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Research article

Feasibility and Effects of Structured Physical Exercise Interventions in Adults with Relapsing-Remitting Multiple Sclerosis: A Pilot Study

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Abstract

Multiple sclerosis (MS) is a chronic neurological disease which affects young adults at a time of maximum personal, professional and social growth. Recent guidelines on physical activity have established that exercise is an essential component of the clinical management of people with MS with mild or moderate degree of disability. The main purpose of this study was to test the feasibility and the effects of two different 40-week structured physical exercise interventions (a supervised high intensity interval training plus home exercise program and a self-applied home-based exercise program) on clinical evolution, psychological wellbeing, quality of life, fatigue, cardiorespiratory fitness, strength and balance of people with MS. Twenty-nine participants with relapsing-remitting MS (RRMS) participated in this study. All of them were fully ambulatory and with minimal disability (Expanded Disability Status Scale <3), for at least the last six months. Participants selected to be part of a combined face-to-face plus home exercise group (CFTFG; n = 8); a self-applied home-based exercise group (HG; n = 11) or a control group (CG; n = 10). A total of 23 participants completed the protocol (79.3%), of which 8 participants (100%) from the CFTFG, 7 (63.6%) from the HG and 8 (80%) from the CG. During the first 20-weeks of training, adherence from the CFTFG reached 77.5% and from the HG reached 50 %. During the second 20-weeks of training, adherence from the CFTFG reached 62.5% and from the HG reached 45.4%. After 20-weeks of training, a significant improvement in the absolute VO_2 peak and in the 30-second sit to stand test was observed in the CFTFG (all $p < .05$). This study confirms that offering a 40-week structured exercise programme to a group of fully ambulatory and minimally disabled persons with RRMS is feasible and safe. Any adverse event related to the trial was reported by the participants.

Key words: Multiple sclerosis; disability; exercise; quality of life; physical fitness.

Introduction

Multiple sclerosis (MS) is a chronic neurological disease which affects young adults at a time of maximum personal, professional and social growth (Mayo et al., 2013). The most common symptoms in MS are muscle weakness, spasticity, excessive fatigue, depression and anxiety, associated with neurodegenerative processes that can generate a vicious cycle of reduced mobility and decreased physical activity (White and Castellano, 2008). The reduction in physical activity increases the risk of secondary diseases such as obesity or cardiovascular disease (Borkoles et al., 2008). At the psychological level, symptoms reduce participation in activities of daily living and thus affect leisure and social relations (Wójcicki et al., 2014). Symptoms may appear suddenly, have a variable course and severity, and may have a devastating effect on health and quality of life over time (Latimer-Cheung et al., 2013; Mayo et al., 2013).

Technological advances to diagnose MS and the emergence of new treatments have helped to improve some forms of the disease course (Miller and Rhoades, 2012). Together with these developments, there is a clear need for strategies that allow patients to enjoy the highest possible quality of life, in accordance with their personal characteristics and with the evolution of the disease. In this regard, it has been suggested that the early initiation of an active lifestyle and exercise in patients with MS could promote neuroprotection, neuroregeneration and neuroplasticity (White and Castellano, 2008).

People with MS present impairments in functional capacity due both to the irreversible effects of the disease and to the reversible effects caused by an inactive lifestyle (Dalgas et al., 2008). However, previous studies have shown that MS patients tolerate exercise well (Padgett and Kasser, 2013); programmed physical exercise is a safe and efficient way of improving quality of life in these patients (Dalgas et al., 2008), optimizing daily functioning and enhancing their participation in different areas of daily life (Padgett and Kasser, 2013). Thus, physical exercise has been proposed as an essential component in clinical management in MS patients (Motl et al., 2011). Recently, the American College of Sports Medicine (American College of Sports Medicine, 2017) has recommended that adults with minimal disability (EDSS 0-2.5) should perform aerobic exercise 3-5 days/week, resistance exercise 2 days/week and flexibility exercise 5-7 days/week.

The aims of this study were to: 1) determine the feasibility of delivering two different structured physical exercise interventions in MS patients [(i) a combined face-to-face high-intensity interval training (HIIT) plus home exercise program and (ii) a home-based exercise program], and 2) assess the effects of these interventions on the clin-

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ical evolution, psychological wellbeing, quality of life, fatigue, cardiorespiratory fitness, strength and balance in MS patients.

Methods

Study design and participants

The study sample comprised 29 participants (21 women and 8 men) with relapsing-remitting multiple sclerosis (RRMS), fully ambulatory and with minimal disability [Expanded Disability Status Scale (EDSS) <3], within the previous six months (Figure 1). All participants read the patient information sheet and provided signed informed consent prior to enrolment. Then, patients opted to join one of the following three groups: the combined face-to-face group (CFTFG), which combined supervised face-to-face HIIT training at the health centre with unsupervised training at home; the home-based exercise group (HG), which followed a home-based physical exercise program delivered by e-mail; or the control group (CG), which did not train. This study follows the Helsinki guidelines for ethical behaviour and was approved by the Clinical Research Ethics Committee of the University Hospital Bellvitge (PR350/13).

The groups followed distinct schedules throughout the 40-weeks of the study. While the CG continued their usual pharmacological treatment and the same lifestyle, the CFTFG and HG continued their usual pharmacological treatment but also participated in physical exercise programs. These programs encouraged CFTFG and HG participants to include exercise in their daily lives in order to improve their physical and functional capacities. The programs also educated patients in the practice of physical exercise in accordance with their abilities and needs. In addition, the exercise programs were developed to improve the health-related physical fitness components, prioritizing endurance and strength training (Appendix 1, 2 and 3).

