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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

The effect of 12 weeks high-intensity interval - and resistance training on mobility and quality of life in multiple sclerosis

Promotor :
Prof. dr. Peter FEYS

Copromotor :
dr. Inez WENS
dr. Ilse BAERT

Miguel-Angel Casado
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Student: Casado Miguel-Angel

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I would like to thank several people who supported me throughout the writing of this master thesis and throughout my period at the University of Hasselt. First of all, I'd sincerely like to thank my promotor, Prof. Dr. Peter Feys, and co-promotors, Dr. Inez Wens and Dr. Ilse Baert. Without their scientific knowledge, encouragement and advice, I wouldn't be able to finish this master thesis and attain my master's degree. I'd like to show my greatest appreciation to Dr. Ilse Baert. Her guidance was indispensable throughout the testing protocol. Further, I would also like to give a special recognition to Dra. Lousin Moumdjian for her expertise and help with the statistical analysis and also to Drs. Charly Keytsman because he constantly led the trainings with full dedication. Also, my gratitude goes to all the subjects who participated. Without them, scientific research wouldn't be possible. The University of Hasselt may not be forgotten in this acknowledgement. This institute has laid the foundations for the man I am today and the therapist I will be in the future. Last but not least, I'd like to show my gratitude to my parents and sisters for the unconditional love and support they gave me. Not only throughout my school career, but throughout my whole life.

As, June 2016 C.M.

Research context

This study is situated in the neurological domain of rehabilitation sciences and physiotherapy. A previous study showed that both high-intensity interval (HIIT) - as endurance training improved the endurance capacity and the muscle strength (in the weaker leg) after 12 weeks in MS (Wens I, et al. 2015). However, the effect of HIIT and resistance training on the functional mobility and quality of life in multiple sclerosis (MS) remains unclear. This research is also part of a multi-centered study within the 'special interest group (SIG) on mobility'. The SIG has also performed several multi-center joint data collection studies. Because multiple centers are participating in the developments of studies, more subjects can be included over whole Europe and rehabilitation effects, as well as psychometric properties of outcome measures, can be investigated with more statistical power.

This master thesis is embedded within an experimental study led by Prof. Dr. Op 't Eijnde Bert and Dr. Wens Inez, entitled: 'Multiple sclerosis: associated cardio-metabolic risks and impact of exercise therapy.'. In this study, the cardiovascular profile of patients with MS was measured in rest after following a program including high-intensity interval – and resistance training. The parameters of this study were: total cholesterol, high density lipids (HDL), low density lipids (LDL), triglycerides, C - reactive protein, insulin, glucose, fat percentage, fat and fat-free mass, smoking behavior, blood pressure, heart rate and the maximum rate of oxygen consumption (VO^2max). In this research, the student was responsible for the data acquisition, the data analysis and the reproduction of the results. The necessary files for the data acquisition were provided by Dr. Baert Ilse. Dra. Moumdjian Lousin helped the student with the statistics. Recruitment of subjects was done by Prof. Dr. Op 't Eijnde Bert and Dr. Wens Inez. All the trainings were led by Drs. Keytsman Charly.

Reference list

- Wens I, Dalgas U, Vandenabeele F, Grevendonk L, Verboven K, Hansen D, et al. High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. *PLoS ONE* 2015; 10(9):e0133697. doi:10.1371/journal.pone.0133697

Abstract

Background: Combined cardiovascular high-intensity interval – (HIIT) and resistance training improves the strength and endurance properties in Multiple Sclerosis (MS). The effect on mobility and quality of life (QOL) remains unclear.

Objectives: To investigate the effect of a 12 week combined HIIT and resistance training on the mobility and QOL in MS.

Participants: Twenty-seven MS patients were included. These were randomly allocated in the HIIT- (n=16) or control group (n=11). The HIIT-group performed high-intensity interval training for cardiovascular endurance in combination with resistance training for both the upper – as lower limbs while the control group were instructed to sustain their daily care.

Measurements: Seven capacity tests were used as an objective measure for mobility at pre- and post-measure: 25-foot walk test, timed up and go, timed up and go with a cognitive dual-task, four square step test, five times sit-to-stand test, modified five times sit-to-stand test and two minutes walk test. Further, four patient-reported questionnaires were used to evaluate both mobility as QOL: Rivermead mobility index, multiple sclerosis walking scale-12 Euroqol-5 dimensions-5 levels and multiple sclerosis impact scale-29.

Results: The protocol was safe and well tolerated. Only one subject of the HIIT-group and two subjects of the control group dropped out. There were no differences at baseline between the HIIT- and control group. Despite the HIIT-group scored better in all objective measures and in two of the four questionnaires after 12 weeks of training, no significant group over time interactions were obtained. Also, no significant within-group changes over time were reached.

Conclusion: A combined HIIT and resistance training didn't significantly improved the mobility or the QOL. No significant values were reached for both the within-group – and between-groups analysis. Further research is recommended.

Keywords: Multiple sclerosis, High-intensity interval training, HIIT, Resistance training, Mobility, Quality of life, QOL.

1 Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system with a neurodegenerative character. About 2.5 million young to middle aged people are currently suffering from this disease. In Flanders, this correlates with a prevalence of one in one thousand (Pugliatti M, et al. 2006). The loss of myelin, oligodendrocytes and axons in the central nervous system are characterizing for the disease. Fatigue, gait problems, muscle weakness, spasticity and ataxia form a heterogeneous clinical image of the patient (Noseworthy JH, et al. 2000), as well as a diminished aerobic capacity (Mostert S, Kesselring J. 2002). All these symptoms will lead to a reduced functional capacity (Savci S, et al. 2005). These are the reasons why MS patients, in most cases, are less active than healthy subjects (Stuifbergen AK. 1997) and end up in a vicious circle with even more muscle weakness, fatigue and associated health risks (Ng AV, Kent-Braun JA. 1997).

