MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Effects of an individual 12-week community-located "start-to-run" program on physical capacity, walking, fatigue, cognitive function, brain volumes, and structures in persons with multiple sclerosis

Multiple Sclerosis Journal

1–12

DOI: 10.1177/1352458517740211

Peter Feys, Lousin Moumdjian, Florian Van Halewyck, Inez Wens, Bert O Eijnde, Bart Van Wijmeersch, Veronica Popescu and Paul Van Asch

Correspondence to:
P Feys
Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Life Sciences, Hasselt University, REVAL/BIOMED, Agoralaan gebouw A, Diepenbeek 3590, Belgium.
Peter.Feys@uhasselt.be

Peter Feys
Florian Van Halewyck
Inez Wens
Bert O Eijnde
REVAL Rehabilitation Research Center, Faculty of Medicine and Life Science, Hasselt University, Hasselt, Belgium

Lousin Moumdjian
REVAL Rehabilitation Research Center, Faculty of Medicine and Life Science, Hasselt University, Hasselt, Belgium/IPEM Institute for Psychoacoustics and Electronic Music, Faculty of Arts and Philosophy, Ghent University, Ghent, Belgium

Bart Van Wijmeersch
Rehabilitation & MS Centre Overpelt, Overpelt, Belgium/FBI, BIOMED, Faculty of Life Sciences and Physiotherapy, Hasselt University, Hasselt, Belgium

Veronica Popescu
REVAL Rehabilitation Research Center, Faculty of Medicine and Life Science, Hasselt University, Hasselt, Belgium/Rehabilitation & MS Centre Overpelt, Overpelt, Belgium

Paul Van Asch
Fit Up, Physiotherapy Centre, Kontich, Belgium

Abstract

Background: Exercise therapy studies in persons with multiple sclerosis (pwMS) primarily focused on motor outcomes in mid disease stage, while cognitive function and neural correlates were only limitedly addressed.

Objectives: This pragmatic randomized controlled study investigated the effects of a remotely supervised community-located "start-to-run" program on physical and cognitive function, fatigue, quality of life, brain volume, and connectivity.

Method: In all, 42 pwMS were randomized to either experimental (EXP) or waiting list control (WLC) group. The EXP group received individualized training instructions during 12 weeks (3×/week), to be performed in their community aiming to participate in a running event. Measures were physical (VO_{2max}, sit-to-stand test, Six-Minute Walk Test (6MWT), Multiple Sclerosis Walking Scale-12 (MSWS-12)) and cognitive function (Rao's Brief Repeatable Battery (BRB), Paced Auditory Serial Attention Test (PASAT)), fatigue (Fatigue Scale for Motor and Cognitive Function (FSMC)), quality of life (Multiple Sclerosis Impact Scale-29 (MSIS-29)), and imaging. Brain volumes and diffusion tensor imaging (DTI) were quantified using FSL-SIENA/FIRST and FSL-TBSS.

Results: In all, 35 pwMS completed the trial. Interaction effects in favor of the EXP group were found for VO_{2max}, sit-to-stand test, MSWS-12, Spatial Recall Test, FSMC, MSIS-29, and pallidum volume. VO_{2max} improved by 1.5 mL/kg/min, MSWS-12 by 4, FSMC by 11, and MSIS-29 by 14 points. The Spatial Recall Test improved by more than 10%.

Conclusion: Community-located run training improved aerobic capacity, functional mobility, visuospatial memory, fatigue, and quality of life and pallidum volume in pwMS.

Keywords: Multiple sclerosis, running, community, walking, cognitive function, exercise, neuroplasticity

Date received: 10 March 2017; revised: 23 September 2017; accepted: 25 September 2017

Introduction

Persons with multiple sclerosis (pwMS) have an overall sedentary lifestyle that increases morbidity and cardiovascular risk.[1,2] As such, physical training shifted over years for being regarded with caution toward an important part of MS treatment. Exercise therapy and enhanced physical activity were shown not to increase relapse risk rate.[3] In fact, exercise therapy, with mainly resistance and endurance training under investigation, leads to important benefits in motor function as muscle strength and walking.[4–6] Currently, the impact of exercise on preservation or even restoring neural capacity is under investigation.[7–10]

So far, exercise therapy studies in MS predominantly focused on pwMS in the Expanded Disability Status

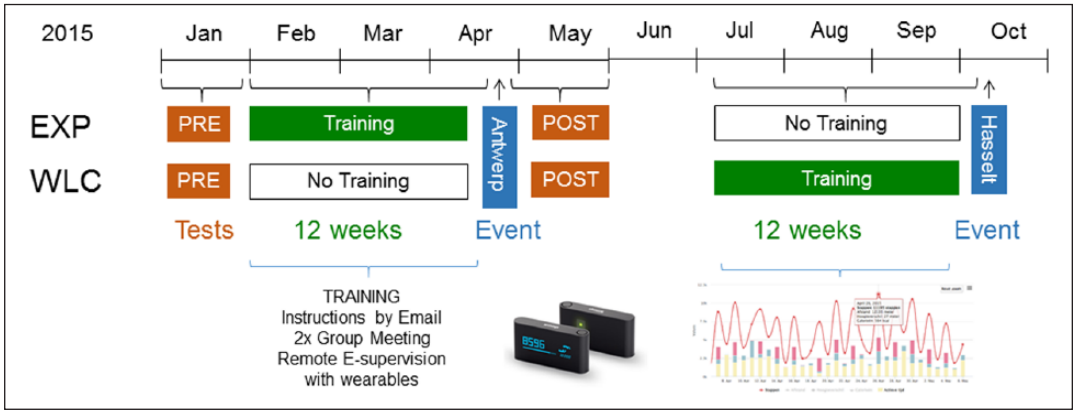

Figure 1. Illustration of the experimental design and methods of training supervision.

