2016•2017
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Effect of high-intensity interval and resistance training on cardiovascular risk factors in MS patients

Promotor :
Prof. dr. Bert OP 'T EIJNDE

Copromotor :
dr. Inez WENS

Tobias Severijns , Ferdy Wijckmans
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

universiteit hasselt
KNOWLEDGE IN ACTION

Universiteit Hasselt | Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Universiteit Hasselt | Campus Diepenbeek | Agoralaan Gebouw D | BE-3590 Diepenbeek

universiteit hasselt
KNOWLEDGE IN ACTION

2016•2017

FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Effect of high-intensity interval and resistance training on cardiovascular risk factors in MS patients

Promotor :
Prof. dr. Bert OP 'T EIJNDE

Copromotor :
dr. Inez WENS

Tobias Severijns , Ferdy Wijckmans

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

universiteit hasselt

KNOWLEDGE IN ACTION

Acknowledgement

First of all, we would like to take this opportunity to thank everyone who contributed to this master thesis. First, our promotor Prof. Dr. Op ‘t Eijnde Bert and co-promotor Dr. Wens Inez for their guidance throughout the first and second part of this thesis.

Furthermore, we want to express our gratitude to Hasselt University and the REVAL Rehabilitation Research Center for the opportunity to perform this master thesis and use their professional equipment to make this research possible.

Bilzen, Maaseik, June 2017 *S.T., W.F.*

Research Framework

This research study fits in the domain of cardiorespiratory and internal diseases as well as the neurological subdomain of the rehabilitation sciences and physiotherapy department of Hasselt University and is constructed according to the central format.

In healthy people, lowered physical activity levels can lead to secondary health problems, such as cardiovascular diseases. Physical exercise can reverse these inactivity related health problems. In multiple sclerosis (MS) population groups, where there is a higher prevalence of cardiovascular risk factors, physical activity safely and efficiently improves physical deconditioning, potentially leading to a decrease in cardiovascular risk factors. The effect size of low to moderate intensity exercise, however, is small. Here, higher intensity exercise might improve therapy outcomes.

In a study of Wens et al. (2016), positive effects of high intensity interval training in combination with resistance training (HIITR) on muscle strength and endurance capacity were demonstrated. In this paper, the effect of HIITR on cardiovascular risk factors was studied through a quasi-experimental study. Outcome measures are: endurance capacity, body composition, physical activity level, isometric muscle strength, oral glucose tolerance, blood lipids and lipoprotein - cholesterol.

The research topic and protocol were provided by our promotor Prof. dr. Bert Op ‘t Eijnde and co-promotor dr. Inez wens. Dr. Inez Wens, Charly Keytsman and colleagues at REVAL center of Hasselt University performed practical research and data-collection. Furthermore, data processing, interpretation of results and the academic writing process was performed by both master students independently, under guidance of promotor Prof. dr. Bert Op ‘t Eijnde and co-promotor dr. Inez Wens.

This thesis is a duo-thesis and every part individually accomplished by both master students is clearly described in table 6.

1. Abstract

Background: Previous research suggests a reduced physical activity level in patients with multiple sclerosis (pwMS), possibly leading to an increase in cardiovascular risk factors. Here, and similar to healthy subjects, exercise training of higher intensity (HIT) might improve therapy outcome. The aim of this study was to investigate the effect of high-intensity interval training in combination with resistance training HIITR on cardiovascular risk factors.

Methods: Twenty-nine pwMS were assigned to a sedentary control group (SED) or a 12-week high intensity interval plus resistance training group (HIITR). At baseline and after 12 weeks, oral glucose tolerance tests (OGTT), body composition measurements (DEXA) and cardiopulmonary exercise tests (CPET) were carried out. Isometric knee flexor/extensor strength (F_{iso}), the physical activity scale for individuals with physical disabilities (PASIPD), blood lipids and lipoprotein-cholesterol were also assessed.

Results: In pwMS, 12-weeks of HIITR increased isometric knee flexor/extensor strength values and endurance capacity ($P < 0.05$). Furthermore, a decrease was evident in OGTT/plasma value (120 minutes post exercise) and in HOMA value, by 5.20±6.24% ($P = 0.047$) and 12.26±12.78% ($P = 0.026$), respectively. However, most plasma glucose and serum insulin levels did not significantly differ from SED. No significant between group differences were found in body composition, PASIPD and blood lipid levels.

Discussion and conclusion: Twelve weeks of HIITR, in pwMS, significantly improved muscle strength and endurance capacity, while no significant improvements in most cardiovascular risk factors were found. A reduction in HOMA value, however, might indicate a slightly decreased risk on developing IGT.

Keywords: Multiple sclerosis, High-intensity interval training, resistance training, oral glucose tolerance, body composition, endurance capacity, isometric muscle strength, physical activity level, blood lipids, lipoprotein – cholesterol.

2. Introduction

Multiple sclerosis (MS) is a progressive demyelinating disease of the central nervous system, affecting approximately 2.300.000 people worldwide. The early course of MS is marked by episodes of neurological dysfunction that generally recover. However, as the disease progresses, pathological changes become dominant and neurological degeneration is present. A wide range of heterogeneous neurological and peripheral symptoms characterizes MS. Most common symptoms being fatigue and muscle weakness, which, amongst others, lead to a decrease in physical activity, functional capacity as well as a reduction in health-related quality of life (HRQOL).[1-3] Neurologically, metabolic changes within axons and demyelination of the central nervous system are present.[1; 4]

In healthy population groups, lowered physical activity levels can lead to secondary health problems such as cardiovascular diseases, obesity and type 2 diabetes, preceded by impaired glucose tolerance (IGT). Cardiovascular disease (CVD) includes coronary heart diseases (CHD), cerebrovascular diseases and peripheral arterial diseases. Common risk factors are abdominal obesity, low high-density lipoprotein (HDL), high low-density lipoprotein (LDL), hypertension and glucose intolerance. In MS, there is a higher prevalence of CVD compared to healthy subjects. Hypertension, hyperlipidaemia and type 2 diabetes are frequently observed in the MS population.[5-7] In a recent study by Wens, I (2013), it was demonstrated there were elevated impaired fasting glucose concentrations and there was higher IGT-prevalence in MS.[8] However, it is not clear whether an increased risk of CVD is related to an increased risk of obesity or changes in body composition, hypertension, dyslipidaemia or type II diabetes in pwMS.

Physical exercise can reverse these secondary health problems related to physical inactivity in other populations. Cardiovascular disease risk can be reduced by about 20-30% by moderate level of leisure time physical activity. It can even be further reduced by 30-40% by high level of leisure time physical activity in healthy subjects.[9] Research in pwMS suggests that lower physical activity levels correlate with an increase in abdominal fat accumulation, higher levels of triglycerides, lower levels of HDL, reduced insulin sensitivity, an increase in fatigue and a decrease in endurance capacity and muscle strength.[10; 11] Consequently, increasing physical activity is an interesting tool that safely and efficiently improves physical deconditioning in

MS.[12-14] Indeed, low-to moderate endurance training is well tolerated in pwMS and improves maximum aerobic capacity and HRQOL.[14-16] The effect size of low to moderate intensity exercise, however, is small. Here, and similar to healthy controls and other disease populations, higher intensity (HIT) exercise might improve therapy outcome.[11; 17]

In previous studies in pwMS, it has been concluded that high intensity interval training and resistance training, as separate training modalities, are safe and well tolerated.[14-16; 18] The effect of combining these two training modalities has only been sparsely investigated among pwMS, concluding that high intensity aerobic exercise in combination with resistance training is indeed safe and improves glucose tolerance.[17]

In accordance with the above line of reasoning, this study aims to investigate the effects of a 12-week high intensity interval and resistance training program on cardiovascular risk factors in pwMS. We hypothesize that HIIT has beneficial effects on cardiovascular risk factors in pwMS.

