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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Impact of periodized home-based rehabilitation and B-alanine supplementation on exercise capacity in Multiple Sclerosis: a feasibility study

Ine Nieste
Maarten Van Herck

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Bert OP 'T EIJNDE

COPROMOTOR :
De heer Charly KEYTSMAN

2017
2018

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First of all we would like to express our very great appreciation to our co-supervisor Drs. Charly Keytsman and supervisor Prof Dr. Bert Op 't Eijnde for the advice, positive feedback and assistance during the research project.

The past two years were a pleasant cooperation in which we have had the opportunity to explore the scientific aspect of physiotherapy. We learned to coordinate, to communicate and to work together as one team and besides teammates, we became close friends.

Furthermore, we would like to thank the Rehabilitation Research Centre REVAL of Hasselt University for provision of their infrastructure and facilities.

At last our special thanks are extended to the participants of this trial who participated on a voluntary basis. This accomplishment would not have been possible without their participation.

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Context of the master thesis

This master's thesis is part of the research domain rehabilitation of cardiorespiratory and internal disorders in a neurological population. In particular, it focusses on the cardiorespiratory rehabilitation in persons with Multiple Sclerosis (PwMS).

The heterogeneity of symptoms in Multiple Sclerosis (MS) often leads to a sedentary lifestyle, known as disuse-related physical inactivity[1, 2]. Such inactivity causes a vicious circle of physical and functional deterioration and negatively influences exercise capacity[3], muscle characteristics[2, 4] and quality of life (QoL)[3, 5, 6]. Since pharmacological treatments have little impact on these secondary symptoms, exercise therapy is a potent strategy to tackle these deficits and the vicious circle of decreased exercise tolerance and greater disability[7].

Exercise therapy has been shown to increase exercise tolerance, muscle strength, QoL and various other functional measures in PwMS[8, 9]. More importantly, high-intensity interval training (HIIT) shows superior results on exercise capacity and muscle characteristics compared to continuous endurance training[10]. HIIT is a time-efficient strategy to implement training in daily living[11]. However, PwMS seem to express higher subjective fatigue following HIIT[12] and reduced adherence[13]. In an attempt to improve exercise performance, HIIT-related feasibility and adherence; a periodized, HIIT-oriented, home-based, remotely supervised exercise program in combination with β-alanine (BA) supplementation is investigated. BA, an ergogenic aid used to enhance muscle carnosine content[14, 15] (which is lowered in PwMS[16]) and consequently high intense training efficiency[17, 18], might lead to improved rehabilitation outcomes in PwMS when combined with an exercise program.

This master's thesis is executed in cooperation with another master student (Kristof Geladé) under the supervision of Doctor of Philosophy (PhD) student Charly Keytsman (co-supervisor) and Prof. Dr. Bert Op 't Eijnde (supervisor) and is part of a broader research project that is currently on-going at Hasselt University (UHasselt). This research project (code:17.09/reva17.02) investigates the impact of β-alanine supplementation on the effects of a home-based rehabilitation program in PwMS.

This experimental study is part of a PhD project of Drs. Charly Keytsman and was conducted as master's thesis project by Maarten Van Herck and Ine Nieste. The study was executed

during the first and second master year at the Rehabilitation Research Centre (REVAL) of UHasselt in Diepenbeek, Belgium.

Aim of this master's thesis was to answer the following research question: "What are the effects of a home-based, periodized rehabilitation program and β-alanine supplementation on exercise capacity and body composition in persons with MS?"

References

1. Blikman LJ, van Meeteren J, Horemans HL, et al. Is physical behavior affected in fatigued persons with multiple sclerosis? *Archives of physical medicine and rehabilitation* 2015; 96: 24-29. 2014/09/23. DOI: 10.1016/j.apmr.2014.08.023.
2. Wens I, Dalgas U, Vandenabeele F, et al. Multiple sclerosis affects skeletal muscle characteristics. *PLoS One* 2014; 9: e108158. 2014/09/30. DOI: 10.1371/journal.pone.0108158.
3. Heine M, van de Port I, Rietberg MB, et al. Exercise therapy for fatigue in multiple sclerosis. *The Cochrane database of systematic reviews* 2015: Cd009956. 2015/09/12. DOI: 10.1002/14651858.CD009956.pub2.
4. Kent-Braun JA, Ng AV, Castro M, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *Journal of applied physiology (Bethesda, Md : 1985)* 1997; 83: 1998-2004. 1998/02/14.
5. Wens I, Eijnde BO and Hansen D. Muscular, cardiac, ventilatory and metabolic dysfunction in patients with multiple sclerosis: Implications for screening, clinical care and endurance and resistance exercise therapy, a scoping review. *Journal of the neurological sciences* 2016; 367: 107-121. 2016/07/18. DOI: 10.1016/j.jns.2016.05.050.
6. Zwibel HL and Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. *The American journal of managed care* 2011; 17 Suppl 5 Improving: S139-145. 2011/07/27.
7. Durstine JL, Painter P, Franklin BA, et al. Physical activity for the chronically ill and disabled. *Sports medicine (Auckland, NZ)* 2000; 30: 207-219. 2000/09/22.
8. Jelinek GA, De Livera AM, Marck CH, et al. Lifestyle, medication and socio-demographic determinants of mental and physical health-related quality of life in people with multiple sclerosis. *BMC neurology* 2016; 16: 235. 2016/11/24. DOI: 10.1186/s12883-016-0763-4.
9. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Archives of physical medicine and rehabilitation* 2013; 94: 1800-1828.e1803. 2013/05/15. DOI: 10.1016/j.apmr.2013.04.020.
10. Wens I, Dalgas U, Vandenabeele F, et al. High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. *PLoS One* 2015; 10: e0133697. 2015/09/30. DOI: 10.1371/journal.pone.0133697.
11. Zaenker P, Favret F, Lonsdorfer E, et al. High-intensity interval training combined with resistance training improves physiological capacities, strength and quality of life in multiple sclerosis patients: a pilot study. *European journal of physical and rehabilitation medicine* 2018; 54: 58-67. 2017/07/07. DOI: 10.23736/s1973-9087.17.04637-8.
12. Dawes H, Collett J, Meaney A, et al. Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis. *Neurorehabilitation and neural repair* 2014; 28: 139-148. 2013/09/13. DOI: 10.1177/1545968313503218.
13. Collett J, Dawes H, Meaney A, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2011; 17: 594-603. 2011/01/21. DOI: 10.1177/1352458510391836.
14. Harris RC, Tallon MJ, Dunnett M, et al. The absorption of orally supplied beta-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. *Amino acids* 2006; 30: 279-289. 2006/03/24. DOI: 10.1007/s00726-006-0299-9.
15. Stellingwerff T, Anwander H, Egger A, et al. Effect of two beta-alanine dosing protocols on muscle carnosine synthesis and washout. *Amino acids* 2012; 42: 2461-2472. 2011/08/19. DOI: 10.1007/s00726-011-1054-4.
16. Keytsman C, Blancquaert L, Wens I, et al. Muscle carnosine in experimental autoimmune encephalomyelitis and multiple sclerosis. *Multiple sclerosis and related disorders* 2018; 21: 24-29. 2018/02/18. DOI: 10.1016/j.msard.2018.02.013.
17. Saunders B, Elliott-Sale K, Artioli GG, et al. beta-alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis. *Br J Sports Med* 2017; 51: 658-669. 2016/11/01. DOI: 10.1136/bjsports-2016-096396.
18. Bellinger PM. beta-Alanine supplementation for athletic performance: an update. *Journal of strength and conditioning research* 2014; 28: 1751-1770. 2013/11/28. DOI: 10.1519/jsc.0000000000000327.

Content

1. Abstract

Background: High-Intensity interval training (HIIT) improves exercise capacity in persons with MS (PwMS). However, PwMS are reported to show reduced adherence to this exercise type, possibly due to its highly demanding nature. Hence, measures to improve HIIT feasibility and adherence are worthwhile investigating. A potential strategy might be to implement periodization principles and β-alanine (BA) supplementation, both commonly used in athletic populations to enhance HIIT efficiency. This has never been investigated in PwMS yet.

Aim of the study: To investigate the feasibility and effects of a HIIT-oriented, periodized, home-based training program on exercise capacity and body composition in PwMS and the ability of BA to fortify these effects.

Methods: This double-blinded, placebo-controlled, randomized feasibility study consisted of 24 weeks periodized, home-based training. A 3-week training cycle (1 volume, 1 HIIT and 1 recuperation week) was repeated eight times. PwMS (EDSS: 1.83 ±1.13) and healthy controls (HC) were allocated to a BA (MS_{BA}, n: 12; HC_{BA}, n: 11) or matching placebo group (MS_{PL}, n: 11; HC_{PL}, n: 11). Exercise capacity (VO_{2max}, time-to-exhaustion: TTE, recovery: HRR, total work done: TWD and maximal workload) and body composition (fat mass: FM, lean mass: LM, fat percentage: FAT%) were assessed at pre- and post-intervention.

