2015•2016
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
*master in de revalidatiewetenschappen en de kinesitherapie*

# Masterproef

## The effect of community-based running training on physical function in patients with multiple sclerosis: a randomized controlled trial

Promotor :
Prof. dr. Peter FEYS

Copromotor :
Mevrouw Lousin MOUMDJIAN

Niels Velkeneers
*Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie*

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KNOWLEDGE IN ACTION

# The effect of community-based running training on physical function in patients with multiple sclerosis: a randomized controlled trial

MS RUN Project

Promotor:

Prof. dr. Peter FEYS

Co-Promotor:

Lousin MOUMDJIAN

Student:

Niels Velkeneers

**Acknowledgement**

I would like to thank everyone who supported me during the completion of this master thesis. First, I would like to sincerely thank my promoter Prof. dr. Peter Feys for giving me the opportunity to be part of this project and his patience, knowledge and advice during every stage of the process. I also would like to thank Dr. Florian Van Halewyck and Lousin Moumdjian for their support and guidance during this entire project, especially in collecting and processing all data.

Next, I want to thank all participants for their motivation during the entire study and that they were willing to spend their time for this research, because the measurements were time-consuming. I learned a lot about their individual differences and experiences of multiple sclerosis that will help me later in my professional career.

I also want to thank my fellow students, members of Move to Sport and all researchers at REVAL for their help and support at different stages of this study. Finally, I would like to thank my friends and parents for their mental and emotional support during these past years. Without their support, it was impossible to achieve this.

Geetbets, 16/06/2016 N.V.

**Research Context**

This randomized controlled trial focuses on the impact of community-based running training on physical function in persons with Multiple Sclerosis (pwMS). Multiple Sclerosis (MS) is one of the major causes of non-traumatic neurologic disability in young adults[1], which can cause a wide range of symptoms limiting the quality of life of pwMS[2]. For many years, pwMS were advised to avoid physical activity, because it can trigger fatigue and exacerbations[3]. But since it's known that exercise is well tolerated and have beneficial effects, much research has been done on the impact of exercise therapy in pwMS[4]. Supervised training has shown a beneficial contribution in the overall rehabilitation[4], while research in less controlled settings are limited.

This study contributes to the research domain of neurological rehabilitation and is part of a larger research project, which is led by Prof. Dr. Peter Feys (promotor), Prof. Dr. Bert Op't Eijnde, Dr. Florian Van Halewyck and Dr. Inez Wens. In this MS RUN study, the effect of rehabilitation therapy on neuroplasticity, cognitive and motor functioning in pwMS is investigated in collaboration with the non-profit association Move To Sport (www.movetosport.be). This non-profit association, founded by Paul Van Asch, encourages people with chronic conditions to have a more physical lifestyle.
During this MS RUN project, participants trained for 12 weeks until they were able to run five kilometers at a public event. Cognitive and motor functioning were investigated before and after the community-based running training, at REVAL, study center for rehabilitation research in Diepenbeek (Belgium). The testing of this study was conducted in collaboration with the studies of Sarah Delva and Andrea Dufour, who were investigating cognitive function and dual tasks respectively. The MRI scans were examined in the University Hospital of Antwerp (Belgium). These results were investigated in the study of Yannick Dello.

I had a small contribution in the determination of the study design, which was mainly determined by Prof. Dr. Peter Feys (promotor), Prof. Dr. Bert Op't Eijnde and Paul Van Asch. I helped with the translation of a questionnaire about perceived symptoms and with the recruitment of participants by sending flyers to a network of neurologists and physiotherapists. After recruitment, I have guided and instructed participants during the information meetings, baseline testing and group-training sessions. During investigations, I collected all data of motor function tests (total distance covered during the 6-Minute Walk Test (6MWT) with Borg Ratings of Perceived Exertion (Borg RPE Scale) and Visual Analogue Scale (VAS) for perceived symptoms, Timed 25-Foot Walk (T25FW), Five repetition Sit-to-Stand Test (5STS)) and assisted during cognitive testing.

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**Abstract**

**Background:** Supervised endurance training in Multiple Sclerosis (MS) is well investigated, however research in less controlled settings are limited.

**Objective:** The aim of this study was to investigate the effect of community-based running training on physical functioning in patients with Multiple Sclerosis (pwMS), in a randomized controlled trial.

**Methods:** Forty-two pwMS (mild disability, Expanded Disability Status Scale (EDSS) between 0.5 and 3.0) were randomized into a group who received 12-week (3 training sessions/week) community-based running training (RT) (*n* = 21) or into a waitlist control group (WLC) (*n* = 21) who were advised not to change their physical activity. Both groups were investigated at baseline and after 12 weeks. Primary, physical fitness, walking capacity and functional mobility were examined. Secondary, self-reported physical activity, exercise related self-efficacy and the physical and psychological impact of MS were evaluated.

**Results:** Thirty-five pwMS completed the study. At baseline, significant differences in age, body weight and body mass index were found. No differences in primary and secondary outcome parameters were found at baseline. Significant group x time interactions were found in $Wattage_{MAX}$ (p=0.0002)), impact of MS on walking disability (MSWS-12 (p=0.0389)) and lower limb functional mobility (5STS (p=0.0182)). Post hoc tests revealed significant improvements in the RT-group, which was not found in the WLC group for all three parameters. For $VO_2max$ (p=0.0127), a significant group effect was present after 12 weeks. No meaningful improvements in walking capacity were found. Secondary, a significant group x time interaction in physical impact of MS (MSIS-29 (p=0.0021)) was found. Post hoc tests revealed significant improvements in the RT-group, which was not found in the WLC group.

