. Significance was defined at p value <0.05.

RESULTS

Of the 66 RRMS participants, 61 completed the current study, with a completion rate of 92.4%. Reasons for drop-out are listed in Fig. 1. The exercise program was well tolerated by both overweight and normal-weight persons with MS, and no adverse events were reported by study participants or personal (i.e., stroke, illness, low back pain, knee pain, fall and etc.). The exercise program was well attended by both exercise groups. Of the 24 exercise sessions, overweight and normal weight participants attended 22.2 ± 1.9 and 22 ± 1.6 sessions, respectively. This reflects 92.5 and 91.7 percent compliance with the exercise sessions.

Baseline results

Results indicated main effects of weight status on baseline values of fatigue ($p=0.045$, $F=4.2$), TUG ($p=0.042$, $F=4.34$) and $V_{O_{2peak}}$ ($p=0.020$, $F=5.73$). $V_{O_{2peak}}$ was significantly higher, whereas TUG and fatigue were significantly lower in normal weight than overweight groups at baseline. Weight ($p=0.001$, $F=271.72$) and BMI ($p=0.001$, $F=400.10$) were significantly higher in

overweight groups at baseline. There were no differences in depression between groups at baseline ($p>0.05$, table 1).

Primary endpoint results

There were no significant interactions between weight status and condition on any of the primary endpoints ($p>0.05$). There were significant main effects of condition on fatigue ($F=12.7$, $p=0.001$, $\eta_p^2=0.18$) and depression ($F=8.69$, $p=0.005$, $\eta_p^2=0.13$). The exercise conditions had statistically significant improvements for fatigue and depression, whereas the control showed no significant changes (Fig. 2).

Secondary endpoint results

We observed the absence of significant interaction effects for $V_{O_{2peak}}$ ($F=1.89$, $p=0.17$) and TUG ($F=0.40$, $p=0.52$). There were significant conditions main effects on $V_{O_{2peak}}$ ($F=21.06$, $p=0.001$, $\eta_p^2=0.27$) and TUG ($F=11.57$, $p=0.001$, $\eta_p^2=0.17$). Those in the exercise condition had significant improvements in aerobic capacity and walking performance, whereas the control did not (Fig. 2). There was neither a significant interaction ($F=0.78$, $p=0.38$) nor main effects ($p>0.05$) for change in BMI.

Correlation

Pearson correlations (scatterplots in Fig. 3) indicated a significant negative correlation between changes in VO_{2peak} and changes in fatigue ($r=-0.59$), depression ($r=-0.50$) and TUG ($r=-0.31$, $p<0.05$) across all participants. The change in VO_{2peak} within the exercise condition had a stronger negative correlation with changes in fatigue ($r=-0.62$), depression ($r=-0.54$) and TUG ($r=-0.46$, $p<0.05$).

DISCUSSION

This is the first randomized controlled trial comparing the effects of interval training involving lower and upper body cycling exercise at moderate-intensity on fatigue, depression and functional parameters in persons with MS while considering weight as a moderating factor. Our results indicate that overweight and normal weight persons with MS had similar benefits from the exercise program for fatigue and depression as well as VO_{2peak} and TUG; however, overweight participants had a poorer status at baseline for fatigue and VO_{2peak} . There was a clear relationship between changes in aerobic capacity with changes in fatigue, depression and walking ability in the exercise training condition, indicating the role of training adaptation for improving outcomes in MS.

Based on the available literature [7, 21, 30, 31], there are few randomized controlled trials that concurrently considered ‘fatigue’ and ‘depression’ as primary endpoints of exercise training in persons with MS. Our results confirm previous studies that report beneficial effects of exercise training for improving fatigue and depression in persons with MS [11, 31]. Indeed, a previous meta-analyses [2, 7, 31] reported that exercise training has small to moderate effects on fatigue and depression (the overall weighted mean effect size < -0.50), whereas in the present

study the effect size estimated by η^2 for the two-factor ANOVA test ($\eta^2 > 0.14$) indicated a large effect of exercise training on fatigue and depression. This may be explained by our focus on fatigue and depression as primary rather than secondary, exploratory end-points.

Previous studies that were part of a Meta-analysis did not consider participants' weight status. These studies used different exercise types to estimate the effect size of exercise and did not distinguish between exercise types. In the present study, we used moderate-intensity (60-75% W_{peak}) interval exercise. Strong evidence suggests that interval training exercise has a wide range of beneficial effects. These effects include increasing both anaerobic and aerobic capacity [25, 32], delaying the onset of fatigue [25], improving skeletal muscle function [33], improving psychological indicators [34], and decreasing cardiovascular risk [32, 33]. However, most MS studies [2, 7, 21, 31] have used resistance, endurance and aquatic exercise as interventions, and as a result, the effects of interval exercise has received less attention [25]. We provide novel evidence that interval type training can be beneficial for fatigue and depression in persons with MS.