CFTFG: during the first 20 weeks, supervised sessions were performed twice per week and were carried out at the health centre while 4 sessions were carried out at home. The duration of the supervised session was 1.5 hours and the duration of the home session incremented from 15 min (weeks 1 to 4) to 1.5 hours (weeks 17 to 20). During the second 20-weeks period, participants exercised independently at home (Figure 2).

HG: the home-based exercise group performed 6 training sessions per week at home throughout the duration of the study (40 weeks). The duration of each session was 1.5 hours. During the first four weeks the participants attended one weekly session at the health centre where they were taught the exercises that formed the basis of the program. After these four weeks, they attended two more refresher sessions (weeks 12 and 20). From week 20 onwards they continued exercising independently at home (Figure 2).

Each participant from CFTFG and the home-based exercise group received a fit ball (O'Live Fitness Ball ®. Aerobic & Fitness. Barcelona. Spain) and two latex exercise bands with different levels of resistance (Thera-Band ® The hygienic Corporation. Akron. OH).

During the first 20 weeks, the aerobic training during the face-to-face sessions of the CFTFG group included HIIT on a stationary bicycle. The training load was adjusted according to the results obtained on a test carried out every four weeks, at an intensity of 17/18 on the Borg scale (Borg, 1990). Participants were able to achieve these intensities when training at home. The HIIT was complemented with aerobic sessions at an intensity of 13-15 on the Borg scale. In the HG, the intensity increased from 50% to 85% of the maximum age-predicted heart rate.

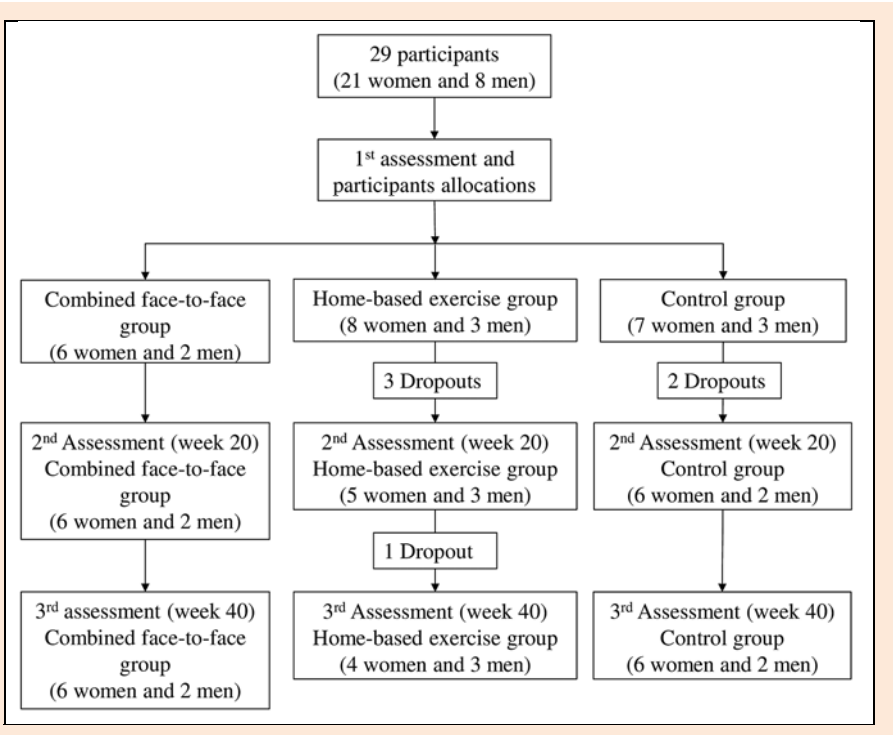

Figure 1. Flowchart showing the study process.

