Effect of High-Intensity Exercise on Multiple Sclerosis Function and Phosphorous Magnetic Resonance Spectroscopy Outcomes

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ABSTRACT

ORBAN, A., B. GARG, M. K. SAMMI, D. N. BOURDETTE, W. D. ROONEY, K. KUEHL, and R. I. SPAIN. Effect of High-Intensity Exercise on Multiple Sclerosis Function and Phosphorous Magnetic Resonance Spectroscopy Outcomes. Med. Sci. Sports Exerc., Vol. 51, No. 7, pp. 1380–1386, 2019. Purpose: We determined if a high-intensity aerobic exercise program would be safe, improve expected fitness and clinical outcomes, and alter exploratory phosphorous magnetic resonance spectroscopy (31P MRS) outcomes in persons with multiple sclerosis (PwMS). Methods: This open-label prospective pilot study compared two cohorts of ambulatory PwMS matched for age, sex and VO2max. Cohorts underwent 8 wk of high-intensity aerobic exercise (MS-Ex, n = 10) or guided stretching (MS-Ctr, n = 7). Aerobic exercise consisted of four 30-min sessions per week while maintaining ≥70% maximal HR. Changes in cardiorespiratory fitness, clinical outcomes, and 31P MRS of tibialis anterior (TA) muscle and brain were compared. Cross-sectional 31P MRS comparisons were made between all MS participants and a separate matched healthy control population. Results: The MS-Ex cohort achieved target increases in VO2max (mean, +12.7%; P = <0.001, between-group improvement, P = 0.03). One participant was withdrawn for exercise-induced syncope. The MS-Ex cohort had within-group improvements in fat mass (−5.8%; P = 0.04), lean muscle mass (+2.6%; P = 0.02), Symbol Digit Modalities Test (+15.1%; P = 0.04), and cognitive subscore of the Modified Fatigue Impact Scale (−26%; P = 0.03), whereas only the physical subscore of the Modified Fatigue Impact Scale improved in MS-Ctr (−16.1%; P = 0.007). 31P MRS revealed significant within-group increases in MS-Ex participants in TA rate constant of phosphocreatine (PCr) recovery (+31.5%; P = 0.03) and adenosine triphosphate/PCr (+3.2%; P = 0.01), and near significant between-group increases in TA PCr recovery rate constant (P = 0.05) but no significant changes in brain 31P MRS after exercise. Conclusions: High-intensity aerobic exercise in PwMS improved expected cardiorespiratory and clinical outcomes but provoked one serious adverse event. The 31P MRS may serve to explore underlying mechanisms by which aerobic exercise exerts cerebral benefits. Key Words: MULTIPLE SCLEROSIS, PHOSPHORUS MR SPECTROSCOPY, AEROBIC EXERCISE, COGNITION, CLINICAL TRIAL.

Although PwMS are reported to have lower baseline fitness, they generally respond as expected to aerobic exercise interventions (2,3). These aerobic exercise programs are typically of moderate intensity defined using the American College of Sport Medicine’s Guidelines for Exercise Testing and Prescription as 50% to 70% VO2max as opposed to high intensity (>70%) (4). The most frequently reported clinical benefits of aerobic exercise in MS are improving fatigue, cognition, and mobility, all of which are common, disabling, and stubbornly treatment-resistant symptoms in MS (5).

The cerebral benefits of aerobic exercise are well established. In rodents, physical activity increases levels of brain-derived neurotrophic factor and growth factors associated with improved cognition, and both preventing demyelination and promoting hippocampal neurogenesis and synaptic plasticity (6). Healthy adults show increased hippocampal volumes accompanied by improvements in memory after a 12-month aerobic exercise intervention compared with stretching (7). These changes may be associated with improved cerebral perfusion and IGF-1 levels (8). Exercise also delays onset and slows...
progression of cognitive impairment and brain atrophy in older adults without neurologic disease (9).

