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Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial.

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Abstract

Background: Exercise programmes that can demonstrate evidence of long-lasting clinical effectiveness are needed for people with multiple sclerosis (PwMS).

Objective: The objective of this study was to assess the effects of a practically implemented exercise programme on self-directed exercise behaviour and important health outcomes in PwMS to nine months of follow-up.

Methods: We conducted a parallel-arm, randomised controlled trial: 120 PwMS (Expanded Disability Status Scale (EDSS) 1.0–6.5) randomised to a three-month exercise intervention plus usual care, or usual care only. Two supervised plus one home-exercise session (weeks 1–6) were followed by one supervised and two home-exercise sessions (weeks 7–12). Cognitive-behavioural techniques promoted long-term exercise behaviour change. Outcomes were blindly assessed at baseline and at three and nine months after randomisation. The primary outcome was self-reported exercise behaviour (Godin Leisure Time Exercise Questionnaire (GLTEQ)). Secondary outcomes included fatigue and health-related quality of life (HRQoL).

Results: The intervention increased self-reported exercise (9.6 points; 95% CI: 2.0 to 17.3 points; $p = 0.01$) and improved fatigue ($p < 0.0001$) and many HRQoL domains ($p \leq 0.03$) at three months. The improvements in emotional well-being ($p = 0.01$), social function ($p = 0.004$) and overall quality of life ($p = 0.001$) were sustained for nine months.

Conclusion: This pragmatic approach to implementing exercise increases self-reported exercise behaviour, improves fatigue and leads to a sustained enhancement of HRQoL domains in PwMS.

Introduction

Supervised facility-based exercise programmes can offer comprehensive support and guidance for people with multiple sclerosis (PwMS) but over the long term are likely to prove difficult because of time barriers, transport issues and health constraints (e.g. fatigue).¹ A major challenge is to develop pragmatic and cost-effective exercise programmes that can safely engage PwMS in exercise and provide robust evidence of a long-lasting impact on important health outcomes. Interventions that promote and provide support for sustainable home-based exercise, including use of community facilities, may help to overcome some of these problems but, to date, only very few studies have assessed the health impacts of exercise in community-based settings.^{2–4} The inclusion of cognitive-behavioural strategies might also be effective for increasing confidence for self-directed exercise, as reported in other clinical populations.^{5–7}

Here, we report the effects of a pragmatic EXercise Intervention for people with MS (EXIMS) on self-directed exercise behaviour and important health outcomes, including fatigue and health-related quality of life (HRQoL). We hypothesised that participants randomised to the intervention group (EXIMS) would show an increase in physical activity levels and improvements in a range of health outcomes up to nine months of follow-up in comparison with participants randomised to usual care alone.

Materials and Methods

Controlled Trial

This was a two-arm, parallel, randomised controlled trial. PwMS were randomised (1:1) to receive either the EXIMS intervention plus usual care or usual care only. Full details of the protocol have been published previously.⁸ This study was approved by the South Yorkshire Research Ethics Committee and conducted according to the principles

of the Declaration of Helsinki. Written informed consent was obtained from participants before entering the study.

Recruitment of participants and baseline assessment

A total of 120 PwMS were recruited via the Sheffield MS Clinic and flyers/community adverts displayed at the local South Yorkshire MS Society branches. All patients were assessed by a consultant neurologist with an interest in MS prior to entering the trial. The inclusion criteria for the trial were clinical diagnosis of MS, as defined by the modified McDonald criteria,⁹ with an Expanded Disability Status Scale (EDSS) score of 1.0–6.5, and able to walk a 10-metre distance; aged 18–65 years; clinically stable for at least four weeks prior to entering the study; physically able to participate in exercise three times per week; able to provide written informed consent. Participants on disease-modifying therapy (interferon beta, glatiramer acetate and natalizumab) had been stable on this treatment for at least three months. Exclusion criteria were comorbid conditions impairing the ability to be physically active three times per week; unwilling to be randomised; living more than 20 miles from the trial centre; already engaged in structured exercise or brisk walking ≥ 3 times per week for ≥ 30 minutes per session for at least six months.

Randomisation and concealed allocation

Minimisation was used to balance the potentially confounding variables of gender and EDSS score (low: 1.0–3.5; higher: 4.0–6.5). Treatment allocation was concealed from the study researchers by using a distant randomisation service at the University of York, UK. The allocation was not disclosed to members of the research team until participants had completed their baseline assessments. Due to the nature of the

intervention, neither the participants nor researchers involved in the day-to-day running of the trial could be blinded to treatment allocation.

Pragmatic exercise intervention

An exercise physiologist supervised the delivery of the intervention but with physiotherapist input during the early stages of the programme. During weeks 1–6, participants attended two supervised sessions per week at a university exercise research facility and engaged in one additional self-directed exercise session in their home environment. Supervised exercise sessions involved up to three participants and lasted for approximately one hour. Studies show that aerobic exercise, resistance exercise and combined programmes bring health benefits to PwMS.^{10,11} Hence, the programme was designed to be pragmatic and accessible, taking into account exercise preferences and giving choices. Aerobic exercise was the core exercise modality as it is accessible (i.e. includes community-based walking exercise) and does not require equipment. Participants were asked to complete short bouts (e.g. 5 × 3 minutes, with two-minute rest intervals) of low to moderate intensity aerobic exercise (e.g. stepping ergometer, cycle-ergometer, treadmill walking, rowing ergometer, arm-cranking) at 50%–69% of predicted maximum heart rate (220–age) or 12–14 on the Borg Ratings of Perceived Exertion Scale.¹² Intensity was monitored continuously during exercise training sessions. As the intervention progressed, participants were encouraged to participate in longer periods of aerobic exercise (e.g. 5 × 4 minutes) or to take shorter rests between bouts.