**Conclusion:** Community-based running training improved physical fitness, functional mobility and impact of MS in persons with mild disability. The study demonstrated feasibility of unsupervised running training.

**Keywords**

Multiple Sclerosis, community-based, running training, physical function, physical fitness, walking capacity, functional mobility

## Introduction

Multiple sclerosis (MS) is a chronic and progressive disease that affects the central nervous system (CNS), characterised by neurodegeneration, demyelination and inflammation[1]. With a total prevalence rate of 83 per 100 000 adults in Europe for the past three decades[2], it can be assumed that MS is the major cause of non-traumatic neurologic disability in young adults[3]. MS is more common in women[4] and regions populated by northern Europeans[5] and usually starts in the third or fourth decade of life[3]. By increasing MS disease progression, patients with multiple sclerosis (pwMS) experience a wide range of symptoms such as muscle weakness, spasticity, pain, cognition, fatigue, bladder and bowel dysfunction, based on the extent and location of lesions[6]. The clinical course and prognosis of MS are complex and unpredictable[7].

For many years pwMS were advised not to participate in physical exercise, to minimize the risk of exacerbations and symptoms of fatigue[8]. However, during the last decades it became clear that exercise is generally safe for pwMS[9] and has no significant influence on relapse activity[10]. Several studies demonstrated that exercise have beneficial effects on pwMS[11]. Exercise can be an effective tool for improving walking mobility[12], fatigue[13] and physical fitness[14] in the overall rehabilitation in MS. PwMS tend to be less physically active compared to healthy adults[15]. Because of their sedentary lifestyle, MS has been associated with an increased risk for chronic health conditions related to physical inactivity, such as cardiovascular disease[16] and other secondary diseases[17–19]. Walking impairment is also one of the most common consequences of MS that limits the quality of life of pwMS[20]. In the study of Larocca[21], 70% of pwMS reported that walking difficulty was the most challenging aspect of their disease.

Supervised endurance training has shown improvements in both physical fitness[22–24] and walking capacity[25,26]. However research in less controlled settings, like home-based training are limited and was mostly targeting balance and lower limb muscle strenght[27–29]. Lot of research has been done about the effect of bicycle training, while fewer studies investigated the effect of running training. Three studies[30–32] evaluated the effects of treadmill training, however the effects of unsupervised running training has never been investigated.

This study investigated the effects of community-based running training on physical function in pwMS. Participants who received 12-week running training were compared with a waitlist control group, who were advised not to change their physical habits. Exercise intensity was based on their individual exercise capacity and focused on improving cardiovascular endurance. Before and after the training intervention, pwMS underwent physical function tests investigating physical fitness, walking capacity and functional mobility primary. While secondary, self-reported physical activity, exercise related self-efficacy and physical and psychological impact of MS were evaluated. We hypothesize that community-based endurance training will improve physical fitness and walking capacity in pwMS.

## Materials and methods

### *Study Design*

This study used a randomized controlled trial to investigate the impact of community-based running training on physical functioning in MS-patients with mild disability. After recruitment, participants were invited to an information meeting about the course of the study and experimental procedures. Baseline testing ($t_1$) started with filling out questionnaires and determination of body height and body weight. With the Nine Hole Peg Test (9HPT) and Timed 25-Foot Walk (T25FW), two of thee parts of the MS Functional Composite Score (MSFC)[33] were used to describe the global impression of the participant. Subsequently, the 5-Repetition Sit-to-Stand Test (5STS) was performed before a Six-Minute Walk Test (6MWT). After a break of 30 minutes, physical fitness was investigated using a maximal graded exercise test on a bicycle ergometer.

After $t_1$, participants were randomized into a running-training (RT) group or to a waitlist control (WLC) group who were encouraged not to increase their physical activity during the study. Participants of the RT-group performed 12-week community-based running training. The exercise intensity was based on their individual exercise capacity and was gradually increased until participants were able to run five kilometers. After this 12-week training period ($t_2$), all participants underwent physical function tests similar to baseline testing. All measurements took place at REVAL, Diepenbeek.

*Participants*

Forty-two PwMS were recruited via a network of neurologists and physiotherapists in different hospitals and MS centers (MS Center Melsbroek, Belgium and MS Center Overpelt, Belgium) and via social media (MS-Liga Flanders). The participants met the following inclusion criteria: an Expanded Disability Status Scale[34] (EDSS) score between 0.5 and 3.0; male or female; older than 18 years; being able to walk five kilometers (but not being able to run five kilometers) at the start of the study; provided written informed consent. Participants were excluded if they wear a pacemaker (for MRI scans) or if they had an acute exacerbation of their MS symptoms within the last three months prior to the study.

Before the study, participants were informed about the course and possible risks of the experimental procedures and signed an informed consent. The study was approved by the Medical Ethical Committee of Hasselt University, Belgium, and the Ethical Committee of Virga Jesse Hospital, Belgium.

*Maximal Graded Exercise Testing*

Individual physical fitness level was assessed by a maximal graded exercise test on a bicycle ergometer. The exercise protocol started with a 10-min warming up. Participants were allowed to cycle at a comfortable pace with exercise intensity (Watt, W) between 30 and 35W, but they were instructed to reach 75 revolutions per minute (rpm) at the end of the warming up.

Maximal graded exercise testing started with a resistance of 30W and 20W for male and female participants, respectively. All participants were instructed to cycle at a frequency of 75 rpm while exercise intensity was gradually increased with 15W for men and 10W for women every minute. After voluntary exhaustion was reached, participants could recover for 2 minutes.