Results: Thirty-six subjects completed the intervention (MS_{BA}, n: 11; HC_{BA}, n: 8; MS_{PL}, n: 7; HC_{PL}, n: 10). Main time effects were found for load (+10.95%), VO_{2max} (+6.17%) TTE (+12.42%), TWD (+22.49%), FM (-6.05%) and FAT% (-4.04%). No main group, intervention nor interaction effects were found ($p>0.05$). Training adherence was 86-92%.

Conclusion: A HIIT-oriented home-based training program seems feasible and enhances exercise capacity in PwMS and HC. Supplementation of BA showed no additional effects.

Keywords: Multiple Sclerosis, β-alanine supplementation, exercise therapy, home-based training, training periodization, exercise capacity, body composition.

Trial Registration: ClinicalTrials.gov NCT03418376

2. Introduction

Multiple Sclerosis (MS) is a progressive, autoimmune, neurodegenerative disorder of the central nervous system, characterized by chronic inflammatory processes that cause demyelination and axonal damage[1]. Clinical manifestations include spasticity, tremor, paralysis, increased fatigue, decreased mobility, walking difficulties, muscle weakness and cognitive abnormalities[2]. These manifestations often lead to disuse and a more sedentary lifestyle[3, 4]. This disease-induced physical inactivity causes a vicious circle of decreased exercise tolerance and even greater disability[5, 6], thereby negatively influencing quality of life (QoL)[7]. Recent immune-modulatory therapies effectively decrease MS relapse rates and disease severity, but fail to slow the disease processes and accumulation of MS-related disabilities. Therefore, alternative solutions are warranted.

Exercise therapy, currently known to be safe, well tolerated[8] and efficient at counteracting negative effects on mobility, muscular strength, physical fitness and fatigue[9, 10], has become a cornerstone of rehabilitation in persons with MS (PwMS). Surprisingly and in an attempt to further improve exercise therapy outcome in MS, superior results were found following high intensity interval training (HIIT, 1-5 high-intensity exercise bouts ranging from 6s to 4min interspersed by recovery periods of 30s – 4 min, 8-12w)[11] on exercise capacity and muscle strength (+25-60%), compared to moderate intensity training[12, 13]. Although no adverse events are reported in literature[13-15], adherence to HIIT is reported to be rather low in PwMS (53-72%) compared to continuous, low intensity exercise (95%)[16]. Possibly, a rehabilitation program consisting of purely high intense modalities is too demanding (intensity = 100% of maximum heart rate) and requires perseverance. In fact, Perri et al. (2002) reported that prescription of higher exercise intensities appeared to significantly decrease training adherence, leading to reduced exercise output[17]. This supports the necessity of alternative training programs (with inclusion of HIIT components) to augment long-term feasibility and adherence in patients[18].

In sports communities, training programs are designed to ensure optimal performance throughout the entire season while preventing overload and/or injuries. Training is divided in periodically alternating blocks of 1-4 weeks. Each block represents a different training goal, to ensure adequate stimuli and adaptations[19-21]. This periodization principle could be used for PwMS as well in order to comply with the HIIT requirements and on the same time, enhance

feasibility by alternating HIIT blocks with other training modalities. Additionally, training performance and thus clinical outcomes might even be improved, since current rehabilitation principles (continuous, linear progressions of the same stimulus and training of multiple abilities simultaneously) result in suboptimal stimuli and adaptations[21-23]. However, principles of periodization have never been explored in the rehabilitation of PwMS.

Although exercise therapy has proven to be effective in terms of functional parameters and QoL in MS, only 43 percent of PwMS is reported to participate in an exercise program[24]. Multiple barriers to engage in physical activity (PA) are identified in literature, being: lack of time, distance, transportation, neurological disability, specialist availability and insurance coverage[25, 26]. These barriers cause rehabilitation to be of short term and often reactive to a functional decline[26], which limits long-term benefits. Possibly, if PwMS would be able to self-manage their exercise therapy and transportation is no longer of concern, higher activity levels might be established. This could be achieved by home-based rehabilitation, which has already been shown to be safe and effective for improving function and symptoms in MS[27, 28].

Ergogenic supplements are widely used in athletic populations to enhance training efficiency and could be particularly useful in a context of maximum intensity (i.e. HIIT). Hence, supplements able to compensate for such high training demands have been extensively studied, which has led to the disclosure of ergogenic effects of β-alanine (BA) in exercise types lasting 60-240s[29, 30]. BA is the rate-limiting precursor of carnosine[31], which is an important intramuscular buffer of exercise-induced acidosis during high-intensity exercise[31]. Interestingly, recent evidence shows significant reductions in muscle carnosine content (MCC) in PwMS compared to healthy controls (HC)[14]. Additionally, PwMS are reported to have higher blood lactate concentrations[32] which could, based on the above line of reasoning, possibly account for the higher degrees of subjective leg fatigue and overall perceived exertion during/after HIIT reported in MS[11, 33, 34]. Oral ingestion of BA has been shown to increase MCC in healthy persons[35], and in an animal MS model (Experimental Autoimmune Encephalomyelitis, EAE)[14]. Furthermore, MCC elevations are already shown to exert ergogenic effects in athletes[30], but have never been investigated in PwMS yet.

Therefore, the aim of the present study was to investigate the effect and feasibility of a HIIT-oriented, periodized, long-term (home-based) training program on exercise capacity and body composition in MS and the ability of BA to fortify these effects.

3. Materials & Methods

3.1. Subjects

Participants were recruited through local advertisement in cooperation with the non-profit association 'Move To Sport'. Sixty-six subjects were assessed for eligibility and 45 were enrolled in the study following written informed consent, of which 23 persons with MS (PwMS; EDSS range 0-4, mean: 1.83 ±1.13) and 22 healthy controls (HC). A flowchart of participants' inclusion can be found in Figure 1. Subjects were asked to maintain their usual medication constant the entire study course and were excluded if they experienced an acute MS exacerbation 3 months prior to the start of the study, were already taking nutritional supplements in the previous 6 months, had an EDSS score > 4, were aged < 18 years, or had contraindications to participate in moderate- to high intense physical exercise. The study was approved by the local Ethical Committee of the Jessa hospital and Hasselt University (7/02/2017, 17.09/REVA17.02) and was performed in accordance with the Declaration of Helsinki. This study was registered at ClinicalTrials.gov (NCT03418376) at initial release.

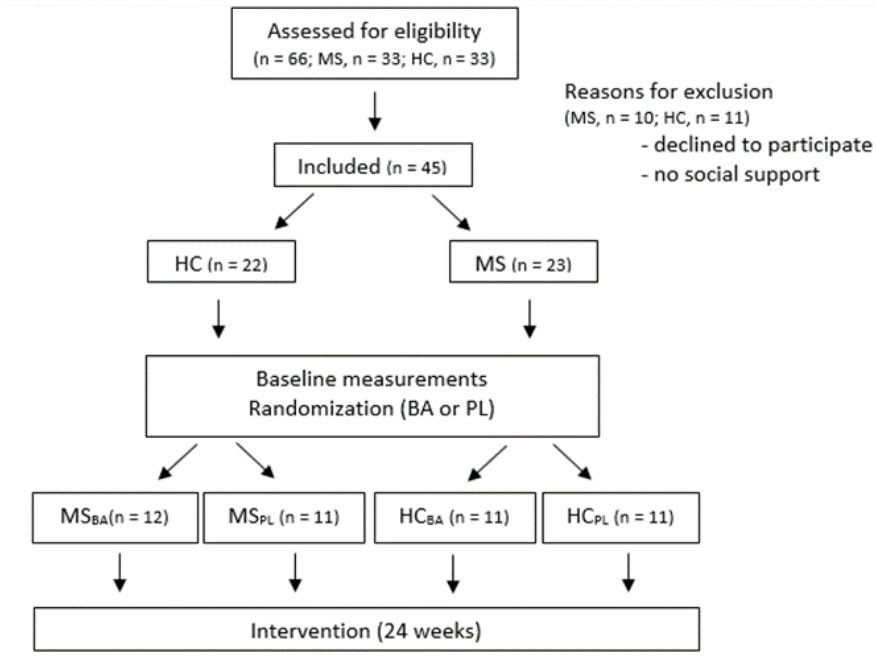

Figure 1. Flowchart of participants' inclusion

Sixty-six persons met the eligibility criteria of which 45 persons (HC: n = 22, MS: n = 23) were included and randomized over four groups. Abbreviations: BA, β-alanine; HC, Healthy Controls; MS, Multiple Sclerosis; MSK, Musculoskeletal; PL, Placebo.

3.2. Study design

The current feasibility study was conducted between March 2017 and September 2017, whereas patient recruitment started February 2016. All measurements took place at the Rehabilitation Research Centre of Hasselt University (REVAL) in Diepenbeek, Belgium. Medical safety was evaluated by a trained professional before any other measurement took place. Exercise capacity and body composition were measured two weeks before start of the intervention (w0) and one week after completion (w26), as represented in Figure 2. After baseline measurements, PwMS and HC were allocated to either β-alanine (BA) or Placebo (PL) supplementation using randomization software. Four groups were formed (cfr. Figure 1): PwMS and BA (MS_{BA}, n = 12), PwMS and PL (MS_{PL}, n = 11), HC and BA (HC_{BA} , n = 11) and HC and PL (HC_{PL}, n = 11). Subjects and affect-assessors were blinded to supplementation protocol. The intervention consisted of 24 weeks home-based training (identical for all groups) and supplementation of either BA or PL. Personalized training schedules were sent by mail and adherence to it was monitored using smartwatches and an online registration system (flow.polar.com). Smartwatches (Polar M200) were distributed during an information session at baseline. After baseline measures, one habituation week (w1) was organized to prevent technical issues during the intervention.