3. Methods

3.1 Participants

After informed consent was obtained, a total of 29 MS patients, older than 18 years, were enrolled in this study. To be included, McDonald criteria (EDSS range 0-6) had to be used in the diagnosis of MS. Exclusion criteria for pwMS were having another chronic illness, pregnancy, being an athlete or physically active adult (> 30 MET*h/week), not being able to perform high-intensity exercise, having any indications to refrain from engaging in physical activity and/or participating in another study. Furthermore, pwMS were rejected if an acute MS exacerbation was evident within six months preceding study take-off. The participants were recruited in Belgium from the MS clinic Overpelt database, through local advertisements and via the REVAL Hasselt Database.

This quasi-experimental study was authorized by the medical ethics committee of Jessa Hospital Hasselt (s1 protocol) and Hasselt University. All mentioned measurements were performed per the Declaration of Helsinki and public health criteria.

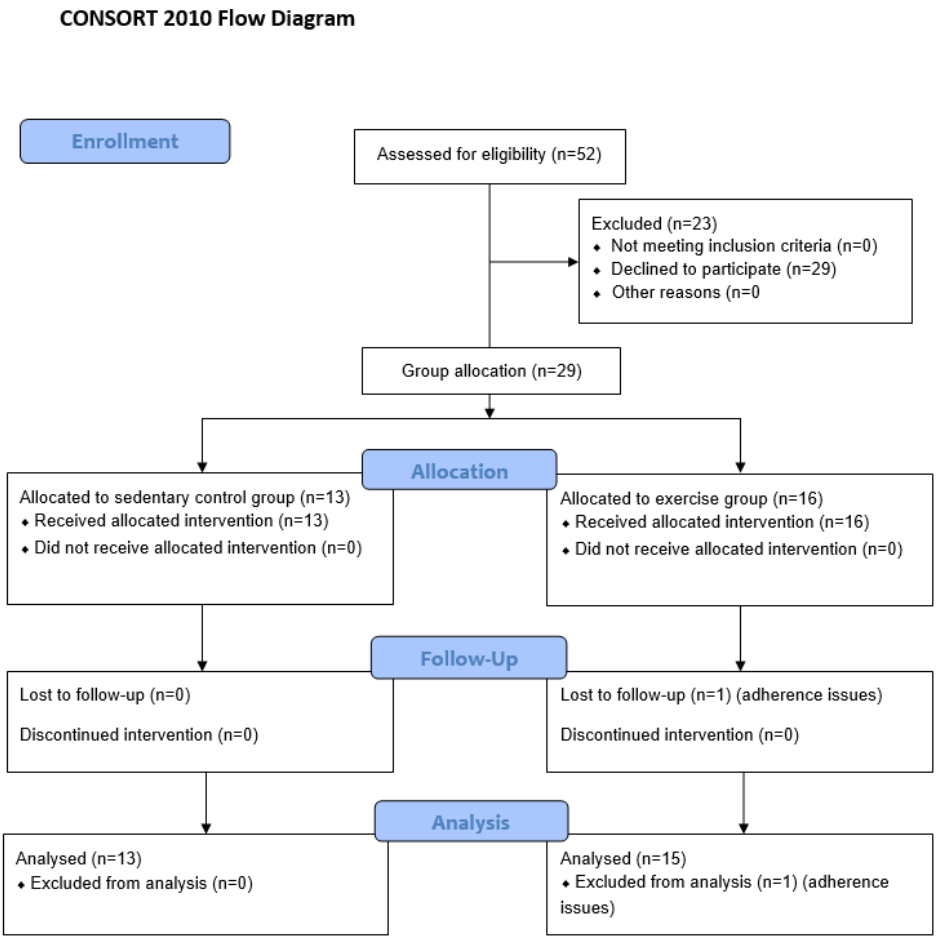

Figure 1. Consort flow diagram concerning enrolment, allocation, follow-up and analysis of subjects.

3.2 Study Protocol

3.2.1 Pre-intervention measurements

Following study inclusion, baseline measurements were performed. Consisting of a cardiopulmonary exercise test (CPET), a body composition measurement (DEXA), the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD), isometric knee flexor and extensor muscle strength measurements (F_{iso}) an oral glucose tolerance test (OGTT), and blood lipids, lipoprotein-cholesterol blood samples (BLG).

3.2.2 Intervention program

After pre-intervention measurements, subjects were allocated to either a sedentary control group (SED) or an intervention group (HIITR). Participants could indicate which group (SED or HIITR) had their preference, and were divided in one of two groups as such. HIITR consisted of a 12-week high-intensity interval training program combined with resistance training, whereas SED subjects remained physically inactive during the study course. Both subjects and research workers participating in this quasi experimental trial were not blinded to group allocation.

HIITR (High-Intensity Interval Training combined with Resistance Training)

Following pre-intervention measurements and group allocation, the HIITR group engaged in a twelve-week exercise program, which took place at the Rehabilitation Research Centre of Hasselt University. All training sessions were supervised by researchers and physiotherapists. Participants had to complete 5 training sessions per 2 weeks (3 sittings in one week and 2 sittings in the other week). Training sessions were interspersed by minimal 24 hours of rest, to guarantee sufficient recuperation and to minimize training related injuries. HIIT consisted of cardiovascular training and resistance training

Cardiovascular training: Exercise programs were adjusted so the patient could execute them at high workload, which, in the primary six weeks, was determined as the hearth rate represented by 100% of the maximal cycling resistance from the baseline's maximal CPET. Progressing through the intervention program, patients had to reach the HR_{max} during each training session. Every session commenced with 5 minutes of warm-up executed on a cycle ergometer. Following warm-up, high intensity cycle interval training was completed. Throughout the first six weeks, training length gradually rose from 5 x 1 minutes of maximal

exercise interspersed by 1-minute rest intervals to 5 x 2 minutes and 1-minute rest intervals. During the second six-week training period, the heart rate rose to a level corresponding to 100 to 120% of the maximal workload. Concluding each session, extremities were stretched. Adherence to exercise and adverse events were monitored by means of an exercise diary.

Resistance training: Every session was accompanied by a resistance training program. A well-balanced program, consisting of six different muscle strengthening exercises targeting all major muscle groups of the body, was executed at moderate to high intensity. Following exercises, using Technogym equipment, were performed: leg press, leg curl, leg extension, vertical traction, arm curl and chest press. Workout intensity and length were adapted from 1 x 10 repetitions to 2 x 20 repetitions at maximal achievable resistance. The amount of repetitions was determined in advance, while intensity was based on subject's impairment levels and possibilities. Considering regularly reported leg strength variations in both legs in pwMS, resistance training of the lower extremities was executed unilaterally.