Scale (EDSS) range between 3 and 5.5. However, also pwMS in the early disease phase show reduced aerobic capacity, walking, and jogging functions requiring adapted exercise therapy programs.[11–14] Also, non-motor symptoms such as abnormal fatigue and cognitive impairments occur at an early stage.[15,16] An interaction of above-mentioned dysfunctions clearly impacts on quality of life. In this framework, there is emerging interest in investigating whether exercise has impact on fatigue, cognitive function, and quality of life.[17–20]

In particular, aerobic capacity is a key feature of health and performance given its associations with muscle strength, walking, fatigue, information processing speed, as well as overall and regional brain volumes such as the thalamus, basal ganglia, and hippocampus.[14,21,22] Endurance training was shown to improve aerobic capacity in pwMS,[18,23,24] as well as walking, functional mobility, fatigue, and quality of life.[4,17,25] The effect of exercise (modality) on type of cognitive symptoms is not yet well understood.[18,26] In addition, few studies in MS have investigated exercise effects on neural correlates,[9,10,22] despite promising results in the healthy population.[27,28] Most studies applied (treadmill) walking or bicycle training.[29–31] So far, physical benefits of exercise were mainly demonstrated in studies applying directly supervised interventions.[4,6] Unsupervised studies in a home or community setting seemed less effective,[6] likely because the prescribed exercise volume and intensity were not fully reached. This advocates for alternative supervision strategies and motivational methods to increase adherence.

This pragmatic randomized controlled trial investigated the multi-dimensional effects of remotely supervised community-located running training in pwMS with mild disability. pwMS who performed a 12-week running training program with the aim to run 5 km on a public event were compared with a waitlist control group. The primary outcome measures were physical fitness, walking capacity and perceived ability, functional mobility, and quality of life. Secondary outcome measures were fatigue, cognitive function, brain volumes, and structural connectivity.

Methods

Participants

Adults with MS were recruited through announcements at REVAL rehabilitation research institute (UHasselt), Flemish MS rehabilitation centers and MS Society, and Move-to-Sport. Adults diagnosed with MS were included based on the ability to walk 5 km without rest or use of assistive device. Interested pwMS attended an information session and jointly walked 5 km for verification of their ability. Exclusion criteria were reports to have run 5 km in the preceding 6 months or a relapse occurring in the preceding 3 months. The Medical Ethics Committees of the Jessa Hospital and Hasselt University approved the study. Participants signed an informed consent.

Experimental design and intervention

Figure 1 illustrates the trial design and training supervision. pwMS were assigned to the experimental (EXP) or the "waiting list control" (WLC) group prior to baseline testing. Both groups shared the goal to run 5 km during a public event. The EXP group ran on 26 April 2015 (Antwerp 10 Miles) and the WLC group on 11 October 2015 (Dwars door Hasselt). Patients were tested at two time points (0 and 12 weeks). The EXP group completed a 12-week gradual "start-to-run" program in between time points. The WLC group

was offered a comparable training program after the final measurements.

pwMS received training instructions by email. They were asked to train three times weekly according to a personalized training intensity schedule that was based on their baseline aerobic capacity. An illustration of a training protocol is provided in supplementary material S1. During the first weeks, training consisted of longer walking bouts, interspersed with short 1′ running bouts. The relative amount of running gradually increased until participants were able to run 5 km without interruption at 12 weeks. pwMS wore an activity tracker (Withings Pulse Ox) at the waist that registered the intensity of steps per minute. Participants were asked to weekly upload data to allow remote supervision of the training adherence by the research assistant. If a participant had been inactive, a phone call was made for enquiry. Besides, two group training sessions were organized (weeks 4 and 8) at a 400-m outdoor running track at KULeuven. Participants performed their individual training session simultaneously, while being observed by the project dedicated researcher (MSc exercise physiology and PhD) and master students (rehabilitation sciences and physiotherapy). This allowed to monitor individual progress and discuss potential risk for injuries. In addition, the sessions included elements of education, individual knowledge acquisition also related to observing others, and communication within the context of shared experiences and social interactions.

Outcome measures and test procedures

First, descriptive characteristics and outcomes were registered. After 30′ rest, physical tests were performed. Following another 1.5-hour rest, cognitive function tests were performed. Evaluation was performed at REVAL by a study nurse, a PhD student in Rehabilitation Sciences and Physiotherapy, and the project dedicated researcher (MSc in exercise physiology, PhD). Evaluation was standardized by an instruction booklet, composed under supervision of senior researchers and a neuropsychologist, and practiced during tester training sessions preceding the trial. Neural imaging was recorded at UZA (University Hospital Antwerp, in Wilrijk) on another day mostly within 1-week time period.

Descriptive outcomes. The MS Functional Composite (MSFC) score consisted of the Nine Hole Peg Test (9HPT), Timed 25-Foot Walk (T25FW), and Paced Auditory Serial Attention Test (PASAT). Self-report measures documented mood and self-efficacy applying the Hospital Anxiety and Depression Scale (HADS) and the Exercise Self-Efficacy Scale (ESES), respectively.[32]

Primary outcomes. Aerobic capacity was assessed on an electronically braked cycle ergometer (eBike Basic®; General Electric GmbH, Bitz, Germany) with continuous pulmonary gas exchange analysis (Oxycon, Erich Jaeger GmbH, Germany), and heart rate (HR) monitoring (Polar®). Oxygen uptake (VO_2), expiratory volume, and respiratory exchange ratio were collected breath-by-breath and averaged every minute.

After 10′ warming up, participants performed a maximal graded exercise test (75 r/min; female: 20 W + 10 W/min; male: 30 W + 15 W/min) to volitional fatigue. Maximal exercise intensity was expressed in workload (W_{max}), HR (HR_{max}), and aerobic capacity (VO_{2max}; mL/kg/min) at the level of voluntary exhaustion. Walking was determined using the Six-Minute Walk Test (6MWT; m), performed at maximal speed according to instructions of Goldman et al.,[33] and the Multiple Sclerosis Walking Scale-12 (MSWS-12; range 0–100).[34] The 5-repetition Sit-to-Stand (5-STS) test evaluated functional strength of the lower limbs and dynamic balance.[35] Quality of life was measured by the Multiple Sclerosis Impact Scale-29 (MSIS-29).[36]

Secondary outcomes. The Fatigue Scale for Motor and Cognitive Function (FSMC) documented perceived fatigue.[37] For *cognitive function*, the PASAT and Rao's Brief Repeatable Battery (BRB) were applied, including the Digit Symbol Substitution Test (DSST), Word List Generation (WLG), Selective Reminding Test (SRT), and the Spatial Recall Test (SPART).[38–40] The DSST measured sustained attention and information processing speed by presenting a random sequence of numbers to be complemented with the respective symbol during 120″. The phonemic WLG examined verbal fluency during 15″ starting with letters "N," "A," or "K." The SRT assessed long-term memory distinguishing long-term storage (LTS) and consistent long-term retrieval (CLTR). The examiner verbally presented 12 words which the patient had to recall. This was repeated until one could repeat all 12. The SPART is a visuospatial learning and delayed recall test. A checkerboard with seven checkers in specified places was presented during 10″. Immediately after, and after another 30′, the patient was requested to place them back on a blank checkerboard. The total score is a sum of the correct checkers.