Where appropriate, participants also performed exercises for strength and control. The prescribed strength training was based on individual functional needs, as assessed by the trial physiotherapist (NS). Strength training was undertaken by 48 of 60 participants

in the intervention group and typically involved two to six different resistance exercises (e.g. wall press-ups, arm-curls, leg abduction, wall squats and/or regular squats, knee extensions, calf raises, sit-to-stand) each session. Body resistance, light weights and Therabands were used to provide resistance and one to three sets of five to 20 repetitions were performed, depending on level of disability and strength, as well as stage of the programme (exercises were progressed according to individual capabilities and strength gains). Balance board, balance exercises and exercise ball work were included where control and coordination were a problem and static stretching exercises for large skeletal muscle groups were also included in the sessions if appropriate.

During weeks 7–12 participants attended the centre once per week and completed two additional self-directed exercise sessions in their home or local community. The home-exercise sessions were intended to mirror the supervised sessions in terms of intensity and duration of aerobic exercise, and also included tailored exercises for strength, flexibility and balance. Participants were encouraged to seek out opportunities to exercise in the local community (e.g. healthy living centres, health walks, fitness centres, swimming pools, etc.), based on their individual preferences. Details of supervised and home-exercise sessions were recorded in an exercise log.

The supervised exercise sessions incorporated cognitive-behavioural techniques (e.g. goal setting, finding social support, understanding the costs/benefits of exercise, etc.) to promote long-term participation in physical activity. Using the Transtheoretical Model¹³ as a guiding framework, this aspect of the intervention was aimed at equipping PwMS with the skills, knowledge and confidence to engage in a more physically active lifestyle. The cognitive-behavioural elements were integrated into the exercise sessions using strategies appropriate to the conversation, stage of change and concerns/questions raised by participants. Further details of the theoretical model

for facilitating physical activity behaviour change have been published previously.⁸ Participants in the usual care group were offered three exercise sessions at the university exercise research facility and individual exercise advice after the study.

Outcome measures

Outcomes were assessed at baseline, and at three months (post-intervention) and nine months after randomisation. The primary outcome was self-reported exercise behaviour at three months using the Godin Leisure Time Exercise Questionnaire (GLTEQ).¹⁴ The GLTEQ asks participants to recall the frequency of strenuous, moderate and mild intensity exercise for periods >15 minutes over the past seven days and is a valid measure of habitual exercise in PwMS.¹⁵ Daily movement and step counts were objectively assessed using an accelerometer (Actigraph GT2M accelerometer, Actigraph, LLC, FL, USA), worn on the waist during waking hours, except when bathing/showering or swimming. Accelerometers were programmed for an epoch length of one minute and the average daily movement count (vertical axis) and daily step count over a seven-day period were recorded.

Secondary outcomes included fatigue, HRQoL, functional ability and neurological impairment. Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS).¹⁶ HRQoL was measured using the MSQoL-54.¹⁷ The Multiple Sclerosis Functional Composite (MSFC)¹⁸ was used as a measure of clinical functional ability. It includes a timed 25-foot walk and measures of arm/hand function (9-hole peg test) and cognitive function (Paced Auditory Serial Addition Test: PASAT). Functional exercise capacity was assessed using the six-minute walk test (6MWT).¹⁹ The EDSS²⁰ (neurological impairment and disability) was assessed by a single trained consultant neurologist according to standard clinical procedures²¹ in the hospital setting. Other outcomes

were blindly assessed by an experienced researcher not directly involved with the day-to-day running of the trial.

Sample size

The sample size estimation was based on self-reported physical activity data (GLTEQ) from our pilot study.²² It was estimated that a sample of 50 patients for each group would be sufficient to detect a moderate effect size difference (80% power and a 5% significance level) in GLTEQ (standard deviation, SD = 2.29). Hence, we aimed to recruit 60 participants for each group to allow for a 15% loss to follow-up at the primary time point (based on our pilot study data).²²

Statistical analysis

Repeated-measures mixed modelling was used to compare outcomes between the randomised groups at the three- and nine-month follow-ups, adjusting for baseline score, EDSS and gender. The distribution of the majority of outcomes were skewed, therefore the analyses were bootstrapped (1000 replications) to provide more reliable estimates. All analyses were by intention to treat, whereby participants were analysed in the arm to which they were randomised irrespective of whether they complied with the intervention. Multiple imputation of missing values was performed using the imputation by chained equations (ICE) command in Stata 12. Variables included in the imputation were age, gender, baseline EDSS, and baseline, three- and nine-month follow-up scores for all outcomes. Five imputations were carried out and mixed-model analysis was performed on each imputed dataset. The adjusted means and confidence intervals (CIs) from each analysis were then consolidated using Rubin's rules. Sensitivity analysis was performed to determine the effect of outliers in the GLTEQ scores by their removal from the analysis. Bivariate associations between key variables

were analysed using the Pearson Product Moment correlation coefficient. No corrections for multiple testing were made in the analysis. Analyses were undertaken by the trial statistician, blinded to treatment allocation, using STATA 12 and results are generally reported as means and CIs.

Results

Table 1. Baseline characteristics of participants allocated to usual care only or usual care plus EXIMS. Values are numbers (percentages) or mean \pm SD.