The symptomatic and neuroanatomic benefits of physical activity in MS are also evident. Cross-sectional studies in MS reveal positive associations between levels of physical activity and walking performance with fatigue, cognitive processing speed, brain volumes, and tract integrity (10–12). Longitudinal studies of aerobic exercise generally, although not invariably, demonstrate improvements in fitness and MS symptoms (3,13,14). The variations in results may be due to differences between studies in choice of exercise modality, duration, intensity, comparator group activity and outcome measures. Changes in peripheral cytokines, brain-derived neurotrophic factor, and immunological factors have also been variably noted in response to aerobic exercise in MS and other populations (8,15,16).

What are the underlying mechanisms by which aerobic exercise improves brain functional outcomes and increases volumes and tract integrity? One hypothesis is that the improved mitochondrial function in skeletal muscle resulting from aerobic exercise could also occur in the brain. Improved mitochondrial function, in turn, would reduce oxidative damage, prevent apoptosis, and have restorative properties leading to improved functional outcomes (17). Skeletal muscle mitochondrial function can be demonstrated using phosphorous MR spectroscopy (31P MRS). This technique is primarily used to measure the resynthesis of phosphocreatine (PCr) after exercise as a measure of the oxidative capacity of skeletal muscle as well as demonstrating the three adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphate (Pi) peaks (18). The resynthesis of PCr, measured as a rate constant of recovery (kPCr), was shown to be lower in dorsiflexor muscles of PwMS than controls immediately after exercise (19). Increased kPCr indicates the improved ability of muscle to restore PCr/ATP ratios depletions by exercise suggesting improved mitochondrial function (18). The introduction of high field (7 T) MRI has now improved the signal to noise ratio allowing a similar evaluation of energy peaks, although not kPCr, in the brain (20). To our knowledge, these outcomes have not been explored as a potential marker of mitochondrial function in relation to an aerobic exercise protocol.

In this pilot study, we hypothesized that compared with a stretching control, a short duration, high-intensity exercise program would be well tolerated and would improve the expected outcomes of cardiorespiratory fitness, body composition, and MS symptoms of cognitive dysfunction and fatigue in PwMS. As an exploratory outcome, we hypothesized that 31P MRS would detect altered ratios of ATP, PCr, and Pi in the brain mirroring the expected changes in the of the tibialis anterior (TA) muscle in response to the exercise intervention.

**MATERIALS AND METHODS**

**Study Design**

The unblended prospective pilot cohort study (NCT02263339) protocol was approved by the Institutional Review Board at Oregon Health and Science University (OHSU). Written informed consent was obtained from study participants before enrollment.

**Participants**

Persons with MS were recruited on a convenience basis from the OHSU MS Clinic and local community. Inclusion criteria were ages 18 to 65 yr, diagnosis of relapsing remitting MS (2010 McDonald criteria), and fully ambulatory (Expanded Disability Status Scale, ≤4.0) (21). Exclusion criteria were MS exacerbation or the use of intravenous corticosteroids or antibiotics within 30 d of screening, contraindications to MRI, or uncontrolled cardiopulmonary disease. There were no specific criteria for fatigue or cognition at baseline. MS-exercise (MS-Ex) participants were recruited first, followed by MS-control (MS-Ctr). Cohorts were matched for sex, age ±10 yr, and baseline aerobic fitness (incremental maximal exercise test, VO2max) ±10%. A third cohort of healthy controls (HC) matched to the MS-Ex cohort for sex; age, ±10 yr; and baseline VO2max test, ±10% was recruited for cross-sectional comparison of 31P MRS outcomes.

**Study Interventions**

The aerobic exercise intervention consisted of four sessions per week of aerobic exercise for 30 min maintained at a target HR for eight consecutive weeks. Exercise training target HR was at least 70% of measured maximal HR for each subject. This target HR was determined by the HR during exercise testing when the RER was between 0.9 and 0.99 which is just below the anaerobic threshold. This allowed subjects to aerobically exercise train without being anaerobic. Aerobic exercise sessions were directly supervised by an exercise physiologist at the OHSU Human Performance Laboratory (HPL). Participants exercised on a treadmill (n = 9) or cycle ergometer (n = 1) chosen by the physiologist based on individual abilities. The study goal was a 5% to 15% increase in VO2max per expert opinion (K.K.) given expectations for a population with a chronic disease. The control intervention was a guided static stretching program for 30 min·d−1, 4 d·wk−1, for 8 wk. Initial training and a paper guide to the stretches was provided by an exercise physiologist at the HPL, followed by HPL visits every 2 wk for the same exercise physiologist to review stretching logs and encourage adherence to the program. All study participants were instructed to avoid any other change to baseline activity levels or dietary habits for the duration of the study. Reports of adverse events were collected during study visits and reviewed descriptively, and compliance with study visits was tabulated.