Brain volume and structural connectivity were analyzed based on three-dimensional (3D)-T1 and

diffusion tensor imaging (DTI) sequences recorded on a 3-T scanner at UZA (Magnetom Trio Tim; Siemens AG, Erlangen, Germany) using a 32-channel head coil. The percentage brain volume change was calculated on the 3D-T1 images using the FSL software library using SIENA, SIENAX, FIRST, and TBSS all part of FSL.[41] Structural connectivity was analyzed with voxelwise statistical analysis of the fractional anisotropy (FA), carried out using Tract-Based Spatial Statistics.[42] Detailed analyses are described in supplementary material S2.

Statistical analyses

SAS JMP pro11.2 was used for analyses. Baseline descriptive outcomes were compared between groups using an unpaired *t*-test. Normality was evaluated through visual inspection of a residual quantile plot. Groups were compared by means of a linear mixed model analysis which accounts for fixed and random effects (participants). These models adjust for confounding variables and dropout. Intention-to-treat analysis was performed. The group (EXP–WLC), time (0–12 weeks), and the group × time interaction effects were investigated. Tukey's post hoc test was applied where appropriate to correct for multiple comparisons. Significance level was set at $p < 0.05$.

Results

Participants

Figure 2 illustrates the participant's flow. A total of 50 candidates attended an information session, after which eight pwMS were not included: two were not able to walk 5 km without rest or aid, four declined due to the demanding training program, and two pwMS indicated lacking sufficient social support. The 42 remaining participants were randomized prior to baseline testing. During the 12 weeks, seven patients dropped out of the EXP ($n = 3$) and WLC ($n = 4$). Reasons were experiencing the combination with work too exhausting, moving to another country in between tests, and encountering subjective discomfort during tests. Baseline characteristics are shown in Table 1. No significant differences between the EXP and WLC group were found except for age and body mass index with the EXP group being younger and having lower weight.

Four pwMS (two in each group) were not imaged due to contraindications for magnetic resonance (MR) scanning and logistical reasons. One scan from a participant in each group had to be excluded due to errors in the automated segmentation. Brain images of 15 and 14 pwMS in the EXP and WLC groups, respectively, were included.

Training adherence and adverse events

Participants who completed the training program showed high adherence. The EXP group completed 607 of 648 prescribed sessions (94%). In all, 25 of 41 missed training sessions were related to training-related complaints, such as repetitive strain injury of the ankle ($n = 2$; 9 sessions), training-related fatigue ($n = 2$; 7 sessions), hip and groin pain ($n = 1$; 6 sessions), and calf muscle strain ($n = 1$; 3 sessions). The remaining missed sessions were caused by external factors such as work, holiday, and flu. One participant missed the first 18 training sessions due to relapse-related hospitalization, while another participant missed first 12 training sessions due to psychosocial problems. Both participants continued training until they completed a full 12 weeks and were then tested.

Effects of the training program

The results of 12 weeks' running training versus no training are shown in Table 2 (clinical measures) and Table 3 (MR imaging (MRI) measures).

The primary outcomes did not differ between groups at baseline. Significant group × time interactions and post hoc tests showed higher workload ($Wattage_{MAX}$), aerobic capacity (VO_2max), and the 5-STS(s) in the EXP group, while no changes occurred in the WLC group. Walking capacity (6MWT) did not change significantly in contrast to a significant group × time interaction effect for the MSWS-12. There was a trend in the EXP group for less impact of MS on walking ability after 12 weeks, while the opposite occurred in the WLC group. A significant group × time interaction effect was found in the physical subscale of the MSIS-29. Post hoc tests revealed a borderline significant reduced impact of MS in the EXP group and no change in the WLC group. A borderline interaction effect was found in the psychological subscale in favor of the EXP group.

For the secondary measures, baseline fatigue and cognitive function were not different between groups except for the DSST, with worse performance for the WLC group. The SPART revealed a significant group × time interaction effect with post hoc tests revealing a significant improvement in the EXP group while there was no change in the WLC group. There were no significant effects in any other cognitive test although generally improvements were found in the EXP group. There were significant group × time

