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Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities

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Abstract

Background: The most effective exercise dose has yet to be established for multiple sclerosis (MS).
Objective: The aim of this study was to investigate the effect of different exercise intensities in people with MS.
Methods: We completed a randomized comparator study of three cycling exercise intensities, with blinded assessment, was carried out in Oxford. Sixty-one adults with MS who fulfilled inclusion criteria were randomized at entry into the study, using a computer-generated list held by an exercise professional, into either: continuous (at 45% peak power, $n = 20$), intermittent (30 sec on, 30 sec off at 90% peak power, $n = 21$) or combined (10 min intermittent at 90% peak power then 10 min continuous at 45% peak power, $n = 20$) exercise for 20 min twice a week for 12 weeks in a leisure facility. Groups were assessed at: baseline, halfway (6 weeks), end intervention (12 weeks) and follow-up (24 weeks). Primary outcome measure was 2 min walk.
Results: Fifty-five participants were included in the analysis ($n =$ continuous 20, intermittent 18, combined 17). No differences were found between groups. After 6 weeks, considering all participants, 2 min walk distance increased by 6.96 ± 2.56 m (95% CI: 1.81 to 12.10, effect size (es): 0.25, $p < 0.01$). The continuous group increased by 4.71 ± 4.24 m (95% CI: −3.80 to 13.22, es: 0.06), intermittent by 12.94 ± 4.71 m (95% CI: 3.97 to 21.92, es: 0.28) and combined by 3.22 ± 4.60 m (95% CI: −6.01 to 12.46, es: 0.04). Two minute walk did not significantly change between further assessments. Between 6 and 12 weeks there was a drop in attendance that seemed to be associated with the intermittent and combined groups; these groups also had a greater number of adverse events (leg pain during cycling most common) and dropouts ($n =$ continuous 1, intermittent 5, combined 10). Considering all participants, 6 weeks of cycling exercise produced benefits in mobility that were maintained with further sessions.
Conclusion: While no differences were found between groups, greater benefit may be associated with higher-intensity exercise, but this may be less well tolerated.

CONSORT - trial registration number (ISRCTN89009719)

Keywords

dose, exercise, mobility, multiple sclerosis, randomized trial, rehabilitation

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Introduction

The evidence for regular participation in physical activity for healthy adults and children is compelling. Physical activity contributes to well-being and good health for all[1,2] and the risks associated with participating in physical activity at levels that promote health and well-being are low.[1] A Cochrane systematic review of exercise therapy

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for people with multiple sclerosis (MS) confirms there is good evidence that exercise can be beneficial for mobility, isometric muscle strength, physical fitness and mood.[3]

However, many questions remain regarding optimal, safe exercise prescription for people at different stages of MS. Importantly, while government guidelines exist for healthy adults regarding safe effective levels of physical activity for health and well-being, no such evidence exists for people with MS. It remains to be established what dose of exercise is best and whether there is an exercise dose that is too high and may cause harm. We do not know how many times a week a person should train and whether they should train in short hard bursts or train for longer but less intensely.

To date, exercise studies in people with MS have generally not adequately controlled or monitored the frequency, duration and intensity of exercise.[4,5] To understand exercise in this group better and to enable comparison between exercise therapies, it is recommended that dose is experimentally controlled and measured.[3] Furthermore, there is consensus among reviews of the MS exercise literature that there is a need for studies to utilize experimental designs and reporting that adhere to good methodological principles, in order to provide evidence for exercise prescription.[3–5]

In order to explore safe effective exercise intensity, we conducted a single-blind randomized trial comparing low, high and a combination of low and high-intensity exercise delivered on a cycle ergometer. The study was designed so that the exercise dose was carefully controlled and monitored, and progressed with each group receiving the same frequency and duration of exercise and performing the same relative amount of total work per session.

Materials and methods

Design

This is a randomized comparator study of three parallel intervention groups, with assessment to assess superiority performed by an assessor blinded to group allocation. Participants recruited to the study were allocated the next available study number by the blinded assessor. The study number related to a computer-generated randomization list drawn up by a statistician (blocks sequence generation) to randomize participants into continuous, intermittent or combined groups. The list was held by two registered exercise professionals who then delivered the intervention. Group allocation was concealed from the assessor until the end of the study.

Setting

Assessments were carried out in Oxford, either at the Nuffield Orthopaedic Centre or at Oxford Brookes University. The intervention exercise sessions were carried out at Oxford Brookes University and at four community leisure centres in the Thames Valley and West London.