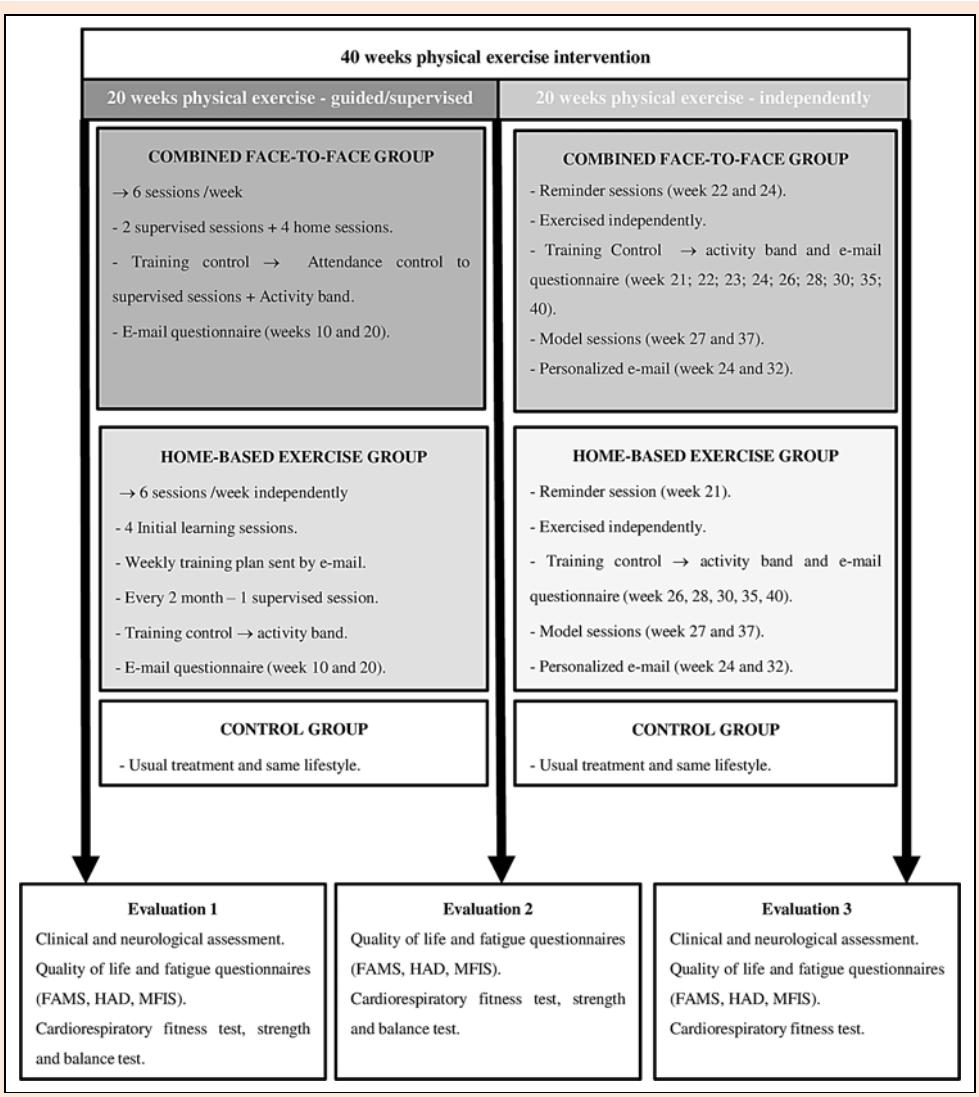

Figure 2. **Design of 40 weeks physical exercise intervention.**

In both groups, the strength training was carried out using two latex exercise bands (red or green) (Thera-Band ® The Hygenic Corporation. Akron. OH) and/or body-weight resistance exercise. These exercises developed the large muscle groups of the trunk and the lower and upper limbs. The endurance and strength training was complemented with exercises for joint mobility, balance (mainly static), stretching exercises and body awareness work.

During these 40 weeks, attendance at the sessions and meetings was recorded in both groups, and the home sessions were monitored by the use of an activity band (Polar Loop. Polar Electro. Finland). Additional information was also obtained from e-mail questionnaires (Google forms. Google Inc. Mountain View. California).

Testing procedures

All participants underwent three evaluations: the first prior to start the intervention (E1), the second after 20 weeks (E2) and the third after 40 weeks (E3). These evaluations comprised clinical and neurological assessments, quality of life and fatigue scales [the Modified Fatigue Impact Scale (MFIS)], Hospital Anxiety and Depression scale (HAD) and Functional Assessment of Multiple Sclerosis (FAMS), and a maximal cardiorespiratory fitness test. Lower limb strength and balance test were assessed prior to the intervention and after 20-weeks.

Anthropometric measurements

Height was measured to the nearest 0.1 cm by using a stadiometer (Seca 225, Seca, Hamburg, Germany).Weight was measured to the nearest 0.1 kg on a digital scale (Tanita MC-780U, Arlington Heights, IL, USA) with the participants wearing light weight clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Clinical and neurological assessments

The participants' neurological impairment and degree of disability were assessed with the EDSS and the number of acute exacerbations of MS symptoms.

Feasibility evaluation criteria

Feasibility was measured as the adherence to the exercise program, and completion rates to the program. Adherence represented the percentage of participants who performed the programmed sessions. Completion rate represents the

percentage of participants out of the total participants that completed the study.

Questionnaires

Psychological wellbeing: The 14-item HAD questionnaire measures the degree of anxiety and depression. HAD has often been used in patients with chronic fatigue syndrome (McCue et al., 2006).

Fatigue: The 21-item MFIS (Fisk et al., 1994) questionnaire is based on interviews with MS patients concerning the impact of fatigue on their lives.

Quality of life: The FAMS is a multidimensional self-report scale designed specifically to measure the quality of life of people with MS. Each participant was assessed by means of the Spanish version of the FAMS scale (Chang et al., 2002).

Cardiorespiratory fitness test

All tests were conducted in the morning at a room temperature of 22 to 24 ºC and a relative physical humidity of 55 to 65%. The participants were tested on a precalibrated cycle ergometer (Excalibur, Lode, Groningen, the Netherlands), cycling at 50 rpm. After a 4-min period cycling at 0 W, participants followed a 20 W/min ramp protocol up to exhaustion. VO_2peak (L/min), relative VO_2peak (ml/kg/min) and respiratory exchange ratio (RER) were measured through breath-by-breath with an automatic gas analysis system (Metasys TR-plus, Brainware SA, La Valette, France) equipped with a pneumotachometer and using a two-way mask (Hans Rudolph, Kansas, USA). Gas and volume calibrations were performed before each test, according to the manufacturer's guidelines.

A 12-lead electrocardiogram and heart rate (HR) were monitored continuously during the test (CardioScan v.4.0, DM Software, Stateline, Nevada, USA).

The 30-second sit to stand test

The participants were asked to sit down and stand upright as often as possible for 30 s without using their hands. The instructors did not record the result if participants could not stand up from a chair without supporting themselves with their arms on arm rests, knees, or walking aid (after attempts of the test instructor to motivate participants to do so). In the general older population, it was found that the 30-s sit to stand test is a reliable and valid measure of lower body strength (Jones et al., 1999).

Balance measurements

Postural sway was assessed with a pressure platform (Podoprint Balance Platform, Namrol, Barcelona, Spain). All participants performed a double leg stance with eyes open and eyes closed. They were instructed to stand erect on the platform with no shoes, motionless and with the arms by their sides. Heels were separated by 3 cm and toes formed a 30º angle. The software requires each participant to maintain this position for 52 s. Three trials were performed with a 60 s rest between them. Total travel distance (TTD), radial area (RA), mean mediolateral (MLD) and mean antero-posterior (APD) displacements of the center of pressure (COP) were measured at a frequency of 100Hz using manufacturer's specific software (PodoPrint v 2.6, Namrol, Barcelona, Spain).