However, 80% of the MS patients live longer than 35 years with this progressive disease. Immune-modulated therapies are capable of decreasing the number of isolated attacks and the speed of degeneration (Koch-Henriksen N, et al. 1998), but active rehabilitation is also needed to reduce the disability. Pharmacologic therapy alone isn't enough, especially in the progressive types of MS and in severe disabled persons. There is evidence that MS patients can ameliorate their muscle strength, exercise tolerance, functional capacity and quality of life through exercise (Motl RW, et al. 2008; Stuifbergen AK, et al. 2006).

In the past, several studies have researched the effect of endurance – and/or strength training in MS. Wens I, et al. (2015) reported that both high-intensity interval – (HIIT) as high-intensity continuous training, in combination with resistance training, improved the strength of the knee flexors and extensors in comparison with a control group in MS after three months of training. The mean cross-sectional area of the vastus lateralis muscle and self-reported physical activity also increased in both exercise groups (Wens I, et al. 2015). Endurance and lean tissue mass only increased in the HIIT-group (Wens I, et al. 2015). Previous investigation also showed that in MS, continue high-intensity resistance training of the lower limbs for 12 weeks, significantly improved the functionality (measured by the five times chair stand, the ascending stair climbing test, 10-meter walk test and the 6-minutes walk test) in comparison to control subjects (Dalgas U, et al. 2009). Moradi M, et al. (2015) showed that moderate-to-high intensity resistance training of both the upper – as lower limbs for eight weeks, in a small sample of male MS subjects, significantly improved the ambulatory function in comparison to a control group. Balance did not change after eight weeks. Also an eight week progressive resistance training on a cycle ergometer, in combination with balance training, significantly improved balance, fatigue, depression and the fear of falling in MS without worsening the symptoms (Cakit BD, et al. 2010). In another study, 312 participants with mild to severe relapsing-remitting type of MS improved their walking after following a rehabilitation program for three weeks (Kalron A, et al. 2015). The program included goal directed physical therapy, moderately intense aerobic exercise training on a cycle ergometer and aquatic exercise which focused on appropriate movements of body structures.

However, not much is known about the effect of three months HIIT and moderate-to-high resistance training on the mobility and quality of life (QOL) in MS. In Gibala MJ. & McGee SL. (2008) HIIT was described as a repeated exercise at high-intensity for 30 seconds to several minutes with a 1 to 5 minutes rest period. Previous research showed that an eight week HIIT significantly improved, in comparison with moderate controlled training (MCT), the walking capacity on the six minutes walking test (6MWT) in patients with coronary artery disease (CAD) (Villelabeitia Jaureguizar MD., et al. 2016). Villelabeitia Jaureguizar MD, et al. (2016) also reported that both protocols improved the quality of life in CAD. After participating to a six week HIIT-protocol in combination with balance training, patients with osteoarthritis (OA) showed less joint pain and an improvement in balance, function and mobility (Bressel E., et al. 2014). Further on, in young boys with ADHD, HIIT showed a significant improvement in motor skills like manual dexterity and ball skills (Meβler CF., et al. 2016). In the same study, HIIT was more effective than traditional multimodal therapy for aspects of quality of life like self-esteem and interaction in a social environment (Meβler CF., et al. 2016).

The impact of HIIT on mobility and quality of life remains unclear in many neurologic conditions, including MS. The present study investigated the effect over twelve weeks of HIIT combined with resistance training on the mobility and quality of life in MS.

2 Methods

2.1 Participants

In this randomized controlled trial, the recruitment of participants happened throughout different channels: a) the REVAL-database with data from former study participants, b) in cooperation with the MS-liga Limburg, c) in cooperation with prof. Van Wijmeersch from the MS- and rehabilitation center in Overpelt and d) through flyers at different physiotherapists and hospitals. To be included in the study, all participants needed the diagnosis of MS according the Mcdonald criteria (Polman CH., et al. 2010) and an Expanded Disability Status Scale (EDSS) ≥ 2 and ≤ 6.5 (Kurtzke JF. 1983). The EDSS was determined by a neurologist. In the last month before participation, participants weren't allowed to have a relapse, to change their disease modifying treatment or to receive corticoid-therapy to be included in the study. Patients were excluded if they couldn't understand and perform instructions or if they suffered from other medical conditions that could interfere their mobility (e.g. stroke, fractures …). All of the subjects read and signed an informed consent (approved by the Ethical Committee of Jessa Hospital in December 2014) before participation. The descriptive characteristics of every participant were measured at baseline and included: age (years), gender (male/female), height (centimetre), weight (kilogram), disease duration (years), type of MS (relapsing remitting, primary progressive, secondary progressive, relapsing progressive), level of disability through EDSS (0-10), the use of disease-modifying and symptomatic drug use, the use of a walking device (including assistive devices and orthoses), the history of (injurious) falling in the past six months, the employment status (working 100%/working 50%/working 25%/retired/payment/unemployed) and the living arrangement (alone/alone with child(ren)/with partner/with partner and child(ren)). The severity of fatigue of the participant was evaluated through the Fatigue Scale for Motor and Cognitive functions (FSMC) (Penner IK, et al. 2009). The cognitive function of the participant was evaluated through the Symbol Digit Modalities Test (SDMT) (Smith A. 1982) and the Performance Scale mobility ($PS_{mobility}$) (Marrie RA, Goldman M. 2007), which compared the participant's condition of mobility in the past 4 weeks to the condition before MS, was also evaluated at baseline.

2.2 Experimental design

In this single blinded randomized controlled trial (RCT), participants were allocated ad random in the HIIT - or control group. The HIIT-group underwent a twelve week training program including a high-intensity interval training on a cycle ergometer (TechnoGym®) and a moderate-to-high resistance program for both the legs as the arms. Participants trained at a ratio of five times in two weeks (e.g. three times during the first week and two times during the second week). The control group was instructed to sustain their daily care (e.g. physiotherapy, speech therapy, occupational therapy and/or neuropsychology.