Maximal exercise intensity ($W_{max}$) could be determined after voluntary exhaustion. Heart rate (HR) was monitored every minute during the test using a heart rate monitor (Polar®). Maximal heart rate ($HR_{max}$) was defined as the highest HR value reached during the test. Aerobic capacity ($VO_{2max}$) was continuously monitored by ergospirometry.

*Functional Walking Capacity and Functional Mobility*

Functional walking capacity was determined using the Six-Minute Walk Test (6MWT) and Timed 25-Foot Walk (T25FW), measuring walking endurance and walking speed, respectively. The impact of MS on walking disability was evaluated using the Multiple Sclerosis Walking Scale-12 (MSWS-12). The 5-repetition Sit-to-Stand Test (5STS) was used for the evaluation of functional mobility of the lower limbs.

The 6MWT is an objective assessment of the walking distance. Participants were instructed to walk as mush distance as possible in six minutes time at their maximal walking speed[35]. During the 6MWT, participants walked back and forth a 30-meter hallway turning around cones. The total distance (m) covered during the 6MWT was registered, with longer distances indicating better mobility[36,37]. The 6MWT has been shown to be a good predictor of the habitual walking performance[38]. After 6MWT, ratings of perceived exertion (RPE) was subjectively determined using a Borg RPE scale (6-20 scale)[39].
The T25FW is a quantitative measurement of walking speed. Participants were instructed to walk as fast they can across a clearly marked 25 ft line. Time (s) was recorded by the average of two consecutive trials[33,35].

The impact of MS on walking disability during the past 2 weeks was evaluated using the Multiple Sclerosis Walking Scale-12 (MSWS-12)[40]. 12 items were rated on a 5-point scale from 1 (not at all) to 5 (extremely). The total score was transformed to a scale with a range of 0 to 100, with lower scores indicating less walking disability[41].
Lower limb muscle strength and balance performance were evaluated by the 5-repetition Sit-to-Stand Test (5STS)[42]. The 5STS-test is a measurement of time (s) needed to complete 5 repetitions of the Sit-to-Stand movement, after the assessor gave a standardized instruction[42].

*Secondary Outcome*

*Physical activity:* Physical activity was measured by the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD)[43]. 13 items about participation in recreational, occupational activities and household over the past 7 days were scored in categories of number of days a week and hours daily[43].

*MS health status:* The physical (20 items) and psychological (9 items) impact of MS from patient's perspective is measured by the Multiple Sclerosis Impact Scale (MSIS-29)[44]. Physical and psychological summary scores are generated by summing individual scores and then transformed to a 0-100 scale, with a higher score indicating worse health[44].

*Self-efficacy:* The Exercise Self-Efficacy Scale (ESES)[45] is a self-reported measurement of how confident pwMS are during exercise and physical activities. 10 items were scored on a 4-point scale, with a total score range between 10 and 40. Higher score indicates more self-efficacy during exercise[45].

*Training*

Following baseline testing ($t_1$), all participants were randomized into a WLC-group or an ET-group. Participants of the WLC-group were advised not to increase their physical activity, whereas ET-group participants received 12-week community-based endurance training focusing on improving cardiovascular endurance. For twelve weeks, ET-group trained with a frequency of three training sessions per week. Training intensity was based on their individual exercise capacity, determined with a maximal graded exercise test on a bicycle ergometer. After $t_1$, participants of the ET-group were divided into a group with low, moderate or good exercise capacity. All groups started exercising with a different training intensity, which was gradually increased until participants were able to run five kilometers. During 12-weeks of training, all participants in the RT-group were provided with a smart activity tracker of Withings®. This online platform provided a visualization of the training adherence. Group-training sessions were organized in week 4 and 8. An example of a training schedule can be found in Appendix 1.

*Statistical Analysis*

All data were analyzed using JMP Pro 12, statistical discovery software from SAS. With an unpaired t-test, data between both groups was compared, except for gender, which was compared using Fisher's exact test. A mixed-model analysis was used for comparing Time x Group effect. The level of significance was set with a p-value $< 0.05$.

## Results

### *Participants*

Figure 1 shows a flowchart of the experimental design and included participants. Eight participants withdrew before baseline testing. Forty-two participants were randomized into a WLC-group (*n*=21) or into an RT-group (*n*=21). Baseline characteristics and measurements are shown in table 1. Significant differences in age (p=0.0028), body weight (p=0.0146) and body mass index (p=0.0301) were observed between the RT-group and the WLC-group at baseline. Thirty-five participants completed the study and were analyzed after 12 weeks. Seven participants withdrew during the study (dropout rate of 7/42 (17%)), with a dropout of three and four participants in the in the RT-group and WLC-group, respectively.

**Table 1.** Participant characteristics and baseline measures

| Variable | RT-Group | WLC-Group | p-value |
|---|---|---|---|
| **Age (yrs)** | 36.64 ± 8.53 (19.5-51.3) | 44.35 ± 8.54 (29.2-62.4) | 0.0028 |
| **Height (m)** | 1.68 ± 0.06 (1.57-1.79) | 1.69 ± 0.07 (1.55-1.80) | n.s. |
| **Weight (kg)** | 67.2 ± 15.22 (50.7-105.0) | 76.13 ± 9.55 (58.0-92.0) | 0.0146 |
| **Body Mass Index** | 24.04 ± 5.79 (16.56-40.01) | 26.96 ± 3.66 (20.07-32.63) | 0.0301 |
| **Disease duration (yrs)** | 8.10 ± 6.09 (0.66-19.11) | 9.24 ± 5.30 (0.62-21.93) | n.s. |
| **Gender (M/F)** | 1/20 | 3/18 | n.s. |
| **T25FW** | 4.14 ± 0.50 (3.38-5.25) | 3.95 ± 0.60 (3.08-5.20) | n.s. |
| **9HPT: Dominant Hand** | 17.96 ± 1.88 (15.1-22.0) | 19.28 ± 3.33 (14.3-23.8) | n.s. |
| **9HPT: Non-Dominant Hand** | 19.20 ± 2.29 (16.1-23.8) | 19.92 ± 3.42 (16.0-27.7) | n.s. |