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normality of the distribution of all variables. For the categorical variables, chi-square tests were employed to detect group differences. For the continuous variables, linear mixed-effect models were used to assess between and within groups effects with Bonferroni post hoc tests.

All data are reported as means and standard error of the mean (SEM) unless otherwise specified. Statistical significance was set at $p < 0.05$. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 19.0 (IBM SPSS Statistics, Chicago, IL, USA).

Results

The characteristics and anthropometric measurements of the 29 participants are presented in Table 1.

Expanded disability status scale

In the clinical follow-up, none of the groups presented changes on the EDSS. The number of acute exacerbations of MS symptoms between the year prior to the study and the first year of follow-up fell by 40% in the CFTFG; there were no relapses in the HG, compared with 12.5% in the CG (Table 2).

Table 1. Participants' characteristics. Values are mean (Standard Error of Mean).

Variables	CFTFG			HG			CG		
	E1	E2	E3	E1	E2	E3	E1	E2	E3
Age (yrs)	42 (1)	42 (1)	42 (1)	42 (1)	42 (1)	43 (1)	42 (1)	43 (1)	43 (1)
Height (m)	1.67 (.03)	1.67 (.03)	1.67 (.03)	1.69 (.03)	1.69 (.03)	1.69 (.03)	1.63 (.03)	1.63 (.03)	1.63 (.03)
Weight (kg)	72.8 (4.9)	74.1 (4.9)	72.9 (4.9)	74.7 (4.6)	72.7 (4.6)	71.7 (4.7)*	63.1 (4.6)	63.8 (4.6)	62.8 (4.7)
BMI	26.1 (1.7)	26.8 (1.7)	26.2 (1.7)	26.2 (1.6)	25.4 (1.6)	25.1 (1.6)*	23.6 (1.6)	23.8 (1.6)	23.5 (1.6)

CFTFG (combined face-to-face group); HG (home-based group); CG (control group); E (evaluation); BMI (body mass index). * Significant differences ($p < 0.05$) when compared to E1.

Table 2. Changes experienced at the clinical follow-up by the patients participating in the study.

Variables	Expanded Disability Status Scale Mean - median (min; max)		% of patients affected by new acute exacerbations in a year *	
	Start of study	End of study	prior to the study	during the study
Combined face-to-face group	1.3 – 1.5 (0; 2)	1.4 – 1.5 (0; 2)	40	20
Home-based exercise group	1.7 – 1.5 (1; 2.5)	1.7 – 1.5 (1; 2.5)	0	0
Control group	1.6 – 1.5 (1; 2.5)	1.63 – 1.75 (1; 2.5)	0	12.5

* Between-groups differences ($\chi 2 = 11.1$, $p = 0.025$)

Table 3. Participants' scores on the HAD, MFIS and FAMS scales throughout the study. Values are mean (Standard Error of Mean).

Variables	CFTFG			HG			CG		
	E1	E2	E3	E1	E2	E3	E1	E2	E3
HAD									
Anxiety	15.3 (1.2)	14.6 (1.2)	14.8 (1.2)	14.5 (1.2)	14.2 (1.3)	16.2 (1.3)	14.6 (1.1)	14.1 (1.2)	14.8 (1.2)
Depression	15.3 (1.1)	16.6 (1.1)	16.6 (1.1)	17.4 (1.1)	17.2 (1.2)	17.8 (1.2)	18.2 (1.1)	18.2 (1.1)	18.1 (1.1)
MFIS									
Physical subscale	17.9 (3.2)	15.0 (3.2)	14.5 (3.2)	14.9 (3.2)	14.0 (3.3)	12.8 (3.3)	9.4 (3.0)	12.1 (3.2)	9.9 (3.1)
Cognitive subscale	12.5 (2.5)	12.3 (2.5)	10.8 (2.5)	8.6 (2.5)	8.8 (2.6)	7.9 (2.6)	6.9 (2.4)	9.6 (2.5)	8.0 (2.4)
Psychosocial subscale	1.5 (.7)	2.9 (.7)	2.6 (.7)	2.6 (0.7)	1.8 (.8)	1.7 (.8)	1.3 (.7)	1.8 (.8)	1.7 (.7)
Total MFIS	31.9 (5.2)	30.1 (5.2)	27.9 (5.2)	26.1 (5.2)	24.4 (5.4)	22.3 (5.4)	17.7 (4.9)	23.5 (5.2)	19.7 (5.1)
FAMS									
Mobility	21.8 (1.8)	21.9 (1.8)	22.4 (1.8)	21.1 (1.8)	22.1 (1.8)	21.7 (1.8)	22.7 (1.7)	22.7 (1.8)	23.0 (1.7)
Symptoms	20.5 (1.7)	21.8 (1.7)	22.6 (1.7)	21.1 (1.7)	23.7 (1.7)	23.0 (1.7)	23.2 (1.6)	22.3 (1.6)	21.9 (1.6)
Emotional Well-Being	22.3 (1.6)	21.6 (1.6)	22.9 (1.6)	23.3 (1.6)	23.1 (1.7)	24.0 (1.7)	25.1 (1.5)	25.7 (1.7)	24.1 (1.6)
General Contentment	20.3 (1.5)	20.9 (1.5)	20.9 (1.5)	20.4 (1.5)	21.1 (1.5)	22.3 (1.5)	23.2 (1.4)	22.4 (1.5)	21.8 (1.4)
Thinking and Fatigue	19.3 (2.6)	21.6 (2.6)	19.3 (2.6)	26.0 (2.6)	24.8 (2.7)	25.9 (2.7)	24.6 (2.5)	27.0 (2.6)	24.4 (2.5)
Family/Social Well-Being	22.4 (1.3)	21.6 (1.3)	21.1 (1.3)	22.8 (1.3)	24.2 (1.3)	24.6 (1.3)	25.6 (1.2)	24.6 (1.3)	24.5 (1.2)
Total FAMS	126.4 (7.7)	129.4 (7.7)	129.1 (7.7)	134.6 (7.7)	138.9 (7.9)	141.5 (7.8)	144.3 (7.2)	144.8 (7.6)	139.7 (7.4)

CFTFG (combined face-to-face group); HG (home-based group); CG (control group); E (evaluation); HAD (Hospital Anxiety and Depression scale); MFIS (Modified Fatigue Impact Scale); FAMS (Functional Assessment of Multiple Sclerosis).