Characteristics	Usual care group(<i>n</i> = 60)	EXIMS group(<i>n</i> = 60)
Age (years)	46.0 \pm 8.4	45.7 \pm 9.1
Female	43 (71.7%)	43 (71.7%)
White	57 (95%)	54 (90%)
Employed full time	16 (27%)	9 (15%)
Employed part time	14 (23%)	17 (28%)
Time since MS diagnosis (years)	9.2 \pm 7.9	8.4 \pm 7.4
EDSS score subgroup	3.8 \pm 1.5	3.8 \pm 1.5
0–3.5	28 (47%)	29 (48%)
4.5–6.5	32 (53%)	31 (52%)
Mean score	3.8 \pm 1.5	3.8 \pm 1.5
MS subtype		
Relapsing-remitting	47 (78%)	51 (85%)
Secondary progressive	11 (18%)	7 (12%)
Primary progressive	2 (3%)	2 (3%)
Anthropometric variables and blood pressure		
Height (m)	1.68 \pm 0.07	1.68 \pm 0.08
Body mass (kg)	76.4 \pm 15.5	79.4 \pm 17.8
BMI (kg/m^2)	27.1 \pm 5.8	28.0 \pm 5.4
Waist circumference (cm)	92.8 \pm 13.6	95.1 \pm 14.4
Waist:Hip ratio	0.86 \pm 0.08	0.87 \pm 0.09
Systolic blood pressure (mm Hg)	129 \pm 16	126 \pm 14
Diastolic blood pressure (mm Hg)	82 \pm 10	83 \pm 10

MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; BMI: body mass index.

Participant flow and recruitment

The trial took place from March 2009 to August 2012. Of 349 potential participants who were assessed for eligibility, 120 (34%) were randomised (Figure 1). The two groups had similar demographic, anthropometric and MS disease characteristics at baseline (Table 1). In the two years preceding the study, 55 relapses were experienced by 30

participants in the usual care group in comparison to 54 relapses experienced by 33 participants in the exercise group.

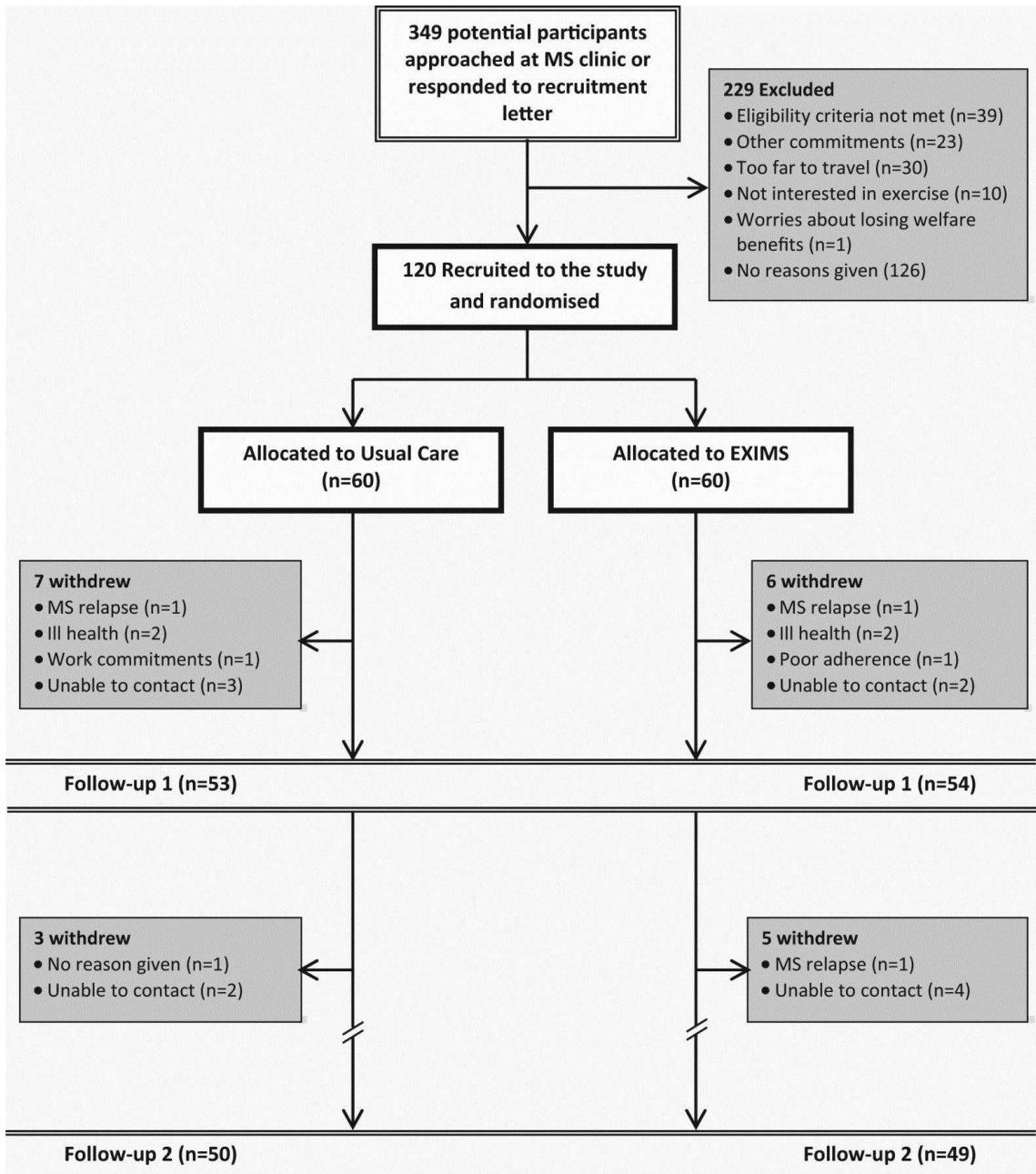


Figure 1. Flow of participants through the trial. EXIMS: pragmatic EXercise Intervention for people with MS.