*Values are means and standard deviation (lowest and highest value)*

Abbreviations: RT = Running Training; WLC = Waitlist Control; T25FW = Timed 25-Foot Walk; 9HPT = Nine-Hole Peg Test; yrs = Years; m = Meter; kg = Kilogram; M = Male; F = Female; n.s. = Not Significant;

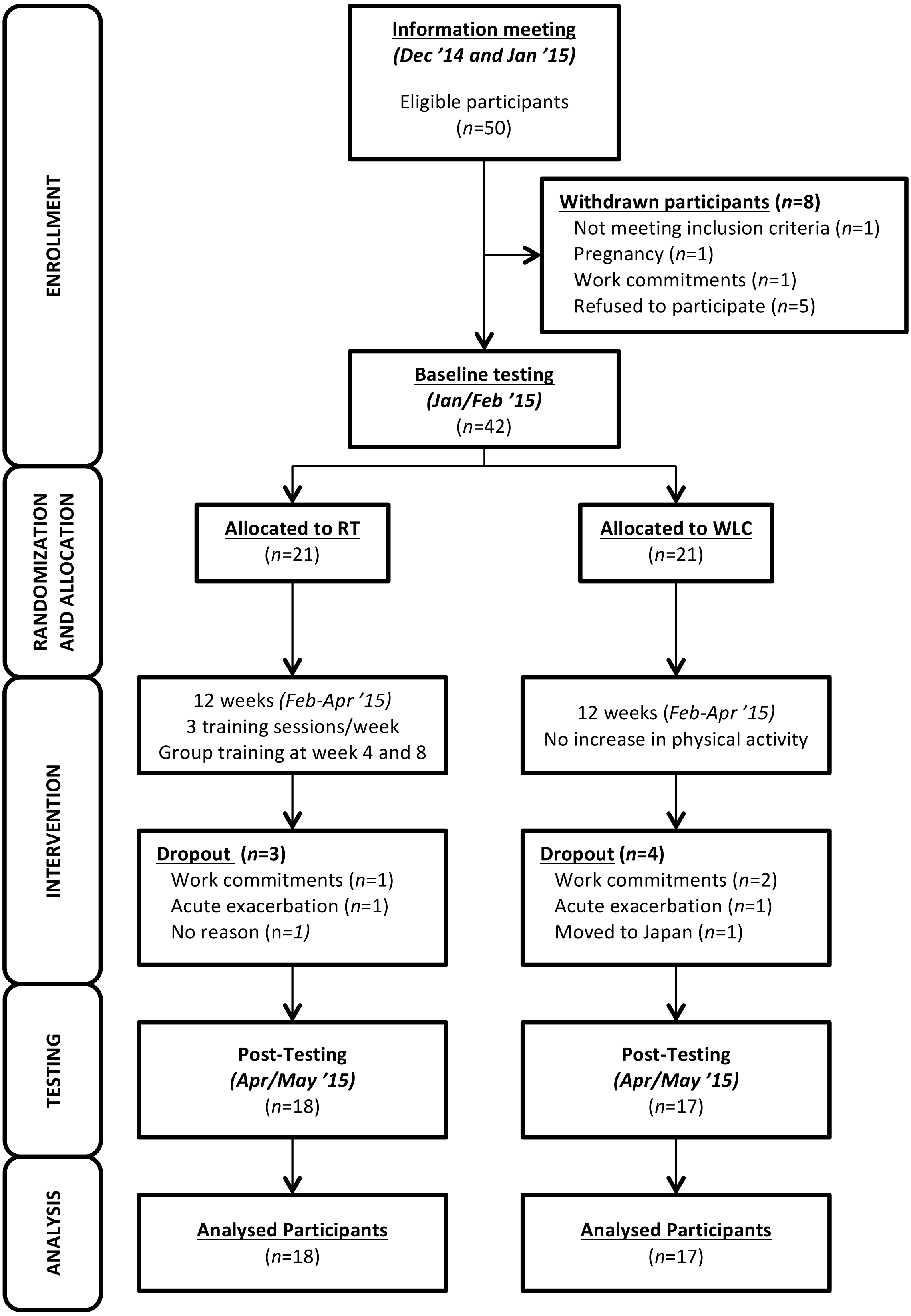


**Figure 1.** Flowchart of experimental design and included participants

Abbreviations: RT = Running Training; WLC = Waitlist Control Group; Dec = December; Jan = January; Feb = February; Apr = April

*Training adherence and training related complaints*

All participants who completed the community-based running training performed a very good training adherence. In general, participants of the RT-group completed 607 training sessions of the 648 training sessions prescribed, leading to an average adherence rate of 94%. 25 of the 41 missed training sessions were related to training related complaints, which are listed in Table 2. The remaining missed training sessions were caused by extern factors, like work, holiday and flu. One participant missed first 18 training sessions due to hospitalization, while another participant missed first 12 training sessions due to psychosocial problems. Both participants missed the start of their training program, but continued training until they reached 12 weeks of training. They were tested at 18 and 16 weeks respectively after baseline training.