2.3 Intervention

The HIIT-group underwent a HIIT for endurance and a moderate-to-high resistance program for strength. In between the days of training, there was minimally one day of rest to ensure the recovery of each participant. At the start of every training, each participant warmed up on a cycle ergometer (TechnoGym®) for 5 minutes. In the first six weeks of training, the exercise intensity for the HIIT increased gradually from 5X1 minute to 5X2 minutes at 100% of the maximal workload (comparable with 80 to 90% of the maximal heart rate, measured at baseline). The rest interval was each time 1 minute. In the next six weeks, the HIIT-group trained 5X2 minutes with a rest interval of 1 minute. During the last six weeks, the heart rate was increased to obtain a level corresponding to 100–120% of the maximal work load. This work load was comparable to 90–100% of the maximal heart rate, measured at baseline. The participants trained their endurance on a cycle ergometer (TechnoGym®) while wearing a heart rate sensor (Polar®). If the hearth rate didn't increase anymore, the physiotherapist automatically increased the resistance. If this program was too heavy for a participant, the participant received an individual follow-up with emphasis to interval.

Because a difference in strength between the two legs is common in MS (Thoumie P., et al. 2005), the lower limbs performed the resistance training separately. Leg press, leg curl and leg extension were the three exercises for the lower limbs while vertical traction, arm curl and chest press were the exercises for the upper limbs. All the exercises were performed on fitness equipment of TechnoGym®. The volume increased from 1X10 repetitions to 2X20 repetitions of maximum attainable weight. The intensity corresponded to a rating of 14-16 on the Borg scale (/20) for perceived exertion. The upper limbs were only trained for esthetic reasons. The training took place at the training center of REVAL and was under supervision of 1 physiotherapist with the aid of master students rehabilitation sciences and physiotherapy at the University of Hasselt. There was always a 1:1 ratio between the trainers and the participants.

As mentioned before, the control group were instructed to sustain their daily care (e.g. physiotherapy, speech therapy, occupational therapy and/or neuropsychology).

2.4 Measure for endurance and strength

All outcome measures were measured at baseline and after twelve weeks of training (post-measure). The capacity of endurance was measured by means of an electronically braked cycle ergometer (eBike Basic, General Electric GmbH) with pulmonary gas exchange analysis (Jaeger Oxycon) and linked with the maximum heart rate. Male participants started at a resistance of 30 watt and increased with 15 watt each minute while females started at 20 watt and increased each minute with 10 watt. Both the maximal voluntary isometric and dynamic strength of the knee extensors and flexors were measured by means of an isokinetic dynamometer (System 3, Biodex, ENRAF-NONIUS).

2.5 Outcome measures

Both objective measurements (capacity tests) as questionnaires (patient-reported) were used to analyze the effect of HIIT and resistance training on mobility and quality of life (QOL) in MS. Participants were instructed to perform the capacity tests as fast, but as safe, as possible.

2.5.1 Capacity tests

- Timed 25-Foot Walk (T25FW)

Fischer JS., et al. (2009) mentionned that in the T25FW, the walking speed (seconds) was measured over a short distance (25 feet; 7.62 meters). The participant was able to use an assistive device. The T25FW was performed two times. The mean of the two performances was used in the analyse. A shorter time was related to a better mobility.

- Timed up and go (TUG)

The TUG was used to analyze the dynamic balance. The participant needed to stand up from a chair (with or without the use of the arms), walk a distance of three meters, turn around, walk back and sit down on the chair (Podsiadlo D, Richardson S. 1991). The time (in seconds) of the task started at the moment the assessor gave the command “start” and ended when the participant sat back in the chair. The participant was able to use an assistive device. The TUG was performed two times. The mean of the two performances was used in the analyse. A shorter time was related to a better mobility.

- Timed up and go with a cognitive dual-task ($TUG_{cognitive}$)

The $TUG_{cognitive}$ was the same test as the TUG, but with a cognitive dual-task. The dual-task included the subtraction of 3 from 50. If the participant was wrong at one point of the subtraction, he/she was instructed to continue from that number on. The participant was able to use an assistive device. The $TUG_{cognitive}$ was performed two times. The mean of the two performances was used in the analyse. A shorter time was related to a better mobility.

- Two minute walk test (2MWT)

In this long walking capacity test, the participant was instructed to cover a maximum distance in two minutes by walking (Butland RJ, et al. 1982). This test was measured in meters. The more meters a participant covered, the better the mobility. The participant was permitted to rest while the test was running, but the time continued. The use of a walking aid was tolerated.

- Four square step test (FSST)

This test was performed with eather canes or tape on the floor. This test was used to measure the dynamic standing balance of the participant (Dite W, Temple VA. 2002). The goal of this test was to step forward, sideways to both sides and backwards as fast as possible. A faster time meant a better mobility. This test was performed two times. The best time was used for the analyse.

- Five repetition sit-to-stand test (5STS)

Both balance as strength of the lower extremities were needed to perform this test quickly. In the FSST, the participant needed to stand up and sit down as fast as possible for 5 times (McCarthy EK, e.a. 2004). The use of the arms was not allowed. The time was measured in seconds. Only one attempt was allowed.

- Modified five repetition sit-to-stand test ($_{\text{modified}}$5STS)

The $_{\text{modified}}$5STS was basically the same test as the 5STS, but the use of the arms was allowed. The same procedures as in the 5STS were followed. This modified version was included as some of the particpants may not be able to perform the 5STS without use of the arms.

2.5.2 Patient-reported questionnaires

- Rivermead motor index (RMI)

The RMI was used to measure the level of reduction in mobility (Collen FM, e.a. 1991). The standard form was used, in which participants needed to say ‘yes’ (= 1) or ‘no’ (= 0). Fifteen questions (e.g. ‘rolling over in bed’, ‘standing up from bed and moving to a chair’, ‘the ability to take the stairs with or without help', 'the ability to walk/run 10 meters in 4 seconds', …) were asked. The maximal score was 15. The higher the score, the less the reduction in mobility.