Participants

After National Health Service (NHS) ethical approval (08/H0604/3) had been obtained, 61 people with MS were recruited to the study in accordance with the declaration of Helsinki between June 2008 and April 2009. Candidates for the study were people with MS over 18 years of age identified through local neurologists or self-referral. Local MS society branches were made aware of the trial and given contact details; individuals from the branches were then able to self-refer to the study. If they were recruited through this method, their general practitioner or consultant neurologist was contacted to ensure suitability. They were not admitted to the study if any of the following criteria were present: (1) a medical condition or complication that would preclude safe participation in exercise, as indicated by the referring neurologist or their general practitioner; (2) unable to walk for 2 min, with walking aid as necessary; (3) not able to sit on a cycle ergometer and complete 60 s unloaded exercise; (4) a relapse or sudden change in their MS symptoms within the previous 2 weeks; (5) a condition affecting the central nervous system other than MS; or (6) insufficient mental capacity to consent.

Intervention

The intervention schedule for all groups was two exercise sessions per week for 12 weeks. Each exercise session consisted of 20 min on a static bike at a convenient time (including non-working hours and weekends) at one of the participating centres. If participants could not achieve 20 min of exercise they were encouraged to continue for as long as possible by the delivering exercise professional. A cadence of 50 rpm was intended throughout the exercise; if participants could not achieve 50 rpm they were encouraged to cycle as fast as possible (but not less than 40 rpm). Participants were randomized into three groups. Groups were primarily designed so that the same relative work was performed per session but delivered at different intensities. The intensity of each group was selected so that the exercise was achievable while being sufficient to elicit a training response at each intensity.[6] Relative exercise intensity was determined for each individual from a baseline fitness test and progressed at a 6 week fitness test.

- The combined group performed 10 min of intermittent cycling (30 s cycling/30 s rest) at 90% peak

workload immediately followed by 10 min continuous cycling at 45% peak workload (Combined).
- The continuous group performed continuous cycling at 45% of the peak workload from the exercise test (Continuous).
- The intermittent group performed 30 s cycling followed by 30 s rest at 90% of the peak workload from exercise test (Intermittent).

To monitor the delivery of intervention and the fidelity of the exercise delivery between exercise professionals, detailed training data were recorded by the exercise professionals during the exercise sessions. Reporting this information is beyond the scope of the current report. However, exercise session heart rate and attendance are displayed (Table 3). Heart rate data were recorded throughout training and are reported from the first exercise sessions during week 1 and week 11 as a percentage of maximum heart rate calculated from age (% max heart rate = 220 − age).

Assessment

Assessments were performed at baseline, 6 weeks (halfway through intervention), 12 weeks (end intervention) and 24 weeks (follow-up). Measurements were made by the same assessor blinded to intervention allocation. No instruction regarding the continuation of exercise was given to the participants during the follow-up period.

Function

The primary outcome measure for the study was the 2 min walk test. Participants were asked to walk as far as they could in 2 min along a 16 m indoor walkway, turning around cones at each end; the distance walked was measured.[7] Walking was also assessed using the timed up and go test (TUG), and for this test participants were required to stand up from a chair, walk 3 m around a cone, return to the chair and sit down as fast as they could.[8] The time taken to complete the TUG was recorded. Walking tests were performed once per assessment; no encouragement was given during the tests. Leg extensor power was measured using a 'leg power meter' (Medical Laboratory Workshops, Nottingham, UK).[9] The maximum power achieved from each leg separately was recorded and reported as an average of the two legs.

Questionnaires

At each assessment the following questionnaires were administered: the Barthel Index (Barthel) was used to measure independence in activities of daily living (0–20 scale, with 20 indicating greatest independence); perceived health status was measured using the Short Form (36) Health Survey (SF-36)[10] (0–100 scale, with 100 indicating high health status); and fatigue was measured using the Fatigue Severity Scale (FSS) (average score from nine statements rated 1 to 7, with 7 indicating strong agreement with the statement).[11]

Exercise test

In order to determine individual fitness levels, a stepwise incremental exercise test was performed on a cycle ergometer (Monarch 874E, Monark Exercise AB, Vansbro, Sweden). Prior to the test participants were asked to refrain from the consumption of alcohol, cigarettes, food and caffeine and to avoid exercise for a period of 3 h, and were also screened for suitability to take part in physical activity using the Physical Activity Readiness Questionnaire (PAR-Q) questionnaire[12] and blood pressure measurement.[6] The test started with unloaded cycling. Participants were asked to maintain a cadence of 50 revolutions per minute (rpm); if participants could not achieve 50 rpm they were encouraged to cycle as fast as the could (but not less than 40 rpm). Every 2 min the external load on the cycle ergometer was increased by 0.5 kg, which equated to 25 W increase in workload at 50 rpm. The test was terminated when the participant reached volitional exhaustion or the cadence dropped by 10 rpm. At the end of each increment heart rate was recorded from a watch receiving telemetry from a monitor strapped around the participant's chest (Polar heart rate monitor, Polar Electro, Finland). The peak power from the test was used to determine the relative exercise intensity during the intervention.