**Table 2.** Summary of training related complaints and frequency of occurrence

| Training related complaints (Number of participants) | Number of missed training sessions |
|---|---|
| **Overuse Injury Ankle (*n*=2)** | 9 |
| **Training Related Fatigue (*n*=2)** | 7 |
| **Hip and Groin Pain (*n*=1)** | 6 |
| **Calf Muscle Strain (*n*=1)** | 3 |

*Physical fitness*

No differences were found comparing physical fitness between both groups at baseline. After 12 weeks, significant group x time interactions were found in maximal exercise intensity ($Wattage_{MAX}$: p=0.0002) and aerobic capacity ($VO_2max$: p=0.0139). Post-hoc test revealed that $Wattage_{MAX}$ significant improved (p<0.0001) in the RT-group, while there was no significant change over time in the WLC-group. For $VO_2max$, there were no significant changes in both RT-group and WLC-group over time. However, a significant group effect was present, with post-hoc test revealing that the differences between groups were significant after 12 weeks (p=0.0127) only. A significant group effect was present comparing maximal heart rate ($HR_{MAX}$: p=0.0464) between both groups. In general, participants in the RT-group demonstrated a higher $HR_{MAX}$ compared with the WLC-group. All differences in physical fitness are shown in table 3.

**Table 3.** Results for physical fitness parameters at 0 and 12 weeks in RT and WLC group

| Variable | Group | Time | | | p-value | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | Week 12 | Delta | Group | Time | Interaction |
| **$VO_2max$ (ml/kg/min)** | **RT** | 23.89 ± 5.92 (14.3-34.2) | 25.39 ± 4.98 (14.9-34.6) | +1.50 (5.91%) | 0.0167 | 0.8853 | 0.0139 |
| | **WLC** | 21.80 ± 4.03 (16.4-32.0) | 20.12 ± 4.82 (13.2-30.8) | -1.68 (7.71%) | | | |
| **$Wattage_{MAX}$ (W)** | **RT** | 127.14 ± 31.49 (70-210) | 145.81 ± 30.50 (100-225) | +18.67 (12.80%) | 0.7351 | 0.0002 | 0.0002 |
| | **WLC** | 133.57 ± 25.06 (80-180) | 133.47 ± 27.11 (90-195) | -0.10 (0.07%) | | | |
| **$HR_{MAX}$ (bpm)** | **RT** | 173.14 ± 12.76 (145-196) | 173.17 ± 10.95 (142-192) | +0.03 (0.02%) | 0.0464 | 0.1696 | 0.1653 |
| | **WLC** | 166.48 ± 17.35 (129-192) | 160.91 ± 20.61 (115-182) | -5.57 (3.35%) | | | |

*Values are means and standard deviation (lowest and highest value)*

Abbreviations: RT = Running Training; WLC = Waitlist Control; $VO_2max$ = Maximal Oxygen Uptake; W = Watt; bpm = Beats Per Minute; $HR_{MAX}$ = Maximum Heart Rate

*Walking capacity and Functional Mobility*

The results of walking capacity and functional mobility are shown in table 4. At baseline, no differences were found comparing walking capacity and functional mobility between both groups. After 12 weeks of training, a significant group x time interaction effect was found in functional mobility, measured by 5STS (p=0.0182). Post-hoc test revealed a significant improvement (p=0.0012) over time in the RT-group, which was not found in the WLC-group. For the MSWS-12 (p=0.0389), a significant group x time interaction effect was found, with participants in the RT-group reported less impact of MS on walking disability, while the opposite happened in the WLC-group. Remarkably, post-hoc test did not show significant differences in any group over time, or differences between groups. No differences were found in walking speed (T25FW), walking endurance (6MWT) and the rating of perceived exertion.

**Table 4.** Results of walking capacity and functional mobility at 0 and 12 weeks in RT and WLC group

| Variable | Group | Time | | | p-value | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | Week 12 | Delta | Group | Time | Interaction |
| **6MWT (m)** | **RT** | 576.38 ± 61.31 (441-687) | 590.42 ± 49.57 (462-660) | +14.04 (2.38%) | 0.5503 | 0.4263 | 0.1447 |
| | **WLC** | 573.91 ± 66.67 (463-717) | 569.70 ± 69.37 (412-678) | -4.21 (0.73%) | | | |
| **Borg 6-20 After 6MWT** | **RT** | 9.90 ± 2.19 (6-15) | 9.97 ± 2.40 (6-15) | +0.07 (0.70%) | 0.1743 | 0.6322 | 0.7570 |
| | **WLC** | 10.55 ± 1.61 (7-13) | 10.84 ± 1.86 (7-14) | +0.29 (2.68%) | | | |
| **T25FW (s)** | **RT** | 4.14 ± 0.50 (3.38-5.25) | 3.98 ± 0.25 (3.57-4.37) | -0.16 (3.86%) | 0.6202 | 0.6111 | 0.1216 |
| | **WLC** | 3.95 ± 0.60 (3.08-5.20) | 4.04 ± 0.43 (3.31-4.84) | +0.09 (2.23%) | | | |
| **MSWS-12 (0-100)** | **RT** | 19.05 ± 16.38 (0-60) | 14.96 ± 12.76 (0-40) | -4.09 (21.47%) | 0.7632 | 0.8552 | 0.0389 |
| | **WLC** | 16.27 ± 18.86 (0-69) | 21.13 ± 26.08 (0-94) | +4.86 (23.00%) | | | |
| **5STS (s)** | **RT** | 10.44 ± 2.43 (6.67-18.16) | 8.73 ± 1.85 (4.86-11.88) | -1.71 (16.38%) | 0.9294 | 0.0022 | 0.0182 |
| | **WLC** | 9.77 ± 2.29 (5.86-15.16) | 9.52 ± 2.19 (6.62-14.91) | -0.25 (2.56%) | | | |