- Multiple Sclerosis walking scale 12 (MSWS-12)

The impact of MS on the participant's walking ability in the last two week was measured with this questionnaire (Hobart JC, et al. 2003). Twelve items were scored from 1-5. A score of 60 was the maximum. Lower scores correlated with a less affected impairment during the last 2 weeks.

- EuroQol 5 dimensions 5 levels (EQ-5D-5L)

This test was divided in a descriptive - and quantitative measure (Herdman M, et al. 2011). In the descriptive part, 5 dimensions were questionned: mobility, self care, usual activities, pain/discomfort and anxiety/depression. Each dimension had 5 levels, ranged from 'no problem' to 'extreme problem'. In this study, this test was reduced to a score on 5. The quantitative part was not used in the analysis.

- Multiple Sclerosis impact scale 29 (MSIS-29)

The MSIS-29 was a self-reported measure which analyzed the impact of MS in the past 2 weeks. The 29 questions were divided in 20 physical items and 9 psycholgical items (Hobart J, e.a. 2001). Each question needed to be answered on a scale from 1 (not at all) to 5 (extremely). In this study, the test was scored on 145. Afterwards, this score was conducted to 100.

2.6 Statistical analysis

SAS 9.2 software (SAS Institute Inc, Cary, USA) was used for the statistical procedure. Because of a small sample size and unequal numbers in both groups, Mann Whitney U test was used to compare the descriptive values of both groups at baseline. Wilcoxon signed rank test (non-parametric test) was used to compare the pre- and post-measure in each group. A 2X2 analysis of variance (ANOVA) was used to test if there were significantly values in group, time and in the group over time interaction. Tukey's multivariate analysis was used in case of significant interaction effects. The differences between the pre- and post-measurements were calculated (delta) as well as the mean of changes in one group (and expressed as a percentage). Statistical significance was set at $p<0.05$. All data were presented as "Mean±SD".

3 Results

3.1 Baseline characteristics

In total, 16 subjects (8 male/8 female) participated in the HIIT-group and 11 subjects (2 male and 9 female) in the control group. No significant differences between the two groups were found for the baseline characteristics. All the baseline characteristics and their values are listed up in Table 1 (demographic data, tests and questionnaires) and Table 2 (medicine use). In the control group, one subject followed physiotherapy, neuropsychotherapy, speech therapy and occupational therapy. Another subject followed both physio- as speech therapy. Three other subjects only followed physiotherapy. Three drop-outs were reported in total (see flowchart presented in figure 1). One subject of the HIIT-group dropped out due to vacation and two subjects of the control group dropped out due to respectively vacation and personal reasons.

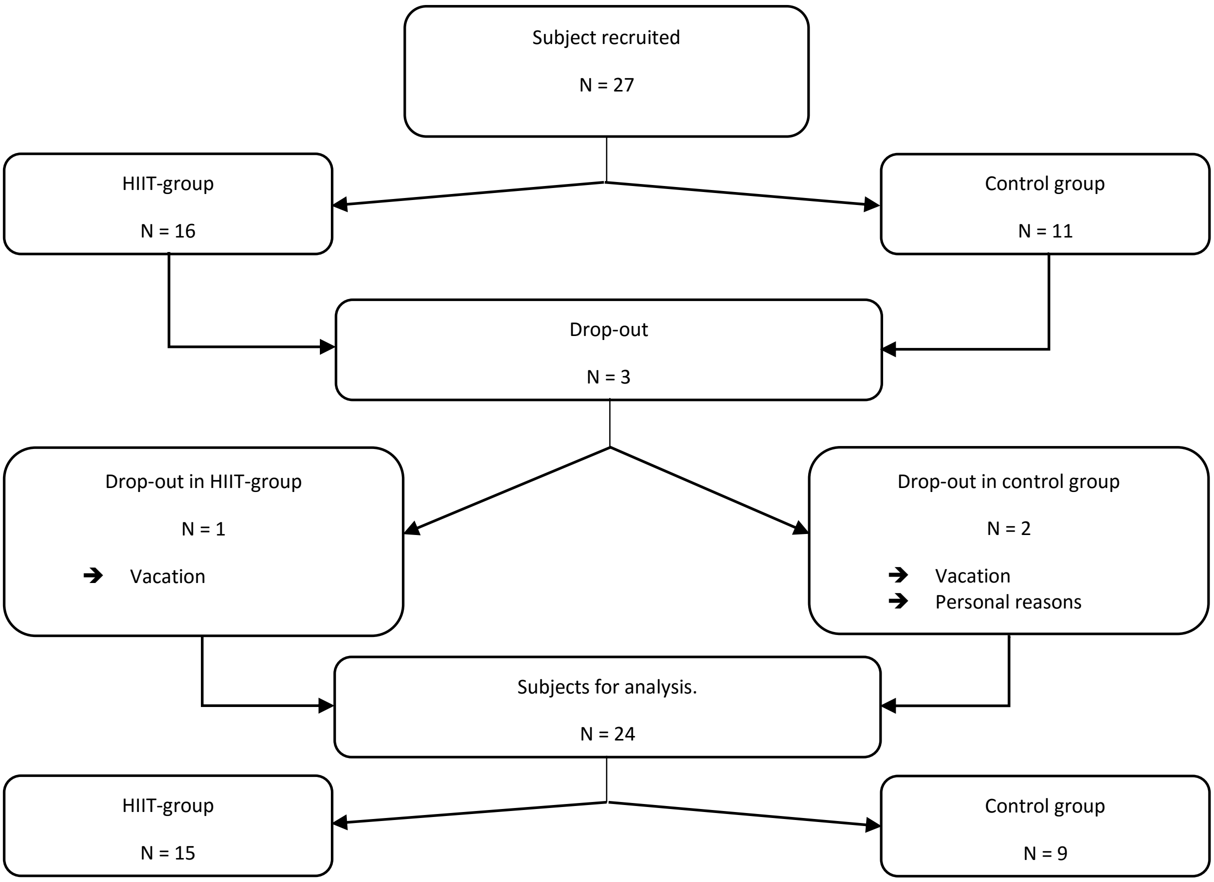

Figure 1. Flowchart of study participants.