**Study Outcomes**

**Cardiorespiratory fitness testing.** All participants underwent measurements of resting systolic blood pressure and HR. After pulmonary function tests, participants completed a physician-supervised, electrocardiogram-monitored VO2max test with measurement of maximal oxygen uptake in accordance with the published guidelines (22). A maximal test was defined as one in which the participant reached a plateau in
oxygen uptake, a RER above 1.1, or in which the participant stopped despite urging by the testing staff. Aerobic capacity outcomes of interest were \( \dot{V}O_{2\text{max}} \) (mL·kg\(^{-1}\)·min\(^{-1}\)), maximum work (W) and total exercise time.

**Body composition testing.** Participants had weight, body mass index, body fat percentage by bioelectrical impedance (Tanita BC-558 bioelectrical impedance analyzer), fat mass and lean mass tested at baseline and after the 8-wk intervention.

**Phosphorus magnetic resonance spectroscopy.** A Siemens 7T Magnetom system (Erlangen, Germany) was used to collect \(^{31}\)P MRS data before and after the study interventions. The \(^{31}\)P MRS TA muscle protocol used a dual-tuned \(^{31}\)P/H surface coil (4 × 9.5 cm oval, with longer axis aligned to the muscle length) positioned over the center of the TA muscle of the right leg. Right legs were positioned in a home-built exercise device consisting of a Plexiglas foot pedal and adjustable rubber band that isolated dorsiflexion of the ankle against a fixed load. \(^{31}\)P MRS protocol of the TA muscle consisted of a 2- to 3-min period of baseline rest, a 3-min exercise period estimated to deactivate phosphocreatine (PCr) by 20% to 40%, and a 4- to 10-min recovery period during which no exercise was performed. The exercise consisted of a foot-flexion exercise synchronized to a metronome set to 40 bpm. \(^{31}\)P spectra were acquired continuously at 1.2-s intervals throughout. For brain, high-resolution MPRAGE anatomic (0.8 mm isotropic) images were acquired for tissue segmentation in a sagittal orientation. A three-dimensional brain \(^{31}\)P MRS was performed using a \(^{31}\)P head coil with a Halo coil setup. Low-resolution phosphorus B\(_1\) maps were acquired for RF coil inhomogeneity correction.

The primary \(^{31}\)P MRS TA outcome of interest was the k\(_{\text{PCR}}\) after a bout of mild exercise. Additionally, ratios of PCR and total ATP to PCR and ratio of total ATP to PCr were captured for both TA and brain. Gamma-ATP (\(\gamma\)-ATP) was used as the marker of total ATP in this study.

**Clinical outcomes.** The Symbol Digit Modalities Test (SDMT), a measure of mental processing speed, was the cognitive measure (24). The patient-reported Modified Fatigue Impact Scale (MFIS), validated for use in MS, assessed fatigue (25). The Symbol Digit Modalities Test (SDMT), a measure of mental processing speed, was the cognitive score (postscore minus prescore) differs between MS-Ex and MS-Control groups and was calculated using independent two-sample \( t \)-tests.

**RESULTS**

The study was conducted between November 2014, and April 2016. Eighteen MS participants consented and started the study. One MS-Ex participant was withdrawn from the study after a near-syncopal event at one visit and a syncopal event after completion of the exercise session on another visit prompting a visit to the emergency department. The participant, whose data were not included in analysis, had a childhood history of exercise-induced syncope thought to have been outgrown. There were no other adverse events. Compliance with study visits was 99.4%. At baseline, 8 of the 10 MS-Ex achieved a Max RER 1.1 or greater, whereas all MS-Ctr and HC participants met this target. At exit, only one MS-Ex participant did not meet RER 1.1. When RER was not met, the \( \dot{V}O_{2\text{max}} \) test was terminated by the participant. MS-Ex and MS-Ctr cohorts did not differ significantly in matching characteristics of age, sex, \( \dot{V}O_{2\text{max}} \) (Table 1). The HC cohort compared for baseline \(^{31}\)P MRS outcomes were younger (36.0 ± 7.5, 46.3 ± 8.9 yr, \( P = 0.01 \)) than the MS participants (Table 5).