*Values are means and standard deviation (lowest and highest value)*

Abbreviations: RT = Running Training; WLC = Waitlist Control; 6MWT = Six-Minute Walk Test; T25FW = Timed 25-Foot Walk; MSWS-12 = 12-Item Multiple Sclerosis Walking Scale; 5STS = 5-Repetition Sit-to-Stand Test; m = Meter; s = Seconds

*Secondary outcomes*

All differences in secondary outcome after community-based running training are shown in table 5. There were no differences in baseline measurements found between both groups. After 12 weeks of training, a significant group x time interaction effect was found in the physical impact of MS, measured by the MSIS-29 (physical items) (p=0.0021). Post-hoc test revealed a borderline significant improvement (p=0.052) in the RT-group, while there was no significant change over time in the WLC-group. No differences were found in self-reported physical activity (PASIPD), exercise related self-efficacy (ESES) and psychological impact of MS (MSIS-19, psychological part)

**Table 5.** Results of secondary outcome parameters at 0 and 12 weeks in RT and WLC group

| Variable | Group | Time | | | p-value | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | Week 12 | Delta | Group | Time | Interaction |
| **PASIPD (0-100)** | **RT** | 15.06 ± 8.14 (3-32) | 17.67 ± 6.85 (6-31) | +2.61 (14.77%) | 0.6828 | 0.1401 | 0.9943 |
| | **WLC** | 14.03 ± 6.43 (4-28) | 16.67 ± 14.26 (1-60) | +2.64 (15.84%) | | | |
| **ESES (0-40)** | **RT** | 30.00 ± 4.16 (25-40) | 32.34 ± 4.46 (25-40) | +2.34 (7.24%) | 0.9663 | 0.0758 | 0.1129 |
| | **WLC** | 31.05 ± 4.82 (22-39) | 31.19 ± 4.44 (23-39) | +0.14 (0.45%) | | | |
| **MSIS-29 Physical (0-100)** | **RT** | 23.51 ± 14.42 (0-50) | 16.33 ± 12.56 (0-36) | -7.18 (30.54%) | 0.8945 | 0.7294 | 0.0021 |
| | **WLC** | 16.43 ± 13.31 (0-41) | 22.25 ± 18.90 (0-61) | +5.82 (26.16%) | | | |
| **MSIS-29 Psychological (0-100)** | **RT** | 30.03 ± 24.31 (3-89) | 22.95 ± 17.22 (0-67) | -7.08 (23.58%) | 0.5158 | 0.3504 | 0.0605 |
| | **WLC** | 21.30 ± 20.77 (3-91) | 23.73 ± 18.00 (0-67) | +2.43 (10.24%) | | | |

*Values are means and standard deviation (lowest and highest value)*

Abbreviations: RT = Running Training; WLC = Waitlist Control; PASIPD = Physical Activity Scale For Individuals With Physical Disabilities; ESES = Exercise Self-Efficacy Scale; MSIS-29 = Multiple Sclerosis Impact Scale;

**Discussion**

This randomized controlled trial investigated the effect of 12-week community-based running training on physical function in pwMS with mild disability. Main results were that community-based running training led to significant improvements in functional mobility and maximal exercise intensity during a maximal graded exercise test on a bicycle ergometer compared with a waitlist control group. No significant changes in walking speed and walking endurance were found in any groups. However, participants of the RT-group reported a decrease of the impact of MS on walking disability and secondary, the impact of MS on physical functioning.

*Training adherence*

The unsupervised community-based running program, remotely instructed, appeared to be feasible. During our 12-week study, there was a dropout rate of 7/42 (17%) in the both groups. This percentage is very similar to previous exercise studies: Geddes et al. reported a drop out of 3/15 (20%) during a 12-week home walking program[46]; van den Berg et al. reported a drop out of 3/19 (16%) during 4 weeks of supervised aerobic treadmill training[30]. Schmidt and Wonneberger, who were investigating the long-term effects of individualized aerobic endurance exercise, reported a high dropout rate of 45/89 (51%), which was assigned to the very long duration (12 months) of the study, with the most prevalent dropout (23 of 45) in the first 3 months of the study[47].
In the studies of Schmidt and Wonneberger[47] and Geddes et al.[46] no adverse effects or increase in fatigue related to the training program were reported. However, in the study of Rampello et al.[26] 2 participants withdrawn from the study due to breathlessness and fatigue related to the training program. We believed that the training related complaints could be related to the higher impact of running training on the musculoskeletal system compared with bicycle training.

During 12 weeks of community-based running training, participants of the RT-group have shown a training adherence rate of 94%, which is comparatively high compared with the training adherence of the study of Geddes et al. (75%)[46] after 4 weeks of supervised aerobic treadmill training and Rampello et al. (87%)[26] after 8 weeks of aerobic training on a bicycle ergometer. We believed that the addition of 2 group-training sessions on a central location had a positive influence on training adherence, because of direct supervision of progress by the researchers and training adaptations if needed as well the social interaction and social support with the other participants. In fact, participants themselves constructed a dedicated Facebook webpage for this project. (https://www.facebook.com/msrunproject).
We also believed that training with a specific purpose (running at a public event) stimulates the participants' motivation to practice in order to achieve that goal. All participants were also aware that they were closely monitored during the training period by means of the Withings® sensor, which could influence training adherence. Participants themselves were also given the option to visualize their running results using an online web platform of the sensor.