Data analysis

To investigate the beneficial effect of exercise on outcome assessments and the differential effect between groups, a pragmatic approach was used to determine sample size. Based on data from a previous study on treadmill training in MS compared with no intervention[13] to identify a change of 10.8 m on the 2 min walk (with an alpha of 0.05 and 90% power), 11 participants would be required. Considering this calculation, the non-specific effect of cycle ergometer training and to allow for dropouts, we aimed to recruit 20 people to each group.

Data were analysed based on the intention-to-treat principle.[14] In this study all participants who received at least one intervention session were included in the analysis. Statistical analysis was performed in SPSS 17. For incomplete data sets multiple imputation, with five imputations, provided multiple statistical estimates for missing data in order to perform the following

statistical analysis.[15] One-way ANOVA was used to assess differences between groups at baseline and difference in intervention sessions attended. Repeated measures ANOVA were used to assess differences between assessments and between groups; alpha was set at $p < 0.05$. Baseline data are reported as means and standard deviations, except for the Barthel ADL index, where the median and range are reported. Assessment data are reported as mean change and standard error from previous assessment; 95% confidence intervals are also reported.

Results

Sixty-one people with MS were recruited from Thames Valley MS society branches and by neurologist referral between June 2008 and April 2009 and randomized into intervention groups. Participant flow is shown in Figure 1. After randomization but prior to receiving the intervention session three people withdrew from the intermittent group: one due to MS relapse and fall, one was unable to tolerate the cycle ergometer used for assessments and one withdrew consent without giving a reason. Three people also withdrew from the combined group: hypertension was discovered in one individual, one was unable to tolerate the cycle ergometer and one withdrew consent without giving a reason. All remaining participants were included in the analysis. Participant descriptives and baseline measures can be found in Table 1. ANOVA revealed no difference in baseline measures between groups.

Results from the intervention are displayed in Table 2. While we had some missing values that required multiple imputation, measure completion was high, with 16% missing values in the primary measure. When between-group measures were considered, no difference was found between intervention groups for any measure ($p > 0.05$). However there were trends in the data.

For the primary outcome measure (the 2 min walk test) the data indicated a trend that 0 to 6 week improvements were greatest in the intermittent group. The mean change for the intermittent group at 6 weeks was 12.94 ± 4.71 m (95% CI: 3.97 to 21.92) compared with 4.71 ± 4.24 m (95% CI: −3.80 to 13.22) for the continuous group and -0.9 ± 1.9 m (95% CI: −4.7 to 2.9) for the combined group. There was a trend for SF-36 score to be maintained in the continuous group after the 6 to 12 week training period, contrary to the total significant reduction in SF-36 observed ($p < 0.05$), with a mean increase in score of 1.6 ± 2.6 (95% CI: −3.7 to 6.9) compared with a reduction in both combined and intermittent scores of -7.6 ± 2.9 (95% CI: −13.3 to −1.9) and -7.6 ± 2.8 (95% CI: −13.2 to −2.06) respectively. The continuous group also showed a trend toward maintaining improvements following the intervention. At the 24 weeks assessment mean change in 2 min walk was -0.03 ± 6.29 m (95% CI: −12.65 to 12.59), TUG was 1.1 ± 1.6 s (95% CI: −2.2 to 4.3) and leg power 1.7 ± 5.1 W (95%: −8.5 to 11.9). There was a trend for more improvement in leg power in the intermittent and combined groups: 12 weeks improvements of 22.8 ± 7.1 W (95% CI: 8.6 to 37.0) and 17.5 ± 7.3 W (95% CI: 2.8 to 32.1) respectively and 7.5 ± 6.7 W (95% CI: −6.0 to 21.0) for the continuous group.

When all participants were considered (Total) (Table 2), repeated measures ANOVA revealed significant improvements in mobility as indicated by 2 min walk distance ($p < 0.01$) and TUG time ($p < 0.05$) at the 6 week assessment. Leg power also improved at the 6 week assessment ($p < 0.01$) and continued to improve at the 12 week assessment ($p < 0.01$). No other difference was found between the 6 and 12 week assessments, except for SF-36 score ($p < 0.05$), which decreased, indicating a reduction in perceived general health status. Twelve weeks after the end of intervention (24 week assessment), TUG performance ($p < 0.05$), leg power ($p < 0.01$) and peak power on the exercise test ($p < 0.05$) had decreased. There was no significant ($p > 0.05$) change in fatigue between assessments as indicated by FSS score.