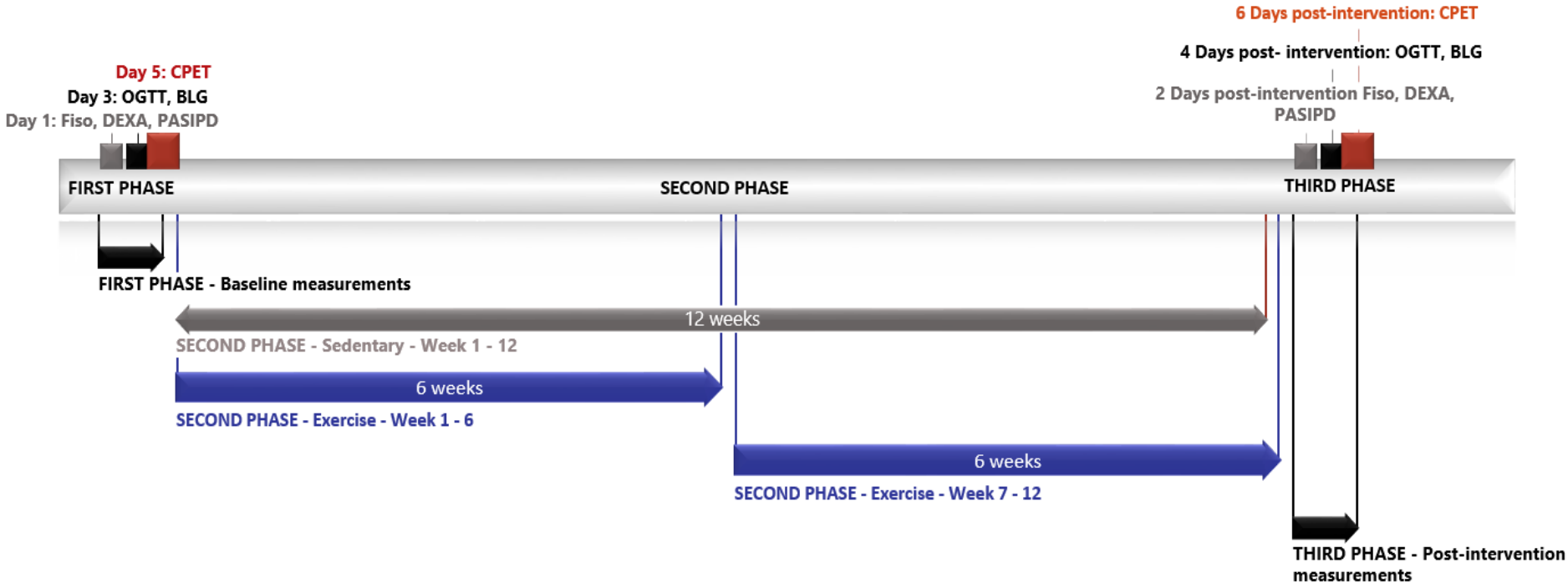

Figure 2. Schematical presentation of the study design.

Abbreviations used: F_{iso}, isometric muscle strength; DEXA, Dual-energy X-ray absorptiometry; PASIPD, physical activity scale for individuals with physical disabilities; OGTT, oral glucose tolerance test; BLG, blood lipids, lipoprotein-cholesterol, and glucose blood samples; CPET, cardio pulmonary exercise test.

3.2.3 Post- intervention measurements

Following HIITR exercise therapy or SED, post-intervention measurements were performed identical to pre-intervention measurements.

3.2.4 Measurements

Outcome Measures

Endurance capacity

Subjects performed a cardiopulmonary exercise test (CPET) on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany) at a cycle pedalling rate of 70 rounds per minute, accompanied by evaluation of respiratory gas exchange (Jaeger Oxycon, Erich Jaeger GmbH, Germany). Commencing every assessment day, calibration was executed. Participants were advised to refrain from any exercise one day in advance as well as the testing day itself, and to only eat a light meal two hours prior to testing. Endurance testing was performed minimal 48 hours apart from isokinetic dynamometer testing to avoid muscle exhaustion conflict. Two different protocols were used for women and men. After a 5-minute cycling warm-up, participants commenced cycling at 20W (women) and 30W (men) for 60 seconds. After this, workload gradually rose with 10W and 15W each minute, respectively, until exhaustion. Two minutes after completing the test, recovery heart rate (HR_{rec}) was taken. Hereafter, participants completed a 5-minute low load cool down. Following parameters were gathered every breath, their mean was computed every 10 seconds: maximal oxygen uptake (VO_2max), expiratory volume (VE), respiratory exchange rate (RER). During the cardiopulmonary exercise test the RER was measured to validate if the test was executed until exhaustion (RER ≥ 1.15). This is the ratio of carbon dioxide output/oxygen uptake (VCO_2/VO_2), measured by gas exchange at the mouth. HR was assessed each minute using a 6-lead electrocardiograph (ECG) apparatus. Furthermore, maximal cycling resistance (W_{max}), test length, maximal heart rate (HR_{max}), maximal and peak lactate levels (Lac_{max}, Lac_{peak}), were reported.[22; 23]

Body composition

Before body composition of all participants was determined, weight and length were measured and BMI was calculated. Thereafter, a Dual Energy X-ray Absorptiometry scan (GE Hologic Series Delphi-A, Vilvoorde, Belgium) assessed total mass, fat mass, lean tissue mass and fat percentage for the whole body. The measurements were taken at baseline and after completing the 12-week training or sedentary program, at the same time of day.

Physical activity level

To determine physical activity level, The Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) was used. This questionnaire consists of 13 items concerning home repair, lawn and garden work, leisure time, sports, ADL and work related physical activity over a period of seven days. Patients were asked at baseline and after the 12-week HIITR exercise or SED program to quantify their physical activity. The amount of days as well as the average hours in a day spent participating in 13 selected activities, over the last seven days, were reported by the participants. A 4-point scale was used, with duration responses from 1(less than one hour) to 4 (more than four hours), and answers concerning frequency ranging from1 (never) to 4 (often). Physical activity was defined as the outcome of the average time used up in one of the 13 selected activities, on a daily base, times a metabolic equivalent value and summed over items. Scores ranged from 0 (no activity) to over 100 MET*h/week (very high). Physical inactivity, determined as < 30 MET*h/week, was a criterion prior to inclusion in the study.[24]

Isometric muscle strength

An isokinetic dynamometer (system 3, Biodex ENRAF-NONIUS, New York, USA) was used to perform isometric muscle strength measurements on leg extension and flexion. The protocol consisted of a 5-minute warm-up period followed by a familiarization procedure, where participants were instructed to execute the knee extension and flexion adequately. Hereafter, maximal voluntary isometric muscle strength, of the knee extensors and flexors (45° and 90°), was measured. For each leg, subjects executed two maximal isometric extensions (four seconds) and two flexions (four seconds), separated by 30 seconds of rest. The highest isometric peak torques for both flexion and extension (Nm) were taken as the maximal

isometric muscle strength for the corresponding leg. The muscle strength of the weakest leg was reported and used for further analysis.

Oral Glucose Tolerance Test

Glucose tolerance in pwMS was investigated through an oral glucose tolerance test (OGTT). A test which is primarily used in diagnosing diabetes by determining plasma glucose concentration. For standardized completion of this test, subjects were instructed to refrain from eating for 10-hours during the night. After this 10-hour fasting period, a glucose bolus of 1 gram per kilogram of bodyweight was administered to participants at 8 AM.

Whole blood glucose concentrations (Analox GM7 Micro-stat; Analox Instruments Ltd., London, UK) were instantly measured by means of capillary blood specimens, taken from a hyperaemic earlobe. This process was executed before and after the administration of the glucose bolus and was monitored using 20-minute intervals in the 2-hour post-glucose load.

Insulin sensitivity and secretion are important contributing factors in the determination of plasma glucose levels, while administering the OGTT. As such, levels of serum insulin were calculated by obtaining 4 ml venous blood samples, in tubes which separated the serum (SST, BD Vacutainer; Becton-Dickinson, Erembodegem, Belgium). This happened at 1 hour intervals. After half an hour, when the blood had the possibility to clot, taken samples were centrifuged for a set period of 10 minutes, at 3500 rounds per minute. In advance of analysation of the batch of serum insulin levels, the serum was collected, frozen and eventually stocked at a temperature of -80°C, as reported by instructions provided by the manufacturer (Mercodia Insulin ELISA, Uppsala, Sweden).