**Changes in cardiorespiratory fitness and body composition.** Nine of 10 MS-Ex achieved the study goal of 5% to 15% increase in \( \dot{V}O_{2\text{max}} \), with mean increase of 12.7% \(( P < 0.001 \)) versus none of the MS-Ctr achieving this goal (mean increase, 1.1%; \( P = 0.82 \); between group difference \( P = 0.03 \)). Eight of 10 MS-Ex achieved ≥10% increase in \( \dot{V}O_{2\text{max}} \) considered clinically meaningful (3). Maximum work and total exercise time also improved in the MS-Ex cohort with significant within- and between-group changes. Neither intervention group demonstrated significant changes in HR or blood pressure parameters. For body composition, percent body fat and lean muscle mass improved within the MS-Ex cohort only (-5.8%, \( P = 0.04 \), and +2.6%, \( P = 0.02 \), respectively).

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**Table 1.** Baseline demographics and matching characteristics between MS-Ex and MS-Ctr cohorts.

| Variables                  | MS-Ex (n = 10) | MS-Ctr (n = 7) | P  
|----------------------------|---------------|---------------|---
| Matching characteristics   |               |               |   
| Age (yr)                   | 44.7 ± 9.4    | 48.7 ± 8.4    | 0.38  
| Females (%)                | 90%           | 86%           | 1.00  
| \( \dot{V}O_{2\text{max}} \) (mL·min\(^{-1}\)·kg\(^{-1}\)) | 30.0 ± 9.3    | 29.0 ± 7.8    | 0.82  
| MS duration (yr)           | 14.6 ± 6.5    | 20.2 ± 10.4   | 0.19  
| EDSS, median (range)       | 3.5 (2.5-4)   | 3 (2-4)       | 0.19  
| Systolic BP (mm Hg)        | 113.9 ± 9.6   | 113.4 ± 7.3   | 0.90  
| HR (bpm)                   | 65.6 ± 11.8   | 67.4 ± 8.2    | 0.59  
| BMI (kg·m\(^{-2}\))        | 26.9 ± 4.4    | 29.6 ± 7.1    | 0.34  
| Body fat by BIA (%)        | 32.9 ± 11.9   | 23.3 ± 7.1    | 0.09  
| \(^{31}\)P MRS TA          |               |               |   
| \( \dot{V}O_{2\text{max}} \) \((\text{s}^{-1})\) | 0.022 ± 0.005 | 0.024 ± 0.010 | 0.64  
| PCr/Pi                     | 6.36 ± 0.61   | 6.64 ± 0.91   | 0.50  
| ATP/Pi                     | 0.92 ± 0.10   | 0.92 ± 0.149  | 0.98  
| ATP/PCr                    | 0.29 ± 0.01   | 0.279 ± 0.020 | 0.16  
| \(^{31}\)P MRS Brain       |               |               |   
| PCr/Pi                     | 4.61 ± 0.44   | 4.34 ± 0.27   | 0.84  
| ATP/Pi                     | 4.61 ± 0.40   | 4.14 ± 0.38   | 0.14  
| ATP/PCr                    | 1.01 ± 0.056  | 0.96 ± 0.05   | 0.05  

All values are mean ± SD unless otherwise indicated.

BIA, bioelectrical impedance analysis; BMI, body mass index; BP, blood pressure; EDSS, Expanded Disability Status Scale.