With regard to safety of and compliance with the three programmes, Figure 1 shows the flow of participants throughout; three participants from the combined exercise group reported adverse events during the exercise intervention phase (tachycardia, leg pain and exacerbation of a knee injury) and a further five participants withdrew from the study (due to personal problems, work commitments and family commitments, and two withdrew consent without giving a reason). In the intermittent group four participants discontinued the intervention due to adverse events (two due to pain during cycling, one because of an exacerbation of MS symptoms and one due to a loss of consciousness during cycling) and one individual withdrew from the study at this stage due to a planned surgical procedure. There were no adverse events associated with the continuous group, but one individual withdrew from the study during the intervention phase.

Forty-one (75%) individuals who received the intervention completed the entire 12 week intervention schedule (Combined: nine (53%); Continuous: 19 (95%); Intermittent: 13 (72%). Table 3 shows the mean intervention sessions attended from 0 to 6 weeks and from 6 to 12 weeks; there were significantly ($p < 0.01$) fewer sessions attended from 6 to12 weeks. Table 3 also shows the mode number of sessions attended from 0 to 6 weeks and from 6 to 12 weeks,

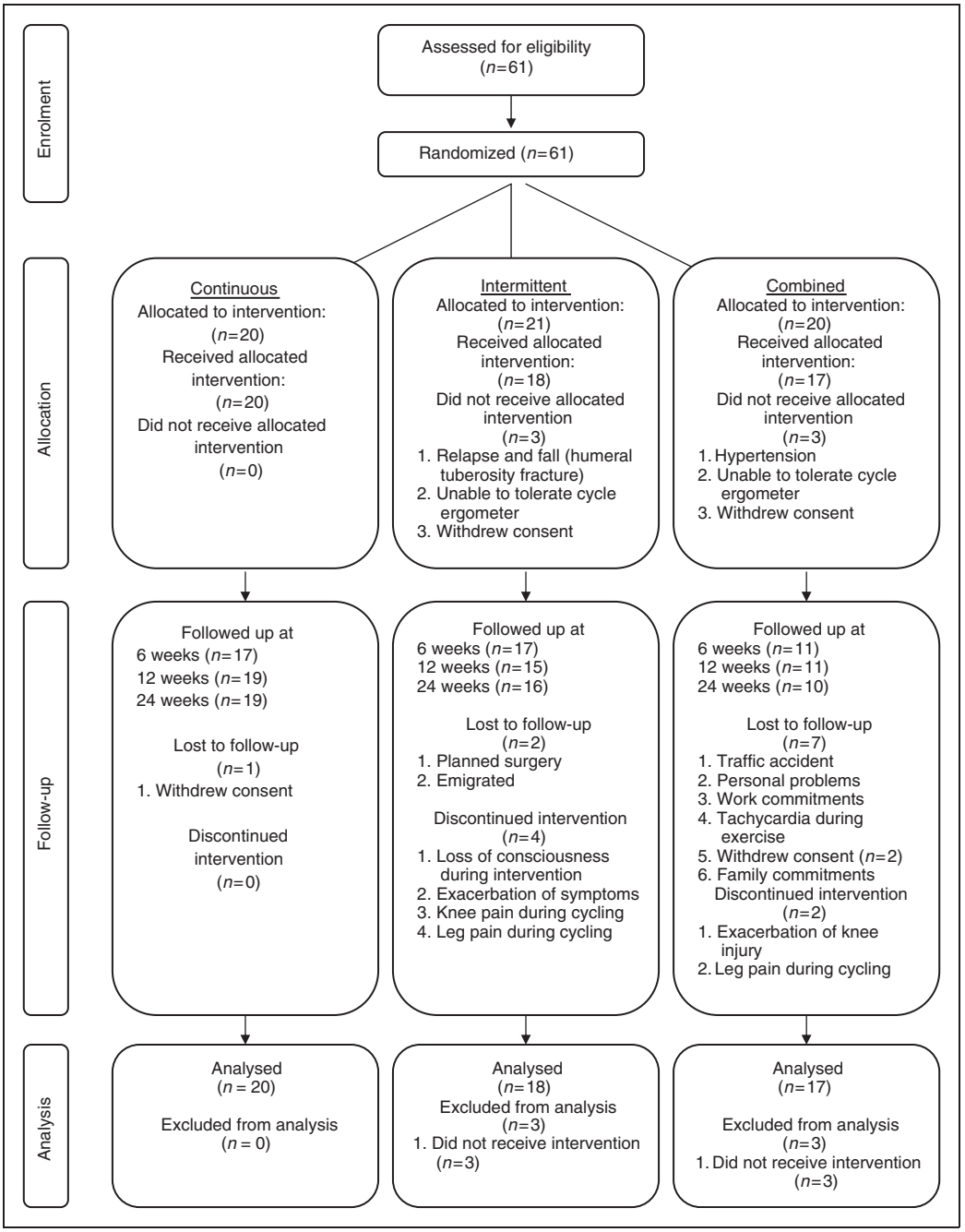

Figure 1. Flow diagram of the progress of participants through the study.