Feasibility

Twenty-three out of 29 participants (79.3%) completed the protocol, 15 of them (78.9%) were members of the physical exercise groups (HG and CFTFG) (Figure 2). Seven participants (63.6%) from the HG and all the participants from the CFTFG completed the 40-week exercise program (p = 0.05).

Adherence from the CFTFG during the first 20 weeks of the supervised sessions (2 sessions/week) reached 77.5%, while in the unsupervised sessions (4 per week) adherence rate was 30%. During the same period, adherence rate of the HG to the program reached 50%.

During weeks 20 to 40, 5 participants from the HG (45.4%) and 5 participants from the CFTFG (62.5%) kept training independently 2 to 6 times a week (p > 0.05). Seven participants from the exercise groups (36.8%) continued training 3 or more times a week during the unsupervised period (weeks 20 to 40), with significant differences between the active groups vs. control group (p = 0.013, statistical power = 75.6%).

The two exercise programs implemented in the present study were safe, well tolerated by all participants and the programs were not related to adverse events.

Questionnaires

No significant within or between group differences were observed throughout the intervention for the HAD; MFIS and FAMS questionnaires (Table 3).

Cardiorespiratory fitness test

No differences were observed between the study groups in terms of peak values. However, a significant difference was observed for absolute VO_2 (L/min) mean values between E1 vs. E2 in the CFTFG ($p = 0.034$, statistical power > 95%) (Table 4).

At ventilatory threshold 1, the CFTFG presented differences in oxygen consumption (p = 0.002) which improved by 3.2 ml/kg/min (95% CI = 4.6 - 1.8; p = 0.006) between the second and the third evaluations; in contrast, oxygen consumption fell in the HG (p = 0.049).

At ventilatory threshold 2, differences in oxygen consumption with regard to the workload were observed (p = 0.047); oxygen consumption fell in the HG between the first and third assessments by 0.07 ml/watt (95% CI 0.03 - 0.12; p = 0.016), but increased in the CFTFG by 29.7 ml/watt (95% CI 55.1 - 4.2, p = 0.032).

The 30-second sit to stand test

In the 30-second sit to stand test, the CFTFG obtained a significant improvement when comparing E2 vs. E1 (p = 0.002; improvement of 33.3%, statistical power > 95%) during the supervised exercise period (weeks 1 to 20). Also, the results obtained by the CG were significantly higher during the E2 than during the E1 (p = 0.026; improvement of 15.3%, statistical power = 75.5 %) (Figure 3).

Table 4. Maximal cardiorespiratory test data for participants from the three groups at each evaluation (baseline: Evaluation 1; after 20 weeks: Evaluation 2; and after 40 weeks: Evaluation 3). Values are mean (Standard Error of Mean).

Variables	CFTFG			HG			CG		
	E1	E2	E3	E1	E2	E3	E1	E2	E3
VO_2 peak (L/min)	1.82 (.20)	2.21 (.21)*	1.91 (.22)	2.07 (.19)	1.85 (.20)	1.71 (.23)	1.71 (.19)	1.65 (.22)	1.33 (.23)
VO_2 peak (ml/kg/min)	26.4 (2.7)	28.7 (2.9)	27.6 (3.0)	28.1 (2.6)	24.6 (2.7)	23.8 (3.1)	27.8 (2.5)	26.8 (2.9)	23.4 (3.1)
VCO_2 (L/min)	2.02 (.22)	2.25 (.24)	2.06 (.25)	2.21 (.21)	1.91 (.23)	1.72 (.26)*	1.80 (.21)	1.62 (.25)	1.44 (.26)
RER	1.10 (.03)	1.02 (.03)*	1.07 (.03)	1.07 (.03)	1.03 (.03)	1.01 (.04)	1.04 (.03)	.99 (.03)	1.09 (.04)**
Peak HR (beat/min)	150 (7)	157 (7)	160 (8)	153 (7)	149 (7)	143 (9)	155 (6)	145 (8)	147 (9)
$VEqO_2$	33.9 (1.6)	30.3 (1.7)*	35.3 (1.8)**	33.1 (1.5)	32.8 (1.6)	30.4 (1.9)	32.3 (1.5)	31.5 (1.8)	33.5 (1.9)
$VEqCO_2$	31.0 (1.0)	29.3 (1.2)	32.1 (1.2)	30.9 (1.0)	31.4 (1.1)	30.5 (1.3)	31.1 (1.0)	31.6 (1.2)	30.0 (1.3)

CFTFG (combined face-to-face group); HG (home-based group); CG (control group); E (evaluation); VO_2 peak (peak oxygen uptake); VCO_2 (carbon dioxide production); RER (respiratory exchange ratio); HR (heart rate); $VEqO_2$ (ventilatory equivalent for O_2); $VEqCO_2$ (ventilatory equivalent for CO_2). * Significant differences ($p < 0.05$) when compared to E1. ** Significant differences ($p < 0.05$) between E2 vs E3.