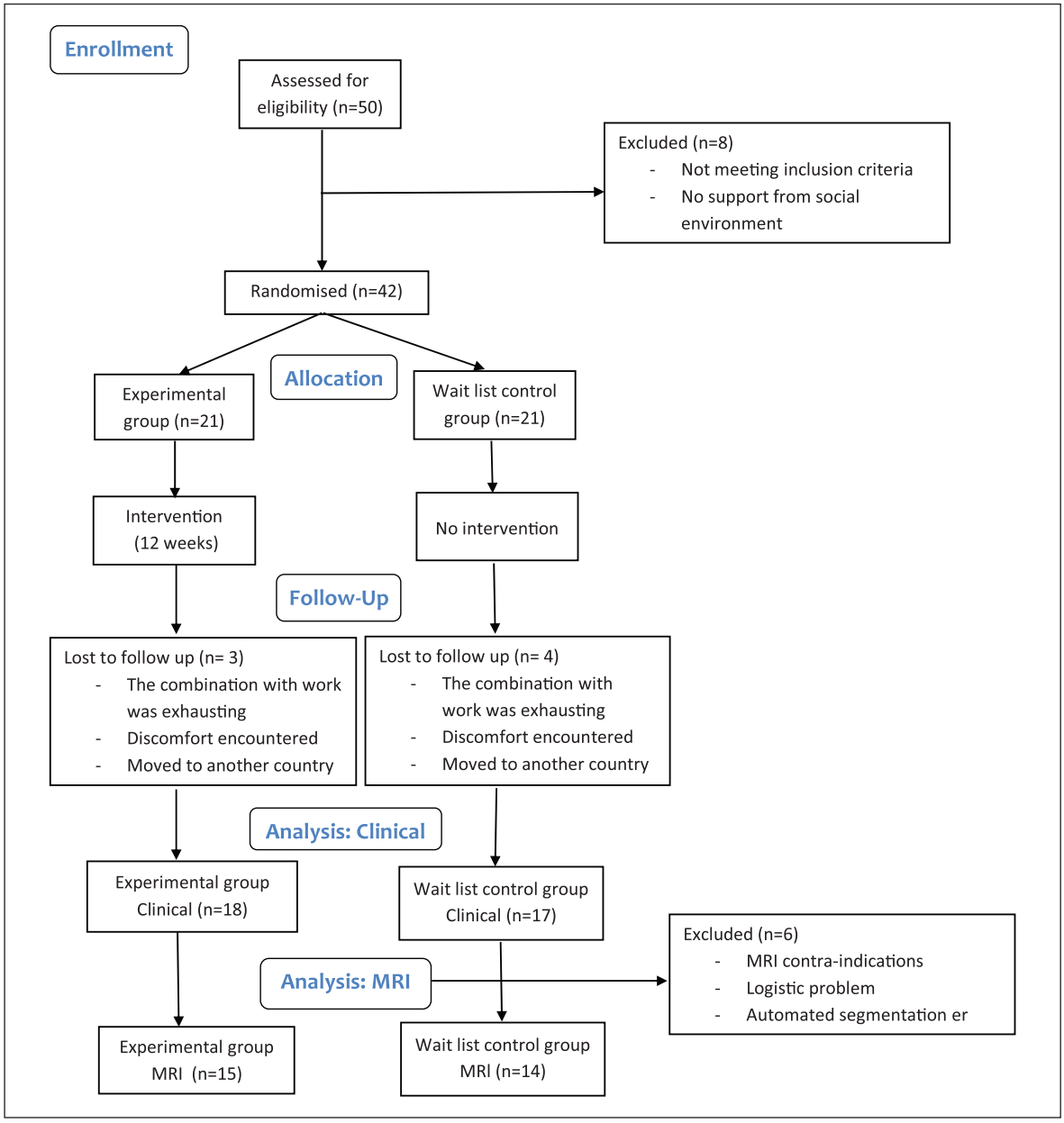

Figure 2. Participant flowchart according to CONSORT.

interaction effects for both the physical and motor domains of the FSMC. Post hoc tests revealed that fatigue was reduced in the EXP group while the WLC group remained unchanged.

Brain volumes did not differ between groups at baseline. The whole as well as gray and white matter volumes of the brain did not change significantly. After 12 weeks, a significant group × time interaction effect was found in the left pallidum with post hoc tests revealing an increased volume in the EXP group which was not present in the WLC group. There was no significant change in any groups in structural connectivity.

Discussion

This pragmatic randomized controlled trial investigated the multi-dimensional effect of 12-week community-located running training in pwMS with mild disability. Participants in the training group adhered well to the remotely supervised program while showing low adverse event rates. Compared to the control group, primary measures such as aerobic capacity,

Table 1. Descriptive characteristics for the experimental (EXP) and waiting list control (WLC) groups, expressed in mean ± SD (Q1–Q3) except for sex (number).

	EXP	WLC	*p*-Value
Demographics			
Age (years)	36.6 ± 8.5 (19.5–51.3)	44.4 ± 8.5 (29.2–62.4)	$p < 0.01$
Sex (M/F)	1/20	3/18	ns
Body mass index	24.0 ± 5.8 (16.6–40.0)	27.0 ± 3.7 (20.1–32.6)	$p < 0.05$
MS			
Disease duration (years)	8.1 ± 6.1 (0.7–19.1)	9.2 ± 5.3 (0.6–21.9)	ns
MS Functional Composite score			
T25FW (s)	4.1 ± 0.5 (3.4–5.3)	4.0 ± 0.6 (3.1–5.2)	ns
9HPT Dominant hand (s)	16.0 ± 1.9 (15.1–22.0)	19.3 ± 3.3 (14.3–23.8)	ns
9HPT Non-dominant hand (s)	19.2 ± 2.3 (16.1–23.8)	19.9 ± 3.4 (16.0–27.7)	ns
PASAT	47.8 ± 7.7 (44.2–51.4)	48 ± 11.0 (42.4–53.6)	ns
ESES			
0–40	30.0 ± 4.2 (25–40)	31.1 ± 4.8 (22–39)	ns
Mood			
HADS anxiety	5.7 ± 4.4 (3.7–7.7)	6.0 ± 4.2 (4.1–7.9)	ns
HADS depression	5.3 ± 4.7 (3.2–7.5)	3.5 ± 3.0 (2.2–4.9)	ns

MS: multiple sclerosis; T25FW: Timed 25-Foot Walk; 9HPT: Nine Hole Peg Test; PASAT: Paced Auditory Serial Attention Test; ESES: Exercise Self-Efficacy Scale; HADS: Hospital Anxiety and Depression Scale; ns: not significant.

perceived walking ability, and physical function–related quality of life improved, as well as secondary measures being fatigue, visuospatial memory, and volume of the left pallidum.

Training adherence and adverse events

A major concern with unsupervised programs is whether participants are actively and safely doing what is instructed. This community-located running program, remotely instructed and supervised, appeared to be feasible. The dropout rate was 15% with plausible reasons, which is lower to previous community-located exercise studies (20% during a 12-week community-located walking program[43] and a 6-month study of which 5 months at home[44]). The training adherence rate (94%) was higher than reported in previous studies (75%–87%) applying aerobic training.[24,43] This can be explained by factors related to a shared goal, intervention plan, and recruitment bias. Participants had a specific common goal which was to run together on a public event. The addition of two group training sessions with direct supervision by the researchers allowed for expert advice and social interaction and peer support. It is noteworthy that unplanned, a dedicated facebook webpage was constructed by the participants themselves. Although we acknowledge its potential reinforcing impact on training adherence and quality of life by peer support, this webpage was not prohibited as social media is part of current reality in many initiatives including that of MS patient societies. It would be useful to include quality research methods related to the experiences of pwMS participating in this type of trials.