with the number of sessions most often attended being greatest for the continuous group. Mean heart rate data recorded every 2 min during the first exercise sessions in week 1 and week 11 are also shown in Table 3. There was no difference between groups in number of sessions attended, but the continuous group showed a trend toward attending more exercise sessions. There was no significant difference in heart rates ($p > 0.05$) recorded during sessions or between groups.

Discussion

When directly comparing different exercise intensities delivered using the same mode of exercise, cycling, and the same relative amount of total work done in a session, we found that 6 weeks of exercise were associated with statistically beneficial effects on mobility and leg power that were at least maintained during a further 6 weeks of exercise for all training programmes with no differences between groups. While we did not find

Table 1. Participant descriptives and baseline measures

	n (Men: Women)	Age (years)	BMI	Time since diagnosis (years)	Disease course	*n* DMT	Barthel index	2 min walk (m)	TUG (s)	Leg power (W)	Peak power on exercise test (W)	FSS	SF-36	Work status
Total	55 (16:39)	52 ± 9	25.2 ± 4.0	13 ± 9	RR = 22, SP = 25, PP = 7, Undefined = 1	14 (26%)	19:13–20	106.1 ± 54.7	18.1 ± 20.6	112.9 ± 72.4	107 ± 49	4.6 ± 1.1	58.6 ± 16.9	Not = 40, PT = 9, FT = 6
Combined	17 (8:9)	55 ± 10	24.9 ± 4.7	12 ± 11	RR = 7, SP = 7, PP = 3, Undefined = 0	6 (35%)	18:15–20	102.7 ± 60.6	20.7 ± 24.1	105.9 ± 66.9	102 ± 53	3.8 ± 1.5	54.3 ± 16.9	Not = 12, PT = 2, FT = 3
Continuous	20 (4:16)	52 ± 8	25.2 ± 3.2	15 ± 8	RR = 8, SP = 10, PP = 2, Undefined = 0	3 (15%)	18:13–20	107.5 ± 59.9	18.8 ± 22.6	111.3 ± 92.2	109 ± 59	4.2 ± 1.1	60.0 ± 17.3	Not = 15, PT = 2, FT = 3
Intermittent	18 (4:14)	50 ± 10	25.6 ± 4.1	11 ± 7	RR = 7, SP = 8, PP = 2, Undefined = 1	5 (28%)	19:15–20	107.8 ± 45.0	14.7 ± 14.6	121.2 ± 72.4	108 ± 32	4.6 ± 1.1	61.8 ± 16.7	Not = 13, PT = 5, FT = 0

Results expressed as mean ± SD (except Barthel index, median:range).
BMI: body mass index (mass/(height^2)). Disease course: *n*DMT: number of participants on disease-modifying therapy, FFS: Fatigue Severity Scale, PP: primary progressive, RR: relapsing–remitting, SP: secondary progressive, TUG: time up and go. Work status: FT: *n* in full-time work (≥37.5 h per week), Not: *n* not working,
PT: *n* in part-time work (<37.5 h per week)