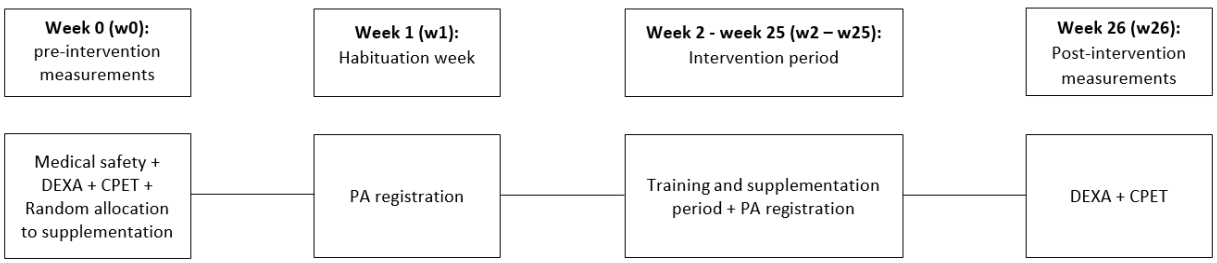

Figure 2. Study design overview

The study was divided into four stages: pre-intervention measurements (w0), one habituation week (w1), an intervention period (w2-w25) and post-intervention measurements (w26). Abbreviations: CPET, Cardiopulmonary Exercise Test; DEXA, Dual-Energy X-ray Absorptiometry; PA, Physical Activity.

3.3. Outcome measures

3.3.1. Exercise capacity

Exercise capacity was evaluated by a cardiopulmonary exercise test (CPET), using a Cyclus2 ergometer (RBM elektronik-automation GmbH, Leipzig, Germany) with pulmonary gas exchange analysis (Metalyzer II® 3B Cortex, Leipzig, Germany). Patients used their own bicycle during the graded exercise test (GXT) and pedaled until volitional exhaustion or failure to maintain a cadence above 60 repetitions per minute (RPM). Initial workload and load progression varied across men and women (30W +15W/min and 20W +10W/min respectively)[36]. Heart rate (HR) was monitored every minute. Oxygen uptake (VO_2) and respiratory exchange ratio (RER) were collected breath-by-breath and averaged every ten seconds. Blood lactate concentrations (La) were evaluated every two minutes from a capillary blood sample of the right earlobe with an Accutrend® Plus system (F. Hoffmann-La Roche Ltd, Basel, Switzerland). This was done in order to verify volitional exhaustion (La > 8 mmol/l blood), together with following criteria: RER > 1.1 and VO2 and HR plateau with increasing workload[37]. Time-to-exhaustion (TTE; min), maximal heart rate (HRmax; bpm), HR after two minutes of recovery (HRrecov; bpm), maximal oxygen uptake (VO_{2max}; ml/kg/min) and maximal workload (Wmax; W) were reported. Total work done (TWD = TTE * average workload /1000; kJ)[38], and heart rate recovery (HRR = HRmax – HRrecov; bpm)[39] were calculated afterwards.

3.3.2. Body composition

A Dual-Energy X-ray Absorptiometry (DEXA) scan (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium) was used to evaluate whole body (with exclusion of the head) fat mass (FM; kg), lean mass (LM; kg) and fat percentage (FAT%; %). Subjects were assessed in a rested state to maximize precision[40].

3.3.3. Physical activity (PA)

Throughout the 24-week training program participants continuously wore a Polar M200 during daytime. Data (amount of training sessions, duration, average HR and HR pattern) was visible for participants and effect-assessors at 'https://flow.polar.com', where adherence (number of executed training sessions and number of HR peaks with >90% of HRmax) was checked.

3.4. Intervention

3.4.1. Supplementation

Participants were supplemented for 24 consecutive weeks. The first 12 weeks (loading phase, w2-13) subjects received a daily dose of 3.2 g (4x800 mg) BA (β-alanine; β-Alanine, Cellulose, HPMC, Magnesium Stearaat, Silicium dioxide, Zinc bisglycinate; Aminolabs® Hasselt, Belgium) and 1.6 g/day (2x800 mg) for the following 12 weeks (maintenance phase, w14-25) or an equivalent amount of PL (Maltodextrin; Cellulose, Glycine, HPMC, Magnesium Stearaat, Silicium dioxide Aminolabs® Hasselt, Belgium). Doses did not exceed 800 mg and were sustained-release tablets to prevent paresthesia[41]. Tablets were ingested at approximately 9 am, 12 am, 3 pm and 6 pm (loading phase) and 9 am and 6 pm (maintenance phase), which is based on a supplementation protocol already reported to effectively elevate muscle carnosine content (MCC) in healthy subjects[35, 42]. Supplements and placebo tablets were provided in identical white tubes and were identical in colour and taste.

3.4.2. Training program

Individualized training schedules were provided every 3-week cycle by mail and were executed outdoor (own bicycle) or indoor (bike rollers or spinning bike). The smartwatches enabled subjects to train at the prescribed exercise intensities (% HRmax). Activity was continuously monitored at 'https://flow.polar.com' in order to provide participants with feedback when deviations from the training protocol were detected. Subjects were instructed to limit their sport activities to the prescribed training protocol and advised to train on specific days. However, deviation was allowed, as long as weekly volumes were reached, sequence of training sessions was preserved and sessions were separated by a 24h period. Duration and intensity gradually increased over time. The 24-week home-based training program consisted of a 3-week training cycle (meso-cycle) which was repeated eight times. One meso-cycle comprised three micro-cycles, of one week each, with the following sequence: high-volume endurance training (week I), high-intensity interval training (HIIT, week II) and a recovery week (week III). Schematic illustration of the training protocol is presented in Figure 3. In the high-volume endurance and HIIT micro-cycle, three training sessions / week were performed. Two sessions in the high-volume endurance week consisted of a moderate intensity and longer duration (2-3hours, 60-80%HRmax) and one session of a higher intensity and shorter duration (1-1.5h, 75-90%). During HIIT sessions, 3 exercise bouts of 60-90seconds (100%HRmax) were

alternated with recuperation bouts of 2-3minutes (low intensity). The recuperation week consisted of one HIIT session (100%HRmax, 3 exercise bouts of 70-90seconds each, 3 minutes recuperation bouts) and one, optional endurance training (2-3h, 70-90% HRmax). Before and after each training session a standardized warming-up (10min, 50-70%HRmax) and cooling-down (10min, 60-80%HRmax) was performed.

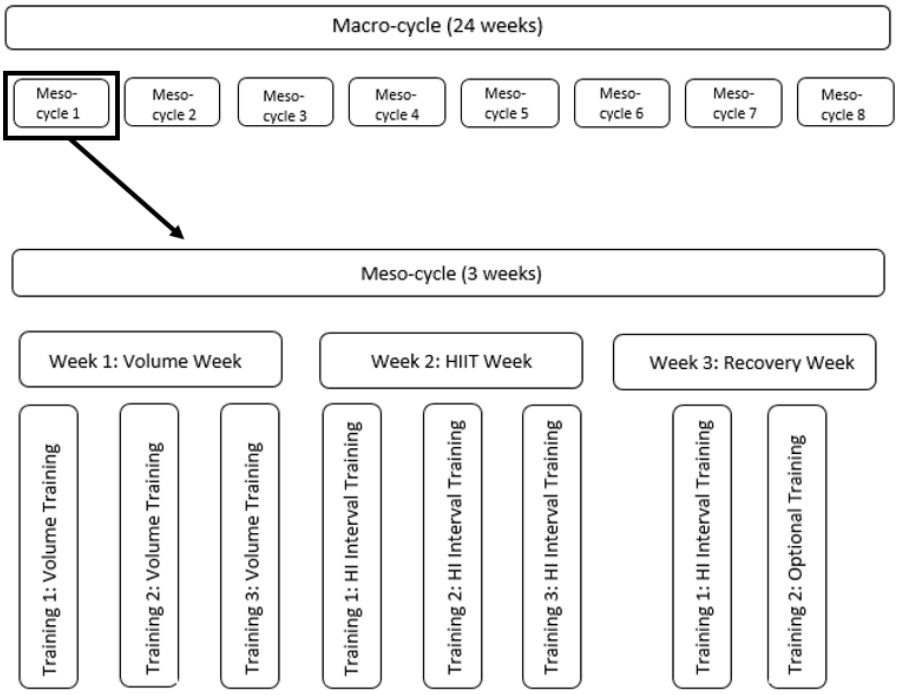

Figure 3. Training protocol

The intervention period (macro-cycle: 24 weeks) consisted of a 3-week training cycle (meso-cycle) which was repeated eight times. One meso-cycle comprised three micro-cycles of one week each: a high-volume endurance training (week I), a high-intensity interval training (week II) and a recovery week (week III). Abbreviations: Hi, High-Intensity; HIIT High-Intensity Interval Training.