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**Statistical Analysis**

Statistical analysis was performed using Stata 13.1 (28). Baseline demographics (Table 1) were analyzed using independent two-sample \( t \)-tests (continuous variables), Fisher Exact tests (categorical variables) and Mann-Whitney \( U \) test (ordinal variables). To determine whether there is any difference between prescore and postscore within each group (Tables 2, 3, and 4), paired \( t \)-tests were used. Pre–post change score was calculated by subtracting prescore from postscore (postscore minus prescore). Between-group change \( P \) value shows if change
respectively), although neither reached a statistically significant improvement over the MS-Ctr cohort (Table 2).

Changes in clinical outcomes of cognition, fatigue, and walking performance. The MS-Ex cohort demonstrated statistically significant improvements in mean SDMT score from baseline (mean, +7 points, +15.1%; P = 0.04), whereas MS-Ctr did not (mean, +1, +1.9%; between-group P = 0.13). Similarly, the cognitive fatigue subscore of the MFIS improved significantly in the MS-Ex cohort from baseline (−26%, P = 0.03) but without a significant between-group difference. Neither cohort exhibited significant changes in the TUG or 6MTW (Table 3).

Changes in $^{31}$P MRS of the right TA and Brain. In the right TA muscle, the MS-Ex cohort demonstrated a significant within-group increase in the $k_{PCr}$ (+31.5%, P = 0.03) and ATP/PCr ratio (+3.2%, P = 0.01). The change in $k_{PCr}$ was nearly but not significantly improved over the MS-Ctr cohort (P = 0.05). No significant changes were seen in $^{31}$P MRS outcomes in the brain after interventions for either cohort (Table 4).

Cross-sectional comparison of $^{31}$P MRS outcomes between matched MS and HC cohorts. Differences in baseline ratios of brain markers of high-energy phosphates were found between the MS and HC participants. These included a greater cerebral Pcr/Pl (MS 4.61 ± 0.44, HC 3.93 ± 0.19, P = 0.002) and lower ATP/PCr (MS 1.01 ± 0.05 vs HC 1.08 ± 0.06, P = 0.001) among the MS cohort. The TA muscle ATP/PCr ratio was significantly lower in the MS participants than HC cohort (0.29 ± 0.01 vs 0.30 ± 0.01, P = 0.02). Additional variables in Table 5 include the matching characteristics between cohorts and baseline differences in functional study outcomes.

**DISCUSSION**

In this 8-wk study, PwMS completing a high-intensity aerobic exercise program demonstrated improvements in cardiorespiratory function, body composition, mental processing speed (SDMT), and cognitive fatigue (MFIS) compared with PwMS doing a stretching program. Overall, the aerobic exercise program was well tolerated; however, the occurrence of exercise-induced near syncope in one MS-Ex subject suggests caution when initiating similar programs. Important to the study design was the matched control group stretching program of equal frequency and duration along with professional support from study staff rather than a waitlist control. Improvement in TA $^{31}$P MRS outcomes supported the VO$^{2max}$ changes found on cardiorespiratory testing. Although cerebral $^{31}$P MRS did not change after the aerobic exercise intervention, cross-sectional differences these markers of brain energy production between MS and matched HC may point to the as yet unknown underlying mechanisms by which aerobic exercise exerts its cognitive benefits.

Although there are now several well-designed studies demonstrating the safety and efficacy of high-intensity aerobic exercise in MS populations, at the time the present study was conceived, this was less clear (3) (29,30). Historically, PwMS were advised to avoid exercise for fear of worsening their disease, in part from overheating. The present study supports that even relatively sedentary PwMS can benefit rapidly from aerobic exercise. The reemergence of exercise-induced syncope in one study participant reminds us that graded intensity and/or direct supervision may be warranted in persons not accustomed to high-intensity exercise. Questions addressed in newer studies include evaluating combinations of aerobic and resistance training as well as developing exercise programs for nonambulatory PwMS to further inform clinical guidelines.