Loss to follow-up and MS relapses

A total of 13 participants (six from the intervention group and seven from the usual care group) were lost to follow-up at three months. An additional eight participants were lost to follow-up at nine months (five from the intervention group and three from the usual care group; Figure 1). Participants that dropped out of the study were slightly younger than the study completers (43.3 vs 46.3 years) and had higher baseline EDSS and total fatigue scores (4.5 vs 3.6 and 48.0 vs 42.6, respectively). During the nine-month study period, 16 MS relapses were experienced by 14 of the usual care participants in comparison to 10 MS relapses experienced by nine participants in the exercise group. Participants were encouraged to rejoin the trial following recovery, and complete or partial follow-up data were obtained for 21 of the 23 relapsing participants.

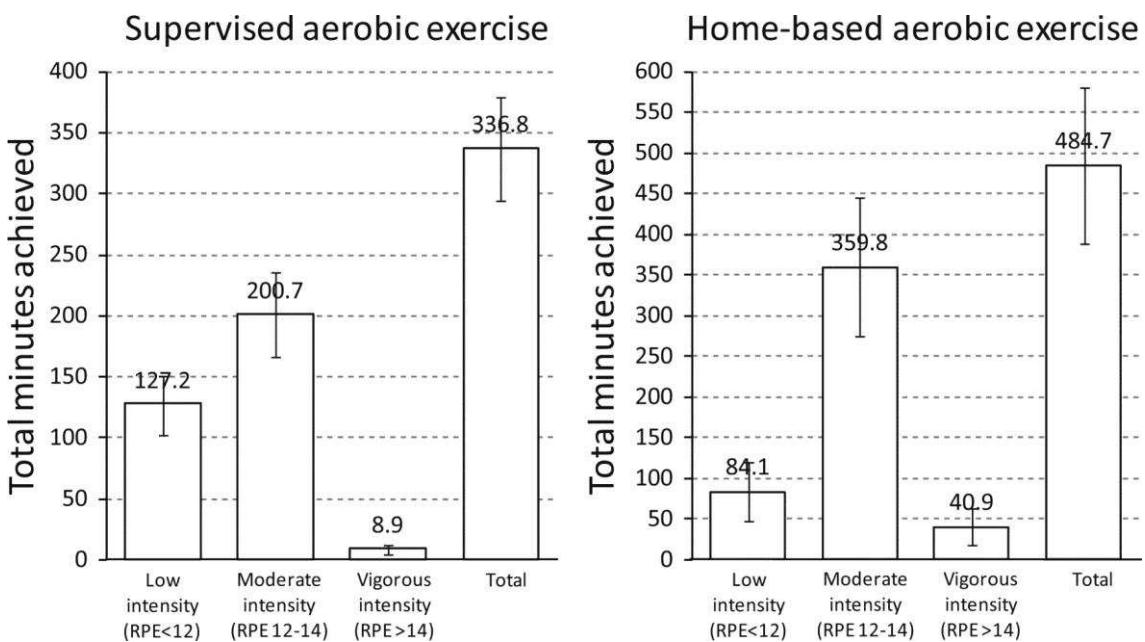


Figure 2. Minutes of supervised and home-based aerobic exercise achieved by the intervention group at different intensities over the supervised period of the study (weeks 1–12). Values are means with error bars representing 95% confidence intervals. RPE: Ratings of Perceived Exertion.

Table 2. Baseline primary and secondary outcome data for participants allocated to usual care only and usual care plus EXIMS. Values are presented as mean \pm SD.

Characteristics	Usual care group		EXIMS group	
	Mean (SD)	N	Mean (SD)	N
Physical activity				
Godin LTEQ score	17.5 (14.8)	59	20.3 (21.9)	58
Accelerometer daily step counts	4695 (2711)	59	4488 (2251)	60
Fatigue				
Physical	21.6 (7.5)	60	22.7 (7.9)	60
Cognitive	17.2 (8.1)	60	18.3 (9.2)	60
Psychosocial	4.0 (2.1)	60	4.1 (2.0)	60
Total MFIS	42.8 (15.7)	60	45.0 (17.0)	60
MSQoL-54				
Physical health	52.2 (30.1)	60	45.7 (28.7)	60
Role limit physical	32.9 (38.6)	60	31.8 (40.7)	59
Role limit emotional	60.6 (43.2)	60	58.8 (43.9)	59
Pain	65.7 (24.1)	60	63.0 (29.6)	60
Emotional well-being	65.1 (18.3)	60	64.2 (18.8)	60
Energy	39.0 (16.5)	60	39.9 (20.1)	60
Health perceptions	42.3 (18.4)	60	42.0 (23.3)	60
Social function	65.3 (24.8)	60	66.0 (23.3)	60
Cognitive function	67.5 (21.0)	60	61.3 (25.0)	60
Health distress	57.8 (26.4)	60	52.5 (28.4)	60
Sexual function	70.0 (32.7)	55	64.4 (31.8)	55
Change in health	45.4 (19.3)	60	44.6 (24.0)	60
Sex satisfaction	52.3 (28.6)	55	53.1 (29.5)	57
Overall quality of life	62.4 (20.3)	60	58.3 (21.8)	60
Physical health component	51.2 (18.8)	60	48.8 (21.5)	60
Mental health component	62.8 (21.7)	60	59.5 (22.5)	60
MSFC				
25-ft walk test (s)	8.9 (10.6)	59	8.2 (6.6)	60
9-hole peg test DH average	25.0 (6.1)	59	26.0 (8.9)	59
9-hole peg test NDH average	29.6 (13.4)	60	27.7 (7.6)	59
PASAT	43.3 (14.2)	60	40.6 (13.8)	60
Six-minute walk test (m)	395 (140)	57	373 (134)	59