3.5. Statistical analysis

All data were analysed using SPSS v. 22.0 (IBM). When assumptions for normality and homoscedasticity were confirmed (Shapiro-Wilk test and Brown-Forsythe test, respectively) for all variables (load, VO_{2max}, TTE, TWD, HRR, FM, LM and FAT%), one-way analysis of variance (ANOVA) was used to compare groups at baseline and to analyse training data. Differences between groups (MS_{BA}, MS_{PL}, HC_{BA} and HC_{PL}) were analysed using mixed model repeated measures ANOVA (within subject variable: time [pre – post intervention], between-subject variables: group [MS – HC] and intervention [BA – PL]). When significant interactions were found, difference scores between groups were analysed post-hoc using unpaired t-tests.

Differences within groups (post minus pre-intervention) were analysed using paired student's t-tests. All data are calculated as means ± standard deviation (SD) and represented as percentages. Differences were considered significant when $p < 0.05$ (2-tailed). Multiple comparison was corrected by means of Bonferroni correction (threshold for statistical significance: $p < 0.05/6$). Intention-to-treat analysis was applied.

4. Results

4.1. Subject characteristics

Gender (p = 0.443), age (p = 0.833), weight (p = 0.484), height (p = 0.245) and BMI (p = 0.551) did not differ between groups. EDSS scores were similar between MS groups (MS_{BA} vs MS_{PL}, p = 0.104). Subject characteristics are presented in Table 1.

Table 1
Subject characteristics

	MS_{BA} (n = 11)	**MS_{PL}** (n = 7)	**HC_{BA}** (n = 8)	**HC_{PL}** (n = 10)	**Total group** (n = 36)	**P-value**
EDSS	1.44 ±1.10	2.42 ±0.97	/	/	1.83 ±1.13	0.104
Gender (m/f)	7/4	4/3	7/1	5/5	23/13	/
Age (y)	41.73 ±10.02	40.71 ±7.39	44.00 ±13.00	39.50 ±11.38	41.44 ±10.39	0.833
Weight (kg)	76.22 ±12.66	73.37 ±10.89	78.87 ±12.59	70.91 ±8.58	74.78 ±11.22	0.484
Height (cm)	172.28 ±9.39	176.31 ±7.76	177.19 ±6.43	170.88 ±5.54	173.77 ±7.66	0.245
BMI (kg/cm^2)	25.78 ±4.28	23.60 ±2.98	25.00 ±2.83	24.28 ±2.61	24.77 ±3.28	0.551

Data are expressed as means ±SD and represent subject characteristics. No between-groups differences were found for EDSS, gender, age, weight, height and BMI. Abbreviations: BA, β-alanine; BMI, Body Mass Index.; EDSS, Expanded Disability Status Scale; f, female; HC, Healthy Controls; m, male; MS, Multiple Sclerosis; PL, Placebo.

4.2. Adherence and adverse events

A drop-out of nine subjects was documented during the course of the study (cfr. Figure 4) due to MS-exacerbations (n: 1), non-exercise related musculoskeletal (MSK) injuries (n: 3), motivation (n: 2) and personal reasons (n: 3). Training adherence was 92% in PwMS, whereas HC completed 86% of the prescribed training sessions. Missed training sessions were due to MS-related exacerbations, holiday, MSK injuries (not related to the exercise program) and personal reasons. No adverse events were reported during the study.

Generally, 34.33% ±25.38 of all high-intensity (HI) bouts (training intensity ≥ 90% of HR_{max}) were reached. No significant difference was found between groups for anaerobic training accomplishment (MS_{BA}: 25.76% ±26.66, MS_{PL}: 40.41% ±19.47, HC_{BA}: 38.88% ±25.13, HC_{PL}: 38.40% ±28.01, p = 0.63).

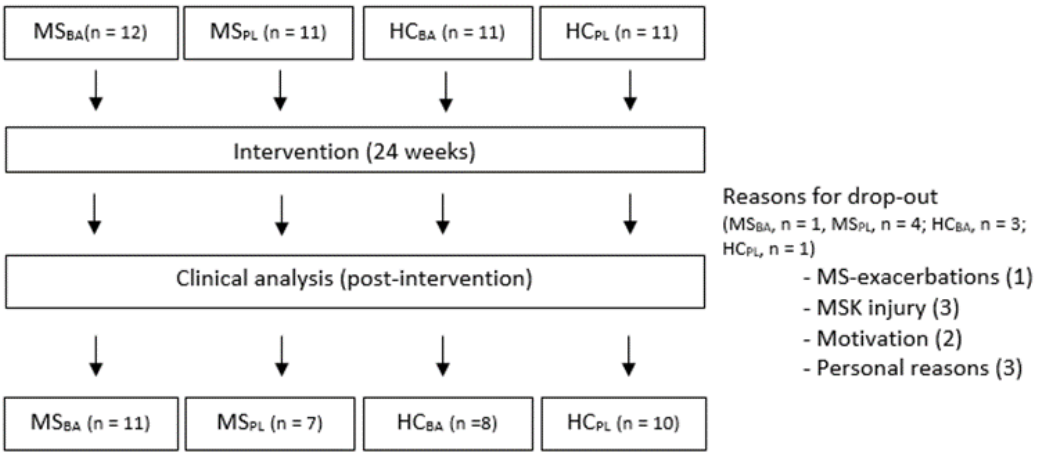

Figure 4. Flowchart of participants' completion

Thirty-six participants completed the intervention (24 weeks). Reasons for drop-out are mentioned (PwMS: 6, HC: 3): MS-exacerbations, MSK-injury, motivation and personal reasons. Abbreviations: BA, β-alanine; HC, Healthy Controls; MS, Multiple Sclerosis; MSK, Musculoskeletal; PL, Placebo.

4.3. Outcome measures and baseline measurements

Primary and secondary outcome measures for all groups at baseline (PRE) and after 24 weeks of training (POST) are presented in Table 2 and Figure 5-6. Groups were comparable at baseline for exercise capacity (p-values between 0.119 and 0.932) and body composition (p-values between 0.405 and 0.975).

4.3.1. Exercise capacity

Main time effects were found for workload (+10.95%, p = 0.000), VO_{2max} (+6.17%, p = 0.001), TTE (+12.42%, p = 0.000) and TWD (+22.49%, p = 0.000). Significant within-group differences were found for workload (+8.77%; +14.47%; +13.15%; +9.00%, p ≤ 0.004), TTE (+12.46%; +14.26%; +13.43%; +10.55%, p ≤ 0.006) and TWD (+19.13%; +25.87%; +29.39%; +18.11%, p ≤ 0.006) in all four groups (MS_{BA}, MS_{PL}, HC_{BA} and HC_{PL} respectively), for VO_{2max} in MS_{PL} (+9.29%, p = 0.010) and HC_{BA} (+11.42%, p = 0.022) and for HRR in MS_{BA} (-13.76%, p = 0.015). No main group, intervention nor interaction effects were found (p > 0.05).

4.3.2. Body composition

Main time effects were found for fat mass (-6.05%, p = 0.009) and fat percentage (-4.04%, p = 0.015). Within-group changes were not significant. No main group, intervention nor interaction were found.

Table 2

Primary and secondary outcome measures for all groups at baseline and after 24 weeks home-based exercise in combination with supplementation of either β-alanine or placebo.

	MS_{BA} (n = 11)		**MS_{PL}** (n = 7)		**HC_{BA}** (n = 8)		**HC_{PL}** (n = 10)	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Load (watt) [c]	217.73 ±45.13	236.82 ±46.65[b]	222.14 ±46.45	254.29 ±47.38[b]	251.88 ±47.35	285.00 ±58.92[b]	239.00 ±59.15	260.50 ±52.09[b]
VO_{2max} ($ml*kg^{-1}*min^{-1}$) [c]	40.36 ±6.52	41.45 ±7.87	41.57 ±7.30	45.43 ±5.16[b]	42.75 ±6.54	47.63 ±7.91[b]	43.40 ±8.59	44.90 ±6.77
TTE (min; abs) [c]	15.49 ±2.75	17.42 ±3.90[b]	15.36 ±1.97	17.55 ±2.49[b]	16.38 ±2.15	18.58 ±2.60[b]	17.94 ±2.86	19.83 ±2.51[b]
TWD (kJ)[c]	113.00 ±35.82	134.62 ±45.80[b]	116.01 ±33.90	146.12 ±41.30[b]	138.13 ±40.65	178.73 ±61.48[b]	142.75 ±46.09	168.60 ±41.52[b]
HRR (bpm)	48.18 ±10.43	41.55 ±10.94[b]	58.71 ±5.16	52.29 ±10.77	49.88 ±11.64	46.75 ±15.14	49.01 ±9.83	49.10 ±12.44
FM (kg) [c]	16.82 ±9.67	16.41 ±10.17	16.18 ±6.31	14.55 ±5.57	15.35 ±5.27	14.07 ±5.49	16.50 ±5.24	15.57 ±5.58
LM (kg)	51.44 ±7.05	50.45 ±7.58	50.54 ±8.45	50.67 ±8.93	56.79 ±8.22	56.72 ±7.86	50.31 ±10.81	50.21 ±10.55
FAT% (%) [c]	23.60 ±10.59	23.50 ±11.57	24.04 ±8.57	22.31 ±7.98	20.95 ±4.75	19.6 ±5.85	25.06 ±8.72	24.08 ±9.28

Data are expressed as means ±SD and represent primary and secondary outcome measures pre- and post-intervention. [c] Main time effects were found for load, VO_{2max}, TTE and TWD. [b] Significant within-group differences were found for load, TTE and TWD in all four groups, for VO_{2max} in MS_{PL} and HC_{BA} and for HRR in MS_{BA}. [a] No between-groups differences were found. Abbreviations: BA, β-alanine; bpm, beats per minute; FAT%, Fat percentage; FM, Fat Mass; HC, Healthy Controls; HRR, Heart Rate Recovery; kJ, Kilojoule; LM, Lean Mass; MS, Multiple Sclerosis; PL, Placebo; TTE, time-to-exhaustion; TWD, Total Work Done; VO_{2max}, maximal oxygen uptake.