The MS-Ex participants in our study demonstrated impressive increases in VO$^{2max}$, with 90% achieving the study goal of ≥5%, and 80% achieving what is now considered a clinically meaningful ≥10% improvement by study end (3). At the same time, the aerobic exercise participants increased their SDMT score by six points more than the MS-Ctr group, an

**TABLE 2. Changes in cardiorespiratory fitness and body composition after interventions between MS-Ex and MS-Ctr cohorts.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>MS-Ex (n = 10)</th>
<th>Post</th>
<th>Pre–Post Change (%, P)</th>
<th>MS-Ctr (n = 7)</th>
<th>Post</th>
<th>Pre–Post Change (%, P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$^{2max}$ (mL·kg$^{-1}$·min$^{-1}$)</td>
<td>30.0 ± 9.3</td>
<td>33.8 ± 8.5</td>
<td>+12.7, &lt;0.001</td>
<td>29.0 ± 7.8</td>
<td>30.3 ± 6.4</td>
<td>+1.1, 0.82</td>
</tr>
<tr>
<td>Maximum work (W)</td>
<td>167.7 ± 52.8</td>
<td>216.6 ± 57.8</td>
<td>+29.1, &lt;0.001</td>
<td>165.3 ± 40.7</td>
<td>184.6 ± 43.5</td>
<td>-0.53, 0.69</td>
</tr>
<tr>
<td>Total exercise time (min)</td>
<td>11.5 ± 2.9</td>
<td>13.8 ± 3.8</td>
<td>+20.5, 0.002</td>
<td>11.9 ± 2.5</td>
<td>11.9 ± 1.7</td>
<td>-0.8, 0.72</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>113.9 ± 9.6</td>
<td>109.7 ± 9.8</td>
<td>-3.7, 0.31</td>
<td>113.4 ± 7.5</td>
<td>109.8 ± 7.5</td>
<td>-3.14, 0.09</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>65.6 ± 11.8</td>
<td>67.4 ± 8.2</td>
<td>+2.7, 0.59</td>
<td>67.4 ± 11.2</td>
<td>66.1 ± 11.2</td>
<td>-1.91, 0.52</td>
</tr>
<tr>
<td>Body fat by BIA (%)</td>
<td>32.9 ± 11.9</td>
<td>31.0 ± 11.0</td>
<td>-5.8, 0.04</td>
<td>23.3 ± 7.1</td>
<td>23.7 ± 6.1</td>
<td>+4.3, 0.56</td>
</tr>
<tr>
<td>Lean muscle mass (kg)</td>
<td>46.7 ± 7.0</td>
<td>47.8 ± 6.8</td>
<td>+2.6, 0.02</td>
<td>61.8 ± 9.7</td>
<td>61.4 ± 11.1</td>
<td>-0.56, 0.71</td>
</tr>
</tbody>
</table>

BIA, bioelectrical impedance analysis.

**TABLE 3. Changes in clinical outcomes of a cognitive test (SDMT), fatigue rating scale (MFIS), and walking performance tests (6MTW and TUG) after interventions between MS-Ex and MS-Ctr cohorts.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>MS-Ex (n = 10)</th>
<th>Post</th>
<th>Pre–Post Change (%, P)</th>
<th>MS-Ctr (n = 7)</th>
<th>Post</th>
<th>Pre–Post Change (%, P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT total score</td>
<td>46.5 ± 13.4</td>
<td>53.5 ± 10.3</td>
<td>+15.1, 0.04</td>
<td>52 ± 6.9</td>
<td>53 ± 5.9</td>
<td>+1.9, 0.59</td>
</tr>
<tr>
<td>MRS total score</td>
<td>313 ± 18.8</td>
<td>236 ± 17.3</td>
<td>-24.6, 0.02</td>
<td>331 ± 16.4</td>
<td>28.8 ± 14.9</td>
<td>-12.9, 0.08</td>
</tr>
<tr>
<td>Physical subscore</td>
<td>13.5 ± 6.7</td>
<td>10.6 ± 6.9</td>
<td>-21.5, 0.19</td>
<td>16.8 ± 7.9</td>
<td>14.1 ± 6.5</td>
<td>-16.1, 0.007</td>
</tr>
<tr>
<td>Cognitive subscore</td>
<td>14.6 ± 11.2</td>
<td>10.8 ± 9.9</td>
<td>-26.0, 0.03</td>
<td>14.4 ± 7.7</td>
<td>12.6 ± 7.8</td>
<td>-12.9, 0.24</td>
</tr>
<tr>
<td>Psychosocial score</td>
<td>3.2 ± 2.3</td>
<td>2.2 ± 2.1</td>
<td>-31.2, 0.05</td>
<td>1.8 ± 1.5</td>
<td>2.1 ± 1.1</td>
<td>+15.4, 0.02</td>
</tr>
<tr>
<td>6MTW distance (m)</td>
<td>429.1 ± 71.2</td>
<td>441.6 ± 58.2</td>
<td>-2.9, 0.47</td>
<td>503.9 ± 90.7</td>
<td>506.7 ± 96.9</td>
<td>+0.6, 0.82</td>
</tr>
<tr>
<td>TUG time (s)</td>
<td>15.1 ± 4.3</td>
<td>12.9 ± 3.2</td>
<td>-14.4, 0.11</td>
<td>12.7 ± 2.5</td>
<td>12.2 ± 2.1</td>
<td>-3.9, 0.17</td>
</tr>
</tbody>
</table>