EXIMS: pragmatic EXercise Intervention for people with MS; LTEQ: Leisure Time Exercise Questionnaire; MFIS: Modified Fatigue Impact Scale; MSQoL-54: MS quality of life-54; MSFC: Multiple Sclerosis Functional Composite; PASAT: Paced Auditory Serial Addition Test; DH: dominant hand; NDH: non-dominant hand.

Adherence to the EXIMS intervention

Adherence to the supervised and home-exercise sessions was very good, with participants attending an average of 16.2 of the 18 supervised sessions (90%; range 7–18 sessions) and participating in an average of 14.6 of the 18 prescribed home-exercise sessions (81%, range 2–18 sessions). Home exercise during the intervention period comprised walking, use of home exercise equipment, public facilities (including swimming) and gardening for the majority of participants. The volumes of supervised

and home-based aerobic exercise are presented in Figure 2. No serious adverse events or serious symptom exacerbations were recorded.

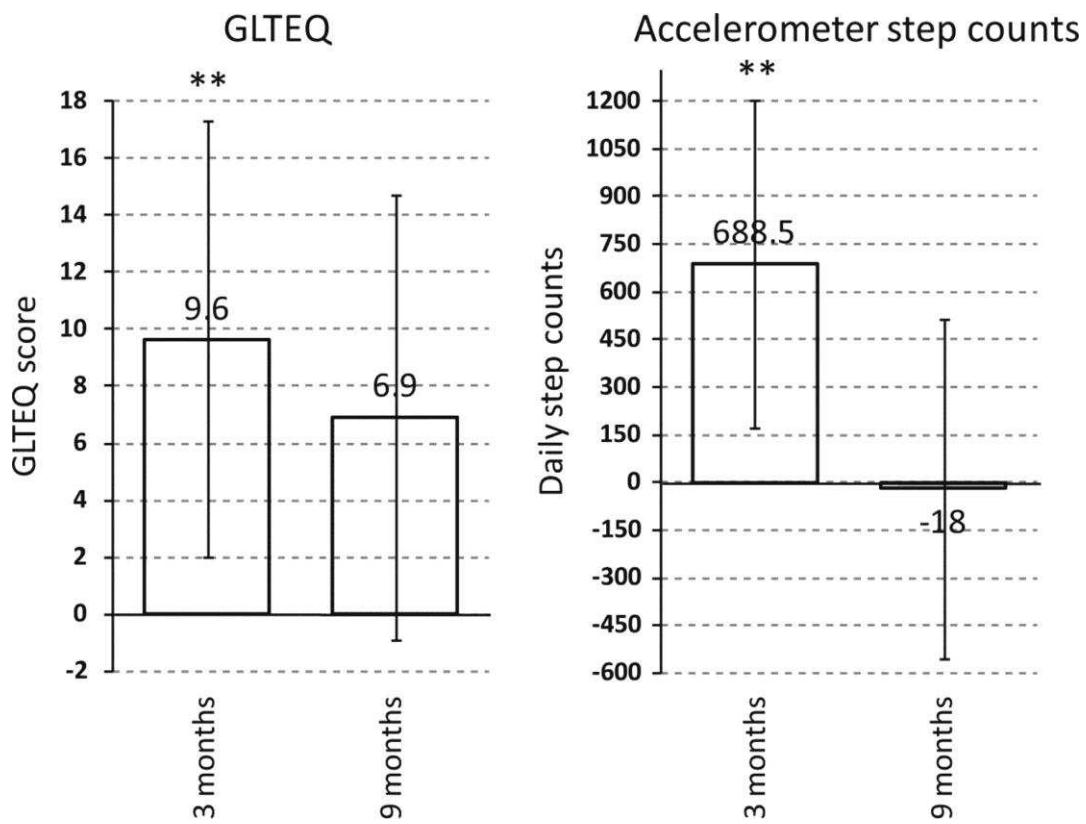


Figure 3. Adjusted mean differences in self-reported exercise (GLTEQ) and accelerometry step counts between the intervention and usual care control groups at 3 months and 9 months (adjusted for baseline, gender and EDSS). Values are means with error bars representing 95% confidence intervals. ** $p \leq 0.01$ between the groups.

GLTEQ: Godin Leisure Time Exercise Questionnaire.