[a] $p < 0.05$ between groups, [b] $p < 0.05$ within groups, [c] $p < 0.05$ within whole group (= main time effect).

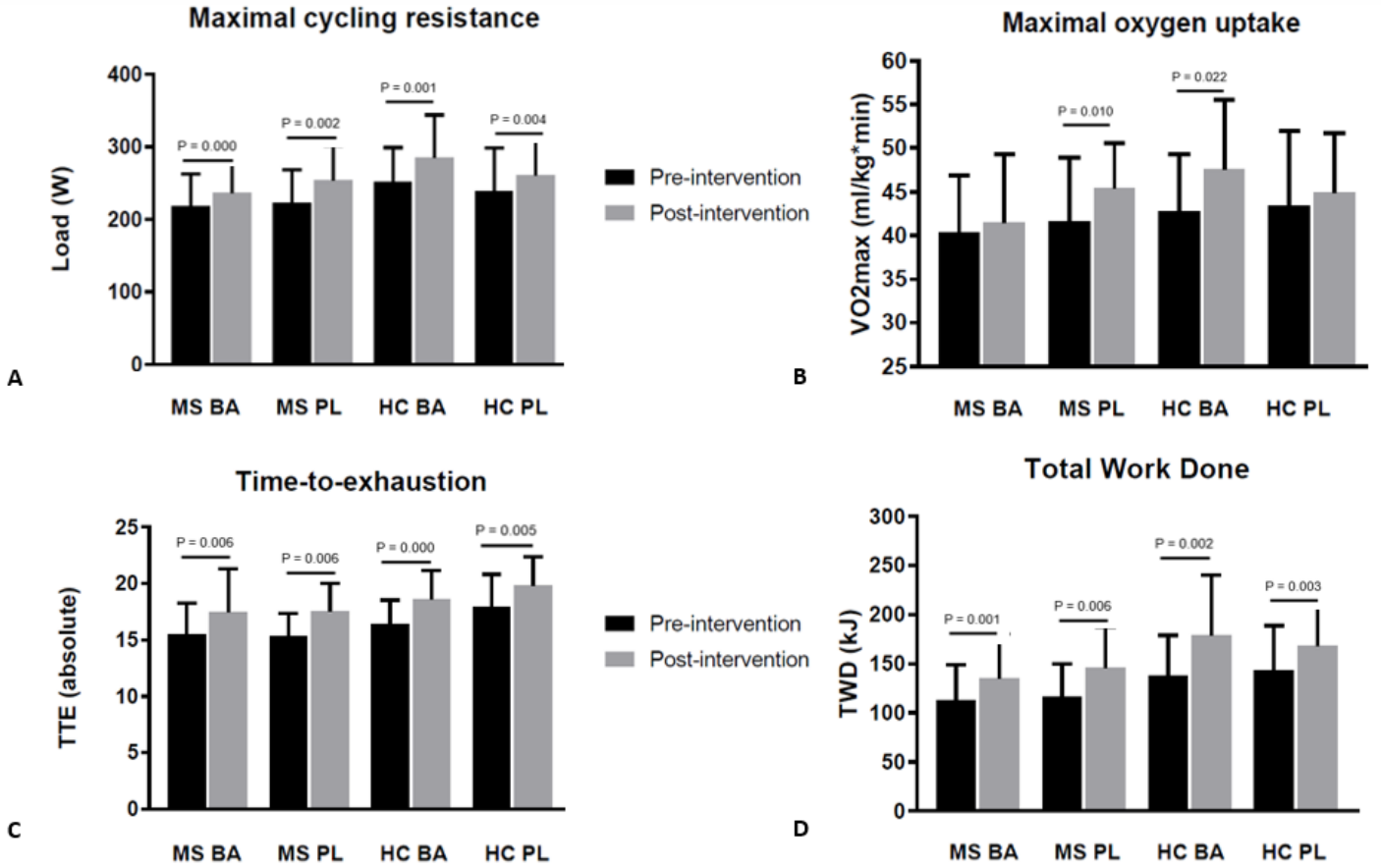

Figure 5. Graphic illustration of outcome measures (A) Maximal cycling resistance (B) Maximal oxygen uptake (C) Time-to-exhaustion and (D) Total work done, for all four groups, at baseline (pre-intervention) and after 24 weeks home-based exercise in combination with supplementation of either β-alanine or placebo (post-intervention).

Means ± SD are represented. Significant within-group changes and corresponding p-values are indicated. Significant within–groups differences were found for workload, TTE and TWD in all four groups and for VO_{2max} in MS_{PL} and HC_{PL}. Abbreviations: BA, β-alanine; HC, Healthy Controls; kJ, Kilojoule; MS, Multiple Sclerosis; PL, Placebo; TTE, time-to-exhaustion; TWD, Total Work Done; VO_{2max}, maximal oxygen uptake; W, Watt.

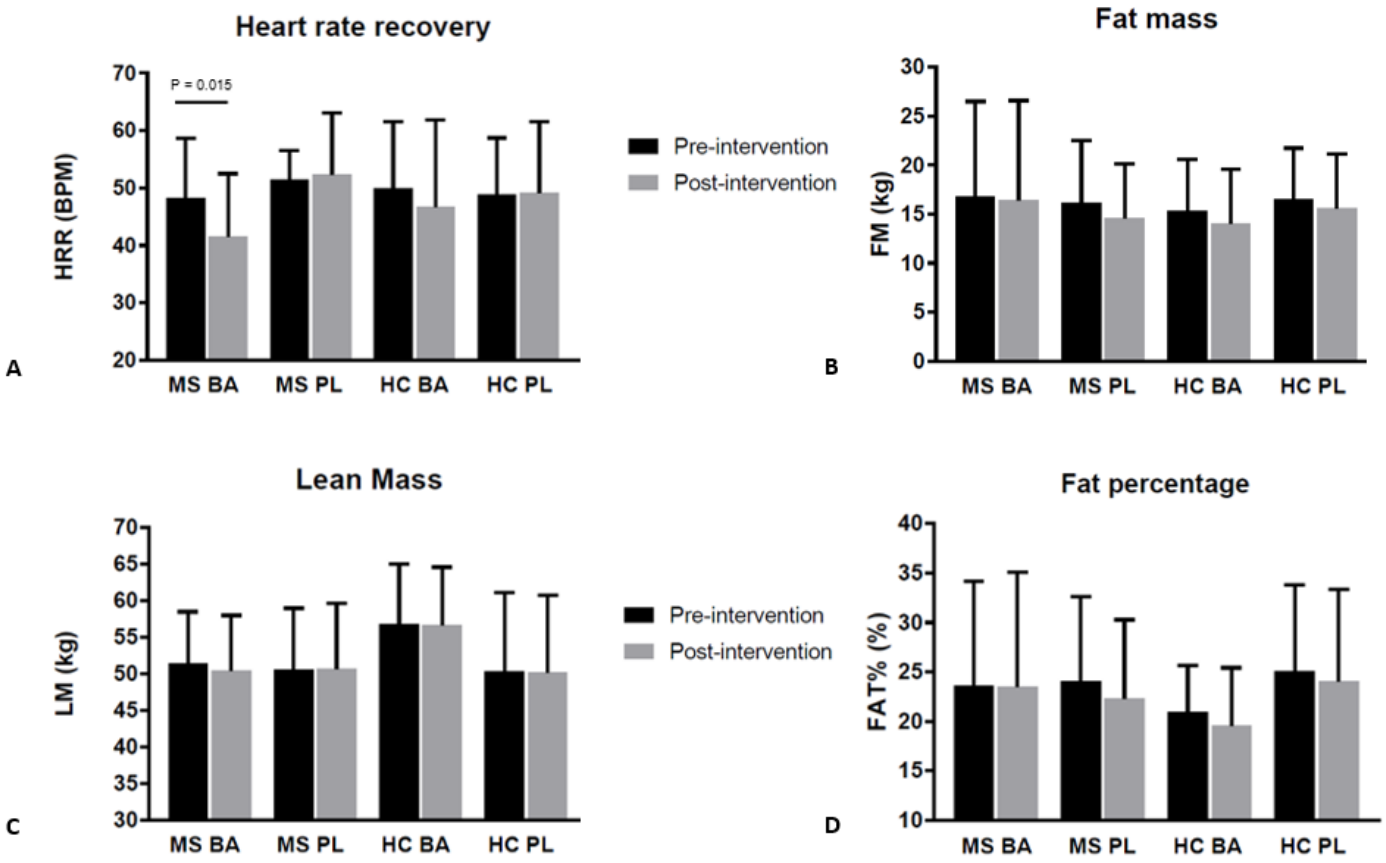

Figure 6. Graphic illustration of outcome measures (A) Heart Rate Recovery (B) Fat Mass (C) Lean Mass and (D) Fat percentage for all four groups, at baseline (pre-intervention) and after 24 weeks home-based exercise in combination with supplementation of either β-alanine or placebo (post-intervention).