Table 1. Baseline characteristics of HIIT- and control group[a,b]

Variable	HIIT	Control	p-value[c]
Gender (M/F)	8/8	2/9	-
Age (years)	63.91 ± 8,4 (49.44-58.39)	52.41 ± 8.78 (46.51-58.31)	.52
Height (centimetre)	170.51 ± 8.96 (165.73-175.28)	167.83 ± 8.11 (162.38-173.28)	.49
Weight (kilogram)	68.98 ± 13.33 (61.88-76.09)	75.26 ± 12.67 (66.75-83.77)	.25
Type MS (RR/SP/PP/RP/missing))	12/3/1/0/0	7/2/0/1/1	-
EDSS (/10)	2.63 ± 1.52 (1.79-3.47)	3.09 ± 1.22 (2.27-3.91)	.35
Disease duration (years)	14.93 ± 8.71 (10.29-19.58)	15.56 ± 8.19 (8.78-22.34)	.86
Number of falls in the past 6 months (none/1/2/3)	14/0/2/0	9/0/1/1	-
Number of injured falls in the past 6 months (none/1/2/3)	15/1/0/0	10/1/0/0	-
Living arrangement (alone/alone with child(ren)/with partner/with partner and child(ren))	1/2/11/2	2/1/6/2	-
Employement status (working 100%/working 50%/working 25%/retired/payment/unemployed)	3/1/1/3/8/0	2/0/0/2/5/2	-
Walking aid (walking stick/none)	1/15.	1/11.	-
Orthosis (unilateral/bilateral/none)	0/0/15	1/0/10	-

Cognitive function, fatigue and perceived mobility[a,b]

Tests and questionnaires	HIIT	Control	p-value[c]
SDMT (/110)	56 ± 12.29 (49.45-62.35)	50.73 ± 12.39 (42.4-59.05)	.2
FSMC cognitive (10-50)	29.81 ± 9.27 (24.87-34.75)	32.18 ± 8.02 (26.79-37.57)	.49
FSMC motor (10-50)	31.63 ± 10.98 (25.78-37.48)	35.09 ± 6.3 (30.86-39.32)	.52
FSMC total score (20-100)	61.44 ± 19.26 (51.17-71.7)	67.27 ± 13.71 (58.06-76.49)	.52
PSmobility (/6)	1.25 ± 1.39 (0.51-1.99)	1.73 ± 1.19 (0.93-2.53)	.24

[a] Abbreviations: EDSS = Expanded Disability Status Scale; F = female; FSMC = Fatigue scale for motor and cognitive functions; HIIT= High-intensity interval training; M = male; MS = multiple sclerosis; PP; $PS_{mobility}$ = Performance scale mobility; RP = relapsing progressive; RR = relapsing remitting; SDMT = Single digit modality test; SP = secondary progressive.

[b] Values are mean ± SD (min-max), categorical data were reported by number.

[c] By Mann-Whitney U test.

Table 2. Medicine use of the HIIT- and control group[a,b]

Medicine	HIIT	Control	p-value
Immuno-suppresive agents (n)	7	5	-
Immuno-modulating agents (n)	7	1	-
Anti-coagulantia (n)	1	2	-
Cholesterol reducers (n)	0	1	-
Anti-diabetica (n)	2	1	-
Anti-epileptica (n)	3	2	-
Anti-hypertensiva (n)	2	2	-
Tremor (n)	1	0	-
Fatigue (n)	0	1	-
Spasticity (n)	2	2	-
Anti-depressiva (n)	3	3	-
Sedativa (n)	1	0	-
Analgetica (n)	1	0	-

[a] Abbreviations: HIIT= High-intensity interval training; n = number.

[b] Values are mean ± SD (min-max), categorical data were reported by number.

3.2 Outcomes

All outcomes and p-values of the capacity tests and questionnaires at baseline and after 12 weeks were shown in Table 3. The percentages of difference between the pre- and post-measure of both the capacity tests and questionnaires and the p-values (measured by Wilcoxon sign rank test) were presented in respectively Table 4 and 5. No significant values were found for the group over time interaction in any of the capacity tests or questionnaires.

Table 3. Outcome measures and p-values of the objective measures and questionnaires [a, b]