Adherence was likely also enhanced through E-monitoring of the physical training by means of a wearable, by participants themselves, and remotely by the researchers. One may comment on the choice of the tracking device, as Withings has not yet been validated in pwMS. We, however, think that its accuracy was sufficient to accurately track whether a training had taken place or not. We acknowledge that the study has a major selection bias. Recruited participants showed only mild walking impairment and likely had high exercise self-efficacy levels as they were willing to engage in an individual community-located running training. They may have been runners previously or being exercise ready to engage in recreational sports. As such, one may not generalize the presented methodology and effects to the whole population of pwMS. Finally, the number of adverse effects in this study, albeit fairly low, was slightly higher than in comparative studies,[24,43] possibly related to the higher impact of running on the musculoskeletal system compared with a bicycle or walking training. Perhaps an extension of the program from 12 to 16 weeks would be beneficial for pwMS to allow a slower increase in running volume.

Table 2. Clinical outcome measures in the various domains at 0 and 12 weeks for both experimental (EXP) and waiting list control (WLC) groups.

Outcome measure	Group	Test point		Delta	*p*-Value		
		Baseline	12 weeks		Group	Time	Interaction
Physical fitness tests							
VO_{2max} (mL/kg/min)	EXP	23.9 ± 5.9	25.4 ± 5.0	+1.5	$p < 0.05$	ns	$p < 0.05$
	WLC	21.8 ± 4.0	20.1 ± 4.8	−1.7			
Workload peak (W)	EXP	127.1 ± 31.5	145.8 ± 30.5	+18.7	ns	$p < 0.001$	$p < 0.001$
	WLC	133.6 ± 25.1	133.5 ± 27.1	−0.1			
Heart rate, HRmax (bpm)	EXP	173.1 ± 12.8	173.2 ± 11.0	+0.0	$p < 0.05$	ns	ns
	WLC	166.5 ± 17.4	160.9 ± 20.6	−5.6			
Motor function tests							
5-STS	EXP	10.4 ± 2.4	8.7 ± 1.9	−1.7	ns	$p < 0.001$	$p < 0.05$
	WLC	9.8 ± 2.3	9.5 ± 2.2	−0.3			
T25FW (s)	EXP	4.1 ± 0.5	4.0 ± 0.3	−0.2	ns	ns	ns
	WLC	4.0 ± 0.6	4.0 ± 0.4	+0.1			
6 MWT (m)	EXP	576.4 ± 61.3	590.4 ± 49.6	+14.0	ns	ns	ns
	WLC	574.0 ± 66.7	569.7 ± 69.4	−4.2			
Cognitive function tests							
DSST	EXP	92.0 ± 15.0	94.3 ± 15.9	+2.3	ns	ns	ns
	WLC	83.5 ± 13.8	85.5 ± 12.2	+2.0			
Word List Generation	EXP	30.6 ± 8.5	32.5 ± 7.4	+1.9	ns	ns	ns
	WLC	80.9 ± 9.7	31.4 ± 7.8	−0.5			
Selective reminding test_LTS	EXP	50.5 ± 6.2	47.2 ± 10.6	3.2	ns	ns	ns
	WLC	49.2 ± 6.8	50.8 ± 7.8	−1.6			
Selective reminding test_CLTR	EXP	58.4 ± 7.2	53.2 ± 10.0	2.1	ns	ns	ns
	WLC	59.7 ± 8.2	62.0 ± 9.3	−2.3			
SPART	EXP	43.1 ± 6.8	48.0 ± 5.8	+5.0	ns	ns	$p < 0.05$
	WLC	44.7 ± 5.0	44.4 ± 6.4	−0.4			
PASAT	EXP	47.8 ± 7.7	50.7 ± 8.3	+2.9	ns	ns	ns
	WLC	48.0 ± 11	48.6 ± 7.2	+0.6			
Self-reported measures							
Walking							
MSWS-12 (0–100)	EXP	19.1 ± 16.4	15.0 ± 12.8	−4.1	ns	ns	$p < 0.05$
	WLC	16.3 ± 18.9	21.1 ± 26.1	+4.9			
Quality of life							
MSIS-29 Physical (0–100)	EXP	23.5 ± 14.4	16.3 ± 12.6	−7.2	ns	ns	$p < 0.01$
	WLC	16.4 ± 13.3	22.3 ± 18.9	+5.8			
MSIS-29 Psychological (0–100)	EXP	30.0 ± 24.3	23.0 ± 17.2	−7.1	ns	ns	$p = 0.06$
	WLC	21.3 ± 20.8	23.7 ± 18.0	+2.4			
Fatigue							
FSMC cognitive domain	EXP	33.4 ± 10.0	28.0 ± 12.6	−5.4	ns	$p < 0.05$	$p < 0.05$
	WLC	28.9 ± 10.0	28.9 ± 10.1	0			
FSMC physical domain	EXP	32.3 ± 8.8	26.2 ± 10.2	−6.0	ns	$p < 0.001$	$p < 0.05$
	WLC	29.3 ± 9.4	29.6 ± 8.2	+0.3			

ns: not significant; 5-STS: 5-repetition Sit-to-Stand; T25FW: Timed 25-Foot Walk; 6MWT: Six-Minute Walk Test; DSST: Digit Symbol Substitution Test; LTS: long-term storage; CLTR: consistent long-term retrieval; SPART: Spatial Recall Test; PASAT: Paced Auditory Serial Attention Test; MSWS-12: Multiple Sclerosis Walking Scale-12; MSIS: Multiple Sclerosis Impact Scale; FSMC: Fatigue Scale for Motor and Cognitive Function.
Data expressed in mean ± SD.

Table 3. MRI outcome measures at 0 and 12 weeks for both experimental (EXP) and waiting list control (WLC) groups.