For the determination of impaired glucose tolerance, as recommended by the World Health Organisation, the glucose concentrations in whole blood had to be transformed to the equivalent concentrations in the pertinent plasma, by applying a factor of 1.11. The classification of impaired fasting glucose is described by the World Health Organisation as a 6.1 to 6.9 mmol/L fasting plasma glucose concentration range. At 2 hours, after administration of the glucose bolus, the range is set at 7.8 to 11.1 mmol/L. The homeostasis model

assessment of insulin resistance was used to detect glucose tolerance level (HOMA-IR=fasting plasma glucose (mmol/L) × fasting serum insulin (mU/l)/22.5).[19-21]

Blood Lipids, Lipoprotein-Cholesterol

A blood test was performed by extracting blood from the vein after a required fasting period of 10 hours. Hereafter, the sample was centrifuged at 2000 rpm for 10 minutes. Directly following centrifugation, blood plasma was frozen in liquid nitrogen and contained at -80°C before further analysis. Total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and plasma triglycerides were investigated in plasma samples. Furthermore, C-reactive protein (CRP) (Beckman Synchron LX 20 Analyzer®, Beckman Coulter Inc., Diamond Diagnostics, USA), and glycosylated haemoglobin (HbA1c) for long-term blood glucose values (Hi-Auto A1c Analyzer®, Menarini Diagnostics Inc., Florence, Italy) were analysed.

3.3 Statistical Analysis

The data analysis was conducted using IBM SPSS statistics 24. Baseline differences between SED and HIITR groups were assessed using an unpaired student's t-test (Mann Whitney U test). Pre-post differences between groups were analysed using an unpaired student's t test (Mann Whitney U test) on the deltas between pre-and post-measurements, whereas within group differences (post minus pre) were analysed with a paired student's t test (Wilcoxon signed rank test). All statistical analyses were independently executed by two researchers. All data are presented as mean ± SE. Relative changes following intervention were calculated as the mean of the individual changes and expressed as a percentage. Statistical significance was achieved when $P \leq 0.05$, whereas $P < 0.01$ indicates the value to be highly statistical significant.

4. Results

4.1 Baseline subject characteristics and adherence to intervention

At baseline, participant and disease characteristics weren't significantly different between the intervention and control group (Table 1). However, pre-intervention outcome measures, such as fat mass (P = 0.039), HbA1c (P = 0.044) and VO_2 max (P = 0.028) were significantly different between groups. Furthermore, more than 90% of all 30 exercise sessions were executed as prescribed in HIITR. Two absences were reported. Reasons for nonappearance were a holiday and domestic reasons. No serious adverse events, nor potentially exercise-induced exacerbations were reported along the course of this study. In the HIITR-group there was one drop-out following adherence issues. (Table 1)

Table 1: Baseline participant and disease characteristics. Data is presented as mean ± SD. Differences between groups (SED, EX) were analysed using an unpaired student's t test (Mann Whitney U test). Abbreviations used: SED, sedentary (usual care); HIITR, high intensity interval training plus resistance training; EDSS, expanded disability status scale; BMI, body mass index.

	SED (n = 13)	***HIITR (n = 16)***	***P-Value***
Age (y)	53.46 ± 2.82	52.69 ± 1.80	0.76
Gender (m/f)	5/8	7/9	1.00
EDSS	3.27 ± 0.40	2.63 ± 0.39	0.31
Weight (kg)	76.63 ± 3.37	68.74 ± 3.30	0.15
Length (m)	1.71 ± 0.02	1.71 ± 0.22	0.97
BMI (kg/m2)	26.30 ± 1.04	23.47 ± 0.78	0.07
Smoke (Yes/no)	2/11	1/4	0.67
Medication BP (Yes/No)	6/7	3/16	0.23

4.2 Outcome measures

Cardiopulmonary exercise test

Endurance capacity:

In SED, there was a significant decline evident, after 12 weeks of refraining from exercise, concerning maximal cycling resistance, test duration and RER max. Values lowered by 10.93±4.47%, 12.14±5.10%, 6.67±3.24%, respectively (P < 0.05).

In contrary, maximal cycling resistance rose by 20.19±2.69% (P = 0.00) and test duration went up by 22.82±2.81% (P = 0.00), within group, after 12 weeks of HIITR. VO_2max, VE and Lac_{peak}

also increased significantly by 23.33±4.41% (P = 0.003), 17.74±4.04% (P = 0.005) and 34.53±8.41% (P = 0.022), correspondingly.

Between groups, there was a significant difference after 12 weeks of HIITR, compared with pre-intervention values, concerning maximal cycling resistance, test duration, VO_2max and expiratory volume (P < 0.01). Peak lactate level also significantly differed between groups (P < 0.05). (table 2)

Body composition

There wasn't any compelling evidence regarding changes in body composition measurements between (SED, HIITR) and within groups (post minus pre). (table 2)

Physical Activity Level

Concerning physical activity level, measured using the PASIPD scale, there weren't any significant changes evident. (table 2)

Isometric muscle strength.

In SED, pre-intervention isometric muscle strength of the strongest leg significantly decreased compared to post-intervention measurements in 45° extension by 12.61±5.68%, 45° flexion by 8.68±3.72% and in 90° extension by 8.34±3.21% (P < 0.05). In HIITR, however, there was a significant increase of 10.68±3.53% and 5.82±3.02% in isometric muscle strength of the strongest leg for extension in 45° and 180°, respectively (P < 0.05).

For SED, no significant differences were found considering the weakest leg. In the contrary, following 12 weeks of HIITR, extension in 45°, 90°, 180° rose by 17.19±3.74%, 19.10±3.62% and 10.33±1.52%, respectively. Isometric flexion strength of the weakest leg rose by 31.61±6.67% (P < 0.05) in 45° and 22.55±4.84% in 90° (P < 0.01).

Significant differences between HIITR and SED groups were evident. In the strongest leg, in 45° and 180° extension and in 45° and 90° of flexion. For the weakest leg, all but flexion in 180° were significantly altered in favour of the HIIITR group (P < 0.05). (Table 3).

Oral glucose tolerance test

Within group differences after 12 weeks of HIITR, were present in OGTT and plasma values measured at 120 minutes after exercise. Both values decreased significantly by 5.20±6.24% ($P = 0.047$). Furthermore, HOMA values lowered after 12 weeks of HIITR by 12.26±12.78% ($P = 0.026$).

No differences were observed between the two groups (SED, HIITR) after 12 weeks regarding OGTT values, plasma glucose levels, serum insulin values and HOMA values ($P > 0.05$). (Table 4)

Blood Lipids, Lipoprotein-Cholesterol

In SED, significant difference within group was absent for all values, except HDL. Here, there was a pre- to post-intervention decline of 7.56±2.34% ($P < 0.01$).

No differences were observed between the two groups (SED, HIITR) after 12 weeks regarding blood lipids, lipoprotein-cholesterol, CRP and HbA1c values ($P > 0.05$). (Table 4)

Table 2: Exercise capacity, body composition and physical activity level at baseline and after 12 weeks of usual care or high intensity aerobic exercise in combination with resistance training. Data is presented as mean ± SD. Pre-post differences between groups (SED, HIITR) were analysed using an unpaired student's t test (Mann Whitney U test) on the deltas between pre-and post-measurements, whereas within group differences (post minus pre) were analysed with a paired student's t test (Wilcoxon signed rank test). SED, sedentary (usual care); HIITR, high intensity interval training plus resistance training; VO_2max, maximum rate of oxygen consumption as measured during incremental exercise; RER, respiratory exchange rate; Lac, lactate; MET, metabolic equivalent of task.