Primary and secondary outcomes

Baseline scores for the primary and secondary outcomes were comparable for the two groups (Table 2). An increase in GLTEQ was observed in the exercise group versus usual care at the primary time point of three months ($p = 0.01$) and a non-significant increase was still apparent after nine months ($p = 0.08$; Figure 3). The improvement in self-reported exercise behaviour was accompanied by increases in objectively

measured daily step counts at three months ($p = 0.009$) in the exercise group versus usual care, but at nine months daily step counts were similar to baseline levels (Figure 3). All dimensions of fatigue were significantly improved in the exercise group in comparison with usual care at three months ($p < 0.0001$), with the change in total fatigue scores being positively correlated with baseline levels (Table 3). Interestingly, volume of supervised aerobic exercise achieved was negatively correlated with the change in total fatigue scores at the three-month follow-up (Table 3). The improvements in fatigue were not maintained at nine months (Table 4). Positive changes in many quality of life domains in favour of the exercise group were also observed at three months, with improvements in emotional well-being ($p = 0.01$), social function ($p = 0.004$) and overall quality of life ($p = 0.001$) being maintained for nine months (Table 4). The exercise intervention had no effect on functional ability or neurological impairment (Table 4). At baseline, EDSS scores were positively correlated with total fatigue scores and negatively correlated with the volume of aerobic exercise achieved (Table 3). Body weight also remained unchanged in both groups but there was evidence of a reduction in waist circumference at both follow-up time points (non-significant at three months) and reduction in diastolic blood pressure at nine months in the exercise group versus usual care (Table 5). Multiple imputation analysis gave similar results to the primary available case analyses, and exclusion of outliers in GLTEQ scores had no impact.

Table 3. Bivariate association between EDSS, total fatigue, GLTEQ and total volumes of supervised and home-based aerobic exercise for the intervention group.

	Total fatigue (B/L)	Δ GLTEQ	Δ Total fatigue	Supervised aerobic exercise (min)	Home-based aerobic exercise (min)
EDSS (B/L)	0.36 ^b	-0.12	0.24	-0.62 ^b	-0.29 ^a
Total fatigue (B/L)		0.03	0.37 ^b	-0.41 ^b	-0.12
Δ GLTEQ			-0.08	0.00	0.03
Δ Total fatigue				-0.32 ^a	-0.05

EDSS: Expanded Disability Status Scale; GLTEQ: Godin Leisure Time Exercise Questionnaire. Values in the table show Pearson Product Moment correlation coefficients. B/L indicates baseline measures; Δ indicates difference between baseline and three-month follow-up; Total volumes of supervised and home-based aerobic exercise are shown in minutes; ^a $p < 0.05$; ^b $p < 0.01$.

Table 4. Secondary outcomes at three months and nine months in participants allocated to usual care and usual care plus EXIMS.

	Follow-up time point (months)	Usual care group mean (sd)	EXIMS group mean (sd)	Difference in adjusted means (95% CI)	Bootstrapped p value
Fatigue					
Physical	3	21.2 (8.9)	17.9 (8.3)	-4.3 (-6.2 to -2.5)	<0.0001
	9	20.7 (8.5)	20.1 (7.8)	-1.2 (-3.0 to 0.7)	0.22
Cognitive	3	17.7 (8.2)	14.9 (9.6)	-3.6 (-5.5 to -1.8)	<0.0001
	9	16.7 (9.6)	16.0 (8.8)	-1.4 (-3.3 to 0.5)	0.15
Psychosocial	3	4.2 (2.1)	2.9 (2.2)	-1.2 (-1.7 to -0.7)	<0.0001
	9	4.0 (2.4)	3.5 (1.9)	-0.3 (-0.8 to 0.3)	0.36
Total MFIS	3	43.2 (17.3)	35.8 (18.2)	-9.2 (-12.8 to -5.7)	<0.0001
	9	41.3 (18.8)	39.6 (16.6)	-2.9 (-6.6 to 0.8)	0.12
MSQoL-54					
Physical health	3	51.4 (31.2)	52.8 (27.4)	6.9 (2.8 to 11.0)	0.001
	9	54.3 (33.1)	51.9 (28.8)	2.9 (-1.5 to 7.3)	0.20
Role limit physical	3	40.2 (42.2)	47.1 (40.4)	7.6 (-1.9 to 17.2)	0.12
	9	39.4 (43.6)	39.6 (41.2)	-0.8 (-10.2 to 8.7)	0.88
Role limit emotional	3	64.1 (42.1)	70.6 (41.4)	7.7 (-4.9 to 20.2)	0.23
	9	61.0 (46.3)	67.4 (39.8)	4.8 (-8.2 to 17.9)	0.47
Pain	3	67.2 (26.6)	70.2 (25.9)	5.4 (0.5 to 10.2)	0.03
	9	64.0 (25.6)	64.5 (28.3)	1.0 (-4.2 to 6.2)	0.70
Emotional well being	3	54.3 (14.2)	60.2 (12.9)	7.3 (3.5 to 11.1)	<0.001
	9	66.2 (21.9)	71.4 (17.5)	5.9 (1.2 to 10.5)	0.01
Energy	3	38.1 (18.9)	53.2 (18.2)	13.6 (8.8 to 18.3)	<0.0001
	9	41.3 (18.3)	46.1 (19.4)	2.5 (-2.2 to 7.2)	0.29
Health perceptions	3	40.3 (20.0)	50.2 (24.0)	9.4 (4.7 to 14.1)	<0.001
	9	44.0 (19.5)	43.9 (19.7)	-1.4 (-6.7 to 3.9)	0.61
Social function	3	67.5 (25.0)	76.9 (21.3)	8.9 (4.2 to 13.5)	<0.0001
	9	65.8 (25.1)	74.1 (21.7)	7.1 (2.2 to 12.0)	0.004
Cognitive function	3	67.6 (21.1)	67.0 (27.4)	4.4 (-0.2 to 9.0)	0.06
	9	69.9 (22.9)	66.4 (27.8)	1.1 (-4.0 to 6.2)	0.68
Health distress	3	61.8 (26.9)	68.7 (24.9)	11.5 (6.6 to 16.4)	<0.001
	9	63.2 (25.8)	61.6 (26.4)	1.3 (-4.5 to 7.0)	0.67
Sexual function	3	70.4 (29.4)	74.1 (30.3)	7.5 (1.3 to 13.7)	0.02
	9	69.4 (29.6)	71.8 (25.9)	4.2 (-2.9 to 11.2)	0.25
Change in health	3	44.5 (22.2)	62.0 (24.5)	17.6 (10.9 to 24.4)	<0.0001
	9	47.3 (20.3)	50.0 (21.9)	3.0 (-3.8 to 9.9)	0.39
Sex satisfaction	3	51.6 (33.5)	64.1 (27.7)	9.8 (2.3 to 17.3)	0.01
	9	56.9 (31.0)	58.0 (25.2)	0.19 (-7.7 to 8.1)	0.96
Overall quality of life	3	60.6 (19.2)	68.1 (20.3)	9.9 (6.3 to 13.5)	<0.0001
	9	60.4 (21.1)	65.9 (20.1)	6.7 (2.6 to 10.7)	0.001
Physical health component	3	52.5 (21.4)	59.7 (20.6)	9.0 (5.6 to 12.4)	<0.0001
	9	53.3 (21.1)	54.1 (21.7)	2.0 (-2.0 to 6.0)	0.32
Mental health component	3	60.8 (20.0)	65.5 (20.2)	7.3 (2.6 to 12.0)	0.002
	9	63.8 (24.1)	65.9 (21.0)	3.5 (-2.1 to 9.2)	0.22
MSFC					
25-ft walk test (s)	3	9.9 (16.4)	6.7 (4.1)	-1.4 (-3.0 to 0.2)	0.09
	9	8.8 (10.8)	7.2 (4.7)	0.4 (-1.0 to 1.9)	0.58
9-Hole pin test DH average	3	25.2 (7.4)	26.4 (13.1)	-0.6 (-1.7 to 0.5)	0.26
	9	25.8 (10.5)	26.9 (14.7)	-1.5 (-3.0 to 0.1)	0.06
9-Hole pin test NDH average	3	28.4 (14.8)	26.8 (7.8)	-0.6 (-1.8 to 0.6)	0.30
	9	29.4 (14.9)	27.0 (7.7)	-0.7 (-1.7 to 0.4)	0.21
PASAT	3	46.0 (13.7)	41.9 (15.0)	-1.8 (-4.4 to 0.8)	0.17
	9	46.9 (13.9)	47.4 (9.9)	2.3 (-0.4 to 5.0)	0.10
Six-minute walk test (m)	3	398 (152)	406 (128)	13 (-6 to 31)	0.18
	9	382 (169)	394 (137)	18 (-9 to 46)	0.20