Variable	Group	Time			p-value [c]		
		Pre	Post	Delta	Group	time	interaction
T25FW (s)	**HIIT**	5.68 ± 1.84 (4.7-6.67)	5.29 ± 1.73 (4.33-6.24)	-.39 ± -11 ((-.37)-(-.43))	.82	.65	.32
	CON	5.3 ± 1.32 (4.42-6.19)	5.59 ± 2.19 (3.91-7.28)	.29 ± .87 ((-.51)-1.09)			
TUG (s)	**HIIT**	8.24 ± 2.63 (6.84-9.64)	7.76 ± 3.87 (5.62-9.9)	-.48 ± 1.24 ((-1.22)-.26)	.92	.67	.35
	CON	7.83 ± 2.01 (6.48-9.18)	8.37 ± 2.66 (6.32-10.41)	.54 ± .65 ((-.16)-1.23)			
$TUG_{cognitive}$ (s)	**HIIT**	9.15 ± 3.46 (7.31-11)	8.36 ± 4.63 (5.79-10.92)	-.79 ± 1.17 ((-1.52)-(-.08))	.9	.29	.54
	CON	9.07 ± 2.56 (7.35-10.79)	9.67 ± 3.68 (6.59-12.74)	.06 ± 1.12 ((-.76)-1.95)			
FSST (s)	**HIIT**	10.06 ± 2.9 (8.51-11.6)	9.73 ± 4.57 (7.19-12.26)	-.33 ± 1.67 ((-1.31)-.66)	.56	.23	.57
	CON	9.6 ± 1.83 (8.37-10.83)	8.97 ± 1.95 (7.47-10.48)	-.63 ± .12 ((-.9)-(-.35))			
5-STS (s)	**HIIT**	12.64 ± 3.18 (10.95-14.33)	12.25 ± 4.99 (9.49-15.01)	-.39 ± 1.81 ((-1.46)-.68)	.47	.55	.92
	CON	11.7 ± 2.71 (9.85-13.49)	11.62 ± 3.93 (8.6-14.65)	-.08 ± 1.22 ((-1.25)-1.16)			
$_{Modified}$5-STS (s)	**HIIT**	11.59 ± 2.72 (10.14-13.03)	10.12 ± 3.83 (8-12.24)	-1.47 ± 1.11 ((-2.14)-(-79))	.62	.03	.78
	CON	10.89 ± 2.91 (8.94-12.85)	10.16 ± 1.9 (8.7-11.61)	-.73 ± -1.01 ((-.24)-(-1.24))			
2-MWT (m)	**HIIT**	172.38 ± 42.14 (149.92-194.83)	178.53 ± 45.55 (153.31-203.76)	6.15 ± 3.41 3.39-8.93	.56	.39	.92
	CON	162.91 ± 28.92 (143.48-182.33)	163.67 ± 41.15 (153.31-203.76)	.76 ± 12.23 ((-11.45)-12.97)			
			Questionnaires				
RMI (/15)	**HIIT**	14 ± 1.21 (13.36-14.65)	14 ± 1.81 (13-15)	0 ± .06 ((-.36)-.35)	.14	.76	.76
	CON	12.91 ± 2.39 (11.31-14.51)	12.78 ± 1.77 (11.4-14.15)	-.13 ± -.62 (.09-(-.36))			
MSWS-12 (/60)	**HIIT**	26.81 ± 14.78 (18.94-34.69)	23.93 ± 13.77 (16.29-31.57)	-2.88 ± -1.01 ((-2.65)-(-3.12))	.37	.15	.8
	CON	30.82 ± 6.48 (26.47-35.17)	29.56 ± 11.77 (20.51-38.6)	-1.26 ± 5.29 ((-5.96)-3.43)			
EQ-5D-5L (/5)	**HIIT**	1.6 ± 0.68 (1.24-1.96)	1.61 ± 0.74 (1.2-2.02)	.01 ± .06 ((-.04)-.06)	.99	.79	.99
	CON	1.6 ± 0.69 (1.15-2.05)	1.71 ± 0.66 (1.2-2.22)	.11 ± -.01 (.05-.17)			
MSIS-29 (/100)	**HIIT**	42.59 ± 18.38 (32.79-52.38)	39.4 ± 17.79 (29.55-31.32)	-3.19 ± -.59 ((-3.24)-(-3.12))	.85	.41	.95
	CON	41.63 ± 8.45 (35.95-47.3)	40.99 ± 10.26 (33.1-48.89)	-.63 ± 1.81 ((-2.85)-1.59)			

[a] Abbreviations: 2-MWT = two minutes walk test; 5-STS = five repetition sit-to-stand test; EQ-5D-5L = Euroqol-5 dimensions-5 levels; FSST = four square step test; m = meter; $_{Modified}$5-STS = modified five repetition sit-to-stand test; MSIS-29 = Multiple Sclerosis impact scale-29; MSWS-12 = Multiple Sclerosis walking scale-12; RMI = Rivermead mobility index; s = seconds; T25FW = timed 25-foot walk; TUG = timed up and go; $TUG_{cognitive}$ = timed up and go cognitive.

[b] Values are mean ± SD (min-max).

[c] By 2X2 ANOVA.

3.2.1 Capacity tests

The results on the capacity tests are shown in table 4. Here, we present the results one by one for the different tests. However, no significant differences over time were found in any group.

- Timed 25 feet walk (T25FW)

The average time for the T25FW in the HIIT-group was 5.68 ± 1.84 seconds at baseline and 5.29 ± 1.73 seconds after twelve weeks of training. The average time for the control group was 5.3 ± 1.32 seconds at baseline and 5.59 ± 2.19 seconds at post-measure. The HIIT-group was 7.03% faster and the control group was 5.47% slower after twelve weeks.

- Timed up and go (TUG)

At baseline, the HIIT-group had a time of 8.24 ± 2.63 seconds. At post-measure, this was 7.76 ± 3.87 seconds. In the control group, the average time was 7.83 ± 2.01 seconds at baseline and 8.37 ± 2.66 seconds at post-measure. The HIIT-group was 5.83% faster and the control group was 6.9% slower at post-measure.

- Timed up and go cognitive ($TUG_{cognitive}$)

The HIIT-group was 8.63% faster after twelve weeks of training (9.15 ± 3.46 seconds at baseline and 8.36 ± 4.63 seconds at post-measure) while the control group was 6.62% slower after 12 weeks (9.07 ± 2.56 seconds at baseline and 9.67 ± 3.68 seconds at post-measure). At post-measure, one subject of the control group wasn’t able to execute this test in a correct way. These values were excluded from the analysis.

- Four square step test (FSST)

Respectively 10.06 ± 2.9 seconds and 9.73 ± 4.57 seconds was the average time that the HIIT-group needed to execute this test at pre- and post-measure. The average time for the control group was respectively 9.6 ± 1.83 seconds at baseline and 8.97 ± 1.95 seconds after twelve weeks. Both groups improved minimally after twelve weeks (3.09% for the HIIT-group and 0.68% for the control group). Both in the HIIT- as the control group was one subject who performed the test with tape instead of canes on the ground.

- Five sit-to-stand (5-STS)

The average time for the 5STS was 12.64 ± 3.18 seconds at baseline and 12.25 ± 4.99 seconds after twelve weeks of training in the HIIT-group. The average time for the control was respectively 11.7 ± 2.71 seconds and 11.62 ± 3.93 seconds. At post-measure, both groups were faster (3.28% for HIIT- and 6.56% for control group).