Psychosocial score includes evaluating combinations of aerobic and resistance training as well as developing exercise programs for nonambulatory PwMS to further inform clinical guidelines.

The MS-Ex participants in our study demonstrated impressive increases in VO$^{2max}$, with 90% achieving the study goal of ≥5%, and 80% achieving what is now considered a clinically meaningful ≥10% improvement by study end (3). At the same time, the aerobic exercise participants increased their SDMT score by six points more than the MS-Ctr group, an
increase that can be considered clinically meaningful (31). The improvements parallel SDMT changes found in other high-intensity aerobic exercise studies with similar VO₂max gains (32). The MFIS is also utilized in aerobic exercise studies and appears sensitive to exercise interventions (13,32). Although not all studies find improvements in cognitive tests and fatigue self-ratings, subgroup analyses sometimes reveal that the most impaired are most likely to demonstrate a benefit, suggesting a ceiling effect of the tests (33). Our study did not select for baseline cognitive impairment or fatigue; however, our comparison with HC demonstrated baseline cross-sectional differences (Table 5). Ceiling effects may have also played a role in the lack of improvement in the 6MWT and TUG walking tests, which have been shown to improve after an exercise intervention in an MS population with a higher level of baseline disability, although baseline 6MWT results was also lower in the MS than HC participants (13). As a pilot study, sample size was not powered on these clinical outcomes which might require larger numbers, longer studies, and possibly measures not thought a priori to change after such a brief intervention, such as patient-reported psychosocial and participation outcomes (34). Overall, the clinical benefits achieved in this study were as expected based on current literature.

The mechanisms by which aerobic exercise improves cognitive function are debated and are likely many. In a recent review, El-Sayes et al. (35) propose a model for neuroplasticity after acute and chronic effects of aerobic exercise starting from molecular and cellular changes, and leading to structural/functional, and finally behavioral changes. This more general model of neuroplasticity appears to hold true for MS as aerobic exercise favorably changes levels of neurotrophins, neurotransmitters, inflammatory factors, hormones, neuromodulators, and more which are also associated with improved cognition, although these findings are neither specific to MS populations, nor are they detected in every study (12,15,36). Although presented sequentially, these structural and behavioral changes can occur early as evidenced by neurogenesis detected in exercising rodents within days, verbal memory and serum matrix metalloproteinases after 3 wk in MS, and increased hippocampal volume and resting-state functional connectivity after 3 months (35,37,38). Our own brain MRI segmentation results on participants in this study did not demonstrate consistent volumetric changes in hippocampal, thalamic, or other brain substructures (see Table, Supplemental Digital Content 1, Changes in deep gray matter volumes after aerobic exercise among the MS-Exercise cohort, http://links.lww.com/MSS/B509). Longer-term exercise studies do more consistently demonstrate growth of brain substructures correlating with cognitive improvement (7,39).

Demonstration of improved bioenergetic function after aerobic exercise in the TA muscle using 31P MRS raises the possibility that aerobic exercise also improves mitochondrial function in the brain. Increased oxygen consumption and glucose metabolism might, in turn, drive the molecular and cellular processes leading to neuroplasticity and improved cognition. We found cross-sectional differences in ATP metabolites between MS and HC populations, similar to Kauv et al. (20), although they expressed the peaks as percentages rather than ratios. Unclear is if the lack of change in metabolite ratios in the MS-Ex cohort after aerobic exercise was a sample size, effect size, or study duration issue, or a true finding. However, the baseline differences encourage further exploration into this potential biomarker by addressing these study design issues.