Means ± SD are represented. Significant within-group changes and corresponding p-values are indicated. No significant within–groups differences were found for FM, FAT% and LM workload, whereas HRR significantly changed in MS_{BA}. Abbreviations: BA, β-alanine; bpm, beats per minute; FAT%, Fat percentage; FM, Fat Mass; HC, Healthy Controls; HRR, Heart Rate Recovery; LM, Lean Mass; MS, Multiple Sclerosis; PL, Placebo.

5. Discussion

The present study is the first to investigate the impact of home-based, HIIT-oriented rehabilitation in PwMS. Twenty-four weeks of training induced significant improvements in exercise capacity and body composition in all participants. The addition of BA-supplementation did not induce superior effects.

Interval training has already been shown to be safe, well-tolerated and to provide superior outcomes compared to continuous training in PwMS[36]. The present study explored several exercise therapy strategies in an attempt to improve HIIT-related feasibility and long-term exercise adherence.

First, periodization principles were applied to comply with HIIT requirements and on the same time, facilitate feasibility by alternating HIIT blocks with volume training sessions and recuperation weeks. In sports communities, this training principle is already known to induce superior effects compared to traditional training organization[20-23] as currently used in rehabilitation settings. Ronnestad et al. (2014)[23] showed that VO_{2max} (+4.6 ±3.7% ml/kg/min) and peak power output (+2.1 ±2.8% watt) significantly improved in trained cyclists after just four weeks of periodized training, while no changes occurred in the continuous progressive exercise group despite similar training volume and intensity[23]. The present study was, to our knowledge, the first to explore these training principles in PwMS. Here, periodization principles induced significant improvements in workload, VO_{2max}, TTE, TWD and body composition (FM and FAT%) in all participants. Moreover, the applied training regimen appeared to elicit similar effects on these parameters in PwMS compared to HC. Furthermore, measures of workload in the current study (+11.01%) seem to confirm the ability of periodized training to provide more optimal stimuli and adaptations[19, 21, 43] in MS compared to traditional training focusing on one or more abilities simultaneously (12 weeks pure HIIT: +7.41%; low intense continuous training: +6.42%; HI and continuous modalities simultaneously: -0.98%) as reported in Collet et al. (2011)[16]. However, more standardized research regarding periodization principles in MS rehabilitation is warranted.

In the present study, heart rate recovery (HRR) and lean mass (LM) were the only outcome measures with no improvements over time. HRR was obtained by subtracting HR measured after exercise cessation from HR max[39]. This is reported to be an important predictor of physical fitness[39, 44] and more importantly, of changes in fitness level after the execution of an

exercise program[45]. Based on its definition and previous findings in literature[39], decreased resting heart rates and thus elevated HRR values are to be expected post-intervention. However, HRR changes in the present study were not significant over time. Moreover, HRR values seemed to decrease after 24 weeks of training. This might be due to the implemented time interval to measure HR after exercise cessation in the present study. In most studies one minute or shorter time intervals are used[39, 46], whereas HR was measured after two minutes of recovery in the current study. Previous research already reported this method to lack sensitivity for detection of changes in physical fitness[39]. Furthermore, a reduction in muscle mass (LM) following 24 weeks of training, though not significant, might seem controversial. However, no addition of resistance training and acidic responses from HIIT, which may have induced protein synthesis inhibition and degradation[47], could explain the current findings. Furthermore, volume training sessions were of such duration (up to 3h) that without concurrent dietary modification (i.e. addition of proteins), muscle degradation might occur[48].

Taking the above line of reasoning into account, the use of periodization principles in the current training protocol improved exercise capacity in all participants, even though initial training levels were already relatively high (VO_{2max} MS: 40.83±6.64ml/kg/min; HC: 43.11±7.54 ml/kg/min) and PwMS were only minimally disabled (mean EDSS: 1.83 ±1.13). Future research should include more disabled PwMS, as training gains of even greater magnitudes may occur based on current findings. Moreover, Figure 5 and 6 show PwMS to achieve similar fitness levels post-intervention as pre-intervention levels of HC. This could imply that 24 weeks of periodized training were able to eliminate existing differences in exercise capacity between mildly disabled PwMS and HC.

Furthermore, HIIT sessions and recuperation weeks significantly reduced total training duration compared to classic training protocols[49], which might beneficially influence participation of PwMS in physical activity since lack of time is experienced as important barrier[25, 26]. Moreover, it appears that alternation of different training modalities made execution of the current training protocol more comfortable and enjoyable, as evident from personal communication with participating subjects. High adherence percentages (86-92%) compared to rather low adherence in previous HI training programs (53-72%, 2 sessions/week, 12weeks)[16], reinforce this finding. It is however difficult to make straightforward

recommendations about feasibility of the currently used periodization principles, as no standardized inventories were administered.

A second strategy we explored was supplementation of BA, for the first time in PwMS, in an attempt to enhance training efficiency during and overall perceived exertion after HIIT[11, 33, 34]. This may be induced through the intramuscular buffering effect on exercise-induced acidosis[31, 50], and thus reduce subjective fatigue perceptions and enhance exercise feasibility. However, under the conditions of the present study, BA did not improve outcome measures of exercise capacity. This is however surprising based on previously described BA-induced training gains in sedentary[38, 51, 52] and athletic populations[29, 30, 53]. Possible explanations for this discordance are low power due to small sample sizes and the inclusion of other than purely HI modalities. However, the aim of the present study was to design a HIIT-oriented training protocol, feasible for PwMS to execute regularly on longer term. For this reason, volume training sessions and recuperation weeks were implemented. As previously described, BA is reported to exert ergogenic effects in exercise types lasting 60-240s[29, 30], and not in exercise durations of >240s[29]. Therefore, total amount of HIIT sessions might have been too limited in the present training study. Furthermore, performance effects of BA were found to be of modest benefit in a recent relative effects analysis but could be meaningful in competitive athletics according to the authors[54]. Taking this into account and knowing most participants did not train on a regular base before start of the intervention, it is possible that adaptation from the training intervention was more influential than the augmentation of MCC and as such, training adaptations dominated supplementation effects[53]. Additionally, a large room for improvement in all subjects might have covered (additional) effects of BA supplementation[53]. No conclusions can be drawn about BA-induced effects on feasibility as no ratings of perceived exertion (RPE) were assessed.

Furthermore, considering the previously described MCC reductions in MS[55] and the reported positive correlation between MCC loading and training gains[52], these results are surprising. However, MCC loading was not measured in the current study and EDSS-scores of participating PwMS (avg. 1.83 ±1.13) were lower compared to EDSS-scores of MS patients with significant MCC reductions (avg. 3.1 ±1.5). Additionally, main reasons for reductions in MCC are sedentarism and progressive denervation[56, 57]. This might be less applicable for the current PwMS since baseline measurements show them to be minimally disabled and relatively fit.

Consequently, carnosine levels did probably not significantly differ between MS and HC at baseline. Furthermore, no conclusions can be drawn for compliance with the supplementation protocol as subjects were not instructed to record supplementation logs. Future research should include larger sample sizes, more disabled PwMS, measurements of MCC and assess compliance with the supplementation protocol.

Third, although exercise programs have proven to be efficient to improve functional parameters and QoL in MS, only 43 percent of PwMS is reported to participate in exercise programs[24]. Lack of time, distance, transportation, specialist availability and insurance coverage appear to be important barriers[25, 26], some of which could, according to the authors, be overcome with home-based rehabilitation. Indeed, the current home-based intervention, which was less time-consuming and did not require transportation to exercise facilities, induced significant improvements in exercise capacity and body composition. Moreover, adherence percentages of the current study seem to support this hypothesis. Training adherence was even 25-30% higher compared to other home-based exercise programs in MS[58, 59]. This is probably due to the implementation of internet-based supervision and feedback[60]. In contrast to the above, accomplishment of anaerobic intensities (i.e. achievement of training intensities ≥90% of HR_{max}) may seem rather low. However, this was probably due to the underestimation of HR during high intense bouts by the currently used device (wrist HR monitor)[61] or rather low warming-up intensities. The gap between HR at 50-70% of HRmax during warming-up and HR during first HI bouts might be too large to reach anaerobic training zones. However, subjects were instructed to perform 'all-out efforts', which guarantees adequate high intensities were reached in the present training program. Nevertheless, future research should implement chest strap monitors instead of wrist sensors in the context of HI exercise[61] and increase intensity of warming-up sessions to at least 80% of HRmax in order to obtain more accurate percentages of HIIT-related feasibility.