There are several possible moderators that may influence the effects of exercise on the symptoms of fatigue and depression. Inactive lifestyles and deconditioning are common among persons with MS, and this contributes to weight gain and subsequently, has a negative effect on the symptoms of fatigue and depression [2]. We observed that exercise is beneficial in persons with MS, but BMI was not a moderator of the changes in fatigue and depression with exercise training. That is, beneficial changes in fatigue and depression were observed after the exercise program in both overweight and normal weight groups. We did not identify any significant weight loss or BMI changes with exercise training. However, by continuing the exercise program (for long-term periods), it may be possible to achieve significant weight loss [35], positively

affecting fatigue and depression over longer periods of time. Therefore, considering the beneficial effects of weight loss based on previous evidence [17, 18], it is recommended performing further studies on the effect of weight loss strategies (i.e., long-term exercise program) on fatigue and depression. It has been demonstrated previously that weight loss can be associated with an increase in 25-hydroxyvitamin D levels, the main circulating vitamin D metabolite [12], and since the level of 25-hydroxyvitamin D is associated with depression [36]; it seems possible that via this pathway, weight loss can have a positive effect on depression during exercise. Additionally, weight loss is associated with a reduction in adipokines, in particular leptin [12]. Leptin is closely related to the symptoms of MS, therefore weight loss will result in a decrease in leptin and potentially improvement in the fatigue profile following exercise training [25].

Numerous primary and secondary pathophysiological pathways have been mentioned that underline the symptoms of fatigue and depression associated with MS [7, 37]. We propose here a potential mechanism by which exercise can alleviate fatigue and depression in MS through improvement in aerobic fitness. Although, we did not observe any interactive effects of exercise and weight status for changes in fitness levels (elevated by Vo_{2peak} and TUG) in the current study, the exercise group main effect was encouraging. A meta-analysis of 4 studies reported non-significant effects of exercise on the TUG test (mean difference = -1.5 sec, 95% CI = 2.19-0.9) [38]. The meta-analysis also reported a positive effect of exercise on other walking ability tests including walking endurance (i.e., 10-m walk test) and speed (i.e., 2- and 6-minute walk test) [38]. It is frequently stated in the literature that walking performance is impaired in person with MS which is commonly assessed using either 10-m walk test, 6-minute walk test and TUG test [38, 39]. TUG reflects walking agility (mobility) which requires several prerequisites for

improvement such as enhancement in aerobic capacity and muscle strength [39]. Exercise can have positive outcomes for walking performance in MS via increases in aerobic capacity and muscular strength, indicators that are normally weaker in person with MS when compared to healthy individuals [25, 39, 40]. Correlation analysis supported this statement and there were moderate correlations observed between improvements in fitness levels and walking performance gain. Although a previous systematic and meta-analysis review suggests a beneficial role of exercise on walking performance [38, 39], it seems that the evidence is not clear and that further studies are needed for clarification. Interestingly, correlational analysis suggested a negative correlation between fitness improvement, fatigue and depression. This suggests that individuals who observed the greatest fitness improvements also had positive changes in fatigue and depression. Therefore, improvement in fitness levels can be considered as a beneficial target for person with MS [41]. The findings of this study suggest that this appears to be independent of weight status, and is positively associated with improvements in psychological indicators (i.e., fatigue and depression).

The current study has some limitations. Firstly, we did not observe significant changes in weight and BMI that could have had an impact on our results. Although BMI was used as a moderating factor and an indicator of body composition in the current study, the lack of weight loss cannot be attributed entirely to the lack of fat loss. During the training program, decreasing fat tissue and increasing muscle tissue may occur simultaneously, therefore, no significant change in weight status was observed. Secondly, BMI is one of the most widely used indexes of body composition in MS studies [12, 13, 16, 25], but it has a lower accuracy than methods such as dual X-ray absorptiometry (DEXA). Therefore using DEXA in future studies would increase internal validity. Thirdly, our intervention included 8-weeks of interval exercise. The short

duration of the exercise program may be one of the reasons for a non-significant change in weight status. Using longer-term durations of exercise may provide more conclusive and complementary results. Moreover, the current study did not have a long term follow up which could indicate a lasting effect of exercise. Finally, regarding the nature of the current study, the small sample size makes interpretations of these data less accurate. In fact, although based on a two-factor ANOVA design and anticipated statistical power of 0.8 with an effect size 0.5 and alpha error 0.05, at least 15 subjects were necessary (G power program 3.0.10, Germany). However, the sample size used in the current study especially in the control groups were small; therefore, further studies should be conducted to investigate further the results presented here.

CONCLUSION

Overall, exercise was efficacious in improving MS-related psychological symptoms, but body weight was not a moderating factor related to the exercise induced changes observed. There were positive correlations found between changes in $Vo2_{peak}$ and improvements in symptoms of fatigue and depression. These findings outlined the important role of exercise-related adaptations for improvement in psychological symptoms (i.e., fatigue and depression) in MS patients. It can be concluded therefore, that the findings from this study indicate, that improvements in fitness levels positively affect psychological parameters in people with MS. These positive outcomes can be achieved by exercise without changes in bodyweight

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Conflict of Interest

Mostafa Khodadust received support from Abadan Islamic Azad University, Abadan, Iran to perform current study. Other authors report no disclosures.

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