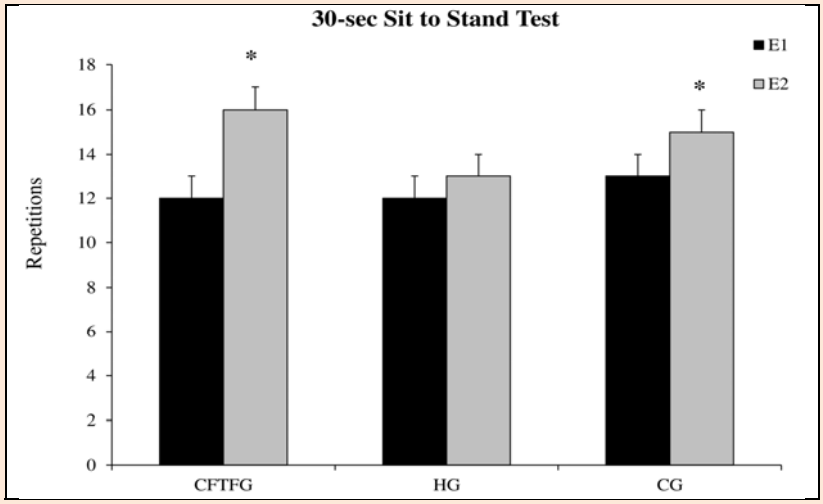

Figure 3. Evolution of the lower limb strength along the intervention in the combined face-to-face group (CFTFG); Home-based group (HG) and Control group (CG) during evaluation 1 (E1) and evaluation 2 (E2). * Statistical differences between E1 vs. E2 ($p < 0.05$).

Table 5. Static balance data for participants from the three groups at each evaluation (baseline: Evaluation 1; after 20 weeks: Evaluation 2; and after 40 weeks: Evaluation 3). Values are mean (Standard Error of Mean).

	CFTFG		HG		CG	
Variables	**E1**	**E2**	**E1**	**E2**	**E1**	**E2**
Balance: Opened Eyes						
COP TTD (mm)	167.0 (18.4)	177.9 (19.4)	146.1 (19.7)	159.2 (20.9)	165.3 (16.5)	224.8 (18.0)*
COP RA (mm^2)	177.8 (70.4)	208.7 (73.6)	158.4 (75.2)	160.3 (79.2)	155.8 (62.9)	199.8 (67.9)
COP APD (mm)	3.9 (.8)	3.8 (.8)	3.1 (.9)	3.2 (.9)	4.2 (.7)	4.7 (.8)
COP MLD (mm)	2.8 (.5)	2.4 (.5)	2.1 (.5)	2.0 (.6)	2.1 (.4)	1.8 (.5)
Balance: Closed Eyes						
COP TTD (mm)	200.1 (34.5)	203.1 (35.5)	239.0 (36.9)	253.7 (38.2)	201.3 (30.9)	230.1 (32.5)
COP RA (mm^2)	204.6 (67.0)	203.1 (70.1)	184.9 (71.6)	200.9 (75.5)	147.7 (59.9)	148.0 (64.7)
COP APD (mm)	3.0 (.9)	3.5 (.9)	4.2 (1.0)	4.0 (1.0)	3.2 (.8)	3.4 (.9)
COP MLD (mm)	3.3 (.5)	2.7 (.5)	2.1 (.5)	2.4 (.5)	2.4 (.4)	2.3 (.5)

CFTFG (combined face-to-face group); HG (home-based group); CG (control group); E (evaluation); COP (center of pressure); TTD (total travel distance); RA (radial area); APD (antero-posterior displacements); MLD (medio-lateral displacements). * Significant differences ($p < 0.05$) between E1 vs E2.

Balance

No significant intervention-related changes were observed in the active groups. The control group presented a slight deterioration, with higher TTD of the COP during the test with open eyes ($p = 0.004$, statistical power > 95%) (Table 5).

Discussion

This study confirms that offering two different 40-week structured exercise programs (HIIT plus home exercise program and a home-based physical exercise program) to a group of fully ambulatory and minimally disabled RRMS patients is feasible, safe and does not produce negative side effects. More than half of the participants continued training regularly and independently after the end of the supervised period of the intervention. In addition, the CFTFG improved the lower limb strength and the aerobic capacity after 20 weeks of exercise.

One of the main objectives of an exercise program designed for a chronic pathology is to achieve a satisfactory level of completion and adherence to the programs. The rate of completion in the current study (78.9%) is similar to that reported by Dalgas et al. (2009) in a shorter supervised intervention (12 weeks of training + 12 weeks of follow-up). In a one-year intervention in healthy sedentary women aged between 50 and 70 years, Cox et al. (2008) obtained a completion rate of ~80%, slightly higher than in the present study. In the current study there were four dropouts in the HG (three of them during the first 20 weeks) while in the CFTFG there were none during the 40 weeks. Different authors associated completion and adherence to exercise interventions with enjoyment of the activity and self-efficacy (Kasser, 2009; McAuley et al., 2007). The dropouts recorded in the HG in the initial phases of the program were not linked to any adverse event or relapse, perhaps reflecting the fact that training on their own may not be a source of enjoyment for sedentary people who already feel weak or fatigued due to the symptoms of their illness and their feelings of physical, psychological or social discomfort (McAuley et al., 2007). On the other hand, group training (i.e. the CFTFG) with people who are in a similar situation, and with whom one can share one's experiences and feelings, seems to promote the idea of exercise as a pleasurable activity and encourage participation over time (Gobbi and Carraro, 2016; Kasser, 2009; Motl et al., 2009).

Kasser (2009) suggests that interventions must be meaningful for participants if their goal is to increase adherence and chances of success.