The study was limited by the small sample size and restricted permitted disability among MS participants which were due to the pilot nature of the study. Other limitations stemmed from the study design including the brevity of cognitive and fatigue testing. The SDMT is measure of mental processing speed and not specific to the cognitive deficits such as learning and memory known to commonly occur in MS. Validated MS batteries of cognitive tests exist that might have greater sensitivity to demonstrate efficacy of the interventions (40). Yet, newer evidence suggests that mental processing speed may be the cognitive domain best associated with aerobic capacity and best stand-alone cognitive task for MS (14,31). Other study limitations include lack of confounder assessments, such as mood and sleep. Finally, the lack of randomized assignment to intervention cohorts tempers the robustness of the conclusions.

### TABLE 5. Cross-sectional comparison between MS participants and a matched HC cohort.

<table>
<thead>
<tr>
<th>Variables</th>
<th>MS (n = 17)</th>
<th>HC (n = 7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.35 ± 9.95</td>
<td>36.0 ± 7.46</td>
<td>0.01</td>
</tr>
<tr>
<td>Females (%)</td>
<td>88%</td>
<td>86%</td>
<td>0.86</td>
</tr>
<tr>
<td>VO₂max (mL min⁻¹ kg⁻¹)</td>
<td>29.61 ± 8.51</td>
<td>34.1 ± 5.43</td>
<td>0.21</td>
</tr>
<tr>
<td>SDMT total score</td>
<td>48.76 ± 11.27</td>
<td>62.57 ± 10.84</td>
<td>0.01</td>
</tr>
<tr>
<td>MRS Total score</td>
<td>32.05 ± 17.35</td>
<td>13.14 ± 9.42</td>
<td>0.01</td>
</tr>
<tr>
<td>6MWT distance (m)</td>
<td>459.75 ± 85.83</td>
<td>567.14 ± 85.82</td>
<td>0.01</td>
</tr>
<tr>
<td>TUG time (s)</td>
<td>14.10 ± 3.78</td>
<td>12.54 ± 1.89</td>
<td>0.31</td>
</tr>
<tr>
<td>31P MRS TA kₑ (s⁻¹)</td>
<td>0.022 ± 0.007</td>
<td>0.028 ± 0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>ATP/Pi</td>
<td>0.92 ± 0.11</td>
<td>0.96 ± 0.06</td>
<td>0.49</td>
</tr>
<tr>
<td>PCr/Pi</td>
<td>6.49 ± 0.74</td>
<td>6.33 ± 0.51</td>
<td>0.62</td>
</tr>
<tr>
<td>ATP/PCr</td>
<td>0.29 ± 0.01</td>
<td>0.20 ± 0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>31P MRS Brain kₑ (s⁻¹)</td>
<td>4.41 ± 0.50</td>
<td>4.25 ± 0.35</td>
<td>0.42</td>
</tr>
<tr>
<td>ATP/Pi</td>
<td>4.49 ± 0.39</td>
<td>3.93 ± 0.19</td>
<td>0.002</td>
</tr>
<tr>
<td>PCr/Pi</td>
<td>0.96 ± 0.05</td>
<td>1.08 ± 0.06</td>
<td>0.001</td>
</tr>
</tbody>
</table>

All values are mean ± SD unless otherwise indicated.
CONCLUSIONS

In conclusion, a brief, high-intensity, aerobic exercise intervention compared with stretching resulted in expected improved fitness, body composition, and clinically significant increases in cognitive performance and cognitive fatigue in PwMS. The adverse event suggests caution when starting high-intensity aerobic exercise in PwMS. The cross-sectional differences in cerebral $^{31}$P MRS encourage further exploration of this potential biomarker of the bioenergetic contributions to neuroplasticity in response to aerobic exercise.

REFERENCES


AEROBIC EXERCISE IMPROVES MULTIPLE SCLEROSIS

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