*The effect of community-based running training on physical fitness and physical activity*

Physical fitness parameters improved after community-based running training. Significant improvements in $Wattage_{MAX}$ were found in the RT-group, while there was no change over time in the WLC-group. In $VO_2max$, a significant difference between two groups was found only in the training group. These findings suggest that improvements in physical fitness could be due to an increase in maximal exercise intensity ($Wattage_{MAX}$ +13%). Several previous studies examining the effects of aerobic training in more supervised settings demonstrated similar effects. The studies of Petajan et al.[24] and Rampello et al.[26] reported improvements of +25% and +20% in $Wattage_{MAX}$ in patients with an average EDSS-score of 3.8 and 3.5 respectively, after supervised aerobic bicycle training. Schulz et al.[48] reported improvements of +6% in $Wattage_{MAX}$ after supervised aerobic bicycle training in patients with an average EDSS-score of 2.0. These studies and our results indicate that greater improvement can be reached in pwMS with more disability.

Despite improvements in physical fitness after community-based running training, these results were not found in physical activity. By analyzing the PASIPD-score, we found small improvements in both RT-group and WLC-group. We believed that this behavioral change could be related to the participation of this study, because all participants were motivated to engage for training and were more aware of their physical activity during the study. It is also conceivable that the increase of physical activity in absolute values were related tot seasonal factors. Baseline testing took place during winter, while it was spring 12 weeks later, which may have an influence on reported physical activity. We note however that changes were small and in fact, not significant.
Comparing the scores of ESES, we found a trend of more self-esteem during exercise in the RT-group (+7%), while nothing changed in the WLC-group. However, this trend was not enough to show significant improvements in self-esteem after an unsupervised training. Participants of the RT-group reported significant lower impact of MS on physical functioning after training. Since it is known that physical fitness is related to disease severity[19],we believed that these findings can be related to the improvements of physical fitness.

*The effect of community-based running training on walking capacity*

Despite no differences in walking capacity were found, the results of this study suggest that community-based running training can significantly improve functional lower limb mobility and impact of MS on walking disability. Participants of the RT-group improved their walking distance from 576m at baseline, to 590m after 12 weeks running training. This results are similar to the findings of Goldman et al. reporting a total walking distance between 595m and 603m in pwMS with mild disability[36]. We believed that the low and not significant improvement in walking distance (+2%) in contrast to improved physical fitness during our study could be explained by a good performance at baseline, which was not able anymore to improve substantially. Greater improvements can be reached in pwMS with more walking disability. Rampello et al. (+7%)[26] and Kileff and Ashburn (+14%)[49] demonstrated significant improvements in walking distance after supervised bicycle training in pwMS with moderate disability.

Geddes et al.[46] reported +16% improvement after a 12-week home walking program. This indicates that more improvements on walking capacity, even in our group, could be reached after a more task-specific walking training. In fact, this study focused on the task running, so one could also state that is rather logical that no impact on walking capacity expressed by speed was present. Although no differences were found during objective measurement of walking capacity, participants of the RT-group reported a significant lower impact of MS on walking disability. We believed that these subjective findings could have a positive influence on patients' ADL (activities of daily living).

Despite no differences in walking capacity were demonstrated, significant improvement in 5STS-test was found, perhaps due to increased muscle strength and dynamic balance because of the running training. The sensitivity of the test in patients with mild disability, may advocate for the value of lower limb strength and balance training in pwMS with mild disability.

*Study limitations and recommendations*

Both groups showed differences in age, body weight and body mass index at baseline. With 4 men out of 42 participants, there was also an unequal distribution of the gender, which was not significant between both groups. Participants of the WLC-control group were significantly older, heavier and had a higher BMI, which could have an influence on physical fitness. Further research using a more heterogeneous group of MS-patients is needed to draw generalized conclusions. Another limitation is that the present study did not report an EDSS-score and type of MS, which would allow comparison with other study results. There was no EDSS available given that we recruited as well via the MS society and via web platforms, and not performed an EDSS status report by a central neurologist.

Using a bicycle ergometer as a tool for measuring maximal exercise capacity during a graded maximal exercise test was not task-specific in a running training program. Maximal exercise testing by running on a treadmill would be more task-specific for determining exercise intensity during running training. One could hypothesize that the improvement in physical fitness and running parameters would even be greater during treadmill-based methods.

Although improvements were demonstrated in physical fitness, these finding were not found in physical activity, measured by questionnaires. Objective research methods using accelerometry could possibly better reveal differences between groups investigating physical activity.

Despite no differences in walking capacity were demonstrated, the 5STS-test was found to be a sensitive test investigating functional mobility (lower limb muscle strength and balance) in pwMS with mild disability. These findings were confirmed during maximal exercise testing, where participants of the RT-group could cycle at a higher resistance. Investigating lower limb muscle strength using a dynamometer is recommended in future research to confirm this hypothesis.

This study investigated the effects of community-based running training only in pwMS with mild disability. This training modality cannot be used in pwMS with a more severe disability, who experiences more walking disability. For these patients, it could be useful to investigate the effect of community-based walking training.

Because of several complaints, reported by the participants, about the increased intensity of training during the last 4 weeks, it could be advisable to prolong the duration of training to 16 instead of 12 weeks.