Learmonth et al. (2012) reported that during their supervised intervention (12-week, 2 sessions/week) with aerobic, strength and balance exercise, the adherence rate to the intervention was 71%. In the current study, the adherence rate of the participants from the CFTFG during the first 20 weeks of the supervised sessions (2 sessions/week) reached 77.5%, while in the unsupervised sessions (3 to 4 a week) the adherence rate was 30%. Possibly, the supervised sessions at the health centre became a source of support; the exercise group seems to offer participants a chance to do something that was good for them as well as providing recreation and social interaction (Kasser, 2009). Learmonth and Motl (2016) identified peer support, the presence of a friendly monitor who is familiar with MS and who is a good motivator, and the feeling of being supervised by a health professional, as facilitators of improvement, and indeed all these aspects featured in the sessions organized for the CFTFG. According to the answers to the questionnaires and the activity band recordings, the adherence rate of the HG during the first 20 weeks of the program reached 50%, a figure well below the rate of 95% obtained by DeBolt and McCubbin (2004) in an 8-week intervention.

To our knowledge, our intervention is the longest of its kind carried out to date. During the unsupervised period of our program, (weeks 20 to 40), 62.5% of the CFTFG and 45.4% of the HG continued training between 2 and 6 times a week. After the 12-week intervention described by Dalgas et al. (2009), participants were encouraged to continue exercising but after a follow-up period of 12 weeks only 20% were found to have done so. Cox et al. (2008) obtained an adherence rate of approximately 64% (3 sessions/week) and reported that the longer the supervised program the greater the continuity over time. Longer supervised interventions make more varied programs possible and thus offer greater choice; they are more attractive, complete, and encourage longer-lasting participation (Asano et al., 2009).

The main difficulties mentioned by participants regarding regular training are the lack of time (that is, the difficulty in combining training with one's working or family life and in making it part of one's everyday routine), the boredom of training alone and, to a lesser extent, fatigue. These difficulties coincide partly with those recorded by Assano et al. (2013), who found fatigue to be the main reason for not training, and lack of time to be the third. These difficulties are also present among the general population. Interestingly, 53.3% of participants indicate that completion of a group session every week might be a feature that facilitates exercise.

During the first 20 weeks the CFTFG carried out two supervised exercise sessions, since there is evidence that moderate-intensity aerobic exercise and strength training twice a week improve functional capacity and muscle function respectively. Some studies also indicate that there may be benefits for mobility and fatigue, while little is known regarding its potential benefits on quality of life (Latimer-Cheung et al., 2013). Interestingly, recent studies suggest an effect of exercise on neuroplasticity. MS patients following moderate aerobic training have displayed volume changes in grey and white matter involved in motor and cognitive function (Klaren et al., 2015; Motl et al., 2015). These structural changes have also been associated with an improvement in learning and memory capacities (Leavitt et al., 2014; Sandroff et al., 2017).

In the present study, the CFTFG achieved significant changes in lower limb strength during the first 20 weeks of the program. These results suggest that at this stage of supervised exercise the intensities achieved were high enough to generate adaptations, whereas in the case of the HG the changes promoted were not significant, probably due to the difficulty to control accurately the volume and intensities during the home-based sessions (Dalgas et al., 2008). DeBolt and McCubbin (2004) suggest that people with MS training at home find it hard to reach a level of intensity that can bring about improvements in power and mobility. Supervision, on the other hand, seems to help participants achieve training intensities high enough to generate adaptations and ensures that the level of training increases appropriately. Platta et al. (2016) suggest that supervised interventions achieve better adherence to exercise prescriptions and increase the likelihood of positive adaptations to training.

During the first 20 weeks in the CFTFG, the sessions included high intensity stationary cycling, which may have improved lower limb strength, as suggested by Collett et al. (2011). In the current study, most of the sessions comprised high intensity interval training, working for 30 seconds at 17-18 RPE and 30 seconds at 11-12 RPE (20-point Borg scale) in three blocks which lasted three minutes at the beginning, and then four or five minutes after week 12. These blocks were combined with strength training and were carried out after warm-up periods and after completing balance and/or mobility training. The more progressive implementation of high intensity training inside a comprehensive framework of activity could explain why it was better tolerated than the high intensity exercise programs proposed by Collett et al. (2011). Between weeks 21 to 40, participants in the current study were encouraged to maintain these high intensity sessions through what were called "superdays" in which stationary cycling was replaced by fitball exercises involving the mobilization of the lower limbs in coordination with the upper limbs at high speed. Half of the participants said that they included one day of high intensity training in their routine; nonetheless the improvements were less marked, which suggested that they were not training at intensities high enough to obtain further improvements.

This study, designed to assess the feasibility and effects of exercise programs in MS, presents some limitations. In the first place, the small sample size (29 MS patients) may have reduced the study's statistical power. Secondly, we allowed participants to choose their group, and drop-outs over the course of the 40 weeks reduced the number of participants available for the study of the selected variables. However, the non-randomization of the sample may actually have been an advantage; according to Saarto et al. (2012), in studies with participants who are keen to improve their lifestyles it is difficult to monitor the mem-

bers of the control group, because they are quite likely to try to apply the measures that the intervention proposes. Another limitation is the timing of the program in relation to the time of year. The second evaluation took place two weeks after Christmas holidays, when there was a significant decrease in the levels of participation (especially in the CFTFG during the month of December). In addition, we did not monitor fatigue before and after each exercise session. Thus, future studies should analyse this outcome when applying the protocol proposed in the current study. Finally, we should mention that diet or other interventions such as massages or psychology were not controlled during the present study and should be taken into account when performing future studies.

The participants of the CFTFG were more clinically active (relapses in the year prior to this study) than the other patients at beginning of the intervention and the reason why there is a downward trend observed in the MFIS probably was a result of the pass of the time and conditioned by this initial higher activity. However, we could not identify significant changes among groups when evaluating anxiety or fatigue (HAD and FAMS scales). Further studies with larger sample sizes should be performed to give light the usefulness of exercise interventions on these items.

In the future, randomized controlled trials with a larger sample of participants with MS should be implemented in order to analyse the effects of these physical exercise programs on cardiorespiratory fitness, strength, balance and clinical evolution. Also, changes in QoL and fatigue scales during the implementation of these protocols may help researchers and practitioners to identify the types of intervention that are of greatest benefit.