6. Recommendations for future research

High to excellent adherence percentages with the current training protocol might bridge the gap between compliance in laboratory compared to real-life settings[18], though more standardized future research is warranted. Hence, following recommendations should be taken into account.

Changes in medication use should be administered. Although subjects were asked to maintain their usual medication constant during the study course, this was not verified post-intervention. Consequently, observed 'training gains' might have originated from possible optimizations of medication use. Furthermore, dietary habits should be analyzed/standardized, since this might have an important impact on carnosine loading[35], but can be equally important for interpretation of changes in body composition (~lean mass). Further, measurements of perceived feasibility should be standardized (i.e. RPE assessments and questionnaires). Moreover, impact of training on daily activity levels could be explored, by comparing activity levels on training days with those on non-training days. This is possible with activity trackers, nowadays often incorporated into HR monitors. Ideally, participating subjects would have been using activity trackers before start of the intervention, which allows comparison between activity levels pre- and post-intervention. Future research should quantify carnosine loading and compliance rate with the supplementation protocol. Finally, larger and more controlled sample sizes are warranted as current findings lack external validity, due to the inclusion of minimally disabled PwMS and the non-representative female-male participant ratio[1].

7. Conclusion

Twenty-four weeks of periodized, home-based training induced significant training gains in PwMS and HC, seemed feasible and provided good adherence. Supplementation of BA did not have additional effects. Further, larger and more controlled research in more disabled PwMS is however warranted to support these findings.

8. List with abbreviations

ANOVA: Analysis of variance

BA: β-alanine

BMI: Body Mass Index

CPET: Cardiopulmonary Exercise Test

DEXA: Dual-Energy X-ray Absorptiometry

EAE: Experimental Autoimmune Encephalomyelitis

FAT%: Fat Percentage

FM: Fat Mass

EDSS: Expanded Disease Severity Scale

GXT: Graded Exercise Test

HC: Healthy Controls

HI: High-Intensity

HIIT: High-Intensity Interval Training

HR: Heart Rate

HRmax: Maximal Heart Rate

HRrecov: HR after two minutes of recovery

HRR: Heart Rate Recovery (= HRmax – HRrecov)

MCC: Muscle Carnosine Content

MS: Multiple Sclerosis

MSK: Musculoskeletal

La: Blood Lactate

LM: Lean Mass

PA: Physical Activity

PRE: Pre-intervention

POST: Post-intervention

PL: Placebo

PwMS: Persons with MS

QoL: Quality of Life

RPE: Ratings of Perceived Exertion

RPM: Repetition Per Minute

REVAL: Rehabilitation Research Centre

RER: Respiratory Exchange Ratio

SD: Standard Deviation

TTE: Time-To-Exhaustion

TWD: Total Work Done

VO_2: Oxygen Uptake

VO_{2max}: Maximal Oxygen Uptake

Wmax: Maximal Workload

References

1. Tullman MJ. Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. *The American journal of managed care* 2013; 19: S15-20. 2013/04/12.
2. Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. *The New England journal of medicine* 2000; 343: 938-952. 2000/09/28. DOI: 10.1056/nejm200009283431307.
3. Wens I, Dalgas U, Vandenabeele F, et al. Multiple sclerosis affects skeletal muscle characteristics. *PLoS One* 2014; 9: e108158. 2014/09/30. DOI: 10.1371/journal.pone.0108158.
4. Blikman LJ, van Meeteren J, Horemans HL, et al. Is physical behavior affected in fatigued persons with multiple sclerosis? *Archives of physical medicine and rehabilitation* 2015; 96: 24-29. 2014/09/23. DOI: 10.1016/j.apmr.2014.08.023.
5. Durstine JL, Painter P, Franklin BA, et al. Physical activity for the chronically ill and disabled. *Sports medicine (Auckland, NZ)* 2000; 30: 207-219. 2000/09/22.
6. Kobelt G. Costs and quality of life for patients with multiple sclerosis in Belgium. *Eur J Health Econ* 2006; 7 Suppl 2: S24-33. 2007/02/24. DOI: 10.1007/s10198-006-0377-7.
7. Zwibel HL and Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. *The American journal of managed care* 2011; 17 Suppl 5 Improving: S139-145. 2011/07/27.
8. Dalgas U, Stenager E, Jakobsen J, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. *Neurology* 2009; 73: 1478-1484. 2009/11/04. DOI: 10.1212/WNL.0b013e3181bf98b4.
9. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Archives of physical medicine and rehabilitation* 2013; 94: 1800-1828.e1803. 2013/05/15. DOI: 10.1016/j.apmr.2013.04.020.
10. Dalgas U, Stenager E and Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2008; 14: 35-53. 2007/09/21. DOI: 10.1177/1352458507079445.
11. Keytsman C, Hansen D, Wens I, et al. Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study. *Disability and rehabilitation* 2017: 1-6. 2017/10/28. DOI: 10.1080/09638288.2017.1395086.
12. Wens I, Dalgas U, Verboven K, et al. Impact of high intensity exercise on muscle morphology in EAE rats. *Physiological research* 2015; 64: 907-923. 2015/06/06.
13. Wens I, Dalgas U, Vandenabeele F, et al. High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. *PLoS One* 2015; 10: e0133697. 2015/09/30. DOI: 10.1371/journal.pone.0133697.
14. Keytsman et al., manuscript under review.
15. Wens I, Dalgas U, Vandenabeele F, et al. High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. *PLoS One* 2015; 10: 13. Article. DOI: 10.1371/journal.pone.0133697.
16. Collett J, Dawes H, Meaney A, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2011; 17: 594-603. 2011/01/21. DOI: 10.1177/1352458510391836.
17. Perri MG, Anton SD, Durning PE, et al. Adherence to exercise prescriptions: effects of prescribing moderate versus higher levels of intensity and frequency. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2002; 21: 452-458. 2002/09/05.
18. Gray SR, Ferguson C, Birch K, et al. High-intensity interval training: key data needed to bridge the gap from laboratory to public health policy. *Br J Sports Med* 2016; 50: 1231-1232. 2016/03/20. DOI: 10.1136/bjsports-2015-095705.

19. Storen O, Bratland-Sanda S, Haave M, et al. Improved VO2max and time trial performance with more high aerobic intensity interval training and reduced training volume: a case study on an elite national cyclist. *Journal of strength and conditioning research* 2012; 26: 2705-2711. 2011/11/30. DOI: 10.1519/JSC.0b013e318241deec.
20. Ronnestad BR, Hansen J, Thyli V, et al. 5-week block periodization increases aerobic power in elite cross-country skiers. *Scand J Med Sci Sports* 2016; 26: 140-146. 2015/02/05. DOI: 10.1111/sms.12418.
21. Issurin VB. New horizons for the methodology and physiology of training periodization. *Sports medicine (Auckland, NZ)* 2010; 40: 189-206. 2010/03/05. DOI: 10.2165/11319770-000000000-00000.
22. Issurin V. Block periodization versus traditional training theory: a review. *The Journal of sports medicine and physical fitness* 2008; 48: 65-75. 2008/01/24.
23. Ronnestad BR, Hansen J and Ellefsen S. Block periodization of high-intensity aerobic intervals provides superior training effects in trained cyclists. *Scand J Med Sci Sports* 2014; 24: 34-42. 2012/06/01. DOI: 10.1111/j.1600-0838.2012.01485.x.
24. Stroud N, Minahan C and Sabapathy S. The perceived benefits and barriers to exercise participation in persons with multiple sclerosis. *Disabil Rehabil* 2009; 31: 2216-2222. Journal Article 2009/11/12 06:00.
25. Asano M, Duquette P, Andersen R, et al. Exercise barriers and preferences among women and men with multiple sclerosis. *Disabil Rehabil* 2013; 35: 353-361. Article. DOI: 10.3109/09638288.2012.742574.
26. Conroy SS, Zhan M, Culpepper WJ, 2nd, et al. Self-directed exercise in multiple sclerosis: Evaluation of a home automated tele-management system. *Journal of telemedicine and telecare* 2017: 1357633x17702757. 2017/04/27. DOI: 10.1177/1357633x17702757.
27. Romberg A, Virtanen A, Ruutiainen J, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. *Neurology* 2004; 63: 2034-2038. 2004/12/15.
28. Khan F and Amatya B. Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. *Archives of physical medicine and rehabilitation* 2017; 98: 353-367. 2016/05/25. DOI: 10.1016/j.apmr.2016.04.016.
29. Hobson RM, Saunders B, Ball G, et al. Effects of beta-alanine supplementation on exercise performance: a meta-analysis. *Amino acids* 2012; 43: 25-37. 2012/01/25. DOI: 10.1007/s00726-011-1200-z.
30. Bellinger PM. beta-ALANINE SUPPLEMENTATION FOR ATHLETIC PERFORMANCE: AN UPDATE. *J Strength Cond Res* 2014; 28: 1751-1770. Review.
31. Boldyrev AA, Aldini G and Derave W. Physiology and pathophysiology of carnosine. *Physiological reviews* 2013; 93: 1803-1845. 2013/10/19. DOI: 10.1152/physrev.00039.2012.
32. Cairns SP. Lactic acid and exercise performance : culprit or friend? *Sports medicine (Auckland, NZ)* 2006; 36: 279-291. 2006/04/01.
33. Collett J, Meaney A, Howells K, et al. Acute recovery from exercise in people with multiple sclerosis: an exploratory study on the effect of exercise intensities. *Disability and rehabilitation* 2017; 39: 551-558. 2016/03/15. DOI: 10.3109/09638288.2016.1152604.
34. Dawes H, Collett J, Meaney A, et al. Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis. *Neurorehabilitation and neural repair* 2014; 28: 139-148. 2013/09/13. DOI: 10.1177/1545968313503218.
35. Harris RC, Tallon MJ, Dunnett M, et al. The absorption of orally supplied beta-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. *Amino acids* 2006; 30: 279-289. 2006/03/24. DOI: 10.1007/s00726-006-0299-9.
36. Wens I, Dalgas U, Vandenabeele F, et al. High Intensity Aerobic and Resistance Exercise Can Improve Glucose Tolerance in Persons With Multiple Sclerosis: A Randomized Controlled Trial. *American journal of physical medicine & rehabilitation* 2017; 96: 161-166. 2016/07/01. DOI: 10.1097/phm.0000000000000563.