Table 2. Difference in outcome measured between assessments

	Difference 0 to 6 weeks	Difference 6 to 12 weeks	Difference 12 to 24 weeks
2 min walk (m)			
Total	7.0 ± 2.6 (1.8 to 12.1)#, 0.25	−1.7 ± 1.5 (−4.6 to 1.3), 0.01	−7.1 ± 3.8 (−14.7 to 0.6), 0.07
Combined	3.2 ± 4.6 (−6.0 to 12.5), 0.04	−0.5 ± 2.6 (−5.7 to 4.8), 0.02	−9.7 ± 6.8 (−23.4 to 4.0), 0.08
Continuous	4.7 ± 4.2 (−3.8 to 13.2), 0.06	−2.1 ± 2.4 (−6.9 to 2.7), 0.03	−0.0 ± 6.3 (−12.7 to 12.6), 0.00
Intermittent	12.9 ± 4.7 (4.0 to 21.9), 0.28	−2.4 ± 2.5 (−7.4 to 2.7), 0.06	−11.4 ± 6.6 (−24.7 to 1.9), 0.20
TUG (s)			
Total	−2.3 ± 1.0 (−4.4 to −0.2)*, 0.09	−0.6 ± 0.4 (−1.4 to 0.1), 0.04	2.4 ± 0.9 (0.5 to 4.2)*, 0.10
Combined	−0.9 ± 1.9 (−4.7 to 2.9), 0.03	−1.7 ± 0.6 (−3.1 to −0.3), 0.14	4.9 ± 1.7 (1.5 to 8.3), 0.20
Continuous	−3.5 ± 1.7 (−6.9 to 0.0), 0.10	−0.3 ± 0.6 (−1.6 to 1), 0.02	1.1 ± 1.6 (−2.2 to 4.3), 0.03
Intermittent	−2.5 ± 1.8 (−6.2 to 1.2), 0.22	0.0 ± 0.7 (−1.3 to 1.4), 0.00	1.1 ± 1.6 (−2.2 to 4.3), 0.16
Leg power (W)			
Total	19.4 ± 4.1 (11.2 to 27.6)#, 0.29	15.9 ± 4.1 (7.8 to 24.1)#, 0.21	−10.9 ± 3.1 (−17.1 to −4.8)#, 0.16
Combined	24.9 ± 7.4 (10.1 to 39.7), 0.47	17.5 ± 7.3 (2.8 to 32.1), 0.33	−16.6 ± 5.5 (−27.7 to −5.6), 0.40
Continuous	20.2 ± 6.8 (6.5 to 33.8), 0.38	7.5 ± 6.7 (−6.0 to 21.0), 0.09	1.7 ± 5.1 (−8.5 to 11.9), 0.01
Intermittent	13.1 ± 7.2 (−1.3 to 27.5), 0.12	22.8 ± 7.1 (8.6 to 37.0), 0.27	−18.0 ± 5.3 (−28.7 to −7.3), 0.35
Peak power on exercise test (W)			
Total	3 ± 2 (−2 to 8), 0.03	2 ± 2 (−2 to 5), 0.02	−29 ± 5 (−39 to −20)*, 0.42
Combined	2 ± 4 (−6 to 10), 0.01	−3 ± 3 (−10 to 4), 0.06	−33 ± 8 (−49 to −16), 0.41
Continuous	0 ± 4 (−8 to 8), 0.00	7 ± 3 (1 to 13), 0.14	−19 ± 8 (−35 to −4), 0.32
Intermittent	7 ± 4 (−1 to 15), 0.23	1 ± 3 (−6 to 8), 0.01	−37 ± 8 (−53 to −20), 0.54
FSS			
Total	0.0 ± 0.1 (−0.2 to 0.2), 0.00	0.0 ± 0.1 (−0.2 to 0.3), 0.00	0.0 ± 0.1 (−0.2 to 0.2), 0.00
Combined	−0.2 ± 0.2 (−0.6 to 0.2), 0.06	−0.0 ± 0.2 (−0.4 to 0.4), 0.00	−0.2 ± 0.2 (−0.5 to 0.3), 0.20
Continuous	0.1 ± 0.2 (−0.3 to 0.4), 0.01	0.0 ± 0.2 (−0.4 to 0.4), 0.00	0.2 ± 0.2 (−0.2 to 0.6), 0.01
Intermittent	0.2 ± 0.2 (−0.2 to 0.6), 0.05	0.1 ± 0.2 (−0.3 to 0.5), 0.01	−0.2 ± 0.2 (−0.5 to 0.2), 0.03
SF36			
Total	1.7 ± 1.4 (−1.0 to 4.5), 0.02	−4.5 ± 1.6 (−7.7 to 1.4)*, 0.11	−1.7 ± 2.4 (−6.6 to 3.1), 0.01
Combined	5.6 ± 2.5 (0.6 to 10.5), 0.18	−7.6 ± 2.9 (−13.3 to −1.9), 0.27	−1.8 ± 4.3 (−10.5 to 6.9), 0.01
Continuous	−0.6 ± 2.3 (−5.2 to 4.0), 0.00	1.6 ± 2.6 (−3.7 to 6.9), 0.03	−4.9 ± 4.0 (−13.0 to 3), 0.10
Intermittent	0.2 ± 2.4 (−4.6 to 5.0), 0.00	−7.6 ± 2.8 (−13.2 to −2.06), 0.27	1.6 ± 4.2 (−6.9 to 10.1), 0.10
Barthel Index			
Total	0.2 ± 0.2 (−0.1 to 0.5), 0.03	−0.6 ± 0.2 (−1.1 to −0.1), 0.11	0.1 ± 0.2 (−0.4 to 0.5), 0.00
Combined	0.0 ± 0.3 (−0.5 to 0.5), 0.00	−0.9 ± 0.4 (−1.7 to −0.0), 0.16	0.4 ± 0.4 (−0.4 to 1.3), 0.07
Continuous	0.8 ± 0.3 (−0.2 to 1.3), 0.27	−0.4 ± 0.4 (−1.2 to 0.4), 0.09	0.0 ± 0.3 (−0.8 to 0.8), 0.00
Intermittent	−0.2 ± 0.3 (−0.7 to 0.4), 0.03	0.5 ± 0.4 (−1.2 to 0.4), 0.08	0.2 ± 0.4 (−1.0 to 0.6), 0.02