Conclusion

Structured exercise programs are well tolerated by RRMS patients. Supervised interventions are able to retain more participants and facilitate high intensity exercise which is well tolerated if applied progressively and adapted to each individual. In view of this positive impact of supervised training, interventions should be designed to enhance the positive aspects of working in small groups, but also to improve the commitment of participants to perform unsupervised exercise sessions in order to maximize the benefits.

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Key points

- Structured exercise programs are well tolerated by patients with relapsing-remitting Multiple Sclerosis and no adverse events were related with the programs.
- Supervised interventions are able to retain more participants and facilitate high intensity exercise which is well tolerated if applied progressively and adapted to each individual.
- Physical exercise interventions should be designed to enhance the positive aspects of working in small groups, but also to improve the commitment of participants to perform unsupervised exercise sessions in order to maximize the benefits.

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APPENDIXES

Appendix 1. Combined face-to-face exercise program (20-weeks period).

Training Period 1								Training Period 2				Training Period 3							
Mesocycle 1				Mesocycle 2				Mesocycle 3				Mesocycle 4				Mesocycle 5			
W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	W 19	W 20
			T1				T2				T3				T4				T5
Borg's scale 12 – 13								Borg's scale 13 – 14											
Warm-up Balance training. Low intensity exercise: walking, joint mobility exercise. **Main part** High intensity interval training (HIIT). Strength training. Core training or aerobic training. **Cool-down** Stretching and body awareness work.																			
Endurance training Ss – 30 min cycling Hs – 45 min walking				**Endurance training** Ss – HIIT 3' x 3sets (rec 3') 3' (30" TR + 30%TR – 30" rec) – Cycling Hs – 60 min walking				**Endurance training** Ss – HIIT 4' x 3sets (rec 3') 4' (30" TR + 30%TR – 30" rec) – Cycling Hs – 75 min walking				**Endurance training** Ss – HIIT 5' x 3sets (rec 3') 5' (30" TR + 30%TR – 30" rec) – Cycling Hs – 85 min walking				**Endurance training** Ss – HIIT 5' x 3sets (rec 3') 5' (30" TR + 30%TR – 30" TR – 20%TR) – Cycling Hs – 90 min walking			
Strength training 12 – 15 rep x 2 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.				**Strength training** 10 – 15 rep x 3 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.				**Strength training** 10 rep x 4 – 5 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.				**Strength training** 10 rep x 4 – 5 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.				**Strength training** 10 rep x 5 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.			
Propioception training Balance training is present during all the program in de Ss. Body awareness work this kind of training appears in some Ss and in a weekly Hs.																			
Flexibility training Stretching is present in all the Ss and Hs. Joint mobility is present along the program but the volume of this kind of training decrease along the program.																			

W: week; T: test; TR: test result; Ss: supervised sessions; Hs: Home sessions; HIIT: High Intensity Interval Training; Min: minute; rec: recuperation; rep: repetition

Appendix 2. Home-based exercise program (20-weeks period).

Training period 1				Training period 2				Training period 3				Training period 4				Training period 5			
Mesocycle 1				Mesocycle 2				Mesocycle 3				Mesocycle 4				Mesocycle 5			
W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	W 19	W 20
Int 50-60	Int 50-60	Int 55-65	Int 55-65	Int 60-70	Int 60-70	Int 65-75	Int 65-75	Int 70-80	Int 70-80	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85
Warm-up: mobility; walking at different intensities; low intensities exercises (5-15min). **Strength training:** calisthenics exercises; resistance exercises with elastic bands. We focused on large muscle groups and antigravity muscle groups (2-3 sets of 8-15 repetitions; 10-20min). **Endurance training:** jogging, running, stepping, fit ball exercise (10-60 min). **Propioception training:** movements in diverse directions and on different surfaces; comparison eyes open/eyes close; single leg static balance, tandem and semi tandem positions (10-30 min) **Cool-down:** Stretching, joint mobility and body awareness work (5-15 min)																			

W: week; Int: Intensity (%); T: test; TR: test result; Ss: supervised sessions; Hs: Home sessions; HIIT: High Intensity Interval Training; Min: minute; rec: recuperation; rep: repetition.

Appendix 3. Independently physical exercise period (weeks 21 to 40).

	W21	W22	W23	W24	W25	W26	W27	W28	W29	W30	W31	W32	W33	W34	W35	W36	W37	W38	W39	W40
Google questionnaire (Q)	Q	Q	Q	Q		Q		Q		Q					Q					Q
Reminder sessions (RS)	RS	RS		RS																
Model Sessions (MS)							MS										MS			
Personalized e-mails (PM)				PM								PM								

Week (W) 20 → Participants received an exercise booklet and guidelines to carry out a self-administered physical exercise program. The participants received instructions to train three to six days a week between 15 to 90 minutes. Once a week the participants carry out a high intensity session (superday; 17-18 Borg's scale). The exercise booklet included: strength exercise, mobility and stretching exercise, balance exercise and instructions for aerobic training.

Reminder sessions (RS) → Structured sessions such as those that should be carried out at home (superday).

Google Questionnaires (Q) → They were used to control the training. Depending on the answers, they received different motivational messages and reminders of activities to be included in the sessions.

Model Sessions (MS) → It was found that the strength and high intensity training were the least present between the sessions that the participants carried out at home. Thus, model sessions were created to maintain the participants' interest on the exercise program and to maintain the strength and superday intensities.

Personalized e-mail → Each participant received a personalized e-mail where he/she was motivated to keep training and adjust the workloads intensities. These e-mails also reminded the importance of strength, balance, stretching, mobility and aerobic training. Also, it was highlighted the importance of intensity for further improvements.