- Modified five sit-to-stand ($_{Modified}$5-STS)

The HIIT-group (11.59 ± 2.72 seconds at baseline and 10.12 ± 3.83 seconds at post-measure) was 12.68% faster and the control group (10.89 ± 2.91 seconds at baseline and 10.16 ± 1.9 seconds at post measure) was 6.7% faster after 12 weeks. The difference between the pre – and post-measure of the $_{modified}$5-STS in the HIIT-group was borderline significant (p=.06), as measured by Wilcoxon signed rank test.

- Two minutes walking test (2-MWT)

For the 2-MWT, the HIIT-group covered on average 172.38 ± 42.14 meters at baseline and 178.53 ± 45.55 meters at post-measure. The average distance for the control group was 162.91 ± 28.92 meters at baseline 163.67 ± 41.15 meters after 12 weeks. Both the HIIT-group (3.57%) as the control group (.47%) covered more distance after 12 weeks.

Table 4. Differences (%) of the objective measures between baseline and after 12 weeks [a]

Variable	Group	Difference between pre- and post-measure (Delta)		
		Percentage [b]	Faster/slower (at post-measure)	p-value [c]
T25FW	HIIT	7,03%	Faster	.34
	CON	5.47%	Slower	.62
TUG	HIIT	5.83%	Faster	.21
	CON	6.9%	Slower	.79
$_{Cognitive}$TUG	HIIT	8.63%	Faster	.22
	CON	6.62%	Slower	.87
FSST	HIIT	3.28%	Faster	.27
	CON	6.56%	Faster	.51
5-STS	HIIT	3.09%	Faster	.38
	CON	.68%	Faster	.79
$_{Modified}$5-STS	HIIT	12.68%	Faster	.06
	CON	6.7%	Faster	.79
2-MWT	HIIT	3.57%	Faster	.69
	CON	.47%	Faster	.54

[a]Abbreviations: 2-MWT = two minutes walk test; 5-STS = five repetition sit-to-stand test; EQ-5D-5L = Euroqol-5 dimensions-5 levels; FSST = four square step test; m = meter; $_{Modified}$5-STS = modified five repetition sit-to-stand test; MSIS-29 = Multiple Sclerosis impact scale-29; MSWS-12 = Multiple Sclerosis walking scale-12; RMI = Rivermead mobility index; s = seconds; T25FW = timed 25-foot walk; TUG = timed up and go; $TUG_{cognitive}$ = timed up and go with cognitive dual-task.

[b] Calculated by: (MeanPost-MeanPre) / MeanPre X 100

[c] By Wilcoxon signed rank test.

3.2.2 *Patient-reported questionnaires*

The results on the patient-reported questionnaires are shown in table 5. Here, we present the results one by one for the different tests. However, no significant differences over time were found in any group.

- Rivermead mobility index (RMI; /15)

The baseline score for the HIIT-group was 14 ± 1.21. After 12 weeks of training, the HIIT-group scored 14 ± 1.81. The control group scored 12.91 ± 2.39 at baseline and 12.78 ± 1.77 at post measure.

- Multiple sclerosis walking scale 12 (MSWS-12; /60)

The HIIT-group (26.81 ± 14.78 at baseline and 23.93 ± 13.77 at post measure) scored 10.73% better after 12 weeks of training and the control group (30.82 ± 6.48 at baseline and 29.56 ± 11.77 seconds at post measure) scored 4.09% better at post-measure.

- EuroQol 5 dimensions 5 levels (EQ-5D-5L; /5)

The average scores on the EQ-5D-5L for the HIIT-group at baseline and after twelve weeks were: 1.6 ± 0.68 and 1.61 ± 0.74. The average score on the EQ-5D-5L for the control group at baseline and after twelve weeks were: 1.6 ± 0.69 and 1.71 ± 0.66.

- Multiple sclerosis impact scale 29 (MSIS-29)

The scores of the HIIT-group were 42.59 ± 18.38 at baseline and 39.4 ± 17.79 after twelve weeks. The scores of the control group were 41.63 ± 8.45 at baseline and 40.99 ± 10.26 after twelve weeks. In percentages, this correlates with an improvement of 7.48% for the HIIT-group and 1.52% for the control group at post-measure.

Table 5. Differences (%) of the questionnaires between baseline and after 12 weeks [a]				
Variable	**Group**	**Difference between pre- and post-measure (Delta)**		
		Percentage [b]	**Better/worse (at post-measure)**	**p-value [c]**
RMI	**HIIT**	0%	No change	.61
	CON	1.01%	Worse	.61
MSWS-12	**HIIT**	10.74	Better	.49
	CON	4.09	Better	.42
EQ-5D-5L	**HIIT**	.63%	Worse	.9
	CON	9.24%	Worse	.42
MSIS-29	**HIIT**	7.48%	Better	.45
	CON	1.52%	Better	.49

[a]Abbreviations: EQ-5D-5L = EuroQol 5 dimensions 5 levels; MSIS-29 = Multiple Sclerosis impact scale 29; MSWS-12 = Multiple Sclerosis walking scale 12; RMI = Rivermead mobility index.

[b] Calculated by: (MeanPost-MeanPre) / MeanPre X 100

[c] By Wilcoxon signed rank test.

4 Discussion

This is the first study that investigated the effect of both a high-intensity interval training as a resistance training on the mobility and quality of life in MS. The HIIT-group followed a program for 12 weeks involving high-intensity interval – and resistance training while the control group was recommended to keep following their daily care. Despites the HIIT-group improved in all objective measures and in two of the four questionnaires after 12 weeks, when expressed in absolute values and percentual changes, no significant values were observed for the group over time interaction. It is concluded that addition of HITT was leading to superior improvements on functional mobility and quality of life.