Results expressed as mean ± SE (95% confidence intervals), effect size (partial eta squared).
*$p < 0.05$, #$p < 0.01$ between assessments.
FFS: Fatigue Severity Scale, PASE: Modified Physical Activity Scale for the elderly, TUG: time up and go.

significant differences between the three different exercise intensity groups, post hoc analysis on the primary outcome measure revealed that the higher-intensity intermittent exercise group would have achieved significantly greater improvements in walking mobility if the study had been powered with a sample size of 123. This finding and the level of compliance support the implementation of a phase III trial.

Importantly, however, we also observed that continuous low-intensity exercise seemed to be better tolerated when the number of adverse events, session attendance and number of withdrawals during the intervention period were considered, suggesting that higher-intensity exercise may be less well tolerated by people with MS. We thus suggest that a future trial exploring exercise intensity should be approached with caution, and that, though higher intensities may offer greater benefits for some, continuous exercise performed at an intensity that falls within an aerobic zone is safe and will benefit mobility and leg power, and should currently be recommended by clinicians for people with MS.

Table 3. Exercise sessions

	0 to 6 weeks	6 to 12 weeks
Sessions attended		
Total	8 ± 3 (10,11)	6 ± 4* (10)
Combined	7 ± 4 (1,10)	5 ± 5 (0)
Continuous	9 ± 3 (11)	7 ± 3 (10)
Intermittent	8 ± 3 (6)	5 ± 4 (0,1,9)
% max heart rate		
Total	66.8 ± 11.6	64.1 ± 8.7
Combined	67.4 ± 14.1	60.6 ± 6.9
Continuous	66.3 ± 9.4	66.5 ± 8.4
Intermittent	66.4 ± 10.3	62.9 ± 9.3

Sessions attended: results expressed as mean ± SD (mode).
% max heart rate: % age predicted maximum heart rate (220 − age), values from training week 1 exercise session (0 to 6 weeks) and week 11 exercise session (6 to 12 weeks).
*Significant difference in number of sessions between 0 to 6 weeks and 6 to 12 weeks ($p < 0.01$).

Our finding that cycling exercise was associated with improvement in walking in people with MS supports the literature that cycling exercise benefits mobility.[16] However, effect sizes suggest that improvements in walking mobility were small. Mean improvement for 2 min walk and TUG at 6 weeks for all training programmes were comparable to 7% and 13% respectively. A 12% increase in walking speed and a 23–24% improvement in TUG has been reported as genuine change for an individual with MS.[8] However, the individual response to the interventions varied considerably, as indicated by large confidence intervals. Rampello et al.[17] found significant improvement in walking distance using the 6 min walk test after 8 weeks of 30 min sessions of aerobic cycling three times weekly at 60% of maximum power. The findings from the present study suggest that mobility improvements may be gained over 6 weeks with an average of only eight sessions of either 20 min continuous, 15 min combined or 10 min intermittent exercise performed in a 20 min session. During the second 6 week period exercise effects were maintained despite individuals only attending an average of six sessions. Although the present study did not include health markers, the effect of exercise intervention on walking is an important consideration when giving exercise guidance for this group. Walking mobility has been reported as the highest concern of people with MS, and it is an important factor in determining independence in activities of daily living and quality of life.[18] Therefore these findings are important to build a picture of a lower minimal exercise dose for functional improvement in people with MS compared with the government guidance for healthy individuals.[1]

Dalgas et al.[5] postulated that intense endurance training might be expected to produce faster and larger training improvements. We did observe a trend towards a better outcome in the 2 min walk in the intermittent high-intensity exercise group. Post hoc analysis shows that a total sample size of 123 would be needed to confirm its superiority (alpha 0.05, power 0.8). In addition, while the present study failed to find significant differences in leg power between groups, the continued improvement in leg power from 6 to 12 weeks may also be more associated with the higher-intensity exercise groups. Certainly the training stimulus associated with high-intensity cycling would be expected to produce greater leg power improvements.[6] It may be that higher-intensity exercise may improve certain functional activities and offer a better outcome for some people with MS.