MFIS: Modified Fatigue Impact Scale; MSQoL-54: MS quality of life-54; MSFC: Multiple Sclerosis Functional Composite; PASAT: Paced Auditory Serial Addition Test; DH: dominant hand; NDH: non-dominant hand; 95% CI: 95% confidence intervals; values are presented as mean (\pm SD), with difference scores adjusted for baseline, gender and Expanded Disability Status Scale (EDSS).

Table 5. Anthropometric, blood pressure and EDSS scores at three- and nine-month follow-ups in participants allocated to usual care only and usual care plus EXIMS.

	Follow-up time point (months)	Usual care group mean (SD)	EXIMS group mean (SD)	Difference in adjusted means (95% CI)	Bootstrapped p value
Body mass (kg)	3	77.0 (15.6)	79.1 (18.0)	0.4 (-0.8 to 1.5)	0.52
	9	77.3 (15.6)	78.8 (18.7)	0.1 (-1.2 to 1.5)	0.88
BMI (kg/m ²)	3	27.2 (5.9)	28.0 (5.2)	0.2 (-0.3 to 0.7)	0.51
	9	27.2 (6.1)	28.0 (5.5)	0.3 (-0.4 to 1.0)	0.40
Waist circumference (cm)	3	90.9 (14.0)	90.5 (14.3)	-1.4 (-2.8 to 0.1)	0.07
	9	91.3 (14.2)	90.5 (14.7)	-2.0 (-3.7 to -0.2)	0.03
Waist:Hip ratio	3	0.85 (0.09)	0.85 (0.09)	-0.002 (-0.02 to 0.01)	0.71
	9	0.85 (0.09)	0.84 (0.09)	-0.01 (-0.02 to 0.002)	0.10
Systolic blood pressure (mm Hg)	3	129.6 (18.4)	125.6 (13.0)	-1.1 (-4.0 to 1.7)	0.44
	9	127.2 (16.4)	124.8 (13.6)	0.1 (-3.1 to 3.3)	0.94
Diastolic blood pressure (mm Hg)	3	83.0 (10.7)	81.9 (8.6)	-1.1 (-3.2 to 0.9)	0.28
	9	83.8 (10.1)	81.5 (8.6)	-2.3 (-4.6 to -0.1)	0.04
EDSS	3	3.9 (1.6)	3.5 (1.3)	-0.1 (-0.4 to 0.2)	0.41
	9	3.9 (1.7)	3.7 (1.5)	-0.1 (-0.4 to 0.2)	0.36

EXIMS: pragmatic EXercise Intervention for people with MS; BMI: body mass index; EDSS: Expanded Disability Status Scale. Values are presented as mean (\pm SD), with difference scores adjusted for baseline, gender and EDSS.