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## Appendix

*Appendix 1: Example training schedule (good exercise capacity)*

| Training Week/Number | Total Distance (km) | Estimated Duration (min.) | Schedule (Including group training at 4.3 and 8.3) | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.1 | 5 | 60 | 60' | | | | | | | | | | | | | | | | | | | |
| 1.2 | 5 | 60 | 60' | | | | | | | | | | | | | | | | | | | |
| 1.3 | 5 | 60 | 60' | | | | | | | | | | | | | | | | | | | |
| 2.1 | 5 | 50 | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' |
| 2.2 | 5 | 48 | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 2' | 3' | 1' | 3' | 2' | 2' |
| 2.3 | 5 | 48 | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 1' | 4' | 2' | 3' | 1' | 3' | 2' | 2' |
| 3.1 | 5 | 47 | 1' | 4' | 1' | 4' | 2' | 3' | 1' | 4' | 2' | 4' | 1' | 4' | 2' | 4' | 1' | 4' | 2' | 3' | | |
| 3.2 | 5 | 47 | 1' | 4' | 1' | 4' | 2' | 3' | 1' | 4' | 2' | 4' | 1' | 4' | 2' | 4' | 1' | 4' | 2' | 3' | | |
| 3.3 | 5 | 45 | 2' | 4' | 2' | 4' | 1' | 4' | 2' | 4' | 2' | 4' | 1' | 4' | 2' | 4' | 3' | 2' | | | | |
| 4.1 | 5 | 43 | 2' | 3' | 2' | 3' | 2' | 3' | 2' | 3' | 1' | 4' | 2' | 3' | 2' | 3' | 2' | 3' | 2' | 1' | | |
| 4.2 | 5 | 43 | 2' | 3' | 2' | 3' | 2' | 3' | 2' | 3' | 1' | 4' | 2' | 3' | 2' | 3' | 2' | 3' | 2' | 1' | | |
| ***<u>4.3</u>*** | 5 | 41 | 2' | 3' | 2' | 3' | 3' | 3' | 2' | 3' | 2' | 3' | 3' | 3' | 2' | 3' | 3' | 1' | | | | |
| 5.1 | 5 | 41 | 2' | 3' | 2' | 3' | 3' | 3' | 2' | 3' | 2' | 3' | 3' | 3' | 2' | 3' | 3' | 1' | | | | |
| 5.2 | 5 | 39 | 2' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 2' | 3' | 3' | 2' | 2' | 2' | 2' | 2' | 3' | 1' | | |
| 5.3 | 5 | 39 | 2' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 2' | 3' | 3' | 2' | 2' | 2' | 2' | 2' | 3' | 1' | | |
| 6.1 | 5 | 39 | 2' | 2' | 3' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 4' | 4' | | | | |
| 6.2 | 5 | 39 | 2' | 2' | 3' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 4' | 4' | | | | |
| 6.3 | 5 | 38 | 2' | 2' | 3' | 2' | 2' | 2' | 4' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 4' | 2' | | | | |
| 7.1 | 5 | 38 | 2' | 2' | 3' | 2' | 2' | 2' | 4' | 2' | 2' | 2' | 3' | 2' | 2' | 2' | 4' | 2' | | | | |
| 7.2 | 5 | 37 | 3' | 2' | 3' | 2' | 4' | 2' | 2' | 2' | 3' | 2' | 4' | 2' | 4' | 2' | | | | | | |
| 7.3 | 5 | 37 | 3' | 2' | 3' | 2' | 4' | 2' | 2' | 2' | 3' | 2' | 4' | 2' | 4' | 2' | | | | | | |
| 8.1 | 5 | 37 | 4' | 2' | 3' | 2' | 4' | 2' | 4' | 2' | 3' | 3' | 5' | 3' | | | | | | | | |
| 8.2 | 5 | 37 | 4' | 2' | 3' | 2' | 4' | 2' | 4' | 2' | 3' | 3' | 5' | 3' | | | | | | | | |
| ***<u>8.3</u>*** | 5 | 36 | 4' | 2' | 3' | 2' | 5' | 2' | 3' | 2' | 4' | 1' | 5' | 3' | | | | | | | | |
| 9.1 | 5 | 35 | 5' | 2' | 5' | 2' | 5' | 2' | 5' | 2' | 5' | 2' | | | | | | | | | | |
| 9.2 | 5 | 35 | 5' | 2' | 4' | 2' | 5' | 2' | 5' | 2' | 6' | 2' | | | | | | | | | | |
| 9.3 | 5 | 35 | 5' | 2' | 6' | 2' | 5' | 2' | 6' | 2' | 3' | 2' | | | | | | | | | | |
| 10.1 | 5 | 34 | 6' | | 2' | 7' | | 2' | 6' | | 2' | 7' | | 2' | | | | | | | | |
| 10.2 | 5 | 33 | 9' | | 2' | 9' | | 2' | 9' | | 2' | | | | | | | | | | | |
| 10.3 | 5 | 33 | 12' | | 2' | 3' | | 2' | 12' | | 2' | | | | | | | | | | | |
| 11.1 | 5 | 32 | 14' | | 2' | 14' | | 2' | | | | | | | | | | | | | | |
| 11.2 | 5 | 31 | 14' | | 1' | 15' | | 1' | | | | | | | | | | | | | | |
| 11.3 | 5 | 31 | 14' | | 1' | 15' | | 1' | | | | | | | | | | | | | | |
| 12.1 | 5 | 31 | 10' | | 1' | 19' | | 1' | | | | | | | | | | | | | | |
| 12.2 | 5 | 30 | 30' | | | | | | | | | | | | | | | | | | | |
| 12.3 | 5 | 30 | 30' | | | | | | | | | | | | | | | | | | | |

| | 
|---|
| Walking ± 5 km/h |
| Running ± 10 km/h |

<u>Abbreviations:</u> km = kilometer; min. = minute; km/h = kilometers per hour

# Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
**The effect of community-based running training on physical function in patients with multiple sclerosis: a randomized controlled trial**

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2016**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

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