Walking speed has been related to muscle strength in people with MS,[19] and intervention utilizing resistance training has been shown to improve lower limb muscle performance and walking mobility measures.[20,21] In the present study leg extensor power was used to measure lower limb muscle performance. Both mobility and leg power increased after 6 weeks of training. However, despite leg power continuing to improve after 12 weeks of training, mobility improvements were stable. This may be due to cycling being more analogous to the muscle action required for leg extensor power measurement than that required for walking. Certainly, task-specific training is associated with improved muscle synergy and coordination.[22]

The present study found no changes in fatigue over the study period, in agreement with the literature that exercise at least does not have a negative effect on fatigue.[5] The FSS has also been used to indicate quality of life (QOL) in people with MS,[23] but, while our FSS data suggest that fatigue was not affected, the SF-36

data (another more widely used measure of QOL[23,24]) suggest that QOL was significantly reduced after 12 weeks of training. This result is contrary to other exercise studies; a meta-analysis on the effect of exercise training on QOL finding small but statistically significant improvements in QOL with exercise in people with MS.[23]. While demonstrating good reliability and internal consistency when used in MS, the SF-36 is criticized for lack of responsiveness in rehabilitation.[10] Although the negative effect on the SF-36 score observed in the present study after 12 weeks of cycling should be treated with caution, it may have importance, since, despite the study being underpowered to detect a between-group effect, the negative effect was more associated with higher-intensity exercise (intermittent and combined). However, other studies with similar within-group sample sizes investigating strengthening and more intensive short periods of exercise have found improvements in the SF-36 after exercise.[24,25]

The adverse events that occurred during the intervention period of the current study were also associated with the higher-intensity exercise groups. In the intermittent group there were four adverse events during the intervention period, and three in the combined group. Two of the adverse events in the intermittent group required inpatient hospitalization, one due to loss of consciousness and one due to exacerbation of MS symptoms. It became apparent that loss of consciousness events were an existing problem of the participant. In agreement with other exercise studies that have reported exacerbation of MS symptoms,[3] it was deemed by the study steering group that the exacerbation of MS symptoms was unlikely to have been caused by the intervention. The reports of leg pain may be of more importance when considering delivering higher-intensity cycling exercise, as two individuals withdrew from the intervention due to leg pain during cycling in the intermittent group and one in the combined group, with a further individual aggravating an existing knee injury. These events suggest that higher-intensity cycling exercise may not be appropriate for some people with MS, and that leg pain should be monitored while delivering the exercise. There was no difference in the number of sessions attended between groups, but a trend toward attending more sessions in the continuous group.

A pragmatic approach was used to determine the sample size of the present study. While the results show that this was insufficient to find differences between groups, this limitation is common among MS exercise studies,[4] and not surprising with the heterogeneous group recruited. Applying CONSORT[26] guidelines to reporting of this trial allows critical appraisal and interpretation of the results and provides evidence for meta-analysis.

Apart from the small sample size, our study has several other limitations. We included only people who were capable of cycling and performing the 2 min walk test. However, we did have a heterogeneous group of individuals, including some people in the very early stages of the disease. While we asked participants to do a fixed dose, we found that many could not maintain the twice weekly intervention schedule, and, although our within-session exercise was carefully controlled, the total dose was much less than we intended. Nonetheless, we unexpectedly found benefits occurring with low doses of exercise. Importantly, we found that an average of eight sessions of 20 mins of cycling exercise had an effect in the first 6 weeks and that an average of six sessions maintained this effect over the following 6 week period, suggesting that lower doses of exercise may benefit people with MS. When participants were measured 12 weeks after training finished, detraining had occurred in mobility measures, with again no difference between groups. Achieving ongoing physical activity would appear to be important for people with MS. Future studies should include health markers in order to further establish health benefits.

Interpreting differences between types of exercise therapy for people with MS from previous research has been found to be difficult due to poorly described interventions and research into different abilities.[4] This research study has utilized a design that controlled and described the intervention and was delivered using the same mode. Thus we can attribute differences between groups to intensity. While we have considered the limitations of the study, the trial has certain strengths, including its design, full recruitment, inclusion of a wide range of abilities, good utility and completion of outcome measures and compliance with the intervention. We thus propose that our observations are important and valid and should be considered in the planning of future trials and in forming the evidence to develop exercise guidance for people with MS.

Conclusions

Cycling exercise delivered over a 6 week period produces significant benefits for mobility and leg power, which are maintained and improved with further weekly sessions. While higher-intensity exercise may offer greater benefits for some, 20 min of continuous cycling exercise with heart rate maintained in an aerobic zone is better tolerated. This approach may be implemented safely in community exercise centres. Further studies may wish to explore optimal exercise frequency for this exercise approach or explore effect over the longer term.

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Conflict of interest statement

None declared.

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