	SED			HIITR			SED/HIITR
	PRE	*POST*	*P-Value*	*PRE*	*POST*	*P-Value*	*Between group*
Exercise capacity:							
Maximal cycling resistance (watt)	113.46 ± 11.40	100.77 ± 10.72	0.03[b]	142.19 ± 16.61	167.50 ± 18.43	0.00[a]	0.00[c]
Test duration (min)	8.54 ± 0.70	7.38 ± 0.64	0.02[b]	10.25 ± 1.09	12.25 ± 1.15	0.00[a]	0.00[c]
VO_2 max (ml/min/kg)	20.78 ± 1.83	21.24 ± 2.09	0.70	26.77 ± 2.15	32.66 ± 2.76	0.00[a]	0.00[c]
VE (l/min)	67.77 ± 5.85	59.77 ± 6.23	0.10	84.40 ± 7.84	99.40 ± 9.64	0.01[a]	0.00[c]
RER max	1.18 ± 0.04	1.09 ± 0.02	0.04[b]	1.24 ± 0.02	1.18 ± 0.04	0.08	0.39
HR rest (beats/min)	81.92 ± 2.43	81.46 ± 2.74	1.00	84.38 ± 3.13	79.81 ± 3.07	0.20	0.28
HR max (beats/min)	145.08 ± 6.21	140.23 ± 6.24	0.41	160.56 ± 3.40	162.19 ± 4.48	0.33	0.22
HR rec (beats/min)	105.15 ± 4.17	108.15 ± 5.64	0.39	117.56 ± 4.82	122.94 ± 4.65	0.12	0.76
Lac max	5.30 ± 0.64	4.62 ± 0.40	0.93	6.05 ± 0.46	5.75 ± 0.37	0.69	0.68
Lac peak	7.58 ± 0.72	6.39 ± 0.48	0.33	8.36 ± 0.74	10.35 ± 0.61	0.02[b]	0.03[d]
Body composition:							
Total mass (kg)	69.82 ± 3.22	70.25 ± 2.95	0.20	62.26 ± 3.11	61.17 ± 2.83	0.21	0.11
Fat mass (kg)	22.58 ± 1.87	23.15 ± 1.73	0.17	17.83 ± 1.19	16.99 ± 1.19	0.32	0.10
Lean tissue mass (kg)	47.16 ± 2.49	47.09 ± 2.39	0.86	44.42 ± 2.67	44.20 ± 2.59	0.49	0.61
Fat percentage (%)	32.37 ± 2.01	33.03 ± 1.96	0.20	29.03 ± 1.67	28.16 ± 1.87	0.30	0.10
Physical activity level (MET*h/week)	22.90 ± 4.59	28.21 ± 8.87	0.65	18.14 ± 3.58	25.88 ± 5.87	0.25	0.54

[a] $P < 0.01$, compared with pre-intervention value, within group
[b] $p < 0.05$, compared with pre-intervention value, within group
[c] $P < 0.01$, compared with pre-intervention value, between group
[d] $p < 0.05$, compared with pre-intervention value, between group

Table 3: Isometric muscle strength of the strongest and weakest leg at baseline and after 12 weeks of usual care or high intensity aerobic exercise in combination with resistance training. Data is presented as mean ± SD. Pre-post differences between groups (SED, HIITR) were analysed using an unpaired student's t test (Mann Whitney U test) on the deltas between pre-and post-measurements, whereas within group differences (post minus pre) were analysed with a paired student's t test (Wilcoxon signed rank test). SED, sedentary (usual care); HIITR, high intensity interval training plus resistance training; Ext, extension; Flex, flexion

	SED			**HIITR**			**SED/HIITR**
	PRE	*POST*	*P-Value*	*PRE*	*POST*	*P-Value*	*Between group*
Strongest leg							
Ext 45° (Nm)	109.67 ± 7.89	98.17 ± 11.53	0.04[b]	111.63 ± 8.76	124.00 ± 10.73	0.02[b]	0.00[c]
Flex 45° (Nm)	69.08 ± 6.36	62.92 ± 6.14	0.05[b]	80,25 ± 6.65	88.86 ± 7.55	0.10	0.01[c]
Ext 90° (Nm)	133.75 ± 11.69	122.50 ± 11.30	0.03[b]	142.38 ± 12.13	144.75 ± 12.42	0.62	0.06
Flex 90° (Nm)	57.33 ± 4.29	53.17 ± 5.53	0.06	62.06 ± 4.92	68.69 ± 5.41	0.09	0.01[d]
Ext 180° (Nm)	73.17 ± 5.94	68.83 ± 5.52	0.05	83.88 ± 7.22	89.88 ± 8.93	0.04[b]	0.01[c]
Flex 180° (Nm)	44.58 ± 3.87	42.50 ± 3.051	0.72	52.69 ± 5.61	56.94 ± 6.01	0.09	0.18
Weakest leg							
Ext 45° (Nm)	100.00 ± 10.40	97.58 ± 11.79	0.43	101.13 ± 11.25	115.38 11.18	0.00[a]	0.01[d]
Flex 45° (Nm)	61.67 ± 8.16	57.08 ± 8.51	0.24	63.69 ± 6.52	76.38 ± 6.54	0.01[b]	0.01[d]
Ext 90° (Nm)	115.58 ± 12.87	113.08 ± 11.98	0.82	111.75 ± 12.36	127.63 ± 11.92	0.01[a]	0.01[c]
Flex 90° (Nm)	51.50 ± 5.79	47.75 ± 6.62	0.15	50.38 ± 4.51	60.88 ± 5.58	0.00[a]	0.00[c]
Ext 180° (Nm)	69.50 ± 6.37	67.17 ± 6.85	0.37	74.13 ± 8.88	80.63 ± 9.22	0.00[a]	0.01[d]
Flex 180° (Nm)	38.58 ± 4.46	37.58 ± 4.38	0.62	42.25 ± 6.17	44.69 ± 5.62	0.44	0.43

[a] P < 0.01, compared with pre-intervention value, within group

[b] p < 0.05, compared with pre-intervention value, within group

[c] P < 0.01, compared with pre-intervention value, between group

[d] p < 0.05, compared with pre-intervention value, between group

Table 4: Glucose tolerance, blood lipids, lipoprotein-cholesterol, and glucose blood samples, heart rate, CRP values and HbA1c levels at baseline and after 12 weeks of usual care or high intensity aerobic exercise in combination with resistance training. Data is presented as mean ± SD. Pre-post differences between groups (SED, HIITR) were analysed using an unpaired student's t test (Mann Whitney U test) on the deltas between pre-and post-measurements, whereas within group differences (post minus pre) were analysed with a paired student's t test (Wilcoxon signed rank test). SED, sedentary (usual care); HIITR, high intensity interval training plus resistance training; OGTT, oral glucose tolerance test; HOMA, homeostatic model assessment; HR, heart rate; LDL, low density lipoproteins; HDL, high density lipoproteins; CRP, c-reactive protein; HbA1c; glycated haemoglobin (A1c).