Outcome measure	Group	Time		*p*-Value		
		Pre	Post	Group	Time	Interaction
Total brain volume	EXP	1526416.8±92610.0	1519198.0±100993.6	ns	ns	ns
	WLC	1540399.0±55295.1	1535597.8±54722.2			
Gray matter volume	EXP	835466.1±48329.8	827432.4±44990.3	ns	ns	ns
	WLC	828207.0±33986.9	820908.8±32468.4			
White matter volume	EXP	690950.7±54156.6	691765.6±62810.6	ns	ns	ns
	WLC	712192.0±33319.9	714689.1±29005.7			
L-thalamus	EXP	10204.0±698.5	10120.4±808.6	ns	ns	ns
	WLC	10396.5±643.5	10397.3±675.6			
L-caudate	EXP	4720.0±605.3	4576.8 ± 410.2	ns	ns	ns
	WLC	4520.4±536.1	4509.6±566.9			
L-putamen	EXP	6210.4±607.6	6249.0±699.5	ns	ns	ns
	WLC	6554.9±652.3	6427.7±604.4			
L-pallidum	EXP	2255.7±201.7	2306.6±194.6	ns	ns	$p<0.05$
	WLC	2364.1±184.2	2323.8±218.2			
L-hippocampus	EXP	5063.3±599.0	4985.0±644.8	ns	ns	ns
	WLC	5206.9±678.9	5234.6±672.5			
L-amygdala	EXP	1711.1±246.5	1679.7±280.1	ns	ns	ns
	WLC	1777.3±340.8	1672.0±422.5			
L-accumbens	EXP	739.3±136.7	735.0±109.6	ns	ns	ns
	WLC	723.5±143.1	726.3±175.5			
R-thalamus	EXP	9973.0±765.1	9911.3±879.8	ns	ns	ns
	WLC	10086.1±566.0	10087.9±556.1			
R-caudate	EXP	4843.3±679.1	4720.7±516.0	ns	ns	ns
	WLC	4678.6±616.7	4645.2±676.8			
R-putamen	EXP	6438.2±601.8	6433.1±643.7	ns	ns	ns
	WLC	6708.4±825.9	6694.6±846.2			
R-pallidum	EXP	2285.5±205.6	2214.2±342.7	ns	ns	ns
	WLC	2395.5±275.4	2378.5±347.1			
R-hippocampus	EXP	5296.8±601.2	5228.0±649.1	ns	ns	ns
	WLC	5480.6±348.5	5428.0±428.2			
R-amygdala	EXP	1767.5±262.9	1821.9±295.0	ns	ns	ns
	WLC	1816.7±265.9	1795.4±354.0			
R-accumbens	EXP	584.8±141.9	576.0±127.2	ns	ns	ns
	WLC	628.4±106.5	621.4±97.3			

ns: not significant.

Physical function and quality of life

The running intervention was successful to increase aerobic capacity. The 6% change in VO_{2max} exceeded biological variability,[45] while the 13% change in workload (in W) was in between the range of 6%–25% found during supervised bicycle training in pwMS with comparable or higher disability.[24,46,47] It is noted, however, that the enhanced aerobic capacity in the EXP group was still below normative values, while change was smaller than those reported in a recent meta-analysis predominantly including studies with direct exercise supervision.[48] Methodologically, one can debate whether the observed change of 1.5 mL/kg/min in EXP was substantial. Only one study published on the test–retest reliability of VO_{2max} in pwMS with low EDSS roughly suggesting 10% as measurement error with an equivalent of 3 mL/kg/min.[14] Heine et al. (2016),[49] however, revealed that the absolute VO_{2max} values were considerably different in three European centers (range, 23.9–32 mL/kg/min) across samples with similar EDSS scores. It was concluded that aerobic

capacity test protocols and the applied equipment substantially impacted on absolute values.

The running training also improved repeated sit-to-stand performance, likely due to increased muscle strength and dynamic balance. In contrast, the 6MWT did not significantly improve, what may be explained by the participant's close-to-normal baseline walking capacity and therefore limited treatment potential in contrast to more disabled patients in previous bicycle or walking training studies.[24,43,50] The EXP group, however, reported less impact of MS on walking ability measured with the MSWS-12, which includes high-level mobility items such as running and stair climbing, distance, and effort of walking. The improved physical function and perceived walking ability were mirrored by reduced perceived impact of MS on physical activities and, although borderline, psychological aspects.

Cognitive function and fatigue

The running intervention improved performance on the SPART, which measures memory and visuospatial perception. Half of participants in the EXP group ($n=9$) scored below the 10th percentile score when taking age and educational adjusted norms into account, and only four subjects after the training. Although changes on the other cognitive tests were almost always largest in the EXP group, no significant interaction effects were found compared to the control group possibly because relatively few patients had considerable cognitive deficits at baseline. It is known that prevalence and severity of cognitive function are increasing with age and disability level.[51] Participants were selected based on preserved walking endurance and engagement for 12 weeks of running training, and not the presence of cognitive dysfunction.

Higher aerobic capacity in pwMS with mild disability has been associated with better information processing speed, however not with visuospatial memory.[52] This may explain the differential effects found on the different cognitive measures. In previous studies, beneficial although inconsistent effects of various physical exercise interventions on memory and attention have been reported.[18,20,44,53] The findings of this study may contribute to a better understanding which physical interventions do target specific cognitive deficits, taking into account patient's characteristics.[20]

pwMS showed moderate to severe fatigue levels at baseline.[37] The running intervention leads to reduced motor and cognitive fatigue. The total score change was above 11, exceeding previously reported threshold for clinical meaningful change being 9.[37] These results are in line with recent reviews and meta-analysis demonstrating a positive effect of exercise training on fatigue, possibly via the mechanism of increased aerobic capacity.[17,48,54,55]

Brain volume and connectivity

To our knowledge, this is one of the first randomized controlled studies in pwMS to report on changes in brain volume after an aerobic exercise program. The volume of the left pallidum increased significantly after 12 weeks of running compared to no change in the control group. This volume change may be biologically plausible given that the pallidum, part of the basal ganglia, is involved in the subtle regulation of voluntary movements that occur on the subconscious level. Previously, it was shown that pallidum was more strongly associated with walking capacity compared to other brain areas.[56] The results do not, however, confirm to previous findings of exercise effects, or cross-sectional associations of aerobic capacity, that indicate on predominantly the hippocampal area added with caudate and thalamic nuclei.[9,10,21,22,55,57] This pragmatic study was, however, not sufficiently powered. A larger sample size and also optimally longer training duration are needed to clarify whether this study is underreporting effects on other neural structures.

The running training program had no effects on structural connectivity. This is seemingly in contrast to previously reported preservation or improved white matter integrity of structures such as the corpus callosum and superior cerebellar peduncle after 3–12 weeks of physical rehabilitation.[8] However, these studies focused on skillful tasks of goal-directed uni- and bilateral arm movements and dynamic balance, respectively. In fact, most of the evidence on effects of rehabilitation on functional and structural brain plasticity did not include endurance training programs.[8]

Considerations

The sample size ($n=42$) in this pragmatic study was rather small. With aerobic capacity as primary outcome measure, the required sample size was 60 in order to achieve 80% power to reject the null hypothesis of equal means with a difference of 3 mL/kg/min[14] and 20% dropout. We advocate to group efforts in a multi-center framework in order not to potentially underreport on the effects of exercise. Another note relates to the sample characteristics. It may be that persons with more motor or cognitive impairments may have shown larger benefits.