37. Heine M, Hoogervorst EL, Hacking HG, et al. Validity of maximal exercise testing in people with multiple sclerosis and low to moderate levels of disability. *Physical therapy* 2014; 94: 1168-1175. 2014/03/29. DOI: 10.2522/ptj.20130418.
38. Stout JR, Graves BS, Smith AE, et al. The effect of beta-alanine supplementation on neuromuscular fatigue in elderly (55-92 Years): a double-blind randomized study. *J Int Soc Sports Nutr* 2008; 5: 21. 2008/11/11. DOI: 10.1186/1550-2783-5-21.
39. Daanen HA, Lamberts RP, Kallen VL, et al. A systematic review on heart-rate recovery to monitor changes in training status in athletes. *International journal of sports physiology and performance* 2012; 7: 251-260. 2012/02/24.
40. Nana A, Slater GJ, Stewart AD, et al. Methodology review: using dual-energy X-ray absorptiometry (DXA) for the assessment of body composition in athletes and active people. *International journal of sport nutrition and exercise metabolism* 2015; 25: 198-215. 2014/07/17. DOI: 10.1123/ijsnem.2013-0228.
41. Artioli GG, Gualano B, Smith A, et al. Role of beta-alanine supplementation on muscle carnosine and exercise performance. *Medicine and science in sports and exercise* 2010; 42: 1162-1173. 2010/05/19. DOI: 10.1249/MSS.0b013e3181c74e38.
42. Stellingwerff T, Anwander H, Egger A, et al. Effect of two beta-alanine dosing protocols on muscle carnosine synthesis and washout. *Amino acids* 2012; 42: 2461-2472. 2011/08/19. DOI: 10.1007/s00726-011-1054-4.
43. Breil FA, Weber SN, Koller S, et al. Block training periodization in alpine skiing: effects of 11-day HIT on VO2max and performance. *Eur J Appl Physiol* 2010; 109: 1077-1086. 2010/04/07. DOI: 10.1007/s00421-010-1455-1.
44. Darr KC, Bassett DR, Morgan BJ, et al. Effects of age and training status on heart rate recovery after peak exercise. *The American journal of physiology* 1988; 254: H340-343. 1988/02/01. DOI: 10.1152/ajpheart.1988.254.2.H340.
45. Giallauria F, Del Forno D, Pilerci F, et al. Improvement of heart rate recovery after exercise training in older people. *Journal of the American Geriatrics Society* 2005; 53: 2037-2038. 2005/11/09. DOI: 10.1111/j.1532-5415.2005.00479_4.x.
46. Watson AM, Brickson SL, Prawda ER, et al. Short-Term Heart Rate Recovery is Related to Aerobic Fitness in Elite Intermittent Sport Athletes. *Journal of strength and conditioning research* 2017; 31: 1055-1061. 2016/07/22. DOI: 10.1519/jsc.0000000000001567.
47. Caso G and Garlick PJ. Control of muscle protein kinetics by acid-base balance. *Current opinion in clinical nutrition and metabolic care* 2005; 8: 73-76. 2004/12/09.
48. Burd NA, Tang JE, Moore DR, et al. Exercise training and protein metabolism: influences of contraction, protein intake, and sex-based differences. *Journal of applied physiology (Bethesda, Md : 1985)* 2009; 106: 1692-1701. 2008/11/28. DOI: 10.1152/japplphysiol.91351.2008.
49. Gillen JB, Martin BJ, MacInnis MJ, et al. Twelve Weeks of Sprint Interval Training Improves Indices of Cardiometabolic Health Similar to Traditional Endurance Training despite a Five-Fold Lower Exercise Volume and Time Commitment. *PLoS One* 2016; 11: e0154075. 2016/04/27. DOI: 10.1371/journal.pone.0154075.
50. Spodaryk K, Szmatlan U and Berger L. The relationship of plasma ammonia and lactate concentrations to perceived exertion in trained and untrained women. *Eur J Appl Physiol Occup Physiol* 1990; 61: 309-312. 1990/01/01.
51. McCormack WP, Stout JR, Emerson NS, et al. Oral nutritional supplement fortified with beta-alanine improves physical working capacity in older adults: a randomized, placebo-controlled study. *Experimental gerontology* 2013; 48: 933-939. 2013/07/09. DOI: 10.1016/j.exger.2013.06.003.
52. del Favero S, Roschel H, Solis MY, et al. Beta-alanine (Carnosyn) supplementation in elderly subjects (60-80 years): effects on muscle carnosine content and physical capacity. *Amino acids* 2012; 43: 49-56. 2011/12/07. DOI: 10.1007/s00726-011-1190-x.

53. Bellinger PM. beta-Alanine supplementation for athletic performance: an update. *Journal of strength and conditioning research* 2014; 28: 1751-1770. 2013/11/28. DOI: 10.1519/jsc.0000000000000327.
54. Trexler ET, Smith-Ryan AE, Stout JR, et al. International society of sports nutrition position stand: Beta-Alanine. *J Int Soc Sports Nutr* 2015; 12: 30. 2015/07/16. DOI: 10.1186/s12970-015-0090-y.
55. Amorini AM, Nociti V, Petzold A, et al. Serum lactate as a novel potential biomarker in multiple sclerosis. *Biochimica et biophysica acta* 2014; 1842: 1137-1143. 2014/04/15. DOI: 10.1016/j.bbadis.2014.04.005.
56. Tallon MJ, Harris RC, Maffulli N, et al. Carnosine, taurine and enzyme activities of human skeletal muscle fibres from elderly subjects with osteoarthritis and young moderately active subjects. *Biogerontology* 2007; 8: 129-137. 2006/09/13. DOI: 10.1007/s10522-006-9038-6.
57. Stuerenburg HJ and Kunze K. Concentrations of free carnosine (a putative membrane-protective antioxidant) in human muscle biopsies and rat muscles. *Archives of gerontology and geriatrics* 1999; 29: 107-113. 2004/09/18.
58. Sosnoff JJ, Finlayson M, McAuley E, et al. Home-based exercise program and fall-risk reduction in older adults with multiple sclerosis: phase 1 randomized controlled trial. *Clinical rehabilitation* 2014; 28: 254-263. 2013/08/29. DOI: 10.1177/0269215513501092.
59. Cakt BD, Nacir B, Genc H, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. *American journal of physical medicine & rehabilitation* 2010; 89: 446-457. 2010/03/11. DOI: 10.1097/PHM.0b013e3181d3e71f.
60. Finkelstein J, Lapshin O, Castro H, et al. Home-based physical telerehabilitation in patients with multiple sclerosis: a pilot study. *J Rehabil Res Dev* 2008; 45: 1361-1373. Journal Article 2008/01/01 00:00.
61. Gillinov S, Etiwy M, Wang R, et al. Variable Accuracy of Wearable Heart Rate Monitors during Aerobic Exercise. *Medicine and science in sports and exercise* 2017; 49: 1697-1703. 2017/07/15. DOI: 10.1249/mss.0000000000001284.

Appendix

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
19/09/'17	Uitleg gebruikte protocol	Promotor: Copromotor: Student(e): Student(e):
11/10/'17	Data overdracht	Promotor: Copromotor: Student(e): Student(e):
7/12/'17	Overlopen data-analyse + overlopen missing data	Promotor: Copromotor: Student(e): Student(e):
30/01/'18	Overlopen gebruikte statistiek	Promotor: Copromotor: Student(e): Student(e):
15/5/'18	Overlopen discussie	Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
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Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2018**

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