	SED			**HIITR**			**SED/HIITR**
	PRE	*POST*	*P-Value*	*PRE*	*POST*	*P-Value*	*Between group*
OGTT0'	5.42 ± 0.20	5.22 ± 0.29	0.67	4.93 ± 0.23	4.64 ± 0.13	0.32	0.96
OGTT30'	9.93 ± 0.53	9.32 ± 0.28	0.29	8.99 ± 0.58	8.60 ± 0.27	0.47	0.64
OGTT60'	10.42 ± 0.89	9.12 ± 0.68	0.10	8.83 ± 0.52	8.80 ± 0.45	0.96	0.21
OGTT90'	8.98 ± 1.04	7.98 ± 0.73	0.13	8.08 ± 0.62	7.06 ± 0.54	0.16	0.68
OGTT120'	7.54 ± 1.06	6.84 ± 0.85	0.11	7.00 ± 0.62	6.20 ± 0.46	0.05[b]	0.98
insulin 0	84.54 ± 16.99	63.08 ± 7.90	0.40	61.31 ± 7.46	50.31 ± 4.45	0.05	0.69
insulin 1	780.30 ± 199.92	803.08 ± 163.41	0.20	601.25 ± 95.65	700.00 ± 106.06	0.44	0.69
Insulin 2	414.85 ± 91.52	400.77 ± 78.08	0.78	394.75 ± 98.54	314.19 ± 45.31	0.71	0.86
Plasma 0' (mmol/L)	6.02 ± 0.23	5.79 ± 0.32	0.67	5.47 ± 0.25	5.15 ± 0.15	0.32	0.96
Plasma 30' (mmol/L)	11.03 ± 0.58	10.34 ± 0.31	0.29	9.98 ± 0.64	9.55 ± 0.30	0.47	0.64
Plasma 60'(mmol/L)	11.57 ± 0.98	10.12 ± 0.76	0.10	9.81 ± 0.57	9.77 ± 0.50	0.96	0.21
Plasma 90' (mmol/L)	9.96 ± 1.16	8.86 ± 0.81	0.13	8.96 ± 0.69	7.84 ± 0.60	0.16	0.68
Plasma 120' (mmol/L)	8.37 ± 1.18	7.59 ± 0.94	0.11	7.77 ± 0.69	6.89 ± 0.51	0.05[b]	0.98
insulin 0' (mg/dl)	11.86 ± 2.38	8.85 ± 1.11	0.40	8.60 ± 1.05	7.06 ± 0.62	0.05	0.71
insulin 60' (mg/dl)	109.44 ± 28.04	112.63 ± 22.92	0.20	84.33 ± 13.42	98.18 ± 14.88	0.44	0.69
insulin 120' (mg/dl)	58.18 ± 12.84	56.21 ± 10.95	0.81	44.10 ± 8.55	44.20 ± 6.79	0.98	0.91
HOMA	3.16 ± 0.61	2.10 ± 0.37	0.13	2.11 ± 0.29	1.60 ± 0.13	0.03[b]	0.76
Total cholesterol (mmol/L)	198.46 ± 10.91	196.31 ± 9.12	0.70	193.56 ± 7.46	188.19 ± 7.02	0.54	0.76
LDL (mmol/L)	113.38 ± 8.77	116.38 ± 8.68	0.53	110.13 ± 6.24	106.88 ± 4.73	0.62	0.48
HDL (mmol/L)	61.85 ± 3.94	56.92 ± 3.57	0.01[a]	62.69 ± 5.38	59.94 ± 4.60	0.20	0.35
Triglycerides (mmol/L)	116.23 ± 16.52	115.23 ± 11.88	0.65	103.56 ± 13.73	106.88 ± 11.36	0.90	0.79
CRP (mg/L)	2.42 ± 0.61	1.79 ± 0.51	0.40	2.09 ± 0.68	1.25 ± 0.27	0.26	0.89
HbA1c	5.48 ± 0.12	5.39 ± 0.05	0.58	5.24 ± 0.07	5.26 ± 0.06	0.72	0.91

[a] P < 0.01, compared with pre-intervention value, within group; [b] p < 0.05, compared with pre-intervention value, within group; [c] P < 0.01, compared with pre-intervention value, between group; [d] p < 0.05, compared with pre-intervention value, between group

5 Discussion

In this quasi-experimental study, the effect of high intensity interval training combined with resistance training on cardiovascular parameters in pwMS was investigated. The exercise group participated in a 12-week exercise program. Significant differences were seen in isometric muscle strength of both legs, particularly in the weakest leg, as well as in exercise capacity values. Considering glucose tolerance, few parameters were significantly altered, however, HOMA values in the exercise group dropped significantly, suggesting a decreased risk for impaired glucose tolerance. No significant changes in body composition, PASIPD or blood lipid levels were documented.

HIITR and cardiovascular risk factors

A systematic review by Wens, I. et al (2013) demonstrated that the prevalence of type 2 diabetes in pwMS is comparable to, or slightly higher than in the general population. Concerning LDL and HDL values, the most valued studies indicated slightly elevated LDL and total cholesterol and lowered HDL values in pwMS.[10; 27]

A previous study observed a higher IGT prevalence in pwMS compared to healthy controls.[8] Physical activity might be able to improve peripheral insulin activity in other patient populations, thus reducing the risk of developing IGT.[9; 28] However, in a recent study in pwMS, no effects on blood glucose and serum insulin were detected after a 24-week mild-to-moderate-intensity resistance and endurance exercise program. Slawta et al. (2003), however, reported lower fasting glucose levels after a low-to-moderate-intensity leisure time physical activity program. Interestingly, high intensity aerobic exercise, combined with resistance training, improved glucose tolerance in pwMS.[17] This indicates that HIITR might be more effective to improve glucose tolerance than mild-to-moderate intensity training programs. In the present study, OGTT and plasma values, measured at 120 minutes post exercise, decreased significantly by 5.20±6.24% for the HIITR group ($P < 0.05$). Furthermore, HOMA values lowered by 12.26±12.78% after 12 weeks of HIITR ($P < 0.05$). Indicating a slightly decreased risk on developing IGT. Post-intervention data concerning blood-lipid levels did not differ significantly from pre-intervention measurements within HIITR ($P > 0.05$). No between group differences were observed for these parameters ($P > 0.05$).

HIITR and endurance capacity

In a study of Wens et al. (2016), positive effects of HIITR on muscle strength and endurance capacity were demonstrated. Therefore, HIITR was chosen as training modality in this quasi experimental study. Findings were similar to the outcomes of Wens et al. (2016). Endurance capacity increased significantly in HIITR. Maximal cycling resistance and test duration rose by 20.19±2.69% (P = 0.000) and 22.82±2.81% (P = 0.000), respectively. VO_2max, expiratory volume and lactate peak also rose significantly by 23.33±4.41% (P = 0.003), 17.74±4.04% (P = 0.005) and 34.53±8.41% (P = 0.022), respectively. Confirming the positive effects of HIITR on endurance capacity in pwMS. In SED, there was a decline evident, after 12 weeks of refraining from exercise, concerning maximal cycling resistance, test duration and RER max, by 10.93±4.47%, 12.14±5.10%, 6.67±3.24%, respectively (P < 0.05). Contributing to physical inactivity in pwMS, possibly leading to a decrease in functional capacity and/or a reduction in HRQOL.[1-3] A highly significant difference, concerning between group treatment effects, was evident. HIITR leads to improvements in maximal cycling resistance, test duration, VO_2max and expiratory volume (P < 0.01). Peak lactate level also significantly differed between groups (P < 0.05). It is advised to engage pwMS in physical activity training programs to decrease regression in endurance capacity caused by physical inactivity, and consequently, slowing potentially time-related decline in functional capacity and HRQOL.