4.1 *The effect of HIIT and resistance training on mobility and QOL*

Evidence is available that exercise could improve both mobility (Garret M, Coote S. 2009; Snook EM, Motl RW. 2009) as QOL (Motl RW, Gosney JL. 2008) in people with MS. Previous study showed that both HIIT as endurance training improved the endurance capacity and the muscle strength (in the weaker leg) after 12 weeks in MS (Wens I, et al. 2015). We could assume that both cardiovascular endurance as muscle strength improved in the present study, because the same protocol as in Wens I, et al. (2015) was used. Current study revealed that an improvement in endurance and muscle strength doesn't necessarily means that this is correlated with an improvement in mobility and QOL in MS. Çakit BD, et al. (2010) showed that MS patients improved their endurance, strength, QOL (Short Form 36, Beck depression scale, fatigue severity scale) and mobility (e.g. TUG, 10 meter walk test, falls efficacy & dynamic gait index) after 8 weeks if they followed a cycling progressive resistance training in combination with balance exercises. In the same study, it was also found that another group, which followed a home-based strength training for the lower limbs, improved their fear of falling if this was combined with balance exercises (Çakit BD, et al. 2010). Functional therapy is also a primary outcome measure in the study of Kalron A et al. (2015). In this study, a big sample of RRMS-patients followed a program of three weeks including functional therapy (e.g. strength, balance, gait …), proprioceptive therapy and aerobic exercise at moderately intensity on a cycle ergometer (Kalron A et al. 2015). All the mobility outcomes (10 – and 20-meter walk test, TUG, 2MWT) were significantly improved in the MS group (Kalron A et al. 2015).

There is also evidence that progressive resistance training of both upper- as lower limbs over 12 weeks could improve the ambulatory function in male MS patients in comparison to a control group (Moradi M, et al. 2015). The difference between the study of Moradi M, et al. (2015) and current study is the fact that we used the Borg scale of perceived exertion (patient-reported) to determine progression, while Moradi M, et al. (2015) based their resistance training on ACSM's (American college of Sports Medicine) guidelines, which may be more objective. Remarkable is the fact that in both Moradi M, et al. (2015) as in our study, balance didn't improve through training. Just like in our training program, no functional and/or proprioceptive training was performed. In contrast to these findings, Broekmans T, et al. (2011) did not find any change in functional mobility, except for reaching, if MS patients followed a light-to-moderate ACSM-based resistance training over 20 weeks (eventually in combination with electro-stimulation). Yet again, no performed functional training was likely being the reason that no functional gains were found. It is concluded that HIIT is effective to improve physical fitness but is not leading to functional effects. This is suggesting that training programs have very task-specific effects.

4.2 *Safety of the protocol*

It is widely known that MS patients suffer from a large variety of symptoms. One may think high-intensity training could be dangerous for the stability of the clinical image of the MS patient because this could lead to relapses, or induce a higher body temperature during or after the training (Smith RM et al. 2006). A result of an increasing core temperature could be a higher frequency of neurologic symptoms, as reported in 80% of MS patients (Guthrie TC, Nelson DA. 1995). It was recently shown that, in heat-sensitive patients, temporary worsening of symptoms is greater when performing endurance (cycling) training compared to resistance training (Skjerbæk AG, et al. 2013).

Interestingly, no adverse events or incidents were recorded and all the participants could perform the protocol, as prescript. In total, three subjects dropped out due to different reasons, but none because of worsening of symptoms. Previously, it was shown that exercise is safe and not leading to increased risk for relapses (Pilutti LA, et al. 2014). We conclude now that HIIT can be considered as safe.

4.3 *Limitations, strengths and recommendations for further research*

First of all, we only performed secondary analyses on the collected data by Wens I, et al. (in progress) which focused on the cardiovascular profile of the MS patient after a 12-week during high-intensity interval – and resistance training. As a result, no power analysis was performed for the mobility measures. We could have used a power analysis in SAS 9.2 software (SAS Institute Inc, Cary, USA), which not happened for the mobility outcomes. As a result, the sample size was rather small (<30). Secondly, the study included two groups with a difference in numbers. At baseline, the HIIT-group consisted out eight men and eight women while the control group consisted out nine women and only two men. Due to this small sample, also non-parametric tests were used for the analysis. This resulted in less power. Also, only two patient-reported questionnaires were used for the evaluation of both mobility as quality of life. In both cases, these aren't ideal measures. Analysis of quality of life is difficult through objective measures, but the addition of the Multiple Sclerosis Quality Of Life Inventory (Fisher et al., 1999) could be an improvement as this questionnaire is both generic and MS-specific. Intention to treat wasn't used in the analysis because measurement of the drop-outs after twelve weeks wasn't performed.

Strengths of the study were that there was always a 1:1 ratio between trainers and MS patients so that it was guaranteed that the planned training intensity was reached. Also, the MS patients did the pre- and post-tests at about the same time of day so that subjective fatigue did not affect the results of the analysis. Feys P, et al. (2011) showed that this wasn't relevant for the objective measures, but fatigue is increasing according to time of day which could influence the outcome of the questionnaires. Further, the objective measures were alternated with questionnaires. Every participant had enough time to recover from the physical tasks. A minimum of one day of recovery was provided between every day of training, again to exclude the possible feeling of fatigue. All tests were performed in a chilled room. Previous study concluded that a temperature above 20°C could have an influence on fatigue, pain, concentration or a worsening of symptoms (Flensner G, et al. 2011).

We recommend that future study include functional training next to a combination of HIIT and resistance training because Wens I, et al. (2015) already found that HIIT and resistance training has a positive effect on endurance and strength after 12 weeks. Additional functional training could influence the mobility in MS and the corresponding quality of life. Twelve weeks of training is enough to get an improvement in mobility because there already exists studies which remarked improvement in mobility in a shorter amount of time (Kalron A, et al. 2015 & Çakit BD, et al. 2010)

5 Conclusion

No significant improvement in mobility and QOL was obtained after 12 weeks of a combined high-intensity interval- and resistance training. We conclude that the combination of both trainings was safe and well tolerated. Further research with the addition of functional training is recommended.

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