Discussion

This was the first robustly designed randomised controlled trial to investigate the effects of a practically implemented progressive exercise programme on self-directed exercise behaviour and important health outcomes in PwMS up to nine months of follow-up. Significant increases in self-reported exercise behaviour (GLTEQ) and step counts were observed in the intervention group versus controls at three months. A smaller difference in GLTEQ score (6.9 points, 95% CI: -0.9 to 14.7) in favour of the intervention group was also apparent after nine months, though this was not statistically significant and there was no evidence of a sustained increase in step counts at this time point.

Whilst the GLTEQ is reported to be a valid measure of habitual exercise behaviour in PwMS,¹⁵ the possibility that self-reporting bias explains the discrepancy between GLTEQ scores and accelerometry step counts at nine months cannot be overlooked. However, difficulties interpreting accelerometer step-count data in PwMS have been highlighted,²³ and activities such as stationary cycling, seated upper-body exercise,

gardening and swimming can go undetected when using accelerometry. Although body weight remained unchanged, evidence of a reduction in waist circumference at both follow-up time points (non-significant at three months) and the reduction in diastolic blood pressure at nine months provides support for the maintenance of physical activity in the exercise group. These findings also show that the exercise intervention had an important impact on risk factors for cardiovascular disease. Hence, the apparent discrepancy between GLTEQ score and accelerometry step counts may reflect a shift to predominantly undetectable non-ambulatory activities over the study follow-up period, but this needs to be verified by future research. Despite this, our results suggest that the magnitude of change in self-directed exercise behaviour at nine months was reduced and was less clinically relevant.

The exercise group experienced improvements in multidimensional fatigue and in most HRQoL dimensions at three months. These improvements are consistent with previous systematic reviews,^{24,25} although some conflicting evidence also exists.^{26,27} Fatigue negatively affects HRQoL²⁸ and has a major impact on the high levels of unemployment in PwMS,²⁹ with $\geq 75\%$ of the MS population experiencing symptoms persistently or sporadically.³⁰ For these reasons, pragmatic interventions that can alleviate fatigue are likely to have an important impact on HRQoL and ability to remain in employment. Baseline fatigue scores in the exercise group were positively associated with EDSS scores at baseline and the reduction in symptoms observed at the three-month follow-up. This suggests that PwMS experiencing the highest levels of fatigue also experienced the greatest improvements with exercise training. However, higher volumes of supervised aerobic exercise were associated with less pronounced reductions in fatigue, suggesting that there could be an optimum level of aerobic exercise for symptom relief in PwMS. The changes in fatigue and GLTEQ scores were unrelated.

Improvements in emotional well-being, social function and overall HRQoL were maintained to nine months in the exercise group (versus controls), whereas the difference between groups in other HRQoL domains and fatigue was diminished at the final follow-up. The lack of a sustained improvement in other HRQoL domains and fatigue might be explained by a reduction in self-directed exercise over the follow-up period. Although previous studies suggest that short-term exercise interventions can have lasting effects on fatigue and HRQoL up to three months,^{2,31,32} continued engagement in exercise is likely to be needed for the longer-term enhancement of many HRQoL dimensions and MS fatigue. A higher level of contact with participants after the intervention period could have been used to provide additional support and motivation for self-directed exercise. Although this has resource implications, our results suggest that strategies for maintaining contact with participants after an initial period of supervision (e.g. posted literature, mobile phone text messaging, social media, etc.) warrant further investigation.

There were no changes in measures of functional ability (6MWT) or neurological impairment (EDSS and MSFC) and these results are consistent with some^{4,26,31,33,34} but not all previous exercise intervention studies.^{3,26,27} Evidence suggests that regular exercise may be more effective in retarding disease progression in PwMS,³⁵ rather than reversing the neuropathological changes that underpin neurological and functional impairments.³⁶

A key limitation of the study is that it included ambulatory participants with only mild to moderate disease (EDSS ≤ 6.5) and at the present time, the effectiveness of exercise interventions for people with more severe disability is unknown. Many eligible PwMS declined to take part in the study without giving a reason (N = 126; 66%) and a more comprehensive understanding of the barriers and facilitators to exercise in PwMS could be used to inform the design of future programmes. In the remaining 34%, unwillingness to travel, other commitments, not being interested in exercise and

worries about losing welfare benefits were cited as the reasons for not taking part. At least 30 potentially eligible PwMS considered the distance too far to travel (Figure 1), hence, providing the supervised component in a broader range of community settings may help to engage more PwMS in exercise programmes.

In conclusion, the observed improvements in self-directed exercise behaviour, HRQoL and fatigue suggest that EXIMS could be an effective way to practically implement progressive exercise rehabilitation within health care settings. EXIMS provides a tailored programme of preferred supervised and home-based exercises that are appropriate for individuals with different physical abilities and the level of uptake (39%) and high level of adherence (>80%) provides evidence that it is accessible to many PwMS. This study recruited participants with a range of neurological impairment (EDSS: 1.0–6.5), suggesting the results can be generalised to a broad spectrum of ambulatory PwMS. Strategies for promoting continued contact between participants and exercise practitioners beyond the initial period of supervision, however, may be needed to maintain meaningful improvements in important health outcomes.

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