HIITR and isometric muscle strength

At baseline, there were no significant differences between both groups, however, after 12 weeks there was a clear contrast SED and HIITR, in favour of HIITR. Considering pre-intervention values of SED, compelling evidence suggested a significant decline in isometric muscle strength. There was a 12.61±5.68%, 8.68±3.72% and 8.34±3.21% decrease for extension in 45° and 90° and flexion in 45°, respectively (P < 0.05). Furthermore, all isometric muscle strength values in the remaining positions decreased as well over time for the strongest leg (P > 0.05). This regression was conjointly visible in the weakest leg for all muscle positions (P > 0.05). This regression in muscle strength, contributes to the vicious circle of physical inactivity and muscle wasting, potentially leading to a reduction in HRQOL.[1-3] The contrary is visible when looking at post-intervention values of HIITR. Here, progression was noticeable in all muscle positions. With the greatest statistically significant incline situated in the weakest leg. Here, isometric extension force in 45°, 90° and 180° went up by 17.19±3.74%,

19.10±3.62% and 10.33±1.52%, respectively ($P < 0.01$). Isometric flexion force in 45° and 90° rose by 31.61±6.67% ($P < 0.05$) and 22.55±4.84% ($P < 0.01$), correspondingly. HIITR seems to be an effective way to counteract muscle wasting due to MS and improve isometric flexion and extension muscle force, namely for the weakest leg. This might contribute to lowering secondary health complications due to inactivity following muscle weakness.

Safety and tolerability

In previous studies, it has been shown that high intensity interval training, and resistance training are safe and tolerable training modalities for pwMS.[12; 14-16; 18] The combination of both modalities has only been sparsely investigated among pwMS, concluding that combining resistance training with high intensity interval training has a positive effect and is safe amongst pwMS.[17] The reason why it has only been sparsely investigated can be explained by the heat sensitivity phenomenon in pwMS, caused by an exercise induced rise in body temperature, eliciting symptom instability.[25; 26] Interestingly, in recent work, HIIT and HIITR had positive effects on muscle strength and exercise capacity in pwMS, with no dropouts, nor adverse events reported during these studies. In current quasi-experimental study, no adverse events and/or exacerbations were reported, implying that persons with mild to moderate MS can tolerate high intensity exercise programs combined with resistance training.

Limitations

This is one of the first studies investigating the effect of high intensity interval training combined with resistance training on cardiovascular parameters in pwMS, therefore, a priori power analysis couldn't be executed, by cause of the absence of a predefined effect size. A post hoc power analysis however was executed. Indicating a power of 0.82 for $P = 0.05$, an effect size of 0.5 and a total sample size of 29 subjects. Moreover, because of the small group size, non-parametrical testing had been executed, which has less power than parametrical testing.

Also, the studied group was heterogeneous of nature regarding EDSS values. In previous studies, EDSS values seemed to be correlated with glucose tolerance. In future studies, EDSS score should be a confounding factor when recruiting patients.

Furthermore, MS subtypes weren't described. In a previous study by wens et al. (2014), there was an association between MS subtype and IGT. In future research, MS subtypes should be acknowledged and considered in statistical analysis.

Concerning physical activity level, no significant differences were found, measured by PASIPD. This measure, however, is a subjective questionnaire, which could lead to overestimation of physical activity.[24; 29] Future studies could use accelerometers to objectively quantify physical activity.

Further, due to the design, social interactions between MS patients were possible, this could influence intervention results. Also, therapists and patients weren't blinded, hence causing a potential bias in intervention outcomes.

Finally, the main limitation of this trial was that subjects were free to indicate their intervention preference, so no randomisation was possible which could cause a potential allocation bias.

6 Conclusion

Present quasi-experimental study demonstrates the positive effects of a 12-week high intensity interval training program, combined with resistance training, in pwMS, on improving muscle strength and endurance capacity. Furthermore, HIITR is indeed well tolerated and safe amongst pwMS. Concerning cardiovascular risk factors, no significant improvements were found for most parameters. However, HOMA values significantly lowered after 12 weeks of HIITR ($P = 0.026$), indicating a slightly decreased risk on developing IGT.

7 Reference list

1. Compston, A., & Coles, A. (2002). Multiple sclerosis. *Lancet, 359*(9313), 1221-1231. doi:10.1016/s0140-6736(02)08220-x
2. Motl, R. W., Arnett, P. A., Smith, M. M., Barwick, F. H., Ahlstrom, B., & Stover, E. J. (2008). Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis. *Mult Scler, 14*(1), 140-142. doi:10.1177/1352458507079126
3. Ng, A. V., & Kent-Braun, J. A. (1997). Quantitation of lower physical activity in persons with multiple sclerosis. *Med Sci Sports Exerc, 29*(4), 517-523.
4. Campbell, G. R., Worrall, J. T., & Mahad, D. J. (2014). The central role of mitochondria in axonal degeneration in multiple sclerosis. *Mult Scler, 20*(14), 1806-1813. doi:10.1177/1352458514544537
5. Marrie, R. A., Reider, N., Cohen, J., Stuve, O., Trojano, M., Cutter, G., . . . Sorensen, P. S. (2015). A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. *Mult Scler, 21*(3), 318-331. doi:10.1177/1352458514564485
6. Slawta, J. N., McCubbin, J. A., Wilcox, A. R., Fox, S. D., Nalle, D. J., & Anderson, G. (2002). Coronary heart disease risk between active and inactive women with multiple sclerosis. *Med Sci Sports Exerc, 34*(6), 905-912.
7. Wens, I., Dalgas, U., Stenager, E., & Eijnde, B. O. (2013). Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis - a systematic review. *Mult Scler, 19*(12), 1556-1564. doi:10.1177/1352458513504252
8. Wens, I., Dalgas, U., Deckx, N., Cools, N., & Eijnde, B. O. (2014). Does multiple sclerosis affect glucose tolerance? *Mult Scler, 20*(9), 1273-1276. doi:10.1177/1352458513515957
9. Li, J., Loerbroks, A., & Angerer, P. (2013). Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? *Curr Opin Cardiol, 28*(5), 575-583. doi:10.1097/HCO.0b013e328364289c
10. Slawta, J. N., Wilcox, A. R., McCubbin, J. A., Nalle, D. J., Fox, S. D., & Anderson, G. (2003). Health behaviors, body composition, and coronary heart disease risk in women with multiple sclerosis. *Arch Phys Med Rehabil, 84*(12), 1823-1830.

11. Wens, I., Dalgas, U., Vandenabeele, F., Grevendonk, L., Verboven, K., Hansen, D., & Eijnde, B. O. (2015). High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. *PLoS One, 10*(9), e0133697. doi:10.1371/journal.pone.0133697
12. Heine, M., van de Port, I., Rietberg, M. B., van Wegen, E. E., & Kwakkel, G. (2015). Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev*(9), Cd009956. doi:10.1002/14651858.CD009956.pub2
13. Motl, R. W. (2014). Benefits, safety, and prescription of exercise in persons with multiple sclerosis. *Expert Rev Neurother, 14*(12), 1429-1436. doi:10.1586/14737175.2014.983904
14. Motl, R. W., & Gosney, J. L. (2008). Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. *Mult Scler, 14*(1), 129-135. doi:10.1177/1352458507080464
15. Dalgas, U., Ingemann-Hansen, T., & Stenager, E. (2009). Physical Exercise and MS Recommendations. *Int MS J, 16*(1), 5-11.
16. Pilutti, L. A., Platta, M. E., Motl, R. W., & Latimer-Cheung, A. E. (2014). The safety of exercise training in multiple sclerosis: a systematic review. *J Neurol Sci, 343*(1-2), 3-7. doi:10.1016/j.jns.2014.05.016
17. Wens, I., Dalgas, U., Vandenabeele, F., Verboven, K., Hansen, D., Deckx, N., . . . Eijnde, B. O. (2016). High Intensity Aerobic and Resistance Exercise Can Improve Glucose Tolerance in Persons With Multiple Sclerosis: A Randomized Controlled Trial. *Am J Phys Med Rehabil*. doi:10.1097/phm.0000000000000563
18. Kjolhede, T., Vissing, K., & Dalgas, U. (2012). Multiple sclerosis and progressive resistance training: a systematic review. *Mult Scler, 18*(9), 1215-1228. doi:10.1177/1352458512437418
19. Wens, I., Hansen, D., Verboven, K., Deckx, N., Kosten, L., Stevens, A. L., . . . Eijnde, B. O. (2015). Impact of 24 Weeks of Resistance and Endurance Exercise on Glucose Tolerance in Persons with Multiple Sclerosis. *Am J Phys Med Rehabil, 94*(10 Suppl 1), 838-847. doi:10.1097/phm.0000000000000257
20. D'Orazio, P., Burnett, R. W., Fogh-Andersen, N., Jacobs, E., Kuwa, K., Kulpmann, W. R., . . . Okorodudu, A. O. (2006). Approved IFCC recommendation on reporting results for blood glucose: International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division, Working Group on Selective Electrodes and Point-of-Care Testing