The control group was on average older with higher weight, and lower cognitive function on one test, than the experimental group. We do not think this has importantly impacted on the main results as no baseline differences in key outcome measures such as aerobic fitness and brain volumes were present. There was no medically confirmed report on EDSS and type of MS present for each participant, as they were recruited via different channels. This is limiting direct comparison of sample characteristics with other studies. The large distance walked during the 6MWT indicates a high probability that EDSS of participants was lower than 3.[58] For future research, one may consider to include proxy measures as Patient Determined Disease Steps (PDDS) to allow comparisons.[59]

It must be noted that the 12-week intervention was a "start-to-run" training program which also substantially included walking activity while the maximal running dosage was only reached in the final week(s). As such, it can be hypothesized that changes on aerobic capacity, physical and cognitive function, and brain volume and structures would be larger when this intervention would have lasted beyond 3 months.

Conclusion

Community-located run training improved aerobic capacity, functional mobility, visuospatial perception and memory, fatigue, and quality of life in pwMS. The pallidum volume increased which relates to control of automatic motor activities. Further research in well-powered sample is recommended to investigate effects of exercise on cognitive functions and neural correlates.

Acknowledgements

The non-for-profit organization Move to Sport (www.movetosport.be) initiated the study. The authors acknowledge Prof. Dr P. Parizel (UZA Antwerp) for facilitation of neuroimaging at UZA Wilrijk and Novartis and the MS Network Limburg for funding-related operational costs. They thank master students Andrea Dufour, Sara Delvah, Niels Velkeneers, and Yannick Dello for assisting in data collection and processing and Lars Grieten from the Mobile Health Unit of UHasselt for use of the electronic data platform for the step activity data.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) declared receipt of the following financial support for the research, authorship, and/or publication of this article: This study was partially funded by the non-for-profit organisation Move to Sport.

References

1. Veldhuijzen van Zanten JJ, Pilutti LA, Duda JL, et al. Sedentary behaviour in people with multiple sclerosis: Is it time to stand up against MS? *Mult Scler* 2016; 22(10): 1250–1256.
2. Wens I, Dalgas U, Stenager E, et al. Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis: A systematic review. *Mult Scler* 2013; 19: 1556–1564.
3. Pilutti LA, Platta ME, Motl RW, et al. The safety of exercise training in multiple sclerosis: A systematic review. *J Neurol Sci* 2014; 343: 3–7.
4. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: A systematic review to inform guideline development. *Arch Phys Med Rehabil* 2013; 94: 1800–1828.
5. Pearson M, Dieberg G and Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: A meta-analysis. *Arch Phys Med Rehabil* 2015; 96: 1339–1348.e7.
6. Snook EM and Motl RW. Effect of exercise training on walking mobility in multiple sclerosis: A meta-analysis. *Neurorehabil Neural Repair* 2009; 23: 108–116.
7. Dalgas U and Stenager E. Exercise and disease progression in multiple sclerosis: Can exercise slow down the progression of multiple sclerosis? *Ther Adv Neurol Disord* 2012; 5: 81–95.
8. Prosperini L, Piattella MC, Gianni C, et al. Functional and structural brain plasticity enhanced by motor and cognitive rehabilitation in multiple sclerosis. *Neural Plast* 2015; 2015: 481574.
9. Sandroff BM, Johnson CL and Motl RW. Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: A novel application of magnetic resonance elastography. *Neuroradiology* 2017; 59: 61–67.
10. Leavitt VM, Cirnigliaro C, Cohen A, et al. Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings. *Neurocase* 2014; 20: 695–697.
11. Kalron A, Achiron A and Dvir Z. Muscular and gait abnormalities in persons with early onset

multiple sclerosis. *J Neurol Phys Ther* 2011; 35: 164–169.

12. Kalron A, Dvir Z, Givon U, et al. Gait and jogging parameters in people with minimally impaired multiple sclerosis. *Gait Posture* 2013; 39(1): 297–302.
13. Neven A, Vanderstraeten A, Janssens D, et al. Understanding walking activity in multiple sclerosis: Step count, walking intensity and uninterrupted walking activity duration related to degree of disability. *Neurol Sci* 2016; 37(9): 1483–1490.
14. Langeskov-Christensen M, Heine M, Kwakkel G, et al. Aerobic capacity in persons with multiple sclerosis: A systematic review and meta-analysis. *Sports Med* 2015; 45: 905–923.
15. Kos D, Kerckhofs E, Nagels G, et al. Origin of fatigue in multiple sclerosis: Review of the literature. *Neurorehabil Neural Repair* 2007; 22(1): 91–100.
16. Amato MP, Ponziani G, Pracucci G, et al. Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. *Arch Neurol* 1995; 52: 168–172.
17. Heine M, van de Port I, Rietberg MB, et al. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev* 2015; 9: CD009956.
18. Briken S, Gold SM, Patra S, et al. Effects of exercise on fitness and cognition in progressive MS: A randomized, controlled pilot trial. *Mult Scler* 2014; 20: 382–390.
19. Kalron A and Zeilig G. Efficacy of exercise intervention programs on cognition in people suffering from multiple sclerosis, stroke and Parkinson's disease: A systematic review and meta-analysis of current evidence. *Neurorehabilitation* 2015; 37(2): 273–289.
20. Sandroff BM, Motl RW, Scudder MR, et al. Systematic, evidence-based review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis. *Neuropsychol Rev* 2016; 26(3): 271–294.
21. Prakash RS, Snook EM, Motl RW, et al. Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis. *Brain Res* 2010; 1341: 41–51.
22. Motl RW, Pilutti LA, Hubbard EA, et al. Cardiorespiratory fitness and its association with thalamic, hippocampal, and basal ganglia volumes in multiple sclerosis. *Neuroimage Clin* 2015; 7: 661–666.
23. Bansi J, Bloch W, Gamper U, et al. Training in MS: Influence of two different endurance training protocols (aquatic versus overland) on cytokine and neurotrophin concentrations during three week randomized controlled trial. *Mult Scler* 2013; 19: 613–621.
24. Rampello A, Franceschini M, Piepoli M, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: A randomized crossover controlled study. *Phys Ther* 2007; 87: 545–555.
25. Motl RW and Sandroff BM. Benefits of exercise training in multiple sclerosis. *Curr Neurol Neurosci Rep* 2015; 15: 62.
26. Motl RW, Sandroff BM and DeLuca J. Exercise training and cognitive rehabilitation: A symbiotic approach for rehabilitating walking and cognitive functions in multiple sclerosis? *Neurorehabil Neural Repair* 2016; 30: 499–511.
27. Hillman CH, Erickson KI and Kramer AF. Be smart, exercise your heart: Exercise effects on brain and cognition. *Nat Rev Neurosci* 2008; 9: 58–65.
28. Hotting K and Roder B. Beneficial effects of physical exercise on neuroplasticity and cognition. *Neurosci Biobehav Rev* 2013; 37: 2243–2257.
29. van den Berg M, Dawes H, Wade DT, et al. Treadmill training for individuals with multiple sclerosis: A pilot randomised trial. *J Neurol Neurosurg Psychiatry* 2006; 77: 531–533.
30. Newman MA, Dawes H, van den Berg M, et al. Can aerobic treadmill training reduce the effort of walking and fatigue in people with multiple sclerosis: A pilot study. *Mult Scler* 2007; 13: 113–119.
31. Schmidt S and Wonneberger M. Long-term endurance exercise improves aerobic capacity in patients with relapsing-remitting multiple sclerosis: Impact of baseline fatigue. *J Neurol Sci* 2014; 336: 29–35.
32. Riazi A, Thompson AJ and Hobart JC. Self-efficacy predicts self-reported health status in multiple sclerosis. *Mult Scler* 2004; 10: 61–66.
33. Goldman MD, Marrie RA and Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler* 2008; 14: 383–390.
34. Hobart JC, Riazi A, Lamping DL, et al. Measuring the impact of MS on walking ability: The 12-item MS Walking Scale (MSWS-12). *Neurology* 2003; 60: 31–36.
35. Moller AB, Bibby BM, Skjerbaek AG, et al. Validity and variability of the 5-repetition sit-to-stand test in patients with multiple sclerosis. *Disabilrehabil* 2012; 34: 2251–2258.
36. Hobart J, Lamping D, Fitzpatrick R, et al. The Multiple Sclerosis Impact Scale (MSIS-29): A new patient-based outcome measure. *Brain* 2001; 124: 962–973.

37. Penner IK, Raselli C, Stocklin M, et al. The Fatigue Scale for Motor and Cognitive Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. *Multscler* 2009; 15: 1509–1517.
38. Strober L, Englert J, Munschauer F, et al. Sensitivity of conventional memory tests in multiple sclerosis: Comparing the Rao Brief Repeatable Neuropsychological Battery and the Minimal Assessment of Cognitive Function in MS. *Mult Scler* 2009; 15: 1077–1084.
39. Boringa JB, Lazeron RH, Reuling IE, et al. The brief repeatable battery of neuropsychological tests: Normative values allow application in multiple sclerosis clinical practice. *Mult Scler* 2001; 7: 263–267.
40. Gontkovsky ST, Vickery CD and Beatty WW. Construct validity of the 7/24 spatial recall test. *Appl Neuropsychol* 2004; 11: 75–84.
41. Patenaude B, Smith SM, Kennedy DN, et al. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage* 2011; 56: 907–922.
42. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006; 31: 1487–1505.
43. Geddes EL, Costello E, Raivel K, et al. The effects of a twelve-week home walking program on cardiovascular parameters and fatigue perception of individuals with multiple sclerosis: A pilot study. *Cardiopulm Phys Ther J* 2009; 20: 5–12.
44. Romberg A, Virtanen A, Ruutiainen J, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: A randomized study. *Neurology* 2004; 63: 2034–2038.
45. Katch VL, Sady SS and Freedson P. Biological variability in maximum aerobic power. *Med Sci Sports Exerc* 1982; 14: 21–25.
46. Petajan JH, Gappmaier E, White AT, et al. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* 1996; 39: 432–441.
47. Schulz KH, Gold SM, Witte J, et al. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. *J Neurol Sci* 2004; 225: 11–18.
48. Platta ME, Ensari I, Motl RW, et al. Effect of exercise training on fitness in multiple sclerosis: A meta-analysis. *Arch Phys Med Rehabil* 2016; 97: 1564–1572.
49. Heine M, Wens I, Langeskov-Christensen M, et al. Cardiopulmonary fitness is related to disease severity in multiple sclerosis. *Mult Scler.* 2016; 22: 231–238.
50. Kileff J and Ashburn A. A pilot study of the effect of aerobic exercise on people with moderate disability multiple sclerosis. *Clin Rehabil* 2005; 19: 165–169.
51. Ruano L, Portaccio E, Goretti B, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. *Mult Scler* 2016; 23(9): 1258–1267.
52. Sandroff BM, Pilutti LA, Benedict RH, et al. Association between physical fitness and cognitive function in multiple sclerosis: Does disability status matter? *Neurorehabil Neural Repair* 2015; 29: 214–223.
53. Sandroff BM, Klaren RE, Pilutti LA, et al. Randomized controlled trial of physical activity, cognition, and walking in multiple sclerosis. *J Neurol* 2014; 261: 363–372.
54. Langeskov-Christensen M, Bisson EJ, Finlayson ML, et al. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review. *J Neurol Sci* 2017; 373: 307–320.
55. Sebastiao E, Hubbard EA, Klaren RE, et al. Fitness and its association with fatigue in persons with multiple sclerosis. *Scand J Med Sci Sports* 2016. Epub ahead of print 17 October 2017. DOI: 10.1111/sms.12752.
56. Motl RW, Hubbard EA, Sreekumar N, et al. Pallidal and caudate volumes correlate with walking function in multiple sclerosis. *J Neurol Sci* 2015; 354: 33–36.
57. Motl RW, Zivadinov R, Bergsland N, et al. Thalamus volume and ambulation in multiple sclerosis: A cross-sectional study. *Neurodegener Dis Manag* 2016; 6: 23–29.
58. Dalgas U, Kjolhede T, Gijbels D, et al. Aerobic intensity and pacing pattern during the six-minute walk test in patients with multiple sclerosis. *J Rehabil Med* 2014; 46: 59–66.
59. Learmonth YC, Motl RW, Sandroff BM, et al. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol* 2013; 13: 37.