(IFCC-SD-WG-SEPOCT). *Clin Chem Lab Med, 44*(12), 1486-1490. doi:10.1515/cclm.2006.275

21. Ryden, L., Grant, P. J., Anker, S. D., Berne, C., Cosentino, F., Danchin, N., . . . Xuereb, R. G. (2013). ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J, 34*(39), 3035-3087. doi:10.1093/eurheartj/eht108
22. Jones, N. L., Makrides, L., Hitchcock, C., Chypchar, T., & McCartney, N. (1985). Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis, 131*(5), 700-708. doi:10.1164/arrd.1985.131.5.700
23. Hansen, D., Wens, I., Kosten, L., Verboven, K., & Eijnde, B. O. (2013). Slowed exercise-onset Vo2 kinetics during submaximal endurance exercise in subjects with multiple sclerosis. *Neurorehabil Neural Repair, 27*(1), 87-95. doi:10.1177/1545968312451916
24. Washburn, R. A., Zhu, W., McAuley, E., Frogley, M., & Figoni, S. F. (2002). The physical activity scale for individuals with physical disabilities: development and evaluation. *Arch Phys Med Rehabil, 83*(2), 193-200.
25. Skjerbaek, A. G., Moller, A. B., Jensen, E., Vissing, K., Sorensen, H., Nybo, L., . . . Dalgas, U. (2013). Heat sensitive persons with multiple sclerosis are more tolerant to resistance exercise than to endurance exercise. *Mult Scler, 19*(7), 932-940. doi:10.1177/1352458512463765
26. Smith, R. M., Adeney-Steel, M., Fulcher, G., & Longley, W. A. (2006). Symptom change with exercise is a temporary phenomenon for people with multiple sclerosis. *Arch Phys Med Rehabil, 87*(5), 723-727. doi:10.1016/j.apmr.2006.01.015
27. White, L. J., McCoy, S. C., Castellano, V., Ferguson, M. A., Hou, W., & Dressendorfer, R. H. (2006). Effect of resistance training on risk of coronary artery disease in women with multiple sclerosis. *Scand J Clin Lab Invest, 66*(4), 351-355. doi:10.1080/00365510600727686
28. Hughes, V. A., Fiatarone, M. A., Fielding, R. A., Kahn, B. B., Ferrara, C. M., Shepherd, P., . . . Evans, W. J. (1993). Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. *Am J Physiol, 264*(6 Pt 1), E855-862.

29. van den Berg-Emons, R. J., L'Ortye, A. A., Buffart, L. M., Nieuwenhuijsen, C., Nooijen, C. F., Bergen, M. P., . . . Bussmann, J. B. (2011). Validation of the Physical Activity Scale for individuals with physical disabilities. *Arch Phys Med Rehabil, 92*(6), 923-928. doi:10.1016/j.apmr.2010.12.006

Table 5: List of abbreviations

BLG	blood lipids, lipoprotein-cholesterol, and glucose blood samples
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CPET	Cardio pulmonary exercise test
CRP	c-reactive protein
CVD	Cardiovascular disease
DEXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
EDSS	Expanded disability status scale
F_{iso}	Isometric muscle strength
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HIIT	High-intensity interval training
HIITR	High-intensity interval plus resistance training
HIT	High intensity training
HOMA	Homeostasis model assessment
HR	Heart rate
HR_{max}	Maximal heart rate
HRQOL	Health related quality of life
HR_{rec}	Heart rate during recovery
IGT	Impaired glucose tolerance
Lac_{max}	Maximal lactate level
Lac_{peak}	Peak lactate level
LDL	Low-density lipoprotein
MET	Metabolic equivalents

MS	Multiple sclerosis
OGTT	Oral glucose tolerance test
PASIPD	Physical activity Scale for individuals with physical disabilities
pwMS	Patient with multiple sclerosis
RER	Respiratory exchange rate
RPE	Rate of perceived exertion
SED	Sedentary
Vco_2/Vo_2	Ratio of carbon dioxide output / oxygen uptake
VE	Expiratory volume
VO_2	Oxygen uptake
W_{max}	Maximal resistance

Table 6: individual accomplishments

	Tobias Severijns	**Ferdy Wijckmans**
Period 1: (19/09/2016 - 20/11/2016)	- Searching articles - Background study	- Searching articles - Background study
Period 2: (21/11/2016 - 23/12/2016)	- Background study - Data processing - Statistical analysis	- Background study
Period 3: (06/02/2017 - 10/03/2017)	- Data processing - Statistical analysis - Interpretation of results	- Double check data processing - Interpretation of results
Period 4: (13/03/2017 - 14/04/2017)	- Extra data processing - Finish writing “Methods” (25%) - Double check “introduction”	- Start academic writing - Finish writing “introduction - Finish writing “Methods” (75%) - Start writing “results” - Figure 1 and 2
Period 5: (17/04/2017 - 19/05/2017)	- Finish writing “research framework” - Finish writing “abstract” - Finish writing “conclusion” - Double check “results” - Double check “discussion”	- Finish writing “results” - Finish writing “discussion” - Double check “research framework” - Double check “abstract” - Double check “conclusion” -
Period 6: (22/05/2017 - 23/06/2017)	- Double check “limitations” - Writing “highlights” - Table: individual accomplishments	- Writing “limitations” - Writing “highlights” - Table 1, 2, 3 and 4 - References

	- Table: list of abbreviations - Final check complete thesis - Finish lay-out - Finish presentation	- Final check complete thesis - Double check lay-out - Double check presentation

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Effect of high-intensity interval and resistance training on cardiovascular risk factors in MS patients

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2017**

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

Niet tegenstaand deze toekenning van het auteursrecht aan de Universiteit Hasselt behoud ik als auteur het recht om de eindverhandeling, - in zijn geheel of gedeeltelijk -, vrij te reproduceren, (her)publiceren of distribueren zonder de toelating te moeten verkrijgen van de Universiteit Hasselt.

Ik bevestig dat de eindverhandeling mijn origineel werk is, en dat ik het recht heb om de rechten te verlenen die in deze overeenkomst worden beschreven. Ik verklaar tevens dat de eindverhandeling, naar mijn weten, het auteursrecht van anderen niet overtreedt.

Ik verklaar tevens dat ik voor het materiaal in de eindverhandeling dat beschermd wordt door het auteursrecht, de nodige toelatingen heb verkregen zodat ik deze ook aan de Universiteit Hasselt kan overdragen en dat dit duidelijk in de tekst en inhoud van de eindverhandeling werd genotificeerd.

Universiteit Hasselt zal mij als auteur(s) van de eindverhandeling identificeren en zal geen wijzigingen aanbrengen aan de eindverhandeling, uitgezonderd deze toegelaten door deze overeenkomst.

Voor akkoord,

Severijns, Tobias **Wijckmans, Ferdy**